Appendix E Evidence tables

Contents

Study	Agrawal et al. (2009)
Pain category	Peripheral pain
Study design	Country: India Design: Parallel Inclusion criteria: Diabetic at least 6 months with good glycaemic control, daily pain of at least moderate severity for >3months, pain intensity of >4 on VASpi, HbA1c <11 Exclusion criteria: Patients with erratic glycaemic control, peripheral vascular disease with absent foot pulses, prescence of foot ulceration, treatment with sublingual glyceryl trinitrate, males on concommitant sildenafil therapy, presence of other causes of neuropathy Study length (days): 84 Intention-to-treat analysis? No
Participants	Total number of patients: 83 Number of males: not reported Underlying cause of neuropathic pain: Painful diabetic neuropathy Mean duration of NP (in months): not reported Baseline pain severity: 7.68 (VASpi) Mean age: 60.74
Intervention(s)	(1) Sodium valproate (fixed dose) + Placebo spray Intervention: valproate Length of treatment (weeks): 12 Fixed/flexible dose regimen: Fixed dose Set dose: 1400mg/d Notes: dose was 20 mg/kg/day (2) Placebo + placebo spray Intervention: placebo Length of treatment (weeks): 12 Fixed/flexible dose regimen: Fixed dose
Concomitant treatments	Drug free baseline period? Yes (duration: 14d) Concomitant pain treatment allowed? No (and no rescue analgesics allowed either)
Outcomes measures and effect sizes	

		SODIUM VALPROATE (FIXED DOSE) + PLACEBO SPRAY			PLACEBO + PLACEBO SPRAY			
		N	k	mean	N	k	mean	Δ
pain score:								
NRS/NRS Pain – 0d	Continuous	20		6.9 (SD 0.447)	20		6.65 (SD 1.12)	
NRS/NRS Pain – 84d	Continuous	20		4.3 (SD 0.85)	20		4.15 (SD 1.12)	MD=0.150 (CI: -0.465, 0.765)
VAS – 0d	Continuous	20		8 (SD 0.805)	20		7.35 (SD 1.16)	
VAS – 84d	Continuous	20		6.15 (SD 1.43)	20		6.9 (SD 1.03)	MD=-0.750 (CI: -1.522, 0.022)

	PPI (from MPQ) – 0d	Continuous	20		3.4 (SD 0.492)	20		2.85 (SD 0.626)	
	PPI (from MPQ) – 84d	Continuous	20		2.7 (SD 0.671)	20		2.55 (SD 0.581)	MD=0.150 (CI: -0.239, 0.539)
	SF McGill – 0d	Continuous	20		24.8 (SD 4.96)	20		22.4 (SD 4.25)	
	SF McGill – 84d	Continuous	20		20.4 (SD 5.99)	20		22.1 (SD 4.38)	MD=-1.750 (CI: -5.004, 1.504)
	adverse events:								
	any adverse event – 84d	Dichotomous	20	4	(20.0%)	21	1	(4.8%)	OR=4.750 (CI: 0.481, 46.906)
	any adverse event – 84d	Dichotomous	20	4	(20.0%)	20	1	(4.8%)	OR=4.750 (CI: 0.481, 46.906)
	headache – 84d	Dichotomous	20	0	(0.0%)	20	0	(0.0%)	OR=1.000 (CI: 0.019, 52.849)
	headache – 84d	Dichotomous	20	0	(0.0%)	21	0	(0.0%)	OR=1.000 (CI: 0.019, 52.849)
	Nausea – 84d	Dichotomous	20	2	(10.0%)	21	1	(4.8%)	OR=2.111 (CI: 0.176, 25.349)
	Nausea – 84d	Dichotomous	20	2	(10.0%)	20	1	(4.8%)	OR=2.111 (CI: 0.176, 25.349)
	Sedation – 84d	Dichotomous	20	1	(5.0%)	21	0	(0.0%)	OR=3.154 (CI: 0.121, 82.165)
	Sedation – 84d	Dichotomous	20	1	(5.0%)	20	0	(0.0%)	OR=3.154 (CI: 0.121, 82.165)
	Weight gain – 84d	Dichotomous	20	0	(0.0%)	20	0	(0.0%)	OR=1.000 (CI: 0.019, 52.849)
	Weight gain – 84d	Dichotomous	20	0	(0.0%)	21	0	(0.0%)	OR=1.000 (CI: 0.019, 52.849)
	treatment withdrawal:								
	due to lack of efficacy – 84d	Dichotomous	20	0	(0.0%)	20	1	(4.8%)	OR=0.317 (CI: 0.012, 8.260)
	due to lack of efficacy – 84d	Dichotomous	20	0	(0.0%)	21	1	(4.8%)	OR=0.317 (CI: 0.012, 8.260)
Comments	-								

Definitions of abbreviations are given at the end of this document.

Study	Arbaiza & Vidal (2007)
Pain category	Peripheral pain
Study design	Country: Peru Design: Parallel Inclusion criteria: NCP of moderate to severe intensity with a duration of at least 3 months Exclusion criteria: Patients who were unable to provide adequate information about their pain, or had mainly somatic, visceral or sympathetically maintained pain. Also excluded were those scheduled for surgery, radiotherapy, chemotherapy or hormone therapy, use of tricyclic antidepressants, tramadol or othe types of opioid, change in dosage of antiepileptics within 30 days prior to the study, respiratory failure, COPD, intracranial hypertension, dependance on opioid analgesics, alcohol or other drugs, history of psychiatric illness Study length (days): 42 Intention-to-treat analysis? No
Participants	Total number of patients: 36 Number of males: 14 (38.9%) Underlying cause of neuropathic pain: Mixed pain (incl cancer&chemotherpy-induced) Mean duration of NP (in months): 4 Baseline pain severity: 7 (NRS (average of arm means)) Mean age: 49.86
Intervention(s)	(1) Tramadol 2.5mg drops (flexible dose) Intervention: tramadol Length of treatment (weeks): 6

	Fixed/flexible dose regimen: Flexible dose Mean dose: 254mg/d Range: 239.8–359.7 Notes: Tramadol was administered 1mg/kg of bodyweight every 6 hours (concentration 2.5mg per drop). Mean number of drops every 6 hours was 27.5 (tramadol) and 25.4 (placebo) (2) Placebo Intervention: placebo Length of treatment (weeks): 6 Fixed/flexible dose regimen: Flexible dose
Concomitant treatments	Drug free baseline period? No Concomitant pain treatment allowed? Yes (Previous anticonvulsants, paracetamol as rescue analgesic)
Outcomes measures and effect sizes	

		TRAMADOL 2.5MG DROPS (FLEXIBLE DOSE)			PLACEBO			
		N	k	mean	N	k	mean	Δ
pain score:								
VAS – 0d	Continuous	18		6.8	18		7	
VAS – 42d	Continuous	13		2.9	12		4.3	MD=-1.400
patient-reported improvement in daily physical and emotional functioning, including sleep:								
NRS Sleep – 42d	Dichotomous	13	3	(23.1%)	12	8	(66.7%)	OR=0.150 (CI: 0.026, 0.874)
major adverse events (defined as leading to withdrawal):								
any major adverse event – 42d	Dichotomous	18	3	(16.7%)	18	0	(0.0%)	OR=8.355 (CI: 0.400, 174.498)
adverse events:								
any adverse event – 42d	Dichotomous	18	7	(38.9%)	18	0	(0.0%)	OR=24.130 (CI: 1.256, 463.720)

Comments	-

Definitions of abbreviations are given at the end of this document.

Study	Arezzo et al. (2008)
Pain category	Peripheral pain
Study design	Country: USA Design: Parallel Inclusion criteria: Duration of PDN >3months, VASpi >40mm (greater than or equal to 4 on NRS over last 7 days), 18 years or older Exclusion criteria: creatinine clearance rates of 60 ml/min or less, conditions that could confound assessment of pain due to PDN, prior use of potential retinotoxins, use of medications and supplemens commonly used for relief of pain, antiepileptics, anti-depressants (except stable SSRIs for anxiety or depression), NSAIDs Study length (days): 91 Intention-to-treat analysis? Yes

Participants	Total number of patients: 167 Number of males: 103 (61.7%) Underlying cause of neuropathic pain: Painful diabetic neuropathy Mean duration of NP (in months): 55.8 Baseline pain severity: 6.43 (NRS) Mean age: 58
Intervention(s)	(1) Pregabalin 600mg/d Intervention: pregabalin Length of treatment (weeks): 13 Fixed/flexible dose regimen: Fixed dose Set dose: 600mg/d Notes: taken in 2 tablets each day; 1 week titration period - starting with single dose of 150 mg/d on day 1, 2-150 mg/d on day 2-6, and 2-300 mg/d on day 7 and continued for remainder of the study (2) Placebo Intervention: placebo Length of treatment (weeks): Fixed/flexible dose regimen: Fixed dose
Concomitant treatments	Drug free baseline period? Yes (duration: 7d) Concomitant pain treatment allowed? Yes (medications to treat NP excluded (including anti-epileptics, anti-depressants, NSAIDs); however, aspirin for cardiac and stroke prophylaxis (up to 325 mg/d), acetaminophen (up to 4 g/d) also allowed, SSRIs for depression or anxiety (if stable), benzodiazepines such as lorazepam for sleep problems (stable dose for greater than 30 days); SSRIs could be considered concomitant medications)

Outcomes measures and effect sizes

		PREGABALIN 600MG/D			PLACEBO			
		N	k	mean	N	k	mean	Δ
pain score:								
NRS/NRS Pain – 0d	Continuous	82		6.28 (SD 1.47)	85		6.58 (SD 1.58)	
patient-reported global improvement:								
PGIC - much worse – 91d	Dichotomous	82	0	(0.0%)	85	0	(0.0%)	OR=1.036 (CI: 0.020, 52.842)
PGIC - moderately worse – 91d	Dichotomous	82	0	(0.0%)	85	2	(2.4%)	OR=0.202 (CI: 0.010, 4.281)
PGIC - minimally worse – 91d	Dichotomous	82	5	(6.1%)	85	10	(11.8%)	OR=0.487 (CI: 0.159, 1.492)
PGIC - no change – 91d	Dichotomous	82	11	(13.4%)	85	28	(32.9%)	OR=0.315 (CI: 0.145, 0.688)
PGIC - minimally better – 91d	Dichotomous	82	14	(17.1%)	85	10	(11.8%)	OR=1.544 (CI: 0.643, 3.705)
PGIC - moderately better – 91d	Dichotomous	82	28	(34.1%)	85	19	(22.4%)	OR=1.801 (CI: 0.908, 3.572)
PGIC - at least moderately better – 91d	Dichotomous	82	52	(63.4%)	85	35	(41.2%)	OR=2.476 (CI: 1.328, 4.618)
PGIC - much better – 91d	Dichotomous	82	24	(29.3%)	85	16	(18.8%)	OR=1.784 (CI: 0.866, 3.675)
patient-reported improvement in daily physical and emotional functioning, including sleep:								
NRS Sleep – 91d	Continuous	82		2.64	85		3.72	MD=-1.080 (CI: -1.750, -0.410)
major adverse events (defined as leading to withdrawal):								
any major adverse event – 91d	Dichotomous	82	14	(17.1%)	85	10	(11.8%)	OR=1.544 (CI: 0.643, 3.705)
adverse events:								
Dizziness – 91d	Dichotomous	82	27	(32.9%)	85	5	(5.9%)	OR=7.855 (CI: 2.849, 21.654)

	Dry mouth – 91d	Dichotomous	82	1	(1.2%)	85	4	(4.7%)	OR=0.250 (CI: 0.027, 2.285)
	euphoria – 91d	Dichotomous	82	0	(0.0%)	85	3	(3.5%)	OR=0.143 (CI: 0.007, 2.809)
	oedema – 91d	Dichotomous	82	0	(0.0%)	85	3	(3.5%)	OR=0.143 (CI: 0.007, 2.809)
	Peripheral oedema – 91d	Dichotomous	82	30	(36.6%)	85	27	(31.8%)	OR=1.239 (CI: 0.653, 2.352)
	Somnolence – 91d	Dichotomous	82	11	(13.4%)	85	5	(5.9%)	OR=2.479 (CI: 0.822, 7.480)
	Weight gain – 91d	Dichotomous	82	12	(14.6%)	85	1	(1.2%)	OR=14.400 (CI: 1.827, 113.492)
	treatment withdrawal:								
	unspecified/other reason – 91d	Dichotomous	82	28	(34.1%)	85	24	(28.2%)	OR=1.318 (CI: 0.683, 2.542)
	use of rescue medication:								
	proportion taking up to 4 g/d of paracetamol – 91d	Dichotomous	82	6	(7.3%)	85	7	(8.2%)	OR=0.880 (CI: 0.283, 2.738)
	ITT/LOCF (last-observation carried forward)								
	pain score:								
	NRS/NRS Pain – 91d	Continuous	82		3.54	85		4.82	MD=-1.280 (CI: -1.960, -0.600)
	NRS/NRS Pain – 91d	Mean change	82		-2.74	85		-1.76	MD=-0.980
	ITT/BOCF (baseline observation carried forward)								
	pain score:								
	NRS/NRS Pain – 91d	Continuous	82		4.32	85		5.03	MD=-0.710 (CI: -1.390, -0.030)
Comments	no comments								

Definitions of abbreviations are given at the end of this document.

Study	Backonja et al. (1998)
Pain category	Peripheral pain
Study design	Country: USA Design: Parallel Inclusion criteria: Painful diabetic neuropathy for of 1-5 years, Pain score VAS at least 40mm Exclusion criteria: Presence of other severe pain that could confound assessment or self evaluation of the pain due to diabetic neuropathy, receipt of any investigational drug within 30 days prior to screening, amputation other than toes, creatinine clearance of less than 60mL/min. Study length (days): 56 Intention-to-treat analysis? Yes
Participants	Total number of patients: 165 Number of males: 99 (60.0%) Underlying cause of neuropathic pain: Painful diabetic neuropathy Mean duration of NP (in months): not reported Baseline pain severity: 6.45 (NRS (average of arm means)) Mean age: 53
Intervention(s)	(1) Gabapentin 3600mg/d Intervention: gabapentin Length of treatment (weeks): 8 Fixed/flexible dose regimen: Fixed dose

	Set dose: 3600mg/d Notes: 4 week titration: week 1: 900 mg/d, week 2: 1800 mg/d, week 3: 2400 mg/d, week 4: 3600 mg/d (2) Placebo Intervention: placebo Length of treatment (weeks): 8 Fixed/flexible dose regimen: Fixed dose
Concomitant treatments	Drug free baseline period? Unclear Concomitant pain treatment allowed? Yes (SSRIs (which could be considered concomitant medications) but others which could affect symptoms of PDN were prohibited; paracetamol or asprin were allowed)

Outcomes measures and effect sizes

		GABAPENTIN 3600MG/D			PLACEBO			
		N	k	mean	N	k	mean	Δ
pain score:								
McGill VAS – 0d	Continuous	82		67.7	79		71.2	
McGill VAS – 56d	Continuous	82		36.9	79		53.8	MD=-16.900
PPI (from MPQ) – 0d	Continuous	81		2.4	79		2.4	
PPI (from MPQ) – 56d	Continuous	81		1.2	79		1.8	MD=-0.600
SF McGill – 0d	Continuous	82		20.5	79		21	
SF McGill – 56d	Continuous	82		10.9	79		16.8	MD=-5.900
patient-reported global improvement:								
PGIC - worse (all grades) – 56d	Dichotomous	79	2	(2.5%)	76	13	(17.1%)	OR=0.126 (CI: 0.027, 0.579)
PGIC - no change or minimally better – 56d	Dichotomous	79	30	(38.0%)	76	38	(50.0%)	OR=0.612 (CI: 0.323, 1.160)
PGIC - at least moderately better – 56d	Dichotomous	79	47	(59.5%)	76	25	(32.9%)	OR=2.996 (CI: 1.554, 5.776)
patient-reported improvement in daily physical and emotional functioning, including sleep:								
POMS – 0d	Continuous	76		33	73		40	
POMS – 56d	Continuous	76		22.8	73		31.9	MD=-9.140 (CI: -17.290, -0.990)
major adverse events (defined as leading to withdrawal):								
any major adverse event – 56d	Dichotomous	84	7	(8.3%)	81	5	(6.2%)	OR=1.382 (CI: 0.420, 4.545)
adverse events:								
Confusion	Dichotomous	84	7	(8.3%)	81	1	(1.2%)	OR=7.273 (CI: 0.874, 60.501)
Diarrhoea	Dichotomous	84	9	(10.7%)	81	7	(8.6%)	OR=1.269 (CI: 0.449, 3.584)
Dizziness – 56d	Dichotomous	84	20	(23.8%)	81	4	(4.9%)	OR=6.016 (CI: 1.956, 18.502)
headache	Dichotomous	84	9	(10.7%)	81	3	(3.7%)	OR=3.120 (CI: 0.813, 11.970)
Nausea – 56d	Dichotomous	84	7	(8.3%)	81	4	(4.9%)	OR=1.750 (CI: 0.492, 6.222)
Somnolence – 56d	Dichotomous	84	19	(22.6%)	81	5	(6.2%)	OR=4.443 (CI: 1.572, 12.561)
overall improvement in quality of life:								
SF36 bodily pain – 0d	Continuous	77		40.6	76		37.5	
SF36 bodily pain – 56d	Continuous	77		55.2	76		47.4	MD=7.800
SF36 vitality – 0d	Continuous	78		41.5	76		40.8	
SF36 vitality – 56d	Continuous	78		53.5	76		43.7	MD=9.800
SF36 mental health – 0d	Continuous	78		72	76		66.5	
SF36 mental health – 56d	Continuous	78		75.7	76		70.4	MD=5.300
treatment withdrawal:								
due to lack of efficacy – 56d	Dichotomous	84	1	(1.2%)	81	5	(6.2%)	OR=0.183 (CI: 0.021, 1.603)
unspecified/other reason – 56d	Dichotomous	84	3	(3.6%)	81	3	(3.7%)	OR=0.963 (CI: 0.189, 4.916)

	protocol deviation – 56d	Dichotomous	84	3	(3.6%)	81	3	(3.7%)	OR=0.963 (CI: 0.189, 4.916)
	ITT/LOCF (last-observation carried forward)								
	pain score:								
	NRS/NRS Pain – 0d[a]	Continuous	82		6.4 (SD 1.36)	80		6.5 (SD 1.57)	
	NRS/NRS Pain – 56d	Continuous	82		3.9	80		5.1	MD=-1.200 (CI: -1.840, -0.560)
	patient-reported improvement in daily physical and emotional functioning, including sleep:								
	NRS Sleep – 0d	Continuous	82		5.2	80		5.1	
	NRS Sleep – 56d	Continuous	82		2.3	80		3.8	MD=-1.470 (CI: -2.170, -0.770)
	Observed cases								
	pain score:								
	NRS/NRS Pain – 0d[a]	Continuous	82		6.4 (SD 1.36)	80		6.5 (SD 1.57)	
	NRS/NRS Pain – 28d[a]	Continuous	70		4.1 (SD 2.38)	65		5 (SD 2.24)	MD=-0.900 (CI: -1.262, -0.538)
	NRS/NRS Pain – 56d[a]	Continuous	70		3.6 (SD 2.3)	65		4.55 (SD 2.42)	MD=-0.950 (CI: -1.357, -0.543)
	patient-reported improvement in daily physical and emotional functioning, including sleep:								
	Normalised (10-pt) sleep interference measure – 0d[b]	Continuous	82		5.2 (SD 2.26)	80		5.1 (SD 2.24)	
	Normalised (10-pt) sleep interference measure – 56d[b]	Continuous	70		1.9 (SD 2.51)	65		2.95 (SD 2.22)	
	NRS Sleep – 0d[a]	Continuous	82		5.2 (SD 2.26)	80		5.1 (SD 2.24)	
	NRS Sleep – 56d[a]	Continuous	70		1.9 (SD 2.51)	65		2.95 (SD 2.22)	MD=-1.050 (CI: -1.474, -0.626)
	[a] SD calculated from unlabelled error bars (assumed to be SEMs) [b] SD calculated from unlabelled error bars (assumed to be SEMs); based on NRS Sleep								
Comments	there was a 1 week baseline period but it is not clear if this was drug-free; ITT analysis included all patients randomised who received at least 1 dose of study medication (however, patients with no data recorded for a particular parameter were automatically excluded from analyses of that parameter)								

Definitions of abbreviations are given at the end of this document.

Study	Backonja et al. (2008)
Pain category	Peripheral pain
Study design	Country: USA Design: Parallel Inclusion criteria: Aged 18 and over with a diagnosis of PHN and an average NPRS score of 3-9 (inclusive) were eligible if at least 6 months had elapsed since vesicle crusting Exclusion criteria: Pain at or around facial area Study length (days): 84 Intention-to-treat analysis? Yes
Participants	Total number of patients: 402 Number of males: 190 (47.3%) Underlying cause of neuropathic pain: Post-herpetic neuralgia Mean duration of NP (in months): 46.8

	Baseline pain severity: 5.9 (NRS (average of arm means)) Mean age: 71.1
Intervention(s)	(1) Capasaicin 8% patch (60 minutes only) Intervention: capsaicin patch Length of treatment (weeks): Fixed/flexible dose regimen: Fixed dose Notes: Study reports 8% capsaicin patch, applied for 60 minutes once (topical anaesthetic cream applied 60 mins before patches) (2) Active placebo patch Intervention: placebo Length of treatment (weeks): Fixed/flexible dose regimen: Fixed dose Notes: As with capsaicin patch, this was applied for 1 hr then removed (topical anaesthetic cream applied 60 mins before patches)
Concomitant treatments	Drug free baseline period? Unclear Concomitant pain treatment allowed? Yes (stable dosages of long-term pain medications for at least 21 days before treatment and must stay on a stable dose during the study duration; opioids rescue meds only up to 5 days after application and then as needed but not permited after day 5, topical medications not allowed)

Outcomes measures and effect sizes

		CAPASAICIN 8% PATCH (60 MINUTES ONLY)			ACTIVE PLACEBO PATCH			
		N	k	mean	N	k	mean	Δ
pain score:								
NRS/NRS Pain – 28d[a]	Percentage change from baseline	190		-30 (SD 2)	202		-22 (SD 1.5)	MD=-8.000 (CI: -8.352, -7.648)
NRS/NRS Pain – 56d[a]	Percentage change from baseline	184		-31.5 (SD 2)	196		-21 (SD 2)	MD=-10.500 (CI: -10.902, -10.098)
NRS/NRS Pain – 84d[a]	Percentage change from baseline	172		-32 (SD 2.5)	185		-23 (SD 3)	MD=-9.000 (CI: -9.571, -8.429)
at least 30% pain reduction (NRS) – 56d[b]	Dichotomous from baseline to average f-u	205	87		197	63		OR=1.568 (CI: 1.043, 2.358)
at least 30% pain reduction (NRS) – 84d[c]	Dichotomous from baseline to average f-u	205	91		197	69		OR=1.481 (CI: 0.991, 2.213)
patient-reported global improvement:								
PGIC - worse (all grades) or no change – 84d	Dichotomous	205	92	(44.9%)	197	111	(56.3%)	OR=0.631 (CI: 0.425, 0.935)
PGIC - better (all grades) – 84d	Dichotomous	205	114	(55.6%)	197	85	(43.1%)	OR=1.651 (CI: 1.113, 2.448)
major adverse events (defined as leading to withdrawal):								
any major adverse event – 84d	Dichotomous	205	1	(0.5%)	197	0	(0.0%)	OR=2.897 (CI: 0.117, 71.547)
adverse events:								
Dizziness – 84d	Dichotomous	205	5	(2.4%)	197	6	(3.0%)	OR=0.796 (CI: 0.239, 2.651)
headache – 84d	Dichotomous	205	7	(3.4%)	197	8	(4.1%)	OR=0.835 (CI: 0.297, 2.348)
Nausea – 84d	Dichotomous	205	8	(3.9%)	197	2	(1.0%)	OR=3.959 (CI: 0.830, 18.881)
oedema – 84d	Dichotomous	205	12	(5.9%)	197	2	(1.0%)	OR=6.062 (CI: 1.339, 27.445)

Pruritus – 84d	Dichotomous	205	10	(4.9%)	197	6	(3.0%)	OR=1.632 (CI: 0.582, 4.580)
site erythema – 84d	Dichotomous	205	193	(94.1%)	197	128	(65.0%)	OR=8.670 (CI: 4.515, 16.649)
site pain – 84d	Dichotomous	205	114	(55.6%)	197	43	(21.8%)	OR=4.487 (CI: 2.901, 6.939)
Vomiting – 84d	Dichotomous	205	6	(2.9%)	197	3	(1.5%)	OR=1.950 (CI: 0.481, 7.906)
treatment withdrawal: due to lack of efficacy – 84d	Dichotomous	205	10	(4.9%)	197	9	(4.6%)	OR=1.071 (CI: 0.426, 2.695)
unspecified/other reason – 84d	Dichotomous	205	4	(2.0%)	197	6	(3.0%)	OR=0.633 (CI: 0.176, 2.280)
lost to follow-up – 84d	Dichotomous	205	3	(1.5%)	197	2	(1.0%)	OR=1.448 (CI: 0.239, 8.760)
poor compliance – 84d	Dichotomous	205	1	(0.5%)	197	1	(0.5%)	OR=0.961 (CI: 0.060, 15.467)
All withdrawals – 84d	Dichotomous	205	19	(9.3%)	197	18	(9.1%)	OR=1.016 (CI: 0.516, 1.998)

[a] extracted from graph
[b] Baseline to weeks 2-8
[c] Baseline to weeks 2-12

Graph from which NRS data extracted appeared to have an error: the key appeared reversed with control doing better than the intervention group. However, as the data in the text stated that the intervention group had better pain relief, it was presumed that the key on the graph was incorrect.

Comments	study had a baseline screening period of at least 14 days (unclear if any of this was drug-free); 1 patient randomised to intervention had the control patch instead - they were included in the intervention group for efficacy analyses but in the control group for safety analyses; authors did not use week 1 scores so as to avoid potentially confounding effect of opioid rescue medications taken during days 0 to 5

Definitions of abbreviations are given at the end of this document.

Study	Bansal et al. (2009)
Pain category	Peripheral pain
Study design	Country: India Design: Crossover Inclusion criteria: 18 and 75 years with PDN from Type 2 diabetes mellitus for at least 1 month, and having pain of more than 50% as assessed by VAS were eligible to be recruited in the study Exclusion criteria: clinically significant or unstable medical or psychiatric illnesses, history of renal or liver disease, epilepsy, psychiatric illness, uncontrolled hypertension, malignancy and substance abuse, pregnancy, women intending to become pregnant, lactating mothers, patietns with evidence of other causes of neuropathy and painful conditions, those taking anticonvulsants, antidepressants, local anaesthetics and opioids, and recent treatment with any investigational drugs within the last 30 days Study length (days): 98 Intention-to-treat analysis? Yes
Participants	Total number of patients: 51 Number of males: 19 (37.3%)

	Underlying cause of neuropathic pain: Painful diabetic neuropathy Mean duration of NP (in months): 12 Baseline pain severity: 70 (VAS (median)) Mean age: 54.5
Intervention(s)	(1) Amitriptyline flexi-dose (10-50mg) Intervention: amitriptyline Length of treatment (weeks): 5 Fixed/flexible dose regimen: Flexible dose Mean dose: 16mg/d Range: 10–50 Notes: starting dose was 10 mg and upward titration (if required) after 1 week and then after 3 weeks, depending on therapeutic response (2) Pregabalin flexi-dose (150-600mg) Intervention: pregabalin Length of treatment (weeks): 5 Fixed/flexible dose regimen: Flexible dose Mean dose: 218mg/d Range: 150–600 Notes: starting dose was 75 mg and upward titration (if required) after 1 week and then after 3 weeks, depending on therapeutic response
Concomitant treatments	Drug free baseline period? Yes (duration: 7d) Concomitant pain treatment allowed? No (those taking anti-convulsants, anti-depressants, local anaesthetics and opioids were all excluded; any treatments for DPN were discontinued for 1 week; rescue medications allowed (up to 3g/day of paracetamol) during the run-in period and washout period.)

Outcomes measures and effect sizes

		AMITRIPTYLINE FLEXI-DOSE (10-50MG)			PREGABALIN FLEXI-DOSE (150-600MG)			
		N	k	mean	N	k	mean	Δ
pain score:								
VAS – 0d	Continuous	44		med: 70[a]	44		med: 70[b]	
VAS – 35d	Continuous	44		med: 42.5[c]	44		med: 40[d]	
at least 50% pain reduction (VAS) – 35d	Dichotomous	51	15	(29.4%)	51	21	(41.2%)	
SF McGill – 0d	Continuous	44		med: 9[e]	44		med: 9[f]	
SF McGill – 35d	Continuous	44		med: 5[g]	44		med: 4[h]	
major adverse events (defined as leading to withdrawal):								
any major adverse event – 35d	Dichotomous	51	17[i]	(33.3%)	51	6[i]	(11.8%)	OR=3.988 (CI: 1.391, 11.434)
any major adverse event – 35d	Dichotomous	44	17[i]	(33.3%)	44	6[i]	(11.8%)	OR=3.988 (CI: 1.391, 11.434)
adverse events:								
Confusion – 35d	Dichotomous	44	0	(0.0%)	44	1	(2.0%)	OR=0.326 (CI: 0.013, 8.219)
Confusion – 35d	Dichotomous	51	0	(0.0%)	51	1	(2.0%)	OR=0.326 (CI: 0.013, 8.219)
Constipation – 35d	Dichotomous	44	2	(3.9%)	44	3	(5.9%)	OR=0.651 (CI: 0.103, 4.099)

	Constipation – 35d	Dichotomous	51	2	(3.9%)	51	3	(5.9%)	OR=0.651 (CI: 0.103, 4.099)
	daytime somnolence – 35d	Dichotomous	51	2	(3.9%)	51	3	(5.9%)	OR=0.651 (CI: 0.103, 4.099)
	daytime somnolence – 35d	Dichotomous	44	2	(3.9%)	44	3	(5.9%)	OR=0.651 (CI: 0.103, 4.099)
	Dizziness – 35d	Dichotomous	51	2	(3.9%)	51	3	(5.9%)	OR=0.651 (CI: 0.103, 4.099)
	Dizziness – 35d	Dichotomous	44	2	(3.9%)	44	3	(5.9%)	OR=0.651 (CI: 0.103, 4.099)
	Dry mouth – 35d	Dichotomous	51	2	(3.9%)	51	0	(0.0%)	OR=5.235 (CI: 0.244, 112.252)
	Dry mouth – 35d	Dichotomous	44	2	(3.9%)	44	0	(0.0%)	OR=5.235 (CI: 0.244, 112.252)
	flu-like symptoms – 35d	Dichotomous	51	0	(0.0%)	51	1	(2.0%)	OR=0.326 (CI: 0.013, 8.219)
	flu-like symptoms – 35d	Dichotomous	44	0	(0.0%)	44	1	(2.0%)	OR=0.326 (CI: 0.013, 8.219)
	headache – 35d	Dichotomous	51	0	(0.0%)	51	1	(2.0%)	OR=0.326 (CI: 0.013, 8.219)
	headache – 35d	Dichotomous	44	0	(0.0%)	44	1	(2.0%)	OR=0.326 (CI: 0.013, 8.219)
	increase in sleep duration – 35d	Dichotomous	44	18	(35.3%)	44	6	(11.8%)	OR=4.385 (CI: 1.534, 12.530)
	increase in sleep duration – 35d	Dichotomous	51	18	(35.3%)	51	6	(11.8%)	OR=4.385 (CI: 1.534, 12.530)
	Peripheral oedema – 35d	Dichotomous	51	0	(0.0%)	51	2	(3.9%)	OR=0.191 (CI: 0.009, 4.096)
	Peripheral oedema – 35d	Dichotomous	44	0	(0.0%)	44	2	(3.9%)	OR=0.191 (CI: 0.009, 4.096)
	Postural hypotension – 35d	Dichotomous	51	1	(2.0%)	51	0	(0.0%)	OR=3.069 (CI: 0.122, 77.410)
	Postural hypotension – 35d	Dichotomous	44	1	(2.0%)	44	0	(0.0%)	OR=3.069 (CI: 0.122, 77.410)
	tiredness – 35d	Dichotomous	44	5	(9.8%)	44	0	(0.0%)	OR=12.392 (CI: 0.664, 231.291)
	tiredness – 35d	Dichotomous	51	5	(9.8%)	51	0	(0.0%)	OR=12.392 (CI: 0.664, 231.291)
	Urine retention – 35d[k]	Dichotomous	44	2	(3.9%)	44	0	(0.0%)	OR=5.235 (CI: 0.244, 112.252)
	Urine retention – 35d[k]	Dichotomous	51	2	(3.9%)	51	0	(0.0%)	OR=5.235 (CI: 0.244, 112.252)
	use of rescue medication: proportion taking up to 3 g/d of paracetamol – 35d	Dichotomous	51	2	(3.9%)	51	0	(0.0%)	OR=5.235 (CI: 0.244, 112.252)
	proportion taking up to 3 g/d of paracetamol – 35d	Dichotomous	44	2	(3.9%)	44	0	(0.0%)	OR=5.235 (CI: 0.244, 112.252)

[a] IQR: 70-80
[b] IQR: 65-75
[c] IQR: 30-57
[d] IQR: 30-60
[e] IQR: 9-11

	[f] IQR: 8-11 [g] IQR: 3-6 [h] IQR: 3-7 [i] due to dizziness, postural hypotension, difficulty with urination and constipation, dry mouth, daytime somnolence and increased sleep [j] due to daytime somnolence, peripheral oedema and constipation [k] defined as difficulty in urination
Comments	patients with prior exposure to gabapentin, pregabalin, amitriptyline, or other medications for DPN were permitted to enter (regardless of dose used and duration of treatment); authors report that ITT was performed but 7 dropouts were not included in the ITT analysis as they did not receive a single dose of both treatments

Definitions of abbreviations are given at the end of this document.

Study	Bernstein et al. (1989)
Pain category	Peripheral pain
Study design	Country: USA Design: Parallel Inclusion criteria: Aged 54 and 90 years with severe intractable PHN for at least 12 months poorly or incompletely controlled with oral analgesics, antidepressants or anticonvulsants Exclusion criteria: None described Study length (days): 42 Intention-to-treat analysis? No
Participants	Total number of patients: 32 Number of males: 12 (37.5%) Underlying cause of neuropathic pain: Post-herpetic neuralgia Mean duration of NP (in months): 35.9 Baseline pain severity: 71.25 (VAS (average of arm means)) Mean age: 72.45
Intervention(s)	(1) Capsaicin 0.075% applied 3-4 times per day Intervention: capsaicin cream Length of treatment (weeks): 6 Fixed/flexible dose regimen: Flexible dose Notes: patients were instructed to use the cream 3-4 times per day (2) Placebo Intervention: placebo Length of treatment (weeks): 6 Fixed/flexible dose regimen: Flexible dose Notes: Unclear if the placebo was active or not
Concomitant treatments	Drug free baseline period? No Concomitant pain treatment allowed? Yes (previous oral medications for pain)

Outcomes measures and effect sizes			CAPSAICIN 0.075% APPLIED 3-4 TIMES PER DAY			PLACEBO			
			N	k	mean	N	k	mean	Δ
pain score:									
VAS – 0d		Continuous	16		71	16		71.5	
VAS – 42d		Continuous	16		50	16		72.5	MD=-22.500
at least 30% pain reduction (VAS) – 28d[a]		Dichotomous	16	9	(56.3%)	16	3	(18.8%)	
at least 30% pain reduction (VAS) – 42d[a]		Dichotomous	16	9	(56.3%)	16	1	(6.3%)	OR=11.667 (CI: 1.227, 110.953)
adverse events:									
Burning pain – 42d[b]		Dichotomous	16	5	(31.3%)	16	2	(12.5%)	OR=3.182 (CI: 0.516, 19.639)
[a] 40% reduction recorded as 30% reduction [b] Ns estimated as exact numbers not reported									
Comments	while there was no drug-free baseline period, all topical medications were discontinued at least 7 days before the study (oral medications were allowed); 3 patients were lost to follow-up but it was not clear what group they were in and no reasons were given								

Definitions of abbreviations are given at the end of this document.

Study	Beydoun et al. (2006)
Pain category	Peripheral pain
Study design	Country: USA Design: Parallel Inclusion criteria: Painful diabetic neuropathy of 6 month to 5 years VASpi at least 50mm Exclusion criteria: Patients with other types of pain, clinically significant medical or psychiatric illness, history of hyponatremia or non compliance, drug or alcohol abuse in the past year, amputations other than toes, treatment with lithium or MAOI, previous treatment with oxcarbazepine, or history of sensitivity to carbamazepine or its metabolites Study length (days): 112 Intention-to-treat analysis? Yes
Participants	Total number of patients: 347 Number of males: 192 (55.3%) Underlying cause of neuropathic pain: Painful diabetic neuropathy Mean duration of NP (in months): 33.3 Baseline pain severity: 74.35 (VAS (mean of arm means)) Mean age: 60.7
Intervention(s)	(1) oxcarbazepine 600 mg/d Intervention: oxcarbazepine Length of treatment (weeks): 16 Fixed/flexible dose regimen: Fixed dose Set dose: 600mg/d Notes: 4 week titration, 12 week maintenance

(2) oxcarbazepine 1200 mg/d

Intervention: oxcarbazepine
Length of treatment (weeks): 16
Fixed/flexible dose regimen: Fixed dose
Set dose: 1200mg/d
Notes: 4 week titration, 12 week maintenance

(3) oxcarbazepine 1800 mg/d

Intervention: oxcarbazepine
Length of treatment (weeks): 16
Fixed/flexible dose regimen: Fixed dose
Set dose: 1800mg/d
Notes: 4 week titration, 12 week maintenance

(4) Placebo

Intervention: placebo
Length of treatment (weeks): 16
Fixed/flexible dose regimen: Fixed dose

Concomitant treatments

Drug free baseline period? Yes (duration: 14d)

Concomitant pain treatment allowed? Yes (current neuropathic pain treatment regimen must be stopped 2 weeks before entry; however SSRIs (which could be considered concomitant medications) and benzodiazepines were allowed; paracetamol as rescue only)

Outcomes measures and effect sizes

		OXCARBAZEPINE 600 MG/D			PLACEBO			
		N	k	mean	N	k	mean	Δ
pain score:								
VAS – 0d	Continuous	83		76.9 (SD 14.2)	89		70.8 (SD 13.2)	
VAS – 112d	Mean change	83		-25.9	89		-19.1	MD=-6.800
patient-reported global improvement:								
GATE- much/very much improved – 112d[a]	Dichotomous	83	30	(36.1%)	89	33	(37.1%)	OR=0.961 (CI: 0.516, 1.787)
major adverse events (defined as leading to withdrawal):								
any major adverse event – 112d	Dichotomous	83	9	(10.8%)	89	6	(6.7%)	OR=1.682 (CI: 0.572, 4.952)
adverse events:								
Dizziness – 112d	Dichotomous	83	5	(6.0%)	89	2	(2.2%)	OR=2.788 (CI: 0.526, 14.784)
Fatigue – 112d	Dichotomous	83	4	(4.8%)	89	6	(6.7%)	OR=0.700 (CI: 0.190, 2.576)
headache – 112d	Dichotomous	83	9	(10.8%)	89	7	(7.9%)	OR=1.425 (CI: 0.505, 4.017)
Nausea – 112d	Dichotomous	83	2	(2.4%)	89	5	(5.6%)	OR=0.415 (CI: 0.078, 2.199)
Somnolence – 112d	Dichotomous	83	2	(2.4%)	89	3	(3.4%)	OR=0.708 (CI: 0.115, 4.346)
treatment withdrawal:								
due to lack of efficacy – 112d	Dichotomous	83	2	(2.4%)	89	5	(5.6%)	OR=0.415 (CI: 0.078, 2.199)
unspecified/other reason – 112d	Dichotomous	83	4	(4.8%)	89	5	(5.6%)	OR=0.851 (CI: 0.220, 3.282)
protocol deviation – 112d	Dichotomous	83	1	(1.2%)	89	1	(1.1%)	OR=1.073 (CI: 0.066, 17.439)

[a] approximated to nearest integer (percentages only presented in text)

		OXCARBAZEPINE 1200 MG/D	PLACEBO

		N	k	mean	N	k	mean	Δ
pain score:								
VAS – 0d	Continuous	87		75.7 (SD 13.8)	89		70.8 (SD 13.2)	
VAS – 112d	Mean change	87		-29	89		-19.1	MD=-9.900
patient-reported global improvement:								
GATE- much/very much improved – 112d[a]	Dichotomous	87	44	(50.6%)	89	33	(37.1%)	OR=1.736 (CI: 0.952, 3.168)
major adverse events (defined as leading to withdrawal):								
any major adverse event – 112d	Dichotomous	87	20	(23.0%)	89	6	(6.7%)	OR=4.129 (CI: 1.569, 10.865)
adverse events:								
Dizziness – 112d	Dichotomous	87	16	(18.4%)	89	2	(2.2%)	OR=9.803 (CI: 2.181, 44.066)
Fatigue – 112d	Dichotomous	87	11	(12.6%)	89	6	(6.7%)	OR=2.002 (CI: 0.706, 5.677)
headache – 112d	Dichotomous	87	9	(10.3%)	89	7	(7.9%)	OR=1.352 (CI: 0.480, 3.806)
Nausea – 112d	Dichotomous	87	13	(14.9%)	89	5	(5.6%)	OR=2.951 (CI: 1.005, 8.671)
Somnolence – 112d	Dichotomous	87	5	(5.7%)	89	3	(3.4%)	OR=1.748 (CI: 0.405, 7.549)
treatment withdrawal:								
due to lack of efficacy – 112d	Dichotomous	87	4	(4.6%)	89	5	(5.6%)	OR=0.810 (CI: 0.210, 3.121)
unspecified/other reason – 112d	Dichotomous	87	5	(5.7%)	89	5	(5.6%)	OR=1.024 (CI: 0.286, 3.671)
protocol deviation – 112d	Dichotomous	87	5	(5.7%)	89	1	(1.1%)	OR=5.366 (CI: 0.614, 46.902)

[a] approximated to nearest integer (percentages only presented in text)

		OXCARBAZEPINE 1800 MG/D			PLACEBO			
		N	k	mean	N	k	mean	Δ
pain score:								
VAS – 0d	Continuous	88		71.3 (SD 15.6)	89		70.8 (SD 13.2)	
VAS – 112d	Mean change	88		-26.5	89		-19.1	MD=-7.400
patient-reported global improvement:								
GATE- much/very much improved – 112d[a]	Dichotomous	88	43	(48.9%)	89	33	(37.1%)	OR=1.622 (CI: 0.890, 2.954)
major adverse events (defined as leading to withdrawal):								
any major adverse event – 112d	Dichotomous	88	36	(40.9%)	89	6	(6.7%)	OR=9.577 (CI: 3.774, 24.302)
adverse events:								
Dizziness – 112d	Dichotomous	88	30	(34.1%)	89	2	(2.2%)	OR=22.500 (CI: 5.176, 97.800)
Fatigue – 112d	Dichotomous	88	13	(14.8%)	89	6	(6.7%)	OR=2.398 (CI: 0.868, 6.626)
headache – 112d	Dichotomous	88	10	(11.4%)	89	7	(7.9%)	OR=1.502 (CI: 0.545, 4.142)
Nausea – 112d	Dichotomous	88	17	(19.3%)	89	5	(5.6%)	OR=4.023 (CI: 1.413, 11.449)
Somnolence – 112d	Dichotomous	88	9	(10.2%)	89	3	(3.4%)	OR=3.266 (CI: 0.854, 12.496)
treatment withdrawal:								
due to lack of efficacy – 112d	Dichotomous	88	2	(2.3%)	89	5	(5.6%)	OR=0.391 (CI: 0.074, 2.070)
unspecified/other reason – 112d	Dichotomous	88	8	(9.1%)	89	5	(5.6%)	OR=1.680 (CI: 0.527, 5.351)
protocol deviation – 112d	Dichotomous	88	2	(2.3%)	89	1	(1.1%)	OR=2.047 (CI: 0.182, 22.987)

[a] approximated to nearest integer (percentages only presented in text)

Comments	ITT population included all patients that were randomised and had provided at least one day of electronic diary data for the VAS during treatment (dichotomous outcomes were recorded by reviewers as patient randomised, regardless of data available)

Definitions of abbreviations are given at the end of this document.

Study	Biesbroeck et al. (1995)
Pain category	Peripheral pain
Study design	Country: USA Design: Parallel Inclusion criteria: PDN of at least 24 months aged between 21 and 85, with at least moderate daily pain interfering with activities or sleep Exclusion criteria: - Study length (days): 56 Intention-to-treat analysis? No
Participants	Total number of patients: 235 Number of males: 132 (56.2%) Underlying cause of neuropathic pain: Painful diabetic neuropathy Mean duration of NP (in months): 105.96 Baseline pain severity: 63.1 (VAS) Mean age: 60
Intervention(s)	(1) Amitriptyline 125mg/d + placebo cream Intervention: amitriptyline Length of treatment (weeks): 8 Fixed/flexible dose regimen: Flexible dose Range: 25–125 Notes: maximum of 5 25 mg capsules per day (ie. 125 mg) (2) Topical capasaicin 0.075% applied 4 times per day + placebo capsules Intervention: capsaicin cream Length of treatment (weeks): 8 Fixed/flexible dose regimen: Fixed dose Notes: cream applied to painful area four times daily during the study
Concomitant treatments	Drug free baseline period? Yes (duration: 7d) Concomitant pain treatment allowed? Yes (amitriptyline or other trycyclics and all topical medicines for the affected area were discontinued at least 7 days before the study enrollment but any other long-term therapy associated with neuropathy could be continued without change in dosage or frequency during the study)
Outcomes measures and effect sizes	

		AMITRIPTYLINE 125MG/D + PLACEBO CREAM			TOPICAL CAPASAICIN 0.075% APPLIED 4 TIMES PER DAY + PLACEBO CAPSULES			
		N	k	mean	N	k	mean	Δ
pain score:								
VAS – 0d[a]	Continuous	108		64.5	104		61.7	
VAS – 56d	Mean change	108		-29.1 (SD 3)	104		-26.1 (SD 2.9)	MD=-3.000 (CI: -3.794, -2.206)

	pain relief:							
	VAS/VASpr – 56d	Continuous	108	57 (SD 3.6)	104		55.1 (SD 3.5)	MD=1.900 (CI: 0.944, 2.856)
	adverse events:							
	Burning pain – 56d	Dichotomous	117	2 (1.7%)	118	68	(57.6%)	OR=0.003 (CI: 0.000, 0.052)
	Sedation – 56d	Dichotomous	117	69 (59.0%)	118	0	(0.0%)	OR=339.619 (CI: 20.616, 5594.699)
	[a] change from baseline							
Comments	-							

Definitions of abbreviations are given at the end of this document.

Study	Bone et al. (2002)
Pain category	Mixed (central and peripheral) or unclear if mixed
Study design	Country: UK & Ireland Design: Crossover Inclusion criteria: Phantom limb pain >6 months duration after a previous surgical amputation, aged 18-75 years, pain score of at least 40mm on 100mm VAS Exclusion criteria: Coexisting epilepsy, known allergy to gabapentin, significant hepatic or renal insufficiency, severe hematologic disease, history of illicit drug or alcohol abuse, serious psychiatric condition, severe pain that could confound the assessment Study length (days): 91 Intention-to-treat analysis? Yes
Participants	Total number of patients: 19 Number of males: 15 (78.9%) Underlying cause of neuropathic pain: Phantomb limb pain Mean duration of NP (in months): not reported Baseline pain severity: 6.4 (VAS (average of arm means); duration of time since amputation 18 months) Mean age: 56.25 (SD: 17.5)
Intervention(s)	(1) Gabapentin flexible dose Intervention: gabapentin Length of treatment (weeks): 6 Fixed/flexible dose regimen: Flexible dose Range: 300–2400 Notes: Titrated from 300mg to 2,400mg or maximum tolerated dose (2) Placebo Intervention: placebo Length of treatment (weeks): 6 Fixed/flexible dose regimen: Flexible dose

Concomitant treatments	Drug free baseline period? Unclear Concomitant pain treatment allowed? Yes (tricyclics allowed if stable and did not change during the study period; however, any other anti-convulsant therapy was discontinued before treatment; codeine(30g)/paracetamol(500g) combined tablet was allowed as rescue analgesia (max 2 tablets in 4 hours))

Outcomes measures and effect sizes

		GABAPENTIN FLEXIBLE DOSE			PLACEBO			
		N	k	mean	N	k	mean	Δ
pain score:								
VAS – 0d	Continuous	19		6.1 (SD 1.8)	19		6.7 (SD 1.9)	
VAS – 28d	Continuous	19		4.1 (SD 2.7)	19		4.4 (SD 2.1)	MD=-0.300 (CI: -1.838, 1.238)
VAS – 28d	Mean change	19		-2 (SD 1.2)	19		-2.3 (SD 1.1)	MD=-0.300 (CI: -1.032, 0.432)
VAS – 42d	Continuous	19		2.9 (SD 2.2)	19		5.1 (SD 2.2)	MD=-2.200 (CI: -3.599, -0.801)
VAS – 42d	Mean change	19		-3.2 (SD 2.1)	19		-1.6 (SD 0.7)	MD=1.600 (CI: 0.605, 2.595)
patient-reported improvement in daily physical and emotional functioning, including sleep:								
NRS Sleep – 0d[a]	Continuous	19		4	19		4	
NRS Sleep – 42d[b]	Continuous	19		3	19		4	MD=-1.000
HADS-D – 0d[c]	Continuous	19		14	19		15	
HADS-D – 42d	Continuous	19		12[d]	19		14[c]	MD=-2.000
adverse events:								
Dizziness – 42d	Dichotomous	19	2	(10.5%)	19	1	(5.3%)	OR=2.118 (CI: 0.176, 25.549)
headache – 42d	Dichotomous	19	2	(10.5%)	19	1	(5.3%)	OR=2.118 (CI: 0.176, 25.549)
Nausea – 42d	Dichotomous	19	1	(5.3%)	19	1	(5.3%)	OR=1.000 (CI: 0.058, 17.249)
Somnolence – 42d	Dichotomous	19	7	(36.8%)	19	2	(10.5%)	OR=4.958 (CI: 0.873, 28.152)
use of rescue medication:								
number of tablets (30mg codeine+500mg paracetamol) – 42d	Continuous	19		177 (SD 71)	19		187 (SD 80)	MD=-10.000 (CI: -58.095, 38.095)

[a] IQR: 2-5
[b] IQR: 1-5
[c] IQR: 5-25
[d] IQR: 4-22

Comments	Authors state they use ITT analyses with all randomised patients; 5 patients dropped out of the study (1 protocol violation, 1 withdrew consent and 3 did not complete) but it was not clear which treatment these patients were having when they dropped out

Definitions of abbreviations are given at the end of this document.

Study	Boureau et al. (2003)
Pain category	Peripheral pain
Study design	Country: France Design: Parallel Inclusion criteria: Aged between 18 and 85 years with PHN for at least 3 months for a maximum of 1 year

	Exclusion criteria: Patients with symptoms or history of depression, immune depression, seizures, illicit drug abuse or recent cranial traumatism, severe renal, hepatic, cardiac, or respiratory pathology, hypersensitivity to tramadol or to opioids, pregnant or breastfeeding women, those on monoamine oxidase inhibitors within 15 days of inclusion visit or antidepressants, anticonvulsants, opioids or local/general anaesthesia within 7 days Study length (days): 43 Intention-to-treat analysis? Yes
Participants	Total number of patients: 127 Number of males: 31 (24.4%) Underlying cause of neuropathic pain: Post-herpetic neuralgia Mean duration of NP (in months): 6.85 Baseline pain severity: 60.45 (VAS (average of arm means)) Mean age: 66.8
Intervention(s)	(1) Tramadol up to 400 mg/d Intervention: tramadol Length of treatment (weeks): 6 Fixed/flexible dose regimen: Flexible dose Mean dose: 275.5mg/d Range: 100–400 Notes: started on 100 mg/d and daily dose was increased depending on therapeutic response and on treatment acceptability (but it could not be decreased) - this increased from 1 tablet per day (in the evening) to 4 tablets in those aged up to 75 years and up to 3 tablets in those older than 75 years. Maximum was 400 mgd/ in those 75 or younger and 300 mg/d in those 75 years and older. (2) Placebo Intervention: placebo Length of treatment (weeks): 6 Fixed/flexible dose regimen: Flexible dose Mean dose: 307.3mg/d
Concomitant treatments	Drug free baseline period? Unclear Concomitant pain treatment allowed? No (those on monoamine oxidase inhibitors within 15 days of inclusion visit or antidepressants, anticonvulsants, opioids or local/general anaesthesia within 7 days were all excluded; Paracetamol up to 3g/d was allowed as rescue medication)
Outcomes measures and effect sizes	

		TRAMADOL UP TO 400 MG/D			PLACEBO			
		N	k	mean	N	k	mean	Δ
ITT/LOCF (last-observation carried forward)								
pain score:								
VAS – 0d	Continuous	63		60.5 (SD 13.8)	62		60.4 (SD 13.5)	
VAS – 43d	Continuous	63		25.3 (SD 23)	62		33.6 (SD 25.4)	MD=-8.300 (CI: -16.799, 0.199)
at least 50% pain reduction (VAS) – 43d	Dichotomous	63	41	(65.1%)	62	31	(50.0%)	OR=1.864 (CI: 0.909, 3.823)
adverse events:								
arrhthmias/dysrhythmias – 43d[a]	Dichotomous	63	1	(1.6%)	62	0	(0.0%)	OR=3.000 (CI: 0.120, 75.066)
Nausea – 43d[b]	Dichotomous	63	11	(17.5%)	62	5	(8.1%)	OR=2.412 (CI: 0.785, 7.405)
Urine retention – 43d[c]	Dichotomous	63	1	(1.6%)	62	1	(1.6%)	OR=0.984 (CI: 0.060, 16.087)

	treatment withdrawal:								
	lost to follow-up – 43d	Dichotomous	64	1	(1.6%)	63	1	(1.6%)	OR=0.984 (CI: 0.060, 16.085)
	use of rescue medication:								
	proportion taking up to 3 g/d of paracetamol – 43d	Dichotomous	63	14	(22.2%)	62	25	(40.3%)	OR=0.423 (CI: 0.194, 0.924)
	Per Protocol								
	pain score:								
	VAS – 0d	Continuous	53		60.8 (SD 12.1)	55		60 (SD 13.8)	
	VAS – 15d[d]	Continuous	53		35 (SD 21.1)	55		44 (SD 21.5)	MD=-9.000 (CI: -17.038, -0.962)
	VAS – 22d[d]	Continuous	53		31 (SD 21.1)	55		40 (SD 21.5)	MD=-9.000 (CI: -17.038, -0.962)
	VAS – 43d	Continuous	53		24.6 (SD 22.4)	55		31.8 (SD 25.3)	MD=-7.200 (CI: -16.204, 1.804)
	[a] described in paper as adverse effects 'Cardiovascular System' [b] described in paper as adverse effects 'Digestive System' [c] described in paper as adverse effects 'Urogenital System' [d] extracted from graph; dispersion in graph assumed to be SE (SD was calculated from this)								
Comments	as concomitant drugs were not permitted, those taking monoamine oxidase inhibitors within 15 days of inclusion visit or antidepressants, anti-convulsants, opioids or local/general anaesthesia within 7 days were excluded; ITT population had those from the safety population having at least one VAS measurement at day 43 visit (or at the final visit in case of premature discontinuation) (1 patient from each group was excluded from the efficacy analyses as they had no VAS measurement over the 13 days before the end visit); the per protocol population was those in the ITT population without major protocol deviation)								

Definitions of abbreviations are given at the end of this document.

Study	Breuer et al. (2007)
Pain category	Central pain
Study design	Country: USA Design: Crossover Inclusion criteria: At least 18 years of age, had a diagnosis of probable or definite MS, and reported pain with neuropathic features for at least 3 months, Score of 4 or higher on the 11-point Neuropathic Pain Scale (0=none, 10=the worst imaginable) Exclusion criteria: central pain from another condition, 2 more more MS relapses within the prior 6 months, rapid progressive course of MS, recevied corticosteroids for MS in the 30 days before screening, treatment of epilepsy with anticonvulsants other than lamotrigine, clinically relevant hepatic or renal function, neurologic or psychiatric disease sufficient to potentially compromise compliance or data collection, history of failure ot respond to treatment with lamotrigine, experience with lamotrigine of an adverse event preventing titration to a dose that would have provided pain relief, history of hypersensitivity or serious adverse event to lamotrigine Study length (days): 203 Intention-to-treat analysis? No
Participants	Total number of patients: 18 Number of males: 2 (11.1%) Underlying cause of neuropathic pain: MS neuropathic pain Mean duration of NP (in months): not reported Baseline pain severity: not reported (not reported) Mean age: 49.3

Intervention(s)	(1) Lamotrigine flexible dose Intervention: lamotrigine Length of treatment (weeks): 13 Fixed/flexible dose regimen: Flexible dose Set dose: 400mg/d Range: 25–400 Notes: 8 weeks titration, 3 weeks maintenance, 2 weeks tapering; average dose not reported but 8 of 11 study completers reached the maximum dosage during each of the 2 study periods, of the remaining 3 - dosages of lamotrigine were 50, 100, 300 mg/d (2) placebo Intervention: placebo Length of treatment (weeks): 13 Fixed/flexible dose regimen: Flexible dose
Concomitant treatments	Drug free baseline period? Unclear Concomitant pain treatment allowed? Yes (opioids, non-opioid analgesics (ie. NSAIDs, acetaminophen, lidocaine patch), gabapentin if doses were stable for at least 2 weeks prior to study enrollment and expected to remain stable throughout treatment (use of another anti-convulsants not permitted))
Outcomes measures and effect sizes	

		LAMOTRIGINE FLEXIBLE DOSE			PLACEBO			
		N	k	mean	N	k	mean	Δ
pain score:								
NRS/NRS Pain – 77d	Continuous	15			15			MD=0.820 (CI: -1.532, 3.172)
at least 30% pain reduction (NRS) – 77d	Dichotomous	18	5	(27.8%)	18	2	(11.1%)	OR=3.077 (CI: 0.511, 18.535)
patient-reported improvement in daily physical and emotional functioning, including sleep:								
BPI Sleep – 77d	Continuous	15			15			MD=-0.020 (CI: -1.784, 1.744)
major adverse events (defined as leading to withdrawal):								
any major adverse event – 77d	Dichotomous	18	2	(11.1%)	18	0	(0.0%)	OR=5.606 (CI: 0.251, 125.449)
adverse events:								
Blurred vision – 77d	Dichotomous	18	0	(0.0%)	18	0	(0.0%)	OR=1.000 (CI: 0.019, 53.120)
Constipation – 77d	Dichotomous	18	1	(5.6%)	18	0	(0.0%)	OR=3.171 (CI: 0.121, 83.166)
Dizziness – 77d	Dichotomous	18	0	(0.0%)	18	1	(5.6%)	OR=0.315 (CI: 0.012, 8.269)
feeling drunk/drugged – 77d	Dichotomous	18	1	(5.6%)	18	0	(0.0%)	OR=3.171 (CI: 0.121, 83.166)
frequent urination – 77d	Dichotomous	18	1	(5.6%)	18	0	(0.0%)	OR=3.171 (CI: 0.121, 83.166)
oedema – 77d	Dichotomous	18	1	(5.6%)	18	3	(16.7%)	OR=0.294 (CI: 0.028, 3.138)
Rash – 77d	Dichotomous	18	1	(5.6%)	18	0	(0.0%)	OR=3.171 (CI: 0.121, 83.166)
Sedation – 77d	Dichotomous	18	1	(5.6%)	18	0	(0.0%)	OR=3.171 (CI: 0.121, 83.166)
vertigo – 77d	Dichotomous	18	0	(0.0%)	18	0	(0.0%)	OR=1.000 (CI: 0.019, 53.120)
overall improvement in quality of life:								
MSQoL-54 overall rating – 77d	Continuous	15			15			MD=0.050 (CI: -0.930, 1.030)

Comments	study reported use of 1 week baseline period but not clear if this was a drug-free period; total drop-outs (6/18) were reported (2 due to adverse events, 1 receving a corticosteroid and 3 withdrer) but it was not recorded which treatment drug these patients were receiving; one person included had a carryover effect from one treatment ot another; study also reported different aspects of the Neuropathic Pain Scale (NPS) but did not report a summary NPS score; there was a 7-day baseline period; all patients who completed at least one treatment period were included in the analysis; 1 patient withdrew before randomisation, 2 after randomisation but before taking any drugs because of either non compliance or an unknown reason (the remaining 15

	patients were included in the authors' safety analysis)

Definitions of abbreviations are given at the end of this document.

Study	Cardenas et al. (2002)
Pain category	Mixed (central and peripheral) or unclear if mixed
Study design	Country: USA Design: Parallel Inclusion criteria: Age 18 to 65 years, injury more than 6 months ago, duration of pain at least 3 months averaging at least 3 on a 0 to 10 scale Exclusion criteria: history of cardiovascular disease, absnormal ECG, seizures, hyperthyroidism, glaucoma, pregnancy or ineffective contraception method, any type of antidepressant medication, consumption of more than 2 alcoholic drinks per day, met psychiatric diagnostic criteria for major depressive episode Study length (days): 42 Intention-to-treat analysis? Yes
Participants	Total number of patients: 84 Number of males: 67 (79.8%) Underlying cause of neuropathic pain: Spinal cord injury pain Mean duration of NP (in months): 168.25 Baseline pain severity: 5.25 (NRS (average of arm means)) Mean age: 41.45
Intervention(s)	(1) Amitriptyline (10-125mg/d) Intervention: amitriptyline Length of treatment (weeks): 6 Fixed/flexible dose regimen: Flexible dose Median dose: 50mg/d Range: 10–125 Notes: week 1: 10 mg/d, week 2: 25 mg/d then increasing weekly by 25 mg/d to a possible maximum of 125 mg/d (50 mg/d was the median maximum and week 6 dose) (2) Placebo (active benztropine 0.5mg/d) Intervention: placebo Length of treatment (weeks): 6 Fixed/flexible dose regimen: Fixed dose Set dose: 0.5mg/d Notes: benztropine was used to mimic dry mouth associated with amitriptyline
Concomitant treatments	Drug free baseline period? No Concomitant pain treatment allowed? Unclear (current use of any antidepressant medication was exclusion criteria but it was not clear about permissions for other pain medications)

Outcomes measures and effect sizes

		AMITRIPTYLINE (10-125MG/D)			PLACEBO (ACTIVE BENZTROPINE 0.5MG/D)			
		N	k	mean	N	k	mean	Δ
pain score:								
NRS/NRS Pain – 0d	Continuous	44		5.5 (SD 1.8)	40		5 (SD 1.7)	
NRS/NRS Pain – 42d	Continuous	44		4.5 (SD 1.9)	40		4 (SD 2)	MD=0.500 (CI: -0.336, 1.336)
SF McGill – 0d	Continuous	44		17.5 (SD 9.8)	40		15.7 (SD 7.4)	
SF McGill – 42d	Continuous	44		14.6 (SD 9.7)	40		12.8 (SD 8)	MD=1.800 (CI: -1.990, 5.590)
patient-reported improvement in daily physical and emotional functioning, including sleep:								
CES-D – 0d	Continuous	44		17.1 (SD 9.7)	40		13.3 (SD 8.6)	
CES-D – 42d	Continuous	44		13.4 (SD 10.9)	40		11.2 (SD 8.6)	MD=2.200 (CI: -1.980, 6.380)
BPI (modified) – 0d	Continuous	44		34.8 (SD 24.5)[a]	40		34.7 (SD 24.3)[b]	
BPI (modified) – 42d	Continuous	44		29.8 (SD 22.4)[a]	40		24.4 (SD 20.4)[b]	MD=5.400 (CI: -3.753, 14.553)
major adverse events (defined as leading to withdrawal):								
any major adverse event – 42d	Dichotomous	44	7	(15.9%)	40	2	(5.0%)	OR=3.595 (CI: 0.701, 18.445)
adverse events:								OR=6.831 (CI: 0.342,
Blurred vision – 42d	Dichotomous	44	3	(6.8%)	40	0	(0.0%)	136.478)
Constipation	Dichotomous	44	14	(31.8%)	40	9	(22.5%)	OR=1.607 (CI: 0.606, 4.267)
Diarrhoea	Dichotomous	44	4	(9.1%)	40	3	(7.5%)	OR=1.233 (CI: 0.259, 5.883)
Dizziness[c]	Dichotomous	44	0	(0.0%)	40	3	(7.5%)	OR=0.120 (CI: 0.006, 2.406)
drowsiness/tiredness/fatigue – 42d	Dichotomous	44	14	(31.8%)	40	10	(25.0%)	OR=1.400 (CI: 0.538, 3.643)
Dry mouth – 42d	Dichotomous	44	17	(38.6%)	40	14	(35.0%)	OR=1.169 (CI: 0.481, 2.845)
headache	Dichotomous	44	4	(9.1%)	40	0	(0.0%)	OR=9.000 (CI: 0.469, 172.647)
irritability	Dichotomous	44	4	(9.1%)	40	0	(0.0%)	OR=9.000 (CI: 0.469, 172.647)
nausea/vomiting	Dichotomous	44	0	(0.0%)	40	3	(7.5%)	OR=0.120 (CI: 0.006, 2.406)
palpitation	Dichotomous	44	4	(9.1%)	40	0	(0.0%)	OR=9.000 (CI: 0.469, 172.647)
sleep disturbance	Dichotomous	44	0	(0.0%)	40	3	(7.5%)	OR=0.120 (CI: 0.006, 2.406)
Urine retention	Dichotomous	44	5	(11.4%)	40	5	(12.5%)	OR=0.897 (CI: 0.240, 3.363)
treatment withdrawal:								
unspecified/other reason – 42d	Dichotomous	44	0	(0.0%)	40	1	(2.5%)	OR=0.296 (CI: 0.012, 7.473)
lost to follow-up – 42d	Dichotomous	44	1	(2.3%)	40	0	(0.0%)	OR=2.793 (CI: 0.111, 70.545)

[a] BPI form was modified by: assessing interference with mobility instead of interference with walking ability (as some participants were non-ambulatory), adding 3 items: pain interference with self-care, recreational activities, and social activities

[b] BPI form was modified by: assessing interference with mobility instead of interference with walking ability (as some participants were non-ambulatory), adding 3 items: pain interference with self-care, recreational activities, and social activities

[c] defined as 'dizziness/light-headedness'

Comments

some participants did have depression (score of 16 or greater on CES-D) but randomisation was stratified so these patients were split equallly between the groups

Definitions of abbreviations are given at the end of this document.

Study	Chandra et al. (2006)
Pain category	Peripheral pain
Study design	Country: India Design: Parallel Inclusion criteria: Participants with at least 8 week history of PHN after healing of rash with at least 40mm on 100mm VAS Exclusion criteria: Prior treatment with nortriptyline, gabapentin or demonstrated hypersensitivity to the drugs or their ingredients, neurolytic or neurosurgical therapy for PHN, immunocompromised state, hepatic or renal insufficiency, significant haemotological disease, history of severe pain other than that caused by PHN, history of use of experimental drugs or participation in a clinical study within 2 months of screening, a history of ilicit drug or alcohol abuse within the last year, any serious medical or psychological condition, muscle relaxants, anti-convulsants, topical analgesics and anti-viral agents were discontinued for at least 1 week prior to screening Study length (days): 63 Intention-to-treat analysis? Yes
Participants	Total number of patients: 76 Number of males: 34 (44.7%) Underlying cause of neuropathic pain: Post-herpetic neuralgia Mean duration of NP (in months): not reported Baseline pain severity: 5.7 (NRS (average of arm means) (5.05 is average VAS score)) Mean age: 54
Intervention(s)	(1) Nortriptyline 100mg/d Intervention: nortriptyline Length of treatment (weeks): 9 Fixed/flexible dose regimen: Flexible dose Notes: started at 25 mg twice daily and escalated every 2 weeks if drugs were well-tolerated: 25 mg 3x per day at 2 week and 2-25 mg 3x per day at 4 weeks; 2/3 of patients responded at a daily dose of 75 mg (2) Gabapentin 2700mg/d Intervention: gabapentin Length of treatment (weeks): 9 Fixed/flexible dose regimen: Flexible dose Notes: started at 300 mg 3x daily and escalated every 2 weeks if drugs were well-tolerated: 2-300 mg 3x per day at 2 week and 3-300 mg 3x per day at 4 weeks; nearly 80% of patients responded at a daily dose of 2700 mg
Concomitant treatments	Drug free baseline period? Yes (duration: 7d) Concomitant pain treatment allowed? Unclear (muscle relaxants, anti-convulsants, topical analgesics and anti-viral agents were discontinued for at least 1 week prior to screening but there is no comment about whether or not other anti-depressants were allowed during treatment; non-opioids were allowed as rescue analgesics)
Outcomes measures and effect sizes	**NORTRIPTYLINE 100MG/D** **GABAPENTIN 2700MG/D** **N k mean N k mean Δ**

pain score:								
NRS/NRS Pain – 0d	Continuous	36		5.8 (SD 1.4)	34		5.6 (SD 1.1)	
NRS/NRS Pain – 63d	Mean change	36		-2.18 (SD 1.9)	34		-1.97 (SD 1.68)	MD=-0.210 (CI: -1.049, 0.629)
VAS – 0d	Continuous	36		5.3 (SD 1.3)	34		4.8 (SD 1.2)	
VAS – 63d	Mean change	36		-2.37 (SD 2.22)	34		-2 (SD 1.99)	MD=-0.370 (CI: -1.357, 0.617)
at least 50% pain reduction (NRS) – 63d	Dichotomous	36	9	(25.0%)	34	7	(20.6%)	OR=1.286 (CI: 0.418, 3.951)
SF McGill – 0d	Continuous	36		10.8 (SD 4)	34		10.4 (SD 4.4)	
SF McGill – 63d	Mean change	36		-3.8 (SD 2.94)	34		-3.44 (SD 3.52)	MD=-0.360 (CI: -1.884, 1.164)
adverse events:								
Constipation – 63d	Dichotomous	36	8	(22.2%)	34	0	(0.0%)	OR=20.579 (CI: 1.138, 372.137)
Drowsiness – 63d[a]	Dichotomous	36	6	(16.7%)	34	4	(11.8%)	OR=1.500 (CI: 0.384, 5.860)
Dry mouth – 63d	Dichotomous	36	18	(50.0%)	34	0	(0.0%)	OR=69.000 (CI: 3.931, 1211.166)
Fatigue – 63d	Dichotomous	36	0	(0.0%)	34	1	(2.9%)	OR=0.306 (CI: 0.012, 7.771)
Postural hypotension – 63d	Dichotomous	36	12	(33.3%)	34	0	(0.0%)	OR=35.204 (CI: 1.989, 623.221)
treatment withdrawal:								
unspecified/other reason – 63d	Dichotomous	36	0	(0.0%)	34	1	(2.9%)	OR=0.306 (CI: 0.012, 7.771)
lost to follow-up – 63d	Dichotomous	36	2	(5.6%)	34	3	(8.8%)	OR=0.608 (CI: 0.095, 3.882)

[a] described in paper as sleepiness

Comments	-

Definitions of abbreviations are given at the end of this document.

Study	Cheville et al. (2009)
Pain category	Peripheral pain
Study design	Country: USA Design: Crossover Inclusion criteria: persistent postsurgical neuropathic pain for at least one month, at least 4 (of 10) neuropathic features, age 18 years or greater Exclusion criteria: recent history of drug or alcohol abuse, life expectation >6 months, without clinical evident cognitive or psychiatric morbidity, pregnancy or nursing, non-surgical pain etiologies (ie. Malignancy, dermal pathology, etc), concurrent radiation therapy to painful area, skin problems at the site, use of topical medicines on the site, history of allergy or intolerance to amide local anaesthetics, use of class 1 antiarrhythmic drugs Study length (days): 56 Intention-to-treat analysis? Yes
Participants	Total number of patients: 28 Number of males: 9 (32.1%) Underlying cause of neuropathic pain: Post-surgical pain after surgery for cancer Mean duration of NP (in months): not reported Baseline pain severity: 4.9 (NRS) Mean age: 61.8
Intervention(s)	(1) Lidocaine patch 5% - flexible dose Intervention: lidocaine (topical) Length of treatment (weeks): 4

	Fixed/flexible dose regimen: Flexible dose Notes: maximum of 3 patches for 18 hours or their bedtime during study period (2) placebo Intervention: placebo Length of treatment (weeks): 4 Fixed/flexible dose regimen: Flexible dose
Concomitant treatments	Drug free baseline period? No Concomitant pain treatment allowed? Yes (any stable, pre-existing oral analgesics (including opioid, non-opioid and adjuvant analgesics) but introduction of new analgesics or adjuvant drugs led to study withdrawal; participants were allowed to stop or decrease analgesic use)

Outcomes measures and effect sizes

		LIDOCAINE PATCH 5% - FLEXIBLE DOSE			PLACEBO			
		N	k	mean	N	k	mean	Δ
patient-reported improvement in daily physical and emotional functioning, including sleep:								
BPI – 28d[a]	Mean change	28		-1.8	28		-0.1	MD=-1.700
BPI Mood – 28d[a]	Mean change	28		-2.5	28		-0.5	MD=-2.000
BPI Sleep – 28d[a]	Mean change	28		-0.9	28		0.3	MD=-1.200
BPI general activity – 28d[a]	Mean change	28		-1.6	28		-0.2	MD=-1.400
BPI walking ability – 28d[a]	Mean change	28		-1.8	28		-0.6	MD=-1.200
BPI normal work – 28d[a]	Mean change	28		-2.3	28		0	MD=-2.300
BPI relationship with other people – 28d[a]	Mean change	28		-1.5	28		0.8	MD=-2.300
BPI enjoyment of life – 28d[a]	Mean change	28		-1.9	28		-0.4	MD=-1.500
major adverse events (defined as leading to withdrawal):								
any major adverse event – 28d	Dichotomous	28	2	(7.1%)	28	0	(0.0%)	OR=5.377 (CI: 0.247, 117.247)
treatment withdrawal:								
unspecified/other reason – 28d	Dichotomous	28	5	(17.9%)	28	3	(10.7%)	OR=1.812 (CI: 0.389, 8.444)
treatment phase 1								
pain score:								
NRS/NRS Pain – 0d[b]	Continuous	14		4.6 (SD 1.8)	14		5.1 (SD 1.9)	
NRS/NRS Pain – 28d[c]	Continuous	14		4.4 (SD 2.12)	14		4.8 (SD 1.71)	MD=-0.400 (CI: -1.827, 1.027)

NRS/NRS Pain – 28d[d]	Mean change	13	-0.85 (SD 1)	8	-0.6 (SD 1.1)	MD=-0.250 (CI: -1.186, 0.686)
treatment phase 2						
pain score: NRS/NRS Pain – 28d[d]	Continuous	10	-1.5 (SD 1.4)	7	-0.8 (SD 2)	MD=-0.700 (CI: -2.417, 1.017)

[a] not certain of denominator
[b] first randomisation period only
[c] not certain of denominator; first randomisation period only
[d] estimated from graph

Comments	no washout, but analysis of carry over effects showed no significant interactions; the study was stopped early due to a slow recruitment rate - it is not clear if the study reached an adequate sample size as the sample size calculation was not provided; 2 patients of the 30 randomised dropped out before using the study medication

Definitions of abbreviations are given at the end of this document.

Study	Clifford et al. (2012)
Pain category	Peripheral pain
Study design	Country: not clear Design: Parallel Inclusion criteria: =18 years with HIV distal sensory polyneuropathy for =2 months and average baseline NRS of 3-9 Exclusion criteria: prior use of the study drug, topically applied pain medication, initiation or cesstion of treatment with neurotoxic ARVs, parenteral opioids, other possible cause of peripheral neuropathy, implanted device for NP Study length (days): 84 Intention-to-treat analysis? Yes
Participants	Total number of patients: 494 Number of males: 432 (87.4%) Underlying cause of neuropathic pain: HIV-related neuropathy Mean duration of NP (in months): 72.6 Baseline pain severity: 6 (NRS (average of arm means)) Mean age: 49.7
Intervention(s)	(1) Capsaicin 8% (60 minutes) Intervention: capsaicin patch Length of treatment (weeks): Fixed/flexible dose regimen: Fixed dose Notes: study reports 8% capsaicin patch applied for 60 minutes once (2) Capsaicin 8% (30 minutes) Intervention: capsaicin patch

Length of treatment (weeks):
Fixed/flexible dose regimen: Fixed dose
Notes: study reports 8% capsaicin patch applied for 30 minutes once

(3) Active placebo (0.04% capaicin) (60 minutes)

Intervention: placebo
Length of treatment (weeks):
Fixed/flexible dose regimen: Fixed dose

(4) Active placebo (0.04% capsaicin) (30 minutes)

Intervention: placebo
Length of treatment (weeks):
Fixed/flexible dose regimen: Fixed dose

(5) Capsaicin 8% (30 or 60 minutes)

Intervention: capsaicin patch
Length of treatment (weeks):
Fixed/flexible dose regimen: Fixed dose
Notes: both 60 and 30 minute patches combined

(6) Active placebo (0.04%) (30 or 60 minutes)

Intervention: placebo
Length of treatment (weeks):
Fixed/flexible dose regimen: Fixed dose
Notes: both 60 and 30 minute patches combined

Concomitant treatments

Drug free baseline period? Unclear

Concomitant pain treatment allowed? Yes (stable dosages of chronic pain medications such as anticonvulsants, SSRIs, opioids, NSAIDs, or salicylates at least 21 days before the patch application and for the study duration; acetaminophen up to 3g/d as rescue analgesics, opioid oral pain medication for up to 5 days after treatment for treatment-associated discomfort)

Outcomes measures and effect sizes

		CAPSAICIN 8% (60 MINUTES)			CAPSAICIN 8% (30 MINUTES)			
		N	k	mean	N	k	mean	Δ
pain score:								
NRS/NRS Pain – 0d	Continuous	165		6.2 (SD 1.28)	167		6 (SD 1.29)	
NRS/NRS Pain – 28d[a]	Percentage change from baseline	165		-32.7 (SD 39.2)	167		-29 (SD 32.3)	MD=-3.700 (CI: -11.429, 4.029)
NRS/NRS Pain – 49d[b]	Percentage change from baseline	165		-32.8 (SD 15.4)	167		-26.2 (SD 15.5)	MD=-6.600 (CI: -9.926, -3.274)
NRS/NRS Pain – 56d[a]	Percentage change from baseline	165		-35.1 (SD 47.5)	167		-25.9 (SD 31.7)	MD=-9.200 (CI: -17.898, -0.502)
NRS/NRS Pain – 84d[a]	Percentage change from baseline	165		-36.4 (SD 50.1)	167		-25.8 (SD 32.3)	MD=-10.600 (CI: -19.680, -1.520)
major adverse events (defined as leading to withdrawal):								
any major adverse event – 70d	Dichotomous	165	1	(0.6%)	167	0	(0.0%)	OR=3.055 (CI: 0.124, 75.529)
adverse events:								
Diarrhoea – 70d	Dichotomous	165	7	(4.2%)	167	6	(3.6%)	OR=1.189 (CI: 0.391, 3.616)

erythema (not restricted to site) – 70d	Dichotomous	165	2	(1.2%)	167	3	(1.8%)	OR=0.671 (CI: 0.111, 4.067)
Nausea – 70d	Dichotomous	165	6	(3.6%)	167	5	(3.0%)	OR=1.223 (CI: 0.366, 4.087)
Peripheral oedema – 70d	Dichotomous	165	3	(1.8%)	167	1	(0.6%)	OR=3.074 (CI: 0.316, 29.860)
Pruritus – 70d	Dichotomous	165	4	(2.4%)	167	8	(4.8%)	OR=0.494 (CI: 0.146, 1.673)
site erythema – 70d	Dichotomous	165	97	(58.8%)	167	79	(47.3%)	OR=1.589 (CI: 1.029, 2.453)
site pain – 70d	Dichotomous	165	139	(84.2%)	167	135	(80.8%)	OR=1.267 (CI: 0.717, 2.239)
site papules – 70d	Dichotomous	165	7	(4.2%)	167	5	(3.0%)	OR=1.435 (CI: 0.446, 4.617)
treatment withdrawal:								
due to lack of efficacy – 70d	Dichotomous	165	1	(0.6%)	167	0	(0.0%)	OR=3.055 (CI: 0.124, 75.529)
unspecified/other reason – 70d	Dichotomous	165	6	(3.6%)	167	7	(4.2%)	OR=0.863 (CI: 0.284, 2.623)
lost to follow-up – 70d	Dichotomous	165	2	(1.2%)	167	3	(1.8%)	OR=0.671 (CI: 0.111, 4.067)
poor compliance – 70d	Dichotomous	165	1	(0.6%)	167	1	(0.6%)	OR=1.012 (CI: 0.063, 16.319)
ITT/LOCF (last-observation carried forward)								
pain score:								
NRS/NRS Pain – 49d[c]	Mean value over whole trial period	165		4.1 (SD 2.57)	167		4.5 (SD 1.29)	MD=-0.400 (CI: -0.838, 0.038)
NRS/NRS Pain – 49d[d]	Mean difference from baseline to average f-u	165		-2 (SD 2.57)	167		-1.6 (SD 1.29)	MD=-0.400 (CI: -0.838, 0.038)
at least 30% pain reduction (NRS) – 84d[e]	Dichotomous from baseline to average f-u	165	79		167	65		OR=1.442 (CI: 0.932, 2.229)
patient-reported global improvement:								
PGIC - worse (all grades) or no change – 70d	Dichotomous	165	99	(60.0%)	167	102	(61.1%)	OR=0.956 (CI: 0.616, 1.484)
PGIC - better (all grades) – 70d	Dichotomous	165	66	(40.0%)	167	65	(38.9%)	OR=1.046 (CI: 0.674, 1.625)

[a] %age change from baseline and SEs estimated from graph; denominators are estimates
[b] %age change in LS mean from baseline; from baseline to weeks 2 to 12
[c] least squares mean; mean value from weeks 2 to 12
[d] least squares; mean difference from baseline to weeks 2 to 12
[e] least squares; mean difference from baseline to weeks 2 to 12; approximated to nearest integer (percentages only presented in text)

		CAPSAICIN 8% (60 MINUTES)			**ACTIVE PLACEBO (0.04% CAPAICIN) (60 MINUTES)**			
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**
pain score:								
NRS/NRS Pain – 0d	Continuous	165		6.2 (SD 1.28)	89		5.9 (SD 1.89)	
NRS/NRS Pain – 28d[a]	Percentage change from baseline	165		-32.7 (SD 39.2)	89		-27.7 (SD 25.5)	MD=-5.000 (CI: -12.984, 2.984)
NRS/NRS Pain – 49d[b]	Percentage change from baseline	165		-32.8 (SD 15.4)	89		-30 (SD 15.6)	MD=-2.800 (CI: -6.799, 1.199)

NRS/NRS Pain – 56d[a]	Percentage change from baseline	165		-35.1 (SD 47.5)	89		-35.1 (SD 27.4)	MD=0.000 (CI: -9.214, 9.214)
NRS/NRS Pain – 84d[a]	Percentage change from baseline	165		-36.4 (SD 50.1)	89		-37.1 (SD 26.4)	MD=0.700 (CI: -8.710, 10.110)
major adverse events (defined as leading to withdrawal):								
any major adverse event – 70d	Dichotomous	165	1	(0.6%)	90	1	(1.1%)	OR=0.543 (CI: 0.034, 8.781)
adverse events:								
Diarrhoea – 70d	Dichotomous	165	7	(4.2%)	90	1	(1.1%)	OR=3.943 (CI: 0.477, 32.566)
erythema (not restricted to site) – 70d	Dichotomous	165	2	(1.2%)	90	5	(5.6%)	OR=0.209 (CI: 0.040, 1.098)
Nausea – 70d	Dichotomous	165	6	(3.6%)	90	3	(3.3%)	OR=1.094 (CI: 0.267, 4.484)
Peripheral oedema – 70d	Dichotomous	165	3	(1.8%)	90	2	(2.2%)	OR=0.815 (CI: 0.134, 4.969)
Pruritus – 70d	Dichotomous	165	4	(2.4%)	90	2	(2.2%)	OR=1.093 (CI: 0.196, 6.087)
site erythema – 70d	Dichotomous	165	97	(58.8%)	90	34	(37.8%)	OR=2.349 (CI: 1.387, 3.979)
site pain – 70d	Dichotomous	165	139	(84.2%)	90	29	(32.2%)	OR=11.245 (CI: 6.117, 20.675)
site papules – 70d	Dichotomous	165	7	(4.2%)	90	0	(0.0%)	OR=8.565 (CI: 0.484, 151.711)
treatment withdrawal:								
due to lack of efficacy – 70d	Dichotomous	165	1	(0.6%)	90	1	(1.1%)	OR=0.543 (CI: 0.034, 8.781)
unspecified/other reason – 70d	Dichotomous	165	6	(3.6%)	90	4	(4.4%)	OR=0.811 (CI: 0.223, 2.953)
lost to follow-up – 70d	Dichotomous	165	2	(1.2%)	90	0	(0.0%)	OR=2.768 (CI: 0.131, 58.275)
poor compliance – 70d	Dichotomous	165	1	(0.6%)	90	2	(2.2%)	OR=0.268 (CI: 0.024, 3.000)
ITT/LOCF (last-observation carried forward)								
pain score:								
NRS/NRS Pain – 49d[c]	Mean value over whole trial period	165		4.1 (SD 2.57)	89		4.2 (SD 1.89)	MD=-0.100 (CI: -0.654, 0.454)
NRS/NRS Pain – 49d[d]	Mean difference from baseline to average f-u	165		-2 (SD 2.57)	89		-1.8 (SD 1.89)	MD=-0.200 (CI: -0.754, 0.354)
at least 30% pain reduction (NRS) – 84d	Dichotomous from baseline to average f-u	165	79	[e]	90	40	[d]	OR=1.148 (CI: 0.685, 1.924)
patient-reported global improvement:								
PGIC - worse (all grades) or no change – 70d	Dichotomous	165	99	(60.0%)	90	26	(28.9%)	OR=3.692 (CI: 2.126, 6.413)
PGIC - better (all grades) – 70d	Dichotomous	165	66	(40.0%)	90	63	(70.0%)	OR=0.286 (CI: 0.165, 0.494)

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[d] least squares; mean difference from baseline to weeks 2 to 12
[e] least squares; mean difference from baseline to weeks 2 to 12; approximated to nearest integer (percentages only presented in text)

		CAPSAICIN 8% (30 MINUTES)			ACTIVE PLACEBO (0.04% CAPSAICIN) (30 MINUTES)			
		N	k	mean	N	k	mean	Δ
pain score:								
NRS/NRS Pain – 0d	Continuous	167		6 (SD 1.29)	73		5.9 (SD 1.71)	
NRS/NRS Pain – 28d[a]	Percentage change from baseline	167		-29 (SD 32.3)	73		-20.4 (SD 13.7)	MD=-8.600 (CI: -14.417, -2.783)
NRS/NRS Pain – 49d[b]	Percentage change from baseline	167		-26.2 (SD 15.5)	73		-19.1 (SD 15.4)	MD=-7.100 (CI: -11.340, -2.860)
NRS/NRS Pain – 56d[a]	Percentage change from baseline	167		-25.9 (SD 31.7)	73		-19.7 (SD 13.7)	MD=-6.200 (CI: -11.935, -0.465)
NRS/NRS Pain – 84d[a]	Percentage change from baseline	167		-25.8 (SD 32.3)	73		-17.3 (SD 13.2)	MD=-8.500 (CI: -14.265, -2.735)
major adverse events (defined as leading to withdrawal):								
any major adverse event – 70d	Dichotomous	167	0	(0.0%)	72	0	(0.0%)	OR=0.433 (CI: 0.009, 22.026)
adverse events:								
Diarrhoea – 70d	Dichotomous	167	6	(3.6%)	72	1	(1.4%)	OR=2.646 (CI: 0.313, 22.385)
erythema (not restricted to site) – 70d	Dichotomous	167	3	(1.8%)	72	4	(5.6%)	OR=0.311 (CI: 0.068, 1.427)
Nausea – 70d	Dichotomous	167	5	(3.0%)	72	1	(1.4%)	OR=2.191 (CI: 0.251, 19.098)
Peripheral oedema – 70d	Dichotomous	167	1	(0.6%)	72	3	(4.2%)	OR=0.139 (CI: 0.014, 1.355)
Pruritus – 70d	Dichotomous	167	8	(4.8%)	72	0	(0.0%)	OR=7.727 (CI: 0.440, 135.694)
site erythema – 70d	Dichotomous	167	79	(47.3%)	72	24	(33.3%)	OR=1.795 (CI: 1.009, 3.196)
site pain – 70d	Dichotomous	167	135	(80.8%)	72	33	(45.8%)	OR=4.986 (CI: 2.729, 9.110)
site papules – 70d	Dichotomous	167	5	(3.0%)	72	0	(0.0%)	OR=4.908 (CI: 0.268, 89.933)
treatment withdrawal:								
due to lack of efficacy – 70d	Dichotomous	167	0	(0.0%)	72	0	(0.0%)	OR=0.433 (CI: 0.009, 22.026)
unspecified/other reason – 70d	Dichotomous	167	7	(4.2%)	72	0	(0.0%)	OR=6.776 (CI: 0.382, 120.236)
lost to follow-up – 70d	Dichotomous	167	3	(1.8%)	72	2	(2.8%)	OR=0.640 (CI: 0.105, 3.916)
poor compliance – 70d	Dichotomous	167	1	(0.6%)	72	0	(0.0%)	OR=1.306 (CI: 0.053, 32.449)
ITT/LOCF (last-observation carried forward)								
pain score:								
NRS/NRS Pain – 49d[c]	Mean value over whole trial period	167		4.5 (SD 1.29)	73		4.9 (SD 1.71)	MD=-0.400 (CI: -0.838, 0.038)
NRS/NRS Pain – 49d[d]	Mean difference from baseline to average f-u	167		-1.6 (SD 1.29)	73		-1.1 (SD 1.71)	MD=-0.500 (CI: -0.938, -0.062)
at least 30% pain reduction (NRS) – 84d	Dichotomous from baseline to average f-u	167	65	[e]	72	19	[d]	OR=1.778 (CI: 0.966, 3.270)

patient-reported global improvement:								
PGIC - worse (all grades) or no change – 70d	Dichotomous	167	102	(61.1%)	72	34	(47.2%)	OR=1.754 (CI: 1.004, 3.063)
PGIC - better (all grades) – 70d	Dichotomous	167	65	(38.9%)	72	39	(54.2%)	OR=0.539 (CI: 0.309, 0.942)
overall improvement in quality of life:								
SF36 Physical – 70d	Mean change	167		9	73		-1.7	MD=10.700
SF36 role physical – 70d	Mean change	167		11.5	73		3.5	MD=8.000
SF36 social functioning – 70d	Mean change	167		11	73		1.3	MD=9.700

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[c] least squares mean; mean value from weeks 2 to 12
[d] least squares; mean difference from baseline to weeks 2 to 12
[e] least squares; mean difference from baseline to weeks 2 to 12; approximated to nearest integer (percentages only presented in text)

		CAPSAICIN 8% (30 OR 60 MINUTES)			**ACTIVE PLACEBO (0.04%) (30 OR 60 MINUTES)**			
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**
pain score:								
NRS/NRS Pain – 0d	Continuous	332		6.1 (SD 1.82)	162		5.9 (SD 1.27)	
NRS/NRS Pain – 49d[a]	Percentage change from baseline	332		-29.5 (SD 28.2)	162		-24.5 (SD 15.3)	MD=-5.000 (CI: -8.842, -1.158)
major adverse events (defined as leading to withdrawal):								
any major adverse event – 70d	Dichotomous	332	2	(0.6%)	162	0	(0.0%)	OR=2.458 (CI: 0.117, 51.505)
adverse events:								
Diarrhoea – 70d	Dichotomous	332	13	(3.9%)	162	2	(1.2%)	OR=3.260 (CI: 0.727, 14.622)
erythema (not restricted to site) – 70d	Dichotomous	332	5	(1.5%)	162	9	(5.6%)	OR=0.260 (CI: 0.086, 0.789)
Nausea – 70d	Dichotomous	332	11	(3.3%)	162	4	(2.5%)	OR=1.354 (CI: 0.424, 4.318)
Peripheral oedema – 70d	Dichotomous	332	4	(1.2%)	162	5	(3.1%)	OR=0.383 (CI: 0.101, 1.446)
Pruritus – 70d	Dichotomous	332	12	(3.6%)	162	2	(1.2%)	OR=3.000 (CI: 0.663, 13.566)
site erythema – 70d	Dichotomous	332	176	(53.0%)	162	58	(35.8%)	OR=2.023 (CI: 1.374, 2.978)
site pain – 70d	Dichotomous	332	274	(82.5%)	162	62	(38.3%)	OR=7.620 (CI: 4.981, 11.655)
site papules – 70d	Dichotomous	332	12	(3.6%)	162	0	(0.0%)	OR=12.676 (CI: 0.746, 215.437)
ITT/LOCF (last-observation carried forward)								
pain score:								
NRS/NRS Pain – 49d[b]	Mean value over whole trial period	332		4.3 (SD 1.82)	162		4.6 (SD 2.55)	MD=-0.300 (CI: -0.738, 0.138)
NRS/NRS Pain – 49d[c]	Mean difference from baseline to average f-u	332		-1.8 (SD 1.82)	162		-1.4 (SD 2.55)	MD=-0.400 (CI: -0.838, 0.038)

	at least 30% pain reduction (NRS) – 84d[d]	Dichotomous from baseline to average f-u	332	143		162	58		OR=1.357 (CI: 0.921, 1.999)
	patient-reported global improvement:								
	PGIC - worse (all grades) or no change – 70d	Dichotomous	332	265	(79.8%)	162	107	(66.0%)	OR=2.033 (CI: 1.334, 3.099)
	PGIC - better (all grades) – 70d	Dichotomous	332	67	(20.2%)	162	55	(34.0%)	OR=0.492 (CI: 0.323, 0.750)

[a] %age change in LS mean from baseline; from baseline to weeks 2 to 12
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[c] least squares; mean difference from baseline to weeks 2 to 12
[d] least squares; mean difference from baseline to weeks 2 to 12; approximated to nearest integer (percentages only presented in text)

authors state that covariate analysis found use of concomitant NP medication usage, age, baseline pain and percent decrease in pain during the patch application had significant affects on pain reduction.

Comments	14 day baseline screening period; pre-treatment with lidocaine; McGill Pain Questionnaire also administered but differences were not significant; covariate analysis found concomitant medication use, age, pre-lidocaine pain, % decrease of pain during lidocaine application were all significant; one patient randomised to receive 30-minute control patch actually was treated with 60-minute control patch - this patient was included as randomised in the efficacy analyses but in the 60-minute group for the safety analyses

Definitions of abbreviations are given at the end of this document.

Study	Davidoff et al. (1987)
Pain category	Mixed (central and peripheral) or unclear if mixed
Study design	Country: USA Design: Parallel Inclusion criteria: Patients with dysesthetic pain following traumatic myelopathy for at least 1 month, and initial onset within the first post injury year. Patients had failed to respond to conventional treatment, and had a pain induced functional impairment Exclusion criteria: Under 18 years of age, lacked English fluency, recent history of alcohol or substance abuse Study length (days): 56 Intention-to-treat analysis? No
Participants	Total number of patients: 18 Number of males: 16 (88.9%) Underlying cause of neuropathic pain: Spinal cord injury pain Mean duration of NP (in months): 49.3 Baseline pain severity: 2.25 (PPI from MPQ (average of arm means) (duration of NP and age are average of arm means)) Mean age: 39.1
Intervention(s)	(1) Trazodone hydrochloride 150mg/d Intervention: trazodone

	Length of treatment (weeks): 6 Fixed/flexible dose regimen: Fixed dose Set dose: 150mg/d Notes: 1 capsule per day for 3 days, 2 capsules per day for the next 4 days, 3 per day for the remaining 5 weeks of the study (2) Placebo Intervention: placebo Length of treatment (weeks): 6 Fixed/flexible dose regimen: Fixed dose
Concomitant treatments	Drug free baseline period? No Concomitant pain treatment allowed? Unclear
Outcomes measures and effect sizes	

		TRAZODONE HYDROCHLORIDE 150MG/D			PLACEBO			
		N	k	mean	N	k	mean	Δ
pain score:								
PPI (from MPQ) – 0d	Continuous	9		2.1 (SD 0.45)	9		2.4 (SD 0.45)	
PPI (from MPQ) – 42d	Continuous	9		2.6 (SD 0.3)	9		1.7 (SD 0.3)	MD=0.900 (CI: 0.623, 1.177)
adverse events:								
any adverse event – 42d	Dichotomous	9	4	(44.4%)	9	1	(11.1%)	OR=6.400 (CI: 0.547, 74.891)
Constipation – 42d	Dichotomous	9	0	(0.0%)	9	0	(0.0%)	OR=1.000 (CI: 0.018, 55.799)
Dizziness – 42d	Dichotomous	9	2	(22.2%)	9	0	(0.0%)	OR=6.333 (CI: 0.262, 152.863)
Drowsiness – 42d	Dichotomous	9	4	(44.4%)	9	1	(11.1%)	OR=6.400 (CI: 0.547, 74.891)
Dry mouth – 42d	Dichotomous	9	2	(22.2%)	9	0	(0.0%)	OR=6.333 (CI: 0.262, 152.863)
Infection – 42d[a]	Dichotomous	9	2	(22.2%)	9	0	(0.0%)	OR=6.333 (CI: 0.262, 152.863)
Urine retention – 42d	Dichotomous	9	1	(11.1%)	9	0	(0.0%)	OR=3.353 (CI: 0.120, 93.835)
average per day								
pain score:								
Sternbach Pain Intensity (1-100) – 0d	Continuous	9		57.9 (SD 33.3)	9		55.7 (SD 31.2)	
Sternbach Pain Intensity (1-100) – 42d	Continuous	9		61.7 (SD 20.4)	9		63.4 (SD 25.2)	MD=-1.700 (CI: -22.882, 19.482)
average per week								
pain score:								
Sternbach Pain Intensity (1-100) – 0d	Continuous	9		69.7 (SD 26.1)	9		65.6 (SD 28.8)	
Sternbach Pain Intensity (1-100) – 42d	Continuous	9		73.9 (SD 14.1)	9		68.3 (SD 20.7)	MD=5.600 (CI: -10.763, 21.963)

[a] urinary tract infection

Comments	-

Definitions of abbreviations are given at the end of this document.

Study	Dogra et al. (2005)
Pain category	Peripheral pain
Study design	Country: USA Design: Parallel

	Inclusion criteria: 6 months to 5 years history of PDN, at least 50mm on VAS-100mm Exclusion criteria: Other types of pain, current or prior use of oxcarbazepine, presence of skin lesions that could affect the ability to assess their neuropathic pain, amputation (other than toes), renal insufficiency, Hyponatraemia, chronic infectios diseases, hypersensitivity to oxcarbazepine or carbamazepine. Study length (days): 112 Intention-to-treat analysis? Yes
Participants	Total number of patients: 146 Number of males: 85 (58.2%) Underlying cause of neuropathic pain: Painful diabetic neuropathy Mean duration of NP (in months): 31.8 Baseline pain severity: 72.9 (VAS (average of arm means)) Mean age: 60.1
Intervention(s)	(1) Oxcarbazepine flexible dose (300-1800mg/d) Intervention: oxcarbazepine Length of treatment (weeks): 16 Fixed/flexible dose regimen: Flexible dose Mean dose: 1445mg/d Range: 300–1800 Notes: 4 week titration, 12 week maintenance; started on 300 mg/d and increased after 3 days to 300 mg 2x per day, then titrated as tolerated to a maximum of 900 mg 2x per day in increments of 300 mg every 5 days over the 4 week titration period (2) Placebo Intervention: placebo Length of treatment (weeks): 16 Fixed/flexible dose regimen: Flexible dose
Concomitant treatments	Drug free baseline period? Yes (duration: 14d) Concomitant pain treatment allowed? Yes (clonazepam, oral corticosteroids, TCAs, AEDs, mexiletine hydrochloride, dextromethorphan, capsaicin or any other medication that could affect neuropathic pain were not permitted; however, SSRIs and benzodiazepines apart from clonazepam were permitted; Paracetamol 2000mg/d (as rescue medication))
Outcomes measures and effect sizes	

		OXCARBAZEPINE FLEXIBLE DOSE (300-1800MG/D)			PLACEBO			
		N	k	mean	N	k	mean	Δ
patient-reported improvement in daily physical and emotional functioning, including sleep:								
POMS – 0d	Continuous	59		31.5 (SD 11)[a]	69		32.9 (SD 16.4)[b]	
POMS – 122d	Continuous	59		31.5 (SD 15.4)[a]	69		26.2 (SD 13.5)[b]	

ITT/LOCF (last-observation carried forward)								
pain score:								
VAS – 0d	Continuous	69		71.5 (SD 15.8)	77		74.3 (SD 13.7)	
VAS – 28d[c]	Continuous	69		55 (SD 24.5)	77		65 (SD 22)	MD=-10.000 (CI: -17.587, -2.413)
VAS – 56d[c]	Continuous	69		49.5 (SD 29)	77		61.5 (SD 23.5)	MD=-12.000 (CI: -20.624, -3.376)
VAS – 84d[c]	Continuous	69		50 (SD 29.5)	77		61 (SD 26)	MD=-11.000 (CI: -20.065, -1.935)
VAS – 122d	Mean change	69		-24.3 (SD 27.2)	77		-14.7 (SD 26.4)	MD=-9.600 (CI: -18.316, -0.884)
VAS – 122d	Continuous	69		47.2 (SD 27.8)	77		59.6 (SD 27.4)	MD=-12.400 (CI: -21.371, -3.429)
at least 30% pain reduction (VAS) – 122d	Dichotomous	69	31	(44.9%)	77	22	(28.6%)	OR=2.039 (CI: 1.028, 4.047)
at least 50% pain reduction (VAS) – 122d	Dichotomous	69	24	(34.8%)	77	14	(18.2%)	OR=2.400 (CI: 1.120, 5.143)
patient-reported global improvement:								
GATE- at least much improved – 122d	Dichotomous	69	33	(47.8%)	77	17	(22.1%)	OR=3.235 (CI: 1.581, 6.622)
major adverse events (defined as leading to withdrawal):								
any major adverse event – 122d	Dichotomous	69	19	(27.5%)	77	6	(7.8%)	OR=4.497 (CI: 1.677, 12.060)
adverse events:								
Blurred vision	Dichotomous	69	1	(1.4%)	77	1	(1.3%)	OR=1.118 (CI: 0.069, 18.216)
Diarrhoea	Dichotomous	69	1	(1.4%)	77	4	(5.2%)	OR=0.268 (CI: 0.029, 2.461)
Dizziness – 122d	Dichotomous	69	7	(10.1%)	77	1	(1.3%)	OR=8.581 (CI: 1.028, 71.627)
Fatigue – 122d	Dichotomous	69	3	(4.3%)	77	1	(1.3%)	OR=3.455 (CI: 0.351, 34.014)
headache	Dichotomous	69	5	(7.2%)	77	1	(1.3%)	OR=5.938 (CI: 0.676, 52.139)
Nausea – 122d	Dichotomous	69	2	(2.9%)	77	1	(1.3%)	OR=2.269 (CI: 0.201, 25.585)
Somnolence – 122d	Dichotomous	69	5	(7.2%)	77	0	(0.0%)	OR=13.217 (CI: 0.717, 243.557)
Vomiting	Dichotomous	69	2	(2.9%)	77	1	(1.3%)	OR=2.269 (CI: 0.201, 25.585)
treatment withdrawal:								
due to lack of efficacy – 122d	Dichotomous	69	0	(0.0%)	77	2	(2.6%)	OR=0.217 (CI: 0.010, 4.605)
unspecified/other reason – 122d	Dichotomous	69	5	(7.2%)	77	6	(7.8%)	OR=0.924 (CI: 0.269, 3.175)
protocol deviation – 122d	Dichotomous	69	1	(1.4%)	77	1	(1.3%)	OR=1.118 (CI: 0.069, 18.216)
use of rescue medication:								
mean daily dose[d]	Continuous	69		915 (SD 895)	77		947 (SD 970)	MD=-32.000 (CI: -334.550, 270.550)
Treatment completers								
pain score:								
VAS – 0d	Continuous	44		69 (SD 16)	58		73 (SD 12.5)	
VAS – 122d	Continuous	44		39.6 (SD 25.9)	58		56.1 (SD 27.4)	MD=-16.500 (CI: -26.906, -6.094)
VAS – 122d	Mean change	44		-29.4 (SD 27.1)	58		-16.9 (SD 28.1)	MD=-12.500 (CI: -23.290, -1.710)

[a] includes patients who completed this survey (n = 59)
[b] includes patients who completed this survey (n = 69)
[c] Estimated from graph
[d] mg/d

Comments	there was a 2 week screening phase - unclear if this included a drug-free phase (however, as concomitant medications were not allowed)

Definitions of abbreviations are given at the end of this document.

Study	Donofrio & Capsaicin study (1992)
Pain category	Peripheral pain
Study design	Country: USA Design: Parallel Inclusion criteria: Participants with PDN or radiculopathy aged between 18 and 85 years Exclusion criteria: pregnancy, another skin condition in the area affected by the enruopathy, unstable or uncontrolled diabetes, another organic disease or disorder not under long-term control Study length (days): 56 Intention-to-treat analysis? No
Participants	Total number of patients: 277 Number of males: 139 (50.2%) Underlying cause of neuropathic pain: Painful diabetic neuropathy or radiculopathy Mean duration of NP (in months): not reported Baseline pain severity: 76 (VAS (89% had peripheral polyneuroapthy with 5 year mean pain duration, 7% had radiculopathy with 3 year mean pain duration, 4% had both peripheral polyneuropathy and radiculopathy with 2 year mean pain duration)) Mean age: 60
Intervention(s)	(1) Capsaicin 0.075% fixed dosage (applied 4x per day) Intervention: capsaicin cream Length of treatment (weeks): 8 Fixed/flexible dose regimen: Fixed dose (2) Placebo (vehicle) Intervention: placebo Length of treatment (weeks): 8 Fixed/flexible dose regimen: Fixed dose
Concomitant treatments	Drug free baseline period? No Concomitant pain treatment allowed? Yes (medication dosage of previous oral pain medications that were not expected to change (otherwise, ineligible for study))
Outcomes measures and effect sizes	See table below

		CAPSAICIN 0.075% FIXED DOSAGE (APPLIED 4X PER DAY)			PLACEBO (VEHICLE)			
		N	k	mean	N	k	mean	Δ
pain score: VAS – 56d[a]	Percentage change from baseline	119		-38.1	131		-27.4	MD=-10.700
VAS – 56d	Continuous	120		58.4	131		45.2	MD=13.200

	major adverse events (defined as leading to withdrawal):								
	any major adverse event – 56d	Dichotomous	138	18	(13.0%)	139	5	(3.6%)	OR=4.020 (CI: 1.448, 11.159)
	adverse events:								
	Burning pain – 56d	Dichotomous	138	87	(63.0%)	139	23	(16.5%)	OR=8.604 (CI: 4.888, 15.143)
	Rash – 56d	Dichotomous	138	10	(7.2%)	139	4	(2.9%)	OR=2.637 (CI: 0.807, 8.619)
	treatment withdrawal:								
	due to lack of efficacy – 56d	Dichotomous	138	0	(0.0%)	139	2	(1.4%)	OR=0.199 (CI: 0.009, 4.174)
	unspecified/other reason – 56d	Dichotomous	138	13	(9.4%)	139	7	(5.0%)	OR=1.961 (CI: 0.758, 5.075)
	poor compliance – 56d	Dichotomous	138	7	(5.1%)	139	6	(4.3%)	OR=1.184 (CI: 0.388, 3.619)
	[a] percentage improvement from baseline								
Comments	new oral analgesic usage, antiinflammatories or CNS-acting drugs were not allowed during the study, topic medications previously applied were discontinued for at least 7 days before the study								

Definitions of abbreviations are given at the end of this document.

Study	Dworkin et al. (2003)
Pain category	Peripheral pain
Study design	Country: USA Design: Parallel Inclusion criteria: Pain for 3 or more months following herpes zoster rash healing, at least 40mm on the VAS100mm Exclusion criteria: Those who had previously failed to respond to gabapentin Study length (days): 56 Intention-to-treat analysis? Yes
Participants	Total number of patients: 173 Number of males: 81 (46.8%) Underlying cause of neuropathic pain: Post-herpetic neuralgia Mean duration of NP (in months): 33.8 Baseline pain severity: 6.4 (NRS) Mean age: 71.5
Intervention(s)	(1) Pregabalin 300 mgd or 600mg/d Intervention: pregabalin Length of treatment (weeks): 8 Fixed/flexible dose regimen: Fixed dose Set dose: 600mg/d Notes: start at 150 mg/d (50 mg 3x) for first 3 days and 300 mg/d (100 mg 3x) for remainder at firset treatment week; those with creatinine clearance > 60

	ml/min were given 300 mg/d (200 mg 3x) at the start of the 2nd week (2) Placebo Intervention: placebo Length of treatment (weeks): 8 Fixed/flexible dose regimen: Fixed dose
Concomitant treatments	Drug free baseline period? Yes (duration: 7d) Concomitant pain treatment allowed? Yes (Some existing medications allowed if stable doses for at least 30 day: narcotic and non-narcotic analgesics, NSAIDs, antidepressants, acetaminophen (no more than 4g/d), aspirin, anti-depressants including SSRIs; prohibited medications requiring 7 day washout included: benzodiazepine, skeletal muscle relaxant, orallly administered steroids, local and topical agents for PHN and anti-convulsants (including gabapentin) (injected local anaesthetics or steroids were not permitted within one month of baseline))
Outcomes measures and effect sizes	

		PREGABALIN 300 MGD OR 600MG/D			PLACEBO			
		N	k	mean	N	k	mean	Δ
pain score:								
NRS/NRS Pain – 0d	Continuous	89		6.3 (SD 1.4)	84		6.4 (SD 1.5)	
NRS/NRS Pain – 56d	Continuous	88		3.6 (SD 2.25)	84		5.29 (SD 2.2)	MD=-1.690 (CI: -2.330, -1.050)
at least 30% pain reduction – 56d[a]	Dichotomous	89	56	(62.9%)	84	21	(25.0%)	OR=5.091 (CI: 2.645, 9.800)
at least 50% pain reduction – 56d[a]	Dichotomous	89	44	(49.4%)	84	17	(20.2%)	OR=3.854 (CI: 1.962, 7.571)
McGill VAS – 56d[b]	Continuous	89		38.7 (SD 27.4)	84		56.3 (SD 26.9)	MD=-17.620 (CI: -25.375, -9.865)
PPI (from MPQ) – 56d[b]	Continuous	89		1.58 (SD 1.13)	84		1.98 (SD 1.1)	MD=-0.400 (CI: -0.710, -0.090)
patient-reported global improvement:								
PGIC - worse (all grades) – 56d	Dichotomous	89	3	(3.4%)	84	12	(14.3%)	OR=0.209 (CI: 0.057, 0.771)
PGIC - no change – 56d	Dichotomous	89	11	(12.4%)	84	50	(59.5%)	OR=0.096 (CI: 0.045, 0.206)
PGIC - better (all grades) – 56d	Dichotomous	89	71	(79.8%)	84	22	(26.2%)	OR=11.116 (CI: 5.465, 22.610)
patient-reported improvement in daily physical and emotional functioning, including sleep:								
MOS sleep problems index – 56d[b]	Continuous	85		26.6 (SD 16.3)	82		36.4 (SD 15.8)	MD=-9.800 (CI: -14.490, -5.110)
major adverse events (defined as leading to withdrawal):								
any major adverse event – 56d	Dichotomous	89	28	(31.5%)	84	4	(4.8%)	OR=9.180 (CI: 3.058, 27.561)
adverse events:								
Confusion – 56d	Dichotomous	89	6	(6.7%)	84	0	(0.0%)	OR=13.156 (CI: 0.729, 237.259)
Diarrhoea – 56d	Dichotomous	89	6	(6.7%)	84	4	(4.8%)	OR=1.446 (CI: 0.393, 5.315)
Dizziness – 56d	Dichotomous	89	25	(28.1%)	84	10	(11.9%)	OR=2.891 (CI: 1.291, 6.472)
Dry mouth – 56d	Dichotomous	89	10	(11.2%)	84	2	(2.4%)	OR=5.190 (CI: 1.102, 24.435)
Gait disturbance – 56d	Dichotomous	89	7	(7.9%)	84	1	(1.2%)	OR=7.085 (CI: 0.853, 58.876)
headache – 56d	Dichotomous	89	7	(7.9%)	84	7	(8.3%)	OR=0.939 (CI: 0.315, 2.801)
Peripheral oedema – 56d	Dichotomous	89	17	(19.1%)	84	2	(2.4%)	OR=9.681 (CI: 2.162, 43.340)
Somnolence – 56d	Dichotomous	89	22	(24.7%)	84	6	(7.1%)	OR=4.269 (CI: 1.635, 11.148)
overall improvement in quality of life:								
SF36 Mental – 56d[b]	Continuous	86		77.5 (SD 14.3)	83		73.7 (SD 14)	MD=3.810 (CI: -0.275, 7.895)
SF36 Physical – 56d[b]	Continuous	85		62.2 (SD 18.1)	83		61.4 (SD 17.3)	MD=0.840 (CI: -4.600, 6.280)
treatment withdrawal:								
due to lack of efficacy – 56d	Dichotomous	89	0	(0.0%)	84	6	(7.1%)	OR=0.067 (CI: 0.004, 1.217)
withdrawal of consent – 56d	Dichotomous	89	1	(1.1%)	84	0	(0.0%)	OR=2.864 (CI: 0.115, 71.295)
poor compliance – 56d	Dichotomous	89	2	(2.2%)	84	0	(0.0%)	OR=4.829 (CI: 0.228, 102.063)

	[a] calculated from percentages [b] baseline not reported
Comments	-

Definitions of abbreviations are given at the end of this document.

Study	Eisenberg et al. (2001)
Pain category	Peripheral pain
Study design	Country: Israel Design: Parallel Inclusion criteria: People with Type 1 or 2 diabetes, with evidence of peripheral neuropathy, and with no changes in their anithyperglycaemic medications within Exclusion criteria: Under the age of 18, older than 75 years, impaired renal or liver function, known epilepsy, presence for other painful conditions, receipt of anticonvulsants antidepressants or membrane stablilising agents for reasons other than pain relief, opioids, participation in any clinical trial in the 30 days prior to screening. Study length (days): 77 Intention-to-treat analysis? Yes
Participants	Total number of patients: 53 Number of males: 33 (62.3%) Underlying cause of neuropathic pain: Painful diabetic neuropathy Mean duration of NP (in months): 44.4 Baseline pain severity: 6.5 (NRS) Mean age: 55.25
Intervention(s)	(1) Lamotrigine 400 mg/d Intervention: lamotrigine Length of treatment (weeks): 8 Fixed/flexible dose regimen: Fixed dose Set dose: 400mg/d Notes: titrated from 25 to 400 mg over a 6-week period (2) Placebo Intervention: placebo Length of treatment (weeks): 8 Fixed/flexible dose regimen: Fixed dose
Concomitant treatments	Drug free baseline period? Yes (duration: 3d) Concomitant pain treatment allowed? No (analgesics (including anti-convulsants, anti-depressants, membrane stablizers and opioids) were discontinued at least 3 days before treatment; Paracetamol, dipyrone or NSAIDs as rescue)
Outcomes measures and	**LAMOTRIGINE 400 MG/D** **PLACEBO**

effect sizes

		N	k	mean	N	k	mean	Δ
pain score:								
NRS/NRS Pain – 0d	Continuous	27		6.4 (SD 0.52)	26		6.5 (SD 0.51)	
NRS/NRS Pain – 56d	Continuous	27		4.2 (SD 0.52)	26		5.3 (SD 0.51)	MD=-1.100 (CI: -1.376, -0.824)
at least 50% pain reduction – 46d[a]	Dichotomous	27	12	(44.4%)	26	5	(19.2%)	OR=3.360 (CI: 0.976, 11.563)
McGill Pain Questionnaire – 0d[b]	Continuous	27		12 (SD 3.92)	26		11.1 (SD 3.75)	
McGill Pain Questionnaire – 56d[b]	Continuous	27		12.5 (SD 4.41)	26		10.7 (SD 4.69)	MD=1.800 (CI: -0.653, 4.253)
patient-reported improvement in daily physical and emotional functioning, including sleep:								
BDI – 0d	Continuous	27		14.1 (SD 7.35)	26		17.1 (SD 10.3)	
BDI – 56d	Continuous	27		14.5 (SD 10.3)	26		15.9 (SD 10.3)	MD=-1.400 (CI: -6.949, 4.149)
major adverse events (defined as leading to withdrawal):								
any major adverse event – 56d	Dichotomous	27	2	(7.4%)	26	2	(7.7%)	OR=0.960 (CI: 0.125, 7.371)
adverse events:								
Dizziness – 56d	Dichotomous	27	3	(11.1%)	26	4	(15.4%)	OR=0.688 (CI: 0.138, 3.422)
Drowsiness	Dichotomous	27	1	(3.7%)	26	4	(15.4%)	OR=0.212 (CI: 0.022, 2.035)
epigastric pain	Dichotomous	27	3	(11.1%)	26	1	(3.8%)	OR=3.125 (CI: 0.304, 32.165)
headache	Dichotomous	27	2	(7.4%)	26	2	(7.7%)	OR=0.960 (CI: 0.125, 7.371)
Nausea – 56d	Dichotomous	27	4	(14.8%)	26	4	(15.4%)	OR=0.957 (CI: 0.213, 4.305)
Rash – 56d	Dichotomous	27	2	(7.4%)	26	0	(0.0%)	OR=5.196 (CI: 0.238, 113.586)
treatment withdrawal:								
unspecified/other reason – 56d	Dichotomous	27	1[c]	(3.7%)	26	2[d]	(7.7%)	OR=0.462 (CI: 0.039, 5.422)
protocol deviation	Dichotomous	27	0	(0.0%)	26	1	(3.8%)	OR=0.309 (CI: 0.012, 7.937)
poor compliance	Dichotomous	27	2	(7.4%)	26	3	(11.5%)	OR=0.613 (CI: 0.094, 4.006)
use of rescue medication:								
proportion requiring at least 1 tablet of rescue medication	Dichotomous	24	7	(29.2%)	26	3	(11.5%)	
proportion requiring at least 1 tablet of rescue medication	Dichotomous	27	2	(7.4%)	26	3	(11.5%)	OR=0.613 (CI: 0.094, 4.006)

[a] Measured during last 3 weeks of treatment
[b] MPQ words
[c] personal reasons
[d] personal reasons or car accident

Comments: -

Definitions of abbreviations are given at the end of this document.

Study	Falah et al. (2012)
Pain category	Central pain
Study design	Country: Denmark Design: Crossover Inclusion criteria: 18 years and older with signs and symptoms consistent with central neuropathic pain due to multiple sclerosis (MS confirmed by a specialist in neurology using Poser criteria as patients were typically recruited before McDonald criteria were used; central NP signs and symptoms included pain in a body area with sensory abnormality on clinical examination or quantitative sensory examination corresponding to at least one lesion of the CNS), median total pain of at least 5 on 11-point NRS Exclusion criteria: causes other than central NP due to MS, previous allergic reaction/severe adverse reactions to levetiracetam, pregnancy and lactation,

	severe terminal illness or concomitant treatment with antidepressants, other anticonvulsants or opioids that could not be discontinued Study length (days): 105 Intention-to-treat analysis? Yes
Participants	Total number of patients: 30 Number of males: 22 (73.3%) Underlying cause of neuropathic pain: MS neuropathic pain Mean duration of NP (in months): 60 Baseline pain severity: 5.8 (NRS (median) (also, median duration of NP and age)) Mean age: 47
Intervention(s)	(1) levetiracetam flexible dose Intervention: levetiracetam Length of treatment (weeks): 6 Fixed/flexible dose regimen: Flexible dose Range: 2000–3000 Notes: slow titration in the first 15 days up to 3000 mg/d but those with unacceptable side effects were permitted to lower their dose to 2000-2500 mg/d; actual numbers of patients achieving these different dosage levels was not reported; 7 of 37 eligible patients were withdrawan prior to randomisation for reasons including that they could not stop current pain treatment or failed to meet inclusion criteria (2) placebo Intervention: placebo Length of treatment (weeks): 6 Fixed/flexible dose regimen: Flexible dose
Concomitant treatments	Drug free baseline period? Yes (duration: 7d) Concomitant pain treatment allowed? No (all concomitant treatments for NP (anti-depressants, other anti-convulsants, opioids) were either discontinued or patients on these were excluded; up to six tablets of 500 mg paracetamol and one tablet of 50 mg of tramadol could be used daily as escape medication)
Outcomes measures and effect sizes	

		LEVETIRACETAM FLEXIBLE DOSE			PLACEBO			
		N	k	mean	N	k	mean	Δ
ITT/LOCF (last-observation carried forward)								
pain score:								
NRS/NRS Pain – 0d	Continuous	27		5.8 (SD 1.4)	27		5.8 (SD 1.4)	
NRS/NRS Pain – 42d	Continuous	27		5.3 (SD 2)	27		5.7 (SD 1.8)	MD=-0.400 (CI: -1.415, 0.615)
patient-reported improvement in daily physical and emotional functioning, including sleep:								
Normalised (10-pt) sleep interference measure – 0d[a]	Continuous	27		4.4 (SD 2.5)	27		4.4 (SD 2.5)	
Normalised (10-pt) sleep interference measure – 42d[a]	Continuous	27		3.6 (SD 2.8)	27		4.1 (SD 2.9)	
NRS Sleep – 0d	Continuous	27		4.4 (SD 2.5)	27		4.4 (SD 2.5)	

	NRS Sleep – 42d	Continuous	27		3.6 (SD 2.8)	27		4.1 (SD 2.9)	MD=-0.500 (CI: -2.021, 1.021)
	major adverse events (defined as leading to withdrawal):								
	any major adverse event – 42d	Dichotomous	30	4[b]	(13.3%)	30	1[c]	(3.3%)	OR=4.462 (CI: 0.468, 42.514)
	adverse events:								
	Blurred vision – 42d[d]	Dichotomous	30	1	(3.3%)	30	0	(0.0%)	OR=3.102 (CI: 0.121, 79.228)
	Constipation – 42d	Dichotomous	30	1	(3.3%)	30	3	(10.0%)	OR=0.310 (CI: 0.030, 3.168)
	Diarrhoea – 42d	Dichotomous	30	2	(6.7%)	30	2	(6.7%)	OR=1.000 (CI: 0.131, 7.605)
	Dizziness – 42d	Dichotomous	30	8	(26.7%)	30	0	(0.0%)	OR=23.044 (CI: 1.263, 420.370)
	Drowsiness – 42d[e]	Dichotomous	30	9	(30.0%)	30	5	(16.7%)	OR=2.143 (CI: 0.622, 7.387)
	Fatigue – 42d	Dichotomous	30	6	(20.0%)	30	1	(3.3%)	OR=7.250 (CI: 0.815, 64.457)
	headache – 42d	Dichotomous	30	6	(20.0%)	30	3	(10.0%)	OR=2.250 (CI: 0.507, 9.993)
	mental change – 42d	Dichotomous	30	3	(10.0%)	30	0	(0.0%)	OR=7.764 (CI: 0.384, 157.138)
	mood disturbance – 42d[f]	Dichotomous	30	5	(16.7%)	30	1	(3.3%)	OR=5.800 (CI: 0.635, 53.012)
	Nausea – 42d	Dichotomous	30	4	(13.3%)	30	1	(3.3%)	OR=4.462 (CI: 0.468, 42.514)
	other – 42d[g]	Dichotomous	30	13	(43.3%)	30	4	(13.3%)	OR=4.971 (CI: 1.387, 17.816)
	parasthesia – 42d	Dichotomous	30	3	(10.0%)	30	2	(6.7%)	OR=1.556 (CI: 0.241, 10.049)
	sleep disturbance – 42d	Dichotomous	30	2	(6.7%)	30	0	(0.0%)	OR=5.351 (CI: 0.246, 116.310)
	vertigo – 42d[h]	Dichotomous	30	2	(6.7%)	30	1	(3.3%)	OR=2.071 (CI: 0.178, 24.148)
	treatment withdrawal:								
	due to lack of efficacy – 42d	Dichotomous	30	1	(3.3%)	30	0	(0.0%)	OR=3.102 (CI: 0.121, 79.228)
	unspecified/other reason – 42d	Dichotomous	30	1[i]	(3.3%)	30	0	(0.0%)	OR=3.102 (CI: 0.121, 79.228)
	use of rescue medication:								
	500 mg paracetamol tablets per week – 0d	Continuous	27		16.8 (SD 16.9)	27		16.8 (SD 16.9)	
	500 mg paracetamol tablets per week – 42d	Continuous	27		17.6 (SD 17.7)	27		18.2 (SD 17.6)	MD=-0.600 (CI: -10.015, 8.815)
	50 mg tramadol tablets per week – 0d	Continuous	27		1.4 (SD 3)	27		1.4 (SD 3)	
	50 mg tramadol tablets per week – 42d	Continuous	27		0.9 (SD 2.4)	27		1.3 (SD 2.5)	MD=-0.400 (CI: -1.707, 0.907)
	Per Protocol								
	pain score:								
	NRS/NRS Pain – 0d	Continuous	23		5.8 (SD 1.5)	23		5.8 (SD 1.5)	
	NRS/NRS Pain – 42d	Continuous	23		5.4 (SD 2.1)	23		5.7 (SD 1.9)	MD=-0.300 (CI: -1.457, 0.857)

[a] based on NRS Sleep
[b] 1 fatigue, 2 dizziness, 1 tiredness
[c] influenza and tiredness
[d] defined in study as 'double vision'
[e] defined in study as 'tiredness'
[f] defined in study as 'mood swings'
[g] no other details provided
[h] defined in study as 'balance problems'
[i] because of MS attack

Comments	Study reports the use of tramadol (one of the other drugs being considered in this guideline) as rescue medication - there were a number of patients who were receiving this at baseline as a rescue medication (but it was not clear how many exactly); ITT analysis seems to have been done but not all patients randomised were included in the analysis; 19 patients had prior treatment with drugs specific for NP (ie. Antidepressants, etc) and 3 had been treatd with more than three different drugs; 27 patients were included in the data analysis (4 of the 23 who completed the study had sufficient data from both treatment periods to be included)

Definitions of abbreviations are given at the end of this document.

Study	Finnerup et al. (2002)
Pain category	Mixed (central and peripheral) or unclear if mixed
Study design	Country: Denmark Design: Crossover Inclusion criteria: neurpathic pain after traumatic SCI or at below level of spinal lesion, aged 18-70 and pain intensity of 3 or more on the 0-10 point numeric rating scale. Exclusion criteria: Concomitant cerebral damage or dementia, pregnant or lactating women and fertile women with inappropriate contraception, previous allergic reaction or hypersensitivity to lamotrigine, serious hepatic or renal disease or other significant illness Study length (days): 147 Intention-to-treat analysis? Unclear
Participants	Total number of patients: 30 Number of males: 18 (60.0%) Underlying cause of neuropathic pain: Spinal cord injury pain Mean duration of NP (in months): 84 Baseline pain severity: 5 (median NRS (and median duration of NP)) Mean age: 49
Intervention(s)	(1) lamotrigine 200 mg/d Intervention: lamotrigine Length of treatment (weeks): 9 Fixed/flexible dose regimen: Flexible dose Range: 200–400 Notes: tablets containing 25mg or 100mg were administered as single or divided doses. The dose was gradually increased from 25mg to 400mg. Patients were permitted to reduce the dose if they experience adverse events, but the final dose had to be at least 200mg and continued for at least 2 weeks to complete the trial. (2) Placebo Intervention: placebo Length of treatment (weeks): 9 Fixed/flexible dose regimen: Flexible dose
Concomitant treatments	Drug free baseline period? Unclear Concomitant pain treatment allowed? Yes (treatment with spasmolytics, sedatives for insomnia and simple analgesics for other type of pain was allowed in a constant and unchanged dose during the trial.)
Outcomes measures and effect sizes	

		LAMOTRIGINE 200 MG/D			PLACEBO			
		N	k	mean	N	k	mean	Δ
pain score:								
NRS/NRS Pain – 0d[a]	Continuous	22		med: 5	22		med: 5	
NRS/NRS Pain – 28d[b]	Continuous	22		med: 4	22		med: 4.5	
NRS/NRS Pain – 56d[b]	Continuous	22		med: 3	22		med: 4	

	NRS/NRS Pain – 63d	Mean change	22		med: 1	22		med: 0	
	NRS/NRS Pain – 63d[b]	Continuous	22		med: 3	22		med: 4	
	McGill Pain Questionnaire – 0d[c]	Continuous	22		med: 21.5	22		med: 21.5	
	McGill Pain Questionnaire – 63d	Continuous	22		med: 19[d]	22		med: 18.5[e]	
	patient-reported improvement in daily physical and emotional functioning, including sleep:								
	NRS Sleep – 0d[f]	Continuous	22		med: 1.5	22		med: 1.5	
	NRS Sleep – 63d[g]	Continuous	22		med: 0	22		med: 1	
	major adverse events (defined as leading to withdrawal):								
	any major adverse event	Dichotomous	30	1	(3.3%)	30	2	(6.7%)	OR=0.483 (CI: 0.041, 5.628)
	adverse events:								
	any adverse event – 63d	Dichotomous	30	13	(43.3%)	30	14	(46.7%)	OR=0.874 (CI: 0.316, 2.418)
	moderate to severe – 63d	Dichotomous	30	5	(16.7%)	30	4	(13.3%)	OR=1.300 (CI: 0.313, 5.404)
	skin-related side effects – 63d	Dichotomous	30	4	(13.3%)	30	4	(13.3%)	OR=1.000 (CI: 0.226, 4.431)
	overall improvement in quality of life:								
	SF36 Mental – 0d[h]	Continuous	22		med: 60.7	22		med: 60.7	
	SF36 Mental – 63d	Continuous	22		med: 60.7[i]	22		med: 61.9[j]	
	SF36 Physical – 0d[k]	Continuous	22		med: 33.5	22		med: 33.5	
	SF36 Physical – 63d	Continuous	22		med: 32.6[l]	22		med: 33.9[m]	
	treatment withdrawal:								
	unspecified/other reason	Dichotomous	30	2[n]	(6.7%)	30	1[o]	(3.3%)	OR=2.071 (CI: 0.178, 24.148)
	withdrawal of consent	Dichotomous	30	0	(0.0%)	30	1	(3.3%)	OR=0.322 (CI: 0.013, 8.235)
	protocol deviation	Dichotomous	30	0	(0.0%)	30	1	(3.3%)	OR=0.322 (CI: 0.013, 8.235)
	use of rescue medication:								
	number of people using paracetamol weekly – 0d[p]	Continuous	22		med: 0	22		med: 0	
	number of people using paracetamol weekly – 63d	Continuous	22		med: 0[f]	22		med: 0[q]	

[a] IQR: 3-8 (value for all patients in both groups)
[b] estimated from graph
[c] IQR: 11-31
[d] IQR: 13-27
[e] IQR: 9-32
[f] IQR: 0-4
[g] IQR: 0-3
[h] IQR: 58-67
[i] IQR: 54-67
[j] IQR: 58-68
[k] IQR: 30-38
[l] IQR: 28-42
[m] IQR: 29-37
[n] one patient left the country and another patient had a new trauma
[o] patient was unable to complete without usual medication
[p] IQR: 0-7
[q] IQR: 0-6

Comments	Analyses were made on patients who achieved at least 200mg/d for at least 2 weeks (study population). The last observation carried over method was implemented to the diary account for early discontinuation; other missing data were not replaced. Dichotomous outcomes have been reported as intention-to-treat here (with patients randomised as denominator). There is some inconsistency between the flow diagram of patients in the study and the text regarding the reasons why 8 patients withdrew from the study - the reasons which were in the flow diagram were extracted here.

Definitions of abbreviations are given at the end of this document.

Study	Finnerup et al. (2009)
Pain category	Mixed (central and peripheral) or unclear if mixed
Study design	Country: Denmark Design: Crossover Inclusion criteria: 18 years and older with at and/or below level neuropathic pain for at least 3 months due to trauma or disease of the spinal cord or cauda equina with a median pain intensity of 4 or more on a 0-10 point NRS during a 1 week baseline period. Exclusion criteria: Concomitant cerebral damage, pregancy or lactation, alcohol or substance abuse, hypersensitivity to levetriacetam or pyrrolidine derivates, epilepsy, psychiatric disease, depression, severe liver disease or impaired renal function. Study length (days): 84 Intention-to-treat analysis? No
Participants	Total number of patients: 24 Number of males: 21 (87.5%) Underlying cause of neuropathic pain: Spinal cord injury pain Mean duration of NP (in months): not reported Baseline pain severity: 6 (NRS) Mean age: 51 (SD: 11.2)
Intervention(s)	(1) levetiracetam Intervention: levetiracetam Length of treatment (weeks): 5 Fixed/flexible dose regimen: Flexible dose Range: 2000–3000 Notes: the dose was gradually increased from 1000mg (wk 1), 2000 mg (wk 2), and 3000mg (wk 3). Patients were permitted to reduce the final dose to 2000 or 2500mg daily if they experienced adverse effects. The final dose had to be at least 2000mg to be included in the trial (21 achieved maximum dosage and 3 had 2000 mg/d) (2) Placebo Intervention: placebo Length of treatment (weeks): 5 Fixed/flexible dose regimen: Flexible dose
Concomitant treatments	Drug free baseline period? Unclear Concomitant pain treatment allowed? Yes (spasmolytics, gabapentin, pregabalin, opioids and simple analgesics for pain (NSAIDs, paracetamol, acetylsalicylic acid) were allowed in a constant and unchanged dose during the trial (anti-depressants were slowly tapered off at least 1 week before entering the trial))
Outcomes measures and effect sizes	

		LEVETIRACETAM			PLACEBO			
		N	k	mean	N	k	mean	Δ
pain score: NRS/NRS Pain – 0d[a]	Continuous	24		med: 6 [rng 4–9]	24		med: 6 [rng 4–9]	

	NRS/NRS Pain – 35d	Continuous	24		med: 6 [rng 3–9.5]	24	med: 7 [rng 3–9.5]	
	at least 30% pain reduction (NRS)[b]	Dichotomous	36	3	(8.3%)	36	4 (11.1%)	OR=0.727 (CI: 0.151, 3.510)
	at least 50% pain reduction (NRS)	Dichotomous	36	1	(2.8%)	36	1 (2.8%)	OR=1.000 (CI: 0.060, 16.629)
	patient-reported global improvement:							
	PGIC - worse (all grades)[c]	Dichotomous	36	7	(19.4%)	36	2 (5.6%)	OR=4.103 (CI: 0.790, 21.318)
	PGIC - no change[c]	Dichotomous	36	16	(44.4%)	36	20 (55.6%)	OR=0.640 (CI: 0.253, 1.622)
	PGIC - minimally better[d]	Dichotomous	36	2	(5.6%)	36	1 (2.8%)	OR=2.059 (CI: 0.178, 23.773)
	PGIC - moderately better[e]	Dichotomous	36	1	(2.8%)	36	1 (2.8%)	OR=1.000 (CI: 0.060, 16.629)
	PGIC - at least moderately better[f]	Dichotomous	36	1	(2.8%)	36	1 (2.8%)	OR=1.000 (CI: 0.060, 16.629)
	PGIC - much better[g]	Dichotomous	36	0	(0.0%)	36	0 (0.0%)	OR=1.000 (CI: 0.019, 51.764)
	patient-reported improvement in daily physical and emotional functioning, including sleep:							
	NRS Sleep – 0d[a]	Continuous	24		med: 4 [rng 0–8]	24	med: 4 [rng 0–8]	
	NRS Sleep – 35d	Continuous	24		med: 3 [rng 0–9]	24	med: 3.5 [rng 0–9]	
	major adverse events (defined as leading to withdrawal):							
	any major adverse event	Dichotomous	36	7	(19.4%)	36	2 (5.6%)	OR=4.103 (CI: 0.790, 21.318)
	adverse events:							
	any adverse event – 35d	Dichotomous	36	14	(38.9%)	36	11 (30.6%)	OR=1.446 (CI: 0.545, 3.837)
	balance disorder – 35d	Dichotomous	36	5	(13.9%)	36	1 (2.8%)	OR=5.645 (CI: 0.625, 50.987)
	Dizziness – 35d	Dichotomous	36	6	(16.7%)	36	2 (5.6%)	OR=3.400 (CI: 0.638, 18.132)
	Dry mouth – 35d	Dichotomous	36	1	(2.8%)	36	2 (5.6%)	OR=0.486 (CI: 0.042, 5.608)
	headache – 35d	Dichotomous	36	0	(0.0%)	36	1 (2.8%)	OR=0.324 (CI: 0.013, 8.227)
	moderate to severe – 35d	Dichotomous	36	9	(25.0%)	36	4 (11.1%)	OR=2.667 (CI: 0.738, 9.633)
	Somnolence – 35d	Dichotomous	36	11	(30.6%)	36	4 (11.1%)	OR=3.520 (CI: 1.000, 12.388)
	treatment withdrawal:							
	unspecified/other reason	Dichotomous	36	1[h]	(2.8%)	36	1[i] (2.8%)	OR=1.000 (CI: 0.060, 16.629)
	protocol deviation	Dichotomous	36	1	(2.8%)	36	0 (0.0%)	OR=3.085 (CI: 0.122, 78.271)
	use of rescue medication:							
	proportion taking up to 3 g/d of paracetamol – 0d[a]	Continuous	24		med: 0 [rng 0–56]	24	med: 0 [rng 0–56]	
	proportion taking up to 3 g/d of paracetamol – 35d	Continuous	24		med: 0 [rng 0–56]	24	med: 0 [rng 0–56]	

[a] average of patients in both groups at baseline
[b] 33% pain reduction
[c] estimated from graph
[d] defined in study as 'slight'; estimated from graph
[e] defined in study as 'some'; estimated from graph
[f] combined 'some' with 'a lot'; estimated from graph
[g] defined in study as 'a lot'; estimated from graph
[h] patient had an 'accident with fracture'
[i] increased pain

Comments	2 dropped out before randomisation because they could not be effectively tapered from amitriptyline or escitalopram; 12 dropped out after randomisation - only 24 patients achieved 2000 mg/d for at least 2 weeks and these comprise the study population (however, we have recorded the dichotomous outcomes using intention-to-treat analysis with all those randomised in the denominator)

Definitions of abbreviations are given at the end of this document.

Study	Freynhagen et al. (2005)
Pain category	Peripheral pain

Study design	Country: USA, Germany, Poland Design: Parallel Inclusion criteria: participants with PDN for at least 6 months or PHN for at least 3 months, scoring at least 40mm on VAS Exclusion criteria: unstable medical or psychiatric condition, malignancy within the past 2 years (except basal cell carcinoma), abnormal ECG, ellicit drugs or alcohol abuse in last 2 years, hepatitis B or C or HIV, neurologic disorders, severe pain unrelated to primary diagnosis (ie. PDN/PHN), any potentially sensiation-altering skin conditions that could confound assessment of NP, amputations other than toes, untreated hyperthyroidism (if PDN), neurolytic or neurosurgical therapy (PHN), drugs commonly used to treat NP (including non-SSRIs, benzodiazepines, capsaicin, opiods, NSAIDs, etc - see list of permitted drug use under 'notes') Study length (days): 84 Intention-to-treat analysis? Yes
Participants	Total number of patients: 338 Number of males: 183 (54.1%) Underlying cause of neuropathic pain: Painful diabetic neuropathy or PHN Mean duration of NP (in months): 46.8 Baseline pain severity: 6.85 (NRS (average of means)) Mean age: 62.2
Intervention(s)	(1) Pregabalin (flexible dose) Intervention: pregabalin Length of treatment (weeks): 12 Fixed/flexible dose regimen: Flexible dose Mean dose: 372.2mg/d Range: 150–600 Notes: weekly dosage escalation based on patients tolerability and individual response; single downward dosage titration was allowed after week 1 or at or after week 2, 3, or 4 (and then the patient remained on that dosage for the remainder of the study) (2) Pregabalin (600 mg/d) Intervention: pregabalin Length of treatment (weeks): 12 Fixed/flexible dose regimen: Fixed dose Set dose: 600mg/d Mean dose: 481.5mg/d Notes: 300 mg/d for 1 week and then 600 mg/d for remaining period (3) Placebo Intervention: placebo Length of treatment (weeks): 12 Fixed/flexible dose regimen: Fixed dose (4) Pregabalin (flexi and fixed dosages) Intervention: pregabalin Length of treatment (weeks): Fixed/flexible dose regimen: Flexible dose
Concomitant	Drug free baseline period? Yes (duration: 7d)

treatments	Concomitant pain treatment allowed? Yes (drugs commonly used to treat NP excluded including non-SSRIs, benzodiazepines, capsaicin, opiods, NSAIDs; SSRIs for depression, aspirin for MI and stroke prophylaxis, short-acting benzodiazepines for insomnia were allowed during the study (SSRIs could be considered concomitant medications); Paracetamol as rescue analgesics)

Outcomes measures and effect sizes

		PREGABALIN (FLEXIBLE DOSE)			PREGABALIN (600 MG/D)			
		N	k	mean	N	k	mean	Δ
pain score:								
at least 30% pain reduction (NRS) – 84d	Dichotomous	141	83	(58.9%)	132	88	(66.7%)	OR=0.716 (CI: 0.437, 1.172)
at least 50% pain reduction (NRS) – 84d	Dichotomous	141	68	(48.2%)	132	69	(52.3%)	OR=0.851 (CI: 0.529, 1.368)
patient-reported global improvement:								
PGIC - worse (all grades) – 84d	Dichotomous	141	13	(9.2%)	132	16	(12.1%)	OR=0.736 (CI: 0.340, 1.596)
PGIC - no change – 84d	Dichotomous	141	24	(17.0%)	132	21	(15.9%)	OR=1.084 (CI: 0.571, 2.058)
PGIC - minimally better – 84d	Dichotomous	141	31	(22.0%)	132	24	(18.2%)	OR=1.268 (CI: 0.699, 2.300)
PGIC - at least moderately better – 84d	Dichotomous	141	73	(51.8%)	132	71	(53.8%)	OR=0.922 (CI: 0.573, 1.484)
major adverse events (defined as leading to withdrawal):								
any major adverse event – 84d	Dichotomous	141	24	(17.0%)	132	33	(25.0%)	OR=0.615 (CI: 0.341, 1.110)
adverse events:								
Dizziness – 84d	Dichotomous	141	27	(19.1%)	132	38	(28.8%)	OR=0.586 (CI: 0.333, 1.030)
Nausea – 84d	Dichotomous	141	7	(5.0%)	132	14	(10.6%)	OR=0.440 (CI: 0.172, 1.128)
Peripheral oedema – 84d	Dichotomous	141	23	(16.3%)	132	10	(7.6%)	OR=2.378 (CI: 1.085, 5.210)
Somnolence – 84d	Dichotomous	141	15	(10.6%)	132	17	(12.9%)	OR=0.805 (CI: 0.385, 1.686)
Weight gain – 84d	Dichotomous	141	17	(12.1%)	132	18	(13.6%)	OR=0.868 (CI: 0.427, 1.766)
treatment withdrawal:								
due to lack of efficacy – 84d	Dichotomous	141	12	(8.5%)	132	11	(8.3%)	OR=1.023 (CI: 0.435, 2.406)
unspecified/other reason – 84d	Dichotomous	141	10	(7.1%)	132	3	(2.3%)	OR=3.282 (CI: 0.883, 12.201)
poor compliance – 84d	Dichotomous	141	3	(2.1%)	132	3	(2.3%)	OR=0.935 (CI: 0.185, 4.715)

		PREGABALIN (FLEXIBLE DOSE)			PLACEBO			
		N	k	mean	N	k	mean	Δ
pain score:								
at least 30% pain reduction (NRS) – 84d	Dichotomous	141	83	(58.9%)	65	24	(36.9%)	OR=2.445 (CI: 1.335, 4.478)
at least 50% pain reduction (NRS) – 84d	Dichotomous	141	68	(48.2%)	65	16	(24.6%)	OR=2.853 (CI: 1.483, 5.486)
patient-reported global improvement:								
PGIC - worse (all grades) – 84d	Dichotomous	141	13	(9.2%)	65	11	(16.9%)	OR=0.499 (CI: 0.210, 1.183)
PGIC - no change – 84d	Dichotomous	141	24	(17.0%)	65	23	(35.4%)	OR=0.375 (CI: 0.191, 0.733)
PGIC - minimally better – 84d	Dichotomous	141	31	(22.0%)	65	11	(16.9%)	OR=1.383 (CI: 0.646, 2.961)
PGIC - at least moderately better – 84d	Dichotomous	141	73	(51.8%)	65	20	(30.8%)	OR=2.415 (CI: 1.297, 4.498)
major adverse events (defined as leading to withdrawal):								
any major adverse event – 84d	Dichotomous	141	24	(17.0%)	65	5	(7.7%)	OR=2.462 (CI: 0.894, 6.775)
adverse events:								
Dizziness – 84d	Dichotomous	141	27	(19.1%)	65	3	(4.6%)	OR=4.895 (CI: 1.427, 16.784)
Nausea – 84d	Dichotomous	141	7	(5.0%)	65	1	(1.5%)	OR=3.343 (CI: 0.403, 27.752)
Peripheral oedema – 84d	Dichotomous	141	23	(16.3%)	65	2	(3.1%)	OR=6.140 (CI: 1.402, 26.889)
Somnolence – 84d	Dichotomous	141	15	(10.6%)	65	0	(0.0%)	OR=16.051 (CI: 0.945, 272.521)
Weight gain – 84d	Dichotomous	141	17	(12.1%)	65	2	(3.1%)	OR=4.319 (CI: 0.967, 19.281)

treatment withdrawal:									
due to lack of efficacy – 84d	Dichotomous	141	12	(8.5%)	65	19	(29.2%)	OR=0.225 (CI: 0.101, 0.500)	
unspecified/other reason – 84d	Dichotomous	141	10	(7.1%)	65	4	(6.2%)	OR=1.164 (CI: 0.351, 3.860)	
poor compliance – 84d	Dichotomous	141	3	(2.1%)	65	2	(3.1%)	OR=0.685 (CI: 0.112, 4.200)	

		PREGABALIN (600 MG/D)			PLACEBO			
		N	k	mean	N	k	mean	Δ
pain score:								
at least 30% pain reduction (NRS) – 84d	Dichotomous	132	88	(66.7%)	65	24	(36.9%)	OR=3.417 (CI: 1.838, 6.353)
at least 50% pain reduction (NRS) – 84d	Dichotomous	132	69	(52.3%)	65	16	(24.6%)	OR=3.354 (CI: 1.734, 6.487)
patient-reported global improvement:								
PGIC - worse (all grades) – 84d	Dichotomous	132	16	(12.1%)	65	11	(16.9%)	OR=0.677 (CI: 0.294, 1.557)
PGIC - no change – 84d	Dichotomous	132	21	(15.9%)	65	23	(35.4%)	OR=0.345 (CI: 0.173, 0.689)
PGIC - minimally better – 84d	Dichotomous	132	24	(18.2%)	65	11	(16.9%)	OR=1.091 (CI: 0.498, 2.391)
PGIC - at least moderately better – 84d	Dichotomous	132	71	(53.8%)	65	20	(30.8%)	OR=2.619 (CI: 1.397, 4.908)
major adverse events (defined as leading to withdrawal):								
any major adverse event – 84d	Dichotomous	132	33	(25.0%)	65	5	(7.7%)	OR=4.000 (CI: 1.481, 10.805)
adverse events:								
Dizziness – 84d	Dichotomous	132	38	(28.8%)	65	3	(4.6%)	OR=8.355 (CI: 2.471, 28.252)
Nausea – 84d	Dichotomous	132	14	(10.6%)	65	1	(1.5%)	OR=7.593 (CI: 0.976, 59.069)
Peripheral oedema – 84d	Dichotomous	132	10	(7.6%)	65	2	(3.1%)	OR=2.582 (CI: 0.549, 12.145)
Somnolence – 84d	Dichotomous	132	17	(12.9%)	65	0	(0.0%)	OR=19.848 (CI: 1.174, 335.477)
Weight gain – 84d	Dichotomous	132	18	(13.6%)	65	2	(3.1%)	OR=4.974 (CI: 1.118, 22.133)
treatment withdrawal:								
due to lack of efficacy – 84d	Dichotomous	132	11	(8.3%)	65	19	(29.2%)	OR=0.220 (CI: 0.097, 0.498)
unspecified/other reason – 84d	Dichotomous	132	3	(2.3%)	65	4	(6.2%)	OR=0.355 (CI: 0.077, 1.634)
poor compliance – 84d	Dichotomous	132	3	(2.3%)	65	2	(3.1%)	OR=0.733 (CI: 0.119, 4.496)

		PLACEBO			PREGABALIN (FLEXI AND FIXED DOSAGES)			
		N	k	mean	N	k	mean	Δ
patient-reported global improvement:								
PGIC - worse (all grades) – 84d	Dichotomous	65	11	(16.9%)	273	29	(10.6%)	
PGIC - no change – 84d	Dichotomous	65	23	(35.4%)	273	45	(16.5%)	
PGIC - minimally better – 84d	Dichotomous	65	11	(16.9%)	273	76	(27.8%)	
PGIC - at least moderately better – 84d	Dichotomous	65	20	(30.8%)	273	149	(54.6%)	

Comments	patients with previous exposure to gabapentin was permitted to enter the study; SSRIs for depression, aspirin for MI and stroke prophylaxis, short-acting benzodiazepines for insomnia were allowed during the study

Definitions of abbreviations are given at the end of this document.

Study	Gao et al. (2010)
Pain category	Peripheral pain

Study design	Country: China Design: Parallel Inclusion criteria: Patients 18 years or older with a diagnosos of PDN and an average brief pain inventory (BPI) score of 4 or higher were eligible if they have daily pain for at least 6 months Exclusion criteria: If they had mania, bipolar disorder, psychosis, or were at risk of suicide as judged by the investigator or had a rating of >2 on question 9 of the BDI-II, taking any monoamine oxidase inhibitors within 14 days before visit 2 Study length (days): 84 Intention-to-treat analysis? Yes
Participants	Total number of patients: 215 Number of males: 101 (47.0%) Underlying cause of neuropathic pain: Painful diabetic neuropathy Mean duration of NP (in months): 3.2 Baseline pain severity: 5.5 (BPI average pain) Mean age: 59.25
Intervention(s)	(1) Duloxetine (flexible dose 30-120mg/d) Intervention: duloxetine Length of treatment (weeks): 12 Fixed/flexible dose regimen: Flexible dose Range: 60–120 Notes: started at 30 mg/d for 1 week, then increased to 60 mg/d, then increased to 120 mg once daily any time after 2 weeks if patients did not respond to 60mg/d (2) Placebo Intervention: placebo Length of treatment (weeks): 12 Fixed/flexible dose regimen: Flexible dose
Concomitant treatments	Drug free baseline period? No Concomitant pain treatment allowed? Unclear (authors appear to only state that use of monoamine oxidase inhibitors within 14 days of randomisation were excluded; unclear if others were permitted)
Outcomes measures and effect sizes	

		DULOXETINE (FLEXIBLE DOSE 30-120MG/D)			PLACEBO			
		N	k	mean	N	k	mean	Δ
pain score:								
at least 30% pain reduction – 84d[a]	Dichotomous	106	74	(69.8%)	109	67	(61.5%)	OR=1.450 (CI: 0.823, 2.554)
at least 50% pain reduction – 84d[a]	Dichotomous	106	57	(53.8%)	109	55	(50.5%)	OR=1.142 (CI: 0.669, 1.951)
BPI (severity) – 84d	Continuous	106		-2.72 (SD 2.68)	109		-1.99 (SD 2.61)	MD=-0.730 (CI: -1.437, -0.023)
BPI average pain – 84d[b]	Continuous	106		-2.69 (SD 1.96)	109		-2.31 (SD 1.88)	MD=-0.380 (CI: -0.893, 0.133)

patient-reported global improvement: PGI-I – 84d[b]	Mean change	106		2.32 (SD 1.13)	109		2.64 (SD 1.04)	MD=-0.320 (CI: -0.611, -0.029)
patient-reported improvement in daily physical and emotional functioning, including sleep:								
Normalised (10-pt) sleep interference measure – 84d[c]	Mean change	106		-2.85 (SD 2.88)	109		-2.67 (SD 2.82)	
BPI – 84d	Mean change	106		-2.28 (SD 2.16)	109		-1.88 (SD 2.09)	MD=-0.400 (CI: -0.968, 0.168)
BPI Mood – 84d	Mean change	106		-2.32 (SD 2.47)	109		-1.85 (SD 2.4)	MD=-0.470 (CI: -1.122, 0.182)
BPI Sleep – 84d	Mean change	106		-2.85 (SD 2.88)	109		-2.67 (SD 2.82)	MD=-0.180 (CI: -0.942, 0.582)
BPI general activity – 84d	Mean change	106		-2.5 (SD 2.57)	109		-1.96 (SD 2.51)	MD=-0.540 (CI: -1.219, 0.139)
BPI walking ability – 84d	Mean change	106		-2.45 (SD 2.47)	109		-1.82 (SD 2.4)	MD=-0.630 (CI: -1.282, 0.022)
BPI normal work – 84d	Mean change	106		-2.01 (SD 2.37)	109		-1.7 (SD 2.3)	MD=-0.310 (CI: -0.934, 0.314)
BPI relationship with other people – 84d	Mean change	106		-1.45 (SD 2.27)	109		-1.13 (SD 2.19)	MD=-0.320 (CI: -0.916, 0.276)
BPI enjoyment of life – 84d	Continuous	106		-1.94 (SD 2.47)	109		-1.65 (SD 2.4)	MD=-0.290 (CI: -0.942, 0.362)
major adverse events (defined as leading to withdrawal):								
any major adverse event – 84d	Dichotomous	106	15	(14.2%)	109	4	(3.7%)	OR=4.327 (CI: 1.386, 13.504)
adverse events:								
asthenia – 84d	Dichotomous	106	6	(5.7%)	109	1	(0.9%)	OR=6.480 (CI: 0.767, 54.769)
Constipation – 84d	Dichotomous	106	11	(10.4%)	109	9	(8.3%)	OR=1.287 (CI: 0.510, 3.243)
Diarrhoea – 84d	Dichotomous	106	10	(9.4%)	109	6	(5.5%)	OR=1.788 (CI: 0.626, 5.108)
Dizziness – 84d	Dichotomous	106	16	(15.1%)	109	12	(11.0%)	OR=1.437 (CI: 0.645, 3.203)
Dry mouth – 84d	Dichotomous	106	6	(5.7%)	109	3	(2.8%)	OR=2.120 (CI: 0.516, 8.706)
Fatigue – 84d	Dichotomous	106	8	(7.5%)	109	8	(7.3%)	OR=1.031 (CI: 0.372, 2.854)
headache – 84d	Dichotomous	106	6	(5.7%)	109	6	(5.5%)	OR=1.030 (CI: 0.321, 3.301)
lethargy – 84d	Dichotomous	106	11	(10.4%)	109	4	(3.7%)	OR=3.039 (CI: 0.936, 9.867)
Nausea – 84d	Dichotomous	106	32	(30.2%)	109	13	(11.9%)	OR=3.193 (CI: 1.566, 6.511)
Pruritus – 84d	Dichotomous	106	3	(2.8%)	109	8	(7.3%)	OR=0.368 (CI: 0.095, 1.426)
Somnolence – 84d	Dichotomous	106	17	(16.0%)	109	6	(5.5%)	OR=3.279 (CI: 1.239, 8.676)
Vomiting – 84d	Dichotomous	106	6	(5.7%)	109	5	(4.6%)	OR=1.248 (CI: 0.369, 4.219)
overall improvement in quality of life: EQ-5D - health status index – 84d	Mean change	106		0.12 (SD 0.206)[d]	109		0.14 (SD 0.209)[e]	MD=-0.020 (CI: -0.075, 0.035)

EQ-5D - health status index – 84d	Mean change	106		0.12 (SD 0.206)[d]	109		0.14 (SD 0.209)[e]	MD=0.030 (CI: -0.025, 0.085)
EQ-5D - health status index – 84d	Mean change	106		0.17 (SD 0.206)[e]	109		0.1 (SD 0.209)[d]	MD=-0.020 (CI: -0.075, 0.035)
EQ-5D - health status index – 84d	Mean change	106		0.17 (SD 0.206)[e]	109		0.1 (SD 0.209)[d]	MD=0.030 (CI: -0.025, 0.085)
EQ-5D - health status index – 84d[e]	Mean change	106		0.17 (SD 0.206)	109		0.14 (SD 0.209)	MD=-0.020 (CI: -0.075, 0.035)
EQ-5D - health status index – 84d[e]	Mean change	106		0.17 (SD 0.206)	109		0.14 (SD 0.209)	MD=0.030 (CI: -0.025, 0.085)
EQ-5D - health status index – 84d[d]	Mean change	106		0.12 (SD 0.206)	109		0.1 (SD 0.209)	MD=-0.020 (CI: -0.075, 0.035)
EQ-5D - health status index – 84d[d]	Mean change	106		0.12 (SD 0.206)	109		0.1 (SD 0.209)	MD=0.030 (CI: -0.025, 0.085)
treatment withdrawal: due to lack of efficacy – 84d	Dichotomous	106	1	(0.9%)	109	4	(3.7%)	OR=0.250 (CI: 0.027, 2.274)
withdrawal of consent – 84d	Dichotomous	106	2	(1.9%)	109	3	(2.8%)	OR=0.679 (CI: 0.111, 4.150)
protocol deviation – 84d	Dichotomous	106	1	(0.9%)	109	6	(5.5%)	OR=0.163 (CI: 0.019, 1.382)

[a] this is based on BPI average pain
[b] least squares mean change
[c] based on BPI Sleep
[d] EQ-5D US
[e] EQ-5D UK

Comments	screening period for 3 to 30 days before randomisation - unclear if any part of this was drug-free (unclear if many concomitant drugs were allowed)

Definitions of abbreviations are given at the end of this document.

Study	Gilron et al. (2012)
Pain category	Peripheral pain
Study design	Country: Canada Design: Crossover Inclusion criteria: PHN or PDN, daily pain score of at least 4 (on NRS 0-10) for at least 6 months prior to trial, aspartate aminotransferase and alanine aminotransferase concentration of 120% of the upper limit of normal or less, serum creatinine concentration of 150% fo the upper limit of normal or less and haemoglobin A1c conctration of less than 13% Exclusion criteria: patient history or lab results suggestion inherited neuropathy or neuropathy from other causes, major organ system disease, cardiovascular autonomic neuropathy, baseline postrual hypotension of more than 20 mm Hg, sedation or ataxia dur to concomitant drugs or other caseus, urinary symptoms indicatve of benign prostatic hyupertrophy, psychiatric or substance abuse disorder, hypersensitivyt toa ny of the study drugs or coexisting disorder causing pain as severe as neuropathic pain, no use of contraception in women of child-bearing age Study length (days): 133 Intention-to-treat analysis? Yes
Participants	Total number of patients: 56 Number of males: 35 (62.5%)

	Underlying cause of neuropathic pain: Painful diabetic neuropathy or PHN Mean duration of NP (in months): 48 Baseline pain severity: 5.4 (NRS) Mean age: 64.5
Intervention(s)	(1) Gabapentin flexible-dose Intervention: gabapentin Length of treatment (weeks): 5 Fixed/flexible dose regimen: Flexible dose Mean dose: 2433mg/d (SD: 106) Notes: First 24 days of the 6 week period was titration, days 25-31 was the maintenance phase (at max tolerated dose), days 32-35 were dose taper phase and days 36-42 were drug washout phase; (dispersion given is SE, not SD) (2) Nortriptyline flexible-dose Intervention: nortriptyline Length of treatment (weeks): 5 Fixed/flexible dose regimen: Flexible dose Mean dose: 61.6mg/d (SD: 3.6) Notes: First 24 days of the 6 week period was titration, days 25-31 was the maintenance phase (at max tolerated dose), days 32-35 were dose taper phase and days 36-42 were drug washout phase; (dispersion given is SE, not SD) (3) Gabapentin and nortriptyline flexible-dose Intervention: gabapentin+nortriptyline Length of treatment (weeks): 5 Fixed/flexible dose regimen: Flexible dose Notes: First 24 days of the 6 week period was titration, days 25-31 was the maintenance phase (at max tolerated dose), days 32-35 were dose taper phase and days 36-42 were drug washout phase; mean amximum tolerated dose was 2180 mg (SE 108) of gabapentin and 50.1 mg (SE 3.5)
Concomitant treatments	Drug free baseline period? Yes (duration: 7d) Concomitant pain treatment allowed? Yes (only steady dosages of opioids, NSAIDs, or paracetamol (not tricyclics, gabapentin or pregabalin or procedural pain treatments like nerve blocks))
Outcomes measures and effect sizes	

		GABAPENTIN FLEXIBLE-DOSE			NORTRIPTYLINE FLEXIBLE-DOSE			
		N	k	mean	N	k	mean	Δ
pain score:								
NRS/NRS Pain – 0d	Continuous	56		5.4 (SD 1.53)	56		5.4 (SD 1.53)	
NRS/NRS Pain – 35d	Continuous	46		3.2 (SD 2.42)	50		2.9 (SD 1.8)	MD=0.300 (CI: -0.560, 1.160)
BPI average pain – 0d	Continuous	56		4.9 (SD 1.5)	56		4.9 (SD 1.5)	
BPI average pain – 35d	Continuous	46		3.3 (SD 2.03)	50		3.1 (SD 1.41)	MD=0.200 (CI: -0.507, 0.907)
McGill VAS – 0d	Continuous	56		4.3 (SD 2.99)	56		4.3 (SD 2.99)	
McGill VAS – 35d	Continuous	46		2.4 (SD 2.03)	50		2.5 (SD 2.12)	MD=-0.100 (CI: -0.932, 0.732)
PPI (from MPQ) – 0d	Continuous	56		2 (SD 1.5)	56		2 (SD 1.5)	
PPI (from MPQ) – 35d	Continuous	46		1.5 (SD 1.36)	50		1.6 (SD 0.707)	MD=-0.100 (CI: -0.538, 0.338)

patient-reported improvement in daily physical and emotional functioning, including sleep:									
Normalised (10-pt) sleep interference measure – 0d[a]	Continuous	56		5.1 (SD 2.99)	56		5.1 (SD 2.99)		
Normalised (10-pt) sleep interference measure – 35d[a]	Continuous	46		2.2 (SD 2.03)	50		2.3 (SD 2.12)	MD=-0.100 (CI: -0.930, 0.730)	
BDI – 0d	Continuous	56		8.3 (SD 5.24)	56		8.3 (SD 5.24)		
BDI – 35d	Continuous	46		5.8 (SD 3.39)	50		6.8 (SD 3.54)	MD=-1.000 (CI: -2.386, 0.386)	
BPI Sleep – 0d	Continuous	56		5.1 (SD 2.99)	56		5.1 (SD 2.99)		
BPI Sleep – 35d	Continuous	46		2.2 (SD 2.03)	50		2.3 (SD 2.12)	MD=-0.100 (CI: -0.932, 0.732)	
overall improvement in quality of life:									
SF36 – 0d	Continuous	56		56.8 (SD 15.7)	56		56.8 (SD 15.7)		
SF36 – 35d	Continuous	46		65.4 (SD 12.2)	50		63.1 (SD 12.7)	MD=2.300 (CI: -2.689, 7.289)	
treatment withdrawal:									
due to lack of efficacy – 35d	Dichotomous	56	0	(0.0%)	56	1	(1.8%)	OR=0.327 (CI: 0.013, 8.211)	
unspecified/other reason – 35d	Dichotomous	56	2[b]	(3.6%)	56	1[c]	(1.8%)	OR=2.037 (CI: 0.179, 23.130)	
protocol deviation – 35d	Dichotomous	56	1	(1.8%)	56	0	(0.0%)	OR=3.054 (CI: 0.122, 76.588)	
during dose titration									
adverse events:									
Blurred vision – 35d	Dichotomous	56	3	(5.4%)	56	0	(0.0%)	OR=7.393 (CI: 0.373, 146.518)	
Constipation – 35d	Dichotomous	56	44	(78.6%)	56	6	(10.7%)	OR=30.556 (CI: 10.582, 88.232)	
Dizziness – 35d	Dichotomous	56	7	(12.5%)	56	6	(10.7%)	OR=1.190 (CI: 0.373, 3.795)	
Dry mouth – 35d	Dichotomous	56	11	(19.6%)	56	29	(51.8%)	OR=0.228 (CI: 0.098, 0.528)	
Fatigue – 35d	Dichotomous	56	7	(12.5%)	56	9	(16.1%)	OR=0.746 (CI: 0.257, 2.166)	
feeling drunk/drugged – 35d	Dichotomous	56	6	(10.7%)	56	1	(1.8%)	OR=6.600 (CI: 0.768, 56.738)	
headache – 35d	Dichotomous	56	7	(12.5%)	56	5	(8.9%)	OR=1.457 (CI: 0.433, 4.900)	
impaired attention – 35d	Dichotomous	56	6	(10.7%)	56	0	(0.0%)	OR=14.545 (CI: 0.799, 264.698)	
mood disturbance – 35d	Dichotomous	56	1	(1.8%)	56	4	(7.1%)	OR=0.236 (CI: 0.026, 2.185)	
oedema – 35d	Dichotomous	56	5	(8.9%)	56	2	(3.6%)	OR=2.647 (CI: 0.491, 14.258)	
Pruritus – 35d	Dichotomous	56	0	(0.0%)	56	3	(5.4%)	OR=0.135 (CI: 0.007, 2.681)	
Somnolence – 35d	Dichotomous	56	9	(16.1%)	56	8	(14.3%)	OR=1.149 (CI: 0.409, 3.231)	
Urine retention – 35d	Dichotomous	56	2	(3.6%)	56	4	(7.1%)	OR=0.481 (CI: 0.085, 2.742)	
Weight gain – 35d	Dichotomous	56	3	(5.4%)	56	1	(1.8%)	OR=3.113 (CI: 0.314, 30.878)	
at maximum tolerated dose									
adverse events:									
Blurred vision – 35d	Dichotomous	56	1	(1.8%)	56	0	(0.0%)	OR=3.054 (CI: 0.122, 76.588)	
Constipation – 35d	Dichotomous	56	1	(1.8%)	56	1	(1.8%)	OR=1.000 (CI: 0.061, 16.394)	
Dizziness – 35d	Dichotomous	56	4	(7.1%)	56	2	(3.6%)	OR=2.077 (CI: 0.365, 11.828)	
Dry mouth – 35d	Dichotomous	56	8	(14.3%)	56	29	(51.8%)	OR=0.155 (CI: 0.062, 0.387)	
Fatigue – 35d	Dichotomous	56	2	(3.6%)	56	6	(10.7%)	OR=0.309 (CI: 0.060, 1.600)	

feeling drunk/drugged – 35d	Dichotomous	56	1	(1.8%)	56	0	(0.0%)	OR=3.054 (CI: 0.122, 76.588)
headache – 35d	Dichotomous	56	2	(3.6%)	56	2	(3.6%)	OR=1.000 (CI: 0.136, 7.359)
impaired attention – 35d	Dichotomous	56	2	(3.6%)	56	0	(0.0%)	OR=5.183 (CI: 0.243, 110.450)
mood disturbance – 35d	Dichotomous	56	1	(1.8%)	56	3	(5.4%)	OR=0.321 (CI: 0.032, 3.186)
oedema – 35d	Dichotomous	56	4	(7.1%)	56	2	(3.6%)	OR=2.077 (CI: 0.365, 11.828)
Pruritus – 35d	Dichotomous	56	1	(1.8%)	56	1	(1.8%)	OR=1.000 (CI: 0.061, 16.394)
Somnolence – 35d	Dichotomous	56	1	(1.8%)	56	1	(1.8%)	OR=1.000 (CI: 0.061, 16.394)
Urine retention – 35d	Dichotomous	56	1	(1.8%)	56	3	(5.4%)	OR=0.321 (CI: 0.032, 3.186)
Weight gain – 35d	Dichotomous	56	1	(1.8%)	56	1	(1.8%)	OR=1.000 (CI: 0.061, 16.394)

[a] based on BPI Sleep
[b] depression and development of painful arthritic disorder (likely unrelated)
[c] onset of sciatica (likely unrelated)

		GABAPENTIN FLEXIBLE-DOSE			GABAPENTIN AND NORTRIPTYLINE FLEXIBLE-DOSE			
		N	k	mean	N	k	mean	Δ
pain score:								
NRS/NRS Pain – 0d	Continuous	56		5.4 (SD 1.53)	56		5.4 (SD 1.53)	
NRS/NRS Pain – 35d	Continuous	46		3.2 (SD 2.42)	50		2.3 (SD 1.8)	MD=0.900 (CI: 0.040, 1.760)
BPI average pain – 0d	Continuous	56		4.9 (SD 1.5)	56		4.9 (SD 1.5)	
BPI average pain – 35d	Continuous	46		3.3 (SD 2.03)	50		2.5 (SD 1.41)	MD=0.800 (CI: 0.093, 1.507)
McGill VAS – 0d	Continuous	56		4.3 (SD 2.99)	56		4.3 (SD 2.99)	
McGill VAS – 35d	Continuous	46		2.4 (SD 2.03)	50		2 (SD 2.12)	MD=0.400 (CI: -0.432, 1.232)
PPI (from MPQ) – 0d	Continuous	56		2 (SD 1.5)	56		2 (SD 1.5)	
PPI (from MPQ) – 35d	Continuous	46		1.5 (SD 1.36)	50		1.3 (SD 0.707)	MD=0.200 (CI: -0.238, 0.638)
patient-reported improvement in daily physical and emotional functioning, including sleep:								
Normalised (10-pt) sleep interference measure – 0d[a]	Continuous	56		5.1 (SD 2.99)	56		5.1 (SD 2.99)	
Normalised (10-pt) sleep interference measure – 35d[a]	Continuous	46		2.2 (SD 2.03)	50		1 (SD 2.12)	MD=1.200 (CI: 0.370, 2.030)
BDI – 0d	Continuous	56		8.3 (SD 5.24)	56		8.3 (SD 5.24)	
BDI – 35d	Continuous	46		5.8 (SD 3.39)	50		5.4 (SD 3.54)	MD=0.400 (CI: -0.986, 1.786)
BPI Sleep – 0d	Continuous	56		5.1 (SD 2.99)	56		5.1 (SD 2.99)	
BPI Sleep – 35d	Continuous	46		2.2 (SD 2.03)	50		1 (SD 2.12)	MD=1.200 (CI: 0.368, 2.032)
overall improvement in quality of life:								
SF36 – 0d	Continuous	56		56.8 (SD 15.7)	56		56.8 (SD 15.7)	

SF36 – 35d	Continuous	46		65.4 (SD 12.2)	50		66.3 (SD 12.7)	MD=-0.900 (CI: -5.889, 4.089)
treatment withdrawal:								
due to lack of efficacy – 35d	Dichotomous	56	0	(0.0%)	56	0	(0.0%)	OR=1.000 (CI: 0.020, 51.277)
unspecified/other reason – 35d	Dichotomous	56	2[b]	(3.6%)	56	0	(0.0%)	OR=5.183 (CI: 0.243, 110.450)
protocol deviation – 35d	Dichotomous	56	1	(1.8%)	56	0	(0.0%)	OR=3.054 (CI: 0.122, 76.588)
during dose titration								
adverse events:								
Blurred vision – 35d	Dichotomous	56	3	(5.4%)	56	0	(0.0%)	OR=7.393 (CI: 0.373, 146.518)
Constipation – 35d	Dichotomous	56	44	(78.6%)	56	5	(8.9%)	OR=37.400 (CI: 12.221, 114.454)
Dizziness – 35d	Dichotomous	56	7	(12.5%)	56	6	(10.7%)	OR=1.190 (CI: 0.373, 3.795)
Dry mouth – 35d	Dichotomous	56	11	(19.6%)	56	27	(48.2%)	OR=0.263 (CI: 0.113, 0.610)
Fatigue – 35d	Dichotomous	56	7	(12.5%)	56	6	(10.7%)	OR=1.190 (CI: 0.373, 3.795)
feeling drunk/drugged – 35d	Dichotomous	56	6	(10.7%)	56	4	(7.1%)	OR=1.560 (CI: 0.415, 5.859)
headache – 35d	Dichotomous	56	7	(12.5%)	56	2	(3.6%)	OR=3.857 (CI: 0.765, 19.458)
impaired attention – 35d	Dichotomous	56	6	(10.7%)	56	3	(5.4%)	OR=2.120 (CI: 0.503, 8.937)
mood disturbance – 35d	Dichotomous	56	1	(1.8%)	56	1	(1.8%)	OR=1.000 (CI: 0.061, 16.394)
oedema – 35d	Dichotomous	56	5	(8.9%)	56	3	(5.4%)	OR=1.732 (CI: 0.393, 7.625)
Pruritus – 35d	Dichotomous	56	0	(0.0%)	56	0	(0.0%)	OR=1.000 (CI: 0.020, 51.277)
Somnolence – 35d	Dichotomous	56	9	(16.1%)	56	9	(16.1%)	OR=1.000 (CI: 0.365, 2.742)
Urine retention – 35d	Dichotomous	56	2	(3.6%)	56	3	(5.4%)	OR=0.654 (CI: 0.105, 4.074)
Weight gain – 35d	Dichotomous	56	3	(5.4%)	56	3	(5.4%)	OR=1.000 (CI: 0.193, 5.181)
at maximum tolerated dose								
adverse events:								
Blurred vision – 35d	Dichotomous	56	1	(1.8%)	56	1	(1.8%)	OR=1.000 (CI: 0.061, 16.394)
Constipation – 35d	Dichotomous	56	1	(1.8%)	56	1	(1.8%)	OR=1.000 (CI: 0.061, 16.394)
Dizziness – 35d	Dichotomous	56	4	(7.1%)	56	4	(7.1%)	OR=1.000 (CI: 0.237, 4.213)
Dry mouth – 35d	Dichotomous	56	8	(14.3%)	56	30	(53.6%)	OR=0.144 (CI: 0.058, 0.360)
Fatigue – 35d	Dichotomous	56	2	(3.6%)	56	4	(7.1%)	OR=0.481 (CI: 0.085, 2.742)
feeling drunk/drugged – 35d	Dichotomous	56	1	(1.8%)	56	2	(3.6%)	OR=0.491 (CI: 0.043, 5.574)
headache – 35d	Dichotomous	56	2	(3.6%)	56	1	(1.8%)	OR=2.037 (CI: 0.179, 23.130)

impaired attention – 35d	Dichotomous	56	2	(3.6%)	56	2	(3.6%)	OR=1.000 (CI: 0.136, 7.359)
mood disturbance – 35d	Dichotomous	56	1	(1.8%)	56	0	(0.0%)	OR=3.054 (CI: 0.122, 76.588)
oedema – 35d	Dichotomous	56	4	(7.1%)	56	4	(7.1%)	OR=1.000 (CI: 0.237, 4.213)
Pruritus – 35d	Dichotomous	56	1	(1.8%)	56	0	(0.0%)	OR=3.054 (CI: 0.122, 76.588)
Somnolence – 35d	Dichotomous	56	1	(1.8%)	56	4	(7.1%)	OR=0.236 (CI: 0.026, 2.185)
Urine retention – 35d	Dichotomous	56	1	(1.8%)	56	2	(3.6%)	OR=0.491 (CI: 0.043, 5.574)
Weight gain – 35d	Dichotomous	56	1	(1.8%)	56	0	(0.0%)	OR=3.054 (CI: 0.122, 76.588)

[a] based on BPI Sleep
[b] depression and development of painful arthritic disorder (likely unrelated)

		NORTRIPTYLINE FLEXIBLE-DOSE			GABAPENTIN AND NORTRIPTYLINE FLEXIBLE-DOSE			
		N	k	mean	N	k	mean	Δ
pain score:								
NRS/NRS Pain – 0d	Continuous	56		5.4 (SD 1.53)	56		5.4 (SD 1.53)	
NRS/NRS Pain – 35d	Continuous	50		2.9 (SD 1.8)	50		2.3 (SD 1.8)	MD=0.600 (CI: -0.107, 1.307)
BPI average pain – 0d	Continuous	56		4.9 (SD 1.5)	56		4.9 (SD 1.5)	
BPI average pain – 35d	Continuous	50		3.1 (SD 1.41)	50		2.5 (SD 1.41)	MD=0.600 (CI: 0.046, 1.154)
McGill VAS – 0d	Continuous	56		4.3 (SD 2.99)	56		4.3 (SD 2.99)	
McGill VAS – 35d	Continuous	50		2.5 (SD 2.12)	50		2 (SD 2.12)	MD=0.500 (CI: -0.332, 1.332)
PPI (from MPQ) – 0d	Continuous	56		2 (SD 1.5)	56		2 (SD 1.5)	
PPI (from MPQ) – 35d	Continuous	50		1.6 (SD 0.707)	50		1.3 (SD 0.707)	MD=0.300 (CI: 0.023, 0.577)
patient-reported improvement in daily physical and emotional functioning, including sleep:								
Normalised (10-pt) sleep interference measure – 0d[a]	Continuous	56		5.1 (SD 2.99)	56		5.1 (SD 2.99)	
Normalised (10-pt) sleep interference measure – 35d[a]	Continuous	50		2.3 (SD 2.12)	50		1 (SD 2.12)	MD=1.300 (CI: 0.469, 2.131)
BDI – 0d	Continuous	56		8.3 (SD 5.24)	56		8.3 (SD 5.24)	
BDI – 35d	Continuous	50		6.8 (SD 3.54)	50		5.4 (SD 3.54)	MD=1.400 (CI: 0.014, 2.786)
BPI Sleep – 0d	Continuous	56		5.1 (SD 2.99)	56		5.1 (SD 2.99)	
BPI Sleep – 35d	Continuous	50		2.3 (SD 2.12)	50		1 (SD 2.12)	MD=1.300 (CI: 0.468, 2.132)
overall improvement in quality of life:								
SF36 – 0d	Continuous	56		56.8 (SD 15.7)	56		56.8 (SD 15.7)	
SF36 – 35d	Continuous	50		63.1 (SD 12.7)	50		66.3 (SD 12.7)	MD=-3.200 (CI: -8.189, 1.789)

treatment withdrawal:									
due to lack of efficacy – 35d	Dichotomous	56	1	(1.8%)	56	0	(0.0%)	OR=3.054 (CI: 0.122, 76.588)
unspecified/other reason – 35d	Dichotomous	56	1[b]	(1.8%)	56	0	(0.0%)	OR=3.054 (CI: 0.122, 76.588)
protocol deviation – 35d	Dichotomous	56	0	(0.0%)	56	0	(0.0%)	OR=1.000 (CI: 0.020, 51.277)
during dose titration								
adverse events:								
Blurred vision – 35d	Dichotomous	56	0	(0.0%)	56	0	(0.0%)	OR=1.000 (CI: 0.020, 51.277)
Constipation – 35d	Dichotomous	56	6	(10.7%)	56	5	(8.9%)	OR=1.224 (CI: 0.351, 4.269)
Dizziness – 35d	Dichotomous	56	6	(10.7%)	56	6	(10.7%)	OR=1.000 (CI: 0.302, 3.312)
Dry mouth – 35d	Dichotomous	56	29	(51.8%)	56	27	(48.2%)	OR=1.154 (CI: 0.550, 2.421)
Fatigue – 35d	Dichotomous	56	9	(16.1%)	56	6	(10.7%)	OR=1.596 (CI: 0.527, 4.828)
feeling drunk/drugged – 35d	Dichotomous	56	1	(1.8%)	56	4	(7.1%)	OR=0.236 (CI: 0.026, 2.185)
headache – 35d	Dichotomous	56	5	(8.9%)	56	2	(3.6%)	OR=2.647 (CI: 0.491, 14.258)
impaired attention – 35d	Dichotomous	56	0	(0.0%)	56	3	(5.4%)	OR=0.135 (CI: 0.007, 2.681)
mood disturbance – 35d	Dichotomous	56	4	(7.1%)	56	1	(1.8%)	OR=4.231 (CI: 0.458, 39.105)
oedema – 35d	Dichotomous	56	2	(3.6%)	56	3	(5.4%)	OR=0.654 (CI: 0.105, 4.074)
Pruritus – 35d	Dichotomous	56	3	(5.4%)	56	0	(0.0%)	OR=7.393 (CI: 0.373, 146.518)
Somnolence – 35d	Dichotomous	56	8	(14.3%)	56	9	(16.1%)	OR=0.870 (CI: 0.310, 2.447)
Urine retention – 35d	Dichotomous	56	4	(7.1%)	56	3	(5.4%)	OR=1.359 (CI: 0.290, 6.371)
Weight gain – 35d	Dichotomous	56	1	(1.8%)	56	3	(5.4%)	OR=0.321 (CI: 0.032, 3.186)
at maximum tolerated dose								
adverse events:								
Blurred vision – 35d	Dichotomous	56	0	(0.0%)	56	1	(1.8%)	OR=0.327 (CI: 0.013, 8.211)
Constipation – 35d	Dichotomous	56	1	(1.8%)	56	1	(1.8%)	OR=1.000 (CI: 0.061, 16.394)
Dizziness – 35d	Dichotomous	56	2	(3.6%)	56	4	(7.1%)	OR=0.481 (CI: 0.085, 2.742)
Dry mouth – 35d	Dichotomous	56	29	(51.8%)	56	30	(53.6%)	OR=0.931 (CI: 0.443, 1.955)
Fatigue – 35d	Dichotomous	56	6	(10.7%)	56	4	(7.1%)	OR=1.560 (CI: 0.415, 5.859)
feeling drunk/drugged – 35d	Dichotomous	56	0	(0.0%)	56	2	(3.6%)	OR=0.193 (CI: 0.009, 4.111)
headache – 35d	Dichotomous	56	2	(3.6%)	56	1	(1.8%)	OR=2.037 (CI: 0.179, 23.130)
impaired attention – 35d	Dichotomous	56	0	(0.0%)	56	2	(3.6%)	OR=0.193 (CI: 0.009, 4.111)

	mood disturbance – 35d	Dichotomous	56	3	(5.4%)	56	0	(0.0%)	OR=7.393 (CI: 0.373, 146.518)
	oedema – 35d	Dichotomous	56	2	(3.6%)	56	4	(7.1%)	OR=0.481 (CI: 0.085, 2.742)
	Pruritus – 35d	Dichotomous	56	1	(1.8%)	56	0	(0.0%)	OR=3.054 (CI: 0.122, 76.588)
	Somnolence – 35d	Dichotomous	56	1	(1.8%)	56	4	(7.1%)	OR=0.236 (CI: 0.026, 2.185)
	Urine retention – 35d	Dichotomous	56	3	(5.4%)	56	2	(3.6%)	OR=1.528 (CI: 0.245, 9.517)
	Weight gain – 35d	Dichotomous	56	1	(1.8%)	56	0	(0.0%)	OR=3.054 (CI: 0.122, 76.588)
	[a] based on BPI Sleep [b] onset of sciatica (likely unrelated)								
Comments	only								

Definitions of abbreviations are given at the end of this document.

Study	Gimbel et al. (2003)
Pain category	Peripheral pain
Study design	Country: USA Design: Parallel Inclusion criteria: PDN in both feet, average of at least 5 on an NRS 11 point for more than half a day for at least 3 months Exclusion criteria: unstable or poorly controlled diabetes, chronic pain unrelated to PDN, history of substance or alcohol abuse in last 10 years, =2.5 mg/dl serum creatinine levels, =3 times the upper limit of normal hepatic dysfunction, hypersensitivity to oxycodone or opioids, rapidly escalating pain or recent neurologic deficit in previous month, total fo more than 3 doses per day or short-acting opioids formulation in preceeding 2 weeks, pregnancy, breastfeeding, autonomic neuropathy or gastrointestinal dysfunction that could compromise drug absorportion or increase risk from therapy Study length (days): 42 Intention-to-treat analysis? Yes
Participants	Total number of patients: 159 Number of males: 83 (52.2%) Underlying cause of neuropathic pain: Painful diabetic neuropathy Mean duration of NP (in months): not reported Baseline pain severity: 6.9 (NRS) Mean age: 58.9 (SD: 11.3)
Intervention(s)	(1) Oxycodone (oral) (flexible dose 60 to 120 mg/d) Intervention: oxycodone Length of treatment (weeks): 6 Fixed/flexible dose regimen: Flexible dose Mean dose: 37mg/d (SD: 21) Range: 10–120

	Notes: 10 mg every 12 hours to start to a maximum of 6 tablets (or 60 mg) every 12 hours (2) Placebo Intervention: placebo Length of treatment (weeks): 6 Fixed/flexible dose regimen: Flexible dose
Concomitant treatments	Drug free baseline period? Yes (duration: 3d) Concomitant pain treatment allowed? Unclear (all pre-study opioids were discontinued (those on long-acting opioid formulations were excluded); non-opioid analgesics (ie. NSAIDs or acetaminophen) could be continued if they were at stable dosages for at least 3 weeks before the study and this was monitored at least study visit; unclear about other drugs (ie. Anti-depressants))
Outcomes measures and effect sizes	

		OXYCODONE (ORAL) (FLEXIBLE DOSE 60 TO 120 MG/D)			PLACEBO			
		N	k	mean	N	k	mean	Δ
pain score:								
NRS/NRS Pain – 0d[a]	Continuous	82		7 (SD 2.35)	77		6.9 (SD 2.28)	
NRS/NRS Pain – 28d[a]	Continuous	82		4.1 (SD 2.35)	77		4.7 (SD 2.28)	MD=-0.600 (CI: -1.321, 0.121)
NRS/NRS Pain – 42d[b]	Mean change	82		-2.1 (SD 2.28)	77		-1.1 (SD 2.28)	MD=-1.000 (CI: -1.710, -0.290)
NRS/NRS Pain – 42d[b]	Continuous	82		4.1 (SD 2.35)	77		5.3 (SD 2.28)	MD=-1.200 (CI: -1.921, -0.479)
patient-reported improvement in daily physical and emotional functioning, including sleep:								
Normalised (10-pt) sleep interference measure – 0d[c]	Continuous	82		6.1 (SD 2.17)	77		5.4 (SD 2.11)	
Normalised (10-pt) sleep interference measure – 42d[c]	Continuous	82		1.2 (SD 2.17)	77		0.5 (SD 2.11)	
BPI Mood – 0d	Continuous	82		3.2 (SD 2.9)	77		3.7 (SD 2.81)	
BPI Mood – 42d	Mean change	82		-2.6 (SD 2.81)	77		-2.1 (SD 2.81)	MD=-0.500 (CI: -1.373, 0.373)
BPI Sleep – 0d	Continuous	82		3.6 (SD 2.9)	77		5.3 (SD 2.72)	
BPI Sleep – 42d	Mean change	82		-3.3 (SD 2.9)	77		-1.5 (SD 2.81)	MD=-1.800 (CI: -2.687, -0.913)
NRS Sleep – 42d[b]	Mean change	82		1.2 (SD 2.17)	77		0.5 (SD 2.11)	MD=0.700 (CI: 0.035, 1.365)
NRS Sleep – 42d[b]	Continuous	82		6.1 (SD 2.17)	77		5.4 (SD 2.11)	MD=0.700 (CI: 0.035, 1.365)
BPI general activity – 0d	Continuous	82		3.5 (SD 2.63)	77		4.1 (SD 2.54)	
BPI general activity – 42d	Mean change	82		-2.4 (SD 2.63)	77		-1.8 (SD 2.54)	MD=-0.600 (CI: -1.404, 0.204)
BPI walking ability – 0d	Continuous	82		4.2 (SD 2.9)	77		4.5 (SD 2.81)	
BPI walking ability – 42d	Mean change	82		-2.4 (SD 2.99)	77		-2 (SD 2.9)	MD=-0.400 (CI: -1.315, 0.515)

BPI normal work – 0d	Continuous	82		3.9 (SD 2.81)	77		4.4 (SD 2.72)	
BPI normal work – 42d	Mean change	82		-2.4 (SD 2.81)	77		-1.9 (SD 2.81)	MD=-0.500 (CI: -1.373, 0.373)
BPI relationship with other people – 0d	Continuous	82		2.4 (SD 2.44)	77		3.2 (SD 2.37)	
BPI relationship with other people – 42d	Mean change	82		-2 (SD 2.44)	77		-1.3 (SD 2.37)	MD=-0.700 (CI: -1.448, 0.048)
BPI enjoyment of life – 0d	Continuous	82		3.6 (SD 2.81)	77		4.6 (SD 2.81)	
BPI enjoyment of life – 42d	Mean change	82		-3.2 (SD 2.81)	77		-2.2 (SD 2.81)	MD=-1.000 (CI: -1.873, -0.127)
BPI interference score – 0d	Continuous	82		3.5 (SD 2.35)	77		4.3 (SD 2.37)	
BPI interference score – 42d	Mean change	82		-2.6 (SD 2.35)	77		-1.8 (SD 2.37)	MD=-0.800 (CI: -1.535, -0.065)
BPI average pain intensity – 0d	Continuous	82		4.2 (SD 2.54)	77		5.2 (SD 2.46)	
BPI average pain intensity – 42d	Mean change	82		-2.6 (SD 2.54)	77		-1.5 (SD 2.54)	MD=-1.100 (CI: -1.890, -0.310)
major adverse events (defined as leading to withdrawal):								
any major adverse event – 42d	Dichotomous	82	7	(8.5%)	77	4	(5.2%)	OR=1.703 (CI: 0.478, 6.066)
adverse events:								
asthenia – 42d	Dichotomous	82	12	(14.6%)	77	5	(6.5%)	OR=2.469 (CI: 0.827, 7.371)
Constipation – 42d	Dichotomous	82	35	(42.7%)	77	11	(14.3%)	OR=4.468 (CI: 2.061, 9.688)
Dizziness – 42d	Dichotomous	82	26	(31.7%)	77	8	(10.4%)	OR=4.004 (CI: 1.682, 9.532)
Dry mouth – 42d	Dichotomous	82	13	(15.9%)	77	2	(2.6%)	OR=7.065 (CI: 1.539, 32.439)
headache – 42d	Dichotomous	82	9	(11.0%)	77	18	(23.4%)	OR=0.404 (CI: 0.169, 0.965)
Nausea – 42d	Dichotomous	82	30	(36.6%)	77	6	(7.8%)	OR=6.827 (CI: 2.649, 17.595)
Pruritus – 42d	Dichotomous	82	20	(24.4%)	77	6	(7.8%)	OR=3.817 (CI: 1.441, 10.108)
Somnolence – 42d	Dichotomous	82	33	(40.2%)	77	1	(1.3%)	OR=51.184 (CI: 6.779, 386.452)
Vomiting – 42d	Dichotomous	82	17	(20.7%)	77	2	(2.6%)	OR=9.808 (CI: 2.183, 44.058)
treatment withdrawal:								
due to lack of efficacy – 42d	Dichotomous	82	1	(1.2%)	77	11	(14.3%)	OR=0.074 (CI: 0.009, 0.589)
unspecified/other reason – 42d	Dichotomous	82	7	(8.5%)	77	5	(6.5%)	OR=1.344 (CI: 0.408, 4.428)
protocol deviation – 42d	Dichotomous	82	2	(2.4%)	77	5	(6.5%)	OR=0.360 (CI: 0.068, 1.913)
lost to follow-up – 42d	Dichotomous	82	2	(2.4%)	77	0	(0.0%)	OR=4.814 (CI: 0.227, 101.880)

[a] least squares mean; estimated from graph
[b] least squares mean
[c] least squares mean; based on NRS Sleep

Comments	initial washout/screening phase was 3-7 days

Definitions of abbreviations are given at the end of this document.

Study	Goldstein et al. (2005)
Pain category	Peripheral pain
Study design	Country: USA Design: Parallel Inclusion criteria: Participants with PDN with at least 4 on the 24h Average Pain Score (NRS 11-point), With a mean duration of PDN for at least 6 months which had to have begun in the feet with symetrical onset Exclusion criteria: Particpants who met DSM-IV criteria for axis 1 diagnosis of major depressive disorder, depression-partial remission, dysthymic disorder, Generalised anxiety disorder, alcohol or eating disorders, pain that was not distinguishable from or unrelated to dabetic neuropathy. Patients were also excluded if they has a history of substance abuse, taken excluded medications within 7 days of study, received treatment with MAOI or fluoxetine within 30 days of study, or had opioid use within 3 days of study Study length (days): 84 Intention-to-treat analysis? Yes
Participants	Total number of patients: 457 Number of males: 281 (61.5%) Underlying cause of neuropathic pain: Painful diabetic neuropathy Mean duration of NP (in months): 44.4 Baseline pain severity: 5.9 (NRS) Mean age: 60.1 (SD: 10.9)
Intervention(s)	(1) duloxetine 20mg/d Intervention: duloxetine Length of treatment (weeks): 12 Fixed/flexible dose regimen: Fixed dose Set dose: 20mg/d (2) duloxetine 60mg/d Intervention: duloxetine Length of treatment (weeks): 12 Fixed/flexible dose regimen: Fixed dose Set dose: 60mg/d (3) duloxetine 120mg/d Intervention: duloxetine Length of treatment (weeks): 12 Fixed/flexible dose regimen: Fixed dose Set dose: 120mg/d (4) placebo Intervention: placebo

	Length of treatment (weeks): 12 Fixed/flexible dose regimen: Fixed dose
Concomitant treatments	Drug free baseline period? Unclear Concomitant pain treatment allowed? Unclear (Paracetamol (max 4g/d) but no other analgesics medications for PDN (unclear about anti-depressants but patients considered depressed were excluded))
Outcomes measures and effect sizes	

		DULOXETINE 20MG/D			PLACEBO			
		N	k	mean	N	k	mean	Δ
pain score:								
NRS/NRS Pain – 0d	Continuous	115		5.9 (SD 1.6)	115		5.8 (SD 1.5)	
NRS/NRS Pain – 84d	Mean change	91		-2.36 (SD 2)	88		-1.91 (SD 2.06)	MD=-0.450 (CI: -1.046, 0.146)
at least 50% pain reduction (NRS) – 84d	Dichotomous	115	46	(40.0%)	115	29	(25.2%)	OR=1.977 (CI: 1.127, 3.469)
BPI (severity) – 84d	Mean change	110		-2.25 (SD 2.2)	112		-2.04 (SD 2.22)	MD=-0.210 (CI: -0.792, 0.372)
SF McGill – 84d	Mean change	88		-7.23 (SD 6.29)	96		-5.39 (SD 6.47)	MD=-1.840 (CI: -3.683, 0.003)
patient-reported global improvement:								
PGI-I – 84d	Continuous	108		2.68 (SD 1.25)	111		2.91 (SD 1.26)	MD=-0.230 (CI: -0.563, 0.103)
patient-reported improvement in daily physical and emotional functioning, including sleep:								
BDI – 84d	Continuous	82		-2.44 (SD 4.35)	79		-1.74 (SD 4.27)	MD=-0.700 (CI: -2.030, 0.630)
major adverse events (defined as leading to withdrawal):								
any major adverse event – 84d	Dichotomous	115	5	(4.3%)	115	6	(5.2%)	OR=0.826 (CI: 0.245, 2.786)
adverse events:								
Constipation	Dichotomous	115	6	(5.2%)	115	4	(3.5%)	OR=1.528 (CI: 0.419, 5.563)
Dizziness – 84d	Dichotomous	115	7	(6.1%)	115	8	(7.0%)	OR=0.867 (CI: 0.304, 2.475)
Dry mouth – 84d	Dichotomous	115	6	(5.2%)	115	7	(6.1%)	OR=0.849 (CI: 0.276, 2.609)
Nausea – 84d	Dichotomous	115	16	(13.9%)	115	11	(9.6%)	OR=1.528 (CI: 0.676, 3.454)
Somnolence – 84d	Dichotomous	115	9	(7.8%)	115	9	(7.8%)	OR=1.000 (CI: 0.382, 2.618)
overall improvement in quality of life:								
SF36 Mental – 84d	Continuous	102		0.02 (SD 7.68)	102		-1.09 (SD 7.76)	MD=1.110 (CI: -1.008, 3.228)
SF36 Physical – 84d	Continuous	98		3.67 (SD 7.72)	102		3.94 (SD 7.78)	MD=-0.270 (CI: -2.418, 1.878)
EQ-5D - health status index – 84d	Continuous	101		0.1 (SD 0.201)	107		0.08 (SD 0.207)	MD=0.020 (CI: -0.035, 0.075)
SF36 bodily pain – 84d	Continuous	102		13.2 (SD 19.3)	107		10.3 (SD 19.6)	MD=2.900 (CI: -2.367, 8.167)
SF36 general health – 84d	Continuous	100		3.94 (SD 16.5)	106		2.03 (SD 16.7)	MD=1.910 (CI: -2.613, 6.433)
SF36 mental health – 84d	Continuous	102		0.74 (SD 17)	107		-2.63 (SD 17.5)	MD=3.370 (CI: -1.301, 8.041)
treatment withdrawal:								
due to lack of efficacy – 84d	Dichotomous	115	2	(1.7%)	115	4	(3.5%)	OR=0.491 (CI: 0.088, 2.736)
unspecified/other reason – 84d	Dichotomous	115	7	(6.1%)	115	14	(12.2%)	OR=0.468 (CI: 0.181, 1.205)
protocol deviation – 84d	Dichotomous	115	6	(5.2%)	115	3	(2.6%)	OR=2.055 (CI: 0.501, 8.424)
lost to follow-up – 84d	Dichotomous	115	4	(3.5%)	115	1	(0.9%)	OR=4.108 (CI: 0.452, 37.330)

		DULOXETINE 60MG/D			PLACEBO			
		N	k	mean	N	k	mean	Δ
pain score:								
NRS/NRS Pain – 0d	Continuous	114		6 (SD 1.7)	115		5.8 (SD 1.5)	

NRS/NRS Pain – 84d	Mean difference over whole trial period	88			88			MD=-1.170 (CI: -1.840, -0.500)
NRS/NRS Pain – 84d	Mean change	88		-2.89 (SD 2.06)	88		-1.91 (SD 2.06)	MD=-0.980 (CI: -1.590, -0.370)
at least 50% pain reduction (NRS) – 84d	Dichotomous	114	55	(48.2%)	115	29	(25.2%)	OR=2.764 (CI: 1.581, 4.833)
BPI (severity) – 84d	Mean change	113		-2.81 (SD 2.23)	112		-2.04 (SD 2.22)	MD=-0.770 (CI: -1.352, -0.188)
SF McGill – 84d	Mean change	95		-8.25 (SD 6.34)	96		-5.39 (SD 6.47)	MD=-2.860 (CI: -4.676, -1.044)
patient-reported global improvement:								
PGI-I – 84d	Continuous	111		2.21 (SD 1.26)	111		2.91 (SD 1.26)	MD=-0.700 (CI: -1.033, -0.367)
patient-reported improvement in daily physical and emotional functioning, including sleep:								
BDI – 84d	Continuous	78		-2.71 (SD 4.33)	79		-1.74 (SD 4.27)	MD=-0.970 (CI: -2.314, 0.374)
major adverse events (defined as leading to withdrawal):								
any major adverse event – 84d	Dichotomous	114	15	(13.2%)	115	6	(5.2%)	OR=2.753 (CI: 1.028, 7.371)
adverse events:								
Constipation	Dichotomous	114	17	(14.9%)	115	4	(3.5%)	OR=4.863 (CI: 1.582, 14.947)
Dizziness – 84d	Dichotomous	114	11	(9.6%)	115	8	(7.0%)	OR=1.428 (CI: 0.552, 3.694)
Dry mouth – 84d	Dichotomous	114	8	(7.0%)	115	7	(6.1%)	OR=1.164 (CI: 0.408, 3.325)
Nausea – 84d	Dichotomous	114	19	(16.7%)	115	11	(9.6%)	OR=1.891 (CI: 0.856, 4.179)
Somnolence – 84d	Dichotomous	114	23	(20.2%)	115	9	(7.8%)	OR=2.977 (CI: 1.311, 6.758)
overall improvement in quality of life:								
SF36 Mental – 84d	Continuous	101		0.63 (SD 7.75)	102		-1.09 (SD 7.76)	MD=1.720 (CI: -0.413, 3.853)
SF36 Physical – 84d	Continuous	101		5.86 (SD 7.74)	102		3.94 (SD 7.78)	MD=1.920 (CI: -0.214, 4.054)
EQ-5D - health status index – 84d	Continuous	104		0.13 (SD 0.204)	107		0.08 (SD 0.207)	MD=0.050 (CI: -0.005, 0.105)
SF36 bodily pain – 84d	Continuous	104		18 (SD 19.3)	107		10.3 (SD 19.6)	MD=7.680 (CI: 2.441, 12.919)
SF36 general health – 84d	Continuous	103		5.66 (SD 16.5)	106		2.03 (SD 16.7)	MD=3.630 (CI: -0.868, 8.128)
SF36 mental health – 84d	Continuous	104		2.99 (SD 16.8)	107		-2.63 (SD 17.5)	MD=5.620 (CI: 0.991, 10.249)
treatment withdrawal:								
due to lack of efficacy – 84d	Dichotomous	114	1	(0.9%)	115	4	(3.5%)	OR=0.246 (CI: 0.027, 2.232)
unspecified/other reason – 84d	Dichotomous	114	7	(6.1%)	115	14	(12.2%)	OR=0.472 (CI: 0.183, 1.217)
protocol deviation – 84d	Dichotomous	114	2	(1.8%)	115	3	(2.6%)	OR=0.667 (CI: 0.109, 4.067)
lost to follow-up – 84d	Dichotomous	114	3	(2.6%)	115	1	(0.9%)	OR=3.081 (CI: 0.316, 30.069)

		DULOXETINE 120MG/D			**PLACEBO**			
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**
pain score:								
NRS/NRS Pain – 0d	Continuous	113		5.9 (SD 1.4)	115		5.8 (SD 1.5)	
NRS/NRS Pain – 84d	Mean change	80			88			MD=-1.330 (CI: -1.954, -0.706)
NRS/NRS Pain – 84d	Mean difference over whole trial period	113			115			MD=-1.450 (CI: -2.125, -0.775)

	at least 50% pain reduction (NRS) – 84d	Dichotomous	113	57	(50.4%)	115	29	(25.2%)	OR=3.018 (CI: 1.725, 5.282)
	BPI (severity) – 84d	Mean change	109		-3.07 (SD 2.3)	112		-2.04 (SD 2.22)	MD=-1.030 (CI: -1.626, -0.434)
	SF McGill – 84d	Mean change	99		-9.18 (SD 6.37)	96		-5.39 (SD 6.47)	MD=-3.790 (CI: -5.592, -1.988)
	patient-reported global improvement:								
	PGI-I – 84d	Continuous	109		2.24 (SD 1.25)	111		2.91 (SD 1.26)	MD=-0.670 (CI: -1.003, -0.337)
	patient-reported improvement in daily physical and emotional functioning, including sleep:								
	BDI – 84d	Continuous	74		-3.11 (SD 4.3)	79		-1.74 (SD 4.27)	MD=-1.370 (CI: -2.728, -0.012)
	major adverse events (defined as leading to withdrawal):								
	any major adverse event – 84d	Dichotomous	113	22	(19.5%)	115	6	(5.2%)	OR=4.392 (CI: 1.708, 11.295)
	adverse events:								
	Constipation	Dichotomous	113	12	(10.6%)	115	4	(3.5%)	OR=3.297 (CI: 1.030, 10.551)
	Dizziness – 84d	Dichotomous	113	26	(23.0%)	115	8	(7.0%)	OR=3.997 (CI: 1.723, 9.272)
	Dry mouth – 84d	Dichotomous	113	17	(15.0%)	115	7	(6.1%)	OR=2.732 (CI: 1.086, 6.870)
	Nausea – 84d	Dichotomous	113	31	(27.4%)	115	11	(9.6%)	OR=3.574 (CI: 1.695, 7.539)
	Somnolence – 84d	Dichotomous	113	32	(28.3%)	115	9	(7.8%)	OR=4.653 (CI: 2.103, 10.294)
	overall improvement in quality of life:								
	SF36 Mental – 84d	Continuous	101		1.84 (SD 7.69)	102		-1.09 (SD 7.76)	MD=2.930 (CI: 0.806, 5.054)
	SF36 Physical – 84d	Continuous	101		5.58 (SD 7.64)	102		3.94 (SD 7.78)	MD=1.640 (CI: -0.480, 3.760)
	EQ-5D - health status index – 84d	Continuous	105		0.13 (SD 0.205)	107		0.08 (SD 0.207)	MD=0.050 (CI: -0.005, 0.105)
	SF36 bodily pain – 84d	Continuous	105		18.3 (SD 19.3)	107		10.3 (SD 19.6)	MD=8.000 (CI: 2.775, 13.225)
	SF36 general health – 84d	Continuous	102		9.56 (SD 16.6)	106		2.03 (SD 16.7)	MD=7.530 (CI: 3.010, 12.050)
	SF36 mental health – 84d	Continuous	105		5.14 (SD 16.6)	107		-2.63 (SD 17.5)	MD=7.770 (CI: 3.182, 12.358)
	treatment withdrawal:								
	due to lack of efficacy – 84d	Dichotomous	113	2	(1.8%)	115	4	(3.5%)	OR=0.500 (CI: 0.090, 2.786)
	unspecified/other reason – 84d	Dichotomous	113	5	(4.4%)	115	14	(12.2%)	OR=0.334 (CI: 0.116, 0.961)
	protocol deviation – 84d	Dichotomous	113	2	(1.8%)	115	3	(2.6%)	OR=0.673 (CI: 0.110, 4.104)
	lost to follow-up – 84d	Dichotomous	113	2	(1.8%)	115	1	(0.9%)	OR=2.054 (CI: 0.184, 22.976)
Comments	there was a 1-2 week screening phase (unclear if this included a drug-free phase); unspecified reason' for withdrawal includes 'sponsor's decision', 'personal conflict'/'patients decision', 'physician's decision'; ITT included all randomised patients in the safety analyses and all randomised patients with at least one post-baseline assessment in the efficacy assessment								

Definitions of abbreviations are given at the end of this document.

Study	Gordh et al. (2008)
Pain category	Peripheral pain
Study design	Country: Denmark, Sweden, Finland, Norway Design: Crossover Inclusion criteria: neuropathic pain for at least 6 months, with pain intensity at least 30m on VAS-100mm, at least 18 years old, either hyper- or hypo-

	phenomena on sensibility tests Exclusion criteria: pregnancy, lactating, previous treatment with gabapentin, decreased renal function, serious hepatic, respiratory or haematologic disease, unstable cardiovascular disease, other pain that could confound assessment of neuropathic pain, history of chronic alcohol or drug abuse within previous 3 years Study length (days): 35 Intention-to-treat analysis? Yes
Participants	Total number of patients: 120 Number of males: 56 (46.7%) Underlying cause of neuropathic pain: Nerve injury neuropathic pain Mean duration of NP (in months): not reported Baseline pain severity: 53.15 (VAS (average of arm means) (duration of pain was 6-12 months in 13 patients, more than 5 years in another 13 patients, and between 1 and 5 years for the remaining patients)) Mean age: 48.8
Intervention(s)	(1) gabapentin (flexible dose) Intervention: gabapentin Length of treatment (weeks): 5 Fixed/flexible dose regimen: Flexible dose Mean dose: 2243mg/d Notes: paper says it is a fixed dose treatment phase but then states the dose was increased until maximum pain relief at a tolerable dose was achieved and gave a maximum daily dose; titration started at 300 mg (2) placebo Intervention: placebo Length of treatment (weeks): 5 Fixed/flexible dose regimen: Flexible dose
Concomitant treatments	Drug free baseline period? Unclear Concomitant pain treatment allowed? No (TENS, daily intake of opioids and drugs that might affect the neuropathic pain (ie. Anti-depressants, skeletal muscle relaxants with centrally acting probabilities, antiepileptic drugs, mexiletine, dextromethorphan, capsaicin, anxiolytics) were prohibited; however, occasional use of NSAIDs for other types of pain and the use of benzodiazepines, zolpidem or zopiclon was allowed if they were prescribed before screening; paracetamol with codeine and dextropropoxyphene allowed as rescue medication)
Outcomes measures and effect sizes	

		GABAPENTIN (FLEXIBLE DOSE)			PLACEBO			
		N	k	mean	N	k	mean	Δ
ITT population								
pain score:								
at least 30% pain reduction (VAS) – 35d	Dichotomous	120	31	(25.8%)	120	14	(11.7%)	OR=2.637 (CI: 1.321, 5.264)
at least 50% pain reduction (VAS) – 35d	Dichotomous	120	22	(18.3%)	120	8	(6.7%)	OR=3.143 (CI: 1.339, 7.378)
major adverse events (defined as leading to withdrawal):								
any major adverse event – 35d	Dichotomous	120	7	(5.8%)	120	4	(3.3%)	OR=1.796 (CI: 0.512, 6.305)

adverse events:									
Confusion – 35d	Dichotomous	120	16	(13.3%)	120	2	(1.7%)	OR=9.077 (CI: 2.039, 40.413)	
dizziness or vertigo – 35d	Dichotomous	120	39	(32.5%)	120	9	(7.5%)	OR=5.938 (CI: 2.724, 12.946)	
Dry mouth – 35d	Dichotomous	120	9	(7.5%)	120	3	(2.5%)	OR=3.162 (CI: 0.834, 11.983)	
headache – 35d[a]	Dichotomous	120	18	(15.0%)	120	20	(16.7%)	OR=0.882 (CI: 0.441, 1.766)	
Infection – 35d	Dichotomous	120	10	(8.3%)	120	15	(12.5%)	OR=0.636 (CI: 0.274, 1.479)	
nausea/vomiting – 35d	Dichotomous	120	8	(6.7%)	120	10	(8.3%)	OR=0.786 (CI: 0.299, 2.065)	
skin-related side effects – 35d[b]	Dichotomous	120	10	(8.3%)	120	5	(4.2%)	OR=2.091 (CI: 0.693, 6.312)	
tiredness – 35d[c]	Dichotomous	120	31	(25.8%)	120	17	(14.2%)	OR=2.110 (CI: 1.095, 4.067)	
treatment withdrawal:									
due to lack of efficacy – 35d	Dichotomous	120	1	(0.8%)	120	2	(1.7%)	OR=0.496 (CI: 0.044, 5.542)	
unspecified/other reason – 35d	Dichotomous	120	1	(0.8%)	120	5	(4.2%)	OR=0.193 (CI: 0.022, 1.680)	
withdrawal of consent – 35d	Dichotomous	120	1	(0.8%)	120	1	(0.8%)	OR=1.000 (CI: 0.062, 16.174)	
poor compliance – 35d	Dichotomous	120	2	(1.7%)	120	1	(0.8%)	OR=2.017 (CI: 0.180, 22.545)	
use of rescue medication:									
proportion taking NSAIDs – 35d	Dichotomous	120	10	(8.3%)	120	7	(5.8%)	OR=1.468 (CI: 0.539, 3.993)	
proportion using pain medication – 35d[d]	Dichotomous	120	40	(33.3%)	120	45	(37.5%)	OR=0.833 (CI: 0.491, 1.415)	
treatment phase 1									
pain score:									
VAS – 0d	Continuous	48		52.2 (SD 16.4)	50		54.1 (SD 15.4)		
VAS – 35d	Mean change	48		7.2 (SD 17.8)	50		6.9 (SD 15.5)	MD=0.300 (CI: -6.319, 6.919)	
VAS – 35d	Continuous	48		45.2 (SD 23.6)	50		47.1 (SD 22.2)	MD=-1.900 (CI: -10.980, 7.180)	
patient-reported improvement in daily physical and emotional functioning, including sleep:									
Normalised (10-pt) sleep interference measure – 0d	Continuous	48		3.79 (SD 2.6)	50		3.74 (SD 2.18)		
Normalised (10-pt) sleep interference measure – 35d	Continuous	48		2.8 (SD 2.61)	50		3.14 (SD 2.09)	MD=-0.340 (CI: -1.278, 0.598)	
Normalised (10-pt) sleep interference measure – 35d	Mean change	48		-1.02 (SD 1.56)	50		-0.63 (SD 1.25)	MD=-0.390 (CI: -0.951, 0.171)	
VAS Sleep – 0d	Continuous	48		37.9 (SD 26)	50		37.4 (SD 21.8)		
VAS Sleep – 35d	Mean change	48		-10.2 (SD 15.6)	50		-6.3 (SD 12.5)	MD=3.900 (CI: -1.711, 9.511)	
VAS Sleep – 35d	Continuous	48		28 (SD 26.1)	50		31.4 (SD 20.9)	MD=-3.400 (CI: -12.785, 5.985)	
treatment phase 2									
pain score:									
VAS – 0d	Continuous	50		52.6 (SD 21.1)	48		50.9 (SD 21.6)		
VAS – 35d	Continuous	50		47.2 (SD 25.1)	48		49.9 (SD 24.3)	MD=46.700 (CI: 39.221, 54.179)	
VAS – 35d	Continuous	50		47.2 (SD 25.1)	48		0.5 (SD 9.7)	MD=46.700 (CI: 39.221, 54.179)	
patient-reported improvement in daily physical and emotional functioning, including sleep:									
Normalised (10-pt) sleep interference measure – 0d	Continuous	50		3.29 (SD 2.11)	48		3.23 (SD 2.55)		
Normalised (10-pt) sleep interference measure – 35d	Continuous	50		2.86 (SD 2.26)	48		3.1 (SD 2.65)	MD=-0.240 (CI: -1.217, 0.737)	
Normalised (10-pt) sleep interference measure – 35d	Mean change	50		-0.38 (SD 0.93)	48		-0.05 (SD 1.05)	MD=-0.330 (CI: -0.723, 0.063)	
VAS Sleep – 0d	Continuous	50		32.9 (SD 21.1)	48		32.3 (SD 25.5)		

	VAS Sleep – 35d	Mean change	50	-3.8 (SD 9.3)	48	-0.5 (SD 10.5)	MD=3.300 (CI: -0.633, 7.233)
	VAS Sleep – 35d	Continuous	50	28.6 (SD 22.6)	48	31 (SD 26.5)	MD=-2.400 (CI: -12.169, 7.369)

[a] including migraine
[b] 'skin disorders'
[c] malaise and tiredness

Comments	it was unclear if the run-in period of 2 weeks included a drug-free period (it might have as concomitant drugs were not permitted); At baseline, 38% used analgesics, 11% NSAIDs, 10% sedatives and 9% anti-depressants (those in the placebo-gabapentin arm were the majority of those taking analgesics during treatment periods and also took more NSAIDs during treatment periods); PGIC data collected and authors state that more patients state that they improved during gabapentin than placebo but actual data not shown; ITT population used for continuous outcomes is all the patients who had completed both treatment periods (per protocol was all those in the ITT population with no major protocol deviations); all dichotomous outcomes use all patients randomised as the denominator; the study reported that statistically more patients responded to gabapentin if response was defined as 30% or more reduction in pain intensity but there was no difference if 50% or more reduction was considered a response (actual data was not reported in the study)

Definitions of abbreviations are given at the end of this document.

Study	Graff-Radford et al. (2000)
Pain category	Peripheral pain
Study design	Country: USA Design: Parallel Inclusion criteria: Duration of pain for at least 6 months Exclusion criteria: Not described Study length (days): 56 Intention-to-treat analysis? No
Participants	Total number of patients: 50 Number of males: 27 (54.0%) Underlying cause of neuropathic pain: Post-herpetic neuralgia Mean duration of NP (in months): 24.25 Baseline pain severity: 54.91 (VAS (average of arm means) (duration of NP is also average of arm means)) Mean age: 72.9 (SD: 10.1)
Intervention(s)	(1) Amitriptyline up to 200mg/d Intervention: amitriptyline Length of treatment (weeks): 8 Fixed/flexible dose regimen: Flexible dose Notes: maximum of 200 mg or maximum tolerated dosage (2) active placebo Intervention: placebo Length of treatment (weeks): 8 Fixed/flexible dose regimen: Flexible dose

	Notes: aim to produce dry mouth and constipation
Concomitant treatments	Drug free baseline period? No Concomitant pain treatment allowed? Unclear
Outcomes measures and effect sizes	

		AMITRIPTYLINE UP TO 200MG/D			ACTIVE PLACEBO			
		N	k	mean	N	k	mean	Δ
pain score:								
VAS – 0d	Continuous	11		55.9 (SD 19.6)	13		53.9 (SD 17)	
VAS – 56d	Continuous	11		26.6 (SD 16.8)	13		48.5 (SD 25)	MD=-21.930 (CI: -38.745, -5.115)
McGill Pain Questionnaire – 0d	Continuous	11		22.5 (SD 14)	13		21.5 (SD 10.9)	
McGill Pain Questionnaire – 56d	Continuous	11		17.4 (SD 10.9)	13		17.8 (SD 13.9)	MD=-0.470 (CI: -10.423, 9.483)
patient-reported improvement in daily physical and emotional functioning, including sleep:								
BDI – 0d[a]	Continuous	11		12.1 (SD 7.3)	13		13.2 (SD 6.7)	
BDI – 56d[a]	Continuous	11		11.1 (SD 7.5)	13		14 (SD 14.3)	MD=-2.900 (CI: -11.848, 6.048)
adverse events:								
Sedation – 56d	Dichotomous	12	1	(8.3%)	13	0	(0.0%)	OR=3.522 (CI: 0.130, 95.086)
treatment withdrawal:								
unspecified/other reason – 56d	Dichotomous	12	1	(8.3%)	13	0	(0.0%)	OR=3.522 (CI: 0.130, 95.086)

[a] Ns inferred

Comments	the patient who withdrew because of an adverse event had excessive sedation (same patient recorded for adverse event and withdrawal above); amitriptyline group had significantly more occurences of dry mouth but actual figures were not reported

Definitions of abbreviations are given at the end of this document.

Study	Grosskopf et al. (2006)
Pain category	Peripheral pain
Study design	Country: USA, Germany, UK Design: Parallel Inclusion criteria: PDN for at least 6 months to 5 years, with at least pain rating of 50mm on the VAS-100mm, and stable glycaemic control Exclusion criteria: Other pain that could confound assessment, previous or current oxcarbazepine treatment, skin conditions that could affect assessment of pain, amputations (except toes), renal insufficiency, serum sodium levels <135mmol/l, chronic infectiois disease, hypersensitivity to oxcarbazepine or carbamazepine. Study length (days): 112 Intention-to-treat analysis? Yes
Participants	Total number of patients: 141 Number of males: 78 (55.3%) Underlying cause of neuropathic pain: Painful diabetic neuropathy Mean duration of NP (in months): 34.8

	Baseline pain severity: 71.4 (VAS) Mean age: 61.1 (SD: 10.5)
Intervention(s)	(1) oxcarbazepine (flexible dose) Intervention: oxcarbazepine Length of treatment (weeks): 16 Fixed/flexible dose regimen: Flexible dose Mean dose: 1091mg/d (SD: 222) Range: 300–1200 Notes: 4 week titration, 12 week maintenance; started at 300 mg/d and then increased over 4 weeks to a maximum tolerated dose or a mximum of 600 mg twice per day (1200 mg) (2) Placebo Intervention: placebo Length of treatment (weeks): Fixed/flexible dose regimen: Flexible dose
Concomitant treatments	Drug free baseline period? Yes (duration: 14d) Concomitant pain treatment allowed? No (Paracetamol only (up to 4g/d). No other analgesics (or drugs with analgesics or anti-hyperalgesic properties) allowed)

Outcomes measures and effect sizes

		OXCARBAZEPINE (FLEXIBLE DOSE)			PLACEBO			
		N	k	mean	N	k	mean	Δ
pain score:								
VAS – 0d	Continuous	71		72 (SD 14.2)	70		70.7 (SD 13.6)	
VAS – 112d[a]	Percentage change from baseline	42		27.9	53		31.1	MD=-3.200
adverse events:								
Dizziness[b]	Dichotomous	71	4	(5.6%)	70	1	(1.4%)	OR=4.119 (CI: 0.449, 37.813)
headache[b]	Dichotomous	71	3	(4.2%)	70	0	(0.0%)	OR=7.204 (CI: 0.365, 142.092)
Nausea[b]	Dichotomous	71	2	(2.8%)	70	1	(1.4%)	OR=2.000 (CI: 0.177, 22.571)
treatment withdrawal:								
due to lack of efficacy – 112d	Dichotomous	71	3	(4.2%)	70	3	(4.3%)	OR=0.985 (CI: 0.192, 5.056)
unspecified/other reason – 112d	Dichotomous	71	4	(5.6%)	70	5	(7.1%)	OR=0.776 (CI: 0.200, 3.019)
protocol deviation – 112d	Dichotomous	71	4	(5.6%)	70	5	(7.1%)	OR=0.776 (CI: 0.200, 3.019)
Adverse events – 112d	Dichotomous	71	18	(25.4%)	70	4	(5.7%)	OR=5.604 (CI: 1.788, 17.559)

[a] numerators not reported for this outcome so they are estimates (as completed, not ITT population)
[b] estimated from percentage bar chart

Comments	ITT population consisted fo all randomised patients who provided at least 1 day of electronic diary data for the VAS during treatment

Definitions of abbreviations are given at the end of this document.

Study	Guan et al. (2011)

Pain category	Peripheral pain
Study design	Country: China Design: Parallel Inclusion criteria: 18-75 years with moderate to severe neuropathic pain caused by PHN or PDN (PDN: HBA1c =11% and between 1 and 5 years of distal, symmetrical sensorimotor polyneuropathy; PHN: pain for at least 3 months after herpes virus), mean score over 4 days =40 cm on MPQ VAS Exclusion criteria: other unrelated neurological disorders, clinically significant or unstable medical or psychiatric conditions, abnormal ECG or hematology findings, creatinin clearance <60ml/min,taking other drugs for neuropathic pain (apart from SSRIs being used for depression lasting 30 days or NSAIDs for 7 days if on stable dose) or therapies (massage, mind care, bodybuilding, yoga, Chinese traditional medicine) for 30 days before treatment Study length (days): 63 Intention-to-treat analysis? Yes
Participants	Total number of patients: 309 Number of males: 99 (32.0%) Underlying cause of neuropathic pain: Painful diabetic neuropathy or PHN Mean duration of NP (in months): 25.2 Baseline pain severity: 6.35 (NRS (average of arm means)) Mean age: 60.05
Intervention(s)	(1) pregabalin (flexible dose) Intervention: pregabalin Length of treatment (weeks): 8 Fixed/flexible dose regimen: Flexible dose Range: 150–600 Notes: dosages only flexible for first 4 weeks, after which they were maintained on the same dosage (2) placebo Intervention: placebo Length of treatment (weeks): Fixed/flexible dose regimen: Flexible dose
Concomitant treatments	Drug free baseline period? Yes (duration: 7d) Concomitant pain treatment allowed? Yes (most drugs used to treat NP excluded, however, those already on stable doses of SSRI for depression lasting 30 days (SSRIs could be considered concomitant medications) or NSAIDs for 7 days were allowed to continue with this stable dose (other treatments, like traditional Chinese medicines, physical therapies, massage, yoga, etc were not allowed))
Outcomes measures and effect sizes	

		PREGABALIN (FLEXIBLE DOSE)			PLACEBO			
		N	k	mean	N	k	mean	Δ
pain score:								
NRS/NRS Pain – 0d[a]	Continuous	206		6.3 (SD 1.58)	102		6.4 (SD 1.53)	
NRS/NRS Pain – 28d[b]	Continuous	196		4.2 (SD 1.96)	93		4.6 (SD 1.83)	MD=-0.400 (CI: -0.863, 0.063)
NRS/NRS Pain – 56d[a]	Continuous	186		3.7 (SD 1.91)	85		4.3 (SD 1.75)	MD=-0.600 (CI: -1.063, -0.137)
at least 30% pain reduction (NRS) – 56d	Dichotomous	203	130	(64.0%)	102	53	(52.0%)	OR=1.646 (CI: 1.016, 2.668)

major adverse events (defined as leading to withdrawal):									
any major adverse event – 56d	Dichotomous	206	11	(5.3%)	102	4	(3.9%)	OR=1.382 (CI: 0.429, 4.452)	
adverse events:									
Dizziness – 56d	Dichotomous	206	23	(11.2%)	102	7	(6.9%)	OR=1.706 (CI: 0.706, 4.119)	
lethargy – 56d	Dichotomous	206	16	(7.8%)	102	3	(2.9%)	OR=2.779 (CI: 0.791, 9.766)	
oedema	Dichotomous	206	15	(7.3%)	102	2	(2.0%)	OR=3.927 (CI: 0.880, 17.512)	
Somnolence – 56d	Dichotomous	206	10	(4.9%)	102	1	(1.0%)	OR=5.153 (CI: 0.651, 40.821)	
Weight gain – 56d	Dichotomous	206	5	(2.4%)	102	1	(1.0%)	OR=2.512 (CI: 0.290, 21.792)	
treatment withdrawal:									
unspecified/other reason – 56d	Dichotomous	206	2	(1.0%)	102	0	(0.0%)	OR=2.506 (CI: 0.119, 52.686)	
withdrawal of consent – 56d	Dichotomous	206	5	(2.4%)	102	3	(2.9%)	OR=0.821 (CI: 0.192, 3.505)	
protocol deviation – 56d	Dichotomous	206	2	(1.0%)	102	3	(2.9%)	OR=0.324 (CI: 0.053, 1.967)	
lost to follow-up – 56d	Dichotomous	206	5	(2.4%)	102	7	(6.9%)	OR=0.338 (CI: 0.104, 1.091)	
ITT/LOCF (last-observation carried forward)									
pain score:									
NRS/NRS Pain – 56d	Continuous	206			102			MD=-0.600 (CI: -1.050, -0.150)	
McGill VAS – 56d	Continuous	206			102			MD=-6.560 (CI: -11.650, -1.470)	
PPI (from MPQ) – 56d	Continuous	206			102			MD=-0.350 (CI: -0.580, -0.120)	
patient-reported improvement in daily physical and emotional functioning, including sleep:									
NRS Sleep – 56d	Continuous	206			102			MD=-0.500 (CI: -0.930, -0.070)	

[a] least squares mean
[b] least squares mean; estimated from graph

Comments	duration of PDN (2.9 years) was longer than PHN (1.3 years); 1 patient in the pregabalin arm dropped out after randomisation but before receiving study medication

Definitions of abbreviations are given at the end of this document.

Study	Hahn et al. (2004)
Pain category	Peripheral pain
Study design	Country: Germany Design: Parallel Inclusion criteria: HIV related sensory neuropathies, =18 years old, completed baseline pain diary Exclusion criteria: pregnancy, alternative causes for neuropathy, acute or chronic pancreatitis or chronic renal insufficiency, elevated parameters of lipase and/or amylase, use of tricyclic or tetracyclic antidepressants, other anticonvulsants, topical capsaicin, mexiletine, alpha-liponic acid, systemtic corticosteroids or immunie modulators, central analgesics, had previously had nerve blocks or acupuncture (NSAIDs were discontinued or reduced to a minimum) Study length (days): 42 Intention-to-treat analysis? No
Participants	Total number of patients: 26 Number of males: 20 (76.9%)

	Underlying cause of neuropathic pain: HIV-related neuropathy Mean duration of NP (in months): 152 Baseline pain severity: 4.9 (10-cm VAS (mean of medians for each arm)) Mean age: 45
Intervention(s)	(1) Gabapentin flexible (up to 2400 mg/d) Intervention: gabapentin Length of treatment (weeks): 6 Fixed/flexible dose regimen: Flexible dose Range: 1200–2400 Notes: dose escalated from 400mg to 1200mg over 2 weeks then maintained this if beneficial. If not dose increased to 2400mg. (2) Placebo Intervention: placebo Length of treatment (weeks): 6 Fixed/flexible dose regimen: Flexible dose
Concomitant treatments	Drug free baseline period? No Concomitant pain treatment allowed? No (NSAIDs were either discontinued or reduced to a minimum (so some may still be on NSAIDs); tricyclic or tetracyclic antidepressants, other anticonvulsants, topical capsaicin, mexiletine, alpha-liponic acid, systemtic corticosteroids or immunie modulators, central analgesics were all excluded)

Outcomes measures and effect sizes

		GABAPENTIN FLEXIBLE (UP TO 2400 MG/D)			PLACEBO			
		N	k	mean	N	k	mean	Δ
pain score:								
VAS – 0d	Continuous	15		med: 5.1 [rng 1.7–8.7]	11		med: 4.7 [rng 1.5–9.3]	
VAS – 28d	Continuous	15		med: 2.85	11		med: 3.3	
VAS – 28d	Mean change	15		med: -2.25	11		med: -1.4	
patient-reported improvement in daily physical and emotional functioning, including sleep:								
VAS Sleep – 0d	Continuous	15		med: 4.5 [rng 1.6–7]	11		med: 5.6 [rng 0.2–7.8]	
VAS Sleep – 28d	Continuous	15		med: 2.3	11		med: 4.95	
major adverse events (defined as leading to withdrawal):								
any major adverse event – 28d	Dichotomous	15	1	(6.7%)	11	0	(0.0%)	OR=2.379 (CI: 0.088, 64.050)
adverse events:								
Dizziness – 28d	Dichotomous	15	9	(60.0%)	11	5	(45.5%)	OR=1.800 (CI: 0.373, 8.681)
Gait disturbance – 28d	Dichotomous	15	7	(46.7%)	11	3	(27.3%)	OR=2.333 (CI: 0.439, 12.398)
Nausea – 28d	Dichotomous	15	5	(33.3%)	11	2	(18.2%)	OR=2.250 (CI: 0.346, 14.611)
Somnolence – 28d	Dichotomous	15	12	(80.0%)	11	2	(18.2%)	OR=18.000 (CI: 2.468, 131.285)
treatment withdrawal:								
due to lack of efficacy – 42d	Dichotomous	15	1	(6.7%)	11	0	(0.0%)	OR=2.379 (CI: 0.088, 64.050)
unspecified/other reason – 42d	Dichotomous	15	0	(0.0%)	11	1	(9.1%)	OR=0.226 (CI: 0.008, 6.092)

Comments	-

Definitions of abbreviations are given at the end of this document.

Study	Hanna et al. (2008)
Pain category	Peripheral pain
Study design	Country: Australia and Europe Design: Parallel Inclusion criteria: PDN of at least 3 months who were on a stable max tolerated dose of gabapentin for at least 1 month but were still experiencing moderate to severe pain (score s of at least 5 on the SF-BPI 11 point scale) Exclusion criteria: >11% HbA1c, long-acting opioids in the previous month or previous use of oxycodone in combination with gabapentin Study length (days): 84 Intention-to-treat analysis? Yes
Participants	Total number of patients: 338 Number of males: 210 (62.1%) Underlying cause of neuropathic pain: Painful diabetic neuropathy Mean duration of NP (in months): not reported Baseline pain severity: not reported (baseline pain severity and mean duration of NP not reported) Mean age: 60.1
Intervention(s)	(1) Gabapentin (flexible dose) + placebo Intervention: gabapentin Length of treatment (weeks): 12 Fixed/flexible dose regimen: Flexible dose Mean dose: 1383.625731mg/d Median dose: 1383.625731mg/d Range: 1383.625731–1383.625731 Notes: Maximum tolerated dose from previous gabapentin treatment. Most participants on 600mg/d to 1800 mg/d (2) Gabapentin (flexible dose) + Oxycodone Intervention: gabapentin+oxycodone Length of treatment (weeks): 12 Fixed/flexible dose regimen: Flexible dose Notes: Unclear dose (max tolerated). Escalated from 5mg/d to 80mg/d for some patients. No mean. Unclear how many achielved min max dose. Mean gabapentin dose = 1447.27mg/d
Concomitant treatments	Drug free baseline period? No Concomitant pain treatment allowed? Yes (use of tricyclics or NSAIDs at least 3 weeks before screening and on a stable dose (6.4% were on amitiptyline for depression) or those on aspirin for cardiovascular indication was allowed. Paracetamol allowed as rescue medication; those on long-acting opioids in the previous month or had previously used oxycodone with gabapentin were excluded)
Outcomes measures and effect sizes	

	GABAPENTIN (FLEXIBLE DOSE) + PLACEBO			GABAPENTIN (FLEXIBLE DOSE) + OXYCODONE			
	N	k	mean	N	k	mean	Δ

pain score:								
Box NRS – 0d	Continuous	165		6.5 (SD 1.71)	163		6.4 (SD 1.76)	
Box NRS – 28d	Mean change	165		-0.9 (SD 1.73)	163		-1.7 (SD 2.14)	MD=0.800 (CI: 0.379, 1.221)
Box NRS – 56d	Mean change	165		-1.4 (SD 2.2)	163		-2.2 (SD 2.49)	MD=0.800 (CI: 0.291, 1.309)
Box NRS – 84d	Mean change	165		-1.5 (SD 2.38)	163		-2.1 (SD 2.61)	MD=0.600 (CI: 0.059, 1.141)
major adverse events (defined as leading to withdrawal):								
any major adverse event – 84d	Dichotomous	169	9[a]	(5.3%)	169	27[b]	(16.0%)	OR=0.296 (CI: 0.135, 0.650)
adverse events:								
any adverse event – 84d	Dichotomous	169	119	(70.4%)	169	147	(87.0%)	OR=0.356 (CI: 0.204, 0.621)
Constipation – 84d	Dichotomous	169	10	(5.9%)	169	45	(26.6%)	OR=0.173 (CI: 0.084, 0.358)
Dizziness – 84d	Dichotomous	169	6	(3.6%)	169	25	(14.8%)	OR=0.212 (CI: 0.085, 0.531)
Fatigue – 84d	Dichotomous	169	14	(8.3%)	169	31	(18.3%)	OR=0.402 (CI: 0.205, 0.787)
GI disorders – 84d	Dichotomous	169	45	(26.6%)	169	91	(53.8%)	OR=0.311 (CI: 0.197, 0.491)
headache – 84d	Dichotomous	169	17	(10.1%)	169	17	(10.1%)	OR=1.000 (CI: 0.492, 2.032)
Infection – 84d	Dichotomous	169	30	(17.8%)	169	50	(29.6%)	OR=0.514 (CI: 0.307, 0.859)
Nausea – 84d	Dichotomous	169	18	(10.7%)	169	43	(25.4%)	OR=0.349 (CI: 0.192, 0.636)
skin-related side effects – 84d	Dichotomous	169	19	(11.2%)	169	34	(20.1%)	OR=0.503 (CI: 0.274, 0.923)
Somnolence – 84d	Dichotomous	169	9	(5.3%)	169	37	(21.9%)	OR=0.201 (CI: 0.093, 0.431)
Vomiting – 84d	Dichotomous	169	7	(4.1%)	169	16	(9.5%)	OR=0.413 (CI: 0.165, 1.032)
treatment withdrawal:								
due to lack of efficacy – 84d	Dichotomous	169	20	(11.8%)	169	6	(3.6%)	OR=3.647 (CI: 1.426, 9.325)
unspecified/other reason – 84d	Dichotomous	169	8	(4.7%)	169	9	(5.3%)	OR=0.883 (CI: 0.332, 2.347)
use of rescue medication:								
average tablets used per 2 week period	Continuous	162		2.1 (SD 2.41)	160		1.6 (SD 2.09)	MD=0.500 (CI: 0.007, 0.993)

[a] 16 had toxicity
[b] 12 had toxicity

Comments	LOCF was used for pain scores, escape medication and sleep assessments - however, it is not clear why denominators reported for efficacy analyses were different than patients randomised

Definitions of abbreviations are given at the end of this document.

Study	Harati et al. (1998)
Pain category	Peripheral pain

Study design	Country: USA Design: Parallel Inclusion criteria: diabetes mellitus with acceptable glycemic control, distal symmetric diabetic neuropathy, moderate pain (on Likert scale) in the lower extremeties for previous 3 months, 19 years or older Exclusion criteria: known contraindication to or prior use of tramadol, peripheral neuropathy from other causes (ie. Alcoholism, connective tissues disease, toxic exposure), severe depression, pain more severe than the neuropathic pain, <30ml/min creatinine clearance, clinical significant medical conditions, history of narcotic or alcohol abuse, use of multiple daily doses of narcotic analgesics or mexiletine on a regular basis, amputations, open ulcers, Charcot joint Study length (days): 42 Intention-to-treat analysis? No
Participants	Total number of patients: 131 Number of males: 78 (59.5%) Underlying cause of neuropathic pain: Painful diabetic neuropathy Mean duration of NP (in months): not reported Baseline pain severity: 2.55 (VRS (5-point Likert)) Mean age: 59
Intervention(s)	(1) Tramadol (oral) up to 400 mg/d Intervention: tramadol Length of treatment (weeks): 7 Fixed/flexible dose regimen: Flexible dose Mean dose: 210mg/d (SD: 113) Notes: started at 50 mg/d and increased in 50 mg increments every 3 days up to 200 mg/d on day 10 - this was maintained until day 14; from day 14-28, dosage could be icnreased by 50 mg/d to obtain optimal pain relief up to 400 mg/d; after day 28, dosage could not be reduced; an alternative scheduled was permitted if patients experienced inadequate pain releif at any time (day 1-4, tramadol was titrated up to 200 mg/d, then from day 5, patients could increase dosage by 50 mg/d but still not to exceed 400 mg/d) (2) placebo Intervention: placebo Length of treatment (weeks): 7 Fixed/flexible dose regimen: Fixed dose
Concomitant treatments	Drug free baseline period? Yes (duration: 7d) Concomitant pain treatment allowed? No (no pain medications other the study meds were permitted (tricyclics, anticonvulsants were discontinued 21 days before randomisation and shorter-acting analgesics were stopped 7 days before randomisation))
Outcomes measures and effect sizes	

		TRAMADOL (ORAL) UP TO 400 MG/D			PLACEBO			
		N	k	mean	N	k	mean	Δ
pain score:								
VRS – 0d[a]	Continuous	65		2.5 (SD 0.806)	66		2.6 (SD 0.812)	
VRS – 42d[a]	Continuous	65		1.4 (SD 0.806)	66		2.2 (SD 0.812)	MD=-0.800 (CI: -1.077, -0.523)
pain relief:								
VRS/VRSpr – 42d[b]	Continuous	65		2.1 (SD 1.61)	66		0.9 (SD 1.62)	MD=1.200 (CI: 0.646, 1.754)

	major adverse events (defined as leading to withdrawal):								
	any major adverse event – 42d	Dichotomous	65	9	(13.8%)	66	1	(1.5%)	OR=10.446 (CI: 1.284, 85.023)
	adverse events:								
	Constipation – 42d	Dichotomous	65	14	(21.5%)	66	2	(3.0%)	OR=8.784 (CI: 1.909, 40.429)
	Diarrhoea – 42d	Dichotomous	65	2	(3.1%)	66	5	(7.6%)	OR=0.387 (CI: 0.072, 2.072)
	Dizziness – 42d	Dichotomous	65	3	(4.6%)	66	0	(0.0%)	OR=7.448 (CI: 0.377, 147.110)
	dyspepsia – 42d	Dichotomous	65	6	(9.2%)	66	2	(3.0%)	OR=3.254 (CI: 0.632, 16.758)
	Fatigue – 42d	Dichotomous	65	3	(4.6%)	66	0	(0.0%)	OR=7.448 (CI: 0.377, 147.110)
	Nausea – 42d	Dichotomous	65	15	(23.1%)	66	2	(3.0%)	OR=9.600 (CI: 2.097, 43.941)
	Pruritus – 42d	Dichotomous	65	4	(6.2%)	66	0	(0.0%)	OR=9.732 (CI: 0.513, 184.497)
	Rash – 42d	Dichotomous	65	4	(6.2%)	66	0	(0.0%)	OR=9.732 (CI: 0.513, 184.497)
	Somnolence – 42d	Dichotomous	65	8	(12.3%)	66	4	(6.1%)	OR=2.175 (CI: 0.621, 7.616)
	Vomiting – 42d	Dichotomous	65	3	(4.6%)	66	0	(0.0%)	OR=7.448 (CI: 0.377, 147.110)
	treatment withdrawal:								
	due to lack of efficacy – 42d	Dichotomous	65	9	(13.8%)	66	22	(33.3%)	OR=0.321 (CI: 0.135, 0.767)
	unspecified/other reason – 42d	Dichotomous	65	2	(3.1%)	66	2	(3.0%)	OR=1.016 (CI: 0.139, 7.436)
	[a] 5-point Likert scale [b] 6-point Likert scale								
Comments	study appeared to use MOS approach to assess quality of life, evaluating activities of daily living and sleep - results for sleep were not reported and results for other aspects of daily living have not been extracted								

Definitions of abbreviations are given at the end of this document.

Study	Holbech et al. (2011)
Pain category	Peripheral pain
Study design	Country: Denmark Design: Crossover Inclusion criteria: 20-80 years with symptoms compatible with polyneuropathy for more than 6 months (distal symmetric pain localisation) plus sensory disturbance in area of pain (polyneuropathy had to be confirmed by clinical signs such as decreased deep tendon reflexes and/or electrophysiological tests and/or quantitative sensory testing), median total pain rating of at least 4 on 11-point NRS after 1 week off pain medication (for those with polyneuropathy due to diabetes, hypothyroidism, etc, the underlying cause had to be stable for at least 3 months before inclusion) Exclusion criteria: causes of pain other than polyneuropathy, previous allergic reactions/severe adverse events to levetiracetam, pregnancy and lactation, severe terminal illness, concomitant use of antidepressants, other anticonvulsants, opioids that could not be discontinued Study length (days): 105 Intention-to-treat analysis? Yes
Participants	Total number of patients: 92 Number of males: 22 (23.9%) Underlying cause of neuropathic pain: Polyneuropathy Mean duration of NP (in months): 49 Baseline pain severity: 5.7 (median NRS (also, median duration of NP and age))

	Mean age: 57
Intervention(s)	(1) Levetiracetam flexible-dose Intervention: levetiracetam Length of treatment (weeks): 6 Fixed/flexible dose regimen: Flexible dose Range: 2000–3000 Notes: slow titration in the first 15 days up to 3000 mg/d but those with unacceptable side effects were permitted to lower their dose to 2000-2500 mg/d; actual numbers of patients achieving these different dosage levels was not reported (2) Placebo Intervention: placebo Length of treatment (weeks): 6 Fixed/flexible dose regimen: Flexible dose
Concomitant treatments	Drug free baseline period? Yes (duration: 7d) Concomitant pain treatment allowed? No (all concomitant treatments for NP were either discontinued or patients excluded (ie. Anti-depressants, other anti-convulsants, opioids); up to 5 500mg tablets of paracetamol and one tablet of 50 mg tramadol were permitted as escape medication)

Outcomes measures and effect sizes

		LEVETIRACETAM FLEXIBLE-DOSE			PLACEBO			
		N	k	mean	N	k	mean	Δ
ITT/LOCF (last-observation carried forward)								
pain score:								
NRS/NRS Pain – 0d	Continuous	35		5.2 (SD 1.6)	35		5.2 (SD 1.6)	
NRS/NRS Pain – 42d	Continuous	35		5.5 (SD 2.5)	35		5.3 (SD 2.3)	MD=0.200 (CI: -0.925, 1.325)
pain relief:								
VRS/VRSpr – 42d	Continuous	35		2.29 (SD 1.13)	35		2.28 (SD 1.19)	MD=0.010 (CI: -0.534, 0.554)
patient-reported improvement in daily physical and emotional functioning, including sleep:								
Normalised (10-pt) sleep interference measure – 0d[a]	Continuous	35		4.8 (SD 2.5)	35		4.8 (SD 2.5)	
Normalised (10-pt) sleep interference measure – 42d[a]	Continuous	35		3.9 (SD 3)	35		4 (SD 2.9)	
NRS Sleep – 0d	Continuous	35		4.8 (SD 2.5)	35		4.8 (SD 2.5)	
NRS Sleep – 42d	Continuous	35		3.8 (SD 3)	35		4 (SD 2.9)	MD=-0.200 (CI: -1.582, 1.182)
major adverse events (defined as leading to withdrawal):								
any major adverse event – 42d	Dichotomous	39	3[b]	(7.7%)	35	0	(0.0%)	OR=6.808 (CI: 0.339, 136.609)
adverse events:								
any adverse event – 42d	Dichotomous	39	22	(56.4%)	39	17	(43.6%)	OR=1.675 (CI: 0.684, 4.099)
Blurred vision – 42d[c]	Dichotomous	39	1	(2.6%)	39	0	(0.0%)	OR=3.078 (CI: 0.122, 77.905)
Constipation – 42d	Dichotomous	39	4	(10.3%)	39	2	(5.1%)	OR=2.114 (CI: 0.364, 12.279)
Dizziness – 42d	Dichotomous	39	5	(12.8%)	39	1	(2.6%)	OR=5.588 (CI: 0.621, 50.249)
Drowsiness – 42d[d]	Dichotomous	39	14	(35.9%)	39	4	(10.3%)	OR=4.900 (CI: 1.441, 16.664)
Dry mouth – 42d	Dichotomous	39	0	(0.0%)	39	1	(2.6%)	OR=0.325 (CI: 0.013, 8.223)
headache – 42d	Dichotomous	39	2	(5.1%)	39	3	(7.7%)	OR=0.649 (CI: 0.102, 4.113)
mental change – 42d[e]	Dichotomous	39	3	(7.7%)	39	0	(0.0%)	OR=7.575 (CI: 0.378, 151.723)

	mood disturbance – 42d	Dichotomous	39	1	(2.6%)	39	1	(2.6%)	OR=1.000 (CI: 0.060, 16.577)
	Nausea – 42d	Dichotomous	39	3	(7.7%)	39	2	(5.1%)	OR=1.542 (CI: 0.243, 9.776)
	oedema – 42d	Dichotomous	39	1	(2.6%)	39	1	(2.6%)	OR=1.000 (CI: 0.060, 16.577)
	sleep disturbance – 42d	Dichotomous	39	1	(2.6%)	39	0	(0.0%)	OR=3.078 (CI: 0.122, 77.905)
	urination difficulties – 42d[f]	Dichotomous	39	6	(15.4%)	39	1	(2.6%)	OR=6.909 (CI: 0.791, 60.377)
	Urine retention – 42d	Dichotomous	39	1	(2.6%)	39	0	(0.0%)	OR=3.078 (CI: 0.122, 77.905)
	treatment withdrawal:								
	due to lack of efficacy – 42d	Dichotomous	39	5[g]	(12.8%)	39	5	(12.8%)	OR=1.000 (CI: 0.265, 3.772)
	unspecified/other reason – 42d	Dichotomous	39	1[h]	(2.6%)	39	0	(0.0%)	OR=3.078 (CI: 0.122, 77.905)
	use of rescue medication:								
	500 mg paracetamol tablets per week – 0d	Continuous	35		14.3 (SD 13.9)	35		12.9 (SD 12.7)	
	500 mg paracetamol tablets per week – 0d	Continuous	35		14.3 (SD 13.9)	35		16.3 (SD 15.4)	
	500 mg paracetamol tablets per week – 0d	Continuous	35		16.3 (SD 15.4)	35		12.9 (SD 12.7)	
	500 mg paracetamol tablets per week – 0d	Continuous	35		16.3 (SD 15.4)	35		16.3 (SD 15.4)	
	500 mg paracetamol tablets per week – 42d	Continuous	0			0			
	50 mg tramadol tablets per week – 0d	Continuous	35		2.6 (SD 3.6)	35		2.6 (SD 3.6)	
	50 mg tramadol tablets per week – 42d	Continuous	35		2 (SD 2.6)	35		1.8 (SD 2.9)	MD=0.200 (CI: -1.090, 1.490)
	Per Protocol								
	pain score:								
	NRS/NRS Pain – 0d	Continuous	26		5.7 (SD 1.7)	26		5.7 (SD 1.7)	
	NRS/NRS Pain – 42d	Continuous	26		5 (SD 2.4)	26		5.1 (SD 2.5)	MD=-0.100 (CI: -1.432, 1.232)

[a] based on NRS Sleep
[b] fatigue for all and both fatigue and sleep disturbance for one patient (one of the patients with fatigue also withdrew because of lack of efficacy)
[c] reported as 'double vision'
[d] reported as 'tiredness'
[e] not otherwise specified
[f] 'micturition difficulties'
[g] 1 of these patients also withdrew because of an adverse event (fatigue)
[h] due to logistic problem (not otherwise described)

Comments	Study reports the use of tramadol (one of the other drugs being considered in this guideline) as rescue medication - there were a number of patients who were receiving this at baseline as a rescue medication (but it was not clear how many exactly); authors report pain relief on a 6-point categorical scale ranging from complete to worse as primary outcome; ITT performed with 35 patients for which data was available for both treatment periods using last observation carried forward (4 withdrew in the first treatment period and were not included in the ITT); 24 patients had previously been treated for polyneuropathic pain and 10 had tried several different types of drugs without success (ie. Imipramine, gabapentoids, SSRI, other anticonvulsants); authors recorded SF-36 scores but did not report the actual figures in the study

Definitions of abbreviations are given at the end of this document.

Study	Huse et al. (2001)
Pain category	Mixed (central and peripheral) or unclear if mixed
Study design	Country: Germany Design: Crossover Inclusion criteria: Unilateral amputees. Presence of phantom limb pain with an intensity of at least 3 on 10cm VAS with the end points no pain and

	unbearable pain aged between 18 and 75 years Exclusion criteria: neurological and psychiatric disorders, presence of severe illness, pregnancy or breastfeeding, women with insufficient contraceptive protection, presence of morphine-specific risk factors (known sensitivity, heightened brain pressure, hypotension with hypovolemia, hyperplasia of the prostate, biliary disease, obstructive and inflammatory bowel disease, pheochromocytoma, hypothyreosis) Study length (days): 70 Intention-to-treat analysis? Yes
Participants	Total number of patients: 12 Number of males: 10 (83.3%) Underlying cause of neuropathic pain: Phantomb limb pain Mean duration of NP (in months): not reported Baseline pain severity: 3.335 (VAS (average of means of phantomb limb [4.65] and stump pain [2.02])) Mean age: 50.58 (SD: 14.01)
Intervention(s)	(1) Morphine sulphate (oral) Intervention: morphine Length of treatment (weeks): 4 Fixed/flexible dose regimen: Flexible dose Range: 70–300 Notes: oral retarded morphine sulphate - treatment phase began with an intravenous morphine test to check response and to confirm no serious side effects before treatment commenced (70-100 mg in 7, 120-160 mg in 4, 300 mg in 1) (2) Placebo Intervention: placebo Length of treatment (weeks): 4 Fixed/flexible dose regimen: Flexible dose Notes: also began with a intravenous test phase
Concomitant treatments	Drug free baseline period? Yes (duration: 28d) Concomitant pain treatment allowed? Unclear (The following description is provided 'the use of all analgesic and psychotropic medication were also noted in a pain diary'. Acetylsalicylic acid or paracetamol up to 6 times 100 mg per day was allowed as rescue medication.)
Outcomes measures and effect sizes	

		MORPHINE SULPHATE (ORAL)			PLACEBO			
		N	k	mean	N	k	mean	Δ
pain score:								
VAS – 0d[a]	Continuous	12		4.05 (SD 1.06)	12		4.05 (SD 1.06)	
VAS – 28d[b]	Continuous	12		3.26 (SD 1.59)	12		3.99 (SD 1.23)	MD=-0.730 (CI: -1.867, 0.407)
at least 50% pain reduction (VAS) – 28d[b]	Dichotomous	12	5	(41.7%)	12	1	(8.3%)	OR=7.857 (CI: 0.752, 82.128)
adverse events:								
Constipation – 28d	Continuous	12		0.03 (SD 0.02)	12		0.02 (SD 0.02)	MD=0.010 (CI: -0.006, 0.026)
Dizziness – 28d	Continuous	12		1.27 (SD 1.8)	12		0.71 (SD 1.47)	MD=0.560 (CI: -0.755, 1.875)
Nausea – 28d	Continuous	12		0.74 (SD 1.24)	12		0.4 (SD 0.66)	MD=0.340 (CI: -0.455, 1.135)
tiredness – 28d	Continuous	12		2.21 (SD 1.84)	12		1.33 (SD 1.79)	MD=0.880 (CI: -0.572, 2.332)
urination difficulties – 28d	Continuous	12		0.01 (SD 0.01)	12		0 (SD 0)	MD=0.010 (CI: 0.004, 0.016)

	vertigo – 28d	Continuous	12	0.98 (SD 1.4)	12	0.42 (SD 0.92)	MD=0.560 (CI: -0.388, 1.508)
	[a] baseline for patients in all arms [b] authors transformed 2cm scales into 10cm scales						
Comments	The study was 12 weeks in duration, with a 4 week drug free baseline, 2 treatment phases of 4 weeks (including a titration period of 2 weeks) seperated by a washout period of 1-2 weeks. Follow up at 6 and 12 months. Authors transformed results from 2cm VAS scales into 10cm scales - this may affect the precision of scale						

Definitions of abbreviations are given at the end of this document.

Study	Irving et al. (2011)
Pain category	Peripheral pain
Study design	Country: USA Design: Parallel Inclusion criteria: Aged 18 and over with a diagnosis of PHN and an average NPRS score of 3-9 (inclusive) were eligible if at least 6 months had elapsed since vesicle crusting Exclusion criteria: Use of any topically applied pain medication on the painful area within 21 days before application of study patch. Pain at or around facial area, pregnancy or use of ineffective method of contraception, significant pain of an etiology other than PHN, current use of an investigational drug or class 1 antiarrhythmic drugs, uncontrolled hypertension, hypersensitivity to capsaicin, local anaesthetics, oxycodone hydrochloride, hydrocodone or adhesives, use of high-dose (> 60 mg/day morphine) opioids not orally or transdermally administered Study length (days): 84 Intention-to-treat analysis? Yes
Participants	Total number of patients: 416 Number of males: 190 (45.7%) Underlying cause of neuropathic pain: Post-herpetic neuralgia Mean duration of NP (in months): 22.4 Baseline pain severity: 5.75 (NRS (average of arm means)) Mean age: 70.3
Intervention(s)	(1) Capasaicin 8% single patch (60 minutes) Intervention: capsaicin patch Length of treatment (weeks): Fixed/flexible dose regimen: Fixed dose Notes: Study reports 8% capsaicin patch, applied for 60 minutes once then removed (topical anaesthetic cream applied 60 mins before patches) (2) Placebo patch (60 minutes) Intervention: placebo Length of treatment (weeks): Fixed/flexible dose regimen: Fixed dose Notes: applied for 1 hr then removed (topical anaesthetic cream applied 60 mins before patches)
Concomitant	Drug free baseline period? No

treatments	Concomitant pain treatment allowed? Yes (Paracetamol up to 3g/d (as rescue medications), stable dosage of anti-convulsants, non-SSRIs, opioids, NSAIDs, salicylates, or paracetamol for at least 21 days before the study patch application and through the study)

Outcomes measures and effect sizes

		CAPASAICIN 8% SINGLE PATCH (60 MINUTES)			PLACEBO PATCH (60 MINUTES)			
		N	k	mean	N	k	mean	Δ
pain score:								
NRS/NRS Pain – 0d	Continuous	212		5.7 (SD 1.6)	204		5.8 (SD 1.57)	
NRS/NRS Pain – 28d[a]	Percentage change from baseline	212		-33 (SD 36.4)	204		-23 (SD 35.7)	MD=-10.000 (CI: -16.930, -3.070)
NRS/NRS Pain – 35d[b]	Mean difference from baseline to average f-u	212		-1.7 (SD 1.75)	204		-1.3 (SD 1.71)	MD=-0.400 (CI: -0.733, -0.067)
NRS/NRS Pain – 49d[c]	Mean difference from baseline to average f-u	212		-1.7 (SD 1.75)	204		-1.4 (SD 1.71)	MD=-0.300 (CI: -0.633, 0.033)
NRS/NRS Pain – 56d[a]	Percentage change from baseline	212		-34.5 (SD 36.4)	204		-27 (SD 35.7)	MD=-7.500 (CI: -14.430, -0.570)
NRS/NRS Pain – 84d[a]	Percentage change from baseline	212		-34 (SD 36.4)	204		-27 (SD 35.7)	MD=-7.000 (CI: -13.930, -0.070)
at least 30% pain reduction (NRS) – 84d	Dichotomous	212	100	(47.2%)	204	71	(34.8%)	OR=1.673 (CI: 1.127, 2.482)
at least 50% pain reduction (NRS) – 84d	Dichotomous	212	63	(29.7%)	204	43	(21.1%)	OR=1.583 (CI: 1.012, 2.476)
patient-reported global improvement:								
PGIC - worse (all grades) or no change – 56d[d]	Dichotomous	212	73	(34.4%)	204	93	(45.6%)	OR=0.653 (CI: 0.435, 0.980)
PGIC - worse (all grades) or no change – 56d[d]	Dichotomous	192	73	(34.4%)	192	93	(45.6%)	OR=0.653 (CI: 0.435, 0.980)
PGIC - worse (all grades) or no change – 84d[d]	Dichotomous	212	79	(37.3%)	204	103	(50.5%)	OR=0.567 (CI: 0.381, 0.846)
PGIC - worse (all grades) or no change – 84d[d]	Dichotomous	202	79	(37.3%)	194	103	(50.5%)	OR=0.567 (CI: 0.381, 0.846)
PGIC - minimally better – 56d[d]	Dichotomous	212	48	(22.6%)	204	50	(24.5%)	OR=0.947 (CI: 0.598, 1.498)
PGIC - minimally better – 56d[d]	Dichotomous	192	48	(22.6%)	192	50	(24.5%)	OR=0.947 (CI: 0.598, 1.498)
PGIC - minimally better – 84d[d]	Dichotomous	212	40	(18.9%)	204	41	(20.1%)	OR=0.921 (CI: 0.565, 1.502)
PGIC - minimally better – 84d[d]	Dichotomous	202	40	(18.9%)	194	41	(20.1%)	OR=0.921 (CI: 0.565, 1.502)
PGIC - at least moderately better – 56d[d]	Dichotomous	192	71	(33.5%)	192	49	(24.0%)	OR=1.712 (CI: 1.106, 2.651)
PGIC - at least moderately better – 56d[d]	Dichotomous	212	71	(33.5%)	204	49	(24.0%)	OR=1.712 (CI: 1.106, 2.651)
PGIC - at least moderately better – 84d[d]	Dichotomous	202	83	(39.2%)	194	50	(24.5%)	OR=2.009 (CI: 1.311, 3.078)
PGIC - at least moderately better – 84d[d]	Dichotomous	212	83	(39.2%)	204	50	(24.5%)	OR=2.009 (CI: 1.311, 3.078)
major adverse events (defined as leading to withdrawal):								
any major adverse event – 84d	Dichotomous	212	3	(1.4%)	204	3	(1.5%)	OR=0.962 (CI: 0.192, 4.821)

adverse events:									
any adverse event – 84d	Dichotomous	212	208	(98.1%)	204	177	(86.8%)	OR=7.932 (CI: 2.723, 23.103)	
Dizziness – 84d	Dichotomous	212	3	(1.4%)	204	6	(2.9%)	OR=0.474 (CI: 0.117, 1.920)	
GI disorders – 84d[e]	Dichotomous	212	21	(9.9%)	204	22	(10.8%)	OR=0.910 (CI: 0.484, 1.710)	
headache – 84d	Dichotomous	212	4	(1.9%)	204	10	(4.9%)	OR=0.373 (CI: 0.115, 1.209)	
Infection – 84d	Dichotomous	212	37[f]	(17.5%)	204	37	(18.1%)	OR=0.954 (CI: 0.577, 1.577)	
Nausea – 84d	Dichotomous	212	11	(5.2%)	204	5	(2.5%)	OR=2.178 (CI: 0.743, 6.383)	
oedema – 84d	Dichotomous	212	13	(6.1%)	204	0	(0.0%)	OR=27.677 (CI: 1.634, 468.713)	
Pruritus – 84d	Dichotomous	212	6	(2.8%)	204	3	(1.5%)	OR=1.951 (CI: 0.481, 7.909)	
Rash – 84d[g]	Dichotomous	212	194	(91.5%)	204	141	(69.1%)	OR=4.816 (CI: 2.732, 8.489)	
site erythema – 84d	Dichotomous	212	194	(91.5%)	204	141	(69.1%)	OR=4.816 (CI: 2.732, 8.489)	
site pain – 84d	Dichotomous	212	134	(63.2%)	204	57	(27.9%)	OR=4.430 (CI: 2.928, 6.703)	
Vomiting – 84d	Dichotomous	212	6	(2.8%)	204	0	(0.0%)	OR=12.874 (CI: 0.721, 230.016)	
treatment withdrawal:									
due to lack of efficacy – 84d	Dichotomous	212	1	(0.5%)	204	5	(2.5%)	OR=0.189 (CI: 0.022, 1.629)	
unspecified/other reason – 84d	Dichotomous	212	7	(3.3%)	204	1	(0.5%)	OR=6.932 (CI: 0.845, 56.847)	
lost to follow-up – 84d	Dichotomous	212	4	(1.9%)	204	5	(2.5%)	OR=0.765 (CI: 0.203, 2.891)	
poor compliance – 84d	Dichotomous	212	3	(1.4%)	204	4	(2.0%)	OR=0.718 (CI: 0.159, 3.247)	

[a] percentage change from baseline; estimated from graph
[b] baseline to weeks 2 to 8
[c] baseline to weeks 2 to 12
[d] denominators inferred from percentages and appear to be subject to some rounding error
[e] includes nausea and vomiting
[f] includes sinusitis and upper respiratory tract infection
[g] described as site erythema in paper

Comments	while there was no drug-free baseline period, those on topical medications were required to stop 21 days before treatment with patch

Definitions of abbreviations are given at the end of this document.

Study	Kalso et al. (1995)
Pain category	Peripheral pain
Study design	Country: Finland Design: Crossover

	Inclusion criteria: patients recruited from a previous questionnaire study with neuropathic pain of moderate severity following treatment for breast cancer in the anterior chest wall, and/or axilla and/or medial upper arm in an area with sensory disturbance Exclusion criteria: relapses or metastases of breast cancer, clinically overt cardiac, renal or hepatic disease Study length (days): 70 Intention-to-treat analysis? No
Participants	Total number of patients: 20 Number of males: 0 (0.0%) Underlying cause of neuropathic pain: Post-surgical pain after surgery for cancer Mean duration of NP (in months): not reported Baseline pain severity: 4.15 (VAS (average of means of those in scar vs arm group) (age is median; median time since breast surgery was 45 months but it was not clear if the pain had existing throughout this period)) Mean age: 56
Intervention(s)	(1) Amitriptyline flexible dose Intervention: amitriptyline Length of treatment (weeks): 4 Fixed/flexible dose regimen: Flexible dose Range: 50–100 Notes: up to maximum tolerated dosage; 13 increased to 100 mg/d (4 tablets) while 2 stayed on 50 mg/d (2 tables) until the end of the study (2) Placebo Intervention: placebo Length of treatment (weeks): 4 Fixed/flexible dose regimen: Flexible dose
Concomitant treatments	Drug free baseline period? Unclear Concomitant pain treatment allowed? Unclear (patients were asked to refrain from using other pain killers during the study but if it was unavoidable that patients must take these, it was recorded in their diary (not clear if this included anti-convulsants or other anti-depressants))

Outcomes measures and effect sizes

		AMITRIPTYLINE FLEXIBLE DOSE			PLACEBO			
		N	k	mean	N	k	mean	Δ
pain score:								
VRS – 28d	Continuous	11			11			MD=-1.838 (CI: -2.961, -0.715)
adverse events:								
Constipation – 28d	Dichotomous	13	8	(61.5%)	13	1	(7.7%)	OR=19.200 (CI: 1.876, 196.539)
Dizziness	Dichotomous	13	1	(7.7%)	13	0	(0.0%)	OR=3.240 (CI: 0.120, 87.125)
Drowsiness[a]	Dichotomous	13	12	(92.3%)	13	8	(61.5%)	OR=7.500 (CI: 0.733, 76.773)
Dry mouth	Dichotomous	13	12	(92.3%)	13	5	(38.5%)	OR=19.200 (CI: 1.876, 196.539)
headache	Dichotomous	13	2	(15.4%)	13	5	(38.5%)	OR=0.291 (CI: 0.045, 1.898)
loss of appetite	Dichotomous	13	3	(23.1%)	13	3	(23.1%)	OR=1.000 (CI: 0.161, 6.200)
Nausea	Dichotomous	13	0	(0.0%)	13	2	(15.4%)	OR=0.170 (CI: 0.007, 3.923)
nightmares	Dichotomous	13	6	(46.2%)	13	5	(38.5%)	OR=1.371 (CI: 0.288, 6.535)
palpitation	Dichotomous	13	6	(46.2%)	13	4	(30.8%)	OR=1.929 (CI: 0.387, 9.601)
urination difficulties	Dichotomous	13	3	(23.1%)	13	1	(7.7%)	OR=3.600 (CI: 0.322, 40.233)

	patients with ipsilateral arm pain							
	pain score:							
	VAS – 0d	Continuous	13		med: 5 [rng 1.7–7.1]	13	med: 5 [rng 1.7–7.1]	
	VAS – 28d	Continuous	11		med: 0.5 [rng 0–3]	11	med: 5 [rng 0–9.4]	
	McGill Pain Questionnaire – 0d	Continuous	13		med: 275 [rng 49–654]	13	med: 275 [rng 49–654]	
	McGill Pain Questionnaire – 28d	Continuous	11		med: 205 [rng 0–404]	11	med: 165 [rng 0–582]	
	VRS – 0d[b]	Continuous	13		3.2 (SD 1.08)	13	3.2 (SD 1.44)	
	VRS – 28d[b]	Continuous	11		0.9 (SD 0.995)	11	3.2 (SD 1.99)	MD=-2.300 (CI: -3.615, -0.985)
	patient-reported improvement in daily physical and emotional functioning, including sleep:							
	disturbed sleep – 0d	Dichotomous	13	8	(61.5%)	13	8 (61.5%)	
	disturbed sleep – 28d	Dichotomous	11	1	(9.1%)	11	6 (54.5%)	OR=0.083 (CI: 0.008, 0.895)
	patients with breast scar pain							
	pain score:							
	VAS – 0d	Continuous	12		med: 3.3 [rng 1.4–6.2]	12	med: 3.3 [rng 1.4–6.2]	
	VAS – 28d	Continuous	10		med: 0.2 [rng 0–4.3]	10	med: 3.1 [rng 0.7–5.5]	
	McGill Pain Questionnaire – 0d	Continuous	12		med: 326 [rng 154–618]	12	med: 326 [rng 154–618]	
	McGill Pain Questionnaire – 28d	Continuous	10		med: 58 [rng 0–305]	10	med: 235 [rng 59–661]	
	VRS – 0d[b]	Continuous	12		2.8 (SD 1.04)	12	2.7 (SD 1.04)	
	VRS – 28d[b]	Continuous	10		1.15 (SD 1.11)	10	2.48 (SD 0.949)	MD=-1.330 (CI: -2.233, -0.427)
	patient-reported improvement in daily physical and emotional functioning, including sleep:							
	disturbed sleep – 0d	Dichotomous	12	6	(50.0%)	12	6 (50.0%)	
	disturbed sleep – 28d	Dichotomous	10	0	(0.0%)	10	6 (60.0%)	OR=0.033 (CI: 0.002, 0.718)
	[a] 'tired' [b] 8 point; mean and its dispersion (assumed to be SEM) extracted from graph							
Comments	3 patients had undergone a modified radical mastectomy and 12 breast conserving surgery; 10/15 had pain in both ipsilateral arm and breast scar region, 2/16 had only breast scar pain and 3/15 had only ipsilateral arm pain; 11 of the 12 with breast scar pain had received postoperative radiotherapy and the other had 2 unsuccessful breast repair operations but did not have postoperative radiotherapy); 5/13 of those with ipsilateral pain had postoperative radiotherapy; none had chemotherapy; 5 patients withdrew (4 because of feeling tired and 1 because of noncompliance) but it was not reported which treatment these patients were receiving at the time of withdrawal; unclear if patient who withdrew from the placebo arm was included in the efficacy results; it apepars that the results presented are separated by those who achieved 50 mg/d and those who achieved 100 mg/d (2 less than 50 mg/d) - only the results for 100 mg/d per day were extracted since it appears that the results for 50 mg/d includes those patients that took 100 mg/d - consequently, these results are likely to include patients who took 50 mg/d at earlier time points (before 28 days)							

Definitions of abbreviations are given at the end of this document.

Study	Kautio et al. (2008)
Pain category	Peripheral pain
Study design	Country: Finland Design: Parallel Inclusion criteria: Cancer and chemotherapy induced neuropathic pain of at least 3 on the NRS 11 point scale Exclusion criteria: neurological disease confusing assessment of symptoms or other possible causes of neuropathy, concomitant medication inhibiting

	norepinephrine uptake, contraindications for amitriptyline (ie. Urinary hesitation), pregnancy or lactating women Study length (days): 56 Intention-to-treat analysis? No
Participants	Total number of patients: 42 Number of males: 12 (28.6%) Underlying cause of neuropathic pain: Chemotherapy-induced pain Mean duration of NP (in months): not reported Baseline pain severity: not reported (not reported) Mean age: 54
Intervention(s)	(1) Amitriptyline up to 50mg/d (most patients) Intervention: amitriptyline Length of treatment (weeks): 8 Fixed/flexible dose regimen: Flexible dose Range: 10–50 Notes: 10 mg/d to start, then increased by 10 mg per week until 50 mg/d if tolerated (dose was reduced 10-25 mg; 15 of 17 patients tolerated the 50 mg/d while 1 reduced from 30 to 10 mg because of tiredness and antoehr from 50 to 25 mg because of tachycardia) (2) Placebo Intervention: placebo Length of treatment (weeks): 8 Fixed/flexible dose regimen: Fixed dose
Concomitant treatments	Drug free baseline period? No Concomitant pain treatment allowed? Unclear (only information about concomitant medications was that those inhibiting norepinephrine uptake were not allowed (not clear about other pain medications))
Outcomes measures and effect sizes	

		AMITRIPTYLINE UP TO 50MG/D (MOST PATIENTS)			PLACEBO			
		N	k	mean	N	k	mean	Δ
major adverse events (defined as leading to withdrawal):								
any major adverse event – 56d[a]	Dichotomous	17	0	(0.0%)	16	3	(18.8%)	OR=0.110 (CI: 0.005, 2.320)
treatment withdrawal:								
unspecified/other reason – 56d	Dichotomous	22	2	(9.1%)	22	2	(9.1%)	OR=1.000 (CI: 0.128, 7.812)
poor compliance – 56d	Dichotomous	22	1	(4.5%)	22	1	(4.5%)	OR=1.000 (CI: 0.059, 17.065)

[a] details of adverse events not reported

Comments	2 additional patients withdrew after randomisation but it was not clear what group they were in - one died (details unspecified) and another withdrew consent before receiving treatment; as a result, denominators used in safety analyses were numbers randomised; study also reported global improvement on a 5-point VRS but it was not possible to compare this with the other studies which reported global improvement on 7 point scales - consequently, this was not extracted

Definitions of abbreviations are given at the end of this document.

Study	Khoromi et al. (2005)
Pain category	Peripheral pain
Study design	Country: USA Design: Crossover Inclusion criteria: age 18-75, evidence of lumbar radiculopathy on the basis of pain in one or both buttocks or legs for at least 3 months for at least 5 days per week and at least one of the following: sharp & shooting pain below the knee, pain evoked by straight leg raising to 60 degrees or less, decreased/absent ankle reflex, weakness of muscles below knee, sensory loss in L4/S1 distribution, electromyographic evidence of L4, L5, or S1 root denervation, imaging evidence of nerve root compression in the lower lumbar region Exclusion criteria: hetaptic and renal dysfunction, pregnancy or lactation, seizure disorder, pain of greater intensity in any other location than the low back or leg, narcotic abuse and/or drug or alcohol abuse in past yeawr, fibromyalgia as defined by American College of Rheumatcology criteria, polyneuropathy and peripheral vascular disease, history of neprolithiasis, narrow angle glaucoma Study length (days): 98 Intention-to-treat analysis? No
Participants	Total number of patients: 42 Number of males: 23 (54.8%) Underlying cause of neuropathic pain: Radiculopathy Mean duration of NP (in months): 75 Baseline pain severity: 4.04 (NRS leg pain (duration of pain and age is average of median ages for the 29 completers and 14 drop outs)) Mean age: 56.75
Intervention(s)	(1) Topiramate 50-400 mg Intervention: topiramate Length of treatment (weeks): 6 Fixed/flexible dose regimen: Flexible dose Range: 50–400 Notes: dosages started at 50 mg in 2 divided dosages the first week and increased by increments of 50 mg in each dosage during weeks 3 and 4 up to a maximum of 400 mg (2) Active placebo (diphenhydramine 6.25-50mg) Intervention: placebo Length of treatment (weeks): 6 Fixed/flexible dose regimen: Flexible dose Range: 6.25–50 Notes: diphenhydramine was used as active placebo because of its side effects (mainly sedation and anticholinergic effects which overlap with those of topiramate); it was started at 6.25mg twice per day in week 1 and then increased by 6.25 mg increments in each dose during week 1 and 2 and then 12.5 mg in week 3 to a maximum of to 50 mg/day in 2 divided dosages; any side effects that were untolerable or interfered with patient's activities resulted in a decrease to the prior dosage
Concomitant treatments	Drug free baseline period? Unclear Concomitant pain treatment allowed? Yes (many patients were taking NSAIDs at baseline, 11 were taking opioids, 11 anti-depressants but none were taking anti-convulsants at baseline; it is assumed patients continued on these during the study as it was not stated otherwise)

Outcomes measures and effect sizes

		TOPIRAMATE 50-400 MG			ACTIVE PLACEBO (DIPHENHYDRAMINE 6.25-50MG)			
		N	k	mean	N	k	mean	Δ
pain score:								
NRS/NRS Pain – 0d[a]	Continuous	29		4.63	29		4.63	
NRS/NRS Pain – 42d[a]	Continuous	29		4.3	29		5.12	MD=-0.820
major adverse events (defined as leading to withdrawal):								
any major adverse event – 42d	Dichotomous	41	10	(24.4%)	41	1[b]	(2.4%)	OR=12.903 (CI: 1.567, 106.264)
adverse events:								
any adverse event – 42d[c]	Dichotomous	41	36	(87.8%)	41	30	(73.2%)	OR=2.640 (CI: 0.825, 8.446)
Blurred vision – 42d	Dichotomous	41	1[c]	(2.4%)	41	0	(0.0%)	OR=3.074 (CI: 0.122, 77.692)
Constipation – 42d	Dichotomous	41	3[b]	(7.3%)	41	0	(0.0%)	OR=7.545 (CI: 0.377, 150.869)
decreased libido – 42d	Dichotomous	41	1[c]	(2.4%)	41	0	(0.0%)	OR=3.074 (CI: 0.122, 77.692)
depression – 42d	Dichotomous	41	3[b]	(7.3%)	41	0	(0.0%)	OR=7.545 (CI: 0.377, 150.869)
Diarrhoea – 42d[c]	Dichotomous	41	13	(31.7%)	41	4	(9.8%)	OR=4.295 (CI: 1.264, 14.597)
Fatigue – 42d	Dichotomous	41	14[d]	(34.1%)	41	13[e]	(31.7%)	OR=1.117 (CI: 0.444, 2.807)
headache – 42d[c]	Dichotomous	41	4	(9.8%)	41	4	(9.8%)	OR=1.000 (CI: 0.232, 4.301)
oedema – 42d	Dichotomous	41	1[c]	(2.4%)	41	0	(0.0%)	OR=3.074 (CI: 0.122, 77.692)
Sedation – 42d[c]	Dichotomous	41	14	(34.1%)	41	1	(2.4%)	OR=20.741 (CI: 2.574, 167.128)
slurred speech – 42d	Dichotomous	41	1[c]	(2.4%)	41	0	(0.0%)	OR=3.074 (CI: 0.122, 77.692)
thirsty/dehydrated – 42d	Dichotomous	41	1[c]	(2.4%)	41	0	(0.0%)	OR=3.074 (CI: 0.122, 77.692)
tremor – 42d	Dichotomous	41	0	(0.0%)	41	1[c]	(2.4%)	OR=0.325 (CI: 0.013, 8.221)
urination difficulties – 42d	Dichotomous	41	1[c]	(2.4%)	41	0	(0.0%)	OR=3.074 (CI: 0.122, 77.692)
leg pain								
pain score:								
NRS/NRS Pain – 0d	Continuous	29		4.04	29		4.04	
NRS/NRS Pain – 42d	Continuous	29		3.06	29		3.8	MD=-0.740
back pain								
pain score:								
NRS/NRS Pain – 0d	Continuous	29		4.69	29		4.69	
NRS/NRS Pain – 42d	Continuous	29		3.33	29		4.2	MD=-0.870

[a] average overall
[b] estimated from percentages
[c] approximated to nearest integer (percentages only presented in text)
[d] reported as 'fatigue/weakness'; approximated to nearest integer (percentages only presented in text)
[e] reported as 'fatigue/weakness'; estimated from percentages

Comments

there was a 2-week taper period between dosages (it is unclear how long the drug-free or wash-out period was in this 2 week period but it was assumed to be similar to the study by the same authors, Khoromi 2007, which was 4 days); no significant period or carry-over effect found; there appears to be a 2-week baseline period but it is not clear if this was a drug-free period; 1 patient dropped out prior to randomisation; many patients were taking NSAIDs at baseline, 11 were taking opioids, 11 anti-depressants but none were taking anti-convulsants; an additional patient dropped out after screening because of ECG showing incidental cardiac abnormality but it was not clear what treatment sequence they had been randomised to

Definitions of abbreviations are given at the end of this document.

Study	Khoromi et al. (2007)
Pain category	Peripheral pain
Study design	Country: USA Design: Crossover Inclusion criteria: 18-65 years old with lumbar radiculopathy including pain in one or both buttocks or legs for 3 months or greater for at least 5 days a week (and at least one of the following features: sharp and shooting pain below the knee, pain evoked by straight leg raising to 60 degrees or less, decreased or absent ankle reflex, weakness of msucles below the knee, sensory loss of L5/S1 distribution, electromyographic evidence for L4, L5, or S1 root denervation, imaging evidence of nerve root compression in the lower lumbar region, average pain of at least 4 on a NRS (11-point) Exclusion criteria: serious medical illness involving other organ systems including diabetes, cancer, prostatic disease requiring urological medications, pregnancy or lactation, history of depression requiring antidepressants within 6 months before study or score of 20 or more on the Beck Depression Inventory, history of narcotic or alcohol abuse, narrow angle glaucoma, seizure disorder, fibromyalgia, pain of greater intensity in any other location than the low back or leg, polyneuropathy or peripheral vascular disease associated with numbness or burning pain in lower extremities, allergy to study drugs, evidence of multisomatoform disorder as assessed by 15-item questionnaire (PHQ-15), unwillingness to be tapered off opioids and then maintained drug-free for 2 weeks prior to randomisation to study medication Study length (days): 266 Intention-to-treat analysis? Yes
Participants	Total number of patients: 55 Number of males: 30 (54.5%) Underlying cause of neuropathic pain: Radiculopathy Mean duration of NP (in months): 60 Baseline pain severity: 4.5 (NRS (baseline data of 28 patients who completed the trial) (age and duration of pain is median)) Mean age: 53
Intervention(s)	(1) Morphine (15-90 mg) Intervention: morphine Length of treatment (weeks): 7 Fixed/flexible dose regimen: Flexible dose Mean dose: 62mg/d Range: 15–90 Notes: 5 weeks dose escalation, 2 weeks maintenance at highest tolerated dosages, 2 weeks dose tapering (2) Nortriptyline (25-100 mg) Intervention: nortriptyline Length of treatment (weeks): 7 Fixed/flexible dose regimen: Flexible dose Mean dose: 84mg/d Range: 25–100 Notes: 5 weeks dose escalation, 2 weeks maintenance at highest tolerated dosages, 2 weeks dose tapering (3) Morphine + nortriptyline Intervention: nortriptyline+morphine Length of treatment (weeks): 7

	Fixed/flexible dose regimen: Flexible dose Notes: 5 weeks dose escalation, 2 weeks maintenance at highest tolerated dosages, 2 weeks dose tapering; mean nortriptyline dosage was 55 mg/day and morphine was 49 mg/day (maximum was 100 mg/d nortriptyline and 90 mg/d morphine) (4) Active placebo (benztropine) Intervention: placebo Length of treatment (weeks): 9 Fixed/flexible dose regimen: Flexible dose Notes: benztrophine 0.25-1 mg (used to cause side effects like ddry mouth and mild constipation to mimic both drugs);2 weeks maintenance at highest tolerated dosages, 2 weeks dose tapering
Concomitant treatments	Drug free baseline period? Yes (duration: 14d) Concomitant pain treatment allowed? Yes (patients were asked not to take opioids - for which there was an initial 2-week drug-free period, SSRIs or tricylic medications; anti-inflammatory medications and acetaminophen were allowed as rescue analgesics up to 6 tablets per day (were not able to make changes to any other non-study medications taken for sciatica so it appears some were allowed))

Outcomes measures and effect sizes

		MORPHINE (15-90 MG)			ACTIVE PLACEBO (BENZTROPINE)			
		N	k	mean	N	k	mean	Δ
pain score:								
NRS/NRS Pain – 0d[a]	Continuous	28		5 (SD 2.25)	28		5 (SD 2.25)	
NRS/NRS Pain – 42d[a]	Continuous	28		3.8 (SD 2.5)	28		3.9 (SD 2.4)	MD=-0.100 (CI: -1.384, 1.184)
patient-reported improvement in daily physical and emotional functioning, including sleep:								
BDI – 0d[b]	Continuous	28		8 (SD 6.7)	28		8 (SD 6.7)	
BDI – 42d[b]	Continuous	28		9.6 (SD 8.5)	28		9 (SD 8.5)	MD=0.600 (CI: -3.852, 5.052)
major adverse events (defined as leading to withdrawal):								
any major adverse event – 42d	Dichotomous	55	5[c]	(9.1%)	55	1[d]	(1.8%)	OR=5.400 (CI: 0.610, 47.828)
adverse events:								
abdominal pain – 42d	Dichotomous	55	1[e]	(1.8%)	55	0	(0.0%)	OR=3.055 (CI: 0.122, 76.643)
any adverse event – 42d[f]	Dichotomous	55	26	(47.3%)	55	14	(25.5%)	OR=2.626 (CI: 1.174, 5.874)
Blurred vision – 42d[f]	Dichotomous	55	2	(3.6%)	55	3	(5.5%)	OR=0.654 (CI: 0.105, 4.076)
Constipation – 42d[f]	Dichotomous	55	18	(32.7%)	55	2	(3.6%)	OR=12.892 (CI: 2.820, 58.946)
Dizziness – 42d	Dichotomous	55	4[f]	(7.3%)	55	1[e]	(1.8%)	OR=4.235 (CI: 0.458, 39.171)
Drowsiness – 42d	Dichotomous	55	7[f]	(12.7%)	55	1[e]	(1.8%)	OR=7.875 (CI: 0.935, 66.337)
Dry mouth – 42d[e]	Dichotomous	55	6	(10.9%)	55	6	(10.9%)	OR=1.000 (CI: 0.302, 3.316)
Fatigue – 42d[g]	Dichotomous	55	2	(3.6%)	55	5	(9.1%)	OR=0.377 (CI: 0.070, 2.034)
headache – 42d[f]	Dichotomous	55	4	(7.3%)	55	4	(7.3%)	OR=1.000 (CI: 0.237, 4.217)
heartburn – 42d[e]	Dichotomous	55	1	(1.8%)	55	1	(1.8%)	OR=1.000 (CI: 0.061, 16.401)
loss of appetite – 42d	Dichotomous	55	2[h]	(3.6%)	55	0[i]	(0.0%)	OR=5.187 (CI: 0.243, 110.569)
Nausea – 42d	Dichotomous	55	2[f]	(3.6%)	55	0	(0.0%)	OR=5.187 (CI: 0.243, 110.569)
Sexual dysfunction – 42d	Dichotomous	55	3[f]	(5.5%)	55	0	(0.0%)	OR=7.400 (CI: 0.373, 146.730)
sleep disturbance – 42d	Dichotomous	55	2[j]	(3.6%)	55	0[k]	(0.0%)	OR=5.187 (CI: 0.243, 110.569)
thirsty/dehydrated – 42d	Dichotomous	55	0	(0.0%)	55	0	(0.0%)	OR=1.000 (CI: 0.019, 51.293)
urination difficulties – 42d	Dichotomous	55	1[e]	(1.8%)	55	0	(0.0%)	OR=3.055 (CI: 0.122, 76.643)
weakness – 42d	Dichotomous	55	0	(0.0%)	55	2[f]	(3.6%)	OR=0.193 (CI: 0.009, 4.110)
Weight gain – 42d	Dichotomous	55	0	(0.0%)	55	0	(0.0%)	OR=1.000 (CI: 0.019, 51.293)
overall improvement in quality of life:								
SF36 Physical – 0d	Continuous	28		48 (SD 26)	28		48 (SD 26)	

SF36 Physical – 42d	Continuous	28		56 (SD 27)	28		51.3 (SD 25.8)	MD=4.700 (CI: -9.132, 18.532)
SF36 general health – 0d	Continuous	28		68 (SD 20)	28		68 (SD 20)	
SF36 general health – 42d	Continuous	28		61 (SD 23)	28		61 (SD 23)	MD=0.000 (CI: -12.048, 12.048)
SF36 mental health – 0d	Continuous	28		74 (SD 16)	28		74 (SD 16)	
SF36 mental health – 42d	Continuous	28		68 (SD 21)	28		69 (SD 24)	MD=-1.000 (CI: -12.812, 10.812)
treatment withdrawal:								
due to lack of efficacy – 42d	Dichotomous	55	0	(0.0%)	55	3	(5.5%)	OR=0.135 (CI: 0.007, 2.680)
unspecified/other reason – 42d	Dichotomous	55	4[l]	(7.3%)	55	4[m]	(7.3%)	OR=1.000 (CI: 0.237, 4.217)
poor compliance – 42d	Dichotomous	55	0	(0.0%)	55	1	(1.8%)	OR=0.327 (CI: 0.013, 8.212)
leg pain								
pain score:								
NRS/NRS Pain – 0d[n]	Continuous	28		4.9 (SD 2.43)	28		4.9 (SD 2.43)	
NRS/NRS Pain – 42d[n]	Continuous	28		3.4 (SD 2.8)	28		3.7 (SD 2.7)	MD=-0.300 (CI: -1.741, 1.141)
back pain								
pain score:								
NRS/NRS Pain – 0d[n]	Continuous	28		4.5 (SD 2.4)	28		4.5 (SD 2.4)	
NRS/NRS Pain – 42d[n]	Continuous	28		3.4 (SD 2.5)	28		3.8 (SD 2.5)	MD=-0.400 (CI: -1.710, 0.910)

[a] overall pain; type of dispersion not stated, but appears to be standard deviation
[b] it was unclear how many patients were included in this outcome
[c] 2 sedation, 1 rash, 1 severe dry mouth, and 1 nausea, vomiting and severe constipation
[d] sedation
[e] approximated to nearest integer (percentages only presented in text)
[f] estimated from percentages
[g] tired/fatigue; estimated from percentages
[h] decreased appetite; estimated from percentages
[i] decreased appetite
[j] insomnia; estimated from percentages
[k] insomnia
[l] 3 moved away and 1 withdrew for personal reasons
[m] 3 moved away and 1 because of unrelated surgery
[n] type of dispersion not stated, but appears to be standard deviation

		NORTRIPTYLINE (25-100 MG)			ACTIVE PLACEBO (BENZTROPINE)			
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**
pain score:								
NRS/NRS Pain – 0d[a]	Continuous	28		5 (SD 2.25)	28		5 (SD 2.25)	
NRS/NRS Pain – 42d[a]	Continuous	28		3.2 (SD 2.4)	28		3.9 (SD 2.4)	MD=-0.700 (CI: -1.957, 0.557)
patient-reported improvement in daily physical and emotional functioning, including sleep:								
BDI – 0d[b]	Continuous	28		8 (SD 6.7)	28		8 (SD 6.7)	
BDI – 42d[b]	Continuous	28		7.3 (SD 7.1)	28		9 (SD 8.5)	MD=-1.700 (CI: -5.802, 2.402)
major adverse events (defined as leading to withdrawal):								
any major adverse event – 42d[c]	Dichotomous	55	2	(3.6%)	55	1	(1.8%)	OR=2.038 (CI: 0.179, 23.151)
adverse events:								
abdominal pain – 42d	Dichotomous	55	1[d]	(1.8%)	55	0	(0.0%)	OR=3.055 (CI: 0.122, 76.643)
any adverse event – 42d[e]	Dichotomous	55	19	(34.5%)	55	14	(25.5%)	OR=1.546 (CI: 0.679, 3.519)
Blurred vision – 42d	Dichotomous	55	0	(0.0%)	55	3[e]	(5.5%)	OR=0.135 (CI: 0.007, 2.680)

Constipation – 42d[e]	Dichotomous	55	7	(12.7%)	55	2	(3.6%)	OR=3.865 (CI: 0.765, 19.514)
Dizziness – 42d	Dichotomous	55	2[e]	(3.6%)	55	1[d]	(1.8%)	OR=2.038 (CI: 0.179, 23.151)
Drowsiness – 42d	Dichotomous	55	2[e]	(3.6%)	55	1[d]	(1.8%)	OR=2.038 (CI: 0.179, 23.151)
Dry mouth – 42d	Dichotomous	55	10[e]	(18.2%)	55	6[d]	(10.9%)	OR=1.815 (CI: 0.610, 5.398)
Fatigue – 42d[f]	Dichotomous	55	3	(5.5%)	55	5	(9.1%)	OR=0.577 (CI: 0.131, 2.542)
headache – 42d[e]	Dichotomous	55	2	(3.6%)	55	4	(7.3%)	OR=0.481 (CI: 0.084, 2.742)
heartburn – 42d	Dichotomous	55	2[e]	(3.6%)	55	1[d]	(1.8%)	OR=2.038 (CI: 0.179, 23.151)
loss of appetite – 42d[g]	Dichotomous	55	0	(0.0%)	55	0	(0.0%)	OR=1.000 (CI: 0.019, 51.293)
Nausea – 42d	Dichotomous	55	0	(0.0%)	55	0	(0.0%)	OR=1.000 (CI: 0.019, 51.293)
Sexual dysfunction – 42d	Dichotomous	55	0	(0.0%)	55	0	(0.0%)	OR=1.000 (CI: 0.019, 51.293)
sleep disturbance – 42d	Dichotomous	55	3[h]	(5.5%)	55	0[i]	(0.0%)	OR=7.400 (CI: 0.373, 146.730)
thirsty/dehydrated – 42d	Dichotomous	55	2[e]	(3.6%)	55	0	(0.0%)	OR=5.187 (CI: 0.243, 110.569)
urination difficulties – 42d	Dichotomous	55	1[d]	(1.8%)	55	0	(0.0%)	OR=3.055 (CI: 0.122, 76.643)
weakness – 42d	Dichotomous	55	0	(0.0%)	55	2[e]	(3.6%)	OR=0.193 (CI: 0.009, 4.110)
Weight gain – 42d	Dichotomous	55	2[e]	(3.6%)	55	0	(0.0%)	OR=5.187 (CI: 0.243, 110.569)
overall improvement in quality of life:								
SF36 Physical – 0d	Continuous	28		48 (SD 26)	28		48 (SD 26)	
SF36 Physical – 42d	Continuous	28		64 (SD 27)	28		51.3 (SD 25.8)	MD=12.700 (CI: -1.132, 26.532)
SF36 general health – 0d	Continuous	28		68 (SD 21)	28		68 (SD 20)	
SF36 general health – 42d	Continuous	28		67 (SD 21)	28		61 (SD 23)	MD=6.000 (CI: -5.536, 17.536)
SF36 mental health – 0d	Continuous	28		74 (SD 16)	28		74 (SD 16)	
SF36 mental health – 42d	Continuous	28		79 (SD 16)	28		69 (SD 24)	MD=10.000 (CI: -0.684, 20.684)
treatment withdrawal:								
due to lack of efficacy – 42d	Dichotomous	55	0	(0.0%)	55	3	(5.5%)	OR=0.135 (CI: 0.007, 2.680)
unspecified/other reason – 42d	Dichotomous	55	1[j]	(1.8%)	55	4[k]	(7.3%)	OR=0.236 (CI: 0.026, 2.184)
poor compliance – 42d	Dichotomous	55	0	(0.0%)	55	1	(1.8%)	OR=0.327 (CI: 0.013, 8.212)
leg pain								
pain score:								
NRS/NRS Pain – 0d[l]	Continuous	28		4.9 (SD 2.43)	28		4.9 (SD 2.43)	
NRS/NRS Pain – 42d[l]	Continuous	28		3 (SD 2.7)	28		3.7 (SD 2.7)	MD=-0.700 (CI: -2.114, 0.714)
back pain								
pain score:								
NRS/NRS Pain – 0d[l]	Continuous	28		4.5 (SD 2.4)	28		4.5 (SD 2.4)	
NRS/NRS Pain – 42d[l]	Continuous	28		2.9 (SD 2.4)	28		3.8 (SD 2.5)	MD=-0.900 (CI: -2.184, 0.384)

[a] overall pain; type of dispersion not stated, but appears to be standard deviation
[b] it was unclear how many patients were included in this outcome
[c] sedation
[d] approximated to nearest integer (percentages only presented in text)
[e] estimated from percentages
[f] tired/fatigue; estimated from percentages
[g] decreased appetite
[h] insomnia; estimated from percentages
[i] insomnia
[j] unrelated medical problem
[k] 3 moved away and 1 because of unrelated surgery
[l] type of dispersion not stated, but appears to be standard deviation

	MORPHINE + NORTRIPTYLINE			ACTIVE PLACEBO (BENZTROPINE)			
	N	k	mean	N	k	mean	Δ

pain score:								
NRS/NRS Pain – 0d[a]	Continuous	28		5 (SD 2.25)	28		5 (SD 2.25)	
NRS/NRS Pain – 42d[a]	Continuous	28		3.4 (SD 2.5)	28		3.9 (SD 2.4)	MD=-0.500 (CI: -1.784, 0.784)
patient-reported improvement in daily physical and emotional functioning, including sleep:								
BDI – 0d[b]	Continuous	28		8 (SD 6.7)	28		8 (SD 6.7)	
BDI – 42d[b]	Continuous	28		6 (SD 5)	28		9 (SD 8.5)	MD=-3.000 (CI: -6.653, 0.653)
major adverse events (defined as leading to withdrawal):								
any major adverse event – 42d	Dichotomous	55	4[c]	(7.3%)	55	1[d]	(1.8%)	OR=4.235 (CI: 0.458, 39.171)
adverse events:								
abdominal pain – 42d	Dichotomous	55	2[e]	(3.6%)	55	0	(0.0%)	OR=5.187 (CI: 0.243, 110.569)
any adverse event – 42d[e]	Dichotomous	55	25	(45.5%)	55	14	(25.5%)	OR=2.440 (CI: 1.090, 5.465)
Blurred vision – 42d	Dichotomous	55	1[f]	(1.8%)	55	3[e]	(5.5%)	OR=0.321 (CI: 0.032, 3.186)
Constipation – 42d	Dichotomous	55	20[f]	(36.4%)	55	2[e]	(3.6%)	OR=15.143 (CI: 3.329, 68.887)
Dizziness – 42d[f]	Dichotomous	55	1	(1.8%)	55	1	(1.8%)	OR=1.000 (CI: 0.061, 16.401)
Drowsiness – 42d	Dichotomous	55	3[e]	(5.5%)	55	1[f]	(1.8%)	OR=3.115 (CI: 0.314, 30.918)
Dry mouth – 42d[f]	Dichotomous	55	8	(14.5%)	55	6	(10.9%)	OR=1.390 (CI: 0.448, 4.310)
Fatigue – 42d[g]	Dichotomous	55	3	(5.5%)	55	5	(9.1%)	OR=0.577 (CI: 0.131, 2.542)
headache – 42d[e]	Dichotomous	55	4	(7.3%)	55	4	(7.3%)	OR=1.000 (CI: 0.237, 4.217)
heartburn – 42d	Dichotomous	55	0	(0.0%)	55	1[f]	(1.8%)	OR=0.327 (CI: 0.013, 8.212)
loss of appetite – 42d	Dichotomous	55	1[h]	(1.8%)	55	0[i]	(0.0%)	OR=3.055 (CI: 0.122, 76.643)
Nausea – 42d	Dichotomous	55	1[f]	(1.8%)	55	0	(0.0%)	OR=3.055 (CI: 0.122, 76.643)
Sexual dysfunction – 42d	Dichotomous	55	1[f]	(1.8%)	55	0	(0.0%)	OR=3.055 (CI: 0.122, 76.643)
sleep disturbance – 42d	Dichotomous	55	3[j]	(5.5%)	55	0[k]	(0.0%)	OR=7.400 (CI: 0.373, 146.730)
thirsty/dehydrated – 42d	Dichotomous	55	0	(0.0%)	55	0	(0.0%)	OR=1.000 (CI: 0.019, 51.293)
urination difficulties – 42d	Dichotomous	55	2[e]	(3.6%)	55	0	(0.0%)	OR=5.187 (CI: 0.243, 110.569)
weakness – 42d[e]	Dichotomous	55	2	(3.6%)	55	2	(3.6%)	OR=1.000 (CI: 0.136, 7.364)
Weight gain – 42d	Dichotomous	55	0	(0.0%)	55	0	(0.0%)	OR=1.000 (CI: 0.019, 51.293)
overall improvement in quality of life:								
SF36 Physical – 0d	Continuous	28		48 (SD 26)	28		48 (SD 26)	
SF36 Physical – 42d	Continuous	28		59 (SD 27)	28		51.3 (SD 25.8)	MD=7.700 (CI: -6.132, 21.532)
SF36 general health – 0d	Continuous	28		68 (SD 20)	28		68 (SD 20)	
SF36 general health – 42d	Continuous	28		66 (SD 20)	28		61 (SD 23)	MD=5.000 (CI: -6.290, 16.290)
SF36 mental health – 0d	Continuous	28		74 (SD 16)	28		74 (SD 16)	
SF36 mental health – 42d	Continuous	28		76 (SD 16)	28		69 (SD 24)	MD=7.000 (CI: -3.684, 17.684)
treatment withdrawal:								
due to lack of efficacy – 42d	Dichotomous	55	0	(0.0%)	55	3	(5.5%)	OR=0.135 (CI: 0.007, 2.680)
unspecified/other reason – 42d	Dichotomous	55	2[l]	(3.6%)	55	4[m]	(7.3%)	OR=0.481 (CI: 0.084, 2.742)
poor compliance – 42d	Dichotomous	55	0	(0.0%)	55	1	(1.8%)	OR=0.327 (CI: 0.013, 8.212)
leg pain								
pain score:								
NRS/NRS Pain – 0d[n]	Continuous	28		4.9 (SD 2.43)	28		4.9 (SD 2.43)	
NRS/NRS Pain – 42d[n]	Continuous	28		3.4 (SD 2.5)	28		3.7 (SD 2.7)	MD=-0.300 (CI: -1.663, 1.063)
back pain								
pain score:								
NRS/NRS Pain – 0d[n]	Continuous	28		4.5 (SD 2.4)	28		4.5 (SD 2.4)	
NRS/NRS Pain – 42d[n]	Continuous	28		3.2 (SD 2.4)	28		3.8 (SD 2.5)	MD=-0.600 (CI: -1.884, 0.684)

[a] overall pain; type of dispersion not stated, but appears to be standard deviation
[b] it was unclear how many patients were included in this outcome

	[c] 2 sedation, 1 nausea and vomiting and 1 rash [d] sedation [e] estimated from percentages [f] approximated to nearest integer (percentages only presented in text) [g] tired/fatigue; estimated from percentages [h] decreased appetite; approximated to nearest integer (percentages only presented in text) [i] decreased appetite [j] insomnia; estimated from percentages [k] insomnia [l] withdrawal for personal reasons [m] 3 moved away and 1 because of unrelated surgery [n] type of dispersion not stated, but appears to be standard deviation
Comments	there was a 2-week taper period between dosages of which 4 days were drug-free but there was no significant period or carry-over effect; ITT analysis did not include patients with results from only one or no treatment arm; of 61 patients that underwent screening, 6 declined to participate before randomisation; global pain relief was reported on a 6-point scale but not extracted as it was not possible to combine with other pain scores or 7-point scales of patient-reported global impression of change

Definitions of abbreviations are given at the end of this document.

Study	Kieburtz et al. (1998)
Pain category	Peripheral pain
Study design	Country: USA Design: Parallel Inclusion criteria: Participants with HIV related neuropathy for at least 2 weeks and rating on the pain intensity scale as at least mild all the time or moderate for a total of 2 hours per day; stable dosage of dideoxynucleoside analogs for at least 8 weeks and cimedtidine for at least 2 weeks, serum liver function enzyme levles < 5 times the upper limit of normal Exclusion criteria: diabetes, cardiac disease, seizure disorder, if pain was clearly attributed to a neuropathic drug, use of cardiac antiarrhythmic agents, tricyclics or tetracyclic antidepressants, >50% change in dosage per week of pain control medications a week before entry Study length (days): 70 Intention-to-treat analysis? No
Participants	Total number of patients: 145 Number of males: 139 (95.9%) Underlying cause of neuropathic pain: HIV-related neuropathy Mean duration of NP (in months): not reported Baseline pain severity: 1.075 (gracely scale (average of arm means)) Mean age: 41
Intervention(s)	(1) Amitriptyline up to 100mg/d Intervention: amitriptyline Length of treatment (weeks): 10 Fixed/flexible dose regimen: Flexible dose Range: 25–100

	Notes: 4 week titration starting at 25 mg/d up to 100 mg per day (2) Placebo Intervention: placebo Length of treatment (weeks): 10 Fixed/flexible dose regimen: Flexible dose
Concomitant treatments	Drug free baseline period? No Concomitant pain treatment allowed? Yes (opioid and non-opioid analgesics (excluding tricyclic antidepressants) were allowed)
Outcomes measures and effect sizes	

		AMITRIPTYLINE UP TO 100MG/D			PLACEBO			
		N	k	mean	N	k	mean	Δ
pain score:								
Gracely pain score – 28d[a]	Mean change	41		-0.235 (SD 0.093)	44		-0.12 (SD 0.28)	MD=-0.115 (CI: -0.202, -0.028)
Gracely pain score – 56d[a]	Mean change	34		-0.367 (SD 0.113)	38		-0.235 (SD 0.095)	MD=-0.132 (CI: -0.181, -0.083)
Gracely pain score – 70d	Mean change	39		-0.31 (SD 0.31)	43		-0.125 (SD 0.105)[b]	MD=-0.110 (CI: -0.242, 0.022)
Gracely pain score – 70d	Mean change	27		-0.31 (SD 0.31)	43		-0.2 (SD 0.3)	MD=-0.030 (CI: -0.130, 0.070)
Gracely pain score – 70d	Mean change	27		-0.31 (SD 0.31)	43		-0.125 (SD 0.105)[b]	MD=-0.030 (CI: -0.130, 0.070)
Gracely pain score – 70d	Mean change	27		-0.23 (SD 0.12)[b]	43		-0.2 (SD 0.3)	MD=-0.030 (CI: -0.130, 0.070)
Gracely pain score – 70d	Mean change	27		-0.23 (SD 0.12)[b]	43		-0.2 (SD 0.3)	MD=-0.110 (CI: -0.242, 0.022)
Gracely pain score – 70d	Mean change	39		-0.31 (SD 0.31)	25		-0.125 (SD 0.105)[b]	MD=-0.030 (CI: -0.130, 0.070)
Gracely pain score – 70d	Mean change	39		-0.31 (SD 0.31)	25		-0.125 (SD 0.105)[b]	MD=-0.110 (CI: -0.242, 0.022)
Gracely pain score – 70d	Mean change	39		-0.31 (SD 0.31)	43		-0.2 (SD 0.3)	MD=-0.110 (CI: -0.242, 0.022)
Gracely pain score – 70d	Mean change	39		-0.23 (SD 0.12)[b]	43		-0.2 (SD 0.3)	MD=-0.110 (CI: -0.242, 0.022)
Gracely pain score – 70d[b]	Mean change	27		-0.23 (SD 0.12)	25		-0.125 (SD 0.105)	MD=-0.030 (CI: -0.130, 0.070)
Gracely pain score – 70d[b]	Mean change	27		-0.23 (SD 0.12)	25		-0.125 (SD 0.105)	MD=-0.110 (CI: -0.242, 0.022)
Gracely pain score – 70d[b]	Mean change	27		-0.23 (SD 0.12)	43		-0.125 (SD 0.105)	MD=-0.030 (CI: -0.130, 0.070)
Gracely pain score – 70d[b]	Mean change	39		-0.23 (SD 0.12)	43		-0.125 (SD 0.105)	MD=-0.110 (CI: -0.242, 0.022)
Gracely pain score – 70d	Mean change	39		-0.31 (SD 0.31)	43		-0.2 (SD 0.3)	MD=-0.030 (CI: -0.130, 0.070)
major adverse events (defined as leading to withdrawal):								
toxicity – 70d	Dichotomous	46	3	(6.5%)	49	1	(2.0%)	OR=3.349 (CI: 0.336, 33.411)
treatment withdrawal:								
unspecified/other reason – 70d	Dichotomous	46	8	(17.4%)	49	10	(20.4%)	OR=0.821 (CI: 0.293, 2.303)
lost to follow-up – 70d	Dichotomous	46	2	(4.3%)	49	1	(2.0%)	OR=2.182 (CI: 0.191, 24.909)

[a] estimated from graph
[b] estimated from graph; unclear why difference from that reported in text at same time point (see above) but possibly to do with diff sample size reported (maybe above was ITT? Not clear)

Comments	study includes a 3rd arm of mexiletine not included here as this drug is not in the scope; study reported no significant changes in pain intensity, mood or quality of life assessments but the data was not reported; 1 patient in each group dropped out prior to receiving the study medication

Definitions of abbreviations are given at the end of this document.

Study	Kim et al. (2011)
Pain category	Central pain
Study design	Country: Asia-pacific

	Design: Parallel Inclusion criteria: Patients with central post stroke pain aged 18 years and older who had had a stroke at least 4 months before randomisation, have CPSP for more than 3 months and a score of 40mm on the SFMPQ-VAS, with an average daily pains score over 40mm in the 7 days prior to randomisation Exclusion criteria: Patients were excluded if there were other potential causes of pain that could not readily be discriminated from the CPSP, if they were pregnant or lactating, if they had skin conditions in the affected dermatone that could have altered skin sensation, or if they had cognitive impairement, unstable psychological, medical or psychiatric conditions. Study length (days): 91 Intention-to-treat analysis? Yes
Participants	Total number of patients: 219 Number of males: 137 (62.6%) Underlying cause of neuropathic pain: Post-stroke pain Mean duration of NP (in months): 28.2 Baseline pain severity: 6.4 (NRS (average of arm means); MPQ VAS average of means is 67.1) Mean age: 58.25
Intervention(s)	(1) Pregabalin (flexible dose) Intervention: pregabalin Length of treatment (weeks): 13 Fixed/flexible dose regimen: Flexible dose Mean dose: 356.8mg/d Range: 125–539.7 Notes: 4-week dose adjustment, 8 maintenance, 1 week taper; start with 150 mg/d for 7 days, 300 mg/d for 7 days, then patients were adjusted over the next 2 weeks based on their clinical response and tolerance (either stay on 300 mg/d or increase to 600 mg/d); all dosages were split into 2 administrations per day; 21 (19%) patients had 150 to < 300 mg/d, 39 (35.5%) had 300 to < 450 mg/d and 50 (45.5%) had 600 mg/d (2) Placebo Intervention: placebo Length of treatment (weeks): 13 Fixed/flexible dose regimen: Flexible dose
Concomitant treatments	Drug free baseline period? Yes (duration: 14d) Concomitant pain treatment allowed? Yes (Pharmacological therapies for pain or insomnia if used in a normal routine more than 30 days prior to randomisation; also patients were required to be stabilised on current pain or analgesic medication)
Outcomes measures and effect sizes	

		PREGABALIN (FLEXIBLE DOSE)			PLACEBO			
		N	k	mean	N	k	mean	Δ
pain score:								
NRS/NRS Pain – 0d	Continuous	110		6.5	109		6.3[a]	
NRS/NRS Pain – 91d	Mean change	110			109			MD=-0.200 (CI: -0.750, 0.350)
NRS/NRS Pain – 91d	Continuous	110		4.9	109		5[a]	MD=-0.100
McGill VAS – 0d	Continuous	110		66.2	109		68	
McGill VAS – 91d	Mean change	110			109			MD=-1.000 (CI: -7.000, 5.000)

McGill VAS – 91d	Continuous	110		48.5	109		51	MD=-2.500
patient-reported global improvement:								
PGIC – 91d	Mean change	110			109			MD=-0.200 (CI: -0.500, 0.100)
PGIC – 91d	Continuous	110		2.9	109		3.1	MD=-0.200
patient-reported improvement in daily physical and emotional functioning, including sleep:								
MOS sleep disturbance – 0d	Continuous	110		41.6	109		42.2	
MOS sleep disturbance – 91d	Continuous	110		27.5	109		32.7	MD=-5.200
MOS sleep quantitiy – 0d	Continuous	110		6.3	109		6.5	
MOS sleep quantitiy – 91d	Continuous	110		6.9	109		6.6	MD=0.300
MOS somnolence – 0d	Continuous	110		41.2	109		38	
MOS somnolence – 91d	Continuous	110		40.3	109		36.9	MD=3.400
HADS-A – 0d	Continuous	110		7.7	109		7.5	
HADS-A – 91d	Mean change	110			109			MD=-1.000 (CI: -1.800, -0.200)
HADS-A – 91d	Continuous	110		5.8	109		6.7	MD=-0.900
HADS-D – 0d	Continuous	110		8.3	109		7.6	
HADS-D – 91d	Mean change	110			109			MD=0.200 (CI: -0.600, 1.000)
HADS-D – 91d	Continuous	110		7.1	109		6.5	MD=0.600
MOS sleep adequacy – 0d	Continuous	110		65.5	109		61	
MOS sleep adequacy – 91d	Continuous	110		66.6	109		60.6	MD=6.000
MOS sleep problems index – 0d	Continuous	110		38.6	109		27.2	
MOS sleep problems index – 91d	Mean change	110			109			MD=-4.200 (CI: -8.400, 0.000)
MOS sleep problems index – 91d	Continuous	110		28.5	109		32.1	MD=-3.600
MOS snoring – 0d	Continuous	110		38.7	109		39.1	
MOS snoring – 91d	Continuous	110		40.8	109		32.6	MD=8.200
MOS short of breath/headache – 0d	Continuous	110		17.5	109		19.4	
MOS short of breath/headache – 91d	Continuous	110		10.9	109		14.4	MD=-3.500
major adverse events (defined as leading to withdrawal):								
any major adverse event – 91d	Dichotomous	110	9	(8.2%)	109	4	(3.7%)	OR=2.339 (CI: 0.698, 7.837)
adverse events:								
any adverse event – 91d	Dichotomous	111	77	(69.4%)	109	60	(55.0%)	OR=1.850 (CI: 1.064, 3.214)
Diarrhoea – 91d	Dichotomous	111	6	(5.4%)	109	2	(1.8%)	OR=3.057 (CI: 0.603, 15.491)
Dizziness – 91d	Dichotomous	111	31	(27.9%)	109	8	(7.3%)	OR=4.892 (CI: 2.132, 11.228)
headache – 91d	Dichotomous	111	7	(6.3%)	109	8	(7.3%)	OR=0.850 (CI: 0.297, 2.430)
oedema – 91d	Dichotomous	111	6	(5.4%)	109	0	(0.0%)	OR=13.493 (CI: 0.751, 242.501)
Peripheral oedema – 91d	Dichotomous	111	11	(9.9%)	109	3	(2.8%)	OR=3.887 (CI: 1.053, 14.340)
Somnolence – 91d	Dichotomous	111	24	(21.6%)	109	5	(4.6%)	OR=5.738 (CI: 2.101, 15.671)
Weight gain – 91d	Dichotomous	111	6	(5.4%)	109	2	(1.8%)	OR=3.057 (CI: 0.603, 15.491)
overall improvement in quality of life:								
EQ-5D - health status index – 0d	Continuous	110		0.4	109		0.4	
EQ-5D - health status index – 91d	Mean change	110			109			MD=0.000 (CI: -0.100, 0.100)
EQ-5D - health status index – 91d	Continuous	110		0.6	109		0.5	MD=0.100
EQ-5D - health status VAS – 0d	Continuous	110		56.9	109		58.8	
EQ-5D - health status VAS – 91d	Continuous	110		64.1	109		61.4	MD=2.700
EQ-5D - health status VAS – 91d	Mean change	110			109			MD=3.000 (CI: -1.850, 7.850)
treatment withdrawal:								
due to lack of efficacy – 91d	Dichotomous	110	0	(0.0%)	109	1	(0.9%)	OR=13.224 (CI: 1.688, 103.576)
due to lack of efficacy – 91d	Dichotomous	111	0	(0.0%)	109	1	(0.9%)	OR=13.224 (CI: 1.688, 103.576)
unspecified/other reason – 91d	Dichotomous	110	8	(7.2%)	109	7	(6.4%)	OR=1.143 (CI: 0.400, 3.269)
unspecified/other reason – 91d	Dichotomous	111	8	(7.2%)	109	7	(6.4%)	OR=1.143 (CI: 0.400, 3.269)
lost to follow-up – 91d	Dichotomous	110	0	(0.0%)	109	7	(6.4%)	OR=0.062 (CI: 0.003, 1.096)

	lost to follow-up – 91d	Dichotomous	111	0	(0.0%)	109	7	(6.4%)	OR=0.062 (CI: 0.003, 1.096)	

[a] tool reportedly used was Daily Pain Rating Scale which was not described. As it is often described as NRS, this was assumed here

Comments	authors state that the majority of patients did not achieve a 30 or 50% reduction with pregabalin but the proportions were not reported; 1 patient in the amitriptyline group dropped out prior to receiving study medication

Definitions of abbreviations are given at the end of this document.

Study	Kochar et al. (2002)
Pain category	Peripheral pain
Study design	Country: India Design: Parallel Inclusion criteria: Patients with type 2 diabetes with painful diabetic neuropathy Exclusion criteria: Patients with liver disease, pulmonary TB, thyroid disorders, uraemia, vitamin deficiency, hereditary and paraneoplastic neuropathy, alcoholism, steroid therapy Study length (days): 28 Intention-to-treat analysis? No
Participants	Total number of patients: 60 Number of males: 29 (48.3%) Underlying cause of neuropathic pain: Painful diabetic neuropathy Mean duration of NP (in months): not reported Baseline pain severity: 4.95 (pain severity on SF MPQ - average of means) Mean age: 56.17
Intervention(s)	(1) sodium Valporate 1200mg/d Intervention: valproate Length of treatment (weeks): 4 Fixed/flexible dose regimen: Fixed dose Set dose: 1200mg/d Notes: 200 mg 3x per day first, then 1200 divided in 3 daily dosages (2) Placebo Intervention: placebo Length of treatment (weeks): 4 Fixed/flexible dose regimen: Fixed dose
Concomitant treatments	Drug free baseline period? No Concomitant pain treatment allowed? Yes (appears that this was allowed - authors state that no patient was allowed to change their analgesic medication for pain control)
Outcomes measures and	**SODIUM VALPORATE 1200MG/D** **PLACEBO**

effect sizes			N	k	mean	N	k	mean	Δ
pain score:									
SF McGill – 0d	Continuous		28		5 (SD 1.95)	24		4.9 (SD 1.85)	
SF McGill – 28d	Continuous		28		3.41 (SD 1.88)	24		4.6 (SD 2.12)	MD=-1.190 (CI: -2.287, -0.093)
major adverse events (defined as leading to withdrawal):									
any major adverse event – 28d	Dichotomous		29	1	(3.4%)	28	0	(0.0%)	OR=3.000 (CI: 0.117, 76.789)
treatment withdrawal:									
due to lack of efficacy	Dichotomous		29	0	(0.0%)	28	2	(7.1%)	OR=0.180 (CI: 0.008, 3.914)
poor compliance	Dichotomous		29	1	(3.4%)	28	2	(7.1%)	OR=0.464 (CI: 0.040, 5.429)
Comments	-								

Definitions of abbreviations are given at the end of this document.

Study	Kochar et al. (2004)
Pain category	Peripheral pain
Study design	Country: India Design: Parallel Inclusion criteria: Diabetes for at least 6 months on stable dosage of insulin or oral hypoglycaemic agent, HbA1c <11, Daily neuropathic pain of at least moderate severity for >3 months, Pain intensity of >4 on VAS Exclusion criteria: People with liver disease, pulmonary tuberculosis, thyroid disorders, uraemia, vitamin deficiency, hereditary and paraneoplastic neuropathy, alcoholism, patients on steroid therapy. Study length (days): 84 Intention-to-treat analysis? No
Participants	Total number of patients: 48 Number of males: 21 (43.8%) Underlying cause of neuropathic pain: Painful diabetic neuropathy Mean duration of NP (in months): not reported Baseline pain severity: 5.855 (VAS (average of arm means)) Mean age: 55.31 (SD: 12)
Intervention(s)	(1) Sodium valproate 500md/d Intervention: valproate Length of treatment (weeks): 12 Fixed/flexible dose regimen: Fixed dose Set dose: 500mg/d (2) Placebo Intervention: placebo Length of treatment (weeks): 12

	Fixed/flexible dose regimen: Fixed dose
Concomitant treatments	Drug free baseline period? Unclear Concomitant pain treatment allowed? Unclear (authors state that patients were not allowed to take analgesics for control of pain - it is unclear if this means just rescue analgesics or if other drugs were not permitted (ie. Anti-depressants, anti-convulsants, etc))
Outcomes measures and effect sizes	

		SODIUM VALPROATE 500MD/D			PLACEBO			
		N	k	mean	N	k	mean	Δ
pain score:								
VAS – 0d	Continuous	21		6 (SD 8.94)	18		5.71 (SD 7.21)	
VAS – 28d	Continuous	21		3.95 (SD 7.97)	18		6 (SD 7.81)	MD=-2.050 (CI: -7.013, 2.913)
VAS – 84d	Continuous	21		3 (SD 9.72)	18		6 (SD 7.81)	MD=-3.000 (CI: -8.502, 2.502)
PPI (from MPQ) – 0d	Continuous	21		2.71 (SD 4.58)	18		2.57 (SD 3.9)	
PPI (from MPQ) – 28d	Continuous	21		1.71 (SD 3.85)	18		2.67 (SD 3.9)	MD=-0.960 (CI: -3.402, 1.482)
PPI (from MPQ) – 84d	Continuous	21		1.33 (SD 3.02)	18		2.61 (SD 3.9)	MD=-1.280 (CI: -3.499, 0.939)
SF McGill – 0d	Continuous	21		19.5 (SD 31.1)	18		17.8 (SD 22.2)	
SF McGill – 28d	Continuous	21		13 (SD 24.8)	18		18.9 (SD 23.2)	MD=-5.910 (CI: -20.989, 9.169)
SF McGill – 84d	Continuous	21		9.66 (SD 27.3)	18		17.9 (SD 23)	MD=-8.220 (CI: -24.009, 7.569)
major adverse events (defined as leading to withdrawal):								
any major adverse event – 84d	Dichotomous	22	1	(4.5%)	21	0	(0.0%)	OR=3.000 (CI: 0.116, 77.833)
adverse events:								
Nausea – 84d	Dichotomous	22	2	(9.1%)	21	0[a]	(0.0%)	OR=5.244 (CI: 0.237, 115.946)
Sedation – 84d	Dichotomous	22	1	(4.5%)	21	0[a]	(0.0%)	OR=3.000 (CI: 0.116, 77.833)
treatment withdrawal:								
protocol deviation – 84d	Dichotomous	22	3	(13.6%)	21	0	(0.0%)	OR=7.718 (CI: 0.374, 159.089)

[a] Safety data not reported for placebo group

Investigators report strongly significant differences between arms; however, raw data appear inconsistent with this. It is possible that the dispersion values that are explicitly labelled as SEMs are, in fact, SDs (they look too big to be SEMs and this would also make the differences more plausibly significant).

Comments	-

Definitions of abbreviations are given at the end of this document.

Study	Kochar et al. (2005)
Pain category	Peripheral pain
Study design	Country: India Design: Parallel Inclusion criteria: adult patients with persistent pain for > 6 months after the onset of herpes zoster rash with at least 50 mm on a 100mm VAS and 4/11 on a Likert scale Exclusion criteria: - Study length (days): 56

	Intention-to-treat analysis? No
Participants	Total number of patients: 48 Number of males: 22 (45.8%) Underlying cause of neuropathic pain: Post-herpetic neuralgia Mean duration of NP (in months): 7.87 Baseline pain severity: 6.55 (NRS (average of arm means) (mean age, baseline pain severity, and duration of PHN are averages of means of the patients completing each treatment group)) Mean age: 57.16
Intervention(s)	(1) Divalproex sodium (valproic acid and sodium valproate 1:1) 1000 mg/d Intervention: valproate Length of treatment (weeks): 8 Fixed/flexible dose regimen: Fixed dose Set dose: 1000mg/d (2) Placebo Intervention: placebo Length of treatment (weeks): 8 Fixed/flexible dose regimen: Fixed dose
Concomitant treatments	Drug free baseline period? No Concomitant pain treatment allowed? No (no other topical or oral drugs were allowed)

Outcomes measures and effect sizes

		DIVALPROEX SODIUM (VALPROIC ACID AND SODIUM VALPROATE 1:1) 1000 MG/D			PLACEBO			
		N	k	mean	N	k	mean	Δ
pain score:								
NRS/NRS Pain – 0d[a]	Continuous	22		6.97 (SD 0.73)	18		6.13 (SD 0.94)	
NRS/NRS Pain – 56d[a]	Continuous	22		3.63 (SD 2.34)	18		5.33 (SD 1.68)	MD=-1.700 (CI: -2.948, -0.452)
VAS – 0d[a]	Continuous	22		70.2 (SD 9.21)	18		63.2 (SD 9.18)	
VAS – 56d[a]	Continuous	22		31.3 (SD 29.8)	18		54.9 (SD 17.5)	MD=-23.670 (CI: -38.521, -8.819)
PPI (from MPQ) – 0d[a]	Continuous	22		4 (SD 0.52)	18		3.68 (SD 0.56)	
PPI (from MPQ) – 56d[a]	Continuous	22		1.95 (SD 1.29)	18		3.22 (SD 1)	MD=-1.270 (CI: -1.980, -0.560)
SF McGill – 0d[a]	Continuous	22		20.5 (SD 2.29)	18		18.1 (SD 3.02)	
SF McGill – 56d[a]	Continuous	22		11.9 (SD 6.52)	18		16.1 (SD 3.4)	MD=-4.210 (CI: -7.355, -1.065)
patient-reported global improvement:								
PGIC - worse (all grades) – 56d[b]	Dichotomous	23	1	(4.3%)	22	2	(9.1%)	OR=0.455 (CI: 0.038, 5.404)

PGIC - no change – 56d[b]	Dichotomous	23	4	(17.4%)	22	12	(54.5%)	OR=0.175 (CI: 0.045, 0.688)
PGIC - minimally better – 56d[b]	Dichotomous	23	4	(17.4%)	22	1	(4.5%)	OR=4.421 (CI: 0.453, 43.115)
PGIC - at least moderately better – 56d[b]	Dichotomous	23	13	(56.5%)	22	3	(13.6%)	OR=8.233 (CI: 1.892, 35.826)
major adverse events (defined as leading to withdrawal):								
any major adverse event – 56d	Dichotomous	23	1[c]	(4.3%)	22	0	(0.0%)	OR=3.000 (CI: 0.116, 77.643)
treatment withdrawal:								
due to lack of efficacy – 56d	Dichotomous	23	0	(0.0%)	22	2	(9.1%)	OR=0.174 (CI: 0.008, 3.848)
poor compliance – 56d	Dichotomous	23	0	(0.0%)	22	2	(9.1%)	OR=0.174 (CI: 0.008, 3.848)

[a] study states dispersion is standard error but it appears more likely that this is standard deviation so it has been recorded this way
[b] estimated from percentages
[c] vertigo

Comments	3 patients excluded after randomisation and before treatment: 1 in each group because of lack of sufficient pain score and 1 in placebo group because of withdrawal of consent; the study reported that 3 patients had nausea, dizziness, drowsiness, and mild change in appetite with the drug but that it subsided over a period of 3-5 days and did not report (it was not reported if any patients in placebo group had any adverse events)

Definitions of abbreviations are given at the end of this document.

Study	Leijon & Boivie (1989)
Pain category	Central pain
Study design	Country: Sweden Design: Crossover Inclusion criteria: central post-stroke pain with unequivocal stroke episode and constant or intermittent pain which started after the stroke Exclusion criteria: nociceptive pain, peripheral neuropathic pain or psychogenic origin; pain with known contraindications to study drugs, patients who could not be evaluated in a satisfactory way, Study length (days): 98 Intention-to-treat analysis? No
Participants	Total number of patients: 15 Number of males: 12 (80.0%) Underlying cause of neuropathic pain: Post-stroke pain Mean duration of NP (in months): 54 Baseline pain severity: not reported (not reported (average duration of pain across all treatment groups)) Mean age: 66
Intervention(s)	(1) Amitriptyline 75 mg/d Intervention: amitriptyline Length of treatment (weeks): 4

Fixed/flexible dose regimen: Fixed dose
Set dose: 75mg/d
Notes: dose escalation from 25 mg to 75 mg

(2) Carbamazepine (600-1200 mg/d)

Intervention: carbamazepine
Length of treatment (weeks): 4
Fixed/flexible dose regimen: Flexible dose
Range: 600–1200
Notes: dose escalation from 200 mg to 800 mg which was the final dose; however, 4 patients with moderate side effects had their dosage decreased so 2 patients finished on 600 mg, 1 on 400 mg and 1 on 200 mg.

(3) Placebo

Intervention: placebo
Length of treatment (weeks): 4
Fixed/flexible dose regimen: Fixed dose
Notes: lactulose

Concomitant treatments

Drug free baseline period? Unclear

Concomitant pain treatment allowed? Yes (However, no patients had used anti-depressants or neurepileptic drugs at the start of the trial; the patient with headache used paracetamol 500 mg 4 times per day, another 2 used TENS, one for nocioceptive knee pain and the other for his central post-stroke pain)

Outcomes measures and effect sizes

		AMITRIPTYLINE 75 MG/D			CARBAMAZEPINE (600-1200 MG/D)			
		N	k	mean	N	k	mean	Δ
pain score:								
VRS – 7d[a]	Continuous	15		4.7 (SD 1.3)	14		4.6 (SD 1.2)	
VRS – 28d	Continuous	15		4.2 (SD 1.6)	14		4.2 (SD 1.7)	
major adverse events (defined as leading to withdrawal):								
any major adverse event – 28d	Dichotomous	15	0	(0.0%)	15	0	(0.0%)	OR=1.000 (CI: 0.019, 53.659)
adverse events:								
any adverse event – 28d	Dichotomous	15	14[b]	(93.3%)	15	14[c]	(93.3%)	OR=1.000 (CI: 0.057, 17.621)
moderate to severe – 28d	Dichotomous	15	2	(13.3%)	15	5	(33.3%)	OR=0.308 (CI: 0.049, 1.928)
treatment withdrawal:								
unspecified/other reason – 28d	Dichotomous	15	0	(0.0%)	15	1[d]	(6.7%)	OR=0.312 (CI: 0.012, 8.285)

[a] baseline data not reported
[b] Dry mouth and tiredness were most frequent (actual rates not reported)
[c] Vertigo, tiredness and gait disturbances were most frequent (actual rates not reported)
[d] medication needed to be stopped because of interaction with coagulant drug the patient was taking (Warfarin)

		AMITRIPTYLINE 75 MG/D			PLACEBO			
		N	k	mean	N	k	mean	Δ
pain score:								
VRS – 7d[a]	Continuous	15		4.7 (SD 1.3)	15		5.5 (SD 1.5)	
VRS – 28d	Continuous	15		4.2 (SD 1.6)	15		5.3 (SD 2)	

major adverse events (defined as leading to withdrawal):									
any major adverse event – 28d	Dichotomous	15	0	(0.0%)	15	0	(0.0%)	OR=1.000 (CI: 0.019, 53.659)	
adverse events:									
any adverse event – 28d	Dichotomous	15	14[b]	(93.3%)	15	7	(46.7%)	OR=16.000 (CI: 1.656, 154.595)	
moderate to severe – 28d	Dichotomous	15	2	(13.3%)	15	1	(6.7%)	OR=2.154 (CI: 0.174, 26.672)	
treatment withdrawal:									
unspecified/other reason – 28d	Dichotomous	15	0	(0.0%)	15	0	(0.0%)	OR=1.000 (CI: 0.019, 53.659)	

[a] baseline data not reported
[b] Dry mouth and tiredness were most frequent (actual rates not reported)

		CARBAMAZEPINE (600-1200 MG/D)			PLACEBO			
		N	k	mean	N	k	mean	Δ
pain score:								
VRS – 7d[a]	Continuous	14		4.6 (SD 1.2)	15		5.5 (SD 1.5)	
VRS – 28d	Continuous	14		4.2 (SD 1.7)	15		5.3 (SD 2)	
major adverse events (defined as leading to withdrawal):								
any major adverse event – 28d	Dichotomous	15	0	(0.0%)	15	0	(0.0%)	OR=1.000 (CI: 0.019, 53.659)
adverse events:								
any adverse event – 28d	Dichotomous	15	14[b]	(93.3%)	15	7	(46.7%)	OR=16.000 (CI: 1.656, 154.595)
moderate to severe – 28d	Dichotomous	15	5	(33.3%)	15	1	(6.7%)	OR=7.000 (CI: 0.705, 69.490)
treatment withdrawal:								
unspecified/other reason – 28d	Dichotomous	15	1[c]	(6.7%)	15	0	(0.0%)	OR=3.207 (CI: 0.121, 85.203)

[a] baseline data not reported
[b] Vertigo, tiredness and gait disturbances were most frequent (actual rates not reported)
[c] medication needed to be stopped because of interaction with coagulant drug the patient was taking (Warfarin)

baseline pain scores not reported

Comments	one patient with an allergy to carbamazepine was randomised only to either amitriptyline or placebo; 5 patients had another chronic pain as well as chronic post-stroke pain (3 low back pain, 4 chronic tension headache and 1 sciatica); almost all patients had low baseline depression scores and no patient appeared to be depressed - there was no significant decrease in depression scores for patients being treated with study drugs when compared to placebo period; study reported global assessment of effect on the pain but this was on a 5-step scale so not combinable with results from 7-point PGIC (authors show a difference in effect of study drugs on this scale but not for placebo); ITT not used by authors but dichotomous outcomes recorded here are done as intention-to-treat

Definitions of abbreviations are given at the end of this document.

Study	Lesser et al. (2004)
Pain category	Peripheral pain
Study design	Country: USA Design: Parallel Inclusion criteria: People over the age of 18 years with diabetes and 1-5 years history of PDN and average weekly pain scores of at least 4 on NRS-11

	point Exclusion criteria: No exclusion criteria described Study length (days): 35 Intention-to-treat analysis? Yes
Participants	Total number of patients: 337 Number of males: 202 (59.9%) Underlying cause of neuropathic pain: Painful diabetic neuropathy Mean duration of NP (in months): not reported Baseline pain severity: 6.4 (NRS) Mean age: 59.9 (SD: 10.5)
Intervention(s)	(1) pregabalin 75mg/d Intervention: pregabalin Length of treatment (weeks): 35 Fixed/flexible dose regimen: Fixed dose Set dose: 75mg/d (2) Pregabalin 300mg/d Intervention: pregabalin Length of treatment (weeks): 35 Fixed/flexible dose regimen: Fixed dose Set dose: 300mg/d (3) pregabalin 600mg/d Intervention: pregabalin Length of treatment (weeks): 35 Fixed/flexible dose regimen: Fixed dose Set dose: 600mg/d (4) Placebo Intervention: placebo Length of treatment (weeks): 35 Fixed/flexible dose regimen: Fixed dose
Concomitant treatments	Drug free baseline period? Unclear Concomitant pain treatment allowed? Yes (patients were allowed to take SSRIs if they were already on stable treatment (and acetaminophen 3g/d was allowed as rescue analgesic) but all other neuropathic pain medications were prohibited)
Outcomes measures and effect sizes	

		PREGABALIN 75MG/D			PLACEBO			
		N	k	mean	N	k	mean	Δ
pain score:								
NRS/NRS Pain – 0d	Continuous	77		6.7 (SD 1.3)	97		6.6 (SD 1.5)	
NRS/NRS Pain – 35d[a]	Continuous	77		4.91 (SD 2.11)	97		5.06 (SD 2.07)	MD=-0.150 (CI: -0.775, 0.475)
McGill VAS – 35d[b]	Continuous	77		49.7 (SD 24)	97		53.5 (SD 24.2)	MD=-3.790 (CI: -11.007, 3.427)

PPI (from MPQ) – 35d[b]	Continuous	77		1.67 (SD 0.965)	97		1.79 (SD 0.985)	MD=-0.120 (CI: -0.411, 0.171)
SF McGill – 35d[b]	Continuous	77		15.1 (SD 7.37)	97		15.1 (SD 9.26)	MD=0.000 (CI: -2.471, 2.471)
major adverse events (defined as leading to withdrawal):								
any major adverse event – 35d	Dichotomous	77	2	(2.6%)	97	3	(3.1%)	OR=0.836 (CI: 0.136, 5.130)
adverse events:								
amnesia	Dichotomous	77	2	(2.6%)	97	1	(1.0%)	OR=2.560 (CI: 0.228, 28.772)
asthenia	Dichotomous	77	3	(3.9%)	97	3	(3.1%)	OR=1.270 (CI: 0.249, 6.477)
Confusion	Dichotomous	77	0	(0.0%)	97	2	(2.1%)	OR=0.246 (CI: 0.012, 5.210)
Constipation	Dichotomous	77	0	(0.0%)	97	1	(1.0%)	OR=0.415 (CI: 0.017, 10.331)
Diarrhoea	Dichotomous	77	4	(5.2%)	97	7	(7.2%)	OR=0.705 (CI: 0.199, 2.500)
Dizziness – 35d	Dichotomous	77	6	(7.8%)	97	5	(5.2%)	OR=1.555 (CI: 0.456, 5.301)
Dry mouth	Dichotomous	77	2	(2.6%)	97	0	(0.0%)	OR=6.457 (CI: 0.305, 136.504)
headache	Dichotomous	77	5	(6.5%)	97	10	(10.3%)	OR=0.604 (CI: 0.198, 1.848)
Infection	Dichotomous	77	3	(3.9%)	97	7	(7.2%)	OR=0.521 (CI: 0.130, 2.086)
Peripheral oedema – 35d	Dichotomous	77	3	(3.9%)	97	2	(2.1%)	OR=1.926 (CI: 0.314, 11.824)
Somnolence – 35d	Dichotomous	77	3	(3.9%)	97	4	(4.1%)	OR=0.943 (CI: 0.205, 4.343)
treatment withdrawal:								
unspecified/other reason – 35d	Dichotomous	77	8	(10.4%)	97	5	(5.2%)	OR=2.133 (CI: 0.669, 6.806)

[a] least squares mean
[b] least squares mean; baseline data doesn't appear to have been reported for this tool

		PREGABALIN 300MG/D			PLACEBO			
		N	k	mean	N	k	mean	Δ
pain score:								
NRS/NRS Pain – 0d	Continuous	81		6.2 (SD 1.4)	97		6.6 (SD 1.5)	
NRS/NRS Pain – 35d[a]	Continuous	81		3.8 (SD 2.07)	97		5.06 (SD 2.07)	MD=-1.260 (CI: -1.870, -0.650)
at least 30% pain reduction – 35d	Dichotomous	81	50	(61.7%)	97	32	(33.0%)	OR=3.276 (CI: 1.769, 6.068)
at least 50% pain reduction – 35d	Dichotomous	81	37	(45.7%)	97	17	(17.5%)	OR=3.957 (CI: 2.001, 7.827)
McGill VAS – 35d[b]	Continuous	81		37.4 (SD 24.2)	97		53.5 (SD 24.2)	MD=-16.090 (CI: -23.235, -8.945)
PPI (from MPQ) – 35d[b]	Continuous	81		1.2 (SD 0.99)	97		1.79 (SD 0.985)	MD=-0.590 (CI: -0.881, -0.299)
SF McGill – 35d[b]	Continuous	81		10.2 (SD 8.28)	97		15.1 (SD 9.26)	MD=-4.890 (CI: -7.468, -2.312)
patient-reported global improvement:								
PGIC - worse (all grades) – 35d	Dichotomous	79	4	(5.1%)	95	10	(10.5%)	OR=0.453 (CI: 0.136, 1.506)
PGIC - no change – 35d	Dichotomous	79	12	(15.2%)	95	32	(33.7%)	OR=0.353 (CI: 0.167, 0.744)
PGIC - minimally better – 35d	Dichotomous	79	19	(24.1%)	95	30	(31.6%)	OR=0.686 (CI: 0.350, 1.345)
PGIC - at least moderately better – 35d	Dichotomous	79	44	(55.7%)	95	23	(24.2%)	OR=3.935 (CI: 2.063, 7.509)
major adverse events (defined as leading to withdrawal):								
any major adverse event – 35d	Dichotomous	81	3	(3.7%)	97	3	(3.1%)	OR=1.205 (CI: 0.237, 6.140)
adverse events:								
amnesia	Dichotomous	81	0	(0.0%)	97	1	(1.0%)	OR=0.395 (CI: 0.016, 9.821)
asthenia	Dichotomous	81	4	(4.9%)	97	3	(3.1%)	OR=1.628 (CI: 0.354, 7.494)
Confusion	Dichotomous	81	4	(4.9%)	97	2	(2.1%)	OR=2.468 (CI: 0.440, 13.832)
Constipation	Dichotomous	81	3	(3.7%)	97	1	(1.0%)	OR=3.692 (CI: 0.377, 36.200)
Diarrhoea	Dichotomous	81	1	(1.2%)	97	7	(7.2%)	OR=0.161 (CI: 0.019, 1.335)
Dizziness – 35d	Dichotomous	81	22	(27.2%)	97	5	(5.2%)	OR=6.861 (CI: 2.463, 19.114)
Dry mouth	Dichotomous	81	6	(7.4%)	97	0	(0.0%)	OR=16.788 (CI: 0.931, 302.705)
headache	Dichotomous	81	7	(8.6%)	97	10	(10.3%)	OR=0.823 (CI: 0.298, 2.270)
Infection	Dichotomous	81	8	(9.9%)	97	7	(7.2%)	OR=1.409 (CI: 0.488, 4.068)

Peripheral oedema – 35d	Dichotomous	81	6	(7.4%)	97	2	(2.1%)	OR=3.800 (CI: 0.746, 19.369)
Somnolence – 35d	Dichotomous	81	19	(23.5%)	97	4	(4.1%)	OR=7.125 (CI: 2.313, 21.948)
treatment withdrawal:								
unspecified/other reason – 35d	Dichotomous	81	2	(2.5%)	97	5	(5.2%)	OR=0.466 (CI: 0.088, 2.467)

[a] least squares mean
[b] least squares mean; baseline data doesn't appear to have been reported for this tool

		PREGABALIN 600MG/D			PLACEBO			
		N	k	mean	N	k	mean	Δ
pain score:								
NRS/NRS Pain – 0d	Continuous	81		6.2 (SD 1.5)	97		6.6 (SD 1.5)	
NRS/NRS Pain – 35d[a]	Continuous	81		3.6 (SD 2.07)	97		5.06 (SD 2.07)	MD=-1.460 (CI: -2.070, -0.850)
at least 30% pain reduction – 35d	Dichotomous	81	53	(65.4%)	97	32	(33.0%)	OR=3.845 (CI: 2.061, 7.173)
at least 50% pain reduction – 35d	Dichotomous	81	39	(48.1%)	97	17	(17.5%)	OR=4.370 (CI: 2.211, 8.635)
McGill VAS – 35d[b]	Continuous	81		34.5 (SD 23.8)	97		53.5 (SD 24.2)	MD=-19.010 (CI: -26.097, -11.923)
PPI (from MPQ) – 35d[b]	Continuous	81		1.18 (SD 0.99)	97		1.79 (SD 0.985)	MD=-0.610 (CI: -0.901, -0.319)
SF McGill – 35d[b]	Continuous	81		9.88 (SD 8.19)	97		15.1 (SD 9.26)	MD=-5.180 (CI: -7.744, -2.616)
patient-reported global improvement:								
PGIC - worse (all grades) – 35d	Dichotomous	78	3	(3.8%)	95	10	(10.5%)	OR=0.340 (CI: 0.090, 1.282)
PGIC - no change – 35d	Dichotomous	78	6	(7.7%)	95	32	(33.7%)	OR=0.164 (CI: 0.064, 0.418)
PGIC - minimally better – 35d	Dichotomous	78	15	(19.2%)	95	30	(31.6%)	OR=0.516 (CI: 0.254, 1.049)
PGIC - at least moderately better – 35d	Dichotomous	78	54	(69.2%)	95	23	(24.2%)	OR=7.043 (CI: 3.597, 13.792)
major adverse events (defined as leading to withdrawal):								
any major adverse event – 35d	Dichotomous	81	10	(12.3%)	97	3	(3.1%)	OR=4.413 (CI: 1.171, 16.628)
adverse events:								
amnesia	Dichotomous	81	5	(6.2%)	97	1	(1.0%)	OR=6.316 (CI: 0.723, 55.206)
asthenia	Dichotomous	81	6	(7.4%)	97	3	(3.1%)	OR=2.507 (CI: 0.607, 10.357)
Confusion	Dichotomous	81	7	(8.6%)	97	2	(2.1%)	OR=4.493 (CI: 0.907, 22.268)
Constipation	Dichotomous	81	7	(8.6%)	97	1	(1.0%)	OR=9.081 (CI: 1.093, 75.438)
Diarrhoea	Dichotomous	81	3	(3.7%)	97	7	(7.2%)	OR=0.495 (CI: 0.124, 1.978)
Dizziness – 35d	Dichotomous	81	32	(39.5%)	97	5	(5.2%)	OR=12.016 (CI: 4.402, 32.802)
Dry mouth	Dichotomous	81	4	(4.9%)	97	0	(0.0%)	OR=11.323 (CI: 0.600, 213.519)
headache	Dichotomous	81	8	(9.9%)	97	10	(10.3%)	OR=0.953 (CI: 0.358, 2.541)
Infection	Dichotomous	81	1	(1.2%)	97	7	(7.2%)	OR=0.161 (CI: 0.019, 1.335)
Peripheral oedema – 35d	Dichotomous	81	11	(13.6%)	97	2	(2.1%)	OR=7.464 (CI: 1.603, 34.746)
Somnolence – 35d	Dichotomous	81	22	(27.2%)	97	4	(4.1%)	OR=8.669 (CI: 2.845, 26.416)
treatment withdrawal:								
unspecified/other reason – 35d	Dichotomous	81	2	(2.5%)	97	5	(5.2%)	OR=0.466 (CI: 0.088, 2.467)

[a] least squares mean
[b] least squares mean; baseline data doesn't appear to have been reported for this tool

Comments	30 and 50% response not reported for 75mg/d dosage; there was a 1 week baseline phase - unclear if this was used as a drug-free period; 1 patient who withdrew after randomisation but before taking study medication was not included in the ITT population (it appears this patient was in the 600 mg/d group but this is not explicitly stated)

Definitions of abbreviations are given at the end of this document.

Study	Levendoglu et al. (2004)
Pain category	Mixed (central and peripheral) or unclear if mixed
Study design	Country: Turkey Design: Crossover Inclusion criteria: Patients with complete traumatic SCI at the thoracic and lumbar level, aged between 20 and 65 years, with NP for more than 6 months confirmed by a physician. Exclusion criteria: Severe cognitive impairment, pregnancy, seizure disorder, the use of anticonvulsants and antidepressants, major depression or a score above 16 on the Beck Depression Inventory, and hypersenstivity to gabapentin Study length (days): 126 Intention-to-treat analysis? Unclear
Participants	Total number of patients: 20 Number of males: 13 (65.0%) Underlying cause of neuropathic pain: Spinal cord injury pain Mean duration of NP (in months): 15.8 Baseline pain severity: 88 (VAS (estimated from graph)) Mean age: 35.9 (SD: 9.8)
Intervention(s)	(1) Gabapentin Intervention: gabapentin Length of treatment (weeks): 8 Fixed/flexible dose regimen: Flexible dose Mean dose: 223.5mg/d Notes: all patients' dosages were titrated up to 3600 mg/d but then titration was reduced in the case of intolerable side effects; values reported here are mean values without side effects while max tolerated dosage was 2850 mg (1200-3600) (2) Placebo Intervention: placebo Length of treatment (weeks): 8 Fixed/flexible dose regimen: Flexible dose
Concomitant treatments	Drug free baseline period? Unclear Concomitant pain treatment allowed? No (Concurrent analgesic medications were not allowed at least 15 days before and during the study. Use with anti-convulsants and anti-depressants was exclusion criteria.)

Outcomes measures and effect sizes

		GABAPENTIN			PLACEBO			
		N	k	mean	N	k	mean	Δ
pain score:								
VAS – 0d[a]	Continuous	20		88	20		88	
VAS – 28d[a]	Continuous	20		46	20		80	MD=-34.000
VAS – 56d[a]	Continuous	20		35	20		78	MD=-43.000
NPS – 0d	Continuous	20		8.5 (SD 0.9)	20		8.4 (SD 0.7)	
NPS – 28d	Continuous	20		4.8 (SD 1.1)	20		7.8 (SD 0.7)	MD=-3.000 (CI: -3.571, -2.429)

	NPS – 56d	Continuous	20		3.2 (SD 1.2)	20	7.4 (SD 0.7)	MD=-4.200 (CI: -4.809, -3.591)
	adverse events:							
	Blurred vision – 56d	Dichotomous	20	0	(0.0%)	20	0 (0.0%)	OR=1.000 (CI: 0.019, 52.849)
	Diarrhoea – 56d	Dichotomous	20	0	(0.0%)	20	0 (0.0%)	OR=1.000 (CI: 0.019, 52.849)
	headache – 56d	Dichotomous	20	1	(5.0%)	20	1 (5.0%)	OR=1.000 (CI: 0.058, 17.181)
	Nausea – 56d	Dichotomous	20	0	(0.0%)	20	1 (5.0%)	OR=0.317 (CI: 0.012, 8.260)
	oedema – 56d	Dichotomous	20	3	(15.0%)	20	0 (0.0%)	OR=8.200 (CI: 0.396, 169.899)
	Sedation – 56d	Dichotomous	20	3	(15.0%)	20	0 (0.0%)	OR=8.200 (CI: 0.396, 169.899)
	vertigo – 56d	Dichotomous	20	3	(15.0%)	20	1 (5.0%)	OR=3.353 (CI: 0.318, 35.364)
	Vomiting – 56d	Dichotomous	20	0	(0.0%)	20	1 (5.0%)	OR=0.317 (CI: 0.012, 8.260)
	weakness – 56d	Dichotomous	20	5	(25.0%)	20	2 (10.0%)	OR=3.000 (CI: 0.507, 17.740)
	[a] estimated from graph							
Comments	-							

Definitions of abbreviations are given at the end of this document.

Study	Low et al. (1995)
Pain category	Peripheral pain
Study design	Country: USA Design: Parallel Inclusion criteria: Bilateral symmetric chronic peripheral neuropathy involving the distal lower extremities for at least 6 months, refractory to at least one other form of treatment Exclusion criteria: unstable symptoms in previous 6 months, women of childbearing age unless they were sterilised or were taking an effective form of contraception Study length (days): 56 Intention-to-treat analysis? Yes
Participants	Total number of patients: 40 Number of males: 24 (60.0%) Underlying cause of neuropathic pain: Polyneuropathy Mean duration of NP (in months): 56 Baseline pain severity: 8.4 (VAS) Mean age: 59
Intervention(s)	(1) Capsaicin 0.075% cream (fixed dose 4x per day) Intervention: capsaicin cream Length of treatment (weeks): 8 Fixed/flexible dose regimen: Fixed dose Notes: Limbs were randomised (2) Placebo Intervention: placebo Length of treatment (weeks): 8

	Fixed/flexible dose regimen: Fixed dose Notes: Limbs were randomised
Concomitant treatments	Drug free baseline period? No Concomitant pain treatment allowed? Unclear
Outcomes measures and effect sizes	

		CAPSAICIN 0.075% CREAM (FIXED DOSE 4X PER DAY)			PLACEBO			
		N	k	mean	N	k	mean	Δ
pain score:								
VAS – 28d[a]	Continuous	40		17	40		26	MD=-9.000
VAS – 56d[a]	Continuous	40		39	40		39	MD=0.000
VAS – 84d[a]	Continuous	40		37	40		35	MD=2.000
adverse events:								
Burning pain – 56d	Dichotomous	40	29	(72.5%)	40	16	(40.0%)	OR=3.955 (CI: 1.546, 10.114)
Pruritus – 56d[b]	Dichotomous	40	4	(10.0%)	40	2	(5.0%)	OR=2.111 (CI: 0.364, 12.240)
Rash – 56d	Dichotomous	40	1	(2.5%)	40	0	(0.0%)	OR=3.076 (CI: 0.122, 77.796)

[a] baseline data not relevant as outcome is pain relief
[b] described as 'itching' in publication

Comments	indication is distal painful polyneuropathy

Definitions of abbreviations are given at the end of this document.

Study	Luria et al. (2000)
Pain category	Peripheral pain
Study design	Country: Israel Design: Parallel Inclusion criteria: PDN with pain intensity of at least 4 on NRS 11 point Exclusion criteria: No exclusion criteria described Study length (days): 70 Intention-to-treat analysis? No
Participants	Total number of patients: 40 Number of males: 22 (55.0%) Underlying cause of neuropathic pain: Painful diabetic neuropathy Mean duration of NP (in months): not reported Baseline pain severity: 6.55 (NRS (average of arm means)) Mean age: 54
Intervention(s)	(1) Lamotrigine 400mg/d Intervention: lamotrigine Length of treatment (weeks): 8

	Fixed/flexible dose regimen: Fixed dose Set dose: 400mg/d Notes: started at 25 mg/d for 2 weeks, increased to 50 mg/d for a further 2 weeks and then 100, 200, 300, 400 mg/d each for 1 week (2) Placebo Intervention: placebo Length of treatment (weeks): 8 Fixed/flexible dose regimen: Fixed dose
Concomitant treatments	Drug free baseline period? Yes (duration: 7d) Concomitant pain treatment allowed? No (Patients were allowed rescue doses of simple analgesics (paracetamol or dipyrone) and NSAIDs)
Outcomes measures and effect sizes	

		LAMOTRIGINE 400MG/D			PLACEBO			
		N	k	mean	N	k	mean	Δ
pain score:								
NRS/NRS Pain – 0d[a]	Continuous	18		6.5 (SD 2.12)	16		6.6 (SD 1.2)	
NRS/NRS Pain – 56d[b]	Continuous	18		3.8 (SD 2.97)	16		5.2 (SD 2)	MD=-1.400 (CI: -3.086, 0.286)
at least 50% pain reduction (NRS) – 56d	Dichotomous	18	9	(50.0%)	16	3	(18.8%)	OR=4.333 (CI: 0.912, 20.595)
major adverse events (defined as leading to withdrawal):								
any major adverse event – 56d	Dichotomous	20	1	(5.0%)	20	0	(0.0%)	OR=3.154 (CI: 0.121, 82.165)
adverse events:								
Drowsiness – 56d	Dichotomous	20	2	(10.0%)	20	3	(15.0%)	OR=0.630 (CI: 0.093, 4.244)
GI disorders	Dichotomous	20	7	(35.0%)	20	4	(20.0%)	OR=2.154 (CI: 0.515, 9.000)
headache	Dichotomous	20	3	(15.0%)	20	1	(5.0%)	OR=3.353 (CI: 0.318, 35.364)
Rash – 56d	Dichotomous	20	2	(10.0%)	20	0	(0.0%)	OR=5.541 (CI: 0.249, 123.079)
treatment withdrawal:								
unspecified/other reason – 56d	Dichotomous	20	0	(0.0%)	20	2[c]	(10.0%)	OR=0.180 (CI: 0.008, 4.009)
protocol deviation – 56d	Dichotomous	20	0	(0.0%)	20	2	(10.0%)	OR=0.180 (CI: 0.008, 4.009)
poor compliance – 56d	Dichotomous	20	1	(5.0%)	20	0	(0.0%)	OR=3.154 (CI: 0.121, 82.165)
Rash – 56d	Dichotomous	20	1	(5.0%)	20	0	(0.0%)	OR=3.154 (CI: 0.121, 82.165)

[a] Ns inferred; demographic data on patients who completed only
[b] Ns inferred
[c] one for personal reasons, one for impotence before treatment but after randomisation

Comments	-

Definitions of abbreviations are given at the end of this document.

Study	Max et al. (1988)
Pain category	Peripheral pain
Study design	Country: USA Design: Crossover Inclusion criteria: daily PHN for at least 3 months, normal cognitive and communicative ability Exclusion criteria: presence of another pain as severe as the PHN, depression severe enough to mandate immediate treatment with tricyclics (ie suicidal

	ideation), medical contraindications to study drugs Study length (days): 105 Intention-to-treat analysis? No
Participants	Total number of patients: 58 Number of males: 31 (53.4%) Underlying cause of neuropathic pain: Post-herpetic neuralgia Mean duration of NP (in months): 19 Baseline pain severity: not reported (not reported (duration of NP is median) (Patient characteristics given are of the 58 patients who completed at least 1 period)) Mean age: 72
Intervention(s)	(1) Amitriptyline flexi-dose Intervention: amitriptyline Length of treatment (weeks): 6 Fixed/flexible dose regimen: Flexible dose Mean dose: 65mg/d Range: 12.5–150 Notes: dose escalation from 12.5 to 150 mg (or until highest tolerable level) (2) Placebo (lactose) Intervention: placebo Length of treatment (weeks): 6 Fixed/flexible dose regimen: Flexible dose Notes: Lactose 250 to 1500 mg/d
Concomitant treatments	Drug free baseline period? Yes (duration: 14d) Concomitant pain treatment allowed? Unclear
Outcomes measures and effect sizes	

		AMITRIPTYLINE FLEXI-DOSE			PLACEBO (LACTOSE)			
		N	k	mean	N	k	mean	Δ
pain score:								
100% pain relief – 42d	Dichotomous	62	1	(1.6%)	62	0	(0.0%)	OR=3.049 (CI: 0.122, 76.298)
major adverse events (defined as leading to withdrawal):								
any major adverse event – 42d	Dichotomous	62	5[a]	(8.1%)	62	3[b]	(4.8%)	OR=1.725 (CI: 0.394, 7.555)
adverse events:								
Dizziness – 42d[c]	Dichotomous	62	11	(17.7%)	62	15	(24.2%)	OR=0.676 (CI: 0.282, 1.618)
Dry mouth – 42d[c]	Dichotomous	62	38	(61.3%)	62	24	(38.7%)	OR=2.507 (CI: 1.217, 5.164)
impaired attention – 42d[d]	Dichotomous	62	4	(6.5%)	62	0	(0.0%)	OR=9.615 (CI: 0.507, 182.506)
mood disturbance – 42d[e]	Dichotomous	62	4	(6.5%)	62	0	(0.0%)	OR=9.615 (CI: 0.507, 182.506)
Sedation – 42d[c]	Dichotomous	62	38	(61.3%)	62	24	(38.7%)	OR=2.507 (CI: 1.217, 5.164)
urination difficulties – 42d[c]	Dichotomous	62	8	(12.9%)	62	0	(0.0%)	OR=19.495 (CI: 1.100, 345.635)

[a] due to urinary retention, sedation ,dizziness, palpitations, or rash
[b] due to dizziness, disorientation, or rash

	[c] calculated from percentages [d] calculated from percentages; reported as 'poor concentration' [e] calculated from percentages; reported as 'mood change'
Comments	crossover study of 2 drugs and placebo but lorazepam is not in scope so data on this drug was not extracted; pain intensity was reported with verbal descriptors (from two 13-word lists) with numerical equivalents of these descriptors - as this was not commonly used in other studies, this was not extracted (as unable to combine data with other studies); pain relief was also reported in a 5 point scale but this was not extracted for similar reasons; as only outcomes distracted were dichotomous, all were extracted on an intention-to-treat basis (ie. all patients randomised were included in the denominator); 21 patients dropped out, 14 for drug reactions (reported here for each group) 3 for no pain relief, 2 for onset of more severe pain not related to neuropathy, 1 acute bereavement, 1 medication error, 1 with no reason given (but treatment group of these later patients was not reported); results of amitriptyline showed a dose response relationship; 15 of 58 patients in the study were considered 'depressed' at baseline, though for most this was mild depression (pain relief was similar in these patients than those without depression)

Definitions of abbreviations are given at the end of this document.

Study	McCleane (1999)
Pain category	Mixed (central and peripheral) or unclear if mixed
Study design	Country: UK Design: Parallel Inclusion criteria: All participants had failed on codeine or NSAID based analgesics Exclusion criteria: People on anticonvulsants, sensitivity to lamotrigine Study length (days): 56 Intention-to-treat analysis? No
Participants	Total number of patients: 100 Number of males: 51 (51.0%) Underlying cause of neuropathic pain: Mixed neuropathic pain Mean duration of NP (in months): 74 Baseline pain severity: 6.76 (VAS) Mean age: 45
Intervention(s)	(1) Lamotrigine 200 mg/d Intervention: lamotrigine Length of treatment (weeks): 8 Fixed/flexible dose regimen: Fixed dose Set dose: 200mg/d Notes: One 25 mg tablet per day for 14 days, then 2 daily for 14 days, 4 for 7 days, 6 for 7 days and then 8 until the end of the study perio (2) Placebo Intervention: placebo Length of treatment (weeks): 8 Fixed/flexible dose regimen: Fixed dose
Concomitant	Drug free baseline period? No

treatments	Concomitant pain treatment allowed? Unclear (those already taking anti-convulsants were excluded but it is not clear if other pain medications were allowed)

Outcomes measures and effect sizes

		LAMOTRIGINE 200 MG/D			PLACEBO			
		N	k	mean	N	k	mean	Δ
pain score:								
VAS – 0d[a]	Continuous	50		6.76	50		6.76	
VAS – 56d[b]	Mean change	50		-0.01	50		0.03	MD=-0.040
at least 50% pain reduction (VAS)	Dichotomous	50	0	(0.0%)	50	0	(0.0%)	
patient-reported improvement in daily physical and emotional functioning, including sleep:								
VAS Sleep – 56d[b]	Mean change	50		-0.27	50		-0.15	MD=-0.120
major adverse events (defined as leading to withdrawal):								
any major adverse event – 56d	Dichotomous	50	5[c]	(10.0%)	50	5[d]	(10.0%)	OR=1.000 (CI: 0.271, 3.694)
treatment withdrawal:								
due to lack of efficacy – 56d	Dichotomous	50	4	(8.0%)	50	2	(4.0%)	OR=2.087 (CI: 0.365, 11.948)
Nausea – 56d	Dichotomous	50	3	(6.0%)	50	5	(10.0%)	OR=0.574 (CI: 0.130, 2.545)
Rash – 56d	Dichotomous	50	2	(4.0%)	50	0	(0.0%)	OR=5.206 (CI: 0.244, 111.238)
Bad Taste of tablets – 56d	Dichotomous	50	1	(2.0%)	50	1	(2.0%)	OR=1.000 (CI: 0.061, 16.444)

[a] Ns inferred from adverse effects data; value is average baseline data across patients in both groups
[b] Ns inferred from adverse effects data
[c] nausea - 3, rash - 2
[d] all because of nausea

Comments	8 additional patients were lost to follow-up but it was not clear which treatment group they were in; patient numbers seem unclear - it appears each group had 50 patients but demographic data only available on 74 (also, final numbers not explained by reported drop-outs); study only reported safety events of each group where people dropped out of the study

Definitions of abbreviations are given at the end of this document.

Study	McCleane (2000)
Pain category	Mixed (central and peripheral) or unclear if mixed
Study design	Country: Ireland Design: Parallel Inclusion criteria: Chronic neuropathic pain, unresponsive or intolerant to analgesics, TCA or NSAIDs Exclusion criteria: known sensitivity to capsaicin or doxepin, broken skin over the painful area, Study length (days): 28 Intention-to-treat analysis? No
Participants	Total number of patients: 100 Number of males: 29 (29.0%) Underlying cause of neuropathic pain: Mixed neuropathic pain

	Mean duration of NP (in months): 58.65 Baseline pain severity: 7.12 (VAS (average of arm means)) Mean age: 46.65
Intervention(s)	(1) Capsaicin 0.025% (fixed dosage 3x per day) Intervention: capsaicin cream Length of treatment (weeks): 4 Fixed/flexible dose regimen: Fixed dose Notes: used equal amount 3 times daily (2) Placebo Intervention: placebo Length of treatment (weeks): 4 Fixed/flexible dose regimen: Fixed dose
Concomitant treatments	Drug free baseline period? No Concomitant pain treatment allowed? Unclear
Outcomes measures and effect sizes	

		CAPSAICIN 0.025% (FIXED DOSAGE 3X PER DAY)			PLACEBO			
		N	k	mean	N	k	mean	Δ
pain score:								
VAS – 0d	Continuous	33		7.11	41		7.13	
VAS – 28d	Mean change	33		-1.12 (SD 1.99)	41		0[a]	MD=-1.120
adverse events:								
Burning pain – 28d[b]	Dichotomous	33	27	(81.8%)	41	22	(53.7%)	OR=3.886 (CI: 1.324, 11.407)
treatment withdrawal:								
poor compliance – 28d	Dichotomous	33	8	(24.2%)	41	3	(7.3%)	OR=4.053 (CI: 0.980, 16.763)

[a] study stated that values for placebo did not change
[b] defined as 'burning discomfort' in study

Comments	study included 2 arms with either topical doxepin or topical doxepin/placebo (both arms excluded because it is not oral administration of doxepin)

Definitions of abbreviations are given at the end of this document.

Study	Mishra et al. (2012)
Pain category	Mixed (central and peripheral) or unclear if mixed
Study design	Country: India Design: Parallel Inclusion criteria: Patients with cancer having neuropathic pain Exclusion criteria: Patients with unstable cardiovascular, respiratory, hepatic or hematological disease or psychological disorder and drug abuse were excluded. Study length (days): 28 Intention-to-treat analysis? Unclear

Participants	Total number of patients: 120 Number of males: not reported Underlying cause of neuropathic pain: Cancer pain Mean duration of NP (in months): not reported Baseline pain severity: 7.6 (VAS (average of arm means)) Mean age: not reported
Intervention(s)	(1) Amitriptyline 100 mg/d Intervention: amitriptyline Length of treatment (weeks): 4 Fixed/flexible dose regimen: Fixed dose Set dose: 100mg/d Notes: 50 mg/d for 1 week, 75 mg/d in second week, 100 mg/d in 3rd week (2) gabapentin 1800 mg/d Intervention: gabapentin Length of treatment (weeks): 4 Fixed/flexible dose regimen: Fixed dose Set dose: 1800mg/d Notes: 900 mg/d for 1 week in divided doses, 1200 mg/d in 2nd week and 1800 mg/d in 3rd week (3) Pregabalin 600 mg/d Intervention: pregabalin Length of treatment (weeks): 4 Fixed/flexible dose regimen: Fixed dose Set dose: 600mg/d Notes: 150 mg/d for 1 week in divided doses, 200 mg/d in 2nd week and 600 mg/d in 3rd week (4) Placebo Intervention: placebo Length of treatment (weeks): 4 Fixed/flexible dose regimen: Fixed dose
Concomitant treatments	Drug free baseline period? No Concomitant pain treatment allowed? Unclear (immediate release morphine was given orally as rescue analgesia)
Outcomes measures and effect sizes	

		AMITRIPTYLINE 100 MG/D			GABAPENTIN 1800 MG/D			
		N	k	mean	N	k	mean	Δ
pain score:								
VAS – 0d	Continuous	30		7.77 (SD 1)	30		7.5 (SD 1.1)	
VAS – 14d[a]	Continuous	30		6.85 (SD 1.2)	30		6.39 (SD 1.6)	MD=0.460 (CI: -0.256, 1.176)
VAS – 21d[a]	Continuous	30		4.85 (SD 1)	30		4.87 (SD 1.28)	MD=-0.020 (CI: -0.601, 0.561)
VAS – 28d	Continuous	30		3.23 (SD 0.7)	30		3.07 (SD 0.8)	MD=0.160 (CI: -0.220, 0.540)
use of rescue medication:								
proportion requiring morphine[b]	Dichotomous	30	17	(56.7%)	30	10	(33.3%)	

[a] Estimated from graphs

[b] calculated from percentage

		AMITRIPTYLINE 100 MG/D			PREGABALIN 600 MG/D			
		N	k	mean	N	k	mean	Δ
pain score:								
VAS – 0d	Continuous	30		7.77 (SD 1)	30		7.77 (SD 0.81)	
VAS – 14d[a]	Continuous	30		6.85 (SD 1.2)	30		6.3 (SD 1.2)	MD=0.550 (CI: -0.057, 1.157)
VAS – 21d[a]	Continuous	30		4.85 (SD 1)	30		4.31 (SD 1.05)	MD=0.540 (CI: 0.021, 1.059)
VAS – 28d	Continuous	30		3.23 (SD 0.7)	30		2.5 (SD 0.7)	MD=0.730 (CI: 0.376, 1.084)
use of rescue medication:								
proportion requiring morphine[b]	Dichotomous	30	17	(56.7%)	30	5	(16.7%)	

[a] Estimated from graphs
[b] calculated from percentage

		AMITRIPTYLINE 100 MG/D			PLACEBO			
		N	k	mean	N	k	mean	Δ
pain score:								
VAS – 0d	Continuous	30		7.77 (SD 1)	30		7.47 (SD 1)	
VAS – 14d[a]	Continuous	30		6.85 (SD 1.2)	30		6.1 (SD 0.8)	MD=0.750 (CI: 0.234, 1.266)
VAS – 21d[a]	Continuous	30		4.85 (SD 1)	30		4.4 (SD 0.6)	MD=0.450 (CI: 0.033, 0.867)
VAS – 28d	Continuous	30		3.23 (SD 0.7)	30		3.4 (SD 0.66)	MD=-0.170 (CI: -0.514, 0.174)
use of rescue medication:								
proportion requiring morphine	Dichotomous	30	17[b]	(56.7%)	30	30	(100.0%)	

[a] Estimated from graphs
[b] calculated from percentage

		GABAPENTIN 1800 MG/D			PREGABALIN 600 MG/D			
		N	k	mean	N	k	mean	Δ
pain score:								
VAS – 0d	Continuous	30		7.5 (SD 1.1)	30		7.77 (SD 0.81)	
VAS – 14d[a]	Continuous	30		6.39 (SD 1.6)	30		6.3 (SD 1.2)	MD=0.090 (CI: -0.626, 0.806)
VAS – 21d[a]	Continuous	30		4.87 (SD 1.28)	30		4.31 (SD 1.05)	MD=0.560 (CI: -0.032, 1.152)
VAS – 28d	Continuous	30		3.07 (SD 0.8)	30		2.5 (SD 0.7)	MD=0.570 (CI: 0.190, 0.950)
use of rescue medication:								
proportion requiring morphine[b]	Dichotomous	30	10	(33.3%)	30	5	(16.7%)	

[a] Estimated from graphs
[b] calculated from percentage

		GABAPENTIN 1800 MG/D			PLACEBO			
		N	k	mean	N	k	mean	Δ
pain score:								
VAS – 0d	Continuous	30		7.5 (SD 1.1)	30		7.47 (SD 1)	

VAS – 14d[a]	Continuous	30		6.39 (SD 1.6)	30		6.1 (SD 0.8)	MD=0.290 (CI: -0.350, 0.930)
VAS – 21d[a]	Continuous	30		4.87 (SD 1.28)	30		4.4 (SD 0.6)	MD=0.470 (CI: -0.036, 0.976)
VAS – 28d	Continuous	30		3.07 (SD 0.8)	30		3.4 (SD 0.66)	MD=-0.330 (CI: -0.701, 0.041)
use of rescue medication:								
proportion requiring morphine	Dichotomous	30	10[b]	(33.3%)	30	30	(100.0%)	

[a] Estimated from graphs
[b] calculated from percentage

		PREGABALIN 600 MG/D			PLACEBO			
		N	k	mean	N	k	mean	Δ
pain score:								
VAS – 0d	Continuous	30		7.77 (SD 0.81)	30		7.47 (SD 1)	
VAS – 14d[a]	Continuous	30		6.3 (SD 1.2)	30		6.1 (SD 0.8)	MD=0.200 (CI: -0.316, 0.716)
VAS – 21d[a]	Continuous	30		4.31 (SD 1.05)	30		4.4 (SD 0.6)	MD=-0.090 (CI: -0.523, 0.343)
VAS – 28d	Continuous	30		2.5 (SD 0.7)	30		3.4 (SD 0.66)	MD=-0.900 (CI: -1.244, -0.556)
use of rescue medication:								
proportion requiring morphine	Dichotomous	30	5[b]	(16.7%)	30	30	(100.0%)	

[a] Estimated from graphs
[b] calculated from percentage

Comments	Function was measured by the Eastern Co-operative Oncology Group (ECOG) scoring but this was not extracted; global pain was reported on a 5-point VRS but this was not extracted as it is not possible to synthesise this with a 7-point PGIC scale; the study reported that the most commonly reported adverse events were dizziness, dry mouth, somnolence, nausea and constipation but did not report actual rates of these events with each treatment arm (however, they did report a scoring of adverse events across all drug in a table); authors state that in patients treated with pregabalin, the maximum number of patients had only mild events compared to other groups while patients with moderate events were maximum in the placebo group.

Definitions of abbreviations are given at the end of this document.

Study	Moon et al. (2010)
Pain category	Peripheral pain
Study design	Country: Korea Design: Parallel Inclusion criteria: Outpatients at least 18 years of age with a diagnosis of peripheral neuropathic pain syndrome for at least 3 months, and a daily pain rating score of at least 4 in the 7 days prior to randomisation Exclusion criteria: pregnancy, lactating women (or of childbearing potential and not using effective contraception), unstable medication conditions, significant medical conditions including neurologic conditions causing severe pain unrelated to DPN, PHN or posttraumatic NP, participation in other studies at the same time or within 30 days before screening, any who had received concomitant transcutaneous electrical nerve stimulation or acupuncture Study length (days): 56 Intention-to-treat analysis? Yes
Participants	Total number of patients: 240 Number of males: 111 (46.3%)

	Underlying cause of neuropathic pain: Peripheral neuropathic pain Mean duration of NP (in months): not reported Baseline pain severity: 6.295 (NRS (average of arm means)) Mean age: 60.5
Intervention(s)	(1) Pregabalin (flexible dose) Intervention: pregabalin Length of treatment (weeks): 8 Fixed/flexible dose regimen: Flexible dose Mean dose: 480mg/d Range: 150–600 Notes: 4 week dose adjustment and 4 week maintenance phase (2) Placebo Intervention: placebo Length of treatment (weeks): 8 Fixed/flexible dose regimen: Flexible dose
Concomitant treatments	Drug free baseline period? No Concomitant pain treatment allowed? Yes (Analgesics and anti-depressants that were maintained at a stable dose during the screening period were allowed to be continued (unclear if other anti-convulsants such as gabapentin were excluded))
Outcomes measures and effect sizes	

		PREGABALIN (FLEXIBLE DOSE)			PLACEBO			
		N	k	mean	N	k	mean	Δ
pain score:								
NRS/NRS Pain – 0d	Continuous	162		6.28 (SD 1.52)	78		6.31 (SD 1.45)	
NRS/NRS Pain – 56d	Continuous	162		4.61 (SD 2.12)	78		5.17 (SD 2.18)	MD=-0.500 (CI: -1.000, 0.000)
at least 30% pain reduction (NRS) – 56d	Dichotomous	162	68	(42.0%)	78	27	(34.6%)	OR=1.366 (CI: 0.780, 2.395)
at least 50% pain reduction (NRS) – 56d	Dichotomous	162	42	(25.9%)	78	11	(14.1%)	OR=2.132 (CI: 1.029, 4.415)
patient-reported global improvement:								
PGIC - worse (all grades) or no change – 56d	Dichotomous	162	44	(27.2%)	78	24	(30.8%)	OR=0.839 (CI: 0.464, 1.517)
PGIC - better (all grades) – 56d	Dichotomous	162	118	(72.8%)	78	54	(69.2%)	OR=1.192 (CI: 0.659, 2.156)
patient-reported improvement in daily physical and emotional functioning, including sleep:								
MOS sleep disturbance – 56d	Continuous	162			78			MD=-0.650 (CI: -1.190, -0.110)
MOS sleep interference – 56d	Continuous	162			78			MD=-5.620 (CI: -10.820, -0.420)
MOS sleep quantitiy – 56d	Continuous	162			78			MD=0.440 (CI: 0.080, 0.800)
MOS somnolence – 56d	Continuous	162			78			MD=4.710 (CI: 0.080, 9.340)
HADS-A – 56d	Continuous	162			78			MD=-0.850 (CI: -1.655, -0.045)
HADS-D – 56d	Continuous	162			78			MD=-0.190 (CI: -1.050, 0.670)
MOS sleep adequacy – 56d	Continuous	162			78			MD=2.150 (CI: -5.330, 9.630)
MOS sleep problems index – 56d	Continuous	162			78			MD=-2.120 (CI: -6.150, 1.910)
MOS snoring – 56d	Continuous	162			78			MD=5.050 (CI: -1.475, 11.575)
MOS short of breath/headache – 56d	Continuous	162			78			MD=-3.090 (CI: -6.810, 0.630)
major adverse events (defined as leading to withdrawal):								
any major adverse event – 56d	Dichotomous	162	8	(4.9%)	78	6	(7.7%)	OR=0.623 (CI: 0.209, 1.863)

	overall improvement in quality of life:									
	EQ-5D - health status index – 56d	Continuous	162			78			MD=0.030 (CI: -0.035, 0.095)	
	EQ-5D - health status VAS – 56d	Continuous	162			78			MD=3.500 (CI: -1.180, 8.180)	
	treatment withdrawal:									
	due to lack of efficacy – 56d	Dichotomous	162	8	(4.9%)	78	6	(7.7%)	OR=0.623 (CI: 0.209, 1.863)	
	unspecified/other reason – 56d	Dichotomous	162	6	(3.7%)	78	2	(2.6%)	OR=1.462 (CI: 0.288, 7.412)	
	withdrawal of consent – 56d	Dichotomous	162	5	(3.1%)	78	4	(5.1%)	OR=0.589 (CI: 0.154, 2.258)	
	Rates of adverse events not reported for placebo									
Comments	diagnoses included DPN, PHN, and posttraumatic neuropathic pain									

Definitions of abbreviations are given at the end of this document.

Study	Morello et al. (1999)
Pain category	Peripheral pain
Study design	Country: USA Design: Crossover Inclusion criteria: PDN for at least 3 months, experienced chronic daily pain for more than 3 months, creatinine clearance of 0.5 ml/s Exclusion criteria: non-DPN pain more severe than DPN pain, allergy or adverse reaction to either drug, severe depression by diagnosis or as assessed with the Beck Depression Inventory, pregnancy, treatment for seizures, cardiovascular symptoms of postural hypotension, sympotomatic coronary artery or peripheral vascular disease, creatinine clearance < 0.5 ml/s, prior treatment with either drug only if the previous dosage exceeding the study's maximum dosage of either drug Study length (days): 105 Intention-to-treat analysis? No
Participants	Total number of patients: 25 Number of males: 24 (96.0%) Underlying cause of neuropathic pain: Painful diabetic neuropathy Mean duration of NP (in months): 68.4 Baseline pain severity: 1.005 (Gracey pain scale (average of arm means, both estimated from graph)) Mean age: 60.4 (SD: 10.8)
Intervention(s)	(1) Amitriptyline flexible dose Intervention: amitriptyline Length of treatment (weeks): 6 Fixed/flexible dose regimen: Flexible dose Mean dose: 59mg/d Range: 25–75 Notes: 2-day titration (2) Gabapentin flexible dose

	Intervention: gabapentin Length of treatment (weeks): 6 Fixed/flexible dose regimen: Flexible dose Mean dose: 1565mg/d Range: 900–1800 Notes: 2-day titration
Concomitant treatments	Drug free baseline period? Yes (duration: 14d) Concomitant pain treatment allowed? No (all were discontinued for 2 weeks before entering the study and throughout the study, including regular use of analgesics; however, up to 4 doses per day of paracetamol (325 mg) was allowed for severe pain or pain other than DPN)

Outcomes measures and effect sizes

		AMITRIPTYLINE FLEXIBLE DOSE			GABAPENTIN FLEXIBLE DOSE			
		N	k	mean	N	k	mean	Δ
pain score:								
100% pain relief – 42d	Dichotomous	25	5	(20.0%)	25	5	(20.0%)	OR=1.000 (CI: 0.250, 3.998)
major adverse events (defined as leading to withdrawal):								
any major adverse event – 42d[a]	Dichotomous	25	3	(12.0%)	25	2	(8.0%)	OR=1.568 (CI: 0.239, 10.300)
adverse events:								
any adverse event – 42d	Dichotomous	25	17	(68.0%)	25	18	(72.0%)	OR=0.826 (CI: 0.246, 2.776)
Blurred vision – 42d	Dichotomous	25	2	(8.0%)	25	1	(4.0%)	OR=2.087 (CI: 0.177, 24.615)
Constipation – 42d	Dichotomous	25	3	(12.0%)	25	5	(20.0%)	OR=0.545 (CI: 0.115, 2.581)
Diarrhoea – 42d	Dichotomous	25	1	(4.0%)	25	2	(8.0%)	OR=0.479 (CI: 0.041, 5.652)
Dizziness – 42d	Dichotomous	25	2	(8.0%)	25	7	(28.0%)	OR=0.224 (CI: 0.041, 1.210)
headache – 42d	Dichotomous	25	3	(12.0%)	25	2	(8.0%)	OR=1.568 (CI: 0.239, 10.300)
lethargy – 42d	Dichotomous	25	5	(20.0%)	25	4	(16.0%)	OR=1.313 (CI: 0.308, 5.598)
Nausea – 42d	Dichotomous	25	1	(4.0%)	25	2	(8.0%)	OR=0.479 (CI: 0.041, 5.652)
oedema – 42d	Dichotomous	25	2	(8.0%)	25	3	(12.0%)	OR=0.638 (CI: 0.097, 4.188)
Pruritus – 42d	Dichotomous	25	3	(12.0%)	25	1	(4.0%)	OR=3.273 (CI: 0.317, 33.837)
Weight gain – 42d	Dichotomous	25	6	(24.0%)	25	0	(0.0%)	OR=17.000 (CI: 0.902, 320.365)
treatment withdrawal:								
due to lack of efficacy – 42d	Dichotomous	25	0	(0.0%)	25	1	(4.0%)	OR=0.320 (CI: 0.012, 8.245)
protocol deviation – 42d	Dichotomous	25	1	(4.0%)	25	0	(0.0%)	OR=3.122 (CI: 0.121, 80.391)
treatment phase 1								
pain score:								
Gracely pain score – 0d[b]	Continuous	10		1.06	9		0.95	
Gracely pain score – 28d[b]	Mean change	10		-0.374	9		-0.261	MD=-0.113
Gracely pain score – 28d[b]	Continuous	10		0.82	9		0.63	MD=0.190
Gracely pain score – 42d	Mean change	10		-0.31 (SD 0.231)	9		-0.44 (SD 0.308)	MD=0.130 (CI: -0.117, 0.377)
Gracely pain score – 42d[b]	Continuous	10		0.52	9		0.68	MD=-0.160
treatment phase 2								
pain score:								
Gracely pain score – 0d[b]	Continuous	9		0.84	10		0.98	
Gracely pain score – 28d[b]	Continuous	9		0.37	10		0.78	MD=-0.410
Gracely pain score – 42d[b]	Continuous	9		0.8	10		0.36	MD=0.440

[a] one of these patients crossed over to the other treatment group
[b] data estimated from graph

Comments	authors did not perform ITT analysis but dichotomous outcomes are recorded here including all patients randomised in the denominator; authors also report proportion of patients with various levels of pain relief but it was not possible to extract this into 30% or 50% response

Definitions of abbreviations are given at the end of this document.

Study	Norrbrink & Lundeberg (2009)
Pain category	Mixed (central and peripheral) or unclear if mixed
Study design	Country: Sweden Design: Parallel Inclusion criteria: Participants between 18 and 70 years of age with no known cognitive dysfunction and currently not using tramadol with an SCI for more than 12 months, pain classified as neuropathic pain at or below the level of leision 14 and of a duration of more than 6 months. Patients had to be naive to tramadol and have no signs of intolerance to treatment with opioids in the past Exclusion criteria: Patients who were pregnant or lactating, patients who had previously taken tramadol, patients who were intolerant of opioids. Study length (days): 28 Intention-to-treat analysis? Yes
Participants	Total number of patients: 35 Number of males: 28 (80.0%) Underlying cause of neuropathic pain: Spinal cord injury pain Mean duration of NP (in months): not reported Baseline pain severity: 5.5 (present pain intensity on combined NRS and VRS (average of arm medians); average of medians for present pain intensity on combined NRS and VRS scale is 4) Mean age: 51.3 (SD: 10.8)
Intervention(s)	(1) Tramadol (flexible dose) Intervention: tramadol Length of treatment (weeks): 4 Fixed/flexible dose regimen: Flexible dose Mean dose: 326mg/d Range: 150–400 Notes: initial dose was 50 mg/d 3 times per day and increased every 5 days by 50 mg until a maximum of 400 mg/d was reached (if optimal pain relief was obtained or if adverse events became intolerabel before maximum dose was reached, patients stopped increasing their dosage) (2) Placebo Intervention: placebo Length of treatment (weeks): 4 Fixed/flexible dose regimen: Flexible dose
Concomitant treatments	Drug free baseline period? No Concomitant pain treatment allowed? Yes (Patients allowed to continue stable pain medication and asked not to make any changes in their current dosages)

Outcomes measures and effect sizes

		TRAMADOL (FLEXIBLE DOSE)			PLACEBO			
		N	k	mean	N	k	mean	Δ
pain score:								
combined NRS & VRS – 0d	Continuous	23		med: 3[a]	12		med: 7[b]	
combined NRS & VRS – 0d	Continuous	23		med: 4[c]	12		med: 5[d]	
combined NRS & VRS – 0d	Continuous	23		med: 4[c]	12		med: 7[b]	
combined NRS & VRS – 0d	Continuous	23		med: 3[a]	12		med: 5[d]	
combined NRS & VRS – 28d	Continuous	23		med: 3[e]	12		med: 5.5[f]	
combined NRS & VRS – 28d	Continuous	23		med: 3[e]	12		med: 6.5[g]	
combined NRS & VRS – 28d	Continuous	23		med: 3[h]	12		med: 5.5[f]	
combined NRS & VRS – 28d	Continuous	23		med: 3[h]	12		med: 6.5[g]	
patient-reported improvement in daily physical and emotional functioning, including sleep:								
HADS-A – 0d	Continuous	23		med: 7[i]	12		med: 9[j]	
HADS-A – 28d	Continuous	23		med: 6[k]	12		med: 9[l]	
HADS-D – 0d	Continuous	23		med: 4[m]	12		med: 4.5[n]	
HADS-D – 28d	Continuous	23		med: 3[o]	12		med: 5[p]	
major adverse events (defined as leading to withdrawal):								
any major adverse event – 28d	Dichotomous	23	11	(47.8%)	12	2	(16.7%)	OR=4.583 (CI: 0.817, 25.714)
adverse events:								
any adverse event – 28d	Dichotomous	23	21	(91.3%)	12	7	(58.3%)	OR=7.500 (CI: 1.180, 47.676)
Constipation – 28d	Dichotomous	23	9	(39.1%)	12	3	(25.0%)	OR=1.929 (CI: 0.409, 9.104)
Dizziness – 28d	Dichotomous	23	12	(52.2%)	12	3	(25.0%)	OR=3.273 (CI: 0.700, 15.291)
Dry mouth – 28d	Dichotomous	23	12	(52.2%)	12	3	(25.0%)	OR=3.273 (CI: 0.700, 15.291)
Nausea – 28d	Dichotomous	23	11	(47.8%)	12	2	(16.7%)	OR=4.583 (CI: 0.817, 25.714)
tiredness – 28d	Dichotomous	23	17	(73.9%)	12	2	(16.7%)	OR=14.167 (CI: 2.387, 84.070)
voiding dysfunction – 28d	Dichotomous	23	1	(4.3%)	12	0	(0.0%)	OR=1.667 (CI: 0.063, 44.047)
treatment withdrawal:								
unspecified/other reason – 28d	Dichotomous	23	11	(47.8%)	12	2	(16.7%)	OR=4.583 (CI: 0.817, 25.714)
Treatment completers								
patient-reported global improvement:								
PGIC - much worse – 28d	Dichotomous	12	0	(0.0%)	10	0	(0.0%)	OR=0.840 (CI: 0.015, 46.086)
PGIC - moderately worse – 28d	Dichotomous	12	0	(0.0%)	10	0	(0.0%)	OR=0.840 (CI: 0.015, 46.086)
PGIC - minimally worse – 28d	Dichotomous	12	0	(0.0%)	10	0	(0.0%)	OR=0.840 (CI: 0.015, 46.086)
PGIC - no change – 28d	Dichotomous	12	5	(41.7%)	10	9	(90.0%)	OR=0.079 (CI: 0.007, 0.843)
PGIC - minimally better – 28d	Dichotomous	12	3	(25.0%)	10	1	(10.0%)	OR=3.000 (CI: 0.260, 34.575)
PGIC - moderately better – 28d	Dichotomous	12	4	(33.3%)	10	0	(0.0%)	OR=11.118 (CI: 0.522, 236.755)
PGIC - at least moderately better – 28d	Dichotomous	12	4	(33.3%)	10	0	(0.0%)	OR=11.118 (CI: 0.522, 236.755)
PGIC - much better – 28d	Dichotomous	12	0	(0.0%)	10	0	(0.0%)	OR=0.840 (CI: 0.015, 46.086)

[a] present pain intensity; IQR given - 2.5;5
[b] general pain intensity; IQR given - 4.5;7
[c] general pain intensity; IQR given - 3;5
[d] present pain intensity; IQR given - 4.5;5.5
[e] general pain intensity; IQR given - 2.5;5
[f] present pain intensity; IQR given - 3.5;7
[g] general pain intensity; IQR given - 6;7.25
[h] present pain intensity; IQR given - 2;4
[i] IQRs also reported 2;9

	[j] IQRs also reported 5.75;13 [k] IQRs also reported 1;8 [l] IQRs also reported 5.5;12 [m] IQRs also reported 2;8.5 [n] IQRs also reported 3;13.5 [o] IQRs also reported 2;6 [p] IQRs also reported 2;4.5
Comments	intentin-to-treat analysis included all patients who received at least one dose of study medication

Definitions of abbreviations are given at the end of this document.

Study	Nurmikko et al. (2007)
Pain category	Peripheral pain
Study design	Country: UK & Belgium Design: Parallel Inclusion criteria: Patients with a current history of unilateral peripheral neuropathic pain and allodynia Exclusion criteria: cannabinoid use or nabilone at least 7 days before randomisation, psychiatric conditions beyond depression, concomitant severe non-neuropathic pain, known hisotyr of alcohol or substance abuse, known hypersensitivity to cannabinoilds, scheduled surgery or anaesthesia, severe cardiovascular condition, poorly controlled hypertension, epilepsy, pregnancy, lactation, significant hepatic or renal impairment Study length (days): 35 Intention-to-treat analysis? Yes
Participants	Total number of patients: 125 Number of males: 51 (40.8%) Underlying cause of neuropathic pain: Peripheral neuropathic pain Mean duration of NP (in months): 75.6 Baseline pain severity: 7.25 (NRS (average of arm means)) Mean age: 53.35
Intervention(s)	(1) Sativex oral spray (flexible dose) Intervention: cannabis sativa extract Length of treatment (weeks): 5 Fixed/flexible dose regimen: Flexible dose Mean dose: 29.43mg/d Notes: Max dose of 8 sprays per 3 hour period and 48 sprays per 24hour period. Each spray delivers 2.7 mg of THC and 2.5mg of CBD; mean number of sprays used daily during the first week was 7.3 (3.5 standard deviation) - this remained stable from the 2nd week onward; over the study period, mean number of daily sprays was 10.9 (6.8 standard deviation) (2) Placebo Intervention: placebo Length of treatment (weeks): 5 Fixed/flexible dose regimen: Flexible dose Notes: mean number of sprays used daily during the first week was 10.9 (3.9 standard deviation) - this remained stable from the 2nd week onward; over

	the study period, mean number of daily sprays was 19 (8.3 standard deviation)
Concomitant treatments	Drug free baseline period? No Concomitant pain treatment allowed? Yes (concomitant analgesia maintained at a stable dose)
Outcomes measures and effect sizes	

		SATIVEX ORAL SPRAY (FLEXIBLE DOSE)			PLACEBO			
		N	k	mean	N	k	mean	Δ
pain score:								
NRS/NRS Pain – 0d	Continuous	63		7.3 (SD 1.4)	62		7.2 (SD 1.5)	
NRS/NRS Pain – 21d[a]	Continuous	63		5.5 (SD 2.81)	62		6.5 (SD 2.41)	MD=-1.000 (CI: -1.918, -0.082)
NRS/NRS Pain – 28d[a]	Continuous	63		5.5 (SD 2.94)	62		6.5 (SD 2.41)	MD=-1.000 (CI: -1.941, -0.059)
NRS/NRS Pain – 35d[a]	Continuous	63		5.82 (SD 3.14)	62		6.68 (SD 2.51)	MD=-0.860 (CI: -1.856, 0.136)
at least 30% pain reduction (NRS) – 35d	Dichotomous	63	16	(25.4%)	62	9	(14.5%)	OR=2.005 (CI: 0.810, 4.961)
at least 50% pain reduction (NRS) – 35d	Dichotomous	63	13	(20.6%)	62	5	(8.1%)	OR=2.964 (CI: 0.988, 8.896)
NPS – 0d[a]	Continuous	63		61.1 (SD 13)	62		62.4 (SD 13.7)	
NPS – 35d[a]	Mean change	63		-10.1	62		-2.04	MD=-8.030 (CI: -13.830, -2.230)
patient-reported global improvement:								
PGIC – 35d	Mean change	63			62			MD=32.260 (CI: 16.400, 48.120)
patient-reported improvement in daily physical and emotional functioning, including sleep:								
NRS Sleep – 0d[a]	Continuous	63		3 (SD 0.8)	62		3 (SD 0.9)	
NRS Sleep – 35d[a]	Mean change	63		-0.79	62		-0.36	MD=-0.430 (CI: -0.670, -0.190)
major adverse events (defined as leading to withdrawal):								
any major adverse event – 35d	Dichotomous	63	11	(17.5%)	62	2	(3.2%)	OR=6.346 (CI: 1.345, 29.951)
adverse events:								
Diarrhoea	Dichotomous	63	4	(6.3%)	62	0	(0.0%)	OR=9.454 (CI: 0.498, 179.405)
Dizziness – 35d	Dichotomous	63	18	(28.6%)	62	9	(14.5%)	OR=2.356 (CI: 0.964, 5.755)
Dry mouth – 35d	Dichotomous	63	11	(17.5%)	62	3	(4.8%)	OR=4.160 (CI: 1.100, 15.729)
Fatigue – 35d	Dichotomous	63	13	(20.6%)	62	5	(8.1%)	OR=2.964 (CI: 0.988, 8.896)
feeling drunk/drugged	Dichotomous	63	6	(9.5%)	62	1	(1.6%)	OR=6.421 (CI: 0.750, 54.990)
headache	Dichotomous	63	6	(9.5%)	62	9	(14.5%)	OR=0.620 (CI: 0.207, 1.860)
Nausea – 35d	Dichotomous	63	14	(22.2%)	62	7	(11.3%)	OR=2.245 (CI: 0.838, 6.015)
Somnolence – 35d	Dichotomous	63	4	(6.3%)	62	1	(1.6%)	OR=4.136 (CI: 0.449, 38.091)
Vomiting	Dichotomous	63	8	(12.7%)	62	3	(4.8%)	OR=2.861 (CI: 0.722, 11.334)
treatment withdrawal:								
due to lack of efficacy – 35d	Dichotomous	63	1	(1.6%)	62	5	(8.1%)	OR=0.184 (CI: 0.021, 1.622)
protocol deviation – 35d	Dichotomous	63	1	(1.6%)	62	0	(0.0%)	OR=3.000 (CI: 0.120, 75.066)
Nausea – 35d	Dichotomous	63	1	(1.6%)	62	0	(0.0%)	OR=3.000 (CI: 0.120, 75.066)
Dizziness – 35d	Dichotomous	63	2	(3.2%)	62	0	(0.0%)	OR=5.081 (CI: 0.239, 108.015)
Vomiting – 35d	Dichotomous	63	2	(3.2%)	62	0	(0.0%)	OR=5.081 (CI: 0.239, 108.015)
Feeling drunk – 35d	Dichotomous	63	1	(1.6%)	62	0	(0.0%)	OR=3.000 (CI: 0.120, 75.066)
diarrhoea – 35d	Dichotomous	63	2	(3.2%)	62	0	(0.0%)	OR=5.081 (CI: 0.239, 108.015)
anorexia – 35d	Dichotomous	63	1	(1.6%)	62	0	(0.0%)	OR=3.000 (CI: 0.120, 75.066)
somnolence – 35d	Dichotomous	63	0	(0.0%)	62	1	(1.6%)	OR=0.323 (CI: 0.013, 8.078)

[a] estimated from graphs

Comments	-

Definitions of abbreviations are given at the end of this document.

Study	Otto et al. (2008)
Pain category	Peripheral pain
Study design	Country: Denmark Design: Crossover Inclusion criteria: age > 20 and < 80 with polyneuropathy for> 6 months (distal bilateral sensory disturbances and decreased deep tendon reflexes) confirmed by electrophysciological tests or quantitative sensory testing; median pain rating of at least 4 on a 0-10 point scale for total pain at study entry after 1 week off pain medication Exclusion criteria: causes of pain other than polyneuropathy, previous allergic reaction to study drug or citalopram, pregnancy or lactation, severe terminal illness or concomitant treatment with monoaminoxidaase inhibitors, antidepressants or anticonvulsants Study length (days): 98 Intention-to-treat analysis? Yes
Participants	Total number of patients: 48 Number of males: 29 (60.4%) Underlying cause of neuropathic pain: Polyneuropathy Mean duration of NP (in months): 48 Baseline pain severity: 5.6 (NRS (median duration of NP, baseline pain intensity, and age)) Mean age: 62
Intervention(s)	(1) Escitalopram 20 mg/d Intervention: escitalopram Length of treatment (weeks): 5 Fixed/flexible dose regimen: Fixed dose Set dose: 20mg/d Notes: from 10 mg/d in the first week to 20 mg/d for the remaining treatment period (2) Placebo Intervention: placebo Length of treatment (weeks): 5 Fixed/flexible dose regimen: Fixed dose
Concomitant treatments	Drug free baseline period? Yes (duration: 7d) Concomitant pain treatment allowed? No (use of monoaminoxidase inhibitors, anti-depressants or anti-convulsants prohibited; up to six tablets of 500 mg paracetamol could be used daily as escape medication)

Outcomes measures and effect sizes

		ESCITALOPRAM 20 MG/D			PLACEBO			
		N	k	mean	N	k	mean	Δ
pain score:								
NRS/NRS Pain – 0d	Continuous	41		5.8 (SD 1.5)	41		5.8 (SD 1.5)	
NRS/NRS Pain – 35d	Continuous	41		4.5 (SD 2.3)	41		5.5 (SD 2.1)	MD=-1.000 (CI: -1.953, -0.047)

	patient-reported improvement in daily physical and emotional functioning, including sleep:							
	Normalised (10-pt) sleep interference measure – 0d[a]	Continuous	41		3.8 (SD 2.6)	41	3.8 (SD 2.6)	
	Normalised (10-pt) sleep interference measure – 35d[a]	Continuous	41		3 (SD 2.4)	41	4 (SD 2.7)	
	NRS Sleep – 0d	Continuous	41		3.8 (SD 2.6)	41	3.8 (SD 2.6)	
	NRS Sleep – 35d	Continuous	41		3 (SD 2.4)	41	4 (SD 2.7)	MD=-1.000 (CI: -2.106, 0.106)
	major adverse events (defined as leading to withdrawal):							
	any major adverse event – 35d	Dichotomous	48	5[b]	(10.4%)	48	1[c] (2.1%)	OR=5.465 (CI: 0.614, 48.662)
	adverse events:							
	any adverse event – 35d	Dichotomous	48	21[d]	(43.8%)	48	18[e] (37.5%)	OR=1.296 (CI: 0.573, 2.933)
	Dizziness – 35d	Dichotomous	48	2	(4.2%)	48	5 (10.4%)	OR=0.374 (CI: 0.069, 2.030)
	Drowsiness – 35d[f]	Dichotomous	48	4	(8.3%)	48	2 (4.2%)	OR=2.091 (CI: 0.364, 11.996)
	Dry mouth – 35d	Dichotomous	48	2	(4.2%)	48	2 (4.2%)	OR=1.000 (CI: 0.135, 7.405)
	nausea/vomiting – 35d	Dichotomous	48	6	(12.5%)	48	4 (8.3%)	OR=1.571 (CI: 0.414, 5.965)
	sleep disturbance – 35d	Dichotomous	48	2	(4.2%)	48	0 (0.0%)	OR=5.215 (CI: 0.244, 111.547)
	Urine retention – 35d	Dichotomous	48	1	(2.1%)	48	0 (0.0%)	OR=3.063 (CI: 0.122, 77.089)
	treatment withdrawal:							
	due to lack of efficacy – 35d	Dichotomous	48	1	(2.1%)	48	2 (4.2%)	OR=0.489 (CI: 0.043, 5.584)
	protocol deviation – 35d	Dichotomous	48	0	(0.0%)	48	1 (2.1%)	OR=0.326 (CI: 0.013, 8.216)
	use of rescue medication:							
	500 mg paracetamol tablets per week – 0d	Continuous	41		19.4 (SD 18)	41	19.4 (SD 18)	
	500 mg paracetamol tablets per week – 35d	Continuous	41		16.3 (SD 17.6)	41	21.2 (SD 17.9)	MD=-4.900 (CI: -12.584, 2.784)
	without depression (on Major Depression Inventory)							
	pain score:							
	NRS/NRS Pain – 0d	Continuous	35		5.7 (SD 1.5)	35	5.7 (SD 1.5)	
	NRS/NRS Pain – 35d	Continuous	35		4.2 (SD 2.2)	35	5.2 (SD 2)	MD=-1.000 (CI: -1.985, -0.015)
	with hyperalgesia							
	pain score:							
	NRS/NRS Pain – 0d	Continuous	20		5.4 (SD 1.3)	20	5.4 (SD 1.3)	
	NRS/NRS Pain – 35d	Continuous	20		3.8 (SD 1.9)	20	5.1 (SD 1.8)	MD=-1.300 (CI: -2.447, -0.153)
	without hyperalgesia							
	pain score:							
	NRS/NRS Pain – 0d	Continuous	21		6.3 (SD 1.6)	21	6.3 (SD 1.6)	
	NRS/NRS Pain – 35d	Continuous	21		5.3 (SD 2.4)	21	6.1 (SD 2.3)	MD=-0.800 (CI: -2.222, 0.622)

[a] based on NRS Sleep
[b] 1 somnolence, impotence, fever, 1 nausea & dizziness, 2 loss of appetite, nausea, dry mouth, 1 headache, blurred vision
[c] dizziness and weight gain
[d] 4 unacceptable, 4 bothering, the rest light or moderate
[e] 4 unacceptable, 1 bothering, the rest light or moderate
[f] defined as 'tiredness'

Comments	1 patient included despite only median of 3, 31 patients had previous unsuccessful treatment for neuropathic pain (though none with escitalopram or another SSRI), all but 31 patients of the 41 in the analysis had depression (from Major Depression Inventory but exact score considered depression on this scale was not reported), authors report pain relief on a 6-point categorical scale ranging from complete to worse as primary outcome; authors appear to do some form of intention-to-treat but not all patients randomised (n=48) were included in the analysis (41 in analysis while 37 completed both treatment arms); authors recorded SF-36 scores but did not report the actual figures in the study

Definitions of abbreviations are given at the end of this document.

Study	Paice et al. (2000)
Pain category	Peripheral pain
Study design	Country: USA Design: Parallel Inclusion criteria: Participants with HIV related symmetrical peripheral neuropathy aged 18 and older Exclusion criteria: pregnancy, lactation, inability to read or speak English, use of dideoxyinosine or dieoxycytosine, use of topical medication on the lower extremities, lesions on the feet or legs that might allow systemtic uptake of the drug Study length (days): 28 Intention-to-treat analysis? No
Participants	Total number of patients: 26 Number of males: 25 (96.2%) Underlying cause of neuropathic pain: HIV-related neuropathy Mean duration of NP (in months): not reported Baseline pain severity: 4.7 (current pain on NRS) Mean age: 40.3 (SD: 6)
Intervention(s)	(1) Capsaicin 0.075% (fixed dose 4x per day) Intervention: capsaicin cream Length of treatment (weeks): 4 Fixed/flexible dose regimen: Fixed dose (2) Placebo Intervention: placebo Length of treatment (weeks): 4 Fixed/flexible dose regimen: Fixed dose
Concomitant treatments	Drug free baseline period? No Concomitant pain treatment allowed? Yes (50% were not on analgesics and the rest were on opioids, fentanyl, acetaminophen/codeine, NSAIDs, tricyclic anti-depressants (n=2), and anti-convulsants (n=1) and a variety used other methods like massage, heat, elevation, acupuncture, etc to relieve pain)
Outcomes measures and effect sizes	

		CAPSAICIN 0.075% (FIXED DOSE 4X PER DAY)			PLACEBO			
		N	k	mean	N	k	mean	Δ
pain score:								
NRS/NRS Pain – 0d[a]	Continuous	15		5.05	11		4.25	
NRS/NRS Pain – 28d[a]	Continuous	6		2.15	8		3.78	MD=-1.630
major adverse events (defined as leading to withdrawal):								
any major adverse event – 28d	Dichotomous	15	5	(33.3%)	11	0	(0.0%)	OR=12.048 (CI: 0.592, 245.275)
treatment withdrawal:								
due to lack of efficacy – 28d	Dichotomous	15	5	(33.3%)	11	0	(0.0%)	OR=12.048 (CI: 0.592, 245.275)
unspecified/other reason – 28d	Dichotomous	15	5	(33.3%)	11	2	(18.2%)	OR=2.250 (CI: 0.346, 14.611)

	[a] data estimated from graph
Comments	BPI and POM recorded but not reported fully (BPI available for treatment arm only)

Definitions of abbreviations are given at the end of this document.

Study	Rao et al. (2007)
Pain category	Peripheral pain
Study design	Country: USA Design: Crossover Inclusion criteria: symptomatic chemotherapy-induced peripheral neuropathy for >1 month with pain scores of =4 on a NRS or =1 on the Eastern Cooperative Oncology Group neuropathy scale Exclusion criteria: preexisting neuropathy from other causes, pregnancy or lactating, patients taking antidepressants, opioids, adjuvant analgesics, topical analgesics and amifostine at baseline Study length (days): 98 Intention-to-treat analysis? Unclear
Participants	Total number of patients: 115 Number of males: 31 (27.0%) Underlying cause of neuropathic pain: Chemotherapy-induced pain Mean duration of NP (in months): not reported Baseline pain severity: 3.95 ('average' pain on NRS (mean of arm means)) Mean age: 59
Intervention(s)	(1) gabapentin up to 2700 mg/d Intervention: gabapentin Length of treatment (weeks): 6 Fixed/flexible dose regimen: Flexible dose Median dose: 2700mg/d Notes: 2700 mg/d was the target dose (lowered if patients showed signs of toxicity); corresponds to 9 capsules a day (2) placebo Intervention: placebo Length of treatment (weeks): 6 Fixed/flexible dose regimen: Flexible dose
Concomitant treatments	Drug free baseline period? No Concomitant pain treatment allowed? Yes (NSAIDs permitted; also, while those on anti-depressants, opioids, adjuvant analgesics, topical analgesics or amifostine at baseline were excluded, these were permitted to be initiated after study entry, if needed)
Outcomes measures and effect sizes	

	GABAPENTIN UP TO 2700 MG/D			PLACEBO			
	N	k	mean	N	k	mean	Δ

pain score:								
McGill Pain Questionnaire – 0d	Continuous	57		29.6	58		23.4	
patient-reported improvement in daily physical and emotional functioning, including sleep:								
BPI – 0d	Continuous	57		3.9	58		3.7	
adverse events:								
Dizziness – 42d	Dichotomous	115	8	(7.0%)	115	4	(3.5%)	OR=2.075 (CI: 0.607, 7.093)
Fatigue – 42d	Dichotomous	115	5	(4.3%)	115	7	(6.1%)	OR=0.701 (CI: 0.216, 2.278)
Rash – 42d	Dichotomous	115	3	(2.6%)	115	0	(0.0%)	OR=7.187 (CI: 0.367, 140.719)
use of rescue medication:								
proportion taking non-opioid analgesics – 0d[a]	Dichotomous	57	19	(33.3%)	58	21	(36.2%)	
treatment phase 1								
pain score:								
NRS/NRS Pain – 0d[b]	Continuous	57		4.3 (SD 2.26)	58		3.6 (SD 2.67)	
NRS/NRS Pain – 28d[c]	Continuous	57		3.35 (SD 2.47)	58		3.2 (SD 1.87)	MD=0.150 (CI: -0.651, 0.951)
NRS/NRS Pain – 42d[b]	Continuous	57		3.3 (SD 2.77)	58		3 (SD 1.25)	MD=0.300 (CI: -0.489, 1.089)
McGill Pain Questionnaire – 42d	Continuous	57		17.6	58		19.9	MD=-2.300
patient-reported improvement in daily physical and emotional functioning, including sleep:								
BPI – 42d	Continuous	57		2.8	58		3.3	MD=-0.500
adverse events:								
any adverse event – 42d	Dichotomous	57	44[d]	(77.2%)	58	50	(86.2%)	OR=0.542 (CI: 0.205, 1.428)
treatment withdrawal:								
unspecified/other reason – 42d[e]	Dichotomous	57	14	(24.6%)	58	11	(19.0%)	OR=1.391 (CI: 0.570, 3.392)
use of rescue medication:								
proportion taking opioids – 42d	Dichotomous	57	8	(14.0%)	58	7	(12.1%)	OR=1.190 (CI: 0.401, 3.529)
proportion taking non-opioid analgesics – 42d	Dichotomous	57	19	(33.3%)	58	29	(50.0%)	OR=0.500 (CI: 0.235, 1.063)
treatment phase 2								
pain score:								
NRS/NRS Pain – 0d[c]	Continuous	58		3.05 (SD 0.23)	57		3.1 (SD 0.288)	
NRS/NRS Pain – 28d[c]	Continuous	58		2.65 (SD 0.295)	57		3.1 (SD 0.256)	MD=-0.450 (CI: -0.551, -0.349)
NRS/NRS Pain – 42d[b]	Continuous	58		2.5 (SD 0.262)	57		3.1 (SD 0.384)	MD=-0.600 (CI: -0.720, -0.480)
McGill Pain Questionnaire – 42d	Continuous	58		24	57		15.1	MD=8.900
patient-reported improvement in daily physical and emotional functioning, including sleep:								
BPI – 42d	Continuous	58		3	57		2.8	MD=0.200
adverse events:								
any adverse event – 42d	Dichotomous	58	31	(53.4%)	57	29	(50.9%)	OR=1.109 (CI: 0.533, 2.305)
treatment withdrawal:								
unspecified/other reason – 42d[e]	Dichotomous	58	7	(12.1%)	57	9	(15.8%)	OR=0.732 (CI: 0.253, 2.120)
use of rescue medication:								
proportion taking opioids – 42d	Dichotomous	58	7	(12.1%)	57	5	(8.8%)	OR=1.427 (CI: 0.425, 4.791)
proportion taking non-opioid analgesics – 42d	Dichotomous	58	18	(31.0%)	57	13	(22.8%)	OR=1.523 (CI: 0.663, 3.500)
grade 2								
adverse events:								
Diarrhoea – 42d[f]	Dichotomous	115	3	(2.6%)	115	1	(0.9%)	OR=3.054 (CI: 0.313, 29.798)
Dizziness – 42d[f]	Dichotomous	115	6	(5.2%)	115	3	(2.6%)	OR=2.055 (CI: 0.501, 8.424)
dyspepsia – 42d[f]	Dichotomous	115	0	(0.0%)	115	3	(2.6%)	OR=0.139 (CI: 0.007, 2.725)

Fatigue – 42d[f]	Dichotomous	115	4	(3.5%)	115	5	(4.3%)	OR=0.793 (CI: 0.207, 3.031)
myalgia – 42d[f]	Dichotomous	115	2	(1.7%)	115	2	(1.7%)	OR=1.000 (CI: 0.138, 7.223)
Nausea – 42d[f]	Dichotomous	115	2	(1.7%)	115	5	(4.3%)	OR=0.389 (CI: 0.074, 2.049)
Rash – 42d[f]	Dichotomous	115	1	(0.9%)	115	0	(0.0%)	OR=3.026 (CI: 0.122, 75.064)
Vomiting – 42d[f]	Dichotomous	115	2	(1.7%)	115	3	(2.6%)	OR=0.661 (CI: 0.108, 4.030)
grade 3								
adverse events:								
deyhydration – 42d[g]	Dichotomous	115	0	(0.0%)	115	1	(0.9%)	OR=0.330 (CI: 0.013, 8.197)
Dizziness – 42d[g]	Dichotomous	115	2	(1.7%)	115	1	(0.9%)	OR=2.018 (CI: 0.180, 22.567)
Fatigue – 42d[g]	Dichotomous	115	1	(0.9%)	115	2	(1.7%)	OR=0.496 (CI: 0.044, 5.543)
Rash – 42d[g]	Dichotomous	115	2	(1.7%)	115	0	(0.0%)	OR=5.088 (CI: 0.242, 107.157)

[a] approximated to nearest integer (percentages only presented in text)
[b] standard errors estimated from graph
[c] extracted from graph
[d] all adverse events graded 2 or more
[e] reasons reported were refusal (presumed to be lack of activity, disease progression, death from cancer, switch to alternative therapy (data on how many patients for each of these reasons not reported)
[f] grade 2
[g] grade 3

Comments	authors report that somnolence and fatigue rates were similar 9but only report actual rates for fatigue in the study)

Definitions of abbreviations are given at the end of this document.

Study	Rao et al. (2008)
Pain category	Peripheral pain
Study design	Country: USA Design: Parallel Inclusion criteria: Participants with cancer pain duration of at least 1 month with daily pain scores of either at least 4 on NRS 11 point or 1 on ENS 4 point Exclusion criteria: preexisting neuropathy from other causes, pregnancy or lactating, patients taking antidepressants, opioids, adjuvant analgesics, topical analgesics and amifostine at baseline Study length (days): 70 Intention-to-treat analysis? No
Participants	Total number of patients: 125 Number of males: 51 (40.8%) Underlying cause of neuropathic pain: Chemotherapy-induced pain Mean duration of NP (in months): not reported Baseline pain severity: 3.9 ('average' pain on NRS (mean of arm means)) Mean age: 61
Intervention(s)	(1) lamotrigine 300mg/d Intervention: lamotrigine Length of treatment (weeks): 10

	Fixed/flexible dose regimen: Flexible dose Notes: 300 mg/d is target dosage - start on 25 mg before bedtme for 2 weeks, 25 mg 2x per day for 2 weeks, 50 mg 2x daily for 2 weeks, 100 mg 2x daily for 2 weeks and then escalated to 150 mg 2x daily for 2 weeks (some were allowed to stop sooner if they wished or any reason before 10 weeks but then were encouraged to taper the drug over a 4-week period) (2) Placebo Intervention: placebo Length of treatment (weeks): 10 Fixed/flexible dose regimen: Flexible dose
Concomitant treatments	Drug free baseline period? Unclear Concomitant pain treatment allowed? No (Anti-depressants, anti-convulsants, opioids, topical analgesics, amifostine not allowed but NSAIDs were permitted)
Outcomes measures and effect sizes	

		LAMOTRIGINE 300MG/D			PLACEBO			
		N	k	mean	N	k	mean	Δ
pain score:								
NRS/NRS Pain – 0d[a]	Continuous	63		4.1 (SD 2.68)	62		3.7 (SD 2.46)	
NRS/NRS Pain – 28d[b]	Continuous	63		4.5 (SD 3.37)	62		3.75 (SD 3.15)	MD=0.750 (CI: -0.394, 1.894)
NRS/NRS Pain – 56d[b]	Continuous	63		3.75 (SD 3.57)	62		3.75 (SD 3.15)	MD=0.000 (CI: -1.180, 1.180)
NRS/NRS Pain – 70d	Mean change	63		-0.3	62		-0.5	MD=0.200
NRS/NRS Pain – 70d[b]	Continuous	63		3.8 (SD 4.17)	62		3.55 (SD 3.35)	MD=0.250 (CI: -1.074, 1.574)
McGill Pain Questionnaire – 0d	Continuous	63		38.3	62		32.5	
McGill Pain Questionnaire – 70d	Mean change	63		-12.3	62		-4	MD=-8.300
patient-reported improvement in daily physical and emotional functioning, including sleep:								
BPI – 0d	Continuous	63		3.8	62		3.8	
BPI – 70d	Mean change	63		-0.1	62		-0.8	MD=0.700
major adverse events (defined as leading to withdrawal):								
any major adverse event – 70d	Dichotomous	63	7	(11.1%)	62	1	(1.6%)	OR=7.625 (CI: 0.909, 63.936)
adverse events:								
any adverse event – 70d[c]	Dichotomous	63	26	(41.3%)	62	28	(45.2%)	OR=0.853 (CI: 0.420, 1.733)
Diarrhoea – 70d	Dichotomous	63	3	(4.8%)	62	1	(1.6%)	OR=3.050 (CI: 0.309, 30.150)
Dizziness – 70d	Dichotomous	63	2	(3.2%)	62	1	(1.6%)	OR=2.000 (CI: 0.177, 22.639)
Fatigue – 70d	Dichotomous	63	1	(1.6%)	62	2	(3.2%)	OR=0.484 (CI: 0.043, 5.477)
Nausea – 70d	Dichotomous	63	2	(3.2%)	62	5	(8.1%)	OR=0.374 (CI: 0.070, 2.004)
Rash – 70d	Dichotomous	63	2	(3.2%)	62	0	(0.0%)	OR=5.081 (CI: 0.239, 108.015)
Vomiting – 70d	Dichotomous	63	2	(3.2%)	62	3	(4.8%)	OR=0.645 (CI: 0.104, 3.998)
treatment withdrawal:								
unspecified/other reason – 70d	Dichotomous	63	22	(34.9%)	62	15	(24.2%)	OR=1.681 (CI: 0.772, 3.662)

[a] SE are estimates from graph
[b] estimated from graph using ruler
[c] adverse events considered ≥grade 2 (not defined)

Comments	underlying cause of pain is actually the chemotherapy rather than cancer

Definitions of abbreviations are given at the end of this document.

Study	Raskin et al. (2004)
Pain category	Peripheral pain
Study design	Country: USA Design: Parallel Inclusion criteria: PDN for at least 3 months but less than 10 years with at least 40mm on VAS Exclusion criteria: Participants who required treatment with anticonvulsants, who had other potential causes of NP, other painful conditions, degenerative neurological disorder,open ulcer, amputation, infection, nephrolithiasis, suicide (or suicidal tendencies), substance abuse, clinically significant medical conditions, malignacy within the past 5 years or major psychiatirc disorder were excluded Study length (days): 84 Intention-to-treat analysis? Yes
Participants	Total number of patients: 323 Number of males: 157 (48.6%) Underlying cause of neuropathic pain: Painful diabetic neuropathy Mean duration of NP (in months): 38.4 Baseline pain severity: 68.55 (VAS (average of arm means)) Mean age: 59.2 (SD: 9.8)
Intervention(s)	(1) Topiramate up to 400mg/d Intervention: topiramate Length of treatment (weeks): 12 Fixed/flexible dose regimen: Flexible dose Mean dose: 161.2mg/d Notes: 161.2 mg/d is average dose across the whole study - average dosage over maintenance period was 320 mg/d; 400 mg/d maximum or maximum tolerated; 25 mg at bedtime to start, then increased by 25 mg on weeks 2, 3 and 4, by 50 mg on weeks 5 and 6 and by 100 mg on weeks 7 and 8 where maximum tolerated or 400 mg/d dosages were maintained until week 12 (2) Placebo Intervention: placebo Length of treatment (weeks): 12 Fixed/flexible dose regimen: Flexible dose
Concomitant treatments	Drug free baseline period? Yes (duration: 21d) Concomitant pain treatment allowed? Yes (treatment with anti-convulsants, TENS, acupuncture, anti-epileptic drugs, anti-depressants (other than SSRIs which were allowed if stable for at least 90 days - these could be considered concomitant medications), alpha-lipoic acid, capsaicin, sedative hypnotics, anaesthetics, analgesics, other topical medications or muscle relaxants all excluded; paracetamol (500 mg) or another short-acting analgesia allowed during first 6 weeks only (apart from 24 hours before each visit) and zaleplon and zolpidem tartarate were permitted at bedtime as needed (up to 3 days per week))
Outcomes measures and effect sizes	**TOPIRAMATE UP TO 400MG/D** — **N** **k** **mean**; **PLACEBO** — **N** **k** **mean**; **Δ**

pain score:								
VAS – 0d	Continuous	208		68 (SD 14.4)	109		69.1 (SD 17.2)	
VAS – 28d[a]	Continuous	208		53.4 (SD 23.4)	109		56.2 (SD 23.5)	MD=-2.875 (CI: -8.315, 2.565)
VAS – 56d[a]	Continuous	208		47.5 (SD 27.4)	109		55.2 (SD 25.4)	MD=-7.688 (CI: -13.745, -1.630)
VAS – 84d	Continuous	208		46.2 (SD 27.8)	109		54 (SD 27.4)	MD=-7.800 (CI: -14.180, -1.420)
at least 30% pain reduction (VAS) – 84d	Dichotomous	214	103	(48.1%)	109	37	(33.9%)	OR=1.806 (CI: 1.119, 2.914)
at least 50% pain reduction (VAS) – 84d	Dichotomous	214	74	(34.6%)	109	23	(21.1%)	OR=1.976 (CI: 1.152, 3.390)
patient-reported improvement in daily physical and emotional functioning, including sleep:								
Normalised (10-pt) sleep interference measure – 0d[b]	Continuous	208		6.5 (SD 2.5)	109		6.2 (SD 2.4)	
Normalised (10-pt) sleep interference measure – 84d[b]	Continuous	208		3.9 (SD 3.1)	109		4.6 (SD 2.9)	
NRS Sleep – 0d	Continuous	208		6.5 (SD 2.5)	109		6.2 (SD 2.4)	
NRS Sleep – 84d	Continuous	208		3.9 (SD 3.1)	109		4.6 (SD 2.9)	MD=-0.700 (CI: -1.388, -0.012)
major adverse events (defined as leading to withdrawal):								
any major adverse event – 84d	Dichotomous	214	52	(24.3%)	109	9	(8.3%)	OR=3.567 (CI: 1.684, 7.552)
adverse events:								
Diarrhoea	Dichotomous	214	24	(11.2%)	109	4	(3.7%)	OR=3.316 (CI: 1.120, 9.813)
Dizziness – 84d	Dichotomous	214	15	(7.0%)	109	6	(5.5%)	OR=1.294 (CI: 0.487, 3.435)
Fatigue – 84d	Dichotomous	214	15	(7.0%)	109	2	(1.8%)	OR=4.033 (CI: 0.905, 17.965)
headache	Dichotomous	214	12	(5.6%)	109	10	(9.2%)	OR=0.588 (CI: 0.246, 1.408)
Infection[c]	Dichotomous	214	19	(8.9%)	109	6	(5.5%)	OR=1.673 (CI: 0.648, 4.318)
Nausea – 84d	Dichotomous	214	20	(9.3%)	109	6	(5.5%)	OR=1.770 (CI: 0.689, 4.545)
parasthesia	Dichotomous	214	18	(8.4%)	109	2	(1.8%)	OR=4.913 (CI: 1.119, 21.578)
Somnolence – 84d	Dichotomous	214	21	(9.8%)	109	4	(3.7%)	OR=2.856 (CI: 0.955, 8.541)
overall improvement in quality of life:								
SF36 Mental – 84d	Continuous	208		46.9 (SD 11.9)	109		49.9 (SD 10.1)	MD=-3.000 (CI: -5.492, -0.508)
SF36 Physical – 84d	Continuous	208		37.2 (SD 10.6)	109		34.9 (SD 9.4)	MD=2.300 (CI: 0.022, 4.578)
treatment withdrawal:								
due to lack of efficacy – 84d	Dichotomous	214	31	(14.5%)	109	16	(14.7%)	OR=0.985 (CI: 0.513, 1.892)
unspecified/other reason – 84d	Dichotomous	214	8	(3.7%)	109	1	(0.9%)	OR=4.194 (CI: 0.518, 33.973)
withdrawal of consent – 84d	Dichotomous	214	7	(3.3%)	109	1	(0.9%)	OR=3.652 (CI: 0.444, 30.069)
lost to follow-up – 84d	Dichotomous	214	4	(1.9%)	109	2	(1.8%)	OR=1.019 (CI: 0.184, 5.653)
use of rescue medication:								
proportion using pain medication – 49d[d]	Dichotomous	158	10	(6.3%)	95	14	(14.7%)	OR=0.391 (CI: 0.166, 0.920)
proportion using pain medication – 63d[e]	Dichotomous	112	2	(1.8%)	91	3	(3.3%)	OR=0.533 (CI: 0.087, 3.262)
proportion using pain medication – 77d[f]	Dichotomous	112	0	(0.0%)	80	3	(3.8%)	OR=0.098 (CI: 0.005, 1.932)

[a] estimated from graph
[b] based on NRS Sleep
[c] upper respiratory tract infection
[d] during weeks 7 and 8; denominator not provided but estimated from % and numerator
[e] during weeks 9 and 10; denominator not provided but estimated from % and numerator
[f] during weeks 11 and 12; denominator not provided but estimated from % and numerator

Comments	up to 28 day screening/washout phase (most drugs had 21 day wash-out but some, including analgesics, anesthetics and other topical pain medications or muscle relaxants had a discontinuation period equal to at least 5 half lives of the medication before randomisation); ITT analysis included all those who received at least one ose of study medication and completed at least one follow-up efficacy assessment

Definitions of abbreviations are given at the end of this document.

Study	Raskin et al. (2005)
Pain category	Peripheral pain
Study design	Country: USA Design: Parallel Inclusion criteria: PDN for at least 6 months with pain score of at least 4 on NRS Exclusion criteria: Pregnant or breastfeeding, prior renal transplant or current renal dialysis, serious unstable illness, symptomatic peripheral vascular disease, or other medical conditions that might compromise the study. Also excluded were people with DSM-IV mental health diagnoses, substance abusers, other medical conditions that could be responsible for neuropathy, MAOI use, prior participation in studies of duloxetine. Chronic use of anti-depressants, anti-emetics, analgesics (apart from paracetamol up to 4g/d and aspirin up to 325 mg/d), anti-manics, anti-migraine medications, anti-psychotics, benzodiazepines, capsaicin, chloral hydrate, guanethidine, topical lidocaine, MAOIs, narcotics, psychostimulants, oral and injective steroids, anti-convulsants Study length (days): 84 Intention-to-treat analysis? No
Participants	Total number of patients: 348 Number of males: 162 (46.6%) Underlying cause of neuropathic pain: Painful diabetic neuropathy Mean duration of NP (in months): 223.6 Baseline pain severity: 5.6 (24-hour average pain severity on NRS) Mean age: 58.8 (SD: 10.1)
Intervention(s)	(1) Duloxetine 60mg/d Intervention: duloxetine Length of treatment (weeks): 12 Fixed/flexible dose regimen: Fixed dose Set dose: 60mg/d (2) Duloxetine 120mg/d Intervention: duloxetine Length of treatment (weeks): 12 Fixed/flexible dose regimen: Fixed dose Set dose: 120mg/d (3) Placebo Intervention: placebo Length of treatment (weeks): 12 Fixed/flexible dose regimen: Fixed dose
Concomitant treatments	Drug free baseline period? Unclear Concomitant pain treatment allowed? No (Chronic use of anti-depressants, anti-emetics, analgesics (apart from paracetamol up to 4g/d and aspirin up to 325 mg/d), anti-manics, anti-migraine medications, anti-psychotics, benzodiazepines, capsaicin, chloral hydrate, guanethidine, topical lidocaine, MAOIs, narcotics, psychostimulants, oral and injective steroids, anti-convulsants was exclusion criteria)

Outcomes measures and effect sizes

		DULOXETINE 60MG/D			DULOXETINE 120MG/D			
		N	k	mean	N	k	mean	Δ
pain score:								
NRS/NRS Pain – 0d	Continuous	116		5.5 (SD 1.1)	116		5.7 (SD 1.3)	
NRS/NRS Pain – 84d	Mean change	113		-2.5 (SD 1.91)	114		-2.47 (SD 1.92)	MD=-0.030 (CI: -0.529, 0.469)
at least 50% pain reduction – 84d	Dichotomous	116	85	(73.3%)	116	79	(68.1%)	OR=1.284 (CI: 0.728, 2.264)
BPI (severity) – 84d	Mean change	108		-2.65 (SD 1.97)	108		-2.62 (SD 1.97)	MD=-0.030 (CI: -0.557, 0.497)
SF McGill – 84d	Mean change	102		-7.47 (SD 6.16)	104		-7.82 (SD 6.22)	MD=0.350 (CI: -1.341, 2.041)
patient-reported improvement in daily physical and emotional functioning, including sleep:								
Normalised (10-pt) sleep interference measure[a]	Mean change	108		-3.3 (SD 2.39)	107		-3 (SD 2.48)	
BPI – 84d	Mean change	108		-2.43 (SD 1.87)	108		-2.54 (SD 1.87)	MD=0.110 (CI: -0.389, 0.609)
BPI Mood – 84d	Mean change	108		-2.32 (SD 2.08)	108		-2.6 (SD 2.08)	MD=0.280 (CI: -0.274, 0.834)
BPI Sleep – 84d	Mean change	108		-3.3 (SD 2.39)	107		-3 (SD 2.48)	MD=-0.300 (CI: -0.952, 0.352)
HDS – 84d	Mean change	103		-1.17 (SD 2.54)	100		-0.65 (SD 2.5)	MD=-0.520 (CI: -1.213, 0.173)
BPI general activity – 84d	Mean change	108		-2.22 (SD 2.29)	108		-2.39 (SD 2.29)	MD=0.170 (CI: -0.440, 0.780)
BPI walking ability – 84d	Mean change	108		-2.5 (SD 2.18)	108		-2.68 (SD 2.29)	MD=0.180 (CI: -0.416, 0.776)
BPI normal work – 84d	Mean change	108		-2.24 (SD 2.08)	108		-2.46 (SD 2.18)	MD=0.220 (CI: -0.348, 0.788)
BPI relationship with other people – 84d	Mean change	108		-1.56 (SD 1.87)	108		-1.78 (SD 1.87)	MD=0.220 (CI: -0.279, 0.719)
BPI enjoyment of life – 84d	Mean change	108		-2.63 (SD 2.29)	108		-2.64 (SD 2.29)	MD=0.010 (CI: -0.600, 0.620)
major adverse events (defined as leading to withdrawal):								
any major adverse event – 84d	Dichotomous	116	5	(4.3%)	116	14	(12.1%)	OR=0.328 (CI: 0.114, 0.943)

[a] based on BPI Sleep

		DULOXETINE 60MG/D			PLACEBO			
		N	k	mean	N	k	mean	Δ
pain score:								
NRS/NRS Pain – 0d	Continuous	116		5.5 (SD 1.1)	116		5.5 (SD 1.3)	
NRS/NRS Pain – 84d	Mean change	113		-2.5 (SD 1.91)	113		-1.56 (SD 1.91)	MD=-0.940 (CI: -1.439, -0.441)
at least 50% pain reduction – 84d	Dichotomous	116	85	(73.3%)	116	51	(44.0%)	OR=3.495 (CI: 2.014, 6.063)
BPI (severity) – 84d	Mean change	108		-2.65 (SD 1.97)	109		-1.82 (SD 1.98)	MD=-0.830 (CI: -1.357, -0.303)
SF McGill – 84d	Mean change	102		-7.47 (SD 6.16)	101		-4.96 (SD 6.03)	MD=-2.510 (CI: -4.187, -0.833)
patient-reported improvement in daily physical and emotional functioning, including sleep:								
Normalised (10-pt) sleep interference measure[a]	Mean change	108		-3.3 (SD 2.39)	108		-2.25 (SD 2.49)	
BPI – 84d	Mean change	108		-2.43 (SD 1.87)	109		-1.56 (SD 1.88)	MD=-0.870 (CI: -1.369, -0.371)
BPI Mood – 84d	Mean change	108		-2.32 (SD 2.08)	109		1.76 (SD 2.09)	MD=-4.080 (CI: -4.634, -3.526)
BPI Sleep – 84d	Mean change	108		-3.3 (SD 2.39)	108		-2.25 (SD 2.49)	MD=-1.050 (CI: -1.702, -0.398)
HDS – 84d	Mean change	103		-1.17 (SD 2.54)	101		-0.55 (SD 2.51)	MD=-0.620 (CI: -1.313, 0.073)
BPI general activity – 84d	Mean change	108		-2.22 (SD 2.29)	108		-1.38 (SD 2.29)	MD=-0.840 (CI: -1.450, -0.230)
BPI walking ability – 84d	Mean change	108		-2.5 (SD 2.18)	108		-1.51 (SD 2.29)	MD=-0.990 (CI: -1.586, -0.394)
BPI normal work – 84d	Mean change	108		-2.24 (SD 2.08)	108		-1.45 (SD 2.08)	MD=-0.790 (CI: -1.344, -0.236)
BPI relationship with other people – 84d	Mean change	108		-1.56 (SD 1.87)	108		-1.19 (SD 1.87)	MD=-0.370 (CI: -0.869, 0.129)
BPI enjoyment of life – 84d	Mean change	108		-2.63 (SD 2.29)	108		-1.79 (SD 2.29)	MD=-0.840 (CI: -1.450, -0.230)

major adverse events (defined as leading to withdrawal): any major adverse event – 84d	Dichotomous	116	5	(4.3%)	116	3	(2.6%)	OR=1.697 (CI: 0.396, 7.270)

[a] based on BPI Sleep

		DULOXETINE 120MG/D			PLACEBO			
		N	k	mean	N	k	mean	Δ
pain score:								
NRS/NRS Pain – 0d	Continuous	116		5.7 (SD 1.3)	116		5.5 (SD 1.3)	
NRS/NRS Pain – 84d	Mean change	114		-2.47 (SD 1.92)	113		-1.56 (SD 1.91)	MD=-0.910 (CI: -1.409, -0.411)
at least 50% pain reduction – 84d	Dichotomous	116	79	(68.1%)	116	51	(44.0%)	OR=2.721 (CI: 1.593, 4.649)
BPI (severity) – 84d	Mean change	108		-2.62 (SD 1.97)	109		-1.82 (SD 1.98)	MD=-0.800 (CI: -1.327, -0.273)
SF McGill – 84d	Mean change	104		-7.82 (SD 6.22)	101		-4.96 (SD 6.03)	MD=-2.860 (CI: -4.537, -1.183)
patient-reported improvement in daily physical and emotional functioning, including sleep:								
Normalised (10-pt) sleep interference measure[a]	Mean change	107		-3 (SD 2.48)	108		-2.25 (SD 2.49)	
BPI – 84d	Mean change	108		-2.54 (SD 1.87)	109		-1.56 (SD 1.88)	MD=-0.980 (CI: -1.479, -0.481)
BPI Mood – 84d	Mean change	108		-2.6 (SD 2.08)	109		1.76 (SD 2.09)	MD=-4.360 (CI: -4.914, -3.806)
BPI Sleep – 84d	Mean change	107		-3 (SD 2.48)	108		-2.25 (SD 2.49)	MD=-0.750 (CI: -1.415, -0.085)
HDS – 84d	Mean change	100		-0.65 (SD 2.5)	101		-0.55 (SD 2.51)	MD=-0.100 (CI: -0.793, 0.593)
BPI general activity – 84d	Mean change	108		-2.39 (SD 2.29)	108		-1.38 (SD 2.29)	MD=-1.010 (CI: -1.620, -0.400)
BPI walking ability – 84d	Mean change	108		-2.68 (SD 2.29)	108		-1.51 (SD 2.29)	MD=-1.170 (CI: -1.780, -0.560)
BPI normal work – 84d	Mean change	108		-2.46 (SD 2.18)	108		-1.45 (SD 2.08)	MD=-1.010 (CI: -1.578, -0.442)
BPI relationship with other people – 84d	Mean change	108		-1.78 (SD 1.87)	108		-1.19 (SD 1.87)	MD=-0.590 (CI: -1.089, -0.091)
BPI enjoyment of life – 84d	Mean change	108		-2.64 (SD 2.29)	108		-1.79 (SD 2.29)	MD=-0.850 (CI: -1.460, -0.240)
major adverse events (defined as leading to withdrawal): any major adverse event – 84d	Dichotomous	116	14	(12.1%)	116	3	(2.6%)	OR=5.170 (CI: 1.444, 18.508)

[a] based on BPI Sleep

Comments	up to 3 week screening phase (study period I) - unclear if there was a drug-free screening period and, if so, how long it was

Definitions of abbreviations are given at the end of this document.

Study	Rauck et al. (2007)
Pain category	Peripheral pain
Study design	Country: not clear Design: Parallel Inclusion criteria: =18 years with type1 or type 2 diabetes, moderate to severe intensity symptoms for 1 to 5 years (=4 on NRS), A1C < 12% Exclusion criteria: pregnant women, those breastfeeding or trying to have children, participation in investigational trial in last 30 days, any other condition to interfer with assessment of NP, major skin ulcers, clinically significant ECG abnormalities, any cardiac disorder putting the patient at risk of arrhythmia and MI, malignancy in last 5 years, history of alcohol or drug abuse in last year, those taking any drugs that may itnerfer with results of trial (including anti-convulsants)

	Study length (days): 98 Intention-to-treat analysis? Yes
Participants	Total number of patients: 119 Number of males: 56 (47.1%) Underlying cause of neuropathic pain: Painful diabetic neuropathy Mean duration of NP (in months): 45 Baseline pain severity: 6.55 (NRS (average of means)) Mean age: 55.05
Intervention(s)	(1) lacosamide up to 400 mg/d Intervention: lacosamide Length of treatment (weeks): 10 Fixed/flexible dose regimen: Flexible dose Notes: up to 400 mg/d or maximum tolerated; starting at 100 mg/d for 3 weeks and then titrating up 100 mg/d at weekly intervals over the next 3 weeks and then maintained for the next 4 week period (2) placebo Intervention: placebo Length of treatment (weeks): 10 Fixed/flexible dose regimen: Flexible dose
Concomitant treatments	Drug free baseline period? No Concomitant pain treatment allowed? Yes (serotonin reuptake inhibitors (with no change in dosage from 30 days before trial), other therapy considered necessary by investigator during trial (even if an 'excluded medication'); paracetamol = 2 g/d as rescue medication, aspirin up to 325 mg/d (for prophylaxis of MI, TIA, or stroke))

Outcomes measures and effect sizes

		LACOSAMIDE UP TO 400 MG/D			PLACEBO			
		N	k	mean	N	k	mean	Δ
pain score:								
NRS/NRS Pain – 0d[a]	Continuous	60		6.6 (SD 1.6)	59		6.5 (SD 1.7)	
NRS/NRS Pain – 70d[b]	Mean change	60		-2.28	59		-3.72	MD=1.440
NRS/NRS Pain – 70d[a]	Continuous	60		3 (SD 2.4)	59		4.5 (SD 2.6)	MD=-1.400 (CI: -2.302, -0.498)
at least 30% pain reduction (NRS) – 70d[c]	Dichotomous	60	36	(60.0%)	59	30	(50.8%)	OR=1.450 (CI: 0.701, 2.997)
patient-reported global improvement:								
PGIC - worse (all grades) – 70d	Dichotomous	60	1	(1.7%)	59	6	(10.2%)	OR=0.150 (CI: 0.017, 1.284)
PGIC - no change – 70d	Dichotomous	60	9	(15.0%)	59	12	(20.3%)	OR=0.691 (CI: 0.267, 1.789)
PGIC - minimally better – 70d	Dichotomous	60	9	(15.0%)	59	13	(22.0%)	OR=0.624 (CI: 0.244, 1.596)
PGIC - moderately better – 70d	Dichotomous	60	13	(21.7%)	59	8	(13.6%)	OR=1.763 (CI: 0.671, 4.632)
PGIC - at least moderately better – 70d	Dichotomous	60	37	(61.7%)	59	26	(44.1%)	OR=2.042 (CI: 0.983, 4.243)
PGIC - much better – 70d	Dichotomous	60	24	(40.0%)	59	18	(30.5%)	OR=1.519 (CI: 0.712, 3.239)
major adverse events (defined as leading to withdrawal):								
any major adverse event – 70d	Dichotomous	60	5	(8.3%)	59	3	(5.1%)	OR=1.697 (CI: 0.387, 7.447)
adverse events:								
any adverse event – 70d	Dichotomous	60	52	(86.7%)	59	44	(74.6%)	OR=2.216 (CI: 0.859, 5.714)
Constipation – 70d	Dichotomous	60	0	(0.0%)	59	3	(5.1%)	OR=0.133 (CI: 0.007, 2.641)

	Diarrhoea – 70d	Dichotomous	60	7	(11.7%)	59	3	(5.1%)	OR=2.465 (CI: 0.606, 10.035)
	Dizziness – 70d	Dichotomous	60	9	(15.0%)	59	5	(8.5%)	OR=1.906 (CI: 0.599, 6.069)
	headache – 70d	Dichotomous	60	13	(21.7%)	59	11	(18.6%)	OR=1.207 (CI: 0.492, 2.963)
	Nausea – 70d	Dichotomous	60	7	(11.7%)	59	4	(6.8%)	OR=1.816 (CI: 0.502, 6.565)
	parasthesia – 70d	Dichotomous	60	1	(1.7%)	59	3	(5.1%)	OR=0.316 (CI: 0.032, 3.132)
	Somnolence – 70d	Dichotomous	60	3	(5.0%)	59	3	(5.1%)	OR=0.982 (CI: 0.190, 5.076)
	treatment withdrawal:								
	due to lack of efficacy – 70d	Dichotomous	60	2	(3.3%)	59	4	(6.8%)	OR=0.474 (CI: 0.083, 2.693)
	unspecified/other reason – 70d	Dichotomous	60	0	(0.0%)	59	1	(1.7%)	OR=0.322 (CI: 0.013, 8.073)
	withdrawal of consent – 70d	Dichotomous	60	4	(6.7%)	59	1	(1.7%)	OR=4.143 (CI: 0.449, 38.216)
	protocol deviation – 70d	Dichotomous	60	2	(3.3%)	59	1	(1.7%)	OR=2.000 (CI: 0.176, 22.670)
	lost to follow-up – 70d	Dichotomous	60	1	(1.7%)	59	1	(1.7%)	OR=0.983 (CI: 0.060, 16.092)
	use of rescue medication:								
	proportion using pain medication	Dichotomous	60	13[d]	(21.7%)	59	21[e]	(35.6%)	OR=0.501 (CI: 0.222, 1.129)
	ITT/LOCF (last-observation carried forward)								
	pain score:								
	NRS/NRS Pain – 0d[a]	Continuous	60		6.6 (SD 1.6)	59		6.5 (SD 1.7)	
	NRS/NRS Pain – 70d[a]	Mean change	60		-2.21	59		-3.11	MD=0.900
	NRS/NRS Pain – 70d[a]	Continuous	60		3.7 (SD 2.6)	59		4.5 (SD 2.6)	MD=-0.900 (CI: -1.743, -0.057)
	McGill VAS – 70d	Continuous	60		-36.1	59		-26	MD=-10.200 (CI: -20.300, -0.100)
	PPI (from MPQ) – 70d	Continuous	60		-1.11	59		-0.71	MD=-0.400 (CI: -0.700, -0.100)
	patient-reported improvement in daily physical and emotional functioning, including sleep:								
	NRS Sleep – 70d	Continuous	60		-3.1	59		-2.06	MD=-1.000 (CI: -1.850, -0.150)
	[a] least squares mean [b] least squares mean, despite being 'as observed' or per protocol, the study reported the same patient numbers as the ITT (perhaps an error?) [c] outcome in the study is at least 2-point reduction in Likert pain score (often referred to as 30% reduction) [d] for 59% of days in the maintenance phase [e] for 67% of days in the maintenance phase								
Comments	phase 2 trial; 4 week run-in phase to determine eligibility - not clear if this was a wash-out phase; SF-36 POMS all measured but only significance reported								

Definitions of abbreviations are given at the end of this document.

Study	Rice & Maton (2001)
Pain category	Peripheral pain
Study design	Country: UK Design: Parallel Inclusion criteria: Pain present for >3 months after healing of herpes zoster, pain score of 4 or more on 11-point Likert scale, at least 18 years; women were required not to be pregnant, not lactating, postmenopausal or surgically sterilised Exclusion criteria: Participants who failed to respond to 1200mg/d gabapentin Study length (days): 49 Intention-to-treat analysis? No
Participants	Total number of patients: 344

	Number of males: 138 (40.1%) Underlying cause of neuropathic pain: Post-herpetic neuralgia Mean duration of NP (in months): 26.4 Baseline pain severity: 6.5 (NRS (average of means)) Mean age: 73
Intervention(s)	(1) Gabapentin 1800mg/d Intervention: gabapentin Length of treatment (weeks): 7 Fixed/flexible dose regimen: Fixed dose Set dose: 1800mg/d Notes: included 4-day forced titration period where gabapentin was increased by 300 mg/d over the firset 4 days up to 1200 mg/d; from day 4-7, dosing was stable but after 1 week, the dose was titrated up to 1800 mg/d (1500 mg/d on day 8 and 1800 mg/d on day 9-14) (2) Gabapentin 2400mg/d Intervention: gabapentin Length of treatment (weeks): 7 Fixed/flexible dose regimen: Fixed dose Set dose: 2400mg/d Notes: included 4-day forced titration period where gabapentin was increased by 300 mg/d over the firset 4 days up to 1200 mg/d; from day 4-7, dosing was stable but after 1 week, the dose was titrated up to 1800 mg/d (1500 mg/d on day 8 and 1800 mg/d on day 9-14); after 2 weeks, patients had their dose titrated up to 2400 mg/d (2100 mg/d on day 15 and 2400 mg/d from day 16 onwards) (3) Placebo Intervention: placebo Length of treatment (weeks): 7 Fixed/flexible dose regimen: Fixed dose
Concomitant treatments	Drug free baseline period? Yes Concomitant pain treatment allowed? Yes (medications allowed included anti-depressants, mild opiates (ie. Codeine, aspirin for MI and TIA prophylaxis) and NSAIDs; paracetamol or paracetamol/codeine allowed as rescue medication; washout period required for benzodiazepines, skeletal muscle relaxants, steroids, capsaicin, mexiletine, dextromorphan, NSAIDs (for PHN) and anti-convulsants, opioids)

Outcomes measures and effect sizes

		GABAPENTIN 1800MG/D			GABAPENTIN 2400MG/D			
		N	k	mean	N	k	mean	Δ
pain score:								
NRS/NRS Pain – 0d	Continuous	115		6.5	108		6.5	
NRS/NRS Pain – 28d[a]	Mean change	93		-2 (SD 0.964)	85		-2.05 (SD 1.38)	MD=0.050 (CI: -0.303, 0.403)
NRS/NRS Pain – 49d	Mean change	93		-2.3 (SD 1.93)[b]	85		-2.5 (SD 1.38)[c]	MD=-4.800 (CI: -5.290, -4.310)
NRS/NRS Pain – 49d	Continuous	93		4.3[d]	85		4.2[e]	MD=0.100
at least 50% pain reduction (NRS) – 49d[f]	Dichotomous	115	30	(26.1%)	108	29	(26.9%)	OR=0.961 (CI: 0.530, 1.744)
McGill Pain Questionnaire – 0d	Continuous	115		17.8 (SD 8.5)	108		19.6 (SD 8.9)	
McGill Pain Questionnaire – 49d	Continuous	106		11.9 (SD 8.8)	97		12.5 (SD 8.3)	MD=-0.600 (CI: -2.953, 1.753)

McGill VAS – 0d	Continuous	115		67 (SD 18)	108		70 (SD 18)	
McGill VAS – 49d	Continuous	106		47 (SD 28)	97		46 (SD 25)	MD=1.000 (CI: -6.291, 8.291)
PPI (from MPQ) – 0d	Continuous	115		2.5 (SD 1.2)	108		2.7 (SD 1.2)	
PPI (from MPQ) – 49d	Continuous	106		1.9 (SD 1.1)	97		1.9 (SD 1.2)	MD=0.000 (CI: -0.318, 0.318)
patient-reported global improvement:								
PGIC - worse (all grades), no change or minimally better – 49d	Dichotomous	115	71	(61.7%)	108	66	(61.1%)	OR=1.027 (CI: 0.599, 1.761)
PGIC - at least moderately better – 49d	Dichotomous	115	44	(38.3%)	108	42	(38.9%)	OR=0.974 (CI: 0.568, 1.670)
major adverse events (defined as leading to withdrawal):								
any major adverse event – 49d	Dichotomous	115	15	(13.0%)	108	19	(17.6%)	OR=0.703 (CI: 0.337, 1.465)
adverse events:								
asthenia – 49d	Dichotomous	115	7	(6.1%)	108	6	(5.6%)	OR=1.102 (CI: 0.358, 3.389)
Diarrhoea – 49d	Dichotomous	115	7	(6.1%)	108	5	(4.6%)	OR=1.335 (CI: 0.411, 4.341)
Dizziness – 49d	Dichotomous	115	36	(31.3%)	108	36	(33.3%)	OR=0.911 (CI: 0.520, 1.598)
Dry mouth – 49d	Dichotomous	115	7	(6.1%)	108	5	(4.6%)	OR=1.335 (CI: 0.411, 4.341)
Peripheral oedema – 49d	Dichotomous	115	6	(5.2%)	108	12	(11.1%)	OR=0.440 (CI: 0.159, 1.218)
Somnolence – 49d	Dichotomous	115	20	(17.4%)	108	22	(20.4%)	OR=0.823 (CI: 0.420, 1.612)
treatment withdrawal:								
due to lack of efficacy – 49d	Dichotomous	115	4	(3.5%)	108	1	(0.9%)	OR=3.856 (CI: 0.424, 35.055)
unspecified/other reason – 49d	Dichotomous	115	3	(2.6%)	108	2	(1.9%)	OR=1.420 (CI: 0.233, 8.664)
poor compliance – 49d	Dichotomous	115	2	(1.7%)	108	1	(0.9%)	OR=1.894 (CI: 0.169, 21.191)

[a] estimated from graph; ns inferred from patient flow chart
[b] a reduction of 34.4%; estimated from graph; ns inferred from patient flow chart
[c] a reduction of 34.5%; estimated from graph; ns inferred from patient flow chart
[d] a reduction of 34.4%; ns inferred from patient flow chart
[e] a reduction of 34.5%; ns inferred from patient flow chart
[f] estimated from percentages; ns inferred from patient flow chart

		GABAPENTIN 1800MG/D			**PLACEBO**			
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**
pain score:								
NRS/NRS Pain – 0d	Continuous	115		6.5	111		6.4[a]	
NRS/NRS Pain – 28d	Mean change	93		-2 (SD 0.964)[b]	94		-0.85 (SD 0.97)[c]	MD=-1.150 (CI: -1.427, -0.873)
NRS/NRS Pain – 49d	Mean change	93		-2.3 (SD 1.93)[d]	94		-1.1 (SD 1.94)[c]	MD=-1.200 (CI: -1.754, -0.646)
NRS/NRS Pain – 49d	Continuous	93		4.3[e]	94		5.3[a]	MD=-1.000
at least 50% pain reduction (NRS) – 49d	Dichotomous	115	30[f]	(26.1%)	111	13[g]	(11.7%)	OR=2.661 (CI: 1.305, 5.426)
McGill Pain Questionnaire – 0d	Continuous	115		17.8 (SD 8.5)	111		17.7 (SD 7.7)	
McGill Pain Questionnaire – 49d	Continuous	106		11.9 (SD 8.8)	105		13.7 (SD 9.5)	MD=-1.800 (CI: -4.271, 0.671)
McGill VAS – 0d	Continuous	115		67 (SD 18)	111		68 (SD 15)	
McGill VAS – 49d	Continuous	106		47 (SD 28)	105		54 (SD 26)	MD=-7.000 (CI: -14.290, 0.290)
PPI (from MPQ) – 0d	Continuous	115		2.5 (SD 1.2)	111		2.4 (SD 1.1)	
PPI (from MPQ) – 49d	Continuous	106		1.9 (SD 1.1)	106		2 (SD 1.3)	MD=-0.100 (CI: -0.424, 0.224)
patient-reported global improvement:								
PGIC - worse (all grades), no change or minimally better – 49d	Dichotomous	115	71	(61.7%)	111	87	(78.4%)	OR=0.445 (CI: 0.247, 0.801)

PGIC - at least moderately better – 49d	Dichotomous	115	44	(38.3%)	111	24	(21.6%)	OR=2.246 (CI: 1.248, 4.044)
major adverse events (defined as leading to withdrawal):								
any major adverse event – 49d	Dichotomous	115	15	(13.0%)	111	7	(6.3%)	OR=2.229 (CI: 0.872, 5.695)
adverse events:								
asthenia – 49d	Dichotomous	115	7	(6.1%)	111	4	(3.6%)	OR=1.734 (CI: 0.493, 6.095)
Diarrhoea – 49d	Dichotomous	115	7	(6.1%)	111	1	(0.9%)	OR=7.130 (CI: 0.863, 58.927)
Dizziness – 49d	Dichotomous	115	36	(31.3%)	111	11	(9.9%)	OR=4.143 (CI: 1.983, 8.656)
Dry mouth – 49d	Dichotomous	115	7	(6.1%)	111	1	(0.9%)	OR=7.130 (CI: 0.863, 58.927)
Peripheral oedema – 49d	Dichotomous	115	6	(5.2%)	111	0	(0.0%)	OR=13.237 (CI: 0.737, 237.829)
Somnolence – 49d	Dichotomous	115	20	(17.4%)	111	7	(6.3%)	OR=3.128 (CI: 1.266, 7.728)
treatment withdrawal:								
due to lack of efficacy – 49d	Dichotomous	115	4	(3.5%)	111	4	(3.6%)	OR=0.964 (CI: 0.235, 3.953)
unspecified/other reason – 49d	Dichotomous	115	3	(2.6%)	111	3	(2.7%)	OR=0.964 (CI: 0.190, 4.882)
poor compliance – 49d	Dichotomous	115	2	(1.7%)	111	3	(2.7%)	OR=0.637 (CI: 0.104, 3.888)

[a] ns inferred from patient flow chart
[b] estimated from graph; ns inferred from patient flow chart
[c] a reduction of 15.7%; estimated from graph; ns inferred from patient flow chart
[d] a reduction of 34.4%; estimated from graph; ns inferred from patient flow chart
[e] a reduction of 34.4%; ns inferred from patient flow chart
[f] estimated from percentages; ns inferred from patient flow chart
[g] estimated from percentages; ns inferred from patient flow chart

		GABAPENTIN 2400MG/D			PLACEBO			
		N	k	mean	N	k	mean	Δ
pain score:								
NRS/NRS Pain – 0d	Continuous	108		6.5	111		6.4[a]	
NRS/NRS Pain – 28d	Mean change	85		-2.05 (SD 1.38)[b]	94		-0.85 (SD 0.97)[c]	MD=-1.200 (CI: -1.553, -0.847)
NRS/NRS Pain – 49d	Mean change	85		-2.5 (SD 1.38)[d]	94		-1.1 (SD 1.94)[c]	MD=3.600 (CI: 3.110, 4.090)
NRS/NRS Pain – 49d	Continuous	85		4.2[e]	94		5.3[a]	MD=-1.100
at least 50% pain reduction (NRS) – 49d	Dichotomous	108	29[f]	(26.9%)	111	13[g]	(11.7%)	OR=2.767 (CI: 1.349, 5.675)
McGill Pain Questionnaire – 0d	Continuous	108		19.6 (SD 8.9)	111		17.7 (SD 7.7)	
McGill Pain Questionnaire – 49d	Continuous	97		12.5 (SD 8.3)	105		13.7 (SD 9.5)	MD=-1.200 (CI: -3.656, 1.256)
McGill VAS – 0d	Continuous	108		70 (SD 18)	111		68 (SD 15)	
McGill VAS – 49d	Continuous	97		46 (SD 25)	105		54 (SD 26)	MD=-8.000 (CI: -15.034, -0.966)
PPI (from MPQ) – 0d	Continuous	108		2.7 (SD 1.2)	111		2.4 (SD 1.1)	
PPI (from MPQ) – 49d	Continuous	97		1.9 (SD 1.2)	106		2 (SD 1.3)	MD=-0.100 (CI: -0.444, 0.244)
patient-reported global improvement:								
PGIC - worse (all grades), no change or minimally better – 49d	Dichotomous	108	66	(61.1%)	111	87	(78.4%)	OR=1.735 (CI: 0.907, 3.319)
PGIC - at least moderately better – 49d	Dichotomous	108	42	(38.9%)	111	24	(21.6%)	OR=0.774 (CI: 0.396, 1.513)
major adverse events (defined as leading to withdrawal):								
any major adverse event – 49d	Dichotomous	108	19	(17.6%)	111	7	(6.3%)	OR=3.172 (CI: 1.275, 7.892)

	adverse events:							
	asthenia – 49d	Dichotomous	108	6	(5.6%)	111	4	(3.6%)	OR=1.574 (CI: 0.431, 5.739)
	Diarrhoea – 49d	Dichotomous	108	5	(4.6%)	111	1	(0.9%)	OR=5.340 (CI: 0.613, 46.478)
	Dizziness – 49d	Dichotomous	108	36	(33.3%)	111	11	(9.9%)	OR=4.545 (CI: 2.169, 9.528)
	Dry mouth – 49d	Dichotomous	108	5	(4.6%)	111	1	(0.9%)	OR=5.340 (CI: 0.613, 46.478)
	Peripheral oedema – 49d	Dichotomous	108	12	(11.1%)	111	0	(0.0%)	OR=28.886 (CI: 1.688, 494.310)
	Somnolence – 49d	Dichotomous	108	22	(20.4%)	111	7	(6.3%)	OR=3.801 (CI: 1.550, 9.322)
	treatment withdrawal:								
	due to lack of efficacy – 49d	Dichotomous	108	1	(0.9%)	111	4	(3.6%)	OR=0.250 (CI: 0.027, 2.274)
	unspecified/other reason – 49d	Dichotomous	108	2	(1.9%)	111	3	(2.7%)	OR=0.679 (CI: 0.111, 4.147)
	poor compliance – 49d	Dichotomous	108	1	(0.9%)	111	3	(2.7%)	OR=0.336 (CI: 0.034, 3.286)
	[a] ns inferred from patient flow chart [b] estimated from graph; ns inferred from patient flow chart [c] a reduction of 15.7%; estimated from graph; ns inferred from patient flow chart [d] a reduction of 34.5%; estimated from graph; ns inferred from patient flow chart [e] a reduction of 34.5%; ns inferred from patient flow chart [f] estimated from percentages; ns inferred from patient flow chart [g] estimated from percentages; ns inferred from patient flow chart								
Comments	14 day washout period required for benzodiazepines, skeletal muscle relaxants, steroids, capsaicin, mexiletine, dextromorphan, NSAIDs (for PHN) and anti-convulsants; 30-day washout required for strong opioids								

Definitions of abbreviations are given at the end of this document.

Study	Richter et al. (2005)
Pain category	Peripheral pain
Study design	Country: USA Design: Parallel Inclusion criteria: PDN for 1 to 5 years with at least 40mm on VAS, an average daily pain score of at least 4 for 4 or more days during baseline Exclusion criteria: neurologic disorders unrelated to diabetic neuropathy, any condition that would confound study assessments, recent treatment with any investigational drug or serious medical problems. Study length (days): 42 Intention-to-treat analysis? Yes
Participants	Total number of patients: 246 Number of males: 149 (60.6%) Underlying cause of neuropathic pain: Painful diabetic neuropathy Mean duration of NP (in months): not reported Baseline pain severity: 6.7 (VAS (average of means)) Mean age: 57
Intervention(s)	(1) Pregabalin 150mg/d Intervention: pregabalin Length of treatment (weeks): 6

Fixed/flexible dose regimen: Fixed dose
Set dose: 150mg/d
Notes: 2 week titration, 4 week maintenance; titrated from 25 mg/d to 150 mg/d

(2) Pregabalin 600mg/d

Intervention: pregabalin
Length of treatment (weeks): 6
Fixed/flexible dose regimen: Fixed dose
Set dose: 600mg/d
Notes: 2 week titration, 4 week maintenance; titrated from 100 mg/d to 600 mg/d

(3) Placebo

Intervention: placebo
Length of treatment (weeks): 6
Fixed/flexible dose regimen: Fixed dose

Concomitant treatments

Drug free baseline period? Yes

Concomitant pain treatment allowed? Yes (Paracetamol and stable dose of SSRIs permitted (SSRIs could be considered concomitant medications); other medications that could affect efficacy or safety were not permitted (anti-epileptic drugs, NSAIDs, opioids, tricyclic anti-depressants, benzodiazepines, muscle relaxants, capsaicin, mexiletine, dextromethorphan))

Outcomes measures and effect sizes

		PREGABALIN 150MG/D			PREGABALIN 600MG/D			
		N	k	mean	N	k	mean	Δ
pain score:								
VAS – 0d[a]	Continuous	79		6.5 (SD 1.3)	82		6.7 (SD 1.7)	
VAS – 42d[a]	Mean change	79		5.11 (SD 2.13)	82		4.29 (SD 2.35)	MD=0.820 (CI: 0.126, 1.514)
VAS – 42d[a]	Continuous	79		4.9 (SD 2.2)	82		4.3 (SD 2.7)	MD=0.600 (CI: -0.160, 1.360)
at least 50% pain reduction (VAS) – 42d	Dichotomous	79	18	(22.8%)	82	33	(40.2%)	OR=0.438 (CI: 0.221, 0.870)
McGill VAS – 42d[a]	Mean change	79		53.3 (SD 24.4)	82		43.4 (SD 24.4)	MD=9.890 (CI: 2.337, 17.443)
PPI (from MPQ) – 42d[a]	Mean change	79		1.78 (SD 1.07)	82		1.3 (SD 1.09)	MD=0.480 (CI: 0.147, 0.813)
SF McGill – 42d[a]	Mean change	79		15.5 (SD 8.8)	82		12.1 (SD 8.78)	MD=3.340 (CI: 0.623, 6.057)
patient-reported global improvement:								
PGIC - worse (all grades) – 42d	Dichotomous	79	8	(10.1%)	82	1	(1.2%)	OR=9.127 (CI: 1.114, 74.765)
PGIC - no change – 42d	Dichotomous	79	27	(34.2%)	82	11	(13.4%)	OR=3.351 (CI: 1.525, 7.363)
PGIC - better (all grades) – 42d	Dichotomous	79	42	(53.2%)	82	69	(84.1%)	OR=0.214 (CI: 0.102, 0.448)
major adverse events (defined as leading to withdrawal):								
any major adverse event – 42d	Dichotomous	79	2	(2.5%)	82	7	(8.5%)	OR=0.278 (CI: 0.056, 1.383)
adverse events:								
asthenia – 42d	Dichotomous	79	3	(3.8%)	82	10	(12.2%)	OR=0.284 (CI: 0.075, 1.074)
Constipation – 42d	Dichotomous	79	3	(3.8%)	82	5	(6.1%)	OR=0.608 (CI: 0.140, 2.633)
Diarrhoea – 42d	Dichotomous	79	4	(5.1%)	82	2	(2.4%)	OR=2.133 (CI: 0.380, 11.990)
Dizziness – 42d	Dichotomous	79	8	(10.1%)	82	31	(37.8%)	OR=0.185 (CI: 0.079, 0.437)
Dry mouth – 42d	Dichotomous	79	0	(0.0%)	82	7	(8.5%)	OR=0.063 (CI: 0.004, 1.128)
headache – 42d	Dichotomous	79	6	(7.6%)	82	13	(15.9%)	OR=0.436 (CI: 0.157, 1.212)
Infection – 42d	Dichotomous	79	10	(12.7%)	82	5	(6.1%)	OR=2.232 (CI: 0.727, 6.851)
Peripheral oedema – 42d	Dichotomous	79	3	(3.8%)	82	14	(17.1%)	OR=0.192 (CI: 0.053, 0.696)
Somnolence – 42d	Dichotomous	79	4	(5.1%)	82	18	(22.0%)	OR=0.190 (CI: 0.061, 0.589)
Weight gain – 42d	Dichotomous	79	1	(1.3%)	82	8	(9.8%)	OR=0.119 (CI: 0.014, 0.971)

treatment withdrawal:								
due to lack of efficacy – 42d	Dichotomous	79	0	(0.0%)	82	1	(1.2%)	OR=0.342 (CI: 0.014, 8.514)
unspecified/other reason – 42d	Dichotomous	79	2	(2.5%)	82	2	(2.4%)	OR=1.039 (CI: 0.143, 7.561)

[a] least squares mean

		PREGABALIN 150MG/D			PLACEBO			
		N	k	mean	N	k	mean	Δ
pain score:								
VAS – 0d[a]	Continuous	79		6.5 (SD 1.3)	82		6.9 (SD 1.6)	
VAS – 42d[a]	Mean change	79		5.11 (SD 2.13)	82		5.55 (SD 2.08)	MD=-0.440 (CI: -1.080, 0.200)
VAS – 42d[a]	Continuous	79		4.9 (SD 2.2)	82		5.8 (SD 2.2)	MD=-0.900 (CI: -1.580, -0.220)
at least 50% pain reduction (VAS) – 42d	Dichotomous	79	18	(22.8%)	85	12	(14.1%)	OR=1.795 (CI: 0.802, 4.018)
McGill VAS – 42d[a]	Mean change	79		53.3 (SD 24.4)	82		58 (SD 24.3)	MD=-4.780 (CI: -12.200, 2.640)
PPI (from MPQ) – 42d[a]	Mean change	79		1.78 (SD 1.07)	82		1.96 (SD 0.996)	MD=-0.170 (CI: -0.485, 0.145)
SF McGill – 42d[a]	Mean change	79		15.5 (SD 8.8)	82		18 (SD 8.69)	MD=-2.490 (CI: -5.140, 0.160)
patient-reported global improvement:								
PGIC - worse (all grades) – 42d	Dichotomous	79	8	(10.1%)	85	8	(9.4%)	OR=1.085 (CI: 0.387, 3.043)
PGIC - no change – 42d	Dichotomous	79	27	(34.2%)	85	31	(36.5%)	OR=0.904 (CI: 0.476, 1.717)
PGIC - better (all grades) – 42d	Dichotomous	79	42	(53.2%)	85	39	(45.9%)	OR=1.339 (CI: 0.724, 2.475)
major adverse events (defined as leading to withdrawal):								
any major adverse event – 42d	Dichotomous	79	2	(2.5%)	85	4	(4.7%)	OR=0.526 (CI: 0.094, 2.954)
adverse events:								
asthenia – 42d	Dichotomous	79	3	(3.8%)	85	3	(3.5%)	OR=1.079 (CI: 0.211, 5.509)
Constipation – 42d	Dichotomous	79	3	(3.8%)	85	4	(4.7%)	OR=0.799 (CI: 0.173, 3.689)
Diarrhoea – 42d	Dichotomous	79	4	(5.1%)	85	3	(3.5%)	OR=1.458 (CI: 0.316, 6.728)
Dizziness – 42d	Dichotomous	79	8	(10.1%)	85	2	(2.4%)	OR=4.676 (CI: 0.962, 22.737)
Dry mouth – 42d	Dichotomous	79	0	(0.0%)	85	2	(2.4%)	OR=0.210 (CI: 0.010, 4.444)
headache – 42d	Dichotomous	79	6	(7.6%)	85	9	(10.6%)	OR=0.694 (CI: 0.235, 2.047)
Infection – 42d	Dichotomous	79	10	(12.7%)	85	8	(9.4%)	OR=1.395 (CI: 0.521, 3.735)
Peripheral oedema – 42d	Dichotomous	79	3	(3.8%)	85	4	(4.7%)	OR=0.799 (CI: 0.173, 3.689)
Somnolence – 42d	Dichotomous	79	4	(5.1%)	85	3	(3.5%)	OR=1.458 (CI: 0.316, 6.728)
Weight gain – 42d	Dichotomous	79	1	(1.3%)	85	0	(0.0%)	OR=3.268 (CI: 0.131, 81.391)
treatment withdrawal:								
due to lack of efficacy – 42d	Dichotomous	79	0	(0.0%)	85	1	(1.2%)	OR=0.354 (CI: 0.014, 8.825)
unspecified/other reason – 42d	Dichotomous	79	2	(2.5%)	85	8	(9.4%)	OR=0.250 (CI: 0.051, 1.215)

[a] least squares mean

		PREGABALIN 600MG/D			PLACEBO			
		N	k	mean	N	k	mean	Δ
pain score:								
VAS – 0d[a]	Continuous	82		6.7 (SD 1.7)	82		6.9 (SD 1.6)	
VAS – 42d[a]	Continuous	82		4.3 (SD 2.7)	82		5.8 (SD 2.2)	MD=-1.500 (CI: -2.254, -0.746)
VAS – 42d[a]	Mean change	82		4.29 (SD 2.35)	82		5.55 (SD 2.08)	MD=-1.264 (CI: -1.890, -0.639)
at least 50% pain reduction (VAS) – 42d	Dichotomous	82	33	(40.2%)	85	12	(14.1%)	OR=4.097 (CI: 1.929, 8.702)
McGill VAS – 42d[a]	Mean change	82		43.4 (SD 24.4)	82		58 (SD 24.3)	MD=-14.670 (CI: -21.925, -7.415)
PPI (from MPQ) – 42d[a]	Mean change	82		1.3 (SD 1.09)	82		1.96 (SD 0.996)	MD=-0.660 (CI: -0.970, -0.350)

	SF McGill – 42d[a]	Mean change	82		12.1 (SD 8.78)	82		18 (SD 8.69)	MD=-5.830 (CI: -8.430, -3.230)
	patient-reported global improvement:								
	PGIC - worse (all grades) – 42d	Dichotomous	82	1	(1.2%)	85	8	(9.4%)	OR=0.119 (CI: 0.015, 0.972)
	PGIC - no change – 42d	Dichotomous	82	11	(13.4%)	85	31	(36.5%)	OR=0.270 (CI: 0.125, 0.585)
	PGIC - better (all grades) – 42d	Dichotomous	82	69	(84.1%)	85	39	(45.9%)	OR=6.260 (CI: 3.016, 12.993)
	major adverse events (defined as leading to withdrawal):								
	any major adverse event – 42d	Dichotomous	82	7	(8.5%)	85	4	(4.7%)	OR=1.890 (CI: 0.532, 6.716)
	adverse events:								
	asthenia – 42d	Dichotomous	82	10	(12.2%)	85	3	(3.5%)	OR=3.796 (CI: 1.006, 14.332)
	Constipation – 42d	Dichotomous	82	5	(6.1%)	85	4	(4.7%)	OR=1.315 (CI: 0.340, 5.079)
	Diarrhoea – 42d	Dichotomous	82	2	(2.4%)	85	3	(3.5%)	OR=0.683 (CI: 0.111, 4.199)
	Dizziness – 42d	Dichotomous	82	31	(37.8%)	85	2	(2.4%)	OR=25.225 (CI: 5.789, 109.911)
	Dry mouth – 42d	Dichotomous	82	7	(8.5%)	85	2	(2.4%)	OR=3.873 (CI: 0.780, 19.227)
	headache – 42d	Dichotomous	82	13	(15.9%)	85	9	(10.6%)	OR=1.591 (CI: 0.640, 3.953)
	Infection – 42d	Dichotomous	82	5	(6.1%)	85	8	(9.4%)	OR=0.625 (CI: 0.196, 1.996)
	Peripheral oedema – 42d	Dichotomous	82	14	(17.1%)	85	4	(4.7%)	OR=4.169 (CI: 1.311, 13.260)
	Somnolence – 42d	Dichotomous	82	18	(22.0%)	85	3	(3.5%)	OR=7.688 (CI: 2.169, 27.243)
	Weight gain – 42d	Dichotomous	82	8	(9.8%)	85	0	(0.0%)	OR=19.510 (CI: 1.107, 343.767)
	treatment withdrawal:								
	due to lack of efficacy – 42d	Dichotomous	82	1	(1.2%)	85	1	(1.2%)	OR=1.037 (CI: 0.064, 16.860)
	unspecified/other reason – 42d	Dichotomous	82	2	(2.4%)	85	8	(9.4%)	OR=0.241 (CI: 0.050, 1.169)
	[a] least squares mean								
Comments	baseline values not given for McGill pain questionnnaire; 14 day washout required for anti-epileptic drugs, NSAIDs; 30 day washout required for opioids, tricyclic anti-depressants, benzodiazepines, muscle relaxants, capsaicin, mexiletine, dextromethorphan; ITT included all randomised patients who received at least one dose of study medication								

Definitions of abbreviations are given at the end of this document.

Study	Rintala et al. (2007)
Pain category	Mixed (central and peripheral) or unclear if mixed
Study design	Country: USA Design: Crossover Inclusion criteria: 18-70 years of age, with SCI at any level and any degree of completeness, the SCI occurred at least 12 months before entering the study, at least 1 chronic (>6months) pain component characteristic of NP, at least 1 NP component rated as at least 5 on 0-10 scale when initially contacted about participating, and lived within 160km of the study centre. Exclusion criteria: Evidence of significant cardiac conduction disturbance, history of seizures, evidence of liver dysfunction indicative of and infectious process or hepaticellular injury, evidence of renal insufficency, taking any contraindicated medication such as MAO inhibitors, recurrent or recent substance abuse problem, evidence of previous allergic reaction to any of the study medications, evidence of a serious psychologic disorder that would prevent giving informed consent or hinder one's ability to to follow through with the study based on the attending physicians clinical judgement, evidence of psychologic or psychosomatic chronic pain based on clinical judgement, pregnancy. Study length (days): 56 Intention-to-treat analysis? Unclear
Participants	Total number of patients: 22

	Number of males: 20 (90.9%) Underlying cause of neuropathic pain: Spinal cord injury pain Mean duration of NP (in months): 7.3 Baseline pain severity: 5.6 (VAS) Mean age: 42.6 (SD: 12.6)
Intervention(s)	(1) Amitriptyline flexible dose Intervention: amitriptyline Length of treatment (weeks): 8 Fixed/flexible dose regimen: Flexible dose Notes: First 4 weeks was titration period; given in 3 daily doses instead of at bedtime because gabapentin was taken 3x daily (2) Gabapentin flexible dose Intervention: gabapentin Length of treatment (weeks): 8 Fixed/flexible dose regimen: Flexible dose Notes: First 4 weeks was titration period (3) Active placebo Intervention: placebo Length of treatment (weeks): 8 Fixed/flexible dose regimen: Flexible dose Notes: no titration period (dose kept constant throughout study period)
Concomitant treatments	Drug free baseline period? Yes (duration: 7d) Concomitant pain treatment allowed? Yes (Participants were not allowed to take any pain medications except for the medication for breakthrough pain (defined as pain above the otherwise stable and persistent pain) that was provided by the study:5 mg oxycodone + 325 mg paracetamol in a packet of 8 tablets (one packet for each day); patients were also allowed to take this medication during the drug-free baseline period)

Outcomes measures and effect sizes

		AMITRIPTYLINE FLEXIBLE DOSE			GABAPENTIN FLEXIBLE DOSE			
		N	k	mean	N	k	mean	Δ
pain score:								
at least 30% pain reduction (VAS) – 56d	Dichotomous	38	12	(31.6%)	38	7	(18.4%)	OR=2.044 (CI: 0.703, 5.947)
major adverse events (defined as leading to withdrawal):								
any major adverse event – 56d	Dichotomous	38	4[a]	(10.5%)	38	5[b]	(13.2%)	OR=0.776 (CI: 0.192, 3.147)
treatment withdrawal:								
unspecified/other reason – 56d	Dichotomous	38	3[c]	(7.9%)	38	1[d]	(2.6%)	OR=3.171 (CI: 0.315, 31.946)
protocol deviation – 56d	Dichotomous	38	0	(0.0%)	38	0	(0.0%)	OR=1.000 (CI: 0.019, 51.692)
lost to follow-up – 56d	Dichotomous	38	0	(0.0%)	38	0	(0.0%)	OR=1.000 (CI: 0.019, 51.692)
Treatment completers								
pain score:								
VAS – 0d[e]	Continuous	22		5.6 (SD 2.2)	22		5.6 (SD 2.2)	

VAS – 56d	Continuous	22		3.46 (SD 2.09)	22		4.85 (SD 2.86)	MD=-1.390 (CI: -2.870, 0.090)
adverse events:								
Constipation – 56d	Count	22	61		22	22		RaR=0.366 (CI: 0.225, 0.596)
Dizziness – 56d	Count	22	17		22	23		RaR=1.353 (CI: 0.723, 2.532)
Drowsiness – 56d	Count	22	57		22	46		RaR=0.807 (CI: 0.547, 1.190)
Dry mouth – 56d	Count	22	134		22	78		RaR=0.582 (CI: 0.440, 0.770)
Fatigue – 56d	Count	22	43		22	45		RaR=1.047 (CI: 0.689, 1.590)
Nausea – 56d	Count	22	19		22	13		RaR=0.684 (CI: 0.338, 1.385)
oedema – 56d	Count	22	12		22	11		RaR=0.917 (CI: 0.404, 2.077)
palpitation – 56d	Count	22	3		22	1		RaR=0.333 (CI: 0.035, 3.205)
Rash – 56d	Count	22	0		22	3		OR=0.124 (CI: 0.006, 2.549)
Urine retention – 56d[f]	Count	22	11		22	2		RaR=0.182 (CI: 0.040, 0.820)
Vomiting – 56d	Count	22	6		22	3		RaR=0.500 (CI: 0.125, 1.999)
Weight gain – 56d	Count	22	1		22	1		RaR=1.000 (CI: 0.063, 15.988)
non-completers								
pain score:								
VAS – 0d[e]	Continuous	16		6.6 (SD 2.3)	16		6.6 (SD 2.3)	
adverse events:								
Constipation – 56d	Count	16	22		16	9		RaR=0.409 (CI: 0.188, 0.888)
Dizziness – 56d	Count	16	9		16	7		RaR=0.778 (CI: 0.290, 2.088)
Drowsiness – 56d	Count	16	24		16	7		RaR=0.292 (CI: 0.126, 0.677)
Dry mouth – 56d	Count	16	39		16	19		RaR=0.487 (CI: 0.282, 0.843)
Fatigue – 56d	Count	16	22		16	8		RaR=0.364 (CI: 0.162, 0.817)
Nausea – 56d	Count	16	7		16	8		RaR=1.143 (CI: 0.414, 3.152)
oedema – 56d	Count	16	0		16	5		OR=0.063 (CI: 0.003, 1.262)
palpitation – 56d	Count	16	1		16	1		RaR=1.000 (CI: 0.063, 15.988)
Rash – 56d	Count	16	1		16	0		RaR=0.333 (CI: 0.014, 8.182)
Urine retention – 56d[f]	Count	16	0		16	1		OR=0.313 (CI: 0.012, 8.279)
Vomiting – 56d	Count	16	0		16	0		OR=1.000 (CI: 0.019, 53.457)
Weight gain – 56d	Count	16	1		16	0		RaR=0.333 (CI: 0.014, 8.182)

Treatment completers with less depressive symptomology (CESD-SF<10)								
pain score:								
VAS – 0d[g]	Continuous	14		5.6 (SD 2.2)	14		5.6 (SD 2.2)	
VAS – 56d[h]	Continuous	14		3 (SD 2.24)	14		3.8 (SD 2.62)	MD=-0.800 (CI: -2.606, 1.006)
VAS – 56d[i]	Percentage change from baseline	14		31.5	14		13.9	MD=17.600
VAS – 56d[i]	Mean change	14		-1.58	14		-0.84	MD=0.740
at least 30% pain reduction (VAS) – 56d[j]	Dichotomous	14	7	(50.0%)	14	6	(42.9%)	OR=1.333 (CI: 0.301, 5.912)
Treatment completers with more depressive symptomology (CESD-SF>or=10)								
pain score:								
VAS – 0d[g]	Continuous	8		5.6 (SD 2.2)	8		5.6 (SD 2.2)	
VAS – 56d	Continuous	8		4.21 (SD 1.95)	8		6.7 (SD 2.33)[h]	MD=-2.490 (CI: -4.595, -0.385)
VAS – 56d[f]	Mean change	8		-3.21	8		-0.7	MD=2.510
VAS – 56d[i]	Percentage change from baseline	8		40.6	8		11.3	MD=29.300
at least 30% pain reduction (VAS) – 56d[j]	Dichotomous	8	5	(62.5%)	8	1	(12.5%)	OR=11.667 (CI: 0.922, 147.563)

[a] causes: suicide ideation in 1, drowsiness/dizziness/falling out of wheelchair in 1, allodynia and pins and needles in extremities in 1 and a variety of reasons (including drowsiness, abdominal pain, rapid heartbeat and chills
[b] causes: shortness of breath in 1, dizziness/fatigue/nausea in 1, increased spasticity and pain in 1, fatigue/drowsiness/constipation/dry mouth in 1 and severe itching in 1
[c] 2 due to medical problems (other than adverse events); 1 moved out of state
[d] due to medical problems (other than adverse events)
[e] pain intensity on average in the baseline week - this is across all patients in each treatment group
[f] defined as 'difficulty emptying bladder'
[g] baseline data for all treatment completers
[h] estimated from graph
[i] values taken from figure
[j] calculated from percentages

		AMITRIPTYLINE FLEXIBLE DOSE			ACTIVE PLACEBO			
		N	k	mean	N	k	mean	Δ
pain score:								
at least 30% pain reduction (VAS) – 56d	Dichotomous	38	12	(31.6%)	38	7	(18.4%)	OR=2.044 (CI: 0.703, 5.947)
major adverse events (defined as leading to withdrawal):								
any major adverse event – 56d	Dichotomous	38	4[a]	(10.5%)	38	2[b]	(5.3%)	OR=2.118 (CI: 0.364, 12.320)
treatment withdrawal:								
unspecified/other reason – 56d	Dichotomous	38	3[c]	(7.9%)	38	1[d]	(2.6%)	OR=3.171 (CI: 0.315, 31.946)
protocol deviation – 56d	Dichotomous	38	0	(0.0%)	38	1	(2.6%)	OR=0.325 (CI: 0.013, 8.224)
lost to follow-up – 56d	Dichotomous	38	0	(0.0%)	38	2	(5.3%)	OR=0.190 (CI: 0.009, 4.084)

	Treatment completers							
	pain score:							
	VAS – 0d[e]	Continuous	22		5.6 (SD 2.2)	22	5.6 (SD 2.2)	
	VAS – 56d	Continuous	22		3.46 (SD 2.09)	22	5.11 (SD 2.54)	MD=-1.650 (CI: -3.024, -0.276)
	adverse events:							
	Constipation – 56d	Count	22	61		22	26	RaR=0.426 (CI: 0.269, 0.675)
	Dizziness – 56d	Count	22	17		22	15	RaR=0.882 (CI: 0.441, 1.767)
	Drowsiness – 56d	Count	22	57		22	49	RaR=0.860 (CI: 0.587, 1.259)
	Dry mouth – 56d	Count	22	134		22	87	RaR=0.649 (CI: 0.496, 0.850)
	Fatigue – 56d	Count	22	43		22	30	RaR=0.698 (CI: 0.438, 1.112)
	Nausea – 56d	Count	22	19		22	6	RaR=0.316 (CI: 0.126, 0.791)
	oedema – 56d	Count	22	12		22	11	RaR=0.917 (CI: 0.404, 2.077)
	palpitation – 56d	Count	22	3		22	5	RaR=1.667 (CI: 0.398, 6.974)
	Rash – 56d	Count	22	0		22	2	OR=0.182 (CI: 0.008, 4.024)
	Urine retention – 56d[f]	Count	22	11		22	3	RaR=0.273 (CI: 0.076, 0.978)
	Vomiting – 56d	Count	22	6		22	1	RaR=0.167 (CI: 0.020, 1.384)
	Weight gain – 56d	Count	22	1		22	0	RaR=0.333 (CI: 0.014, 8.182)
	non-completers							
	pain score:							
	VAS – 0d[e]	Continuous	16		6.6 (SD 2.3)	16	6.6 (SD 2.3)	
	adverse events:							
	Constipation – 56d	Count	16	22		16	9	RaR=0.409 (CI: 0.188, 0.888)
	Dizziness – 56d	Count	16	9		16	7	RaR=0.778 (CI: 0.290, 2.088)
	Drowsiness – 56d	Count	16	24		16	8	RaR=0.333 (CI: 0.150, 0.742)
	Dry mouth – 56d	Count	16	39		16	7	RaR=0.179 (CI: 0.080, 0.401)
	Fatigue – 56d	Count	16	22		16	12	RaR=0.545 (CI: 0.270, 1.102)
	Nausea – 56d	Count	16	7		16	5	RaR=0.714 (CI: 0.227, 2.251)
	oedema – 56d	Count	16	0		16	0	OR=1.000 (CI: 0.019, 53.457)
	palpitation – 56d	Count	16	1		16	1	RaR=1.000 (CI: 0.063, 15.988)
	Rash – 56d	Count	16	1		16	0	RaR=0.333 (CI: 0.014, 8.182)
	Urine retention – 56d[f]	Count	16	0		16	1	OR=0.313 (CI: 0.012, 8.279)

Vomiting – 56d	Count	16	0		16	1		OR=0.313 (CI: 0.012, 8.279)
Weight gain – 56d	Count	16	1		16	0		RaR=0.333 (CI: 0.014, 8.182)
Treatment completers with less depressive symptomology (CESD-SF<10)								
pain score:								
VAS – 0d[g]	Continuous	14		5.6 (SD 2.2)	14		5.6 (SD 2.2)	
VAS – 56d[h]	Continuous	14		3 (SD 2.24)	14		4.2 (SD 2.62)	MD=-1.200 (CI: -3.006, 0.606)
VAS – 56d[i]	Percentage change from baseline	14		31.5	14		16.5	MD=15.000
VAS – 56d[i]	Mean change	14		-1.58	14		-0.4	MD=-1.180
at least 30% pain reduction (VAS) – 56d[j]	Dichotomous	14	7	(50.0%)	14	5	(35.7%)	OR=1.800 (CI: 0.396, 8.182)
Treatment completers with more depressive symptomology (CESD-SF>or=10)								
pain score:								
VAS – 0d[g]	Continuous	8		5.6 (SD 2.2)	8		5.6 (SD 2.2)	
VAS – 56d	Continuous	8		4.21 (SD 1.95)	8		6.68 (SD 1.88)	MD=-2.470 (CI: -4.347, -0.593)
VAS – 56d[i]	Mean change	8		-3.21	8		-0.74	MD=-2.470
VAS – 56d[i]	Percentage change from baseline	8		40.6	8		8.7	MD=31.900
at least 30% pain reduction (VAS) – 56d[j]	Dichotomous	8	5	(62.5%)	8	2	(25.0%)	OR=5.000 (CI: 0.584, 42.797)

[a] causes: suicide ideation in 1, drowsiness/dizziness/falling out of wheelchair in 1, allodynia and pins and needles in extremities in 1 and a variety of reasons (including drowsiness, abdominal pain, rapid heartbeat and chills
[b] causes: palpitations in 1 and fatigue/dizziness/drowsiness in 1
[c] 2 due to medical problems (other than adverse events); 1 moved out of state
[d] due to medical problems (other than adverse events)
[e] pain intensity on average in the baseline week - this is across all patients in each treatment group
[f] defined as 'difficulty emptying bladder'
[g] baseline data for all treatment completers
[h] estimated from graph
[i] values taken from figure
[j] calculated from percentages

		GABAPENTIN FLEXIBLE DOSE			ACTIVE PLACEBO			
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**
pain score:								
at least 30% pain reduction (VAS) – 56d	Dichotomous	38	7	(18.4%)	38	7	(18.4%)	OR=1.000 (CI: 0.314, 3.190)
major adverse events (defined as leading to withdrawal):								
any major adverse event – 56d	Dichotomous	38	5[a]	(13.2%)	38	2[b]	(5.3%)	OR=2.727 (CI: 0.495, 15.026)
treatment withdrawal:								
unspecified/other reason – 56d[c]	Dichotomous	38	1	(2.6%)	38	1	(2.6%)	OR=1.000 (CI: 0.060, 16.594)

protocol deviation – 56d	Dichotomous	38	0	(0.0%)	38	1	(2.6%)	OR=0.325 (CI: 0.013, 8.224)
lost to follow-up – 56d	Dichotomous	38	0	(0.0%)	38	2	(5.3%)	OR=0.190 (CI: 0.009, 4.084)
Treatment completers								
pain score:								
VAS – 0d[d]	Continuous	22		5.6 (SD 2.2)	22		5.6 (SD 2.2)	
VAS – 56d	Continuous	22		4.85 (SD 2.86)	22		5.11 (SD 2.54)	MD=-0.260 (CI: -1.858, 1.338)
adverse events:								
Constipation – 56d	Count	22	22		22	26		RaR=1.178 (CI: 0.668, 2.078)
Dizziness – 56d	Count	22	23		22	15		RaR=0.652 (CI: 0.340, 1.250)
Drowsiness – 56d	Count	22	46		22	49		RaR=1.065 (CI: 0.712, 1.593)
Dry mouth – 56d	Count	22	78		22	87		RaR=1.115 (CI: 0.822, 1.514)
Fatigue – 56d	Count	22	45		22	30		RaR=0.667 (CI: 0.420, 1.058)
Nausea – 56d	Count	22	13		22	6		RaR=0.462 (CI: 0.175, 1.214)
oedema – 56d	Count	22	11		22	11		RaR=1.000 (CI: 0.434, 2.307)
palpitation – 56d	Count	22	1		22	5		RaR=5.000 (CI: 0.584, 42.797)
Rash – 56d	Count	22	3		22	2		RaR=0.667 (CI: 0.111, 3.990)
Urine retention – 56d[e]	Count	22	2		22	3		RaR=1.500 (CI: 0.251, 8.977)
Vomiting – 56d	Count	22	3		22	1		RaR=0.333 (CI: 0.035, 3.205)
Weight gain – 56d	Count	22	1		22	0		RaR=0.333 (CI: 0.014, 8.182)
non-completers								
pain score:								
VAS – 0d[d]	Continuous	16		6.6 (SD 2.3)	16		6.6 (SD 2.3)	
adverse events:								
Constipation – 56d	Count	16	9		16	9		RaR=1.000 (CI: 0.397, 2.519)
Dizziness – 56d	Count	16	7		16	7		RaR=1.000 (CI: 0.351, 2.851)
Drowsiness – 56d	Count	16	7		16	8		RaR=1.143 (CI: 0.414, 3.152)
Dry mouth – 56d	Count	16	19		16	7		RaR=0.368 (CI: 0.155, 0.876)
Fatigue – 56d	Count	16	8		16	12		RaR=1.500 (CI: 0.613, 3.670)
Nausea – 56d	Count	16	8		16	5		RaR=0.625 (CI: 0.204, 1.910)
oedema – 56d	Count	16	5		16	0		RaR=0.091 (CI: 0.005, 1.644)
palpitation – 56d	Count	16	1		16	1		RaR=1.000 (CI: 0.063, 15.988)

Rash – 56d	Count	16	0		16	0		OR=1.000 (CI: 0.019, 53.457)
Urine retention – 56d[e]	Count	16	1		16	1		RaR=1.000 (CI: 0.063, 15.988)
Vomiting – 56d	Count	16	0		16	1		OR=0.313 (CI: 0.012, 8.279)
Weight gain – 56d	Count	16	0		16	0		OR=1.000 (CI: 0.019, 53.457)
Treatment completers with less depressive symptomology (CESD-SF<10)								
pain score:								
VAS – 0d[f]	Continuous	14		5.6 (SD 2.2)	14		5.6 (SD 2.2)	
VAS – 56d[g]	Continuous	14		3.8 (SD 2.62)	14		4.2 (SD 2.62)	MD=-0.400 (CI: -2.341, 1.541)
VAS – 56d[h]	Percentage change from baseline	14		13.9	14		16.5	MD=-2.600
VAS – 56d[h]	Mean change	14		-0.84	14		-0.4	MD=-0.440
at least 30% pain reduction (VAS) – 56d[i]	Dichotomous	14	6	(42.9%)	14	5	(35.7%)	OR=1.350 (CI: 0.295, 6.183)
Treatment completers with more depressive symptomology (CESD-SF>or=10)								
pain score:								
VAS – 0d[f]	Continuous	8		5.6 (SD 2.2)	8		5.6 (SD 2.2)	
VAS – 56d	Continuous	8		6.7 (SD 2.33)[g]	8		6.68 (SD 1.88)	MD=0.020 (CI: -2.055, 2.095)
VAS – 56d[h]	Mean change	8		-0.7	8		-0.74	MD=0.040
VAS – 56d[h]	Percentage change from baseline	8		11.3	8		8.7	MD=2.600
at least 30% pain reduction (VAS) – 56d[i]	Dichotomous	8	1	(12.5%)	8	2	(25.0%)	OR=0.429 (CI: 0.031, 5.985)

[a] causes: shortness of breath in 1, dizziness/fatigue/nausea in 1, increased spasticity and pain in 1, fatigue/drowsiness/constipation/dry mouth in 1 and severe itching in 1
[b] causes: palpitations in 1 and fatigue/dizziness/drowsiness in 1
[c] due to medical problems (other than adverse events)
[d] pain intensity on average in the baseline week - this is across all patients in each treatment group
[e] defined as 'difficulty emptying bladder'
[f] baseline data for all treatment completers
[g] estimated from graph
[h] values taken from figure
[i] calculated from percentages

Comments	participants were those that had given permission to participate in previous studies; patients were randomised into 6 crossover sequences; apart from patients who withdrew from the study before a given time point, most patients were able to tolerate maximum tolerable dosages of whichever medication they were receiving; at least 50% of participants who completed the study received no breakthrough medication in week 8 - the majority of other patients had an average of 2 tablets per day (there was no significant difference in ranks of the drugs for the low or high depressive symptom groups or when the groups were combined)

Definitions of abbreviations are given at the end of this document.

Study	Robinson et al. (2004)

Pain category	Mixed (central and peripheral) or unclear if mixed
Study design	Country: USA Design: Parallel Inclusion criteria: amputation >6 months with pain at least 3 months, average pain at least 2 on 11 point scale Exclusion criteria: age 50 years or older with conduction abnormalities on ECG, pregnancy, history of cardiovascular disease or seizures, on any antidepressant medication, use of more than 2 alcoholic drinks per day Study length (days): 42 Intention-to-treat analysis? Yes
Participants	Total number of patients: 39 Number of males: 33 (84.6%) Underlying cause of neuropathic pain: Phantomb limb pain Mean duration of NP (in months): not reported Baseline pain severity: 3.4 (NRS (average of arm means for both phantomb and residual limb)) Mean age: 44.85
Intervention(s)	(1) Amitriptyline 125 mg/d Intervention: amitriptyline Length of treatment (weeks): 6 Fixed/flexible dose regimen: Fixed dose Set dose: 125mg/d Notes: 10 mg/d in week 1, 25 mg/d in week 2, 50 mg/d in week 3, 75 mg/d in week 4, 100 mg/d in week 5, 125 mg/d in week 6 (2) Placebo (0.5mg benztropine) Intervention: placebo Length of treatment (weeks): 6 Fixed/flexible dose regimen: Fixed dose Set dose: 0.5mg/d Notes: benztropine
Concomitant treatments	Drug free baseline period? Unclear Concomitant pain treatment allowed? Yes (prohibited medications were: drugs and supplements commonly used for DPN (benzodiazepines, skeletal muscle relaxants, capsaicin, narcotics, fatty acid supplements, evening primrose oil, myoinositol, chromium picolinate), anti-convulsants, tricyclic antidepressants and centrally acting analgesics (ie tramadol and dextromethorphan); paracetamol up to 4g/d, aspirin up to 325 mg/d and SSRI (if stable for 30 days) were permitted (SSRIs have also been used to treat neuropathic pain))

Outcomes measures and effect sizes

		AMITRIPTYLINE 125 MG/D			PLACEBO (0.5MG BENZTROPINE)			
		N	k	mean	N	k	mean	Δ
pain score:								
SF McGill – 0d	Continuous	18		13 (SD 10.5)	19		12 (SD 11.1)	
SF McGill – 42d	Continuous	18		11.6 (SD 10)	19		12.5 (SD 8.6)	MD=-0.900 (CI: -6.925, 5.125)

	patient-reported improvement in daily physical and emotional functioning, including sleep:							
	BPI (modified) – 0d	Continuous	18		28.4 (SD 23.9)	19		28.8 (SD 22.3)	
	BPI (modified) – 42d	Continuous	18		30.3 (SD 30.6)	19		24.4 (SD 21.4)	MD=5.900 (CI: -11.200, 23.000)
	major adverse events (defined as leading to withdrawal):							
	any major adverse event – 42d	Dichotomous	20	2	(10.0%)	19	0	(0.0%)	OR=5.270 (CI: 0.237, 117.256)
	adverse events:							
	Blurred vision	Dichotomous	20	1	(5.0%)	19	5	(26.3%)	OR=0.147 (CI: 0.015, 1.406)
	Constipation	Dichotomous	20	4	(20.0%)	19	3	(15.8%)	OR=1.333 (CI: 0.256, 6.940)
	Diarrhoea	Dichotomous	20	1	(5.0%)	19	1	(5.3%)	OR=0.947 (CI: 0.055, 16.309)
	Dizziness	Dichotomous	20	2	(10.0%)	19	3	(15.8%)	OR=0.593 (CI: 0.088, 4.009)
	drowsiness/tiredness/fatigue	Dichotomous	20	9	(45.0%)	19	9	(47.4%)	OR=0.909 (CI: 0.258, 3.204)
	Dry mouth	Dichotomous	20	13	(65.0%)	19	13	(68.4%)	OR=0.857 (CI: 0.226, 3.254)
	headache	Dichotomous	20	0	(0.0%)	19	1	(5.3%)	OR=0.301 (CI: 0.012, 7.850)
	nausea/vomiting	Dichotomous	20	2	(10.0%)	19	0	(0.0%)	OR=5.270 (CI: 0.237, 117.256)
	palpitation	Dichotomous	20	0	(0.0%)	19	2	(10.5%)	OR=0.171 (CI: 0.008, 3.800)
	sleep disturbance	Dichotomous	20	2	(10.0%)	19	2	(10.5%)	OR=0.944 (CI: 0.119, 7.477)
	Urine retention	Dichotomous	20	1	(5.0%)	19	1	(5.3%)	OR=0.947 (CI: 0.055, 16.309)
	Residual (or stump) limb pain pain score:							
	NRS/NRS Pain – 0d	Continuous	6		3.9 (SD 2.6)	7		3 (SD 2.5)	
	NRS/NRS Pain – 42d	Continuous	6		3.1 (SD 2.2)	7		2.3 (SD 2)	MD=0.800 (CI: -1.501, 3.101)
	Phantom limb pain pain score:							
	NRS/NRS Pain – 0d	Continuous	17		3.6 (SD 2.4)	14		3.1 (SD 2.6)	
	NRS/NRS Pain – 42d	Continuous	17		3.1 (SD 2.7)	14		3.1 (SD 2.9)	MD=0.000 (CI: -1.989, 1.989)
Comments	authors added 3 items to the BPI to provide a more broad-based assesment: pain interference with self-care, recreational activities, social activities; there was a 1 week baseline phase but it was not clear if this was drug-free								

Definitions of abbreviations are given at the end of this document.

Study	Rog et al. (2005)
Pain category	Central pain
Study design	Country: UK Design: Parallel Inclusion criteria: with diagnosed MS at least 6 months prior, with central neuropathic pain syndromes of at least 3 months due to MS (where nocioceptive pain was unlikely) Exclusion criteria: spasticity or painless spasms alone or other noncentral pain mechanisms were mroe likely, chronic visceral pain, headache, spasticity-associated aching pain, secondary entrapment syndromes, or acute MS-related pains (ie. Optic neuritis or positive Lhermitte sign alone), cannabis use at least 7 days before, history of major psychiatric disorder other than depression associated with underlying condition, severe concomitant illness, seizures, hisotry or suspicion of substance abuse, concomitant nonneuropathic pain or illness that could cause peripheral neuropathic pain, pregnancy, lactacting, levodopa therapy within 7 days of study entry, known or suspected hypersensitivity to cannabinoids, schoeduled procedures requiring general anaesthetic during study

	Study length (days): 35 Intention-to-treat analysis? Yes
Participants	Total number of patients: 66 Number of males: 14 (21.2%) Underlying cause of neuropathic pain: MS neuropathic pain Mean duration of NP (in months): not reported Baseline pain severity: 6.475 (NRS (average of arm means)) Mean age: 49.2 (SD: 8.3)
Intervention(s)	(1) Sativex Intervention: cannabis sativa extract Length of treatment (weeks): 4 Fixed/flexible dose regimen: Flexible dose Mean dose: 25.9mg/d Notes: each spray had 2.7 mg THC (delta-9-tetrahydrocannabinol) and 2.5 mg CBD (cannabidiol); up to 48 sprays in a 24 hour period but also, no more than 8 sprays in a 3-hour period or no up-titrating a daily dose by more than 50%; in week 4, the mean number of sprays each day was 9.6 (from 2 to 25, SD = 6.1) - this is an equivalent of 25.9 mg THC:24mg CBD (2) placebo Intervention: placebo Length of treatment (weeks): Fixed/flexible dose regimen: Flexible dose Notes: in week 4, the mean number of sprays each day was 19.1 (from 1 to 47, SD = 12.9)
Concomitant treatments	Drug free baseline period? No Concomitant pain treatment allowed? Yes (amitriptyline or other tricyclic antidepressants at max dosage 75 mg/d (stable medication for 15 days prior and throughout treatment period))

Outcomes measures and effect sizes

		SATIVEX			PLACEBO			
		N	k	mean	N	k	mean	Δ
pain score:								
NRS/NRS Pain – 0d	Continuous	33		6.58 (SD 1.69)	32		6.37 (SD 1.73)	
NRS/NRS Pain – 28d	Mean change	33			32			MD=-1.250 (CI: -2.110, -0.390)
NRS/NRS Pain – 28d	Continuous	33		3.85 (SD 2.12)	32		4.96 (SD 2.21)	MD=-1.110 (CI: -2.164, -0.056)
NPS – 0d	Continuous	33		46.9 (SD 15.1)	32		45.8 (SD 16.1)	
NPS – 28d	Mean change	33			32			MD=-6.580 (CI: -12.970, -0.190)
NPS – 28d	Continuous	33		31.9 (SD 15.7)	32		37.7 (SD 18.3)	MD=-5.830 (CI: -14.115, 2.455)
patient-reported global improvement:								
PGIC - much worse – 28d	Dichotomous	34	0	(0.0%)	32	0	(0.0%)	OR=0.942 (CI: 0.018, 48.881)
PGIC - moderately worse – 28d	Dichotomous	34	0	(0.0%)	32	0	(0.0%)	OR=0.942 (CI: 0.018, 48.881)
PGIC - minimally worse – 28d	Dichotomous	34	2	(5.9%)	32	3	(9.4%)	OR=0.604 (CI: 0.094, 3.875)
PGIC - no change – 28d	Dichotomous	34	8	(23.5%)	32	19	(59.4%)	OR=0.211 (CI: 0.073, 0.608)
PGIC - minimally better – 28d	Dichotomous	34	15	(44.1%)	32	6	(18.8%)	OR=3.421 (CI: 1.120, 10.447)
PGIC - moderately better – 28d	Dichotomous	34	8	(23.5%)	32	4	(12.5%)	OR=2.154 (CI: 0.579, 8.011)
PGIC - at least moderately better – 28d	Dichotomous	34	9	(26.5%)	32	4	(12.5%)	OR=2.520 (CI: 0.690, 9.204)

	PGIC - much better – 28d	Dichotomous	34	1	(2.9%)	32	0	(0.0%)	OR=2.910 (CI: 0.114, 74.076)
	patient-reported improvement in daily physical and emotional functioning, including sleep:								
	Normalised (10-pt) sleep interference measure – 0d[a]	Continuous	33		5.26 (SD 2.68)	32		4.47 (SD 2.74)	
	Normalised (10-pt) sleep interference measure – 28d[a]	Continuous	33		2.69 (SD 2.05)	32		3.64 (SD 2.63)	
	NRS Sleep – 0d	Continuous	33		5.26 (SD 2.68)	32		4.47 (SD 2.74)	
	NRS Sleep – 28d	Mean change	33			32			MD=-1.390 (CI: -2.275, -0.505)
	NRS Sleep – 28d	Continuous	33		2.69 (SD 2.05)	32		3.64 (SD 2.63)	MD=-0.950 (CI: -2.098, 0.198)
	major adverse events (defined as leading to withdrawal):								
	any major adverse event – 28d	Dichotomous	34	1	(2.9%)	32	0	(0.0%)	OR=2.910 (CI: 0.114, 74.076)
	adverse events:								
	any adverse event – 28d	Dichotomous	34	30	(88.2%)	32	22	(68.8%)	OR=3.409 (CI: 0.945, 12.303)
	Burning pain[b]	Dichotomous	34	0	(0.0%)	32	1	(3.1%)	OR=0.304 (CI: 0.012, 7.747)
	chest discomfort	Dichotomous	34	0	(0.0%)	32	1	(3.1%)	OR=0.304 (CI: 0.012, 7.747)
	Diarrhoea	Dichotomous	34	2	(5.9%)	32	0	(0.0%)	OR=5.000 (CI: 0.231, 108.254)
	Dissociation – 28d	Dichotomous	34	3	(8.8%)	32	0	(0.0%)	OR=7.222 (CI: 0.358, 145.561)
	Dizziness – 28d	Dichotomous	34	18	(52.9%)	32	5	(15.6%)	OR=6.075 (CI: 1.889, 19.533)
	Dry mouth	Dichotomous	34	4	(11.8%)	32	0	(0.0%)	OR=9.590 (CI: 0.495, 185.669)
	dyspepsia	Dichotomous	34	0	(0.0%)	32	1	(3.1%)	OR=0.304 (CI: 0.012, 7.747)
	euphoria – 28d	Dichotomous	34	2	(5.9%)	32	0	(0.0%)	OR=5.000 (CI: 0.231, 108.254)
	falls – 28d	Dichotomous	34	3	(8.8%)	32	2	(6.3%)	OR=1.452 (CI: 0.226, 9.309)
	Fatigue – 28d	Dichotomous	34	2	(5.9%)	32	2	(6.3%)	OR=0.938 (CI: 0.124, 7.083)
	feeling abnormal – 28d	Dichotomous	34	1	(2.9%)	32	0	(0.0%)	OR=2.910 (CI: 0.114, 74.076)
	feeling drunk/drugged – 28d	Dichotomous	34	1	(2.9%)	32	1	(3.1%)	OR=0.939 (CI: 0.056, 15.679)
	glossodynia	Dichotomous	34	1	(2.9%)	32	3	(9.4%)	OR=0.293 (CI: 0.029, 2.973)
	headache	Dichotomous	34	1	(2.9%)	32	3	(9.4%)	OR=0.293 (CI: 0.029, 2.973)
	impaired attention – 28d	Dichotomous	34	2	(5.9%)	32	0	(0.0%)	OR=5.000 (CI: 0.231, 108.254)
	mouth ulceration	Dichotomous	34	1	(2.9%)	32	0	(0.0%)	OR=2.910 (CI: 0.114, 74.076)
	Nausea	Dichotomous	34	3	(8.8%)	32	2	(6.3%)	OR=1.452 (CI: 0.226, 9.309)
	pharyngitis	Dichotomous	34	2	(5.9%)	32	1	(3.1%)	OR=1.938 (CI: 0.167, 22.469)
	Somnolence	Dichotomous	34	3	(8.8%)	32	0	(0.0%)	OR=7.222 (CI: 0.358, 145.561)
	Vomiting	Dichotomous	34	1	(2.9%)	32	0	(0.0%)	OR=2.910 (CI: 0.114, 74.076)
	weakness – 28d	Dichotomous	34	3	(8.8%)	32	0	(0.0%)	OR=7.222 (CI: 0.358, 145.561)
	treatment withdrawal:								
	withdrawal of consent – 28d	Dichotomous	34	1	(2.9%)	32	0	(0.0%)	OR=2.910 (CI: 0.114, 74.076)
	protocol deviation – 28d	Dichotomous	34	2	(5.9%)	32	0	(0.0%)	OR=5.000 (CI: 0.231, 108.254)
	dysesthetic pain								
	pain score:								
	NRS/NRS Pain – 28d	Mean change	30		-2.4 (SD 1.5)	28		-1.3 (SD 1.7)	MD=-1.100 (CI: -1.927, -0.273)
	painful spasms								
	pain score:								
	NRS/NRS Pain – 28d	Mean change	3		-5.7 (SD 3.5)	4		-2.1 (SD 1.6)	MD=-3.600 (CI: -7.860, 0.660)
	[a] based on NRS Sleep [b] application site burning								
Comments	of 66 patients, 59 were dysesthetic and 7 had painful spasms (and the later had higher baseline NRS-11 pain intensities); dose titration was performed by patients as required (there was no specific target dosage); ITT population included all those who had at least one dose of study medication and some efficacy data; no significant differences in most neuropsychological outcomes or between HADS anxiety and depression scales (actual results not given); there was an initial 7 day screening period where patients were not allowed to have any cannabinoid use								

Definitions of abbreviations are given at the end of this document.

Study	Rosenstock et al. (2004)
Pain category	Peripheral pain
Study design	Country: USA Design: Parallel Inclusion criteria: Aged 18 and over with type 1 or 2 diabetes with symetrical painful symptoms in distal extremities for 1-5 years prior to the study, and whose symptoms were attributable to sensorimotor PDN. Score of at least 40mm on 100mm VAS, and minimum average daily pain score of 4 on an 11 point NRS Exclusion criteria: Other serious or unstable medical conditions including psychiatric disorders and conditions that could confound evaluation of PDN. Participants with amputations other than toes, non-diabetic neurological disorders, skin conditions affecting sensation in painful limbs, serum creatinine clearance <60ml/min, failure to repsond to previous treatment with gabapentin at doese of >1200mg/day for pain associated with PDN, or previous participation in othe rpregabalin clinical trials. Study length (days): 63 Intention-to-treat analysis? Yes
Participants	Total number of patients: 146 Number of males: 82 (56.2%) Underlying cause of neuropathic pain: Painful diabetic neuropathy Mean duration of NP (in months): not reported Baseline pain severity: not reported (not reported) Mean age: 59.7
Intervention(s)	(1) Pregabalin 300mg/day Intervention: pregabalin Length of treatment (weeks): 8 Fixed/flexible dose regimen: Fixed dose Set dose: 300mg/d Notes: no titration period (2) Placebo Intervention: placebo Length of treatment (weeks): 8 Fixed/flexible dose regimen: Fixed dose
Concomitant treatments	Drug free baseline period? No Concomitant pain treatment allowed? Yes (Paracetamol (up to 4g/d), aspirin (up to 325 mg/d), and SSRIs (SSRIs could be considered concomitant medications) provided no doeses changed in 30 days prior to randomisation or during study)
Outcomes measures and effect sizes	**PREGABALIN 300MG/DAY** — **N k mean**; **PLACEBO** — **N k mean**; **Δ**

pain score:								
NRS/NRS Pain – 56d[a]	Continuous	75		3.99 (SD 2.25)	69		5.46 (SD 2.33)	MD=-1.470 (CI: -2.190, -0.750)
at least 50% pain reduction (NRS) – 56d	Dichotomous	76	26[b]	(34.2%)	70	9[c]	(12.9%)	OR=3.926 (CI: 1.656, 9.310)
at least 50% pain reduction (NRS) – 56d	Dichotomous	65	26[b]	(34.2%)	62	9[c]	(12.9%)	OR=3.926 (CI: 1.656, 9.310)
McGill VAS – 56d[a]	Continuous	75		40.8 (SD 26.3)	69		57 (SD 26.7)	MD=-16.190 (CI: -24.855, -7.525)
PPI (from MPQ) – 56d[a]	Continuous	75		1.42 (SD 1.13)	69		1.79 (SD 1.08)	MD=-0.370 (CI: -0.730, -0.010)
SF McGill – 56d[a]	Continuous	75		10.5 (SD 26.3)	69		14.9 (SD 9.39)	MD=-4.410 (CI: -7.325, -1.495)
patient-reported global improvement:								
PGIC - worse (all grades) – 56d	Dichotomous	76	6	(7.9%)	70	13	(18.6%)	OR=0.376 (CI: 0.134, 1.051)
PGIC - no change – 56d	Dichotomous	76	18	(23.7%)	70	29	(41.4%)	OR=0.439 (CI: 0.215, 0.894)
PGIC - better (all grades) – 56d	Dichotomous	76	49	(64.5%)	70	27	(38.6%)	OR=2.890 (CI: 1.475, 5.663)
patient-reported improvement in daily physical and emotional functioning, including sleep:								
POMS – 56d	Continuous	71		23.5 (SD 26.3)[d]	66		33.4 (SD 27.3)	MD=-9.950 (CI: -18.530, -1.370)
NRS Sleep – 56d[a]	Continuous	75		2.78 (SD 2.34)	69		4.32 (SD 2.41)	MD=-1.540 (CI: -2.280, -0.800)
major adverse events (defined as leading to withdrawal):								
any major adverse event – 56d	Dichotomous	76	8	(10.5%)	70	2	(2.9%)	OR=4.000 (CI: 0.819, 19.527)
adverse events:								
asthenia – 56d	Dichotomous	76	3	(3.9%)	70	2	(2.9%)	OR=1.397 (CI: 0.227, 8.619)
Constipation – 56d	Dichotomous	76	4	(5.3%)	70	0	(0.0%)	OR=8.752 (CI: 0.463, 165.559)
Diarrhoea – 56d	Dichotomous	76	3	(3.9%)	70	2	(2.9%)	OR=1.397 (CI: 0.227, 8.619)
Dizziness – 56d	Dichotomous	76	27	(35.5%)	70	8	(11.4%)	OR=4.270 (CI: 1.783, 10.228)
flu-like symptoms – 56d	Dichotomous	76	3	(3.9%)	70	3	(4.3%)	OR=0.918 (CI: 0.179, 4.705)
headache – 56d	Dichotomous	76	5	(6.6%)	70	7	(10.0%)	OR=0.634 (CI: 0.192, 2.097)
hyperglycaemia – 56d	Dichotomous	76	3	(3.9%)	70	0	(0.0%)	OR=6.714 (CI: 0.341, 132.341)
Infection – 56d	Dichotomous	76	11	(14.5%)	70	4	(5.7%)	OR=2.792 (CI: 0.846, 9.220)
Nausea – 56d	Dichotomous	76	6	(7.9%)	70	6	(8.6%)	OR=0.914 (CI: 0.281, 2.979)
Peripheral oedema – 56d	Dichotomous	76	8	(10.5%)	70	1	(1.4%)	OR=8.118 (CI: 0.988, 66.666)
Somnolence – 56d	Dichotomous	76	15	(19.7%)	70	2	(2.9%)	OR=8.361 (CI: 1.837, 38.050)
Vomiting – 56d	Dichotomous	76	3	(3.9%)	70	1	(1.4%)	OR=2.836 (CI: 0.288, 27.917)
overall improvement in quality of life:								
SF36 Mental – 56d[a]	Continuous	72		75.8 (SD 16.1)	69		72.4 (SD 16.4)	MD=3.470 (CI: -1.725, 8.665)
SF36 bodily pain – 56d[a]	Continuous	73		53.8 (SD 19.1)	69		47 (SD 19.7)	MD=6.870 (CI: 0.700, 13.040)
SF36 vitality – 56d[a]	Continuous	72		46.8 (SD 16.6)	69		43.6 (SD 17)	MD=3.240 (CI: -2.130, 8.610)
treatment withdrawal:								
due to lack of efficacy – 56d	Dichotomous	76	1	(1.3%)	70	3	(4.3%)	OR=0.298 (CI: 0.030, 2.932)
unspecified/other reason – 56d	Dichotomous	76	0	(0.0%)	70	1	(1.4%)	OR=0.303 (CI: 0.012, 7.557)
protocol deviation – 56d	Dichotomous	76	2	(2.6%)	70	1	(1.4%)	OR=1.865 (CI: 0.165, 21.030)
lost to follow-up – 56d	Dichotomous	76	0	(0.0%)	70	1	(1.4%)	OR=0.303 (CI: 0.012, 7.557)

[a] Least squares mean
[b] estimated from percentage (40%) so numbers may not be absolutely accurate
[c] estimated from percentage (14.5%) so numbers may not be absolutely accurate
[d] Total mood disturbance, Least squares mean

Comments	-

Definitions of abbreviations are given at the end of this document.

Study	Rossi et al. (2009)

Pain category	Central pain
Study design	Country: Italy Design: Parallel Inclusion criteria: Patients with MS and chronic neuropathic pain, aged 18 to 60 years with normal hematologic exams Exclusion criteria: Patients with trigeminal neuralgia or other painful manifestations, and those suffering from hepatic or renal disturbances, or who had had an MS relapse 0-30 days before randomisation Study length (days): 84 Intention-to-treat analysis? No
Participants	Total number of patients: 20 Number of males: 5 (25.0%) Underlying cause of neuropathic pain: MS neuropathic pain Mean duration of NP (in months): 8.25 Baseline pain severity: 69.65 (mm on VAS (average of arm means)) Mean age: 36.8
Intervention(s)	(1) Levetiracetam 500mg Intervention: levetiracetam Length of treatment (weeks): 12 Fixed/flexible dose regimen: Fixed dose Set dose: 500mg/d Notes: patients started at 1 tablet twice a day during the first week, gradually increasing to 3 twice a day in the 4th week (2) Placebo Intervention: placebo Length of treatment (weeks): Fixed/flexible dose regimen: Fixed dose
Concomitant treatments	Drug free baseline period? No Concomitant pain treatment allowed? No (All previous medications (ie. Gabapentin, carbamazepine, pregabalin, baclofen, amitryptline, duloxetine) at least 2 weeks prior and did not start again until the end of the trial)

Outcomes measures and effect sizes

		LEVETIRACETAM 500MG			PLACEBO			
		N	k	mean	N	k	mean	Δ
pain score:								
VAS – 0d	Continuous	12		73.7 (SD 20)	8		65.6 (SD 17)	
VAS – 28d[a]	Continuous	11		58 (SD 23)	8		65 (SD 19)	MD=-7.000 (CI: -25.923, 11.923)
VAS – 56d[a]	Continuous	11		41 (SD 10)	8		60 (SD 22.5)	MD=-19.000 (CI: -35.674, -2.326)
VAS – 84d[a]	Continuous	10		35 (SD 13)	8		55 (SD 21)	MD=-20.000 (CI: -36.634, -3.366)
major adverse events (defined as leading to withdrawal):								
any major adverse event – 84d	Dichotomous	12	2[b]	(16.7%)	8	0	(0.0%)	OR=4.048 (CI: 0.170, 96.187)
adverse events:								
Dizziness – 84d	Dichotomous	12	1	(8.3%)	8	0	(0.0%)	OR=2.217 (CI: 0.080, 61.403)

	flu	Dichotomous	12	2	(16.7%)	8	3	(37.5%)	OR=0.333 (CI: 0.041, 2.686)
	Nausea – 84d	Dichotomous	12	1	(8.3%)	8	1	(12.5%)	OR=0.636 (CI: 0.034, 11.909)
	Somnolence – 84d	Dichotomous	12	3	(25.0%)	8	0	(0.0%)	OR=6.263 (CI: 0.281, 139.631)
	overall improvement in quality of life:								
	MSQoL-54 overall rating – 0d[c]	Continuous	12		32	8		33	
	MSQoL-54 overall rating – 84d[c]	Continuous	10		67.5	8		37	MD=30.500
	treatment withdrawal:								
	unspecified/other reason – 84d	Dichotomous	12	2	(16.7%)	8	1	(12.5%)	OR=1.400 (CI: 0.105, 18.615)
	[a] SD estimated from graph; number of patients not reported so estimated [b] due to severe pain or somnolence [c] Estimated from graph; number of patients not reported so estimated								
Comments	single blind study (patients only were blind to treatment allocation); study also reprots proportion of patients achieving at least 20 mm reduction on a 100mm VAS scale (ie. 20% reduction)								

Definitions of abbreviations are given at the end of this document.

Study	Rowbotham et al. (1998)
Pain category	Peripheral pain
Study design	Country: USA Design: Parallel Inclusion criteria: Age 18 years and over with pain scores at least 40mm on VAS and at least 4 on average daily pain score with NRS (11 point). Exclusion criteria: Prior treatment with gabapentin or demonstrated hypersensitivity to the drug or its ingredients, neurolytic or neurosurgical therapy for PHN, immunocompromised state, significant heraptic or renal insufficiency, significant haematological disease, severe pain other than that caused by PHN, the use of experimental drugs or participation in a clinical study within 2 months of screening, a history of illicit drug or alcohol abuse within the last year, any serious or unstable medical or psychological condition. Study length (days): 56 Intention-to-treat analysis? No
Participants	Total number of patients: 229 Number of males: 118 (51.5%) Underlying cause of neuropathic pain: Post-herpetic neuralgia Mean duration of NP (in months): not reported Baseline pain severity: 6.4 (NRS (average of means)) Mean age: not reported
Intervention(s)	(1) Gabapentin up to 3600mg/d Intervention: gabapentin Length of treatment (weeks): 8 Fixed/flexible dose regimen: Flexible dose Notes: 4 week titration period, 4 week stable dose period; 83.3% received at least 2400 mg/d and 65% received 3600 mg/d (2) Placebo Intervention: placebo

	Length of treatment (weeks): 8 Fixed/flexible dose regimen: Flexible dose
Concomitant treatments	Drug free baseline period? Yes (duration: 14d) Concomitant pain treatment allowed? Yes (Previously prescribed tricyclic anti-depressants or narcotics were continued; muscle relaxants, anti-convulsants, mexiletine, topical analgesics and anti-viral agents were discontinued 2 weeks before screening)

Outcomes measures and effect sizes

		GABAPENTIN UP TO 3600MG/D			PLACEBO			
		N	k	mean	N	k	mean	Δ
pain score:								
NRS/NRS Pain – 0d	Continuous	109		6.3 (SD 1.7)	116		6.5 (SD 1.7)	
NRS/NRS Pain – 56d	Continuous	109		4.2 (SD 2.3)	116		6 (SD 2.4)	MD=-1.800 (CI: -2.414, -1.186)
NRS/NRS Pain – 56d	Mean change	109		-2.1 (SD 2.1)	116		-0.5 (SD 1.6)	MD=-1.600 (CI: -2.090, -1.110)
SF McGill – 0d	Continuous	104		17.2 (SD 9.6)	110		18.7 (SD 8.5)	
SF McGill – 56d	Mean change	104		-5.8 (SD 8.9)	110		-1.8 (SD 8.9)	MD=-4.000 (CI: -6.386, -1.614)
SF McGill – 56d	Continuous	104		11.4 (SD 9.3)	110		16.8 (SD 10.8)	MD=-5.400 (CI: -8.096, -2.704)
patient-reported global improvement:								
PGIC - worse (all grades) – 56d	Dichotomous	113	3	(2.7%)	116	10	(8.6%)	OR=0.289 (CI: 0.077, 1.079)
PGIC - no change – 56d	Dichotomous	113	25	(22.1%)	116	69	(59.5%)	OR=0.194 (CI: 0.109, 0.345)
PGIC - minimally better – 56d	Dichotomous	113	19	(16.8%)	116	9	(7.8%)	OR=2.403 (CI: 1.037, 5.567)
PGIC - at least moderately better – 56d	Dichotomous	113	47	(41.6%)	116	14	(12.1%)	OR=5.188 (CI: 2.649, 10.163)
patient-reported improvement in daily physical and emotional functioning, including sleep:								
Normalised (10-pt) sleep interference measure – 0d[a]	Continuous	109		4.3 (SD 2.8)	116		4.1 (SD 2.9)	
Normalised (10-pt) sleep interference measure – 56d[a]	Continuous	109		2.4 (SD 2.5)	116		3.6 (SD 3)	
Normalised (10-pt) sleep interference measure – 56d[a]	Mean change	109		-1.9 (SD 2.5)	116		-0.5 (SD 1.6)	
POMS – 0d[b]	Continuous	84		31.9 (SD 35.7)	91		30.6 (SD 36.6)	
POMS – 56d[b]	Mean change	84		-15 (SD 27.9)	91		-2.9 (SD 20.5)	MD=-12.100 (CI: -19.403, -4.797)
POMS – 56d[b]	Continuous	84		16.9 (SD 28.3)	91		27.7 (SD 37.1)	MD=-10.800 (CI: -20.533, -1.067)
NRS Sleep – 0d	Continuous	109		4.3 (SD 2.8)	116		4.1 (SD 2.9)	
NRS Sleep – 56d	Mean change	109		-1.9 (SD 2.5)	116		-0.5 (SD 1.6)	MD=-1.400 (CI: -1.952, -0.848)
NRS Sleep – 56d	Continuous	109		2.4 (SD 2.5)	116		3.6 (SD 3)	MD=-1.200 (CI: -1.920, -0.480)
major adverse events (defined as leading to withdrawal):								
any major adverse event – 56d	Dichotomous	113	21	(18.6%)	116	14	(12.1%)	OR=1.663 (CI: 0.799, 3.460)
adverse events:								
any adverse event – 56d[c]	Dichotomous	113	62	(54.9%)	116	32	(27.6%)	OR=3.191 (CI: 1.840, 5.534)
Dizziness	Dichotomous	113	31	(27.4%)	116	6	(5.2%)	OR=6.931 (CI: 2.763, 17.387)
Infection	Dichotomous	113	9	(8.0%)	116	3	(2.6%)	OR=3.260 (CI: 0.859, 12.368)

	Peripheral oedema	Dichotomous	113	11	(9.7%)	116	4	(3.4%)	OR=3.020 (CI: 0.932, 9.782)
	Somnolence	Dichotomous	113	31	(27.4%)	116	6	(5.2%)	OR=6.931 (CI: 2.763, 17.387)
	overall improvement in quality of life:								
	SF36 Mental – 0d	Continuous	93		67.9 (SD 20)	101		69.2 (SD 20.2)	
	SF36 Mental – 56d	Mean change	93		6.7 (SD 16.5)	101		0.7 (SD 15.4)	MD=6.000 (CI: 1.498, 10.502)
	SF36 Mental – 56d	Continuous	93		74.6 (SD 16.6)	101		69.9 (SD 20.6)	MD=4.700 (CI: -0.546, 9.946)
	SF36 Physical – 0d	Continuous	92		61.7 (SD 24.5)	101		57.6 (SD 29.3)	
	SF36 Physical – 56d	Mean change	92		4.5 (SD 19.4)	101		-0.1 (SD 19.5)	MD=4.600 (CI: -0.893, 10.093)
	SF36 Physical – 56d	Continuous	92		66.2 (SD 24.4)	101		57.5 (SD 30)	MD=8.700 (CI: 1.013, 16.387)
	treatment withdrawal:								
	due to lack of efficacy – 56d	Dichotomous	113	0	(0.0%)	116	2	(1.7%)	OR=0.202 (CI: 0.010, 4.249)
	unspecified/other reason – 56d	Dichotomous	113	2	(1.8%)	116	3	(2.6%)	OR=0.679 (CI: 0.111, 4.140)
	poor compliance – 56d	Dichotomous	113	1	(0.9%)	116	2	(1.7%)	OR=0.509 (CI: 0.046, 5.692)

[a] based on NRS Sleep
[b] results also available for each component of POMS
[c] Any adverse event

Comments	null

Definitions of abbreviations are given at the end of this document.

Study	Rowbotham et al. (2004)
Pain category	Peripheral pain
Study design	Country: USA Design: Parallel Inclusion criteria: Full diabetic neuropathy (no other peripheral neuropathy) of at least moderate severity for 3 months or longer and metabolically stable (type 1 or type 2 diabetes) with at least 40mm on the VASpi, at least 18 years old Exclusion criteria: Presence of clinically significant psychiatric disorders or a history of recent drug or alcohol abuse, major depressive disorder within 6 months of study, BDI score of 13 or more, Raskin Depression Scale score of 9 or more, seizure disorders, clinically significant cardiovascular, renal, or hepatic disease, clinically significant abnormalities in physcial examination results, vital signs, ECG, or lab test results at the start of the study. Additionally, use of investigational drugs or procedures, antipsychotics or electroconvulsive therapy within 30 days of study initiation, antidepressants within 14 days and use of any anxiolytic, sedative-hypnotic, anticonvulsant or any other psychotropic drug or capsaicin product within 7 days of study initiation, patients unable to reduce their analgesic use to a maximum of 1 dose per day by the first day of treatment Study length (days): 56 Intention-to-treat analysis? Yes
Participants	Total number of patients: 244 Number of males: 145 (59.4%) Underlying cause of neuropathic pain: Painful diabetic neuropathy Mean duration of NP (in months): 21.0555555555556 Baseline pain severity: 68.7 (VASpi (average of arm means))

	Mean age: 59
Intervention(s)	(1) Venlafaxine extended-release 75mg/d Intervention: venlafaxine Length of treatment (weeks): 6 Fixed/flexible dose regimen: Fixed dose Set dose: 75mg/d Notes: 37.5 mg/d in week 1, 75 mg/d in week 2 (2) Venlafaxine extended-release 150-225mg/d Intervention: venlafaxine Length of treatment (weeks): 6 Fixed/flexible dose regimen: Flexible dose Range: 150–225 Notes: 37.5 mg/d in week 1, 75 mg/d in week 2, then increased to 150 mg/d during week 3. At week 4, the capsules were adjusted individually according to clinical response and tolerance to a maximum of 3 capsules daily (3) Placebo Intervention: placebo Length of treatment (weeks): 6 Fixed/flexible dose regimen: Fixed dose
Concomitant treatments	Drug free baseline period? Yes (duration: 14d) Concomitant pain treatment allowed? Yes (No antipsychotics, antidepressants, anticonvulsant or any other psychotropic drug or capsaicin product were permitted except for occasional use of zolpidem (< or = 10 mg) or temazepam (< or = 15 mg) for sleep; tramadol was prohibited but other opioids or other analgesics were allowed within the limit of a single dose of a single type of analgesic per day (also, no more than 10 doses per week of the patient's normal analgesic were allowed for severe pain during baseline period))
Outcomes measures and effect sizes	

		VENLAFAXINE EXTENDED-RELEASE 75MG/D			VENLAFAXINE EXTENDED-RELEASE 150-225MG/D			
		N	k	mean	N	k	mean	Δ
pain score:								
VAS – 0d[a]	Continuous	81		69.9	82		67.3	
VAS – 42d[a]	Mean change	81		22.4	82		33.8	MD=-11.400
VAS – 42d[b]	Continuous	81		51	82		59.9	MD=-8.900
at least 50% pain reduction (VAS) – 42d[c]	Dichotomous	82	31	(37.8%)	82	46	(56.1%)	OR=0.476 (CI: 0.255, 0.888)
major adverse events (defined as leading to withdrawal):								
any major adverse event – 42d	Dichotomous	82	6	(7.3%)	82	8	(9.8%)	OR=0.730 (CI: 0.242, 2.207)
adverse events:								
dyspepsia – 42d	Dichotomous	82	7	(8.5%)	82	8	(9.8%)	OR=0.863 (CI: 0.298, 2.502)
myalgia	Dichotomous	82	4[d]	(4.9%)	82	5	(6.1%)	OR=0.790 (CI: 0.204, 3.052)
Nausea – 42d	Dichotomous	82	18	(22.0%)	82	8	(9.8%)	OR=2.602 (CI: 1.060, 6.383)
sleep disturbance	Dichotomous	82	4[e]	(4.9%)	82	8[f]	(9.8%)	OR=0.474 (CI: 0.137, 1.642)

Somnolence – 42d	Dichotomous	82	11	(13.4%)	82	12	(14.6%)	OR=0.904 (CI: 0.374, 2.184)
Vomiting	Dichotomous	82	5	(6.1%)	82	4[d]	(4.9%)	OR=1.266 (CI: 0.328, 4.894)
treatment withdrawal:								
due to lack of efficacy – 42d	Dichotomous	82	2	(2.4%)	82	3	(3.7%)	OR=0.658 (CI: 0.107, 4.047)
unspecified/other reason – 42d	Dichotomous	82	2	(2.4%)	82	2	(2.4%)	OR=1.000 (CI: 0.137, 7.274)
withdrawal of consent – 42d	Dichotomous	82	0	(0.0%)	82	1	(1.2%)	OR=0.329 (CI: 0.013, 8.202)
protocol deviation – 42d	Dichotomous	82	1	(1.2%)	82	2	(2.4%)	OR=0.494 (CI: 0.044, 5.555)
lost to follow-up – 42d	Dichotomous	82	1	(1.2%)	82	2	(2.4%)	OR=0.494 (CI: 0.044, 5.555)
use of rescue medication:								
proportion taking NSAIDs – 42d[g]	Dichotomous	82	33	(40.2%)	82	30	(36.6%)	OR=1.167 (CI: 0.622, 2.192)

[a] Ns inferred from other outcomes
[b] Ns inferred from other outcomes; week 6 mean daily ratings
[c] calculated from percentages
[d] approximated to nearest integer (percentages only presented in text)
[e] 'insomnia';approximated to nearest integer (percentages only presented in text)
[f] 'insomnia'; approximated to nearest integer (percentages only presented in text)
[g] Ns inferred from other outcomes; calculated from percentages; approximated to nearest integer (percentages only presented in text)

		VENLAFAXINE EXTENDED-RELEASE 75MG/D			PLACEBO			
		N	k	mean	N	k	mean	Δ
pain score:								
VAS – 0d[a]	Continuous	81		69.9	80		68.8	
VAS – 42d[a]	Mean change	81		22.4	80		18.7	MD=3.700
VAS – 42d[b]	Continuous	81		51	80		43.6	MD=7.400
at least 50% pain reduction (VAS) – 42d[c]	Dichotomous	82	31	(37.8%)	81	27	(33.3%)	OR=1.216 (CI: 0.639, 2.311)
major adverse events (defined as leading to withdrawal):								
any major adverse event – 42d	Dichotomous	82	6	(7.3%)	81	3	(3.7%)	OR=2.053 (CI: 0.495, 8.504)
adverse events:								
dyspepsia – 42d	Dichotomous	82	7	(8.5%)	81	1	(1.2%)	OR=7.467 (CI: 0.897, 62.134)
myalgia	Dichotomous	82	4[d]	(4.9%)	81	0	(0.0%)	OR=9.344 (CI: 0.495, 176.420)
Nausea – 42d	Dichotomous	82	18	(22.0%)	81	4	(4.9%)	OR=5.414 (CI: 1.744, 16.810)
sleep disturbance	Dichotomous	82	4[e]	(4.9%)	81	3[f]	(3.7%)	OR=1.333 (CI: 0.289, 6.154)
Somnolence – 42d	Dichotomous	82	11	(13.4%)	81	1	(1.2%)	OR=12.394 (CI: 1.561, 98.411)
Vomiting	Dichotomous	82	5	(6.1%)	81	0	(0.0%)	OR=11.568 (CI: 0.629, 212.711)
treatment withdrawal:								
due to lack of efficacy – 42d	Dichotomous	82	2	(2.4%)	81	5	(6.2%)	OR=0.380 (CI: 0.072, 2.018)
unspecified/other reason – 42d	Dichotomous	82	2	(2.4%)	81	2	(2.5%)	OR=0.988 (CI: 0.136, 7.184)
withdrawal of consent – 42d	Dichotomous	82	0	(0.0%)	81	1	(1.2%)	OR=0.325 (CI: 0.013, 8.102)
protocol deviation – 42d	Dichotomous	82	1	(1.2%)	81	0	(0.0%)	OR=3.000 (CI: 0.120, 74.732)
lost to follow-up – 42d	Dichotomous	82	1	(1.2%)	81	1	(1.2%)	OR=0.988 (CI: 0.061, 16.063)
use of rescue medication:								
proportion taking NSAIDs – 42d	Dichotomous	82	33[g]	(40.2%)	81	26[h]	(32.1%)	OR=1.425 (CI: 0.750, 2.708)

[a] Ns inferred from other outcomes
[b] Ns inferred from other outcomes; week 6 mean daily ratings
[c] calculated from percentages
[d] approximated to nearest integer (percentages only presented in text)
[e] 'insomnia';approximated to nearest integer (percentages only presented in text)
[f] 'insomnia'; approximated to nearest integer (percentages only presented in text)
[g] Ns inferred from other outcomes; calculated from percentages; approximated to nearest integer (percentages only presented in text)
[h] Ns inferred from other outcomes; calculated from percentages

		VENLAFAXINE EXTENDED-RELEASE 150-225MG/D			PLACEBO			
		N	k	mean	N	k	mean	Δ
pain score:								
VAS – 0d[a]	Continuous	82		67.3	80		68.8	
VAS – 42d[a]	Mean change	82		33.8	80		18.7	MD=15.100
VAS – 42d[b]	Continuous	82		59.9	80		43.6	MD=16.300
at least 50% pain reduction (VAS) – 42d[c]	Dichotomous	82	46	(56.1%)	81	27	(33.3%)	OR=2.556 (CI: 1.354, 4.824)
major adverse events (defined as leading to withdrawal):								
any major adverse event – 42d	Dichotomous	82	8	(9.8%)	81	3	(3.7%)	OR=2.811 (CI: 0.718, 11.001)
adverse events:								
dyspepsia – 42d	Dichotomous	82	8	(9.8%)	81	1	(1.2%)	OR=8.649 (CI: 1.056, 70.821)
myalgia	Dichotomous	82	5	(6.1%)	81	0	(0.0%)	OR=11.568 (CI: 0.629, 212.711)
Nausea – 42d	Dichotomous	82	8	(9.8%)	81	4	(4.9%)	OR=2.081 (CI: 0.601, 7.205)
sleep disturbance[d]	Dichotomous	82	8	(9.8%)	81	3	(3.7%)	OR=2.811 (CI: 0.718, 11.001)
Somnolence – 42d	Dichotomous	82	12	(14.6%)	81	1	(1.2%)	OR=13.714 (CI: 1.739, 108.148)
Vomiting	Dichotomous	82	4[e]	(4.9%)	81	0	(0.0%)	OR=9.344 (CI: 0.495, 176.420)
treatment withdrawal:								
due to lack of efficacy – 42d	Dichotomous	82	3	(3.7%)	81	5	(6.2%)	OR=0.577 (CI: 0.133, 2.499)
unspecified/other reason – 42d	Dichotomous	82	2	(2.4%)	81	2	(2.5%)	OR=0.988 (CI: 0.136, 7.184)
withdrawal of consent – 42d	Dichotomous	82	1	(1.2%)	81	1	(1.2%)	OR=0.988 (CI: 0.061, 16.063)
protocol deviation – 42d	Dichotomous	82	2	(2.4%)	81	0	(0.0%)	OR=5.062 (CI: 0.239, 107.096)
lost to follow-up – 42d	Dichotomous	82	2	(2.4%)	81	1	(1.2%)	OR=2.000 (CI: 0.178, 22.500)
use of rescue medication:								
proportion taking NSAIDs – 42d	Dichotomous	82	30[f]	(36.6%)	81	26[g]	(32.1%)	OR=1.220 (CI: 0.639, 2.332)

[a] Ns inferred from other outcomes
[b] Ns inferred from other outcomes; week 6 mean daily ratings
[c] calculated from percentages
[d] 'insomnia'; approximated to nearest integer (percentages only presented in text)
[e] approximated to nearest integer (percentages only presented in text)
[f] Ns inferred from other outcomes; calculated from percentages; approximated to nearest integer (percentages only presented in text)
[g] Ns inferred from other outcomes; calculated from percentages

Comments

ITT population included all patients randomised who received at least 1 dose of the assigned treatment and had baseline evaluation and at least 1 score during therapy or within 3 days of the last dose (LOCF was used for those that dropped out; however BOCF was performed as well but results were not presented - authors stated that the results supported the LOCF results).

Definitions of abbreviations are given at the end of this document.

Study	Sabatowski et al. (2004)
Pain category	Peripheral pain
Study design	Country: Europe and Australia Design: Parallel Inclusion criteria: PHN for more than 6 months aged 18 years and over with pain scores at last 40mm on VAS and at least 4 on average daily pain on NRS (11-point) Exclusion criteria: Patients with active malignancy, clinically significant respiratory, haematologic, hepatic, or cardiovascular disease. Patients who had failed to respond to prevuious gabapentin doses of >1200mg for PHN, who had undergone neurolytic or neurosurgical therapy for PHN were also excluded. Patients with a creatinine <30mL/min were also excluded. Study length (days): 56 Intention-to-treat analysis? Yes
Participants	Total number of patients: 238 Number of males: 107 (45.0%) Underlying cause of neuropathic pain: Post-herpetic neuralgia Mean duration of NP (in months): 42.13 Baseline pain severity: 6.8 (NRS (average of means)) Mean age: 72.13
Intervention(s)	(1) Pregabalin 150mg/d Intervention: pregabalin Length of treatment (weeks): 8 Fixed/flexible dose regimen: Fixed dose Set dose: 150mg/d Notes: 1-week forced titration (2) Pregabalin 300mg/d Intervention: pregabalin Length of treatment (weeks): 8 Fixed/flexible dose regimen: Fixed dose Set dose: 300mg/d Notes: 1-week forced titration (3) placebo Intervention: placebo Length of treatment (weeks): 8 Fixed/flexible dose regimen: Fixed dose
Concomitant treatments	Drug free baseline period? No Concomitant pain treatment allowed? Yes (stable regimes of paracetamol (3g/d), NSAIDs, opioid or non-opioid analgesics, anti-depressants)

Outcomes measures and effect sizes

		PREGABALIN 150MG/D			PLACEBO			
		N	k	mean	N	k	mean	Δ
patient-reported global improvement:								
PGIC - worse (all grades) – 56d[a]	Dichotomous	81	17	(21.0%)	81	22	(27.2%)	OR=0.712 (CI: 0.345, 1.471)
PGIC - no change – 56d[a]	Dichotomous	81	19	(23.5%)	81	31	(38.3%)	OR=0.494 (CI: 0.250, 0.977)
PGIC - minimally better – 56d	Dichotomous	81	20	(24.7%)	81	17	(21.0%)	OR=1.234 (CI: 0.592, 2.576)
PGIC - at least moderately better – 56d	Dichotomous	81	25	(30.9%)	81	11	(13.6%)	OR=2.841 (CI: 1.287, 6.269)
major adverse events (defined as leading to withdrawal):								
any major adverse event – 56d	Dichotomous	81	9	(11.1%)	81	8	(9.9%)	OR=1.141 (CI: 0.417, 3.121)
adverse events:								
asthenia	Dichotomous	81	5	(6.2%)	81	4	(4.9%)	OR=1.266 (CI: 0.328, 4.897)
Diarrhoea	Dichotomous	81	4	(4.9%)	81	4	(4.9%)	OR=1.000 (CI: 0.241, 4.143)
Dizziness – 56d	Dichotomous	81	10	(12.3%)	81	12	(14.8%)	OR=0.810 (CI: 0.329, 1.996)
Dry mouth	Dichotomous	81	9	(11.1%)	81	3	(3.7%)	OR=3.250 (CI: 0.846, 12.478)
headache	Dichotomous	81	9	(11.1%)	81	3	(3.7%)	OR=3.250 (CI: 0.846, 12.478)
Peripheral oedema – 56d	Dichotomous	81	2	(2.5%)	81	0	(0.0%)	OR=5.126 (CI: 0.242, 108.454)
Somnolence – 56d	Dichotomous	81	12	(14.8%)	81	6	(7.4%)	OR=2.174 (CI: 0.774, 6.108)
overall improvement in quality of life:								
SF36 Mental – 56d	Continuous	81			81			MD=5.720
treatment withdrawal:								
due to lack of efficacy – 56d	Dichotomous	81	0	(0.0%)	81	7	(8.6%)	OR=0.061 (CI: 0.003, 1.086)
unspecified/other reason – 56d	Dichotomous	81	1	(1.2%)	81	3	(3.7%)	OR=0.325 (CI: 0.033, 3.192)
poor compliance – 56d	Dichotomous	81	0	(0.0%)	81	2	(2.5%)	OR=0.195 (CI: 0.009, 4.128)
ITT/LOCF (last-observation carried forward)								
pain score:								
NRS/NRS Pain – 0d	Continuous	81		6.9 (SD 1.7)	81		6.6 (SD 1.6)	
NRS/NRS Pain – 56d[b]	Continuous	81		5.14 (SD 1.98)	81		6.33 (SD 1.98)	MD=-1.200 (CI: -1.815, -0.585)
at least 50% pain reduction (NRS) – 56d	Dichotomous	81	21	(25.9%)	81	8	(9.9%)	OR=3.194 (CI: 1.321, 7.723)
McGill VAS – 56d[b]	Continuous	80		52 (SD 22.9)	80		62 (SD 22.9)	MD=-10.020 (CI: -20.045, 0.005)
patient-reported improvement in daily physical and emotional functioning, including sleep:								
NRS Sleep – 56d[b]	Continuous	81		3.13 (SD 1.89)	81		4.24 (SD 1.89)	MD=-1.110 (CI: -1.710, -0.510)
Per Protocol								
pain score:								
NRS/NRS Pain – 0d	Continuous	81		6.9 (SD 1.7)	81		6.6 (SD 1.6)	
NRS/NRS Pain – 56d[c]	Continuous	67		5.1 (SD 1.96)	73		6.31 (SD 1.97)	MD=-1.210 (CI: -1.875, -0.545)

[a] approximated to nearest integer (percentages only presented in text)
[b] Least Squares Mean
[c] Least squares mean

		PREGABALIN 300MG/D			PLACEBO			
		N	k	mean	N	k	mean	Δ
patient-reported global improvement:								
PGIC - worse (all grades) – 56d[a]	Dichotomous	76	11	(14.5%)	81	22	(27.2%)	OR=0.454 (CI: 0.203, 1.015)
PGIC - no change – 56d[a]	Dichotomous	76	19	(25.0%)	81	31	(38.3%)	OR=0.538 (CI: 0.271, 1.067)

	PGIC - minimally better – 56d	Dichotomous	76	17	(22.4%)	81	17	(21.0%)	OR=1.085 (CI: 0.507, 2.319)
	PGIC - at least moderately better – 56d	Dichotomous	76	29	(38.2%)	81	11	(13.6%)	OR=3.926 (CI: 1.789, 8.620)
	major adverse events (defined as leading to withdrawal):								
	any major adverse event – 56d	Dichotomous	76	12	(15.8%)	81	8	(9.9%)	OR=1.711 (CI: 0.658, 4.448)
	adverse events:								
	asthenia	Dichotomous	76	2	(2.6%)	81	4	(4.9%)	OR=0.520 (CI: 0.093, 2.926)
	Diarrhoea	Dichotomous	76	4	(5.3%)	81	4	(4.9%)	OR=1.069 (CI: 0.258, 4.436)
	Dizziness – 56d	Dichotomous	76	21	(27.6%)	81	12	(14.8%)	OR=2.195 (CI: 0.994, 4.851)
	Dry mouth	Dichotomous	76	5	(6.6%)	81	3	(3.7%)	OR=1.831 (CI: 0.422, 7.940)
	headache	Dichotomous	76	8	(10.5%)	81	3	(3.7%)	OR=3.059 (CI: 0.780, 11.991)
	Peripheral oedema – 56d	Dichotomous	76	10	(13.2%)	81	0	(0.0%)	OR=25.737 (CI: 1.481, 447.370)
	Somnolence – 56d	Dichotomous	76	18	(23.7%)	81	6	(7.4%)	OR=3.879 (CI: 1.448, 10.393)
	overall improvement in quality of life:								
	SF36 Mental – 56d	Continuous	76			81			MD=6.050
	treatment withdrawal:								
	due to lack of efficacy – 56d	Dichotomous	76	1	(1.3%)	81	7	(8.6%)	OR=0.141 (CI: 0.017, 1.174)
	unspecified/other reason – 56d	Dichotomous	76	2	(2.6%)	81	3	(3.7%)	OR=0.703 (CI: 0.114, 4.325)
	poor compliance – 56d	Dichotomous	76	1	(1.3%)	81	2	(2.5%)	OR=0.527 (CI: 0.047, 5.930)
	ITT/LOCF (last-observation carried forward)								
	pain score:								
	NRS/NRS Pain – 0d	Continuous	76		7 (SD 1.6)	81		6.6 (SD 1.6)	
	NRS/NRS Pain – 56d[b]	Continuous	76		4.76 (SD 2.01)	81		6.33 (SD 1.98)	MD=-1.570 (CI: -2.195, -0.945)
	at least 50% pain reduction (NRS) – 56d	Dichotomous	76	21	(27.6%)	81	8	(9.9%)	OR=3.484 (CI: 1.436, 8.453)
	McGill VAS – 56d[b]	Continuous	76		48.4 (SD 22.9)	80		62 (SD 22.9)	MD=-13.640 (CI: -20.875, -6.405)
	patient-reported improvement in daily physical and emotional functioning, including sleep:								
	NRS Sleep – 56d[b]	Continuous	76		2.18 (SD 1.92)	81		4.24 (SD 1.89)	MD=-1.430 (CI: -2.040, -0.820)
	Per Protocol								
	pain score:								
	NRS/NRS Pain – 0d	Continuous	76		7 (SD 1.6)	81		6.6 (SD 1.6)	
	NRS/NRS Pain – 56d[c]	Continuous	65		4.66 (SD 2.02)	73		6.31 (SD 1.97)	MD=-1.650 (CI: -2.320, -0.980)
	[a] approximated to nearest integer (percentages only presented in text) [b] Least Squares Mean [c] Least squares mean								
Comments	-								

Definitions of abbreviations are given at the end of this document.

Study	Satoh et al. (2011)
Pain category	Peripheral pain
Study design	Country: Japan Design: Parallel Inclusion criteria: Over 18 years of age diagnosed with type 1 or type 2 diabetes at least one year previously and diagnosed with painful distal, symmetrical, sensorimotor polyneuropathy due to diabetes, had a score of >40mm on the VAS of the short form McGill Pain questionnaire and evaluated and recorded pain for at least 4 of the previous 7 days in the daily pain diary prior to treatment, with the mean score being >4 on the 11 point (0-10)

	numeric rating scale Exclusion criteria: Patients with a malignant tumour within the past 2 years, creatine clearance less than 30mL/min, and those who had pain or other skin conditions that may affect evaluation of pain Study length (days): 98 Intention-to-treat analysis? Yes
Participants	Total number of patients: 317 Number of males: 240 (75.7%) Underlying cause of neuropathic pain: Painful diabetic neuropathy Mean duration of NP (in months): 52 Baseline pain severity: 6 (NRS (average of means)) Mean age: 61.6
Intervention(s)	(1) Pregabalin 300mg/d Intervention: pregabalin Length of treatment (weeks): 14 Fixed/flexible dose regimen: Fixed dose Set dose: 300mg/d Notes: 1 week titration, starting from 75 mg 2x daily (2) Pregabalin 600mg/d Intervention: pregabalin Length of treatment (weeks): 14 Fixed/flexible dose regimen: Fixed dose Set dose: 600mg/d Notes: 1 week titration, starting from 75 mg 2x daily (3) Placebo Intervention: placebo Length of treatment (weeks): Fixed/flexible dose regimen: Fixed dose
Concomitant treatments	Drug free baseline period? No Concomitant pain treatment allowed? Unclear
Outcomes measures and effect sizes	

		PREGABALIN 300MG/D			PREGABALIN 600MG/D			
		N	k	mean	N	k	mean	Δ
pain score:								
at least 50% pain reduction (NRS) – 98d	Dichotomous	136	39	(29.1%)	45	16	(35.6%)	OR=0.729 (CI: 0.357, 1.489)
at least 50% pain reduction (NRS) – 98d	Dichotomous	134	39	(29.1%)	45	16	(35.6%)	OR=0.729 (CI: 0.357, 1.489)
major adverse events (defined as leading to withdrawal):								
any major adverse event – 98d	Dichotomous	134	10	(7.5%)	45	12	(26.7%)	OR=0.218 (CI: 0.087, 0.549)
any major adverse event – 98d	Dichotomous	136	10	(7.5%)	45	12	(26.7%)	OR=0.218 (CI: 0.087, 0.549)

adverse events:								
Constipation – 98d	Dichotomous	134	4	(3.0%)	45	2	(4.4%)	OR=0.652 (CI: 0.115, 3.682)
Constipation – 98d	Dichotomous	136	4	(3.0%)	45	2	(4.4%)	OR=0.652 (CI: 0.115, 3.682)
Dizziness – 98d	Dichotomous	136	26	(19.4%)	45	17	(37.8%)	OR=0.389 (CI: 0.186, 0.815)
Dizziness – 98d	Dichotomous	134	26	(19.4%)	45	17	(37.8%)	OR=0.389 (CI: 0.186, 0.815)
Peripheral oedema – 98d	Dichotomous	136	17	(12.7%)	45	6	(13.3%)	OR=0.929 (CI: 0.342, 2.520)
Peripheral oedema – 98d	Dichotomous	134	17	(12.7%)	45	6	(13.3%)	OR=0.929 (CI: 0.342, 2.520)
Somnolence – 98d	Dichotomous	134	28	(20.9%)	45	18	(40.0%)	OR=0.389 (CI: 0.188, 0.805)
Somnolence – 98d	Dichotomous	136	28	(20.9%)	45	18	(40.0%)	OR=0.389 (CI: 0.188, 0.805)
Weight gain – 98d	Dichotomous	134	15	(11.2%)	45	5	(11.1%)	OR=0.992 (CI: 0.339, 2.901)
Weight gain – 98d	Dichotomous	136	15	(11.2%)	45	5	(11.1%)	OR=0.992 (CI: 0.339, 2.901)
treatment withdrawal:								
unspecified/other reason – 98d	Dichotomous	136	10	(7.5%)	45	1	(2.2%)	OR=3.492 (CI: 0.434, 28.066)
unspecified/other reason – 98d	Dichotomous	134	10	(7.5%)	45	1	(2.2%)	OR=3.492 (CI: 0.434, 28.066)

		PREGABALIN 300MG/D			**PLACEBO**			
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**
pain score:								
NRS/NRS Pain – 98d	Continuous	136			136			MD=-0.630 (CI: -1.090, -0.170)
at least 50% pain reduction (NRS) – 98d	Dichotomous	134	39	(29.1%)	135	29	(21.5%)	OR=1.483 (CI: 0.853, 2.580)
at least 50% pain reduction (NRS) – 98d	Dichotomous	136	39	(29.1%)	136	29	(21.5%)	OR=1.483 (CI: 0.853, 2.580)
major adverse events (defined as leading to withdrawal):								
any major adverse event – 98d	Dichotomous	134	10	(7.5%)	135	6	(4.4%)	OR=1.720 (CI: 0.607, 4.872)
any major adverse event – 98d	Dichotomous	136	10	(7.5%)	136	6	(4.4%)	OR=1.720 (CI: 0.607, 4.872)
adverse events:								
Constipation – 98d	Dichotomous	134	4	(3.0%)	135	1	(0.7%)	OR=4.091 (CI: 0.451, 37.083)
Constipation – 98d	Dichotomous	136	4	(3.0%)	136	1	(0.7%)	OR=4.091 (CI: 0.451, 37.083)
Dizziness – 98d	Dichotomous	136	26	(19.4%)	136	9	(6.7%)	OR=3.335 (CI: 1.499, 7.422)
Dizziness – 98d	Dichotomous	134	26	(19.4%)	135	9	(6.7%)	OR=3.335 (CI: 1.499, 7.422)
Peripheral oedema – 98d	Dichotomous	136	17	(12.7%)	136	6	(4.4%)	OR=3.095 (CI: 1.181, 8.111)
Peripheral oedema – 98d	Dichotomous	134	17	(12.7%)	135	6	(4.4%)	OR=3.095 (CI: 1.181, 8.111)
Somnolence – 98d	Dichotomous	134	28	(20.9%)	135	11	(8.1%)	OR=2.946 (CI: 1.401, 6.196)
Somnolence – 98d	Dichotomous	136	28	(20.9%)	136	11	(8.1%)	OR=2.946 (CI: 1.401, 6.196)
Weight gain – 98d	Dichotomous	134	15	(11.2%)	135	3	(2.2%)	OR=5.496 (CI: 1.553, 19.449)
Weight gain – 98d	Dichotomous	136	15	(11.2%)	136	3	(2.2%)	OR=5.496 (CI: 1.553, 19.449)
treatment withdrawal:								
unspecified/other reason – 98d	Dichotomous	136	10	(7.5%)	136	3	(2.2%)	OR=3.519 (CI: 0.947, 13.080)
unspecified/other reason – 98d	Dichotomous	134	10	(7.5%)	135	3	(2.2%)	OR=3.519 (CI: 0.947, 13.080)

		PREGABALIN 600MG/D			**PLACEBO**			
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**
pain score:								
NRS/NRS Pain – 98d	Continuous	45			136			MD=-0.740 (CI: -1.390, -0.090)
at least 50% pain reduction (NRS) – 98d	Dichotomous	45	16	(35.6%)	135	29	(21.5%)	OR=2.036 (CI: 0.976, 4.247)
at least 50% pain reduction (NRS) – 98d	Dichotomous	45	16	(35.6%)	136	29	(21.5%)	OR=2.036 (CI: 0.976, 4.247)

major adverse events (defined as leading to withdrawal):									
any major adverse event – 98d	Dichotomous	45	12	(26.7%)	135	6	(4.4%)	OR=7.879 (CI: 2.752, 22.556)	
any major adverse event – 98d	Dichotomous	45	12	(26.7%)	136	6	(4.4%)	OR=7.879 (CI: 2.752, 22.556)	
adverse events:									
Constipation – 98d	Dichotomous	45	2	(4.4%)	135	1	(0.7%)	OR=6.279 (CI: 0.556, 70.958)	
Constipation – 98d	Dichotomous	45	2	(4.4%)	136	1	(0.7%)	OR=6.279 (CI: 0.556, 70.958)	
Dizziness – 98d	Dichotomous	45	17	(37.8%)	136	9	(6.7%)	OR=8.567 (CI: 3.464, 21.192)	
Dizziness – 98d	Dichotomous	45	17	(37.8%)	135	9	(6.7%)	OR=8.567 (CI: 3.464, 21.192)	
Peripheral oedema – 98d	Dichotomous	45	6	(13.3%)	136	6	(4.4%)	OR=3.333 (CI: 1.017, 10.922)	
Peripheral oedema – 98d	Dichotomous	45	6	(13.3%)	135	6	(4.4%)	OR=3.333 (CI: 1.017, 10.922)	
Somnolence – 98d	Dichotomous	45	18	(40.0%)	135	11	(8.1%)	OR=7.576 (CI: 3.213, 17.862)	
Somnolence – 98d	Dichotomous	45	18	(40.0%)	136	11	(8.1%)	OR=7.576 (CI: 3.213, 17.862)	
Weight gain – 98d	Dichotomous	45	5	(11.1%)	135	3	(2.2%)	OR=5.542 (CI: 1.269, 24.207)	
Weight gain – 98d	Dichotomous	45	5	(11.1%)	136	3	(2.2%)	OR=5.542 (CI: 1.269, 24.207)	
treatment withdrawal:									
unspecified/other reason – 98d	Dichotomous	45	1	(2.2%)	136	3	(2.2%)	OR=1.008 (CI: 0.102, 9.937)	
unspecified/other reason – 98d	Dichotomous	45	1	(2.2%)	135	3	(2.2%)	OR=1.008 (CI: 0.102, 9.937)	

Comments	2 patients treated with 300 mg/d and 1 treated with placebo dropped out prior to receiving study medication

Definitions of abbreviations are given at the end of this document.

Study	Scheffler et al. (1991)
Pain category	Peripheral pain
Study design	Country: USA Design: Parallel Inclusion criteria: Participants with PDN who were unresponsive or intolerant to conventional therapy, with at least moderate to severe pain, aged 18 to 95 years old. Exclusion criteria: uncontrolled diabetes, another skin condition in the area affected Study length (days): 56 Intention-to-treat analysis? No
Participants	Total number of patients: 54 Number of males: 19 (35.2%) Underlying cause of neuropathic pain: Painful diabetic neuropathy Mean duration of NP (in months): 42 Baseline pain severity: 74.8 (VAS (average of means)) Mean age: 60.7
Intervention(s)	(1) 0.075% capsaicin applied to site 4 times per day Intervention: capsaicin cream Length of treatment (weeks): 8 Fixed/flexible dose regimen: Fixed dose

	(2) Placebo Intervention: placebo Length of treatment (weeks): 8 Fixed/flexible dose regimen: Fixed dose
Concomitant treatments	Drug free baseline period? No Concomitant pain treatment allowed? Yes (oral analgesics that were currently being taken (if not expected to change during study))
Outcomes measures and effect sizes	

		0.075% CAPSAICIN APPLIED TO SITE 4 TIMES PER DAY			PLACEBO			
		N	k	mean	N	k	mean	Δ
pain score:								
VAS – 0d	Continuous	28		76.8 (SD 16.1)	26		72.8 (SD 22.3)	
VAS – 28d	Percentage change from baseline	28		-33.1 (SD 34.6)	26		-19.5 (SD 39.3)	MD=-13.600 (CI: -33.403, 6.203)
VAS – 56d	Percentage change from baseline	28		-49.1 (SD 48.1)	26		-16.5 (SD 49.3)	MD=-32.600 (CI: -58.612, -6.588)
pain relief:								
VAS/VASpr – 56d	Continuous	28		65.7 (SD 42.1)	26		38.6 (SD 34.8)	MD=27.100 (CI: 6.558, 47.642)
major adverse events (defined as leading to withdrawal):								
any major adverse event – 56d	Dichotomous	28	3	(10.7%)	26	0	(0.0%)	OR=7.275 (CI: 0.358, 147.973)
adverse events:								
Burning pain – 56d	Dichotomous	28	17	(60.7%)	26	5	(19.2%)	OR=6.491 (CI: 1.887, 22.329)
treatment withdrawal:								
unspecified/other reason – 56d	Dichotomous	28	3	(10.7%)	26	1[a]	(3.8%)	OR=3.000 (CI: 0.292, 30.836)
protocol deviation – 56d	Dichotomous	28	0	(0.0%)	26	1	(3.8%)	OR=0.298 (CI: 0.012, 7.653)
poor compliance – 56d	Dichotomous	28	3	(10.7%)	26	1	(3.8%)	OR=3.000 (CI: 0.292, 30.836)

[a] death related to underlying disease

Comments	use of new oral anlgesics, anti-inflammatory drugs, or central nervous system-acting drugs were not permitted during the study

Definitions of abbreviations are given at the end of this document.

Study	Selvarajah et al. (2010)
Pain category	Peripheral pain
Study design	Country: UK Design: Parallel Inclusion criteria: neuropathay total symptom score 6 > 4 and < 16 for at least 6 months with stable glycaemic control, with persistent pain, despite adequate trial of tricyclic antidepressants

	Exclusion criteria: none reported Study length (days): 84 Intention-to-treat analysis? Yes
Participants	Total number of patients: 30 Number of males: 19 (63.3%) Underlying cause of neuropathic pain: Painful diabetic neuropathy Mean duration of NP (in months): not reported Baseline pain severity: 65.35 (100mm VAS (averaged from both arms)) Mean age: 56.3
Intervention(s)	(1) Sativex Intervention: cannabis sativa extract Length of treatment (weeks): 12 Fixed/flexible dose regimen: Flexible dose Mean dose: 0.7mg/d (SD: 0.38) Notes: up to 4 dosages per day; study medication amount: 0.7 ml +/- 0.38 (2) Placebo Intervention: placebo Length of treatment (weeks): 12 Fixed/flexible dose regimen: Flexible dose Notes: up to 4 dosages per day; study medication amount: 0.73 ml +/- 0.38
Concomitant treatments	Drug free baseline period? No Concomitant pain treatment allowed? Yes (any pre-existing neuropathic pain treatment (including tricyclics))
Outcomes measures and effect sizes	

		SATIVEX			PLACEBO			
		N	k	mean	N	k	mean	Δ
pain score:								
VAS – 0d	Continuous	15		55.8 (SD 26.7)	15		44.9 (SD 21.5)	
VAS – 84d	Continuous	15		40.1 (SD 28.5)	15		25.2 (SD 28.8)	MD=14.900 (CI: -5.604, 35.404)
at least 30% pain reduction (VAS) – 84d	Dichotomous	15	8	(53.3%)	15	9	(60.0%)	OR=0.762 (CI: 0.179, 3.241)
McGill VAS – 0d	Continuous	15		7.6 (SD 1.8)	15		6.9 (SD 1.7)	
McGill VAS – 84d	Continuous	15		5.1 (SD 2.2)	15		3.8 (SD 2.6)	MD=1.300 (CI: -0.424, 3.024)
NPS – 0d	Continuous	15		67.1 (SD 19.4)	15		63.6 (SD 14)	
NPS – 84d	Continuous	15		51.6 (SD 21.9)	15		51.9 (SD 24.1)	MD=-0.300 (CI: -16.779, 16.179)
PPI (from MPQ) – 0d	Continuous	15		2.5 (SD 1.1)	15		2 (SD 1)	
PPI (from MPQ) – 84d	Continuous	15		2.1 (SD 1.1)	15		1.4 (SD 1.7)	MD=0.700 (CI: -0.325, 1.725)
overall improvement in quality of life:								
SF36 Mental – 0d	Continuous	15		57.9 (SD 22.6)	15		57.1 (SD 19.9)	
SF36 Mental – 84d	Continuous	15		64.4 (SD 20.3)	15		59.4 (SD 20.6)	MD=5.000 (CI: -9.636, 19.636)
SF36 Physical – 0d	Continuous	15		26.9 (SD 15.1)	15		30.8 (SD 22.7)	
SF36 Physical – 84d	Continuous	15		30.5 (SD 16.6)	15		36.5 (SD 27.9)	MD=-6.000 (CI: -22.429, 10.429)
EQ-5D - health status index – 0d	Continuous	15		0.4 (SD 0.21)	15		0.43 (SD 0.21)	
EQ-5D - health status index – 84d	Continuous	15		0.54 (SD 0.22)	15		0.6 (SD 0.2)	MD=-0.060 (CI: -0.210, 0.090)

	EQ-5D - health status VAS – 0d	Continuous	15	46 (SD 20.4)	15	44.6 (SD 21.8)	
	EQ-5D - health status VAS – 84d	Continuous	15	58.1 (SD 20.5)	15	56.4 (SD 11.7)	MD=1.700 (CI: -10.245, 13.645)
	SF36 role physical – 0d	Continuous	15	8.9 (SD 27.1)	15	12.5 (SD 23.5)	
	SF36 role physical – 84d	Continuous	15	12.5 (SD 32.1)	15	39.3 (SD 47.7)	MD=-26.800 (CI: -55.896, 2.296)
	SF36 social functioning – 0d	Continuous	15	50.8 (SD 32.5)	15	48.4 (SD 24.9)	
	SF36 social functioning – 84d	Continuous	15	55.4 (SD 25.3)	15	67 (SD 27.6)	MD=-11.600 (CI: -30.548, 7.348)
	SF36 bodily pain – 0d	Continuous	15	22.4 (SD 15.5)	15	25.7 (SD 11.3)	
	SF36 bodily pain – 84d	Continuous	15	35.6 (SD 16.6)	15	41.2 (SD 24.6)	MD=-5.600 (CI: -20.618, 9.418)
	SF36 general health – 0d	Continuous	15	33.5 (SD 18.7)	15	28.4 (SD 20.8)	
	SF36 general health – 84d	Continuous	15	34.1 (SD 18.2)	15	29.6 (SD 19.5)	MD=4.500 (CI: -8.999, 17.999)
	SF36 vitality – 0d	Continuous	15	28.3 (SD 23.2)	15	30.8 (SD 19.2)	
	SF36 vitality – 84d	Continuous	15	33.9 (SD 22.4)	15	39.6 (SD 19.4)	MD=-5.700 (CI: -20.696, 9.296)
	SF36 role emotional – 0d	Continuous	15	38.1 (SD 41.1)	15	33.3 (SD 40.8)	
	SF36 role emotional – 84d	Continuous	15	54.8 (SD 46.4)	15	47.6 (SD 48.4)	MD=7.200 (CI: -26.731, 41.131)
	With depression (HADS-D score ≥10)						
	pain score:						
	VAS – 0d[a]	Continuous		62.3 (SD 22.1)		62.3 (SD 22.1)	
	VAS – 84d	Mean change		-36.7 (SD 28.6)		-26.5 (SD 20.7)	MD=-10.200
	VAS – 84d	Continuous		25.6		35.8	MD=-10.200
	Without depression (HADS-D score <10)						
	pain score:						
	VAS – 0d[b]	Continuous		43.4 (SD 24.3)		43.4 (SD 24.3)	
	VAS – 84d	Continuous		38.5		26.1	MD=12.400
	VAS – 84d	Mean change		-4.9 (SD 14.4)		-17.3 (SD 33.1)	MD=12.400
	[a] average across all 10 patients with depression [b] average across all 18 patients without depression						
Comments	Use of Sativex as adjunct therapy; 1 placebo-treated patient excluded from ITT analysis because of protocol violation; 6 patients withdrew due to adverse events but it wasn't clear which arm these patients were in or what adverse events occurred; concurrent trycylics used and dosages not reported; bottom of the article (which is a 'brief report') states that the costs of publication were defrayed in part by the payment of page charges and, thus, this article must be marked 'advertisement'; further analysis done for patients with and without depression but it was not clear how many patients in each arm were depressed or not depression (of the overall ITT population, 18 had no depression, 10 had depression and 1 patient was excluded because baseline data on HADS-D was incomplete)						

Definitions of abbreviations are given at the end of this document.

Study	Shaibani et al. (2009)
Pain category	Peripheral pain
Study design	Country: USA Design: Parallel Inclusion criteria: =18 years with type1 or type 2 diabetes, symptoms for 6 months to 5 years (=4 on NRS for 7 days prior to randomisation), HbA1C < 12% for at least 3 months Exclusion criteria: other conditions contributing to chronic pain, MI or clinically relevant cardiac dysfunction in last year, chronic alcohol or drug abuse in last year or any drug use that might interfere with trial results, skin ulcers, amputation related to diabetes (other than toe), pregnancy or nursing, less than 2 years postmenopausal Study length (days): 140

	Intention-to-treat analysis? Yes
Participants	Total number of patients: 468 Number of males: 265 (56.6%) Underlying cause of neuropathic pain: Painful diabetic neuropathy Mean duration of NP (in months): 24 Baseline pain severity: 6.3 (NRS (average of arm means)) Mean age: 59.8 (SD: 10)
Intervention(s)	(1) lacosamide 600 Intervention: lacosamide Length of treatment (weeks): 18 Fixed/flexible dose regimen: Fixed dose Set dose: 600mg/d Notes: 6-week forced titration followed by 12-week maintenance (2) lacosamide 400 Intervention: lacosamide Length of treatment (weeks): 18 Fixed/flexible dose regimen: Fixed dose Set dose: 400mg/d Notes: 6-week forced titration followed by 12-week maintenance (3) lacosamide 200 Intervention: lacosamide Length of treatment (weeks): 18 Fixed/flexible dose regimen: Fixed dose Set dose: 200mg/d Notes: 6-week forced titration followed by 12-week maintenance (4) placebo Intervention: placebo Length of treatment (weeks): 18 Fixed/flexible dose regimen: Fixed dose
Concomitant treatments	Drug free baseline period? Yes (duration: 7d) Concomitant pain treatment allowed? Yes (small proportion also had concomitant tricyclic anti-depressants though the changes in pain scores were said to be similar (though anti-convulsants, muscle relaxants, mexiletine, topical analgesics, opioids, or any therapy for neuropathic pain within 7 days of randomisation or during trial not permitted); paracetamol 2 g/day allowed as rescue analgesics)
Outcomes measures and effect sizes	

		LACOSAMIDE 600			PLACEBO			
		N	k	mean	N	k	mean	Δ
pain score:								
NRS/NRS Pain – 0d	Continuous	137		6.3 (SD 1.4)	64		6.2 (SD 1.6)	
NRS/NRS Pain – 63d[a]	Mean difference from baseline to average f-u	131		-1.85	64		-1.27	MD=-0.570 (CI: -1.099, -0.041)

NRS/NRS Pain – 84d[b]	Mean difference from baseline to average f-u	76		-2.81	52		-1.88	MD=-0.930 (CI: -1.596, -0.264)
NRS/NRS Pain – 112d[c]	Mean difference from baseline to average f-u	131		-2.23	64		-1.67	MD=-0.560 (CI: -1.168, 0.048)
at least 30% pain reduction (NRS) – 126d[d]	Dichotomous from baseline to average f-u	131	76		65	29		OR=1.668 (CI: 0.913, 3.045)
at least 30% pain reduction (NRS) – 126d[d]	Dichotomous from baseline to average f-u	131	76		64	29		OR=1.668 (CI: 0.913, 3.045)
at least 50% pain reduction (NRS) – 126d[d]	Dichotomous from baseline to average f-u	131	39		64	17		OR=1.172 (CI: 0.600, 2.289)
at least 50% pain reduction (NRS) – 126d[d]	Dichotomous from baseline to average f-u	131	39		65	17		OR=1.172 (CI: 0.600, 2.289)
patient-reported global improvement:								
PGIC - worse (all grades) – 126d	Dichotomous	137	6	(4.4%)	65	3	(4.6%)	OR=0.947 (CI: 0.229, 3.910)
PGIC - no change – 126d	Dichotomous	137	9	(6.6%)	65	12	(18.5%)	OR=0.311 (CI: 0.124, 0.781)
PGIC - minimally or moderately better – 126d	Dichotomous	137	26	(19.0%)	65	30	(46.2%)	OR=0.273 (CI: 0.143, 0.523)
PGIC - much better – 126d	Dichotomous	137	29	(21.2%)	65	6	(9.2%)	OR=2.640 (CI: 1.037, 6.723)
patient-reported improvement in daily physical and emotional functioning, including sleep:								
NRS Sleep – 112d[e]	Mean difference from baseline to average f-u	131		-2.8 (SD 2.09)	64		-1.9 (SD 2.13)	MD=-0.900 (CI: -1.533, -0.267)
major adverse events (defined as leading to withdrawal):								
any major adverse event – 126d	Dichotomous	137	58	(42.3%)	65	9	(13.8%)	OR=4.568 (CI: 2.092, 9.977)
adverse events:								
any adverse event – 126d	Dichotomous	137	119	(86.9%)	65	55	(84.6%)	OR=1.202 (CI: 0.521, 2.775)
balance disorder – 126d	Dichotomous	137	13	(9.5%)	65	0	(0.0%)	OR=14.205 (CI: 0.831, 242.757)
Blurred vision – 126d	Dichotomous	137	7	(5.1%)	65	0	(0.0%)	OR=7.529 (CI: 0.423, 133.858)
Diarrhoea – 126d	Dichotomous	137	11	(8.0%)	65	5	(7.7%)	OR=1.048 (CI: 0.348, 3.150)
Dizziness – 126d	Dichotomous	137	39	(28.5%)	65	3	(4.6%)	OR=8.224 (CI: 2.436, 27.764)
Fatigue – 126d	Dichotomous	137	6	(4.4%)	65	2	(3.1%)	OR=1.443 (CI: 0.283, 7.351)
headache – 126d	Dichotomous	137	18	(13.1%)	65	8	(12.3%)	OR=1.078 (CI: 0.442, 2.626)
Nausea – 126d	Dichotomous	137	25	(18.2%)	65	4	(6.2%)	OR=3.404 (CI: 1.132, 10.232)
Peripheral oedema – 126d[f]	Dichotomous	137	5	(3.6%)	65	3	(4.6%)	OR=0.783 (CI: 0.181, 3.380)
Pruritus – 126d	Dichotomous	137	7	(5.1%)	65	1	(1.5%)	OR=3.446 (CI: 0.415, 28.612)
Somnolence – 126d	Dichotomous	137	12	(8.8%)	65	0	(0.0%)	OR=13.048 (CI: 0.760, 223.870)
vertigo – 126d	Dichotomous	137	8	(5.8%)	65	1	(1.5%)	OR=3.969 (CI: 0.486, 32.423)
Vomiting – 126d	Dichotomous	137	9	(6.6%)	65	0	(0.0%)	OR=9.685 (CI: 0.555, 169.000)
treatment withdrawal:								
due to lack of efficacy – 126d	Dichotomous	137	7	(5.1%)	65	2	(3.1%)	OR=1.696 (CI: 0.342, 8.401)
unspecified/other reason – 126d	Dichotomous	137	3	(2.2%)	65	2	(3.1%)	OR=0.705 (CI: 0.115, 4.327)
withdrawal of consent – 126d	Dichotomous	137	16	(11.7%)	65	5	(7.7%)	OR=1.587 (CI: 0.555, 4.538)
protocol deviation – 126d	Dichotomous	137	1	(0.7%)	65	2	(3.1%)	OR=0.232 (CI: 0.021, 2.602)

lost to follow-up – 126d	Dichotomous	137	5	(3.6%)	65	1 (1.5%)	OR=2.424 (CI: 0.277, 21.183)
poor compliance – 126d	Dichotomous	137	1	(0.7%)	65	0 (0.0%)	OR=1.440 (CI: 0.058, 35.819)
use of rescue medication:							
rescue medication usage	Percentage change from baseline to average f-u	137		-37[g]	65	-17	MD=-20.000

[a] least squares mean; from baseline to weeks 1 to 18
[b] least squares mean; from baseline to maintenance period (weeks 6-18)
[c] least squares mean; from baseline to last 4 weeks (weeks 14 to 18)
[d] estimated from percentage so may not be completely accurate; from baseline to last 4 weeks (weeks 14 to 18)
[e] from baseline to last 4 weeks (weeks 14 to 18)
[f] estimated from percentage so may not be completely accurate
[g] unclear if this is reduction in the proportion of patients or proportion of drugs used

		LACOSAMIDE 400			PLACEBO			
		N	k	mean	N	k	mean	Δ
pain score:								
NRS/NRS Pain – 0d	Continuous	125		6.4 (SD 1.5)	64		6.2 (SD 1.6)	
NRS/NRS Pain – 63d[a]	Mean difference from baseline to average f-u	120		-1.89	64		-1.27	MD=-0.620 (CI: -1.149, -0.091)
NRS/NRS Pain – 84d[b]	Mean difference from baseline to average f-u	91		-2.77	52		-1.88	MD=-0.890 (CI: -1.537, -0.243)
NRS/NRS Pain – 112d[c]	Mean difference from baseline to average f-u	120		-2.29	64		-1.67	MD=-0.610 (CI: -1.218, -0.002)
NRS/NRS Pain – 126d[d]	Continuous	125		3.9	65		4.4	MD=-0.500
NRS/NRS Pain – 126d[d]	Continuous	125		3.9	52		4.4	MD=-0.500
at least 30% pain reduction (NRS) – 126d[e]	Dichotomous from baseline to average f-u	120	70		64	29		OR=1.690 (CI: 0.917, 3.114)
at least 30% pain reduction (NRS) – 126d[e]	Dichotomous from baseline to average f-u	125	70		65	29		OR=1.690 (CI: 0.917, 3.114)
at least 50% pain reduction (NRS) – 126d[e]	Dichotomous from baseline to average f-u	120	53		64	17		OR=2.187 (CI: 1.129, 4.238)
at least 50% pain reduction (NRS) – 126d[e]	Dichotomous from baseline to average f-u	125	53		65	17		OR=2.187 (CI: 1.129, 4.238)
patient-reported global improvement:								
PGIC - worse (all grades) – 126d	Dichotomous	125	3	(2.4%)	65	3	(4.6%)	OR=0.508 (CI: 0.100, 2.592)
PGIC - no change – 126d	Dichotomous	125	12	(9.6%)	65	12	(18.5%)	OR=0.469 (CI: 0.198, 1.113)
PGIC - minimally or moderately better – 126d	Dichotomous	125	42	(33.6%)	65	30	(46.2%)	OR=0.590 (CI: 0.320, 1.090)
PGIC - much better – 126d	Dichotomous	125	28	(22.4%)	65	6	(9.2%)	OR=2.838 (CI: 1.110, 7.261)
patient-reported improvement in daily physical and emotional functioning, including sleep:								
NRS Sleep – 112d[f]	Mean difference from baseline to average f-u	120		-2.1 (SD 2.07)	64		-1.9 (SD 2.13)	MD=-0.200 (CI: -0.840, 0.440)
major adverse events (defined as leading to withdrawal):								
any major adverse event – 126d	Dichotomous	125	30	(24.0%)	65	9	(13.8%)	OR=1.965 (CI: 0.870, 4.438)
adverse events:								
any adverse event – 126d	Dichotomous	125	99	(79.2%)	65	55	(84.6%)	OR=0.692 (CI: 0.311, 1.541)

balance disorder – 126d	Dichotomous	125	6	(4.8%)	65	0	(0.0%)	OR=7.126 (CI: 0.395, 128.492)
Blurred vision – 126d	Dichotomous	125	3	(2.4%)	65	0	(0.0%)	OR=3.743 (CI: 0.190, 73.566)
Diarrhoea – 126d	Dichotomous	125	6	(4.8%)	65	5	(7.7%)	OR=0.605 (CI: 0.177, 2.063)
Dizziness – 126d	Dichotomous	125	27	(21.6%)	65	3	(4.6%)	OR=5.694 (CI: 1.657, 19.567)
Fatigue – 126d	Dichotomous	125	7	(5.6%)	65	2	(3.1%)	OR=1.869 (CI: 0.377, 9.264)
headache – 126d	Dichotomous	125	10	(8.0%)	65	8	(12.3%)	OR=0.620 (CI: 0.232, 1.655)
Nausea – 126d	Dichotomous	125	9	(7.2%)	65	4	(6.2%)	OR=1.183 (CI: 0.350, 3.999)
Peripheral oedema – 126d[g]	Dichotomous	125	2	(1.6%)	65	3	(4.6%)	OR=0.336 (CI: 0.055, 2.064)
Pruritus – 126d	Dichotomous	125	9	(7.2%)	65	1	(1.5%)	OR=4.966 (CI: 0.615, 40.082)
Somnolence – 126d	Dichotomous	125	10	(8.0%)	65	0	(0.0%)	OR=11.909 (CI: 0.687, 206.539)
vertigo – 126d	Dichotomous	125	1	(0.8%)	65	1	(1.5%)	OR=0.516 (CI: 0.032, 8.388)
Vomiting – 126d	Dichotomous	125	2	(1.6%)	65	0	(0.0%)	OR=2.652 (CI: 0.125, 56.056)
treatment withdrawal:								
due to lack of efficacy – 126d	Dichotomous	125	6	(4.8%)	65	2	(3.1%)	OR=1.588 (CI: 0.311, 8.100)
unspecified/other reason – 126d	Dichotomous	125	2	(1.6%)	65	2	(3.1%)	OR=0.512 (CI: 0.070, 3.722)
withdrawal of consent – 126d	Dichotomous	125	10	(8.0%)	65	5	(7.7%)	OR=1.043 (CI: 0.341, 3.192)
protocol deviation – 126d	Dichotomous	125	3	(2.4%)	65	2	(3.1%)	OR=0.775 (CI: 0.126, 4.756)
lost to follow-up – 126d	Dichotomous	125	2	(1.6%)	65	1	(1.5%)	OR=1.041 (CI: 0.093, 11.696)
poor compliance – 126d	Dichotomous	125	1	(0.8%)	65	0	(0.0%)	OR=1.578 (CI: 0.063, 39.288)
use of rescue medication:								
rescue medication usage	Percentage change from baseline to average f-u	125		-43[h]	65		-17	MD=-26.000

[a] least squares mean; from baseline to weeks 1 to 18
[b] least squares mean; from baseline to maintenance period (weeks 6-18)
[c] least squares mean; from baseline to last 4 weeks (weeks 14 to 18)
[d] not sure about denominator
[e] estimated from percentage so may not be completely accurate; from baseline to last 4 weeks (weeks 14 to 18)
[f] from baseline to last 4 weeks (weeks 14 to 18)
[g] estimated from percentage so may not be completely accurate
[h] unclear if this is reduction in the proportion of patients or proportion of drugs used

		LACOSAMIDE 200			PLACEBO			
		N	k	mean	N	k	mean	Δ
pain score:				6.3 (SD			6.2 (SD	
NRS/NRS Pain – 0d	Continuous	141		1.5)	64		1.6)	
NRS/NRS Pain – 63d[a]	Mean difference from baseline to average f-u	138		-1.73	64		-1.27	MD=-0.450 (CI: -0.960, 0.060)
NRS/NRS Pain – 84d[b]	Mean difference from baseline to average f-u	112		-2.21	52		-1.88	MD=-0.320 (CI: -0.947, 0.307)
NRS/NRS Pain – 112d[c]	Mean difference from baseline to average f-u	138		-2.01	64		-1.67	MD=-0.330 (CI: -0.938, 0.278)
at least 30% pain reduction (NRS) – 126d[d]	Dichotomous from baseline to average f-u	138	75		64	29		OR=1.437 (CI: 0.792, 2.606)

at least 30% pain reduction (NRS) – 126d[d]	Dichotomous from baseline to average f-u	141	75		65	29		OR=1.437 (CI: 0.792, 2.606)
at least 50% pain reduction (NRS) – 126d[d]	Dichotomous from baseline to average f-u	141	37		65	17		OR=1.013 (CI: 0.518, 1.980)
at least 50% pain reduction (NRS) – 126d[d]	Dichotomous from baseline to average f-u	138	37		64	17		OR=1.013 (CI: 0.518, 1.980)
patient-reported global improvement:								
PGIC - worse (all grades) – 126d	Dichotomous	141	8	(5.7%)	65	3	(4.6%)	OR=1.243 (CI: 0.319, 4.847)
PGIC - no change – 126d	Dichotomous	141	29	(20.6%)	65	12	(18.5%)	OR=1.144 (CI: 0.541, 2.416)
PGIC - minimally or moderately better – 126d	Dichotomous	141	42	(29.8%)	65	30	(46.2%)	OR=0.495 (CI: 0.270, 0.908)
PGIC - much better – 126d	Dichotomous	141	26	(18.4%)	65	6	(9.2%)	OR=2.223 (CI: 0.867, 5.700)
major adverse events (defined as leading to withdrawal):								
any major adverse event – 126d	Dichotomous	141	17	(12.1%)	65	9	(13.8%)	OR=0.853 (CI: 0.358, 2.031)
adverse events:								
any adverse event – 126d	Dichotomous	141	113	(80.1%)	65	55	(84.6%)	OR=0.734 (CI: 0.333, 1.618)
balance disorder – 126d	Dichotomous	141	4	(2.8%)	65	0	(0.0%)	OR=4.287 (CI: 0.227, 80.816)
Blurred vision – 126d	Dichotomous	141	2	(1.4%)	65	0	(0.0%)	OR=2.348 (CI: 0.111, 49.598)
Diarrhoea – 126d	Dichotomous	141	9	(6.4%)	65	5	(7.7%)	OR=0.818 (CI: 0.263, 2.546)
Dizziness – 126d	Dichotomous	141	8	(5.7%)	65	3	(4.6%)	OR=1.243 (CI: 0.319, 4.847)
Fatigue – 126d	Dichotomous	141	5	(3.5%)	65	2	(3.1%)	OR=1.158 (CI: 0.219, 6.132)
headache – 126d	Dichotomous	141	14	(9.9%)	65	8	(12.3%)	OR=0.785 (CI: 0.312, 1.977)
Nausea – 126d	Dichotomous	141	14	(9.9%)	65	4	(6.2%)	OR=1.681 (CI: 0.531, 5.322)
Peripheral oedema – 126d[e]	Dichotomous	141	3	(2.1%)	65	3	(4.6%)	OR=0.449 (CI: 0.088, 2.289)
Pruritus – 126d	Dichotomous	141	6	(4.3%)	65	1	(1.5%)	OR=2.844 (CI: 0.335, 24.123)
Somnolence – 126d	Dichotomous	141	7	(5.0%)	65	0	(0.0%)	OR=7.305 (CI: 0.411, 129.858)
vertigo – 126d	Dichotomous	141	1	(0.7%)	65	1	(1.5%)	OR=0.457 (CI: 0.028, 7.424)
Vomiting – 126d	Dichotomous	141	6	(4.3%)	65	0	(0.0%)	OR=6.284 (CI: 0.349, 113.245)
treatment withdrawal:								
due to lack of efficacy – 126d	Dichotomous	141	5	(3.5%)	65	2	(3.1%)	OR=1.158 (CI: 0.219, 6.132)
unspecified/other reason – 126d	Dichotomous	141	1	(0.7%)	65	2	(3.1%)	OR=0.225 (CI: 0.020, 2.527)
withdrawal of consent – 126d	Dichotomous	141	9	(6.4%)	65	5	(7.7%)	OR=0.818 (CI: 0.263, 2.546)
protocol deviation – 126d	Dichotomous	141	4	(2.8%)	65	2	(3.1%)	OR=0.920 (CI: 0.164, 5.154)
lost to follow-up – 126d	Dichotomous	141	9	(6.4%)	65	1	(1.5%)	OR=4.364 (CI: 0.541, 35.189)
poor compliance – 126d	Dichotomous	141	1	(0.7%)	65	0	(0.0%)	OR=1.399 (CI: 0.056, 34.795)
use of rescue medication:								
rescue medication usage	Percentage change from baseline to average f-u	141		-35[f]	65		-17	MD=-18.000

[a] least squares mean; from baseline to weeks 1 to 18
[b] least squares mean; from baseline to maintenance period (weeks 6-18)
[c] least squares mean; from baseline to last 4 weeks (weeks 14 to 18)
[d] estimated from percentage so may not be completely accurate; from baseline to last 4 weeks (weeks 14 to 18)
[e] estimated from percentage so may not be completely accurate
[f] unclear if this is reduction in the proportion of patients or proportion of drugs used

Comments	phase 3 trial; randomisation after 2 week run-in period of which at least one week was considered 'wash-out'; adverse events reported are those occuring in at least 5% of patients; atrial fibrillation occurred twice in one patient treated with 600 mg/d (it is not clear if atrial fibrillation occurred in patients in the other arms)

Definitions of abbreviations are given at the end of this document.

Study	Siddall et al. (2006)
Pain category	Central pain
Study design	Country: Australia Design: Parallel Inclusion criteria: central neuropathic pain associated with SCI (duration at least 3 months), aged 18 years and over, with pain scores at least 40mm on a VAS, and at least 4 on average daily pain on a NRS (11-point), with sound medical and mental health Exclusion criteria: <60 ml/minute creatinine clearance, breastfeadding or pregnant women, women of childbearing potential not using reliable contraception Study length (days): 84 Intention-to-treat analysis? Yes
Participants	Total number of patients: 137 Number of males: 114 (83.2%) Underlying cause of neuropathic pain: Spinal cord injury pain Mean duration of NP (in months): 121.8 Baseline pain severity: 6.635 (NRS (average of means)) Mean age: 50
Intervention(s)	(1) Pregabalin Intervention: pregabalin Length of treatment (weeks): 12 Fixed/flexible dose regimen: Flexible dose Mean dose: 460mg/d Range: 150–600 Notes: 460 mg/d was the average dose after the 3-week stabilisation phase (it was 483 mg/d in the study completers); last dose was 150 mg/d in 11%, 300 mg/d in 33%, and 60- mg/d in 56% (2) Placebo Intervention: placebo Length of treatment (weeks): 12 Fixed/flexible dose regimen: Flexible dose
Concomitant treatments	Drug free baseline period? Yes (duration: 7d) Concomitant pain treatment allowed? Yes (NSAIDs, opioids, non-opioid analgesics, anti-epileptic drugs, anti-depressants if stable for at least 1 month before study, muscle relaxants (those on gabapentin had to discontinue treatment at least one week before the study))
Outcomes	**PREGABALIN** **PLACEBO**

measures and effect sizes			N	k	mean	N	k	mean	Δ
pain score:									
	NRS/NRS Pain – 0d	Continuous	69		6.54 (SD 1.3)	67		6.73 (SD 1.4)	
	NRS/NRS Pain – 84d	Continuous	69		4.62 (SD 2.1)	67		6.27 (SD 2.1)	MD=-1.530 (CI: -2.145, -0.915)
	at least 30% pain reduction (NRS) – 84d	Dichotomous	70	29	(41.4%)	67	11	(16.4%)	OR=3.691 (CI: 1.652, 8.247)
	at least 30% pain reduction (NRS) – 84d	Dichotomous	69	29	(41.4%)	67	11	(16.4%)	OR=3.691 (CI: 1.652, 8.247)
	at least 50% pain reduction (NRS) – 84d	Dichotomous	69	15	(21.4%)	67	5	(7.5%)	OR=3.444 (CI: 1.175, 10.101)
	at least 50% pain reduction (NRS) – 84d	Dichotomous	70	15	(21.4%)	67	5	(7.5%)	OR=3.444 (CI: 1.175, 10.101)
	McGill VAS – 0d	Continuous	69		69.1 (SD 13.6)	67		73.1 (SD 14.5)	
	McGill VAS – 84d	Continuous	69		49.2 (SD 24.1)	67		68.5 (SD 22.2)	MD=-17.600 (CI: -25.200, -10.000)
	PPI (from MPQ) – 0d	Continuous	69		2.46 (SD 0.9)	67		2.63 (SD 1)	
	PPI (from MPQ) – 84d	Continuous	69		1.85 (SD 1.1)	67		2.55 (SD 1)	MD=-0.660 (CI: -0.995, -0.325)
	SF McGill – 0d	Continuous	69		17.4 (SD 9.2)	67		18.4 (SD 9)	
	SF McGill – 84d	Continuous	69		11.7 (SD 9.9)	67		17.5 (SD 10.3)	MD=-4.900 (CI: -7.700, -2.100)
patient-reported global improvement:									
	PGIC - worse (all grades) – 84d	Dichotomous	69	12	(17.1%)	65	20	(29.9%)	OR=0.474 (CI: 0.210, 1.071)
	PGIC - worse (all grades) – 84d	Dichotomous	70	12	(17.1%)	67	20	(29.9%)	OR=0.474 (CI: 0.210, 1.071)
	PGIC - no change – 84d	Dichotomous	70	18	(25.7%)	67	31	(46.3%)	OR=0.387 (CI: 0.187, 0.799)
	PGIC - no change – 84d	Dichotomous	69	18	(25.7%)	65	31	(46.3%)	OR=0.387 (CI: 0.187, 0.799)
	PGIC - better (all grades) – 84d	Dichotomous	69	39	(55.7%)	65	14	(20.9%)	OR=4.736 (CI: 2.217, 10.117)
	PGIC - better (all grades) – 84d	Dichotomous	70	39	(55.7%)	67	14	(20.9%)	OR=4.736 (CI: 2.217, 10.117)
patient-reported improvement in daily physical and emotional functioning, including sleep:									
	Normalised (10-pt) sleep interference measure – 0d[a]	Continuous	69		4.22 (SD 2.6)	66		4.98 (SD 2.6)	
	Normalised (10-pt) sleep interference measure – 84d[a]	Continuous	69		2.79 (SD 2.6)	66		4.71 (SD 2.7)	
	NRS Sleep – 0d	Continuous	69		4.22 (SD 2.6)	66		4.98 (SD 2.6)	
	NRS Sleep – 84d	Continuous	69		2.79 (SD 2.5)	66		4.71 (SD 2.7)	MD=-1.920 (CI: -2.799, -1.041)
	HADS-A – 0d	Continuous	69		6.74 (SD 3.6)	67		8.67 (SD 4.1)	
	HADS-A – 84d	Continuous	69		5.16 (SD 3.4)	67		7.49 (SD 4.3)	MD=-2.330 (CI: -3.635, -1.025)
	HADS-D – 0d	Continuous	69		5.86 (SD 3.7)	67		6.61 (SD 3.7)	
	HADS-D – 84d	Continuous	69		5.44 (SD 4.1)	67		6.29 (SD 4.2)	MD=-0.850 (CI: -2.245, 0.545)
	MOS sleep problems index – 0d	Continuous	69		43.3 (SD 19.8)	67		50.6 (SD 19.1)	
	MOS sleep problems index – 84d	Continuous	69		34.5 (SD 18.3)	67		45.2 (SD 21.3)	MD=-10.700 (CI: -17.383, -4.017)
major adverse events (defined as leading to withdrawal):									
	any major adverse event – 84d	Dichotomous	70	15	(21.4%)	67	9	(13.4%)	OR=1.758 (CI: 0.711, 4.345)
adverse events:									
	amnesia – 84d	Dichotomous	70	7	(10.0%)	67	2	(3.0%)	OR=3.611 (CI: 0.722, 18.052)
	asthenia – 84d	Dichotomous	70	11	(15.7%)	67	4	(6.0%)	OR=2.936 (CI: 0.886, 9.732)
	Blurred vision – 84d[b]	Dichotomous	70	6	(8.6%)	67	2	(3.0%)	OR=3.047 (CI: 0.593, 15.662)
	Cognitive impairment – 84d[c]	Dichotomous	70	6	(8.6%)	67	1	(1.5%)	OR=6.188 (CI: 0.725, 52.840)
	Constipation – 84d	Dichotomous	70	9	(12.9%)	67	4	(6.0%)	OR=2.324 (CI: 0.680, 7.944)
	Dizziness – 84d	Dichotomous	70	17	(24.3%)	67	6	(9.0%)	OR=3.261 (CI: 1.199, 8.872)
	Dry mouth – 84d	Dichotomous	70	11	(15.7%)	67	2	(3.0%)	OR=6.059 (CI: 1.290, 28.472)
	Infection – 84d	Dichotomous	70	6	(8.6%)	67	4	(6.0%)	OR=1.477 (CI: 0.398, 5.484)
	myasthenia – 84d	Dichotomous	70	6	(8.6%)	67	3	(4.5%)	OR=2.000 (CI: 0.479, 8.345)
	oedema – 84d[d]	Dichotomous	70	14	(20.0%)	67	4	(6.0%)	OR=3.938 (CI: 1.224, 12.662)
	Somnolence – 84d	Dichotomous	70	29	(41.4%)	67	6	(9.0%)	OR=7.191 (CI: 2.742, 18.857)
	urination difficulties – 84d[e]	Dichotomous	70	4	(5.7%)	67	2	(3.0%)	OR=1.970 (CI: 0.349, 11.128)
treatment withdrawal:									
	due to lack of efficacy – 84d	Dichotomous	70	5	(7.1%)	67	20	(29.9%)	OR=0.181 (CI: 0.063, 0.516)

	unspecified/other reason – 84d	Dichotomous	70	1	(1.4%)	67	1	(1.5%)	OR=0.957 (CI: 0.059, 15.609)

[a] based on NRS Sleep
[b] defined as 'amblyopia'
[c] Paper reports this as 'thinking abnormal'
[d] Paper reports this as 'oedema'
[e] 'urinary incontinence'

Comments	patients on gabapentin were required to discontinue treatment at least one week before the study; ITT analyses included all those who had at least one dose of study medication and had at least one post-baseline assessment (1 patient in the pregabalin group was not included in the efficacy analyses because there was no on-treatment efficacy assessment

Definitions of abbreviations are given at the end of this document.

Study	Simpson (2001)
Pain category	Peripheral pain
Study design	Country: USA Design: Parallel Inclusion criteria: with PDN for 3 months to 1.5 years, with pain score of at least 40mm on a SF McGill Questionnaire VAS-100mm, average pain rating of at least 4 on a NRS (11-point) Exclusion criteria: severe pain from a cause other than diabetic neuropathy, amputations other than toes, renal failure with creatinine clearance <60 ml/min, use of the following drugs within 30 days of screening: tricyclics, mexiletine, carbamazepine, phenytoin, valproate, dextromethorphan, opioids, capsicin, NSAIDs, skeletal muscle relaxants, benzodiazepines, OTC centrally acting agents Study length (days): 56 Intention-to-treat analysis? No
Participants	Total number of patients: 60 Number of males: 36 (60.0%) Underlying cause of neuropathic pain: Painful diabetic neuropathy Mean duration of NP (in months): not reported Baseline pain severity: 6.45 (NRS (average of arm means)) Mean age: 50
Intervention(s)	(1) Gabapentin flexi Intervention: gabapentin Length of treatment (weeks): 8 Fixed/flexible dose regimen: Flexible dose Notes: max tolerated dosage; week 1: 300 mg/d for 2 days, 300mg twice per day for 2 days, then 300 mg three times per day for 3 days; week 2: 300 mg 2-1-1 for 1 day, 300 mg 2-2-1 for 1 day, 300 mg 2-2-2 for 5 days; week 3: 300 mg 3-2-2 for 1 day, 300 mg 3-3-2 for 1 day, 300 mg 3-3-3 for 5 days; week 4: 300 mg 4-3-3 for 1 day, 300 mg 4-4-3 for 1 day then maintained at 300 mg 4-4-4 (2) placebo Intervention: placebo Length of treatment (weeks): 8

	Fixed/flexible dose regimen: Flexible dose
Concomitant treatments	Drug free baseline period? Unclear Concomitant pain treatment allowed? No (use of the following within 30 days of screening was exclusion criteria and none were allowed during the trial duration: tricyclics, mexiletine, carbamazepine, phenytoin, valproate, dextromethorphan, opioids, capsicin, NSAIDs, skeletal muscle relaxants, benzodiazepines, OTC centrally acting agents)

Outcomes measures and effect sizes

		GABAPENTIN FLEXI			PLACEBO			
		N	k	mean	N	k	mean	Δ
pain score:								
NRS/NRS Pain – 0d	Continuous	27		6.4	27		6.5	
NRS/NRS Pain – 56d	Mean change	27		-2.4	27		-0.5	MD=-1.900
NRS/NRS Pain – 56d	Continuous	27		4	27		6	MD=-2.000
patient-reported global improvement:								
PGIC - worse (all grades) – 56d	Dichotomous	30	1	(3.3%)	30	4	(13.3%)	OR=0.224 (CI: 0.024, 2.136)
PGIC - no change or minimally better – 56d	Dichotomous	30	11	(36.7%)	30	16	(53.3%)	OR=0.507 (CI: 0.180, 1.422)
PGIC - at least moderately better – 56d	Dichotomous	30	15	(50.0%)	30	7	(23.3%)	OR=3.286 (CI: 1.085, 9.952)
patient-reported improvement in daily physical and emotional functioning, including sleep:								
POMS – 56d	Continuous	27		25	27		34	MD=-9.000
major adverse events (defined as leading to withdrawal):								
any major adverse event – 56d	Dichotomous	30	2	(6.7%)	30	2	(6.7%)	OR=1.000 (CI: 0.131, 7.605)
adverse events:								
Confusion – 56d	Dichotomous	30	2	(6.7%)	30	0	(0.0%)	OR=5.351 (CI: 0.246, 116.310)
Diarrhoea – 56d	Dichotomous	30	3	(10.0%)	30	1	(3.3%)	OR=3.222 (CI: 0.316, 32.889)
Dizziness – 56d	Dichotomous	30	6	(20.0%)	30	1	(3.3%)	OR=7.250 (CI: 0.815, 64.457)
headache – 56d	Dichotomous	30	3	(10.0%)	30	1	(3.3%)	OR=3.222 (CI: 0.316, 32.889)
Nausea – 56d	Dichotomous	30	2	(6.7%)	30	1	(3.3%)	OR=2.071 (CI: 0.178, 24.148)
Somnolence – 56d	Dichotomous	30	6	(20.0%)	30	1	(3.3%)	OR=7.250 (CI: 0.815, 64.457)
overall improvement in quality of life:								
SF36 bodily pain – 56d	Continuous	27		60	27		45	MD=15.000
SF36 vitality – 56d	Continuous	27		60	27		40	MD=20.000
SF36 mental health – 56d	Continuous	27		80	27		65	MD=15.000
treatment withdrawal:								
due to lack of efficacy – 56d	Dichotomous	30	1	(3.3%)	30	1	(3.3%)	OR=1.000 (CI: 0.060, 16.763)

Comments	there was a 7-day screening period - unclear if this was drug-free (while no ITT performed, reviewers entered patients randomised into denominators for dichotomous outcomes)

Definitions of abbreviations are given at the end of this document.

Study	Simpson et al. (2000)
Pain category	Peripheral pain
Study design	Country: USA

	Design: Parallel Inclusion criteria: Participants with painful HIV associated polyneuropathy Exclusion criteria: Participants on sodium valproate, alternative causes for neuropathy, pregnancy or breastfeeding, those with acute active opportunistic infectios (excludin oral thrush, orogenital or rectal herpes and mycobacterium avium-intracellular bacteremia) within 2 weeks of randomisation, major active psychiatric disorders, use of chemotherapeutic agents, systemic corticosteroids or immune modulators, addition of dideoxyneucleosides to an already established antiretroviral regimen Study length (days): 98 Intention-to-treat analysis? No
Participants	Total number of patients: 42 Number of males: 24 (57.1%) Underlying cause of neuropathic pain: HIV-related neuropathy Mean duration of NP (in months): not reported Baseline pain severity: 1.07 (Gracely pain score) Mean age: 44.5
Intervention(s)	(1) Lamotrigine 300mg/d Intervention: lamotrigine Length of treatment (weeks): 14 Fixed/flexible dose regimen: Fixed dose Set dose: 300mg/d Notes: 7 week titration, starting at 25 mg/d (weeks 1-2), 25 mg 2x per day (week 3-4), 50 mg 2x per day (week 5), 100 mg 2x per day (week 6), 150 mg 2x per day (week 7-14) (2) Placebo Intervention: placebo Length of treatment (weeks): 14 Fixed/flexible dose regimen: Fixed dose
Concomitant treatments	Drug free baseline period? No Concomitant pain treatment allowed? Unclear (a number of concomitant treatments were excluded but these were mostly not pain medications apart from valproic acid)
Outcomes measures and effect sizes	

		LAMOTRIGINE 300MG/D			PLACEBO			
		N	k	mean	N	k	mean	Δ
pain score:								
Gracely pain score – 0d	Continuous	9		1.09 (SD 0.32)	20		1.05 (SD 0.33)	
Gracely pain score – 98d	Continuous	9		0.52 (SD 0.37)	20		0.88 (SD 0.45)	MD=-0.360 (CI: -0.672, -0.048)
Gracely pain score – 98d	Mean change	9		-0.55 (SD 0.42)	20		-0.18 (SD 0.402)	MD=-0.370 (CI: -0.696, -0.044)
major adverse events (defined as leading to withdrawal):								
any major adverse event – 98d	Dichotomous	20	5	(25.0%)	22	0	(0.0%)	OR=15.968 (CI: 0.822, 310.145)
treatment withdrawal:								
unspecified/other reason – 98d	Dichotomous	20	0	(0.0%)	22	2	(9.1%)	OR=0.200 (CI: 0.009, 4.428)
lost to follow-up – 98d	Dichotomous	20	5	(25.0%)	22	1	(4.5%)	OR=7.000 (CI: 0.740, 66.212)

	Rash – 98d	Dichotomous	20	5	(25.0%)	22	0	(0.0%)	OR=15.968 (CI: 0.822, 310.145)
	Infection – 98d	Dichotomous	20	1	(5.0%)	22	0	(0.0%)	OR=3.462 (CI: 0.133, 89.951)
Comments	-									

Definitions of abbreviations are given at the end of this document.

Study	Simpson et al. (2003)
Pain category	Peripheral pain
Study design	Country: USA Design: Parallel Inclusion criteria: Participants with HIV- related sensory neuropathy (that was not responding to treatment) aged 32 to 67 years with symptoms of neuropathic pain in both distal lower extremities for at least 6 weeks and had either diminished reflexes at the ankles compared to the knees or distal diminution of sensations of vibration, pain or temperature in the legs Exclusion criteria: Previous or current use of lamotrigine, other neurological disorders that could confound diagnosis of peripheral neuropathy such as myelopathy, no prior exposure to dideoxynucleoside analogue antiretroviral therapy (or to have discontinued them within 8 weeks of randomisation or treated with a stable dose for at least 8 weeks before randomisation), use of valproate within 4 weeks of randomisation Study length (days): 77 Intention-to-treat analysis? No
Participants	Total number of patients: 227 Number of males: 197 (86.8%) Underlying cause of neuropathic pain: HIV-related neuropathy Mean duration of NP (in months): not reported Baseline pain severity: 66.625 (VAS (average of arm means)) Mean age: 44.25
Intervention(s)	(1) Lamotrigine 400 or 600 mg/d Intervention: lamotrigine Length of treatment (weeks): 11 Fixed/flexible dose regimen: Flexible dose Mean dose: 379.9333333mg/d Notes: Target dose was 400mg/d but this was increased to 600mg day for those on enzyme inducing drugs; mean maintenance dosage ranged from 377 to 402 mg/d across all patients (2) Placebo Intervention: placebo Length of treatment (weeks): 11 Fixed/flexible dose regimen: Flexible dose
Concomitant treatments	Drug free baseline period? No Concomitant pain treatment allowed? Yes (analgesics could be continued during therapy if they were receiving them at least 4 weeks before randomisation but needed to be maintained on a regular basis throughout the study (ie. tricyclics, class I anti-arrhythmics, anti-convulsants); opioids and

non-opioid medications could be adjusted as needed, other therapies like massage or acupuncture were allowed if they were used for at least 4 weeks before randomisation and the regimen was maintained throughout the study, analgesics for new, acute conditions could be added for non-neuropathic pain for up to 10 days but no new analgesics were allowed for continuous use throughout the study)

Outcomes measures and effect sizes

		LAMOTRIGINE 400 OR 600 MG/D			PLACEBO			
		N	k	mean	N	k	mean	Δ
pain score:								
at least 30% pain reduction (VAS) – 77d	Dichotomous	150	63	(42.0%)	77	20	(26.0%)	OR=2.064 (CI: 1.128, 3.775)
patient-reported global improvement:								
PGIC - at least moderately better – 77d	Dichotomous	150	39	(26.0%)	77	22	(28.6%)	OR=0.878 (CI: 0.475, 1.624)
major adverse events (defined as leading to withdrawal):								
any major adverse event – 77d	Dichotomous	150	4	(2.7%)	77	3	(3.9%)	OR=0.676 (CI: 0.147, 3.099)
adverse events:								
Diarrhoea – 77d	Dichotomous	150	16	(10.7%)	77	7	(9.1%)	OR=1.194 (CI: 0.469, 3.039)
headache – 77d	Dichotomous	150	16	(10.7%)	77	7	(9.1%)	OR=1.194 (CI: 0.469, 3.039)
Infection – 77d	Dichotomous	150	17	(11.3%)	77	7	(9.1%)	OR=1.278 (CI: 0.506, 3.228)
Nausea – 77d	Dichotomous	150	17	(11.3%)	77	8	(10.4%)	OR=1.102 (CI: 0.453, 2.682)
Rash – 77d	Dichotomous	150	21	(14.0%)	77	9	(11.7%)	OR=1.230 (CI: 0.534, 2.833)
treatment withdrawal:								
unspecified/other reason – 77d	Dichotomous	150	2	(1.3%)	77	4	(5.2%)	OR=0.247 (CI: 0.044, 1.378)
withdrawal of consent – 77d	Dichotomous	150	6	(4.0%)	77	1	(1.3%)	OR=3.167 (CI: 0.374, 26.785)
protocol deviation – 77d	Dichotomous	150	8	(5.3%)	77	5	(6.5%)	OR=0.811 (CI: 0.256, 2.569)
lost to follow-up – 77d	Dichotomous	150	8	(5.3%)	77	4	(5.2%)	OR=1.028 (CI: 0.300, 3.528)
ART group								
pain score:								
VAS – 77d	Mean change	45		-27.1	23		-9	MD=-18.100
at least 30% pain reduction (VAS) – 77d	Dichotomous	62	26	(41.9%)	30	5	(16.7%)	OR=3.611 (CI: 1.221, 10.683)
Gracely pain score – 77d	Mean change	45		-0.27	23		-0.1	MD=-0.170
McGill Pain Questionnaire – 77d	Mean change	45		-6.9	23		-1.6	MD=-5.300
patient-reported global improvement:								
PGIC - much worse – 77d	Dichotomous	62	0	(0.0%)	30	0	(0.0%)	OR=0.488 (CI: 0.009, 25.187)
PGIC - moderately worse – 77d	Dichotomous	62	3	(4.8%)	30	4	(13.3%)	OR=0.331 (CI: 0.069, 1.583)
PGIC - minimally worse – 77d	Dichotomous	62	0	(0.0%)	30	2	(6.7%)	OR=0.091 (CI: 0.004, 1.962)
PGIC - no change – 77d	Dichotomous	62	7	(11.3%)	30	5	(16.7%)	OR=0.636 (CI: 0.184, 2.202)
PGIC - minimally better – 77d	Dichotomous	62	11	(17.7%)	30	5	(16.7%)	OR=1.078 (CI: 0.338, 3.441)
PGIC - moderately better – 77d	Dichotomous	62	11	(17.7%)	30	6	(20.0%)	OR=0.863 (CI: 0.285, 2.609)
PGIC - at least moderately better – 77d	Dichotomous	62	24	(38.7%)	30	7	(23.3%)	OR=2.075 (CI: 0.772, 5.576)
PGIC - much better – 77d	Dichotomous	62	13	(21.0%)	30	1	(3.3%)	OR=7.694 (CI: 0.956, 61.903)
treatment withdrawal:								
unspecified/other reason – 77d	Dichotomous	62	1	(1.6%)	30	1	(3.3%)	OR=0.475 (CI: 0.029, 7.872)
withdrawal of consent – 77d	Dichotomous	62	1	(1.6%)	30	0	(0.0%)	OR=1.488 (CI: 0.059, 37.608)
protocol deviation – 77d	Dichotomous	62	4	(6.5%)	30	3	(10.0%)	OR=0.621 (CI: 0.130, 2.969)
lost to follow-up – 77d	Dichotomous	62	6	(9.7%)	30	1	(3.3%)	OR=3.107 (CI: 0.357, 27.050)
No ART group								
pain score:								
VAS – 77d	Mean change	71		-23.3	33		-21.3	MD=-2.000
at least 30% pain reduction (VAS) – 77d	Dichotomous	88	37	(42.0%)	47	15	(31.9%)	OR=1.548 (CI: 0.735, 3.261)
Gracely pain score – 77d	Mean change	71		-0.3	33		-0.27	MD=-0.030
McGill Pain Questionnaire – 77d	Mean change	71		-6.8	33		-8.7	MD=1.900

patient-reported global improvement:									
PGIC - much worse – 77d	Dichotomous	88	0	(0.0%)	47	0	(0.0%)	OR=0.537 (CI: 0.010, 27.480)	
PGIC - moderately worse – 77d	Dichotomous	88	2	(2.3%)	47	1	(2.1%)	OR=1.070 (CI: 0.094, 12.115)	
PGIC - minimally worse – 77d	Dichotomous	88	4	(4.5%)	47	1	(2.1%)	OR=2.190 (CI: 0.238, 20.181)	
PGIC - no change – 77d	Dichotomous	88	16	(18.2%)	47	8	(17.0%)	OR=1.083 (CI: 0.426, 2.756)	
PGIC - minimally better – 77d	Dichotomous	88	7	(8.0%)	47	8	(17.0%)	OR=0.421 (CI: 0.143, 1.245)	
PGIC - moderately better – 77d	Dichotomous	88	16	(18.2%)	47	5	(10.6%)	OR=1.867 (CI: 0.638, 5.463)	
PGIC - at least moderately better – 77d	Dichotomous	88	42	(47.7%)	47	15	(31.9%)	OR=1.948 (CI: 0.927, 4.092)	
PGIC - much better – 77d	Dichotomous	88	26	(29.5%)	47	10	(21.3%)	OR=1.552 (CI: 0.673, 3.577)	
treatment withdrawal:									
unspecified/other reason – 77d	Dichotomous	88	1	(1.1%)	47	3	(6.4%)	OR=0.169 (CI: 0.017, 1.668)	
withdrawal of consent – 77d	Dichotomous	88	5	(5.7%)	47	1	(2.1%)	OR=2.771 (CI: 0.314, 24.442)	
protocol deviation – 77d	Dichotomous	88	4	(4.5%)	47	2	(4.3%)	OR=1.071 (CI: 0.189, 6.077)	
lost to follow-up – 77d	Dichotomous	88	2	(2.3%)	47	3	(6.4%)	OR=0.341 (CI: 0.055, 2.117)	

Comments	ART - neurotoxic antiretrovirals

Definitions of abbreviations are given at the end of this document.

Study	Simpson et al. (2008)
Pain category	Peripheral pain
Study design	Country: USA Design: Parallel Inclusion criteria: at least 2 months of moderate to severe neuropathic pain in both feet secondary to HIV-DSP or neurotoxic antiretroviral drug exposure with average NPRS score of 3 to 9 (inclusive); HIV-DSP diagnosed by neurologist based on pain, burning, or dysesthetic discomfort in both feet, diminshed ankle reflexes, and diminution of vibration, pain or temperature sensation in the distal legs; on stable doses of neurotoxic ARV for at least 8 weeks; stable on other pain medications (anticonvulsants, nonselective serotonin reuptake inhibitor antidepressants, opioids) for at least 21 days Exclusion criteria: pain other than painful HIV-associated neuropathy, another cause for neuropathy (ie. diabetes mellitus, B12 deficiency, alcoholism), abnormalities in cardiac, renal, hepatic, or pulmonary function, hypersensitivity to capsaicin or opioids, those receiving 60 mg morphine equivalent or more Study length (days): 84 Intention-to-treat analysis? Yes
Participants	Total number of patients: 307 Number of males: 286 (93.2%) Underlying cause of neuropathic pain: HIV-related neuropathy Mean duration of NP (in months): 57.68 Baseline pain severity: 5.9 (NPRS (NRS)) Mean age: 47.7
Intervention(s)	(1) Capasaicin 8% patch (30 minutes) Intervention: capsaicin patch Length of treatment (weeks):

	Fixed/flexible dose regimen: Fixed dose Notes: up to four patches; topical local anaesthic (lidocaine 4%) was applied for 60 minutes and then removed with soap and water before patch application. (2) Capasaicin 8% patch (60 minutes) Intervention: capsaicin patch Length of treatment (weeks): Fixed/flexible dose regimen: Fixed dose Notes: up to four patches; topical local anaesthic (lidocaine 4%) was applied for 60 minutes and then removed with soap and water before patch application. (3) Capasaicin 8% patch (90 minutes only) Intervention: capsaicin patch Length of treatment (weeks): Fixed/flexible dose regimen: Fixed dose Notes: up to four patches; topical local anaesthic (lidocaine 4%) was applied for 60 minutes and then removed with soap and water before patch application. (4) Control patch (30, 60 or 90 minutes) Intervention: placebo Length of treatment (weeks): Fixed/flexible dose regimen: Fixed dose Notes: up to four patches; topical local anaesthic (lidocaine 4%) was applied for 60 minutes and then removed with soap and water before patch application. (5) Capsaicin 8% (30, 60 or 90 minutes) Intervention: capsaicin patch Length of treatment (weeks): Fixed/flexible dose regimen: Fixed dose Notes: This is the total of all those in the 3 different time period intervention groups grouped together; up to four patches; topical local anaesthic (lidocaine 4%) was applied for 60 minutes and then removed with soap and water before patch application.
Concomitant treatments	Drug free baseline period? No Concomitant pain treatment allowed? Yes (use of topical analgesics excluded but stable on other pain medications (anticonvulsants, nonselective serotonin reuptake inhibitor antidepressants, opioids) for at least 21 days; patients could also be administered oxycodone hydrochlorite oral solution (1 mg/ml) or equivalent at the onset of treatmetn-associated discomfort; patients could take hydrocodone bitartrate/acetaminophin 5 mg/500 mg for up to 7 days)
Outcomes measures and effect sizes	

		CAPASAICIN 8% PATCH (30 MINUTES)			CONTROL PATCH (30, 60 OR 90 MINUTES)			
		N	k	mean	N	k	mean	Δ
pain score:								
NRS/NRS Pain – 0d	Continuous	72		5.9 (SD 1.6)	82		5.9 (SD 1.6)	
at least 30% pain reduction (NRS) – 84d[a]	Dichotomous from baseline to average f-u	72	30		82	15		OR=3.190 (CI: 1.537, 6.621)
Gracely pain score[a]	Mean difference from baseline to average f-u	72		-0.22 (SD 0.55)	82		-0.04 (SD 0.31)	MD=-0.180 (CI: -0.324, -0.036)

SF McGill[a]	Mean difference from baseline to average f-u	72		-9.02 (SD 9.43)	82		-3.2 (SD 8.77)	MD=-5.820 (CI: -8.709, -2.931)
SF McGill sensory[a]	Mean difference from baseline to average f-u	72		-6.7 (SD 7.02)	82		-2.07 (SD 6.82)	MD=-4.630 (CI: -6.823, -2.437)
Summation of pain – 84d[b]	Percentage change from baseline to average f-u	72		-27.7 (SD 30.9)	82		-10.7 (SD 30.8)	MD=-17.000 (CI: -26.766, -7.234)
patient-reported global improvement:								
PGIC - minimally better	Dichotomous	72	17	(23.6%)	82	11	(13.4%)	OR=1.995 (CI: 0.865, 4.603)
PGIC - better (all grades)	Dichotomous	72	40	(55.6%)	82	20	(24.4%)	OR=3.875 (CI: 1.952, 7.692)
PGIC - moderately better	Dichotomous	72	13	(18.1%)	82	4	(4.9%)	OR=4.297 (CI: 1.333, 13.851)
PGIC - at least moderately better	Dichotomous	72	13	(18.1%)	82	4	(4.9%)	OR=4.297 (CI: 1.333, 13.851)
PGIC - much better	Dichotomous	72	10	(13.9%)	82	5	(6.1%)	OR=2.484 (CI: 0.807, 7.646)

[a] outcome from baseline to weeks 2 to 12

[b] NRS; Baseline to week 2–12; least squares mean

		CAPASAICIN 8% PATCH (60 MINUTES)			CONTROL PATCH (30, 60 OR 90 MINUTES)			
		N	k	mean	N	k	mean	Δ
pain score:								
NRS/NRS Pain – 0d	Continuous	78		5.8 (SD 1.7)	82		5.9 (SD 1.6)	
at least 30% pain reduction (NRS) – 84d[a]	Dichotomous from baseline to average f-u	78	19		82	15		OR=1.438 (CI: 0.671, 3.082)
Gracely pain score[a]	Mean difference from baseline to average f-u	78		-0.24 (SD 0.45)	82		-0.04 (SD 0.31)	MD=-0.200 (CI: -0.320, -0.080)
SF McGill[a]	Mean difference from baseline to average f-u	78		-9.65 (SD 9.75)	82		-3.2 (SD 8.77)	MD=-6.450 (CI: -9.328, -3.572)
SF McGill sensory[a]	Mean difference from baseline to average f-u	78		-7.2 (SD 7.54)	82		-2.07 (SD 6.82)	MD=-5.130 (CI: -7.361, -2.899)
Summation of pain – 84d[b]	Percentage change from baseline to average f-u	78		-15.8 (SD 30.4)	82		-10.7 (SD 30.8)	MD=-5.100 (CI: -14.584, 4.384)
patient-reported global improvement:								
PGIC - minimally better	Dichotomous	78	27	(34.6%)	82	11	(13.4%)	OR=3.417 (CI: 1.554, 7.514)
PGIC - better (all grades)	Dichotomous	78	45	(57.7%)	82	20	(24.4%)	OR=4.227 (CI: 2.152, 8.304)
PGIC - moderately better	Dichotomous	78	11	(14.1%)	82	4	(4.9%)	OR=3.201 (CI: 0.974, 10.524)
PGIC - at least moderately better	Dichotomous	78	11	(14.1%)	82	4	(4.9%)	OR=3.201 (CI: 0.974, 10.524)
PGIC - much better	Dichotomous	78	7	(9.0%)	82	5	(6.1%)	OR=1.518 (CI: 0.461, 5.001)

[a] outcome from baseline to weeks 2 to 12

[b] NRS; Baseline to week 2–12; least squares mean

		CAPASAICIN 8% PATCH (90 MINUTES ONLY)			CONTROL PATCH (30, 60 OR 90 MINUTES)			
		N	k	mean	N	k	mean	Δ
pain score:								
NRS/NRS Pain – 0d	Continuous	75		6.1 (SD 1.6)	82		5.9 (SD 1.6)	
at least 30% pain reduction (NRS) – 84d[a]	Dichotomous from baseline to average f-u	75	27		82	15		OR=2.513 (CI: 1.208, 5.224)
Gracely pain score[a]	Mean difference from baseline to average f-u	75		-0.17 (SD 0.41)	82		-0.04 (SD 0.31)	MD=-0.130 (CI: -0.245, -0.015)
SF McGill[a]	Mean difference from baseline to average f-u	75		-6.29 (SD 9.75)	82		-3.2 (SD 8.77)	MD=-3.090 (CI: -6.001, -0.179)
SF McGill sensory[a]	Mean difference from baseline to average f-u	75		-4.78 (SD 7.25)	82		-2.07 (SD 6.82)	MD=-2.710 (CI: -4.917, -0.503)
Summation of pain – 84d[b]	Percentage change from baseline to average f-u	75		-24.7 (SD 30.6)	82		-10.7 (SD 30.8)	MD=-14.000 (CI: -23.613, -4.387)
patient-reported global improvement:								
PGIC - minimally better	Dichotomous	75	20	(26.7%)	82	11	(13.4%)	OR=2.347 (CI: 1.038, 5.306)
PGIC - better (all grades)	Dichotomous	75	40	(53.3%)	82	20	(24.4%)	OR=3.543 (CI: 1.798, 6.980)
PGIC - moderately better	Dichotomous	75	15	(20.0%)	82	4	(4.9%)	OR=4.875 (CI: 1.539, 15.445)
PGIC - at least moderately better	Dichotomous	75	15	(20.0%)	82	4	(4.9%)	OR=4.875 (CI: 1.539, 15.445)
PGIC - much better	Dichotomous	75	5	(6.7%)	82	5	(6.1%)	OR=1.100 (CI: 0.305, 3.961)

[a] outcome from baseline to weeks 2 to 12

[b] NRS; Baseline to week 2–12; least squares mean

		CONTROL PATCH (30, 60 OR 90 MINUTES)			CAPSAICIN 8% (30, 60 OR 90 MINUTES)			
		N	k	mean	N	k	mean	Δ
pain score:								
NRS/NRS Pain – 0d	Continuous	82		5.9 (SD 1.6)	225		5.9 (SD 1.6)	
Gracely pain score[a]	Mean difference from baseline to average f-u	82		-0.04 (SD 0.31)	225		-0.21 (SD 0.47)	MD=0.170 (CI: 0.079, 0.261)
SF McGill[a]	Mean difference from baseline to average f-u	82		-3.2 (SD 8.77)	225		-8.33 (SD 9.66)	MD=5.130 (CI: 2.850, 7.410)
SF McGill sensory[a]	Mean difference from baseline to average f-u	82		-2.07 (SD 6.82)	225		-6.24 (SD 7.31)	MD=4.170 (CI: 2.412, 5.928)
Summation of pain – 84d[b]	Percentage change from baseline to average f-u	82		-10.7 (SD 30.8)	225		-22.8 (SD 30.6)	MD=12.100 (CI: 4.326, 19.874)
patient-reported global improvement:								
PGIC - minimally better	Dichotomous	82	11	(13.4%)	225	64	(28.4%)	OR=0.390 (CI: 0.194, 0.783)

PGIC - better (all grades)	Dichotomous	82	20	(24.4%)	225	125	(55.6%)	OR=0.258 (CI: 0.146, 0.456)
PGIC - moderately better	Dichotomous	82	4	(4.9%)	225	39	(17.3%)	OR=0.245 (CI: 0.085, 0.708)
PGIC - at least moderately better	Dichotomous	82	4	(4.9%)	225	39	(17.3%)	OR=0.245 (CI: 0.085, 0.708)
PGIC - much better	Dichotomous	82	5	(6.1%)	225	22	(9.8%)	OR=0.599 (CI: 0.219, 1.638)
major adverse events (defined as leading to withdrawal):								
any major adverse event – 84d	Dichotomous	82	1	(1.2%)	225	2	(0.9%)	OR=1.377 (CI: 0.123, 15.386)
adverse events:								
Burning pain – 84d[c]	Dichotomous	82	2	(2.4%)	225	18	(8.0%)	OR=0.288 (CI: 0.065, 1.267)
depression – 84d	Dichotomous	82	1	(1.2%)	225	7	(3.1%)	OR=0.384 (CI: 0.047, 3.174)
Diarrhoea – 84d	Dichotomous	82	3	(3.7%)	225	6	(2.7%)	OR=1.386 (CI: 0.339, 5.675)
Dizziness – 84d	Dichotomous	82	0	(0.0%)	225	5	(2.2%)	OR=0.243 (CI: 0.013, 4.443)
Fatigue – 84d	Dichotomous	82	2	(2.4%)	225	4	(1.8%)	OR=1.381 (CI: 0.248, 7.687)
gastric upset – 84d[d]	Dichotomous	82	2	(2.4%)	225	0	(0.0%)	OR=14.006 (CI: 0.665, 294.862)
GI disorders – 84d[e]	Dichotomous	82	2	(2.4%)	225	0	(0.0%)	OR=14.006 (CI: 0.665, 294.862)
headache – 84d	Dichotomous	82	1	(1.2%)	225	9	(4.0%)	OR=0.296 (CI: 0.037, 2.376)
myalgia – 84d	Dichotomous	82	2	(2.4%)	225	4	(1.8%)	OR=1.381 (CI: 0.248, 7.687)
Nausea – 84d	Dichotomous	82	1	(1.2%)	225	5	(2.2%)	OR=0.543 (CI: 0.063, 4.720)
Pruritus – 84d[f]	Dichotomous	82	5	(6.1%)	225	39	(17.3%)	OR=0.310 (CI: 0.118, 0.815)
Rash – 84d	Dichotomous	82	1	(1.2%)	225	4	(1.8%)	OR=0.682 (CI: 0.075, 6.193)
site pain – 84d	Dichotomous	82	7	(8.5%)	225	47	(20.9%)	OR=0.353 (CI: 0.153, 0.818)
site papules – 84d	Dichotomous	82	1	(1.2%)	225	11	(4.9%)	OR=0.240 (CI: 0.031, 1.890)
sleep disturbance – 84d[g]	Dichotomous	82	1	(1.2%)	225	6	(2.7%)	OR=0.451 (CI: 0.053, 3.801)
urticaria – 84d[h]	Dichotomous	82	1	(1.2%)	225	5	(2.2%)	OR=0.543 (CI: 0.063, 4.720)
Vomiting – 84d	Dichotomous	82	2	(2.4%)	225	1	(0.4%)	OR=5.600 (CI: 0.501, 62.600)
anxiety – 84d	Dichotomous	82	1	(1.2%)	225	4	(1.8%)	OR=0.682 (CI: 0.075, 6.193)
treatment withdrawal:								
due to lack of efficacy	Dichotomous	82	2	(2.4%)	225	1	(0.4%)	OR=5.600 (CI: 0.501, 62.600)
unspecified/other reason	Dichotomous	82	2	(2.4%)	225	5	(2.2%)	OR=1.100 (CI: 0.209, 5.783)

	lost to follow-up	Dichotomous	82	4	(4.9%)		225	13	(5.8%)	OR=0.836 (CI: 0.265, 2.642)
	Death unrelated to treatment	Dichotomous	82	2[i]	(2.4%)		225	1[j]	(0.4%)	OR=5.600 (CI: 0.501, 62.600)

[a] outcome from baseline to weeks 2 to 12

[b] NRS; Baseline to week 2–12; least squares mean
[c] application site burning
[d] gastritis
[e] gastroenteritis
[f] application site pruritus
[g] insomnia
[h] application site urticaria
[i] drug overdose and coma (no more details provided)
[j] sepsis (no other details provided)

Comments	LOCF used for intention-to-treat analyses

Definitions of abbreviations are given at the end of this document.

Study	Simpson et al. (2010)
Pain category	Peripheral pain
Study design	Country: USA Design: Parallel Inclusion criteria: participants with HIV DSP for over 3 months, confirmed by a neurologist with an average score of at least 4 on NPRS. Patients receiving neurotoxix antiretroviral drugs known to cause sensory neuropathy clinically similar to HIV DSP must have been on stable doses for over 3 months before screening. Exclusion criteria: People taking SSRIs and antiepileptics were excluded Study length (days): 98 Intention-to-treat analysis? Yes
Participants	Total number of patients: 302 Number of males: 245 (81.1%) Underlying cause of neuropathic pain: HIV-related neuropathy Mean duration of NP (in months): 62.4 Baseline pain severity: 6.8 (NRS (average of arm means)) Mean age: 47.5
Intervention(s)	(1) Pregabalin flexi Intervention: pregabalin Length of treatment (weeks): 14 Fixed/flexible dose regimen: Flexible dose Mean dose: 385.7mg/d (SD: 160.3)

	Range: 150–600 Notes: 2-week dose adjustment phase (2) Placebo Intervention: placebo Length of treatment (weeks): 14 Fixed/flexible dose regimen: Flexible dose
Concomitant treatments	Drug free baseline period? Yes (duration: 14d) Concomitant pain treatment allowed? Yes (Doses of other pain medications had to be stable for 1 month before treatment and throughout the study, but those taking anti-epileptics or SNRIs were excluded)
Outcomes measures and effect sizes	

		PREGABALIN FLEXI			PLACEBO			
		N	k	mean	N	k	mean	Δ
pain score:								
NRS/NRS Pain – 0d	Continuous	149		6.9 (SD 0.75)	150		6.7 (SD 0.75)	
patient-reported global improvement:								
PGIC - worse (all grades) – 98d[a]	Dichotomous	151	6	(4.0%)	151	12	(7.9%)	OR=0.479 (CI: 0.175, 1.312)
PGIC - no change – 98d[b]	Dichotomous	151	20	(13.2%)	151	38	(25.2%)	OR=0.454 (CI: 0.250, 0.825)
PGIC - better (all grades) – 98d[c]	Dichotomous	151	125	(82.8%)	151	101	(66.9%)	OR=2.380 (CI: 1.385, 4.091)
major adverse events (defined as leading to withdrawal):								
any major adverse event – 98d	Dichotomous	151	7	(4.6%)	151	2	(1.3%)	OR=3.622 (CI: 0.740, 17.725)
adverse events:								
Dizziness – 98d	Dichotomous	151	29	(19.2%)	151	16	(10.6%)	OR=2.006 (CI: 1.039, 3.871)
Dry mouth – 98d	Dichotomous	151	14	(9.3%)	151	1	(0.7%)	OR=15.328 (CI: 1.989, 118.114)
euphoria – 98d	Dichotomous	151	15	(9.9%)	151	1	(0.7%)	OR=16.544 (CI: 2.157, 126.917)
Peripheral oedema – 98d	Dichotomous	151	9	(6.0%)	151	7	(4.6%)	OR=1.304 (CI: 0.473, 3.596)
Somnolence – 98d	Dichotomous	151	35	(23.2%)	151	13	(8.6%)	OR=3.203 (CI: 1.618, 6.340)
treatment withdrawal:								
due to lack of efficacy – 98d	Dichotomous	151	0	(0.0%)	151	3	(2.0%)	OR=0.140 (CI: 0.007, 2.734)
unspecified/other reason – 98d	Dichotomous	151	18	(11.9%)	151	17	(11.3%)	OR=1.067 (CI: 0.527, 2.159)
withdrawal of consent – 98d	Dichotomous	151	5	(3.3%)	151	5	(3.3%)	OR=1.000 (CI: 0.283, 3.528)
ITT/LOCF (last-observation carried forward)								
pain score:								
NRS/NRS Pain – 98d[d]	Mean change	149		-2.88 (SD 0.75)	150		-2.63 (SD 0.75)	MD=-0.250 (CI: -0.420, -0.080)
at least 30% pain reduction – 98d	Dichotomous	151	85	(56.3%)	151	84	(55.6%)	OR=1.027 (CI: 0.652, 1.618)
at least 50% pain reduction – 98d	Dichotomous	151	59	(39.1%)	151	64	(42.4%)	OR=0.872 (CI: 0.551, 1.380)
Per Protocol								
pain score:								
NRS/NRS Pain – 56d[e]	Mean change	149		-3.33	150		-2.53	MD=-0.800
NRS/NRS Pain – 70d[f]	Mean change	149		-3.05 (SD 0.75)	150		-2.65 (SD 0.75)	MD=-0.400 (CI: -0.570, -0.230)
NRS/NRS Pain – 98d[f]	Mean change	149		-3.2 (SD 0.95)	150		-2.7 (SD 1)	MD=-0.500 (CI: -0.721, -0.279)

[a] estimated from percentages and denominator; includes minimally, much and very much worse
[b] estimated from percentages and denominator
[c] estimated from percentages and denominator; includes very much, much , and minimally improved
[d] SE estimated from graph
[e] unclear of patient numbers at this time point - has been estimated

	[f] estimated from graph; unclear of patient numbers at this time point - has been estimated
Comments	HADS score was measured and results said to be not significant but values weren't reported

Definitions of abbreviations are given at the end of this document.

Study	Sindrup et al. (1999)
Pain category	Peripheral pain
Study design	Country: Denmark Design: Crossover Inclusion criteria: 20-80 years with painful polyneuropathy for more than 6 months (diagnosis confirmed with electrophysiology tests - slowing of nerve conduction or reduction of amplitude of sensory action potential), at least 4 on a 0-10 NRS when off medication Exclusion criteria: causes other than polyneuropathy, previous allergic reaction to tramadol or other opioids, treatment with MAOI, pregnancy or breast feeding, epilepsy or severe terminal illness Study length (days): 63 Intention-to-treat analysis? Yes
Participants	Total number of patients: 45 Number of males: 27 (60.0%) Underlying cause of neuropathic pain: Polyneuropathy Mean duration of NP (in months): 1.5 Baseline pain severity: 6.66 (NRS (mean calculated from raw data provided in the study) (median neuropathy duration and age)) Mean age: 58
Intervention(s)	(1) Tramadol (oral) flexible dose Intervention: tramadol Length of treatment (weeks): 4 Fixed/flexible dose regimen: Flexible dose Range: 200–400 Notes: escalated from 200 to 400 mg/d or maximum tolerated (23 had 400 mg/d, 4 had 300 mg/d and 7 had 200 mg/d) (2) Placebo Intervention: placebo Length of treatment (weeks): 4 Fixed/flexible dose regimen: Flexible dose
Concomitant treatments	Drug free baseline period? Yes (duration: 7d) Concomitant pain treatment allowed? Unclear (other neuropathic pain medications were slowly tapered off for a week before the drug-free period so it is assumed that patients were not permitted to be on other pain medications (though it was not clearly specified, nor were the actual pain medications which were not permitted to continue explicitly identified in the paper); paracetamol allowed as rescue analgesic (up to six 500 mg tablets))
Outcomes measures and	**TRAMADOL (ORAL) FLEXIBLE DOSE** **PLACEBO**

effect sizes

		N	k	mean	N	k	mean	Δ
pain score:								
NRS/NRS Pain – 0d[a]	Continuous	34		6.66 (SD 3.83)	34		6.66 (SD 3.83)	
NRS/NRS Pain – 28d[a]	Continuous	34		4.53 (SD 2.7)	34		6.26 (SD 2.4)	MD=-1.730 (CI: -2.944, -0.516)
at least 30% pain reduction (NRS) – 28d[b]	Dichotomous	45	16	(35.6%)	45	6	(13.3%)	OR=3.586 (CI: 1.250, 10.291)
at least 50% pain reduction (NRS) – 28d[b]	Dichotomous	45	11	(24.4%)	45	3	(6.7%)	OR=4.529 (CI: 1.169, 17.547)
major adverse events (defined as leading to withdrawal):								
any major adverse event – 28d	Dichotomous	45	7	(15.6%)	45	2	(4.4%)	OR=3.961 (CI: 0.775, 20.233)
adverse events:								
any adverse event – 28d	Dichotomous	45	28	(62.2%)	45	12	(26.7%)	OR=4.529 (CI: 1.852, 11.077)
Constipation – 28d	Dichotomous	45	10	(22.2%)	45	2	(4.4%)	OR=6.143 (CI: 1.262, 29.895)
Dizziness – 28d	Dichotomous	45	15	(33.3%)	45	2	(4.4%)	OR=10.750 (CI: 2.288, 50.513)
Drowsiness – 28d	Dichotomous	45	19	(42.2%)	45	4	(8.9%)	OR=7.490 (CI: 2.290, 24.496)
Dry mouth – 28d	Dichotomous	45	17	(37.8%)	45	6	(13.3%)	OR=3.946 (CI: 1.381, 11.274)
Nausea – 28d	Dichotomous	45	11	(24.4%)	45	3	(6.7%)	OR=4.529 (CI: 1.169, 17.547)
urination difficulties – 28d[c]	Dichotomous	45	6	(13.3%)	45	1	(2.2%)	OR=6.769 (CI: 0.780, 58.723)
treatment withdrawal:								
unspecified/other reason – 28d	Dichotomous	45	0	(0.0%)	45	1[d]	(2.2%)	OR=0.326 (CI: 0.013, 8.218)
lost to follow-up – 28d	Dichotomous	45	1	(2.2%)	45	0	(0.0%)	OR=3.067 (CI: 0.122, 77.324)
use of rescue medication:								
500 mg paracetamol tablets per week – 28d[e]	Continuous	34		med: 0	34		med: 8	

[a] mean and SD calculated from raw data provided in the study
[b] calculated from raw data provided in the study
[c] described as 'micturation difficulties'
[d] participation in another trial
[e] during the last week

Comments

authors reported the numbers needed to treat to obtain a 50% or greater reduction in pain score but actual number of participants was not reported; ITT analysis seems to have been done but not all patients randomised were included in the analysis; concomitant drugs were slowly tapered over a period of 1 week before the 1-week drug-free baseline period

Definitions of abbreviations are given at the end of this document.

Study	Sindrup et al. (2003)
Pain category	Peripheral pain
Study design	Country: Denmark Design: Crossover Inclusion criteria: 20-80 years old with symptoms compatible with polyneuropathy present for > 6 months (diagnosis confirmed with nerve conduction studies), median pain of at least 4 on 0-10 NRS for individual most bothersome pain symptom Exclusion criteria: causes of pain other than polyneuropathy, previous allergic reaction to study drugs, treamtent with monoamine oxidase inhibotirs or quinidine, cardiac conduction disturbances or recent myocardial infarction, pregnancy, severe terminal illness, inability to sufficiently metabolise sparteine/debrisoquine (both study drugs are metabolised via this enzyme) Study length (days): 77 Intention-to-treat analysis? Yes

Participants	Total number of patients: 40 Number of males: 23 (57.5%) Underlying cause of neuropathic pain: Polyneuropathy Mean duration of NP (in months): 51 Baseline pain severity: 7 (NRS (study population details such as mean duration of NP, age and sex are of the 32 patients completing the trial)) Mean age: 56
Intervention(s)	(1) Venlafaxine (112.5 mg/d) Intervention: venlafaxine Length of treatment (weeks): 4 Fixed/flexible dose regimen: Fixed dose Set dose: 112.5mg/d Notes: 37.5 mg in first week, 75 mg in second, 112.5 mg in last 2 weeks (2) Imipramine (75 mg/d) Intervention: imipramine Length of treatment (weeks): 4 Fixed/flexible dose regimen: Fixed dose Set dose: 75mg/d Notes: 25 mg in first week, 50 mg in second, 75 mg in last 2 weeks (3) Placebo Intervention: placebo Length of treatment (weeks): 4 Fixed/flexible dose regimen: Fixed dose
Concomitant treatments	Drug free baseline period? Yes (duration: 7d) Concomitant pain treatment allowed? Unclear (other neuropathic pain medications were slowly tapered off for a week before the drug-free period so it is assumed that patients were not permitted to be on other pain medications (though it was not clearly specified, nor were the actual pain medications which were not permitted to continue explicitly identified in the paper); paracetamol allowed as rescue analgesic (up to six 500 mg tablets))
Outcomes measures and effect sizes	

		VENLAFAXINE (112.5 MG/D)			IMIPRAMINE (75 MG/D)			
		N	k	mean	N	k	mean	Δ
pain score: Summation of pain – 28d[a]	Percentage change from baseline	32		80 (SD 38)	32		77 (SD 50)	MD=3.000 (CI: -18.759, 24.759)
major adverse events (defined as leading to withdrawal): any major adverse event – 28d	Dichotomous	40	5[b]	(12.5%)	40	1[c]	(2.5%)	OR=5.571 (CI: 0.620, 50.031)
adverse events: any adverse event – 28d	Dichotomous	40	20	(50.0%)	40	20	(50.0%)	OR=1.000 (CI: 0.416, 2.403)
Blurred vision – 28d	Dichotomous	40	1	(2.5%)	40	1	(2.5%)	OR=1.000 (CI: 0.060, 16.562)
Constipation – 28d	Dichotomous	40	1	(2.5%)	40	0	(0.0%)	OR=3.076 (CI: 0.122, 77.796)
Dizziness – 28d	Dichotomous	40	2	(5.0%)	40	3	(7.5%)	OR=0.649 (CI: 0.103, 4.110)
Drowsiness – 28d[d]	Dichotomous	40	9	(22.5%)	40	3	(7.5%)	OR=3.581 (CI: 0.891, 14.391)
Dry mouth – 28d	Dichotomous	40	4	(10.0%)	40	12	(30.0%)	OR=0.259 (CI: 0.075, 0.891)

gastric upset – 28d	Dichotomous	40	3	(7.5%)	40	0	(0.0%)	OR=7.560 (CI: 0.378, 151.285)
headache – 28d	Dichotomous	40	2	(5.0%)	40	3	(7.5%)	OR=0.649 (CI: 0.103, 4.110)
Nausea – 28d	Dichotomous	40	6	(15.0%)	40	5	(12.5%)	OR=1.235 (CI: 0.344, 4.431)
palpitation – 28d	Dichotomous	40	0	(0.0%)	40	1	(2.5%)	OR=0.325 (CI: 0.013, 8.222)
urination difficulties – 28d[e]	Dichotomous	40	2	(5.0%)	40	0	(0.0%)	OR=5.260 (CI: 0.245, 113.106)
treatment withdrawal:								
due to lack of efficacy – 28d	Dichotomous	40	0	(0.0%)	40	1	(2.5%)	OR=0.325 (CI: 0.013, 8.222)
unspecified/other reason – 28d	Dichotomous	40	0	(0.0%)	40	1[f]	(2.5%)	OR=0.325 (CI: 0.013, 8.222)
use of rescue medication:								
500 mg paracetamol tablets per week – 0d	Continuous	32		18 (SD 18)	32		18 (SD 18)	
500 mg paracetamol tablets per week – 28d	Continuous	32		9 (SD 16)	32		8 (SD 15)	MD=1.000 (CI: -6.599, 8.599)
ITT/LOCF (last-observation carried forward)								
pain score:								
NRS/NRS Pain – 0d[g]	Continuous	32		7 (SD 1.5)	32		7 (SD 1.5)	
NRS/NRS Pain – 28d	Continuous	32		5.3 (SD 2.7)	32		5 (SD 2.7)	MD=0.300 (CI: -1.023, 1.623)

[a] summation of results from 4 different 0-10 NRS scales measuring of paroxysmal, constant, touch-evoked and pressure-evoked pain
[b] 1 nausea/dizziness, 1 tiredness/nausea, 1 nausea, 1 nausea/vomiting, 1 unknown
[c] skin rash
[d] 'tiredness'
[e] 'disturbed micturition'
[f] pain data was missing
[g] average at baseline of all patients in each arm

		VENLAFAXINE (112.5 MG/D)			**PLACEBO**			
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**
pain score:	Percentage change from							
Summation of pain – 28d[a]	baseline	32		80 (SD 38)	32		100 (SD 46)	MD=-20.000 (CI: -40.673, 0.673)
major adverse events (defined as leading to withdrawal):								
any major adverse event – 28d	Dichotomous	40	5[b]	(12.5%)	40	2[c]	(5.0%)	OR=2.714 (CI: 0.494, 14.901)
adverse events:								
any adverse event – 28d	Dichotomous	40	20	(50.0%)	40	14	(35.0%)	OR=1.857 (CI: 0.757, 4.558)
Blurred vision – 28d	Dichotomous	40	1	(2.5%)	40	0	(0.0%)	OR=3.076 (CI: 0.122, 77.796)
Constipation – 28d	Dichotomous	40	1	(2.5%)	40	2	(5.0%)	OR=0.487 (CI: 0.042, 5.599)
Dizziness – 28d	Dichotomous	40	2	(5.0%)	40	1	(2.5%)	OR=2.053 (CI: 0.179, 23.589)
Drowsiness – 28d[d]	Dichotomous	40	9	(22.5%)	40	3	(7.5%)	OR=3.581 (CI: 0.891, 14.391)
Dry mouth – 28d	Dichotomous	40	4	(10.0%)	40	3	(7.5%)	OR=1.370 (CI: 0.286, 6.559)
gastric upset – 28d	Dichotomous	40	3	(7.5%)	40	3	(7.5%)	OR=1.000 (CI: 0.189, 5.280)
headache – 28d	Dichotomous	40	2	(5.0%)	40	3	(7.5%)	OR=0.649 (CI: 0.103, 4.110)
Nausea – 28d	Dichotomous	40	6	(15.0%)	40	1	(2.5%)	OR=6.882 (CI: 0.789, 60.060)
palpitation – 28d	Dichotomous	40	0	(0.0%)	40	1	(2.5%)	OR=0.325 (CI: 0.013, 8.222)
urination difficulties – 28d[e]	Dichotomous	40	2	(5.0%)	40	0	(0.0%)	OR=5.260 (CI: 0.245, 113.106)
treatment withdrawal:								
due to lack of efficacy – 28d	Dichotomous	40	0	(0.0%)	40	1	(2.5%)	OR=0.325 (CI: 0.013, 8.222)

unspecified/other reason – 28d	Dichotomous	40	0	(0.0%)	40	0	(0.0%)	OR=1.000 (CI: 0.019, 51.627)
use of rescue medication:								
500 mg paracetamol tablets per week – 0d	Continuous	32		18 (SD 18)	32		18 (SD 18)	
500 mg paracetamol tablets per week – 28d	Continuous	32		9 (SD 16)	32		13 (SD 17)	MD=-4.000 (CI: -12.089, 4.089)
ITT/LOCF (last-observation carried forward)								
pain score:								
NRS/NRS Pain – 0d[f]	Continuous	32		7 (SD 1.5)	32		7 (SD 1.5)	
NRS/NRS Pain – 28d	Continuous	32		5.3 (SD 2.7)	32		6.3 (SD 2.1)	MD=-1.000 (CI: -2.185, 0.185)

[a] summation of results from 4 different 0-10 NRS scales measuring of paroxysmal, constant, touch-evoked and pressure-evoked pain
[b] 1 nausea/dizziness, 1 tiredness/nausea, 1 nausea, 1 nausea/vomiting, 1 unknown
[c] 1 nausea/diarrhoea, 1 vomiting
[d] 'tiredness'
[e] 'disturbed micturition'
[f] average at baseline of all patients in each arm

		IMIPRAMINE (75 MG/D)			PLACEBO			
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**
pain score:								
Summation of pain – 28d[a]	Percentage change from baseline	32		77 (SD 50)	32		100 (SD 46)	MD=-23.000 (CI: -46.540, 0.540)
major adverse events (defined as leading to withdrawal):								
any major adverse event – 28d	Dichotomous	40	1[b]	(2.5%)	40	2[c]	(5.0%)	OR=0.487 (CI: 0.042, 5.599)
adverse events:								
any adverse event – 28d	Dichotomous	40	20	(50.0%)	40	14	(35.0%)	OR=1.857 (CI: 0.757, 4.558)
Blurred vision – 28d	Dichotomous	40	1	(2.5%)	40	0	(0.0%)	OR=3.076 (CI: 0.122, 77.796)
Constipation – 28d	Dichotomous	40	0	(0.0%)	40	2	(5.0%)	OR=0.190 (CI: 0.009, 4.088)
Dizziness – 28d	Dichotomous	40	3	(7.5%)	40	1	(2.5%)	OR=3.162 (CI: 0.315, 31.775)
Drowsiness – 28d[d]	Dichotomous	40	3	(7.5%)	40	3	(7.5%)	OR=1.000 (CI: 0.189, 5.280)
Dry mouth – 28d	Dichotomous	40	12	(30.0%)	40	3	(7.5%)	OR=5.286 (CI: 1.361, 20.534)
gastric upset – 28d	Dichotomous	40	0	(0.0%)	40	3	(7.5%)	OR=0.132 (CI: 0.007, 2.647)
headache – 28d	Dichotomous	40	3	(7.5%)	40	3	(7.5%)	OR=1.000 (CI: 0.189, 5.280)
Nausea – 28d	Dichotomous	40	5	(12.5%)	40	1	(2.5%)	OR=5.571 (CI: 0.620, 50.031)
palpitation – 28d	Dichotomous	40	1	(2.5%)	40	1	(2.5%)	OR=1.000 (CI: 0.060, 16.562)
urination difficulties – 28d[e]	Dichotomous	40	0	(0.0%)	40	0	(0.0%)	OR=1.000 (CI: 0.019, 51.627)
treatment withdrawal:								
due to lack of efficacy – 28d	Dichotomous	40	1	(2.5%)	40	1	(2.5%)	OR=1.000 (CI: 0.060, 16.562)
unspecified/other reason – 28d	Dichotomous	40	1[f]	(2.5%)	40	0	(0.0%)	OR=3.076 (CI: 0.122, 77.796)
use of rescue medication:								
500 mg paracetamol tablets per week – 0d	Continuous	32		18 (SD 18)	32		18 (SD 18)	
500 mg paracetamol tablets per week – 28d	Continuous	32		8 (SD 15)	32		13 (SD 17)	MD=-5.000 (CI: -12.855, 2.855)
ITT/LOCF (last-observation carried forward)								
pain score:								
NRS/NRS Pain – 0d[g]	Continuous	32		7 (SD 1.5)	32		7 (SD 1.5)	
NRS/NRS Pain – 28d	Continuous	32		5 (SD 2.7)	32		6.3 (SD 2.1)	MD=-1.300 (CI: -2.485, -0.115)

[a] summation of results from 4 different 0-10 NRS scales measuring of paroxysmal, constant, touch-evoked and pressure-evoked pain

	[b] skin rash [c] 1 nausea/diarrhoea, 1 vomiting [d] 'tiredness' [e] 'disturbed micturition' [f] pain data was missing [g] average at baseline of all patients in each arm
Comments	an additional 3 patients have missing data: 2 were lost to follow-up and 1 had non compliance and went to the hospital for a urinary tract infection but it was not clear what treatment these patients were receiving at the time; authors state that the study was stopped before the stipulated number of patients had completed te trial because the study drug had expired and new supplies were not available; ITT analysis seems to have been done but not all patients randomised were included in the analysis; concomitant drugs were slowly tapered over a period of 1 week before the 1-week drug-free baseline period

Definitions of abbreviations are given at the end of this document.

Study	Smith et al. (2005)
Pain category	Mixed (central and peripheral) or unclear if mixed
Study design	Country: USA Design: Crossover Inclusion criteria: Lower limb amputation at least 6 months prior, average pain rating in the last month of at least 3 on the NRS (0-10), agreement with the medication schedules and protocols, ability to read and speak English Exclusion criteria: Under the age of 18 years, taking other antiepileptic medication or cimetindine, consuming more than two alcoholic drinks per day, pregnant or breastfeeding, high serum creatinine clearance level or low estimated creatinine clearance in a screening serum creatinine, kidney disease. Study length (days): 119 Intention-to-treat analysis? No
Participants	Total number of patients: 24 Number of males: 18 (75.0%) Underlying cause of neuropathic pain: Phantomb limb pain Mean duration of NP (in months): not reported Baseline pain severity: 4.38 (NRS) Mean age: 52.1 (SD: 15.5)
Intervention(s)	(1) Gabapentin Intervention: gabapentin Length of treatment (weeks): 6 Fixed/flexible dose regimen: Flexible dose Median dose: 3600mg/d Range: 300–3600 Notes: Dose increases followed a standardised titration schedule (300mg increases every 2 to 3 days) unless the pain rating was 0 or side effects were uncomfortable. (2) Placebo Intervention: placebo

	Length of treatment (weeks): 6 Fixed/flexible dose regimen: Flexible dose
Concomitant treatments	Drug free baseline period? Unclear Concomitant pain treatment allowed? Unclear (use of other antiepileptic medication or cimetindine prohibited but unclear about anti-depressants, opioids, etc.)
Outcomes measures and effect sizes	

		GABAPENTIN			PLACEBO			
		N	k	mean	N	k	mean	Δ
pain score:								
SF McGill Affective – 0d	Continuous	24		3.17 (SD 2.81)	24		3.61 (SD 3.35)	
SF McGill Affective – 42d	Continuous	24		3.15 (SD 3.45)	24		2.91 (SD 3.42)	MD=0.240 (CI: -1.704, 2.184)
SF McGill sensory – 0d	Continuous	24		11.7 (SD 7.87)	24		12.5 (SD 7.87)	
SF McGill sensory – 42d	Continuous	24		10.7 (SD 6.84)	24		10.4 (SD 8.78)	MD=0.360 (CI: -4.093, 4.813)
patient-reported improvement in daily physical and emotional functioning, including sleep:								
CES-D – 0d	Continuous	24		17.5 (SD 10.7)	24		18.6 (SD 12.7)	
CES-D – 42d	Continuous	24		13.7 (SD 10.2)	24		14.8 (SD 9.82)	MD=-1.070 (CI: -6.726, 4.586)
BPI (modified) – 0d	Continuous	24		30.5 (SD 22)	24		33.4 (SD 25.2)	
BPI (modified) – 42d	Continuous	24		23.6 (SD 19.4)	24		25.4 (SD 19.3)	MD=-1.770 (CI: -12.715, 9.175)
Residual (or stump) limb pain								
pain score:								
NRS/NRS Pain – 0d	Continuous	24		3.63 (SD 2.75)	24		3.21 (SD 2.43)	
NRS/NRS Pain – 42d	Continuous	24		2.26 (SD 1.94)	24		2.79 (SD 2.28)	MD=-0.530 (CI: -1.728, 0.668)
NRS/NRS Pain – 42d	Mean change	24		-1.22 (SD 2.56)	24		-0.74 (SD 1.94)	MD=-0.480 (CI: -1.765, 0.805)
Phantom limb pain								
pain score:								
NRS/NRS Pain – 0d	Continuous	24		4.38 (SD 2.57)	24		4.09 (SD 2.24)	
NRS/NRS Pain – 42d	Continuous	24		3.43 (SD 2.42)	24		3.6 (SD 2.67)	MD=-0.170 (CI: -1.612, 1.272)
NRS/NRS Pain – 42d	Mean change	24		-0.94 (SD 1.98)	24		-0.49 (SD 2.2)	MD=-0.450 (CI: -1.634, 0.734)

Comments	patient-reported overall benefit from study medication (ie. global benefit) was recorded on a 6-point categorical scale but this was not extracted as it was not possible to synthesise this with the more frequently used 7-poing PGIC; authors modified BPI so the item on 'walking' was changed to 'mobility (ability to get around)' so it incorporated people who were unable to walk and 3 items were added to give a more thorough perspective of pain interference (self-care, recreational activities, social activities)

Definitions of abbreviations are given at the end of this document.

Study	Stacey et al. (2008)
Pain category	Peripheral pain
Study design	Country: USA, Germany, Italy, Spain, UK Design: Parallel Inclusion criteria: PHN for at least 3 months after the herpes zoster episode, with a pain score of at least 40mm on VAS 100mm, average daily pain

	rating of at least 4 on NRS (11 point) Exclusion criteria: Other types of severe pain that might confound assesment, previous neurolytic or neurosurgical therapy for PHN, creatinine clearance less than 60mL/min, women who were pregnant or lactating. Study length (days): 28 Intention-to-treat analysis? Yes
Participants	Total number of patients: 269 Number of males: 150 (55.8%) Underlying cause of neuropathic pain: Post-herpetic neuralgia Mean duration of NP (in months): 30.4 Baseline pain severity: 6.5 (NRS (average of arm means)) Mean age: 67.4
Intervention(s)	(1) Pregabalin flexible dose (150-600mg/d) Intervention: pregabalin Length of treatment (weeks): 4 Fixed/flexible dose regimen: Flexible dose Range: 150–600 Notes: 150 mg/d for first 3 days with subsequent dose adjustment up to a maximum of 600 mg/d by the end of week 2; 45 % were titrated to a maximum daily dose of 600 mg/d (during the first 10 days, the mean daily dose was 206.1 mg and during the last 2 weeks it was 396.1 mg) (2) Pregabalin (300mg/d) Intervention: pregabalin Length of treatment (weeks): 4 Fixed/flexible dose regimen: Fixed dose Set dose: 300mg/d Notes: during the first 10 days, the mean daily dose was 293.6 mg and during the last 2 weeks it was 295.4 mg (3) placebo Intervention: placebo Length of treatment (weeks): 4 Fixed/flexible dose regimen: Fixed dose
Concomitant treatments	Drug free baseline period? No Concomitant pain treatment allowed? Yes (Some concomitant pain treatments that had stable doses for at least 30 days prior to baseline and remained stable throughout trial; however gabapentin (with 3 day taper of medication before randomisation), oxycodone (or other medications including oxycodone), acupunture, local and topic anesthetics, nerve blocks, potential retinotoxins and musculoskeletal relaxants were not permitted)
Outcomes measures and effect sizes	

		PREGABALIN FLEXIBLE DOSE (150-600MG/D)			PREGABALIN (300MG/D)			
		N	k	mean	N	k	mean	Δ
pain score: at least 30% pain reduction (NRS) – 28d	Dichotomous	91	64	(70.3%)	88	51	(58.0%)	OR=1.720 (CI: 0.927, 3.189)

at least 50% pain reduction (NRS) – 28d	Dichotomous	91	42	(46.2%)	88	35	(39.8%)	OR=1.298 (CI: 0.717, 2.349)
SF McGill – 28d	Mean change	91		-37.6	88		-33.2	MD=-4.360
major adverse events (defined as leading to withdrawal):								
any major adverse event – 28d	Dichotomous	91	4	(4.4%)	88	16	(18.2%)	OR=0.207 (CI: 0.066, 0.646)
adverse events:								
amnesia	Dichotomous	91	0	(0.0%)	88	2	(2.3%)	OR=0.189 (CI: 0.009, 3.995)
balance disorder	Dichotomous	91	3	(3.3%)	88	4	(4.5%)	OR=0.716 (CI: 0.156, 3.295)
Blurred vision	Dichotomous	91	4	(4.4%)	88	0	(0.0%)	OR=9.103 (CI: 0.483, 171.612)
Confusion	Dichotomous	91	3	(3.3%)	88	3	(3.4%)	OR=0.966 (CI: 0.190, 4.919)
Dizziness – 28d	Dichotomous	91	22	(24.2%)	88	27	(30.7%)	OR=0.720 (CI: 0.372, 1.394)
euphoria – 28d	Dichotomous	91	2	(2.2%)	88	2	(2.3%)	OR=0.966 (CI: 0.133, 7.014)
Fatigue – 28d	Dichotomous	91	8	(8.8%)	88	5	(5.7%)	OR=1.600 (CI: 0.503, 5.094)
lethargy	Dichotomous	91	0	(0.0%)	88	2	(2.3%)	OR=0.189 (CI: 0.009, 3.995)
Peripheral oedema – 28d	Dichotomous	91	3	(3.3%)	88	3	(3.4%)	OR=0.966 (CI: 0.190, 4.919)
Somnolence – 28d	Dichotomous	91	10	(11.0%)	88	17	(19.3%)	OR=0.516 (CI: 0.222, 1.199)
vertigo	Dichotomous	91	4	(4.4%)	88	2	(2.3%)	OR=1.977 (CI: 0.353, 11.078)
Weight gain – 28d	Dichotomous	91	8	(8.8%)	88	4	(4.5%)	OR=2.024 (CI: 0.587, 6.980)
treatment withdrawal:								
due to lack of efficacy – 28d	Dichotomous	91	1	(1.1%)	88	0	(0.0%)	OR=2.934 (CI: 0.118, 72.985)
unspecified/other reason – 28d	Dichotomous	91	0	(0.0%)	88	2[a]	(2.3%)	OR=0.189 (CI: 0.009, 3.995)

[a] for both patients, authors state: subject defaulted (not clear what this means)

		PREGABALIN FLEXIBLE DOSE (150-600MG/D)			PLACEBO			
		N	k	mean	N	k	mean	Δ
pain score:								
at least 30% pain reduction (NRS) – 28d	Dichotomous	91	64	(70.3%)	90	28	(31.1%)	OR=5.249 (CI: 2.785, 9.891)
at least 50% pain reduction (NRS) – 28d	Dichotomous	91	42	(46.2%)	90	17	(18.9%)	OR=3.681 (CI: 1.884, 7.190)
SF McGill – 28d	Mean change	91		-37.6	90		-21.2	MD=-16.330
major adverse events (defined as leading to withdrawal):								
any major adverse event – 28d	Dichotomous	91	4	(4.4%)	90	4	(4.4%)	OR=0.989 (CI: 0.240, 4.080)
adverse events:								
amnesia	Dichotomous	91	0	(0.0%)	90	0	(0.0%)	OR=0.989 (CI: 0.019, 50.385)
balance disorder	Dichotomous	91	3	(3.3%)	90	0	(0.0%)	OR=7.158 (CI: 0.364, 140.597)
Blurred vision	Dichotomous	91	4	(4.4%)	90	0	(0.0%)	OR=9.309 (CI: 0.494, 175.461)
Confusion	Dichotomous	91	3	(3.3%)	90	0	(0.0%)	OR=7.158 (CI: 0.364, 140.597)
Dizziness – 28d	Dichotomous	91	22	(24.2%)	90	6	(6.7%)	OR=4.464 (CI: 1.714, 11.626)
euphoria – 28d	Dichotomous	91	2	(2.2%)	90	0	(0.0%)	OR=5.056 (CI: 0.239, 106.798)
Fatigue – 28d	Dichotomous	91	8	(8.8%)	90	1	(1.1%)	OR=8.578 (CI: 1.050, 70.070)
lethargy	Dichotomous	91	0	(0.0%)	90	0	(0.0%)	OR=0.989 (CI: 0.019, 50.385)
Peripheral oedema – 28d	Dichotomous	91	3	(3.3%)	90	1	(1.1%)	OR=3.034 (CI: 0.310, 29.731)
Somnolence – 28d	Dichotomous	91	10	(11.0%)	90	2	(2.2%)	OR=5.432 (CI: 1.155, 25.539)
vertigo	Dichotomous	91	4	(4.4%)	90	0	(0.0%)	OR=9.309 (CI: 0.494, 175.461)
Weight gain – 28d	Dichotomous	91	8	(8.8%)	90	0	(0.0%)	OR=18.425 (CI: 1.047, 324.196)
treatment withdrawal:								
due to lack of efficacy – 28d	Dichotomous	91	1	(1.1%)	90	4	(4.4%)	OR=0.239 (CI: 0.026, 2.180)

unspecified/other reason – 28d	Dichotomous	91	0	(0.0%)	90	7[a]	(7.8%)	OR=0.061 (CI: 0.003, 1.082)	

[a] for 3 patients, authors state: subject defaulted (not clear what this means)

		PREGABALIN (300MG/D)			PLACEBO			
		N	k	mean	N	k	mean	Δ
pain score:								
at least 30% pain reduction (NRS) – 28d	Dichotomous	88	51	(58.0%)	90	28	(31.1%)	OR=3.052 (CI: 1.650, 5.646)
at least 50% pain reduction (NRS) – 28d	Dichotomous	88	35	(39.8%)	90	17	(18.9%)	OR=2.836 (CI: 1.438, 5.591)
SF McGill – 28d	Mean change	88		-33.2	90		-21.2	MD=-11.970
major adverse events (defined as leading to withdrawal):								
any major adverse event – 28d	Dichotomous	88	16	(18.2%)	90	4	(4.4%)	OR=4.778 (CI: 1.529, 14.932)
adverse events:								
amnesia	Dichotomous	88	2	(2.3%)	90	0	(0.0%)	OR=5.231 (CI: 0.248, 110.529)
balance disorder	Dichotomous	88	4	(4.5%)	90	0	(0.0%)	OR=9.639 (CI: 0.511, 181.739)
Blurred vision	Dichotomous	88	0	(0.0%)	90	0	(0.0%)	OR=1.023 (CI: 0.020, 52.102)
Confusion	Dichotomous	88	3	(3.4%)	90	0	(0.0%)	OR=7.409 (CI: 0.377, 145.567)
Dizziness – 28d	Dichotomous	88	27	(30.7%)	90	6	(6.7%)	OR=6.197 (CI: 2.411, 15.928)
euphoria – 28d	Dichotomous	88	2	(2.3%)	90	0	(0.0%)	OR=5.231 (CI: 0.248, 110.529)
Fatigue – 28d	Dichotomous	88	5	(5.7%)	90	1	(1.1%)	OR=5.361 (CI: 0.614, 46.852)
lethargy	Dichotomous	88	2	(2.3%)	90	0	(0.0%)	OR=5.231 (CI: 0.248, 110.529)
Peripheral oedema – 28d	Dichotomous	88	3	(3.4%)	90	1	(1.1%)	OR=3.141 (CI: 0.320, 30.790)
Somnolence – 28d	Dichotomous	88	17	(19.3%)	90	2	(2.2%)	OR=10.535 (CI: 2.355, 47.128)
vertigo	Dichotomous	88	2	(2.3%)	90	0	(0.0%)	OR=5.231 (CI: 0.248, 110.529)
Weight gain – 28d	Dichotomous	88	4	(4.5%)	90	0	(0.0%)	OR=9.639 (CI: 0.511, 181.739)
treatment withdrawal:								
due to lack of efficacy – 28d	Dichotomous	88	0	(0.0%)	90	4	(4.4%)	OR=0.109 (CI: 0.006, 2.048)
unspecified/other reason – 28d	Dichotomous	88	2[a]	(2.3%)	90	7[b]	(7.8%)	OR=0.276 (CI: 0.056, 1.366)

[a] for both patients, authors state: subject defaulted (not clear what this means)
[b] for 3 patients, authors state: subject defaulted (not clear what this means)

Comments	there was a 1 week baseline evaluation phase

Definitions of abbreviations are given at the end of this document.

Study	Tandan et al. (1992)
Pain category	Peripheral pain
Study design	Country: USA Design: Parallel Inclusion criteria: PDN of at least moderate intensity of pain and minimum duration of 3 months, aged between 18 to 85 years, daily pain of at least moderate intensity, good long-term control of any associated systematic disease, intolerance or unresponsive to conventional treatments Exclusion criteria: pregnancy, lactating women, patients with other topical medication at the site of application, those in whom the pain was deemed likely to be of pscyhological rather than an organic basis Study length (days): 56

	Intention-to-treat analysis? No
Participants	Total number of patients: 22 Number of males: 11 (50.0%) Underlying cause of neuropathic pain: Painful diabetic neuropathy Mean duration of NP (in months): 16.95 Baseline pain severity: 81.1 (VAS (average of arm means)) Mean age: 54.2
Intervention(s)	(1) 0.075% capsaicin applied to site 4 times per day Intervention: capsaicin cream Length of treatment (weeks): 8 Fixed/flexible dose regimen: Fixed dose (2) Placebo (vehicle) Intervention: placebo Length of treatment (weeks): 8 Fixed/flexible dose regimen: Fixed dose
Concomitant treatments	Drug free baseline period? No Concomitant pain treatment allowed? Yes (other topical medications not allowed; appears that they recorded whether or not patients had any change to ongoing medications (particularly analgesics) at follow-up points)

Outcomes measures and effect sizes

		0.075% CAPSAICIN APPLIED TO SITE 4 TIMES PER DAY			PLACEBO (VEHICLE)			
		N	k	mean	N	k	mean	Δ
pain score:								
VAS – 0d	Continuous	10		75.9	10		86.3	
VAS – 56d	Mean change	10		-16 (SD 18.3)	10		-4.1 (SD 13.3)	MD=-11.900 (CI: -25.935, 2.135)
patient-reported global improvement:								
PGIC - worse (all grades) – 56d	Dichotomous	11	1	(9.1%)	11	0	(0.0%)	OR=3.286 (CI: 0.120, 89.812)
PGIC - no change – 56d	Dichotomous	11	2	(18.2%)	11	8	(72.7%)	OR=0.083 (CI: 0.011, 0.633)
PGIC - better (all grades) – 56d	Dichotomous	11	7	(63.6%)	11	2	(18.2%)	OR=7.875 (CI: 1.105, 56.123)
major adverse events (defined as leading to withdrawal):								
any major adverse event – 56d	Dichotomous	11	1	(9.1%)	11	0	(0.0%)	OR=3.286 (CI: 0.120, 89.812)
adverse events:								
Burning pain – 56d	Dichotomous	11	6	(54.5%)	11	2	(18.2%)	OR=5.400 (CI: 0.778, 37.505)
treatment withdrawal:								
unspecified/other reason – 56d	Dichotomous	11	1	(9.1%)	11	1	(9.1%)	OR=1.000 (CI: 0.055, 18.304)

Comments	-

Definitions of abbreviations are given at the end of this document.

Study	Tasmuth et al. (2002)
Pain category	Peripheral pain
Study design	Country: Finland Design: Crossover Inclusion criteria: Postoperative moderate to severe neuropathic pain in breast cancer patients in the anterior chest wall and/or axilla and/or median upper arm in an area with sensory disturbances Exclusion criteria: relapse or metastases of cancer, clinically overt cardiac, renal or hepatic disease, use of concomitant medications such as monoamine oxidase inhibitors or drugs that are significantly metabolized by the P4502D6 isoenzome or which inhibit this enzyme Study length (days): 70 Intention-to-treat analysis? No
Participants	Total number of patients: 15 Number of males: not reported Underlying cause of neuropathic pain: Post-surgical pain after surgery for cancer Mean duration of NP (in months): not reported Baseline pain severity: 49 (current pain intensity on VAS (55 is median age)) Mean age: 55
Intervention(s)	(1) Venlafaxine flexible dose Intervention: venlafaxine Length of treatment (weeks): 4 Fixed/flexible dose regimen: Flexible dose Range: 18.75–75 Notes: dose escalation from 18.75 mg to 75 mg/d (11 had the maximum dosage) (2) placebo Intervention: placebo Length of treatment (weeks): 4 Fixed/flexible dose regimen: Flexible dose
Concomitant treatments	Drug free baseline period? No Concomitant pain treatment allowed? Unclear (patients were asked to refrain from taking other pain medications but any used were reported in pain diaries)

Outcomes measures and effect sizes

		VENLAFAXINE FLEXIBLE DOSE			PLACEBO			
		N	k	mean	N	k	mean	Δ
pain score:								
VAS – 0d[a]	Continuous	13		med: 49 [rng 20–75]	13		med: 49 [rng 20–75]	
VAS – 28d	Continuous	11		med: 0 [rng 0–35]	11		med: 0.6 [rng 0–70]	
VRS – 0d[b]	Continuous	13		med: 4 [rng 3–5]	13		med: 4 [rng 3–5]	
VRS – 28d	Continuous	11		med: 0 [rng 0–4]	11		med: 1 [rng 0–2]	

pain relief:									
VAS/VASpr – 28d	Continuous	11		med: 42 [rng 0–100]	11		med: 25 [rng 0–100]	
VRS/VRSpr – 28d[c]	Continuous	11		med: 1.5 [rng 0–4]	11		med: 1 [rng 0–3]	
patient-reported improvement in daily physical and emotional functioning, including sleep:								
BDI – 0d	Continuous	11		med: 10 [rng 1–28]	13		med: 10 [rng 1–28]	
BDI – 28d	Continuous	11		med: 7 [rng 1–39]	11		med: 7 [rng 1–11]	
major adverse events (defined as leading to withdrawal):								
any major adverse event – 28d	Dichotomous	15	1[d]	(6.7%)	15	0	(0.0%)	OR=3.207 (CI: 0.121, 85.203)
adverse events:								
Constipation – 28d	Dichotomous	15	4	(26.7%)	15	3	(20.0%)	OR=1.455 (CI: 0.264, 8.009)
Drowsiness – 28d[e]	Dichotomous	15	9	(60.0%)	15	10	(66.7%)	OR=0.750 (CI: 0.169, 3.327)
Dry mouth – 28d	Dichotomous	15	8	(53.3%)	15	6	(40.0%)	OR=1.714 (CI: 0.403, 7.292)
headache – 28d	Dichotomous	15	6	(40.0%)	15	4	(26.7%)	OR=1.833 (CI: 0.392, 8.566)
loss of appetite – 28d	Dichotomous	15	3	(20.0%)	15	4	(26.7%)	OR=0.688 (CI: 0.125, 3.786)
Nausea – 28d	Dichotomous	15	4	(26.7%)	15	4	(26.7%)	OR=1.000 (CI: 0.198, 5.045)
nightmares – 28d	Dichotomous	15	2	(13.3%)	15	4	(26.7%)	OR=0.423 (CI: 0.065, 2.766)
palpitation – 28d	Dichotomous	15	3	(20.0%)	15	3	(20.0%)	OR=1.000 (CI: 0.167, 5.985)
urination difficulties – 28d	Dichotomous	15	2	(13.3%)	15	2	(13.3%)	OR=1.000 (CI: 0.122, 8.210)

[a] mean of patients in both groups
[b] 8 point; mean of patients in both groups
[c] 5 point
[d] due to acute nausea, sweating and headache during the first day of treatment
[e] 'tired'

Comments	5 patients had modified radical mastectomy and 8 had breast-conserving surgery, 8/13 of those who did not withdrawal had pain in the ipsilateral arm and 5 had pain in the breast scar region (4 of these 5 patients and 6 of the 8 who had pain in the ipsilateral arm had postoperative radiotherapy); 1 other patient withdrew due to non compliance but it was not clear which treatment the patient was receiving at the time.

Definitions of abbreviations are given at the end of this document.

Study	Thienel et al. (2004)
Pain category	Peripheral pain
Study design	Country: USA Design: Parallel Inclusion criteria: Adults with diabetes and bilateral and simultaneous symptoms of painful peripheral polyneuropathy for at least 6 months. Anti-diabetic regimens had to be stable for at least 3 months before study entry. HbA1c less than 11% and creatinine clearance of at least 60ml/min Exclusion criteria: Polyneuropathy due to causes other than diabetes, diabetic ulceration of the extremities, non traumatic amputation, hospitalisation within the last 3 months for hyper/hypoglycaemia while adherant to appropriate diabetic therapy, history of unstable medical disease, progressive or degenerative neurological disorders, history of hepatitis or HIV, mental impairment affecting participation, alcohol or drug abuse, malignacy within the past 5 years, nephrolitiasis, previous participation in trial in last 30 days Study length (days): 140 Intention-to-treat analysis? No
Participants	Total number of patients: 1269

	Number of males: 736 (58.0%) Underlying cause of neuropathic pain: Painful diabetic neuropathy Mean duration of NP (in months): 100.8 Baseline pain severity: 58 (VAS (average of arm means)) Mean age: 58 (SD: 10)
Intervention(s)	(1) topiramate 100mg/d Intervention: topiramate Length of treatment (weeks): 20 Fixed/flexible dose regimen: Fixed dose Set dose: 100mg/d Notes: Treatment phase was 18 or 22 weeks (2) topiramate 200mg/d Intervention: topiramate Length of treatment (weeks): 20 Fixed/flexible dose regimen: Fixed dose Set dose: 200mg/d Notes: Treatment phase was 18 or 22 weeks (3) topiramate 400mg/d Intervention: topiramate Length of treatment (weeks): 20 Fixed/flexible dose regimen: Fixed dose Set dose: 400mg/d Notes: Treatment phase was 18 or 22 weeks (4) Placebo Intervention: placebo Length of treatment (weeks): 20 Fixed/flexible dose regimen: Fixed dose Notes: Treatment phase was 18 or 22 weeks
Concomitant treatments	Drug free baseline period? Yes (duration: 28d) Concomitant pain treatment allowed? No (anti-depressants, MAOI, anti-convulsant medications were prohibited; patients requiring chronic use of simple analgesics (including paracetamol and opoioids) were excluded but periodic rescue medication for breakthrough pain was allowed after randomisation)

Outcomes measures and effect sizes

		TOPIRAMATE 100MG/D			PLACEBO			
		N	k	mean	N	k	mean	Δ
major adverse events (defined as leading to withdrawal):								
any major adverse event – 140d[a]	Dichotomous	253	41	(16.2%)	384	32	(8.3%)	OR=2.127 (CI: 1.300, 3.482)
adverse events:								
Cognitive impairment – 140d[b]	Dichotomous	253	8	(3.2%)	384	7	(1.8%)	OR=1.759 (CI: 0.630, 4.911)
Confusion – 140d[a]	Dichotomous	253	8	(3.2%)	384	4	(1.0%)	OR=3.102 (CI: 0.924, 10.412)
Fatigue – 140d[a]	Dichotomous	253	28	(11.1%)	384	42	(10.9%)	OR=1.013 (CI: 0.610, 1.682)
Nausea – 140d[a]	Dichotomous	253	25	(9.9%)	384	27	(7.0%)	OR=1.450 (CI: 0.821, 2.561)

parasthesia – 140d[c]	Dichotomous	253	23	(9.1%)	384	19	(4.9%)	OR=1.921 (CI: 1.024, 3.606)
Somnolence – 140d[a]	Dichotomous	253	20	(7.9%)	384	15	(3.9%)	OR=2.112 (CI: 1.060, 4.207)
treatment withdrawal:								
due to lack of efficacy – 140d[a]	Dichotomous	253	42	(16.6%)	384	82	(21.4%)	OR=0.733 (CI: 0.486, 1.106)
unspecified/other reason – 140d[a]	Dichotomous	253	7	(2.8%)	384	15	(3.9%)	OR=0.700 (CI: 0.281, 1.742)
withdrawal of consent – 140d	Dichotomous	253	18[d]	(7.1%)	384	23[e]	(6.0%)	OR=1.202 (CI: 0.635, 2.276)
lost to follow-up – 140d[a]	Dichotomous	253	8	(3.2%)	384	4	(1.0%)	OR=3.102 (CI: 0.924, 10.412)
use of rescue medication:								
proportion using pain medication – 140d	Dichotomous	253	118[c]	(46.6%)	384	202[f]	(52.6%)	OR=0.788 (CI: 0.573, 1.082)
RCT1								
pain score:								
VAS – 0d[g]	Continuous	128		60.1 (SD 18.4)	136		57.7 (SD 19.1)	
VAS – 140d[g]	Continuous	128		36.1 (SD 28.2)	136		43.1 (SD 27.5)	MD=-7.000 (CI: -13.725, -0.275)
RCT3								
pain score:								
VAS – 0d[h]	Continuous	122		60.4 (SD 18.8)	126		55.3 (SD 21.1)	
VAS – 140d[h]	Continuous	122		44.7 (SD 29.5)	126		37.8 (SD 29.1)	MD=6.900 (CI: -0.395, 14.195)

[a] All 3 RCTs pooled
[b] memory impairment, all 3 RCTs pooled
[c] All 3 RCTs pooled; approximated to nearest integer (percentages only presented in text)
[d] 'patient choice'; All 3 RCTs pooled
[e] All 3 RCTs pooled; 'patient choice'
[f] estimated from percentage; All 3 RCTs pooled
[g] RCT1
[h] RCT3

		TOPIRAMATE 200MG/D			PLACEBO			
		N	k	mean	N	k	mean	Δ
major adverse events (defined as leading to withdrawal):								
any major adverse event – 140d[a]	Dichotomous	372	93	(25.0%)	384	32	(8.3%)	OR=3.667 (CI: 2.382, 5.644)
adverse events:								
Cognitive impairment – 140d[b]	Dichotomous	372	18	(4.8%)	384	7	(1.8%)	OR=2.738 (CI: 1.130, 6.635)
Confusion – 140d[a]	Dichotomous	372	11	(3.0%)	384	4	(1.0%)	OR=2.895 (CI: 0.913, 9.173)
Fatigue – 140d[a]	Dichotomous	372	63	(16.9%)	384	42	(10.9%)	OR=1.660 (CI: 1.091, 2.526)
Nausea – 140d[a]	Dichotomous	372	48	(12.9%)	384	27	(7.0%)	OR=1.959 (CI: 1.194, 3.213)
parasthesia – 140d	Dichotomous	372	52[a]	(14.0%)	384	19[c]	(4.9%)	OR=3.122 (CI: 1.808, 5.391)
Somnolence – 140d[a]	Dichotomous	372	44	(11.8%)	384	15	(3.9%)	OR=3.300 (CI: 1.803, 6.041)
treatment withdrawal:								
due to lack of efficacy – 140d[a]	Dichotomous	372	49	(13.2%)	384	82	(21.4%)	OR=0.559 (CI: 0.379, 0.823)
unspecified/other reason – 140d[a]	Dichotomous	372	20	(5.4%)	384	15	(3.9%)	OR=1.398 (CI: 0.704, 2.773)
withdrawal of consent – 140d	Dichotomous	372	28[d]	(7.5%)	384	23[e]	(6.0%)	OR=1.278 (CI: 0.722, 2.261)
lost to follow-up – 140d[a]	Dichotomous	372	7	(1.9%)	384	4	(1.0%)	OR=1.822 (CI: 0.529, 6.276)
use of rescue medication:								
proportion using pain medication – 140d	Dichotomous	372	196[c]	(52.7%)	384	202[f]	(52.6%)	OR=1.003 (CI: 0.754, 1.335)
RCT1								
pain score:								
VAS – 0d[g]	Continuous	130		55.8 (SD 21.2)	136		57.7 (SD 19.1)	
VAS – 140d[g]	Continuous	130		38.3 (SD 28.4)	136		43.1 (SD 27.5)	MD=-4.800 (CI: -11.523, 1.923)

RCT2						
pain score:						
VAS – 0d[h]	Continuous	116	58 (SD 19.5)	119	57.5 (SD 19.4)	
VAS – 140d[h]	Continuous	116	37.8 (SD 28.4)	119	41.6 (SD 28.6)	MD=-3.800 (CI: -11.088, 3.488)
RCT3						
pain score:						
VAS – 0d[i]	Continuous	123	59.3 (SD 19.2)	126	55.3 (SD 21.1)	
VAS – 140d[i]	Continuous	123	44.7 (SD 28.7)	126	37.8 (SD 29.1)	MD=6.900 (CI: -0.279, 14.079)

[a] All 3 RCTs pooled
[b] memory impairment, all 3 RCTs pooled
[c] All 3 RCTs pooled; approximated to nearest integer (percentages only presented in text)
[d] 'patient choice'; All 3 RCTs pooled
[e] All 3 RCTs pooled; 'patient choice'
[f] estimated from percentage; All 3 RCTs pooled
[g] RCT1
[h] RCT2
[i] RCT3

		TOPIRAMATE 400MG/D			**PLACEBO**			
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**
major adverse events (defined as leading to withdrawal):								
any major adverse event – 140d[a]	Dichotomous	260	79	(30.4%)	384	32	(8.3%)	OR=4.801 (CI: 3.067, 7.515)
adverse events:								
Cognitive impairment – 140d[b]	Dichotomous	260	18	(6.9%)	384	7	(1.8%)	OR=4.006 (CI: 1.649, 9.734)
Confusion – 140d[a]	Dichotomous	260	18	(6.9%)	384	4	(1.0%)	OR=7.066 (CI: 2.363, 21.129)
Fatigue – 140d[a]	Dichotomous	260	52	(20.0%)	384	42	(10.9%)	OR=2.036 (CI: 1.309, 3.166)
Nausea – 140d[a]	Dichotomous	260	33	(12.7%)	384	27	(7.0%)	OR=1.922 (CI: 1.126, 3.282)
parasthesia – 140d[c]	Dichotomous	260	31	(11.9%)	384	19	(4.9%)	OR=2.601 (CI: 1.435, 4.712)
Somnolence – 140d[a]	Dichotomous	260	23	(8.8%)	384	15	(3.9%)	OR=2.387 (CI: 1.221, 4.668)
treatment withdrawal:								
due to lack of efficacy – 140d[a]	Dichotomous	260	32	(12.3%)	384	82	(21.4%)	OR=0.517 (CI: 0.332, 0.805)
unspecified/other reason – 140d[a]	Dichotomous	260	10	(3.8%)	384	15	(3.9%)	OR=0.984 (CI: 0.435, 2.225)
withdrawal of consent – 140d	Dichotomous	260	19[d]	(7.3%)	384	23[e]	(6.0%)	OR=1.237 (CI: 0.660, 2.321)
lost to follow-up – 140d[a]	Dichotomous	260	11	(4.2%)	384	4	(1.0%)	OR=4.197 (CI: 1.322, 13.327)
use of rescue medication:								
proportion using pain medication – 140d	Dichotomous	260	142[c]	(54.6%)	384	202[f]	(52.6%)	OR=1.084 (CI: 0.791, 1.487)
RCT1								
pain score:								
VAS – 0d[g]	Continuous	130		56.3 (SD 20.2)	136		57.7 (SD 19.1)	
VAS – 140d[g]	Continuous	130		39.7 (SD 26.9)	136		43.1 (SD 27.5)	MD=-3.400 (CI: -9.938, 3.138)
RCT2								
pain score:								
VAS – 0d[h]	Continuous	129		57.8 (SD 19.7)	119		57.5 (SD 19.4)	
VAS – 140d[h]	Continuous	129		39.3 (SD 26.3)	119		41.6 (SD 28.6)	MD=-2.300 (CI: -9.156, 4.556)

[a] All 3 RCTs pooled
[b] memory impairment, all 3 RCTs pooled

	[c] All 3 RCTs pooled; approximated to nearest integer (percentages only presented in text) [d] 'patient choice'; All 3 RCTs pooled [e] All 3 RCTs pooled; 'patient choice' [f] estimated from percentage; All 3 RCTs pooled [g] RCT1 [h] RCT2
Comments	This paper combines the results of 3 RCTs some had a treatment phase of 18 weeks, some had a treatment phase of 22 weeks

Definitions of abbreviations are given at the end of this document.

Study	Tolle et al. (2008)
Pain category	Peripheral pain
Study design	Country: USA and Germany Design: Parallel Inclusion criteria: PDN for at least 1 year with a pain score of at least 40mm on a VAS-100mm and average daily pain rating of at least 4 on NRS-11 point Exclusion criteria: Creatinine clearence less than 30mL/min Study length (days): 84 Intention-to-treat analysis? Yes
Participants	Total number of patients: 395 Number of males: 219 (55.4%) Underlying cause of neuropathic pain: Painful diabetic neuropathy Mean duration of NP (in months): not reported Baseline pain severity: 6.425 (NRS (average of all means)) Mean age: 58.61 (SD: 11.5)
Intervention(s)	(1) Pregabalin 150mg/d Intervention: pregabalin Length of treatment (weeks): 12 Fixed/flexible dose regimen: Fixed dose Set dose: 150mg/d Notes: no titration (2) Pregabalin 300mg/d Intervention: pregabalin Length of treatment (weeks): 12 Fixed/flexible dose regimen: Fixed dose Set dose: 300mg/d Notes: 7 day titration from 150 mg/d (3) Pregabalin 300/600mg/d Intervention: pregabalin Length of treatment (weeks): 12

Fixed/flexible dose regimen: Flexible dose
Notes: patients received 300 mg/d or 600 mg/d depending on their creatinine clearance (high [> 60 ml/min] - 600 mg/d, normal [> 30 but < or = 60 ml/min] - 300 mg/d); 7 day titration from 150 mg/d

(4) Placebo

Intervention: placebo
Length of treatment (weeks): 12
Fixed/flexible dose regimen: Fixed dose

(5) Pregabalin (dosages combined)

Intervention: pregabalin
Length of treatment (weeks): 12
Fixed/flexible dose regimen: Fixed dose

Concomitant treatments

Drug free baseline period? Yes (duration: 7d)

Concomitant pain treatment allowed? Yes (excluded: medications and miscellaneous supplements commonly used for relief of neuropathic pain including benzodiazepines (other than stable bedtime dosages for sleep), skeletal muscle relaxants, capsaicin, alpha-lipoid acid, local anaesthtics, opioids including tramadol, memantine, AEDs, anti-depressants (other than SSRI for depression if stable for at least 30 days - SSRIs could be considered concomitant medications), analgesics like NSAIDs and dextromethorphan; unclear if rescue analgesics (such as paracetamol) were allowed)

Outcomes measures and effect sizes

		PREGABALIN 150MG/D			PLACEBO			
		N	k	mean	N	k	mean	Δ
pain score:								
at least 50% pain reduction (NRS) – 84d	Dichotomous	99	28	(28.3%)	96	24	(25.0%)	OR=1.188 (CI: 0.613, 2.304)
at least 50% pain reduction (NRS) – 84d	Dichotomous	82	28	(28.3%)	79	24	(25.0%)	OR=1.188 (CI: 0.613, 2.304)
patient-reported global improvement:								
PGIC - worse (all grades) – 84d	Dichotomous	99	5	(5.1%)	96	9	(9.4%)	OR=0.513 (CI: 0.165, 1.592)
PGIC - worse (all grades) – 84d	Dichotomous	96	5	(5.1%)	93	9	(9.4%)	OR=0.513 (CI: 0.165, 1.592)
PGIC - worse (all grades), no change or minimally better – 84d	Dichotomous	99	52	(52.5%)	96	62	(64.6%)	OR=0.591 (CI: 0.328, 1.065)
PGIC - worse (all grades), no change or minimally better – 84d	Dichotomous	96	52	(52.5%)	93	62	(64.6%)	OR=0.591 (CI: 0.328, 1.065)
PGIC - no change – 84d	Dichotomous	99	21	(21.2%)	96	23	(24.0%)	OR=0.852 (CI: 0.434, 1.674)
PGIC - no change – 84d	Dichotomous	96	21	(21.2%)	93	23	(24.0%)	OR=0.852 (CI: 0.434, 1.674)
PGIC - minimally better – 84d	Dichotomous	99	26	(26.3%)	96	30	(31.3%)	OR=0.780 (CI: 0.417, 1.458)
PGIC - minimally better – 84d	Dichotomous	96	26	(26.3%)	93	30	(31.3%)	OR=0.780 (CI: 0.417, 1.458)
PGIC - at least moderately better – 84d	Dichotomous	99	44	(44.4%)	96	31	(32.3%)	OR=1.692 (CI: 0.939, 3.050)
PGIC - at least moderately better – 84d	Dichotomous	96	44	(44.4%)	93	31	(32.3%)	OR=1.692 (CI: 0.939, 3.050)
patient-reported improvement in daily physical and emotional functioning, including sleep:								
NRS Sleep – 84d	Continuous	96			93			MD=-0.450 (CI: -1.050, 0.150)
major adverse events (defined as leading to withdrawal):								
any major adverse event – 84d	Dichotomous	99	5	(5.1%)	96	3	(3.1%)	OR=1.649 (CI: 0.383, 7.099)
adverse events:								
asthenia – 84d	Dichotomous	99	1	(1.0%)	96	0	(0.0%)	OR=2.939 (CI: 0.118, 73.039)
Dizziness – 84d	Dichotomous	99	3	(3.0%)	96	2	(2.1%)	OR=1.469 (CI: 0.240, 8.990)
Dry mouth – 84d	Dichotomous	99	3	(3.0%)	96	0	(0.0%)	OR=7.000 (CI: 0.357, 137.346)
headache – 84d	Dichotomous	99	5	(5.1%)	96	5	(5.2%)	OR=0.968 (CI: 0.271, 3.456)
oedema – 84d	Dichotomous	99	4	(4.0%)	96	0	(0.0%)	OR=9.094 (CI: 0.483, 171.237)
Peripheral oedema – 84d	Dichotomous	99	5	(5.1%)	96	2	(2.1%)	OR=2.500 (CI: 0.473, 13.208)

Somnolence – 84d	Dichotomous	99	5	(5.1%)	96	1	(1.0%)	OR=5.053 (CI: 0.579, 44.075)
vertigo – 84d	Dichotomous	99	2	(2.0%)	96	0	(0.0%)	OR=4.949 (CI: 0.235, 104.429)
Weight gain – 84d	Dichotomous	99	6	(6.1%)	96	0	(0.0%)	OR=13.417 (CI: 0.745, 241.531)
overall improvement in quality of life:								
EQ-5D - health status index – 84d	Continuous	92			90			MD=0.100 (CI: 0.035, 0.165)
treatment withdrawal:								
due to lack of efficacy – 84d	Dichotomous	99	8	(8.1%)	96	11	(11.5%)	OR=0.679 (CI: 0.261, 1.770)
unspecified/other reason – 84d	Dichotomous	99	4	(4.0%)	96	3	(3.1%)	OR=1.305 (CI: 0.284, 5.992)
poor compliance – 84d	Dichotomous	99	0	(0.0%)	96	0	(0.0%)	OR=0.970 (CI: 0.019, 49.368)
Per Protocol								
pain score:								
NRS/NRS Pain – 84d	Continuous	87			87			MD=-0.400 (CI: -1.040, 0.240)
ITT population								
pain score:								
NRS/NRS Pain – 84d	Continuous	98			96			MD=-0.270 (CI: -0.875, 0.335)

		PREGABALIN 300MG/D			**PLACEBO**			
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**
pain score:								
at least 50% pain reduction (NRS) – 84d	Dichotomous	99	26	(26.3%)	96	24	(25.0%)	OR=1.124 (CI: 0.575, 2.199)
at least 50% pain reduction (NRS) – 84d	Dichotomous	79	26	(26.3%)	79	24	(25.0%)	OR=1.124 (CI: 0.575, 2.199)
patient-reported global improvement:								
PGIC - worse (all grades) – 84d	Dichotomous	99	8	(8.1%)	96	9	(9.4%)	OR=0.868 (CI: 0.320, 2.357)
PGIC - worse (all grades) – 84d	Dichotomous	94	8	(8.1%)	93	9	(9.4%)	OR=0.868 (CI: 0.320, 2.357)
PGIC - worse (all grades), no change or minimally better – 84d	Dichotomous	99	54	(54.5%)	96	62	(64.6%)	OR=0.675 (CI: 0.373, 1.223)
PGIC - worse (all grades), no change or minimally better – 84d	Dichotomous	94	54	(54.5%)	93	62	(64.6%)	OR=0.675 (CI: 0.373, 1.223)
PGIC - no change – 84d	Dichotomous	99	17	(17.2%)	96	23	(24.0%)	OR=0.672 (CI: 0.332, 1.361)
PGIC - no change – 84d	Dichotomous	94	17	(17.2%)	93	23	(24.0%)	OR=0.672 (CI: 0.332, 1.361)
PGIC - minimally better – 84d	Dichotomous	99	29	(29.3%)	96	30	(31.3%)	OR=0.937 (CI: 0.506, 1.736)
PGIC - minimally better – 84d	Dichotomous	94	29	(29.3%)	93	30	(31.3%)	OR=0.937 (CI: 0.506, 1.736)
PGIC - at least moderately better – 84d	Dichotomous	99	40	(40.4%)	96	31	(32.3%)	OR=1.481 (CI: 0.818, 2.684)
PGIC - at least moderately better – 84d	Dichotomous	94	40	(40.4%)	93	31	(32.3%)	OR=1.481 (CI: 0.818, 2.684)
patient-reported improvement in daily physical and emotional functioning, including sleep:								
NRS Sleep – 84d	Continuous	96			93			MD=-0.620 (CI: 0.000, -1.240)
major adverse events (defined as leading to withdrawal):								
any major adverse event – 84d	Dichotomous	99	11	(11.1%)	96	3	(3.1%)	OR=3.875 (CI: 1.046, 14.354)
adverse events:								
asthenia – 84d	Dichotomous	99	4	(4.0%)	96	0	(0.0%)	OR=9.094 (CI: 0.483, 171.237)
Dizziness – 84d	Dichotomous	99	9	(9.1%)	96	2	(2.1%)	OR=4.700 (CI: 0.988, 22.349)
Dry mouth – 84d	Dichotomous	99	5	(5.1%)	96	0	(0.0%)	OR=11.233 (CI: 0.613, 205.976)
headache – 84d	Dichotomous	99	3	(3.0%)	96	5	(5.2%)	OR=0.569 (CI: 0.132, 2.449)
oedema – 84d	Dichotomous	99	12	(12.1%)	96	0	(0.0%)	OR=27.571 (CI: 1.609, 472.600)
Peripheral oedema – 84d	Dichotomous	99	9	(9.1%)	96	2	(2.1%)	OR=4.700 (CI: 0.988, 22.349)
Somnolence – 84d	Dichotomous	99	4	(4.0%)	96	1	(1.0%)	OR=4.000 (CI: 0.439, 36.451)
vertigo – 84d	Dichotomous	99	6	(6.1%)	96	0	(0.0%)	OR=13.417 (CI: 0.745, 241.531)
Weight gain – 84d	Dichotomous	99	6	(6.1%)	96	0	(0.0%)	OR=13.417 (CI: 0.745, 241.531)

overall improvement in quality of life:								
EQ-5D - health status index – 84d	Continuous	92			90			MD=0.080 (CI: 0.015, 0.145)
treatment withdrawal:								
due to lack of efficacy – 84d	Dichotomous	99	5	(5.1%)	96	11	(11.5%)	OR=0.411 (CI: 0.137, 1.231)
unspecified/other reason – 84d	Dichotomous	99	4	(4.0%)	96	3	(3.1%)	OR=1.305 (CI: 0.284, 5.992)
poor compliance – 84d	Dichotomous	99	0	(0.0%)	96	0	(0.0%)	OR=0.970 (CI: 0.019, 49.368)
Per Protocol								
pain score:								
NRS/NRS Pain – 84d	Continuous	89			87			MD=-0.150 (CI: -0.785, 0.485)
ITT population								
pain score:								
NRS/NRS Pain – 84d	Continuous	99			96			MD=-0.100 (CI: -0.700, 0.500)

		PREGABALIN 300/600MG/D			**PLACEBO**			
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**
pain score:								
at least 50% pain reduction (NRS) – 84d	Dichotomous	101	36	(35.6%)	96	24	(25.0%)	OR=1.964 (CI: 1.021, 3.779)
at least 50% pain reduction (NRS) – 84d	Dichotomous	78	36	(35.6%)	79	24	(25.0%)	OR=1.964 (CI: 1.021, 3.779)
patient-reported global improvement:								
PGIC - worse (all grades) – 84d	Dichotomous	101	5	(5.0%)	96	9	(9.4%)	OR=0.519 (CI: 0.167, 1.610)
PGIC - worse (all grades) – 84d	Dichotomous	95	5	(5.0%)	93	9	(9.4%)	OR=0.519 (CI: 0.167, 1.610)
PGIC - worse (all grades), no change or minimally better – 84d	Dichotomous	101	47	(46.5%)	96	62	(64.6%)	OR=0.490 (CI: 0.271, 0.883)
PGIC - worse (all grades), no change or minimally better – 84d	Dichotomous	95	47	(46.5%)	93	62	(64.6%)	OR=0.490 (CI: 0.271, 0.883)
PGIC - no change – 84d	Dichotomous	101	13	(12.9%)	96	23	(24.0%)	OR=0.483 (CI: 0.228, 1.023)
PGIC - no change – 84d	Dichotomous	95	13	(12.9%)	93	23	(24.0%)	OR=0.483 (CI: 0.228, 1.023)
PGIC - minimally better – 84d	Dichotomous	101	29	(28.7%)	96	30	(31.3%)	OR=0.923 (CI: 0.498, 1.709)
PGIC - minimally better – 84d	Dichotomous	95	29	(28.7%)	93	30	(31.3%)	OR=0.923 (CI: 0.498, 1.709)
PGIC - at least moderately better – 84d	Dichotomous	101	48	(47.5%)	96	31	(32.3%)	OR=2.043 (CI: 1.133, 3.683)
PGIC - at least moderately better – 84d	Dichotomous	95	48	(47.5%)	93	31	(32.3%)	OR=2.043 (CI: 1.133, 3.683)
patient-reported improvement in daily physical and emotional functioning, including sleep:								
NRS Sleep – 84d	Continuous	98			93			MD=-1.010 (CI: -1.605, -0.415)
major adverse events (defined as leading to withdrawal):								
any major adverse event – 84d	Dichotomous	101	13	(12.9%)	96	3	(3.1%)	OR=4.580 (CI: 1.262, 16.616)
adverse events:								
asthenia – 84d	Dichotomous	101	5	(5.0%)	96	0	(0.0%)	OR=11.000 (CI: 0.600, 201.678)
Dizziness – 84d	Dichotomous	101	14	(13.9%)	96	2	(2.1%)	OR=7.563 (CI: 1.671, 34.237)
Dry mouth – 84d	Dichotomous	101	7	(6.9%)	96	0	(0.0%)	OR=15.317 (CI: 0.863, 271.978)
headache – 84d	Dichotomous	101	1	(1.0%)	96	5	(5.2%)	OR=0.182 (CI: 0.021, 1.587)
oedema – 84d	Dichotomous	101	4	(4.0%)	96	0	(0.0%)	OR=8.908 (CI: 0.473, 167.701)
Peripheral oedema – 84d	Dichotomous	101	10	(9.9%)	96	2	(2.1%)	OR=5.165 (CI: 1.101, 24.220)
Somnolence – 84d	Dichotomous	101	8	(7.9%)	96	1	(1.0%)	OR=8.172 (CI: 1.002, 66.629)
vertigo – 84d	Dichotomous	101	5	(5.0%)	96	0	(0.0%)	OR=11.000 (CI: 0.600, 201.678)
Weight gain – 84d	Dichotomous	101	7	(6.9%)	96	0	(0.0%)	OR=15.317 (CI: 0.863, 271.978)
overall improvement in quality of life:								
EQ-5D - health status index – 84d	Continuous	90			90			MD=0.140 (CI: 0.075, 0.205)

treatment withdrawal:									
due to lack of efficacy – 84d	Dichotomous	101	3	(3.0%)	96	11	(11.5%)	OR=0.237 (CI: 0.064, 0.876)	
unspecified/other reason – 84d	Dichotomous	101	6	(5.9%)	96	3	(3.1%)	OR=1.958 (CI: 0.476, 8.060)	
poor compliance – 84d	Dichotomous	101	1	(1.0%)	96	0	(0.0%)	OR=2.881 (CI: 0.116, 71.577)	
Per Protocol									
pain score:									
NRS/NRS Pain – 84d	Continuous	85			87			MD=-1.030 (CI: -1.680, -0.380)	
ITT population									
pain score:									
NRS/NRS Pain – 84d	Continuous	101			96			MD=-0.910 (CI: -1.510, -0.310)	

Comments	-

Definitions of abbreviations are given at the end of this document.

Study	van Seventer et al. (2006)
Pain category	Peripheral pain
Study design	Country: unclear Design: Parallel Inclusion criteria: PHN for at least 3 months after herpes zoster episode with pain score of at least 40mm on VAS 100mm, average daily pain rating of at least 4 on NRS 11 point Exclusion criteria: Patients with malignancy (except basal cell carcinoma) within the past 2 years, clinically significant or unstable hepatic, respiratory, or haematological illnesses or psychologic condtitions, unstable cardiovascular disease, immunocomptimised, history of alcohol or drug abuse in the past 2 years, participantion in a clinical trial for an investigational drug or agent within 30 days prior to study, participation in a trial on pregabalin. Study length (days): 91 Intention-to-treat analysis? No
Participants	Total number of patients: 370 Number of males: 168 (45.4%) Underlying cause of neuropathic pain: Post-herpetic neuralgia Mean duration of NP (in months): 40.7 Baseline pain severity: 6.67 (NRS) Mean age: 70.7
Intervention(s)	(1) Pregabalin 150mg/d Intervention: pregabalin Length of treatment (weeks): 13 Fixed/flexible dose regimen: Fixed dose Set dose: 150mg/d Notes: 1 week titration, 12 week maintenance (2) Pregabalin 300mg/d Intervention: pregabalin

Length of treatment (weeks): 13
Fixed/flexible dose regimen: Fixed dose
Set dose: 300mg/d
Notes: 1 week titration, 12 week maintenance

(3) Pregablin 600mg/d

Intervention: pregabalin
Length of treatment (weeks): 13
Fixed/flexible dose regimen: Fixed dose
Set dose: 600mg/d
Notes: 1 week titration, 12 week maintenance

(4) Placebo

Intervention: placebo
Length of treatment (weeks): 13
Fixed/flexible dose regimen: Fixed dose

(5) all pregabalin dosages

Intervention: pregabalin
Length of treatment (weeks):
Fixed/flexible dose regimen: Fixed dose

Concomitant treatments

Drug free baseline period? Yes (duration: 7d)

Concomitant pain treatment allowed? Yes (stable medications (30 days or more) before study entry including non-narcotic analgesics (ie. Noramidopyrine and paracetamol) and stable regimes of opioids, anti-inflammatories were allowed; rescue medications allowed (paracetamol, tramadol, amitriptyline); wash-out required for prohibited medications including skeletal muscle relaxants, steriods, capsaicin, mexiletine, dextromethorphan, anti-epileptics, amantadine, alpha-lipoic acid, hydroxychloroquine, benzodiazepine, thioridazine, deferoxamine)

Outcomes measures and effect sizes

		PREGABALIN 150MG/D			PLACEBO			
		N	k	mean	N	k	mean	Δ
pain score:								
NRS/NRS Pain – 0d	Continuous	87		6.44 (SD 1.58)	93		6.85 (SD 1.49)	
NRS/NRS Pain – 91d[a]	Continuous	87		5.26 (SD 2.24)	93		6.14 (SD 2.22)	MD=-0.880 (CI: -1.530, -0.230)
at least 30% pain reduction (NRS) – 91d	Dichotomous	87	24	(27.6%)	93	10	(10.8%)	OR=3.162 (CI: 1.411, 7.087)
at least 50% pain reduction (NRS) – 91d	Dichotomous	87	16	(18.4%)	93	4	(4.3%)	OR=5.014 (CI: 1.605, 15.665)
patient-reported global improvement:								
PGIC - worse (all grades) or no change – 91d	Dichotomous	87	30	(34.5%)	93	38	(40.9%)	OR=0.762 (CI: 0.416, 1.395)
PGIC - minimally better – 91d	Dichotomous	87	17	(19.5%)	93	11	(11.8%)	OR=1.810 (CI: 0.795, 4.122)
PGIC - at least moderately better – 91d	Dichotomous	87	14	(16.1%)	93	10	(10.8%)	OR=1.592 (CI: 0.667, 3.801)
patient-reported improvement in daily physical and emotional functioning, including sleep:								
NRS Sleep – 91d[b]	Continuous	87		3.07 (SD 2.05)	93		4.1 (SD 2.03)	MD=-1.030 (CI: -1.620, -0.440)
major adverse events (defined as leading to withdrawal):								
any major adverse event – 91d	Dichotomous	87	7	(8.0%)	93	5	(5.4%)	OR=1.540 (CI: 0.470, 5.046)
adverse events:								
asthenia – 91d	Dichotomous	87	4	(4.6%)	93	5	(5.4%)	OR=0.848 (CI: 0.220, 3.267)
Blurred vision – 91d	Dichotomous	87	0	(0.0%)	93	0	(0.0%)	OR=1.069 (CI: 0.021, 54.439)

Confusion – 91d[c]	Dichotomous	87	2	(2.3%)	93	1	(1.1%)	OR=2.165 (CI: 0.193, 24.307)
Constipation – 91d	Dichotomous	87	1	(1.1%)	93	2	(2.2%)	OR=0.529 (CI: 0.047, 5.941)
Diarrhoea – 91d	Dichotomous	87	5	(5.7%)	93	1	(1.1%)	OR=5.610 (CI: 0.642, 49.013)
Dizziness – 91d	Dichotomous	87	14	(16.1%)	93	9	(9.7%)	OR=1.790 (CI: 0.732, 4.377)
Dry mouth – 91d	Dichotomous	87	5	(5.7%)	93	0	(0.0%)	OR=12.467 (CI: 0.679, 228.884)
Gait disturbance – 91d	Dichotomous	87	1	(1.1%)	93	0	(0.0%)	OR=3.243 (CI: 0.130, 80.670)
headache – 91d	Dichotomous	87	4	(4.6%)	93	3	(3.2%)	OR=1.446 (CI: 0.314, 6.653)
Nausea – 91d	Dichotomous	87	1	(1.1%)	93	5	(5.4%)	OR=0.205 (CI: 0.023, 1.788)
oedema – 91d	Dichotomous	87	3	(3.4%)	93	3	(3.2%)	OR=1.071 (CI: 0.210, 5.456)
Peripheral oedema – 91d	Dichotomous	87	11	(12.6%)	93	10	(10.8%)	OR=1.201 (CI: 0.483, 2.988)
Somnolence – 91d	Dichotomous	87	8	(9.2%)	93	4	(4.3%)	OR=2.253 (CI: 0.653, 7.770)
Weight gain – 91d	Dichotomous	87	3	(3.4%)	93	0	(0.0%)	OR=7.746 (CI: 0.394, 152.151)
facial oedema – 91d	Dichotomous	87	3	(3.4%)	93	2	(2.2%)	OR=1.625 (CI: 0.265, 9.965)
treatment withdrawal:								
due to lack of efficacy – 91d	Dichotomous	87	16	(18.4%)	93	22	(23.7%)	OR=0.727 (CI: 0.353, 1.499)
unspecified/other reason – 91d	Dichotomous	87	3	(3.4%)	93	7	(7.5%)	OR=0.439 (CI: 0.110, 1.754)
poor compliance – 91d	Dichotomous	87	0	(0.0%)	93	0	(0.0%)	OR=1.069 (CI: 0.021, 54.439)

[a] least squares mean
[b] least squares mean; baseline not reported
[c] Described as 'thinking abnormal' in evidence table

		PREGABALIN 300MG/D			PLACEBO			
		N	k	mean	N	k	mean	Δ
pain score:								
NRS/NRS Pain – 0d	Continuous	98		6.72 (SD 1.41)	93		6.85 (SD 1.49)	
NRS/NRS Pain – 91d[a]	Continuous	98		5.07 (SD 2.28)	93		6.14 (SD 2.22)	MD=-1.070 (CI: -1.695, -0.445)
at least 30% pain reduction (NRS) – 91d	Dichotomous	98	25	(25.5%)	93	10	(10.8%)	OR=2.842 (CI: 1.280, 6.313)
at least 50% pain reduction (NRS) – 91d	Dichotomous	98	16	(16.3%)	93	4	(4.3%)	OR=4.341 (CI: 1.394, 13.520)
patient-reported global improvement:								
PGIC - worse (all grades) or no change – 91d	Dichotomous	98	32	(32.7%)	93	38	(40.9%)	OR=0.702 (CI: 0.389, 1.267)
PGIC - minimally better – 91d	Dichotomous	98	13	(13.3%)	93	11	(11.8%)	OR=1.140 (CI: 0.483, 2.690)
PGIC - at least moderately better – 91d	Dichotomous	98	17	(17.3%)	93	10	(10.8%)	OR=1.742 (CI: 0.753, 4.031)
patient-reported improvement in daily physical and emotional functioning, including sleep:								
NRS Sleep – 91d[b]	Continuous	98		2.84 (SD 2.08)	93		4.1 (SD 2.03)	MD=-1.260 (CI: -1.840, -0.680)
major adverse events (defined as leading to withdrawal):								
any major adverse event – 91d	Dichotomous	98	15	(15.3%)	93	5	(5.4%)	OR=3.181 (CI: 1.107, 9.141)
adverse events:								
asthenia – 91d	Dichotomous	98	3	(3.1%)	93	5	(5.4%)	OR=0.556 (CI: 0.129, 2.394)
Blurred vision – 91d	Dichotomous	98	2	(2.0%)	93	0	(0.0%)	OR=4.845 (CI: 0.230, 102.259)
Confusion – 91d[c]	Dichotomous	98	2	(2.0%)	93	1	(1.1%)	OR=1.917 (CI: 0.171, 21.499)
Constipation – 91d	Dichotomous	98	8	(8.2%)	93	2	(2.2%)	OR=4.044 (CI: 0.836, 19.570)
Diarrhoea – 91d	Dichotomous	98	0	(0.0%)	93	1	(1.1%)	OR=0.313 (CI: 0.013, 7.781)
Dizziness – 91d	Dichotomous	98	32	(32.7%)	93	9	(9.7%)	OR=4.525 (CI: 2.020, 10.139)
Dry mouth – 91d	Dichotomous	98	4	(4.1%)	93	0	(0.0%)	OR=8.905 (CI: 0.473, 167.718)
Gait disturbance – 91d	Dichotomous	98	2	(2.0%)	93	0	(0.0%)	OR=4.845 (CI: 0.230, 102.259)
headache – 91d	Dichotomous	98	1	(1.0%)	93	3	(3.2%)	OR=0.309 (CI: 0.032, 3.028)
Nausea – 91d	Dichotomous	98	0	(0.0%)	93	5	(5.4%)	OR=0.082 (CI: 0.004, 1.498)

oedema – 91d	Dichotomous	98	3	(3.1%)	93	3	(3.2%)	OR=0.947 (CI: 0.186, 4.816)
Peripheral oedema – 91d	Dichotomous	98	14	(14.3%)	93	10	(10.8%)	OR=1.383 (CI: 0.582, 3.290)
Somnolence – 91d	Dichotomous	98	11	(11.2%)	93	4	(4.3%)	OR=2.813 (CI: 0.863, 9.173)
Weight gain – 91d	Dichotomous	98	8	(8.2%)	93	0	(0.0%)	OR=17.564 (CI: 0.999, 308.770)
facial oedema – 91d	Dichotomous	98	1	(1.0%)	93	2	(2.2%)	OR=0.469 (CI: 0.042, 5.262)
treatment withdrawal:								
due to lack of efficacy – 91d	Dichotomous	98	13	(13.3%)	93	22	(23.7%)	OR=0.494 (CI: 0.232, 1.050)
unspecified/other reason – 91d	Dichotomous	98	7	(7.1%)	93	7	(7.5%)	OR=0.945 (CI: 0.318, 2.806)
poor compliance – 91d	Dichotomous	98	1	(1.0%)	93	0	(0.0%)	OR=2.877 (CI: 0.116, 71.513)

[a] least squares mean
[b] least squares mean; baseline not reported
[c] Described as 'thinking abnormal' in evidence table

		PREGABLIN 600MG/D			PLACEBO			
		N	k	mean	N	k	mean	Δ
pain score:								
NRS/NRS Pain – 0d	Continuous	90		6.65 (SD 1.44)	93		6.85 (SD 1.49)	
NRS/NRS Pain – 91d[a]	Continuous	88		4.35 (SD 2.25)	93		6.14 (SD 2.22)	MD=-1.790 (CI: -2.430, -1.150)
at least 30% pain reduction (NRS) – 91d	Dichotomous	90	31	(34.4%)	93	10	(10.8%)	OR=4.361 (CI: 1.985, 9.581)
at least 50% pain reduction (NRS) – 91d	Dichotomous	90	22	(24.4%)	93	4	(4.3%)	OR=7.199 (CI: 2.370, 21.868)
patient-reported global improvement:								
PGIC - worse (all grades) or no change – 91d	Dichotomous	90	20	(22.2%)	93	38	(40.9%)	OR=0.414 (CI: 0.217, 0.789)
PGIC - minimally better – 91d	Dichotomous	90	18	(20.0%)	93	11	(11.8%)	OR=1.864 (CI: 0.826, 4.207)
PGIC - at least moderately better – 91d	Dichotomous	90	22	(24.4%)	93	10	(10.8%)	OR=2.685 (CI: 1.191, 6.057)
patient-reported improvement in daily physical and emotional functioning, including sleep:								
NRS Sleep – 91d[b]	Continuous	88		2.17 (SD 2.06)	93		4.1 (SD 2.03)	MD=-1.930 (CI: -2.520, -1.340)
major adverse events (defined as leading to withdrawal):								
any major adverse event – 91d	Dichotomous	90	19	(21.1%)	93	5	(5.4%)	OR=4.710 (CI: 1.675, 13.240)
adverse events:								
asthenia – 91d	Dichotomous	90	5	(5.6%)	93	5	(5.4%)	OR=1.035 (CI: 0.289, 3.705)
Blurred vision – 91d	Dichotomous	90	4	(4.4%)	93	0	(0.0%)	OR=9.728 (CI: 0.516, 183.346)
Confusion – 91d[c]	Dichotomous	90	4	(4.4%)	93	1	(1.1%)	OR=4.279 (CI: 0.469, 39.043)
Constipation – 91d	Dichotomous	90	8	(8.9%)	93	2	(2.2%)	OR=4.439 (CI: 0.916, 21.507)
Diarrhoea – 91d	Dichotomous	90	0	(0.0%)	93	1	(1.1%)	OR=0.341 (CI: 0.014, 8.474)
Dizziness – 91d	Dichotomous	90	33	(36.7%)	93	9	(9.7%)	OR=5.404 (CI: 2.403, 12.149)
Dry mouth – 91d	Dichotomous	90	11	(12.2%)	93	0	(0.0%)	OR=27.050 (CI: 1.569, 466.317)
Gait disturbance – 91d	Dichotomous	90	4	(4.4%)	93	0	(0.0%)	OR=9.728 (CI: 0.516, 183.346)
headache – 91d	Dichotomous	90	4	(4.4%)	93	3	(3.2%)	OR=1.395 (CI: 0.303, 6.417)
Nausea – 91d	Dichotomous	90	2	(2.2%)	93	5	(5.4%)	OR=0.400 (CI: 0.076, 2.117)
oedema – 91d	Dichotomous	90	5	(5.6%)	93	3	(3.2%)	OR=1.765 (CI: 0.409, 7.612)
Peripheral oedema – 91d	Dichotomous	90	12	(13.3%)	93	10	(10.8%)	OR=1.277 (CI: 0.522, 3.123)
Somnolence – 91d	Dichotomous	90	23	(25.6%)	93	4	(4.3%)	OR=7.638 (CI: 2.522, 23.133)
Weight gain – 91d	Dichotomous	90	8	(8.9%)	93	0	(0.0%)	OR=19.267 (CI: 1.095, 338.955)
facial oedema – 91d	Dichotomous	90	4	(4.4%)	93	2	(2.2%)	OR=2.116 (CI: 0.378, 11.851)
treatment withdrawal:								
due to lack of efficacy – 91d	Dichotomous	90	6	(6.7%)	93	22	(23.7%)	OR=0.231 (CI: 0.089, 0.600)
unspecified/other reason – 91d	Dichotomous	90	4	(4.4%)	93	7	(7.5%)	OR=0.571 (CI: 0.161, 2.023)

poor compliance – 91d	Dichotomous	90	1	(1.1%)		93	0	(0.0%)		OR=3.134 (CI: 0.126, 77.948)

[a] least squares mean
[b] least squares mean; baseline not reported
[c] Described as 'thinking abnormal' in evidence table

		PLACEBO			ALL PREGABALIN DOSAGES			
		N	k	mean	N	k	mean	Δ
patient-reported global improvement:								
PGIC - worse (all grades) or no change – 91d	Dichotomous	93	38	(40.9%)	275	82	(29.8%)	OR=1.626 (CI: 0.999, 2.648)
PGIC - minimally better – 91d	Dichotomous	93	11	(11.8%)	275	48	(17.5%)	OR=0.634 (CI: 0.314, 1.280)
PGIC - at least moderately better – 91d	Dichotomous	93	10	(10.8%)	275	53	(19.3%)	OR=0.505 (CI: 0.245, 1.038)

Comments	-

Definitions of abbreviations are given at the end of this document.

Study	Vestergaard et al. (2001)
Pain category	Central pain
Study design	Country: Denmark Design: Crossover Inclusion criteria: central post stroke pain for more than 3 months where nocioceptive, periphrral neuropathy and psychogenic origin were considered unlikely, pain score of at least 4 on an NRS (11-point), age >18 years Exclusion criteria: dementia or any other cognitive impairment, diabetic neuropathy, malignant disease, recent myocardial infarction, severe heart insufficiency, liver/renal failure, known allergy to lamotrigine, positive hisotry for alcohol o drug abuse, pregnancy or lactation (those of childbearing age were required to use contraception) Study length (days): 133 Intention-to-treat analysis? Yes
Participants	Total number of patients: 30 Number of males: 18 (60.0%) Underlying cause of neuropathic pain: Post-stroke pain Mean duration of NP (in months): 48 Baseline pain severity: 6 (median NRS (median duration of pain and age)) Mean age: 59
Intervention(s)	(1) Lamotrigine 200 mg/d Intervention: lamotrigine Length of treatment (weeks): 8 Fixed/flexible dose regimen: Fixed dose Set dose: 200mg/d

	Notes: dose gradually increased every 2nd week (25 to 50 to 100 to 200 mg/d) (2) placebo Intervention: placebo Length of treatment (weeks): 8 Fixed/flexible dose regimen: Fixed dose
Concomitant treatments	Drug free baseline period? Unclear Concomitant pain treatment allowed? No (no concomitant use of anti-depressants, anti-epileptics or analgesics allowed, use of monamine oxidase inhibitors were not allowed in the last 14 days before the start of the trial; acetylsalicylic acid (300 mg dailly) as an antithrombolytic agent and paracetamol (500mg as needed) were allowed as rescue medication.)
Outcomes measures and effect sizes	

		LAMOTRIGINE 200 MG/D			PLACEBO			
		N	k	mean	N	k	mean	Δ
pain score:								
NRS/NRS Pain – 0d	Continuous	30		med: 6 [rng 4–10]	30		med: 6 [rng 4–10]	
NRS/NRS Pain – 56d	Continuous	30		med: 5	30		med: 7	
major adverse events (defined as leading to withdrawal):								
any major adverse event – 56d	Dichotomous	30	3[a]	(10.0%)	30	0	(0.0%)	OR=7.764 (CI: 0.384, 157.138)
adverse events:								
any adverse event – 56d	Dichotomous	30	17	(56.7%)	30	18	(60.0%)	OR=0.872 (CI: 0.312, 2.435)
moderate to severe – 56d[b]	Dichotomous	30	6	(20.0%)	30	3	(10.0%)	OR=2.250 (CI: 0.507, 9.993)
skin-related side effects – 56d	Dichotomous	30	5[c]	(16.7%)	30	2	(6.7%)	OR=2.800 (CI: 0.498, 15.734)
treatment withdrawal:								
due to lack of efficacy – 56d	Dichotomous	30	1	(3.3%)	30	3	(10.0%)	OR=0.310 (CI: 0.030, 3.168)
protocol deviation – 56d	Dichotomous	30	0	(0.0%)	30	1[d]	(3.3%)	OR=0.322 (CI: 0.013, 8.235)

[a] these were due to mild rash, severe headache and severe pain
[b] considered by investigators to possibly be related to treatment
[c] 2 had rash
[d] patient took concomitant analgesics

Comments	1 patient withdrew consent before randomisation; an additional patient was withdrawn due to protocol violation (for taking concomitant analgesics) but it was not clear which treatment this was associated with (this was discovered by investigators after completion of the trial); authors reported rates of those who they considered responding to treatment (pain scores lower than the corresponding treatment period values): 12 were considered responders in the lamotrigine group, 3 in the placebo group and 11 had no difference in pain scores; rescue medication usage was reported as low in the study and not statistically significantly different between groups (but more data was not reported); there was a 7-day baseline period (patients on other medications were tapered off before the trial - uncertain if this was done before ths 7-day baseline period [this would then be a drug-free baseline period] or during this period)

Definitions of abbreviations are given at the end of this document.

Study	Vinik et al. (2007)
Pain category	Peripheral pain
Study design	Country: USA

	Design: Parallel Inclusion criteria: PDN for at least 6 months but less than 5 years with an average daily pain score of at least 4 on the NRS 11-point Exclusion criteria: severe pain not associated with PDN, pain from mononeuropathy, osteoarthritis of ankle or foot, gout, bursitis or fascitis, pain from proximal diabetic neuropathy, diabetic mononeuropathy or diabetic truncal neuropathy, diffuse peripheral neuropathy from causes other than diabetes, MS or other conditions associated with central neuropathic pain, acupuncutre or nerve blocks for pain relief within 30 days of screening, prior use of lamotrigine Study length (days): 133 Intention-to-treat analysis? Yes
Participants	Total number of patients: 360 Number of males: 195 (54.2%) Underlying cause of neuropathic pain: Painful diabetic neuropathy Mean duration of NP (in months): not reported Baseline pain severity: 6.275 (NRS (average of arm means)) Mean age: 59.9
Intervention(s)	(1) Lamotrigine 200mg/d Intervention: lamotrigine Length of treatment (weeks): 19 Fixed/flexible dose regimen: Fixed dose Set dose: 200mg/d Notes: 7 week dose escalation and 12 week maintenance phase (2) Lamotrigine 300mg/d Intervention: lamotrigine Length of treatment (weeks): 19 Fixed/flexible dose regimen: Fixed dose Set dose: 300mg/d Notes: 7 week dose escalation and 12 week maintenance phase (3) Lamotrigine 400mg/d Intervention: lamotrigine Length of treatment (weeks): 19 Fixed/flexible dose regimen: Fixed dose Set dose: 400mg/d Notes: 7 week dose escalation and 12 week maintenance phase (4) Placebo Intervention: placebo Length of treatment (weeks): 19 Fixed/flexible dose regimen: Fixed dose
Concomitant treatments	Drug free baseline period? No Concomitant pain treatment allowed? Yes (Paracetamol as rescue, gabapentin and anti-depressents allowed; non-drug therapies like nerve blocks, acupunture or other procedures, analgesics and medications with analgesic properties like dextormethorphan were prohibited)

Outcomes measures and effect sizes

		LAMOTRIGINE 200MG/D			PLACEBO			
		N	k	mean	N	k	mean	Δ
pain score:								
at least 30% pain reduction (NRS) – 133d[a]	Dichotomous	90	25	(27.8%)	90	32	(35.6%)	OR=0.688 (CI: 0.343, 1.380)
at least 50% pain reduction (NRS) – 133d[a]	Dichotomous	90	19	(21.1%)	90	23	(25.6%)	OR=0.791 (CI: 0.364, 1.720)
major adverse events (defined as leading to withdrawal):								
any major adverse event – 133d	Dichotomous	90	10	(11.1%)	90	5	(5.6%)	OR=2.125 (CI: 0.696, 6.487)
adverse events:								
Dizziness – 133d	Dichotomous	90	3	(3.3%)	90	2	(2.2%)	OR=1.517 (CI: 0.247, 9.304)
headache	Dichotomous	90	7	(7.8%)	90	3	(3.3%)	OR=2.446 (CI: 0.612, 9.776)
Nausea – 133d	Dichotomous	90	10	(11.1%)	90	4	(4.4%)	OR=2.688 (CI: 0.810, 8.912)
Rash – 133d	Dichotomous	90	13	(14.4%)	90	8	(8.9%)	OR=1.731 (CI: 0.680, 4.404)
treatment withdrawal:								
unspecified/other reason – 133d	Dichotomous	90	31	(34.4%)	90	28	(31.1%)	OR=1.163 (CI: 0.624, 2.169)

[a] calculated from percentages

		LAMOTRIGINE 300MG/D			PLACEBO			
		N	k	mean	N	k	mean	Δ
pain score:								
at least 30% pain reduction (NRS) – 133d[a]	Dichotomous	90	37	(41.1%)	90	32	(35.6%)	OR=1.000 (CI: 0.516, 1.936)
at least 50% pain reduction (NRS) – 133d[a]	Dichotomous	90	28	(31.1%)	90	23	(25.6%)	OR=1.074 (CI: 0.513, 2.247)
major adverse events (defined as leading to withdrawal):								
any major adverse event – 133d	Dichotomous	90	10	(11.1%)	90	5	(5.6%)	OR=2.125 (CI: 0.696, 6.487)
adverse events:								
Dizziness – 133d	Dichotomous	90	8	(8.9%)	90	2	(2.2%)	OR=4.293 (CI: 0.886, 20.808)
headache	Dichotomous	90	19	(21.1%)	90	3	(3.3%)	OR=7.761 (CI: 2.207, 27.287)
Nausea – 133d	Dichotomous	90	4	(4.4%)	90	4	(4.4%)	OR=1.000 (CI: 0.242, 4.128)
Rash – 133d	Dichotomous	90	7	(7.8%)	90	8	(8.9%)	OR=0.864 (CI: 0.300, 2.493)
treatment withdrawal:								
unspecified/other reason – 133d	Dichotomous	90	34	(37.8%)	90	28	(31.1%)	OR=1.344 (CI: 0.725, 2.492)

[a] calculated from percentages

		LAMOTRIGINE 400MG/D			PLACEBO			
		N	k	mean	N	k	mean	Δ
pain score:								
at least 30% pain reduction (NRS) – 133d[a]	Dichotomous	90	25	(27.8%)	90	32	(35.6%)	OR=0.464 (CI: 0.219, 0.984)
at least 50% pain reduction (NRS) – 133d[a]	Dichotomous	90	16	(17.8%)	90	23	(25.6%)	OR=0.419 (CI: 0.171, 1.028)
major adverse events (defined as leading to withdrawal):								
any major adverse event – 133d	Dichotomous	90	15	(16.7%)	90	5	(5.6%)	OR=3.400 (CI: 1.180, 9.801)
adverse events:								
Dizziness – 133d	Dichotomous	90	10	(11.1%)	90	2	(2.2%)	OR=5.500 (CI: 1.170, 25.863)
headache	Dichotomous	90	14	(15.6%)	90	3	(3.3%)	OR=5.342 (CI: 1.479, 19.298)

	Nausea – 133d	Dichotomous	90	9	(10.0%)	90	4	(4.4%)	OR=2.389 (CI: 0.708, 8.061)
	Rash – 133d	Dichotomous	90	11	(12.2%)	90	8	(8.9%)	OR=1.427 (CI: 0.546, 3.734)
	treatment withdrawal:								
	unspecified/other reason – 133d	Dichotomous	90	45	(50.0%)	90	28	(31.1%)	OR=2.214 (CI: 1.205, 4.068)
	[a] calculated from percentages								
Comments	this entry summaries study 1 from this publication; there was a 7 day baseline period								

Definitions of abbreviations are given at the end of this document.

Study	Vinik et al. (2007)
Pain category	Peripheral pain
Study design	Country: USA Design: Parallel Inclusion criteria: PDN for at least 6 months but less than 5 years with an average daily pain score of at least 4 on the NRS 11-point Exclusion criteria: severe pain not associated with PDN, pain from mononeuropathy, osteoarthritis of ankle or foot, gout, bursitis or fascitis, pain from proximal diabetic neuropathy, diabetic mononeuropathy or diabetic truncal neuropathy, diffuse peripheral neuropathy from causes other than diabetes, MS or other conditions associated with central neuropathic pain, acupuncutre or nerve blocks for pain relief within 30 days of screening, prior use of lamotrigine Study length (days): 133 Intention-to-treat analysis? Yes
Participants	Total number of patients: 360 Number of males: 195 (54.2%) Underlying cause of neuropathic pain: Painful diabetic neuropathy Mean duration of NP (in months): not reported Baseline pain severity: 6.225 (NRS (average of arm means)) Mean age: 59.9
Intervention(s)	(1) Lamotrigine 200mg/d Intervention: lamotrigine Length of treatment (weeks): 19 Fixed/flexible dose regimen: Fixed dose Set dose: 200mg/d (2) Lamotrigine 300mg/d Intervention: lamotrigine Length of treatment (weeks): 19 Fixed/flexible dose regimen: Fixed dose Set dose: 300mg/d (3) Lamotrigine 400mg/d Intervention: lamotrigine Length of treatment (weeks): 19

	Fixed/flexible dose regimen: Fixed dose Set dose: 400mg/d (4) Placebo Intervention: placebo Length of treatment (weeks): 19 Fixed/flexible dose regimen: Fixed dose
Concomitant treatments	Drug free baseline period? No Concomitant pain treatment allowed? Yes (gabapentin and anti-depressents allowed; non-drug therapies like nerve blocks, acupuntures or other procedures, analgesics and medications with analgesic properties like dextormethorphan were prohibited; Paracetamol as rescue permitted)
Outcomes measures and effect sizes	

		LAMOTRIGINE 200MG/D			PLACEBO			
		N	k	mean	N	k	mean	Δ
pain score:								
at least 30% pain reduction (NRS) – 133d[a]	Dichotomous	90	32	(35.6%)	90	25	(27.8%)	OR=0.661 (CI: 0.295, 1.478)
at least 50% pain reduction (NRS) – 133d[a]	Dichotomous	90	21	(23.3%)	90	19	(21.1%)	OR=1.091 (CI: 0.481, 2.474)
major adverse events (defined as leading to withdrawal):								
any major adverse event – 133d	Dichotomous	90	10	(11.1%)	90	9	(10.0%)	OR=1.125 (CI: 0.434, 2.915)
adverse events:								
Dizziness – 133d	Dichotomous	90	4	(4.4%)	90	6	(6.7%)	OR=0.651 (CI: 0.177, 2.390)
Nausea – 133d	Dichotomous	90	11	(12.2%)	90	7	(7.8%)	OR=1.651 (CI: 0.610, 4.472)
Rash – 133d	Dichotomous	90	9	(10.0%)	90	8	(8.9%)	OR=1.139 (CI: 0.419, 3.098)
treatment withdrawal:								
unspecified/other reason – 133d	Dichotomous	90	32	(35.6%)	90	32	(35.6%)	OR=1.000 (CI: 0.543, 1.841)

[a] calculated from percentages

		LAMOTRIGINE 300MG/D			PLACEBO			
		N	k	mean	N	k	mean	Δ
pain score:								
at least 30% pain reduction (NRS) – 133d[a]	Dichotomous	90	28	(31.1%)	90	25	(27.8%)	OR=1.149 (CI: 0.553, 2.388)
at least 50% pain reduction (NRS) – 133d[a]	Dichotomous	90	20	(22.2%)	90	19	(21.1%)	OR=1.091 (CI: 0.481, 2.474)
major adverse events (defined as leading to withdrawal):								
any major adverse event – 133d	Dichotomous	90	9	(10.0%)	90	9	(10.0%)	OR=1.000 (CI: 0.378, 2.648)
adverse events:								
Dizziness – 133d	Dichotomous	90	6	(6.7%)	90	6	(6.7%)	OR=1.000 (CI: 0.310, 3.226)
Nausea – 133d	Dichotomous	90	5	(5.6%)	90	7	(7.8%)	OR=0.697 (CI: 0.213, 2.285)
Rash – 133d	Dichotomous	90	10	(11.1%)	90	8	(8.9%)	OR=1.281 (CI: 0.481, 3.412)
treatment withdrawal:								
unspecified/other reason – 133d	Dichotomous	90	32	(35.6%)	90	32	(35.6%)	OR=1.000 (CI: 0.543, 1.841)

[a] calculated from percentages

		LAMOTRIGINE 400MG/D	PLACEBO

			N	k	mean	N	k	mean	Δ
pain score:									
at least 30% pain reduction (NRS) – 133d[a]	Dichotomous		90	27	(30.0%)	90	25	(27.8%)	OR=0.859 (CI: 0.399, 1.846)
at least 50% pain reduction (NRS) – 133d[a]	Dichotomous		90	20	(22.2%)	90	19	(21.1%)	OR=0.911 (CI: 0.391, 2.122)
major adverse events (defined as leading to withdrawal):									
any major adverse event – 133d	Dichotomous		90	15	(16.7%)	90	9	(10.0%)	OR=1.800 (CI: 0.744, 4.357)
adverse events:									
Dizziness – 133d	Dichotomous		90	9	(10.0%)	90	6	(6.7%)	OR=1.556 (CI: 0.530, 4.568)
Nausea – 133d	Dichotomous		90	5	(5.6%)	90	7	(7.8%)	OR=0.697 (CI: 0.213, 2.285)
Rash – 133d	Dichotomous		90	14	(15.6%)	90	8	(8.9%)	OR=1.888 (CI: 0.750, 4.752)
treatment withdrawal:									
unspecified/other reason – 133d	Dichotomous		90	42	(46.7%)	90	32	(35.6%)	OR=1.586 (CI: 0.872, 2.884)

[a] calculated from percentages

Comments	this entry summaries study 2 from this publication;there was a 7 day baseline period

Definitions of abbreviations are given at the end of this document.

Study	Vranken et al. (2008)
Pain category	Central pain
Study design	Country: Holland Design: Parallel Inclusion criteria: Severe neuropathic pain caused by brain and spinal cord injuries for at least 6 months, with a pain score of at least 60mm on a VAS 100mm Exclusion criteria: pregnancy, history of intolerance, hypersensitivity or known allergy tp pregabalin, known history of significant heaptic, renal or spychiatric disorder, hisotry of galactose intolerance, lactase deficieincy, glucose-galactose malabsorption, < 60ml/min creatinine clearnace Study length (days): 28 Intention-to-treat analysis? Yes
Participants	Total number of patients: 40 Number of males: 19 (47.5%) Underlying cause of neuropathic pain: Central pain Mean duration of NP (in months): not reported Baseline pain severity: 7.5 (VAS (average of means)) Mean age: 54.45
Intervention(s)	(1) Pregabalin (flexible dose) Intervention: pregabalin Length of treatment (weeks): 4 Fixed/flexible dose regimen: Flexible dose Range: 150–600

	Notes: titrated at 3-day intervals (150, 300 or 600 mg/d with 1, 2 or 4 daily capsules) (2) Placebo Intervention: placebo Length of treatment (weeks): 4 Fixed/flexible dose regimen: Flexible dose
Concomitant treatments	Drug free baseline period? No Concomitant pain treatment allowed? Yes (Opioids, anti-depressants, NSAIDs if stable for at least 90 days before study)
Outcomes measures and effect sizes	

		PREGABALIN (FLEXIBLE DOSE)			PLACEBO			
		N	k	mean	N	k	mean	Δ
pain score:								
VAS – 0d	Continuous	20		7.6 (SD 0.8)	20		7.4 (SD 1)	
VAS – 28d	Continuous	20		5.1 (SD 2.9)	20		7.3 (SD 2)	MD=-2.180 (CI: -3.795, -0.565)
major adverse events (defined as leading to withdrawal):								
any major adverse event – 28d	Dichotomous	20	3	(15.0%)	20	3	(15.0%)	OR=1.000 (CI: 0.176, 5.673)
adverse events:								
Cognitive impairment – 28d[a]	Dichotomous	20	6	(30.0%)	20	8	(40.0%)	OR=0.643 (CI: 0.174, 2.381)
Confusion	Dichotomous	20	7	(35.0%)	20	4	(20.0%)	OR=2.154 (CI: 0.515, 9.000)
Dizziness – 28d	Dichotomous	20	7	(35.0%)	20	6	(30.0%)	OR=1.256 (CI: 0.334, 4.733)
Nausea – 28d	Dichotomous	20	6	(30.0%)	20	4	(20.0%)	OR=1.714 (CI: 0.400, 7.340)
Peripheral oedema – 28d	Dichotomous	20	1	(5.0%)	20	4	(20.0%)	OR=0.211 (CI: 0.021, 2.079)
Somnolence – 28d	Dichotomous	20	9	(45.0%)	20	9	(45.0%)	OR=1.000 (CI: 0.288, 3.476)
overall improvement in quality of life:								
SF36 Mental – 0d	Continuous	20		67.5 (SD 19.2)	20		63.2 (SD 22)	
SF36 Mental – 28d	Continuous	20		70.3 (SD 18.8)	20		62 (SD 21.3)	MD=8.300 (CI: -4.151, 20.751)
SF36 Physical – 0d	Continuous	20		31.5 (SD 21.4)	20		30.5 (SD 23.8)	
SF36 Physical – 28d	Continuous	20		34 (SD 23.4)	20		30 (SD 23.5)	MD=4.000 (CI: -10.534, 18.534)
EQ-5D - health status index – 0d	Continuous	20		0.28 (SD 0.32)	20		0.16 (SD 0.34)	
EQ-5D - health status index – 28d	Continuous	20		med: 0.59[b]	20		med: 0.06[c]	
EQ-5D - health status VAS – 0d	Continuous	20		60.4 (SD 17)	20		50.1 (SD 19.7)	
EQ-5D - health status VAS – 28d	Continuous	20		65.7 (SD 17)	20		37.8 (SD 18.5)	MD=27.900 (CI: 16.889, 38.911)
treatment withdrawal:								
due to lack of efficacy – 28d	Dichotomous	20	0	(0.0%)	20	1	(5.0%)	OR=0.317 (CI: 0.012, 8.260)

[a] study reported 'cognitive performance' as adverse event
[b] instead of dispersion, IQR was reported (0.52, 0.67)
[c] instead of dispersion, IQR was reported (-0.17, 0.57)

Comments	those on gabapentin had to discontinue use at least 3 days before the start of the study

Definitions of abbreviations are given at the end of this document.

Study	Vranken et al. (2011)
Pain category	Central pain
Study design	Country: Holland

	Design: Parallel Inclusion criteria: Participants with neuropathic pain caused by spinal cord injury at least 6 months, at least 18 years of age and VAS scale of 6 and higher Exclusion criteria: pregnancy, history of intolerance, hypersensitivity or known allergy to duloxetine, known history of significant hepatic, renal or psychiatric disorder, use of antidepressants for treatment of depression Study length (days): 56 Intention-to-treat analysis? Yes
Participants	Total number of patients: 48 Number of males: not reported Underlying cause of neuropathic pain: Spinal cord injury pain Mean duration of NP (in months): not reported Baseline pain severity: 7.15 (VAS (average of arm means)) Mean age: not reported
Intervention(s)	(1) Duloxetine flexi Intervention: duloxetine Length of treatment (weeks): 8 Fixed/flexible dose regimen: Flexible dose Mean dose: 99.1mg/d (SD: 29.2) Range: 60–120 Notes: Patients received either 60 or 120 mg/d; mean usage at end of study was 99.1 mg (29.2) (2) Placebo Intervention: placebo Length of treatment (weeks): 8 Fixed/flexible dose regimen: Flexible dose
Concomitant treatments	Drug free baseline period? No Concomitant pain treatment allowed? Yes (Oral medication for pain were allowed if neuropathic pain treatment was on a stable regimen at least 6 weeks before study. Anti-depressants discontinued for 30 days prior to starting study. No new analgesic treatment alllowed during study.)

Outcomes measures and effect sizes

		DULOXETINE FLEXI			PLACEBO			
		N	k	mean	N	k	mean	Δ
pain score:								
VAS – 0d[a]	Continuous	24		7.1 (SD 0.8)	24		7.2 (SD 0.8)	
VAS – 28d[b]	Continuous	24		5.3 (SD 2)	24		5.9 (SD 2.1)	MD=-0.600 (CI: -1.760, 0.560)
VAS – 56d[a]	Continuous	24		5 (SD 2)	24		6.1 (SD 1.7)	MD=-1.100 (CI: -2.150, -0.050)
patient-reported global improvement:								
PGIC - much worse – 56d	Dichotomous	24	0	(0.0%)	24	0	(0.0%)	OR=1.000 (CI: 0.019, 52.443)
PGIC - moderately worse – 56d	Dichotomous	24	1	(4.2%)	24	0	(0.0%)	OR=3.128 (CI: 0.121, 80.684)
PGIC - minimally worse – 56d	Dichotomous	24	1	(4.2%)	24	4	(16.7%)	OR=0.217 (CI: 0.022, 2.108)
PGIC - no change – 56d	Dichotomous	24	10	(41.7%)	24	16	(66.7%)	OR=0.357 (CI: 0.110, 1.156)
PGIC - minimally better – 56d	Dichotomous	24	6	(25.0%)	24	4	(16.7%)	OR=1.667 (CI: 0.404, 6.870)
PGIC - moderately better – 56d	Dichotomous	24	4	(16.7%)	24	0	(0.0%)	OR=10.756 (CI: 0.546, 211.777)

	PGIC - at least moderately better – 56d	Dichotomous	24	5	(20.8%)	24	0	(0.0%)	OR=13.821 (CI: 0.719, 265.518)
	PGIC - much better – 56d	Dichotomous	24	1	(4.2%)	24	0	(0.0%)	OR=3.128 (CI: 0.121, 80.684)
	adverse events:								
	Confusion – 56d	Dichotomous	24	3	(12.5%)	24	0	(0.0%)	OR=7.977 (CI: 0.390, 163.333)
	Constipation – 56d	Dichotomous	24	0	(0.0%)	24	2	(8.3%)	OR=0.184 (CI: 0.008, 4.036)
	Dizziness – 56d	Dichotomous	24	4	(16.7%)	24	2	(8.3%)	OR=2.200 (CI: 0.363, 13.338)
	Dry mouth – 56d	Dichotomous	24	1	(4.2%)	24	0	(0.0%)	OR=3.128 (CI: 0.121, 80.684)
	headache – 56d	Dichotomous	24	3	(12.5%)	24	2	(8.3%)	OR=1.571 (CI: 0.238, 10.365)
	nausea/vomiting – 56d	Dichotomous	24	5	(20.8%)	24	2	(8.3%)	OR=2.895 (CI: 0.503, 16.674)
	Somnolence – 56d	Dichotomous	24	12	(50.0%)	24	2	(8.3%)	OR=11.000 (CI: 2.104, 57.504)
	urination difficulties – 56d	Dichotomous	24	2[c]	(8.3%)	24	0[d]	(0.0%)	OR=5.444 (CI: 0.248, 119.632)
	overall improvement in quality of life:								
	SF36 Mental – 0d	Continuous	24		68 (SD 17)	24		72 (SD 19)	
	SF36 Mental – 56d	Continuous	24		73 (SD 19)	24		73 (SD 19)	MD=0.000 (CI: -10.750, 10.750)
	SF36 Physical – 0d	Continuous	24		39 (SD 25)	24		38 (SD 28)	
	SF36 Physical – 56d	Continuous	24		41 (SD 27)	24		39 (SD 25)	MD=2.000 (CI: -12.721, 16.721)
	EQ-5D - health status index – 0d	Continuous	24		0.36 (SD 0.33)	24		0.24 (SD 0.3)	
	EQ-5D - health status index – 56d	Continuous	24		4 (SD 0.31)	24		0.37 (SD 0.34)	MD=3.630 (CI: 3.446, 3.814)
	EQ-5D - health status VAS – 0d	Continuous	24		63 (SD 18)	24		56 (SD 18)	
	EQ-5D - health status VAS – 56d	Continuous	24		59 (SD 21)	24		53 (SD 17)	MD=6.000 (CI: -4.809, 16.809)
	treatment withdrawal:								
	due to lack of efficacy – 56d	Dichotomous	24	1	(4.2%)	24	0	(0.0%)	OR=3.128 (CI: 0.121, 80.684)
	unspecified/other reason – 56d	Dichotomous	24	3	(12.5%)	24	1	(4.2%)	OR=3.286 (CI: 0.317, 34.083)

[a] denominators not reported for this outcome but assumed as ITT
[b] estimated from graph; denominators not reported for this outcome but assumed as ITT
[c] study reported 'micturition'
[d] study reported 'miction'

Comments	-

Definitions of abbreviations are given at the end of this document.

Study	Vrethem et al. (1997)
Pain category	Peripheral pain
Study design	Country: Sweden Design: Crossover Inclusion criteria: polyneuropathy for at least 6 months with no signs of central, nocioceptive or psychogenic pain (polyneuropathy diagnosis required at least 2 of: distal sensory impairment, distal bilateral msucle weakness or atrophy, bileateral decrease or loss of tendon reflexes Exclusion criteria: patients with other neurologic diseases Study length (days): 98 Intention-to-treat analysis? No
Participants	Total number of patients: 37 Number of males: 17 (45.9%) Underlying cause of neuropathic pain: Polyneuropathy Mean duration of NP (in months): 48

	Baseline pain severity: 4.55 (VRS-10-step (average of arm means - diabetic patients had mean 5.0 [1.4] score and non-diabetic patients had 4.1[1.9]) (pain duration is median value)) Mean age: 61
Intervention(s)	(1) Amitriptyline 75 mg/d Intervention: amitriptyline Length of treatment (weeks): 4 Fixed/flexible dose regimen: Fixed dose Set dose: 75mg/d Notes: days 1-3: 25 mg/d, 4-6: 50 mg/d, from day 7: 75 mg/d (2) placebo (lactose) Intervention: placebo Length of treatment (weeks): 4 Fixed/flexible dose regimen: Fixed dose
Concomitant treatments	Drug free baseline period? Unclear Concomitant pain treatment allowed? Yes (appears concomitant drugs were used by some)
Outcomes measures and effect sizes	

		AMITRIPTYLINE 75 MG/D			PLACEBO (LACTOSE)			
		N	k	mean	N	k	mean	Δ
patient-reported improvement in daily physical and emotional functioning, including sleep:								
Better sleep – 28d	Dichotomous	35	11[a]	(31.4%)	33	4	(12.1%)	OR=3.323 (CI: 0.937, 11.782)
major adverse events (defined as leading to withdrawal):								
any major adverse event – 28d	Dichotomous	35	3[b]	(8.6%)	33	0	(0.0%)	OR=7.215 (CI: 0.358, 145.247)
adverse events:								
any adverse event – 28d	Dichotomous	35	24[c]	(68.6%)	33	6[d]	(18.2%)	OR=9.818 (CI: 3.151, 30.594)
Dry mouth – 28d	Dichotomous	35	12[e]	(34.3%)	33	2[f]	(6.1%)	OR=8.087 (CI: 1.647, 39.702)
hyperglycaemia – 28d	Dichotomous	35	1[g]	(2.9%)	33	0	(0.0%)	OR=2.913 (CI: 0.115, 74.063)
Nausea – 28d	Dichotomous	35	1[h]	(2.9%)	33	0	(0.0%)	OR=2.913 (CI: 0.115, 74.063)
Sedation – 28d	Dichotomous	35	12[i]	(34.3%)	33	3[j]	(9.1%)	OR=5.217 (CI: 1.317, 20.673)
tachycardia – 28d	Dichotomous	35	0	(0.0%)	33	0	(0.0%)	OR=0.944 (CI: 0.018, 48.924)
Urine retention – 28d	Dichotomous	35	1[k]	(2.9%)	33	0	(0.0%)	OR=2.913 (CI: 0.115, 74.063)
urticaria – 28d	Dichotomous	35	0	(0.0%)	33	0	(0.0%)	OR=0.944 (CI: 0.018, 48.924)
vertigo – 28d	Dichotomous	35	7[l]	(20.0%)	33	1[h]	(3.0%)	OR=8.000 (CI: 0.926, 69.078)
diabetes								
pain score:								
VRS – 0d[m]	Continuous	17		5.3 (SD 1.4)	17		5.3 (SD 1.4)	
VRS – 28d[n]	Continuous	17		3.65 (SD 1.7)	17		5.5 (SD 1.55)	MD=-1.850 (CI: -2.945, -0.755)
no diabetes								
pain score:								
VRS – 0d[m]	Continuous	17		4.3 (SD 1.76)	17		4.3 (SD 1.76)	
VRS – 28d[n]	Continuous	16		3.55 (SD 1.96)	16		3.85 (SD 2.16)	MD=-0.300 (CI: -1.726, 1.126)

[a] 2 with better sleep did not have better pain relief

	[b] due to hyperglycaemia, severe thirst and urinary retention [c] 17 mild, 4 moderate, 3 severe [d] 4 mild, 2 moderate [e] 10 were mild, 2 moderate [f] 1 was mild [g] severe (not directly related to the treatment but could have been caused by lethargy and slight confusion which made the patient forget her insulin treatment) [h] mild [i] 10 mild, 2 moderate [j] 2 mild, 1 moderate [k] severe [l] 5 mild, 2 moderate [m] measured as daily verbal assessment; average of morning and evening scores [n] measured as daily verbal assessment; average of morning and evening scores taken over the last week (days 22 to 28)
Comments	19 patients were diabetic; 1 patient with severe depression was excluded and treated by a psychiatrist and another discontinued the study after taking only one dose (but it was not clear what treatment the patient was receiving at the time of withdrawal); authors considered at least 20% pain reduction a response to treatment

Definitions of abbreviations are given at the end of this document.

Study	Wade et al. (2004)
Pain category	Central pain
Study design	Country: UK Design: Parallel Inclusion criteria: clinically confirmed MS of any type (undertaken through history, full examination, and full review of hospital notes) that is stable over the preceeding 4 weeks with no relapse (confirmed clinically on study entry) and be on stable regular medication for the past 4 weeks; participants included for pain as the primary symptom were required to have pain that was not obviously musculoskeletal and was at least 50% of maximal severity on a VAS Exclusion criteria: current or past history of drug or alcohol abuse, significant psychiatric illness other than depression associated with MS, serious cardiovascular disorder, significant renal or hepatic impairment or history of epilepsy, planned visit abroad during the active study Study length (days): - Intention-to-treat analysis? Unclear
Participants	Total number of patients: 37 Number of males: not reported Underlying cause of neuropathic pain: MS neuropathic pain Mean duration of NP (in months): not reported Baseline pain severity: not reported ((data on patient demographics is from all 160 patients included in the study with various primary symptoms including pain, tremor, bladder control, spasticity, and spasm)) Mean age: 50.7
Intervention(s)	(1) Sativex pump action spray flexible dose Intervention: cannabis sativa extract Length of treatment (weeks): 6 Fixed/flexible dose regimen: Flexible dose

	Range: 2.5–120 Notes: 2.7 mg THC and 2.5 mg CBD with each spray; contained peppermint flavour and colouring to disguise the taste and appearance of CBME; participants titrated individually and recorded the number of doses they tried in a diary (increments were no more than 120 mg THC and 120 mg CBD per day with no more than 20 mg of each in any 3-hour period); average dose of the subgroup with pain as the primary symptom was not clear (2) Placebo spray flexible dose Intervention: placebo Length of treatment (weeks): 6 Fixed/flexible dose regimen: Flexible dose Notes: contained peppermint flavour and colouring as the active treatment did to disguise the taste and appearance of CBME
Concomitant treatments	Drug free baseline period? No Concomitant pain treatment allowed? Yes (Sativex was taken as adjuvant treatment so patients were asked to continue on concomitant medication)
Outcomes measures and effect sizes	

		SATIVEX PUMP ACTION SPRAY FLEXIBLE DOSE			PLACEBO SPRAY FLEXIBLE DOSE			
		N	k	mean	N	k	mean	Δ
pain score: VAS – 35d[a]	Mean difference from baseline to average f-u	18		-9.83	19		-19.9	MD=10.040 (CI: -6.522, 26.602)

[a] from baseline to last 2 weeks of treatment (so average of weeks 4 to 6 [5 weeks] chosen as endpoint)(dispersion available from inter-arm data only)

Comments	This study has been included, despite the fact that it includes patients with MS with symptoms other than neuropathic pain as the randomisation was stratified by primary MS symptom and results are also separated by symptom. Authors stated that caution was exercised for those taking drugs metabolized by certain cytochrome P450 enzymes such as tricyclic antidepressants and anticonvulsants. Patients were assessed for eligibility after a 2-week baseline period. Other outcomes were reported in the study (including affect on sleep, Beck's Depression Index, safety data, and others) but they have not been extracted as the summary of results included patients with primary symptoms other than pain from MS.

Definitions of abbreviations are given at the end of this document.

Study	Watson & Evans (1992)
Pain category	Peripheral pain
Study design	Country: Canada Design: Parallel Inclusion criteria: Neuropathic post mastectomy pain for more than 3 months with at least moderate or severe pain for at least one half of the day Exclusion criteria: open skin lesionsi n area of pain, other skin conditions in the affected area, severe depression with voiced suicidal intent, another unrelated significant pain problem Study length (days): 42 Intention-to-treat analysis? No
Participants	Total number of patients: 25 Number of males: 0 (0.0%) Underlying cause of neuropathic pain: Post-surgical pain after surgery for cancer

	Mean duration of NP (in months): 48 Baseline pain severity: 59.95 (VAS (average of arm means)) Mean age: 58
Intervention(s)	(1) Capsaicin 0.075% 4x per day Intervention: capsaicin cream Length of treatment (weeks): 6 Fixed/flexible dose regimen: Fixed dose (2) Placebo Intervention: placebo Length of treatment (weeks): 6 Fixed/flexible dose regimen: Fixed dose
Concomitant treatments	Drug free baseline period? No Concomitant pain treatment allowed? Yes (Participants could continue with previous analgesics if needed but no topical agents)

Outcomes measures and effect sizes

		CAPSAICIN 0.075% 4X PER DAY			PLACEBO			
		N	k	mean	N	k	mean	Δ
pain score:								
VAS – 0d	Continuous	13		59.9 (SD 17.1)	10		60 (SD 16.2)	
VAS – 42d	Mean change	12		-17.8 (SD 24.8)	10		-9.6 (SD 25)	MD=-8.200 (CI: -29.084, 12.684)
patient-reported global improvement:								
at least 50% improvement in global ratings of pain status – 42d	Dichotomous	14	8	(57.1%)	11	3	(27.3%)	OR=3.556 (CI: 0.651, 19.412)
major adverse events (defined as leading to withdrawal):								
any major adverse event – 42d	Dichotomous	14	1	(7.1%)	11	0	(0.0%)	OR=2.556 (CI: 0.095, 68.999)
adverse events:								
Burning pain – 42d	Dichotomous	14	12	(85.7%)	11	1	(9.1%)	OR=60.000 (CI: 4.718, 763.007)
treatment withdrawal:								
unspecified/other reason – 42d	Dichotomous	14	1	(7.1%)	11	1	(9.1%)	OR=0.769 (CI: 0.043, 13.866)

Comments	-

Definitions of abbreviations are given at the end of this document.

Study	Watson et al. (1993)
Pain category	Peripheral pain
Study design	Country: USA & Canada Design: Parallel Inclusion criteria: Participants aged 18 and over with PHN for at least 6 months who had been poorly or incompletely controlled with oral analgesics,

	antidepressants or anticonvulsants Exclusion criteria: Pregnant or lactating women, patients with other skin conditions in the dermatome areas of skin affected by PHN Study length (days): 42 Intention-to-treat analysis? No
Participants	Total number of patients: 143 Number of males: 90 (62.9%) Underlying cause of neuropathic pain: Post-herpetic neuralgia Mean duration of NP (in months): 32.2 Baseline pain severity: not reported (actual values not reported (9% in capsaicin and 10% in placebo had very severe initial pain severity while 91% and 90% in these groups, respectively, had moderate/severe initial pain severity)) Mean age: 70.8
Intervention(s)	(1) Capasaicin 0.075% applied 4 times per day Intervention: capsaicin cream Length of treatment (weeks): 6 Fixed/flexible dose regimen: Fixed dose (2) Placebo Intervention: placebo Length of treatment (weeks): 6 Fixed/flexible dose regimen: - Notes: unclear if placebo was active or not
Concomitant treatments	Drug free baseline period? No Concomitant pain treatment allowed? Yes (Previous oral medications for pain (topical excluded); however, 6 patients were excluded because they received concomitant psychoactive medication (this was not reported as exclusion criteria))
Outcomes measures and effect sizes	

		CAPASAICIN 0.075% APPLIED 4 TIMES PER DAY			PLACEBO			
		N	k	mean	N	k	mean	Δ
major adverse events (defined as leading to withdrawal):								
any major adverse event – 42d	Dichotomous	74	18	(24.3%)	69	2	(2.9%)	OR=10.768 (CI: 2.395, 48.420)
adverse events:								
asthenia	Dichotomous	74	3	(4.1%)	69	0	(0.0%)	OR=6.804 (CI: 0.345, 134.164)
Burning pain – 42d	Dichotomous	74	45	(60.8%)	69	23	(33.3%)	OR=3.103 (CI: 1.565, 6.153)
Diarrhoea	Dichotomous	74	0	(0.0%)	69	2	(2.9%)	OR=0.181 (CI: 0.009, 3.842)
Dizziness – 42d	Dichotomous	74	1	(1.4%)	69	0	(0.0%)	OR=2.837 (CI: 0.114, 70.811)
headache	Dichotomous	74	2	(2.7%)	69	0	(0.0%)	OR=4.793 (CI: 0.226, 101.628)
Infection	Dichotomous	74	2	(2.7%)	69	0	(0.0%)	OR=4.793 (CI: 0.226, 101.628)

	Nausea – 42d	Dichotomous	74	2	(2.7%)	69	0	(0.0%)	OR=4.793 (CI: 0.226, 101.628)
	Pain lasting over 12 months								
	pain score: VAS – 28d[a]	Percentage change from baseline			21.5			1.1	MD=20.400
	VAS – 42d[a]	Percentage change from baseline			15			5.2	MD=9.800
	Pain lasting over 6 months								
	pain score: VAS – 28d[a]	Percentage change from baseline			21.8			9	MD=12.800
	VAS – 42d[a]	Percentage change from baseline			20.9			5.8	MD=15.100
	[a] Ns for each arm unclear. Dispersion not reported								
Comments	all topical medications were stopped 7 days before the trial started								

Definitions of abbreviations are given at the end of this document.

Study	Watson et al. (1998)
Pain category	Peripheral pain
Study design	Country: Canada Design: Crossover Inclusion criteria: PHN of more than 3 months duration, with pain of at least moderate severity for at least one-half of the day, no evidence of impaired ability to attend weekly visits or communicate to deal with outcome measures Exclusion criteria: cardiac disease, seizure disorder, severe depression with voiced suicidal intent requiring urgent management, another significant pain problem, alcoholism, previous brain damage caused by head injury, stroke or other causes Study length (days): 70 Intention-to-treat analysis? Unclear
Participants	Total number of patients: 33 Number of males: not reported Underlying cause of neuropathic pain: Post-herpetic neuralgia Mean duration of NP (in months): 13 Baseline pain severity: not reported (not reported (pain duration is median)) Mean age: not reported
Intervention(s)	(1) Amitriptyline flexible dose Intervention: amitriptyline Length of treatment (weeks): 5 Fixed/flexible dose regimen: Flexible dose Range: 10–160 Notes: stable dosage in last 2 weeks (dosages started at 20 mg/d but at 10 mg/d if aged > 65 years); actual dosage unclear - responders (n = 18

	amitriptyline, 17 nortriptyline) had mean 58.09 mg/d (on either drug) while non-responders (13 amitriptyline, 14 nortriptyline) had mean 68.57 mg/d (on either drug) (2) Nortriptyline flexible dose Intervention: nortriptyline Length of treatment (weeks): 5 Fixed/flexible dose regimen: Flexible dose Range: 10–160 Notes: stable dosage in last 2 weeks (dosages started at 20 mg/d but at 10 mg/d if aged > 65 years); actual dosage unclear - responders (n = 18 amitriptyline, 17 nortriptyline) had mean 58.09 mg/d while non-responders (13 amitriptyline, 14 nortriptyline) had mean 68.57 mg/d
Concomitant treatments	Drug free baseline period? Yes (duration: 21d) Concomitant pain treatment allowed? Unclear (anti-depressants and neuroleptic therapy were withdrawn in first 3 week period but patients were allowed to continue with use of analgesics as needed during the trial as they had previously and this was reported daily (but it is unclear if these other analgesics would be concomitant medications or rescue medications))
Outcomes measures and effect sizes	

		AMITRIPTYLINE FLEXIBLE DOSE			NORTRIPTYLINE FLEXIBLE DOSE			
		N	k	mean	N	k	mean	Δ
adverse events:								
Constipation – 35d	Dichotomous	33	10	(30.3%)	33	14	(42.4%)	OR=0.590 (CI: 0.214, 1.626)
dizziness or vertigo – 35d	Dichotomous	33	3	(9.1%)	33	1	(3.0%)	OR=3.200 (CI: 0.315, 32.475)
Drowsiness – 35d	Dichotomous	33	4	(12.1%)	33	6	(18.2%)	OR=0.621 (CI: 0.158, 2.441)
Dry mouth – 35d	Dichotomous	33	28	(84.8%)	33	26	(78.8%)	OR=1.508 (CI: 0.425, 5.346)
headache – 35d	Dichotomous	33	3	(9.1%)	33	3	(9.1%)	OR=1.000 (CI: 0.187, 5.357)
lethargy or fatigue – 35d	Dichotomous	33	1	(3.0%)	33	2	(6.1%)	OR=0.484 (CI: 0.042, 5.617)
Nausea – 35d	Dichotomous	33	1	(3.0%)	33	0	(0.0%)	OR=3.092 (CI: 0.121, 78.704)
Weight gain – 35d	Dichotomous	33	2	(6.1%)	33	0	(0.0%)	OR=5.317 (CI: 0.246, 115.132)

Comments	Actual efficacy data not reported: authors stated that there was no significant difference in VAS pain scores between treatment groups and VAS scores generally decreased over time, VAS for sleep showed increasing and equal effect in both groups, no difference in concomitant rescue analgesic usage; study started with a 3-week period where patietns were withdrawn from antidepressants or neuroleptic therapy but it is unclear how long patients were actually drug-free before they started treatment)

Definitions of abbreviations are given at the end of this document.

Study	Webster et al. (2010)
Pain category	Peripheral pain
Study design	Country: USA Design: Parallel Inclusion criteria: Aged 18 and over with a diagnosis of PHN and an average NPRS score of 3-9 (inclusive) were eligible if at least 3 months had elapsed since vesicle crusting Exclusion criteria: Pain at or around facial area Study length (days): 84

	Intention-to-treat analysis? Yes
Participants	Total number of patients: 155 Number of males: 72 (46.5%) Underlying cause of neuropathic pain: Post-herpetic neuralgia Mean duration of NP (in months): 36 Baseline pain severity: 5.35 (NRS (average of arm means)) Mean age: 70
Intervention(s)	(1) Capasaicin 8% single patch (60 minutes only) Intervention: capsaicin patch Length of treatment (weeks): Fixed/flexible dose regimen: Fixed dose Notes: Study reports 8% capsaicin patch, applied for 60 minutes once then removed (topical anaesthetic cream applied 60 mins before patches) (2) Placebo patch applied for 60 minutes only Intervention: placebo Length of treatment (weeks): Fixed/flexible dose regimen: Fixed dose Notes: 1 hr then removed (topical anaesthetic cream applied 60 mins before patches)
Concomitant treatments	Drug free baseline period? No Concomitant pain treatment allowed? Yes (patients on any chronic pain medications had to be on stable dosages for at least 21 days before study patch application (but this was limited to only 25% of patients on concomitant drugs at study entry); however any topically applied pain medication to the affected area within 21 days before application of study patch was exclusion criteria; use of opioid medication that was not orally or transdermally administered or exceeded total dose of 60 mg/d morphine were excluded; paracetamol up to 2g/d allowed as rescue medication)
Outcomes measures and effect sizes	

		CAPASAICIN 8% SINGLE PATCH (60 MINUTES ONLY)			PLACEBO PATCH APPLIED FOR 60 MINUTES ONLY			
		N	k	mean	N	k	mean	Δ
pain score:								
NRS/NRS Pain – 0d[a]	Continuous	102		5.4 (SD 1.62)	53		5.3 (SD 1.6)	
NRS/NRS Pain – 28d[b]	Percentage change from baseline	102		-37 (SD 40.4)	53		-29 (SD 32.8)	MD=-8.000 (CI: -19.801, 3.801)
NRS/NRS Pain – 35d[c]	Mean difference from baseline to average f-u	102		-1.8 (SD 2.02)	53		-1.6 (SD 1.97)	MD=-0.200 (CI: -0.859, 0.459)
NRS/NRS Pain – 49d[d]	Mean difference from baseline to average f-u	102		-1.8 (SD 2.02)	53		-1.6 (SD 1.97)	MD=-0.200 (CI: -0.859, 0.459)
NRS/NRS Pain – 56d[b]	Percentage change from baseline	102		-37.5 (SD 40.4)	53		-33.5 (SD 43.7)	MD=-4.000 (CI: -18.134, 10.134)
NRS/NRS Pain – 84d[b]	Percentage change from baseline	102		-36.5 (SD 22.7)	53		-39 (SD 29.1)	MD=2.500 (CI: -6.495, 11.495)
at least 30% pain reduction (NRS) – 84d	Dichotomous	102	50	(49.0%)	53	26	(49.1%)	OR=0.999 (CI: 0.514, 1.939)
at least 50% pain reduction (NRS) – 84d	Dichotomous	102	40	(39.2%)	53	19	(35.8%)	OR=1.154 (CI: 0.580, 2.297)

patient-reported global improvement:									
PGIC - worse (all grades) or no change – 28d	Dichotomous	102	60	(58.8%)	53	30	(56.6%)	OR=1.095 (CI: 0.560, 2.143)
PGIC - worse (all grades) or no change – 56d	Dichotomous	102	48	(47.1%)	53	29	(54.7%)	OR=0.736 (CI: 0.378, 1.432)
PGIC - worse (all grades) or no change – 84d	Dichotomous	102	54	(52.9%)	53	35	(66.0%)	OR=0.579 (CI: 0.291, 1.152)
PGIC - better (all grades) – 28d	Dichotomous	102	40	(39.2%)	53	19	(35.8%)	OR=1.154 (CI: 0.580, 2.297)
PGIC - better (all grades) – 56d	Dichotomous	102	43	(42.2%)	53	14	(26.4%)	OR=2.030 (CI: 0.982, 4.197)
PGIC - better (all grades) – 84d	Dichotomous	102	41	(40.2%)	53	15	(28.3%)	OR=1.703 (CI: 0.831, 3.487)
major adverse events (defined as leading to withdrawal):								
any major adverse event – 84d	Dichotomous	102	0	(0.0%)	53	0	(0.0%)	OR=0.522 (CI: 0.010, 26.673)
adverse events:								
any adverse event – 84d	Dichotomous	102	76	(74.5%)	53	28	(52.8%)	OR=2.610 (CI: 1.297, 5.252)
Burning pain – 84d	Dichotomous	102	3	(2.9%)	53	0	(0.0%)	OR=3.764 (CI: 0.191, 74.232)
Dizziness – 84d	Dichotomous	102	1	(1.0%)	53	3	(5.7%)	OR=0.165 (CI: 0.017, 1.627)
Infection – 84d	Dichotomous	102	16	(15.7%)	53	8	(15.1%)	OR=1.047 (CI: 0.416, 2.632)
Pruritus – 84d	Dichotomous	103	17	(16.5%)	53	6	(11.3%)	OR=1.548 (CI: 0.572, 4.194)
Rash – 84d[e]	Dichotomous	103	4	(3.9%)	53	0	(0.0%)	OR=4.839 (CI: 0.256, 91.590)
treatment withdrawal:								
due to lack of efficacy – 84d	Dichotomous	102	3	(2.9%)	53	7	(13.2%)	OR=0.199 (CI: 0.049, 0.805)
unspecified/other reason – 84d	Dichotomous	102	3	(2.9%)	53	1	(1.9%)	OR=1.576 (CI: 0.160, 15.528)
lost to follow-up – 84d	Dichotomous	102	5	(4.9%)	53	0	(0.0%)	OR=6.036 (CI: 0.327, 111.266)
poor compliance – 84d	Dichotomous	102	0	(0.0%)	53	2	(3.8%)	OR=0.100 (CI: 0.005, 2.132)
Patients with >6 months PHN duration								
pain score:								
NRS/NRS Pain – 0d[a]	Continuous	86		5.4 (SD 1.72)	43		5.2 (SD 1.75)	
NRS/NRS Pain – 35d[c]	Mean difference from baseline to average f-u	86		-1.8 (SD 2.02)	43		-1.4 (SD 2.11)	MD=-0.400 (CI: -1.162, 0.362)
NRS/NRS Pain – 49d[d]	Mean difference from baseline to average f-u	86		-1.8 (SD 2.02)	43		-1.3 (SD 2.04)	MD=-0.500 (CI: -1.244, 0.244)
at least 30% pain reduction (NRS) – 84d	Dichotomous	86	43	(50.0%)	43	19	(44.2%)	OR=1.263 (CI: 0.605, 2.636)
at least 50% pain reduction (NRS) – 84d	Dichotomous	86	34	(39.5%)	43	12	(27.9%)	OR=1.689 (CI: 0.763, 3.738)

[a] least squares mean
[b] percentage change from baseline; estimated from graph

	[c] least squares mean; baseline to weeks 2 to 8 [d] least squares mean; baseline to weeks 2 to 12 [e] described as site erythema in paper
Comments	-

Definitions of abbreviations are given at the end of this document.

Study	Webster et al. (2010)
Pain category	Peripheral pain
Study design	Country: USA Design: Parallel Inclusion criteria: Aged 18 and over with a diagnosis of PHN and an average NPRS score of 3-9 (inclusive) were eligible if at least 6 months had elapsed since vesicle crusting Exclusion criteria: Use of any toipcally applied pain medication on the painful area within 21 days of treatment; current use of any investigational drug or class I anti-arrhythmic drug, uncontrolled diabetes mellitus or hypertention, significnat pain of an etiology other than PHN, pain at or around facial area (including above the scalp hairline or near mucous membranes), hypersensitivity to capsaicin, local anesthetics, oxycodone hydrochloride, hydrocodone or adhesives Study length (days): 84 Intention-to-treat analysis? Yes
Participants	Total number of patients: 299 Number of males: 150 (50.2%) Underlying cause of neuropathic pain: Post-herpetic neuralgia Mean duration of NP (in months): 45.6 Baseline pain severity: 5.6 (NRS) Mean age: 71.35
Intervention(s)	(1) Capsaicin 8% single patch applied for 90mins then removed (topical anasthetic cream applied 60 mins before patches) Intervention: capsaicin patch Length of treatment (weeks): Fixed/flexible dose regimen: Fixed dose Notes: Study reports 8% capsaicin patch, applied for 90 minutes once. (2) Capsaicin 8% single patch applied for 60mins then removed (topical anaesthetic cream applied 60 mins before patches) Intervention: capsaicin patch Length of treatment (weeks): Fixed/flexible dose regimen: Fixed dose Notes: Study reports 8% capsaicin patch, applied for 60 minutes once. (3) Capsaicin 8% single patch applied for 30mins then removed (topical anaesthetic cream applied 60 mins before patches) Intervention: capsaicin patch Length of treatment (weeks): Fixed/flexible dose regimen: Fixed dose

Notes: Study reports 8% capsaicin patch, applied for 30 minutes once.

(4) Pooled Placebo patch applied for 30, 60 & 90 mins then removed (topical anaesthetic cream applied 60 mins before patches)

Intervention: placebo
Length of treatment (weeks):
Fixed/flexible dose regimen: Fixed dose
Notes: Study reports pooled results for placebo groups (30,60 and 90 mins)

(5) Pooled capsaicin group

Intervention: capsaicin patch
Length of treatment (weeks):
Fixed/flexible dose regimen: Fixed dose
Notes: Study reports pooled results for intervention groups (30,60 and 90 mins)

Concomitant treatments

Drug free baseline period? No

Concomitant pain treatment allowed? Yes (Paracetamol up to 2g/d (as rescue medication); opioids up to 3 days after patch application; no other topical medications allowed during the study period; concomitant opioids that were not orally or transdermally administered or exceeded a total dose of 60 mg/d morphine equivalent)

Outcomes measures and effect sizes

		CAPSAICIN 8% SINGLE PATCH APPLIED FOR 90MINS THEN REMOVED (TOPICAL ANASTHETIC CREAM APPLIED 60 MINS BEFORE PATCHES)			POOLED PLACEBO PATCH APPLIED FOR 30, 60 & 90 MINS THEN REMOVED (TOPICAL ANAESTHETIC CREAM APPLIED 60 MINS BEFORE PATCHES)			
		N	k	mean	N	k	mean	Δ
pain score:								
NRS/NRS Pain – 0d	Continuous	73		5.6 (SD 0.94)	77		5.3 (SD 1.49)	
NRS/NRS Pain – 35d[a]	Mean difference from baseline to average f-u	73		-1.4 (SD 1.71)	77		-1 (SD 1.67)	MD=-0.400 (CI: -0.941, 0.141)
NRS/NRS Pain – 49d[b]	Mean difference from baseline to average f-u	73		-1.3 (SD 1.62)	77		-0.8 (SD 1.67)	MD=-0.500 (CI: -1.027, 0.027)
at least 30% pain reduction (NRS) – 84d	Dichotomous	73	29	(39.7%)	77	22	(28.6%)	OR=1.648 (CI: 0.834, 3.257)
at least 50% pain reduction (NRS) – 84d	Dichotomous	73	17	(23.3%)	77	8	(10.4%)	OR=2.618 (CI: 1.053, 6.513)
adverse events:								
Nausea – 84d	Dichotomous	73	6[c]	(8.2%)	77	7	(9.1%)	OR=0.896 (CI: 0.286, 2.802)
Pruritus – 84d	Dichotomous	73	6	(8.2%)	77	9	(11.7%)	OR=0.677 (CI: 0.228, 2.006)

[a] least squares mean; baseline to weeks 2 to 8
[b] least squares mean; baseline to weeks 2 to 12
[c] described as site erythema in paper

		CAPSAICIN 8% SINGLE PATCH APPLIED FOR 60MINS THEN REMOVED (TOPICAL ANAESTHETIC CREAM APPLIED 60 MINS BEFORE PATCHES)			POOLED PLACEBO PATCH APPLIED FOR 30, 60 & 90 MINS THEN REMOVED (TOPICAL ANAESTHETIC CREAM APPLIED 60 MINS BEFORE PATCHES)			
		N	k	mean	N	k	mean	Δ
pain score:								
NRS/NRS Pain – 0d	Continuous	77		5.4 (SD 1.75)	77		5.3 (SD 1.49)	
NRS/NRS Pain – 35d[a]	Mean difference from baseline to average f-u	77		-1.3 (SD 1.67)	77		-1 (SD 1.67)	MD=-0.300 (CI: -0.827, 0.227)
NRS/NRS Pain – 49d[b]	Mean difference from baseline to average f-u	77		-1.2 (SD 1.58)	77		-0.8 (SD 1.67)	MD=-0.400 (CI: -0.913, 0.113)
at least 30% pain reduction (NRS) – 84d	Dichotomous	77	27	(35.1%)	77	22	(28.6%)	OR=1.350 (CI: 0.683, 2.667)
at least 50% pain reduction (NRS) – 84d	Dichotomous	77	21	(27.3%)	77	8	(10.4%)	OR=3.234 (CI: 1.332, 7.855)
adverse events:								
Nausea – 84d	Dichotomous	77	3[c]	(3.9%)	77	7	(9.1%)	OR=0.405 (CI: 0.101, 1.630)
Pruritus – 84d	Dichotomous	77	4	(5.2%)	77	9	(11.7%)	OR=0.414 (CI: 0.122, 1.407)

[a] least squares mean; baseline to weeks 2 to 8
[b] least squares mean; baseline to weeks 2 to 12
[c] described as site erythema in paper

		CAPSAICIN 8% SINGLE PATCH APPLIED FOR 30MINS THEN REMOVED (TOPICAL ANAESTHETIC CREAM APPLIED 60 MINS BEFORE PATCHES)			POOLED PLACEBO PATCH APPLIED FOR 30, 60 & 90 MINS THEN REMOVED (TOPICAL ANAESTHETIC CREAM APPLIED 60 MINS BEFORE PATCHES)			
		N	k	mean	N	k	mean	Δ
pain score:								
NRS/NRS Pain – 0d	Continuous	72		5.8 (SD 1.7)	77		5.3 (SD 1.49)	
NRS/NRS Pain – 35d[a]	Mean difference from baseline to average f-u	72		-1.4 (SD 1.7)	77		-1 (SD 1.67)	MD=-0.400 (CI: -0.941, 0.141)
NRS/NRS Pain – 49d[b]	Mean difference from baseline to average f-u	72		-1.3 (SD 1.61)	77		-0.8 (SD 1.67)	MD=-0.500 (CI: -1.027, 0.027)
at least 30% pain reduction (NRS) – 84d	Dichotomous	72	27	(37.5%)	77	22	(28.6%)	OR=1.500 (CI: 0.755, 2.982)
at least 50% pain reduction (NRS) – 84d	Dichotomous	72	17	(23.6%)	77	8	(10.4%)	OR=2.666 (CI: 1.071, 6.636)

adverse events:								
Nausea – 84d	Dichotomous	72	4	(5.6%)	77	7	(9.1%)	OR=0.588 (CI: 0.165, 2.101)
Pruritus – 84d	Dichotomous	72	7	(9.7%)	77	9	(11.7%)	OR=0.814 (CI: 0.286, 2.313)

[a] least squares mean; baseline to weeks 2 to 8
[b] least squares mean; baseline to weeks 2 to 12

		POOLED PLACEBO PATCH APPLIED FOR 30, 60 & 90 MINS THEN REMOVED (TOPICAL ANAESTHETIC CREAM APPLIED 60 MINS BEFORE PATCHES)			POOLED CAPSAICIN GROUP			
		N	k	mean	N	k	mean	Δ
patient-reported global improvement:								
PGIC - worse (all grades) or no change – 28d	Dichotomous	77	45	(58.4%)	222	97	(43.7%)	OR=1.812 (CI: 1.072, 3.064)
PGIC - worse (all grades) or no change – 56d	Dichotomous	77	42	(54.5%)	222	99	(44.6%)	OR=1.491 (CI: 0.886, 2.510)
PGIC - worse (all grades) or no change – 84d	Dichotomous	77	38	(49.4%)	222	99	(44.6%)	OR=1.211 (CI: 0.720, 2.035)
PGIC - better (all grades) – 28d	Dichotomous	77	32[a]	(41.6%)	222	125[b]	(56.3%)	OR=0.552 (CI: 0.326, 0.933)
PGIC - better (all grades) – 56d	Dichotomous	77	35[a]	(45.5%)	222	123[b]	(55.4%)	OR=0.671 (CI: 0.398, 1.129)
PGIC - better (all grades) – 84d	Dichotomous	77	39[a]	(50.6%)	222	123[b]	(55.4%)	OR=0.826 (CI: 0.491, 1.388)
major adverse events (defined as leading to withdrawal):								
any major adverse event – 84d[b]	Dichotomous	77	0	(0.0%)	222	2	(0.9%)	OR=0.569 (CI: 0.027, 11.984)
adverse events:								
Diarrhoea – 84d	Dichotomous	77	3	(3.9%)	222	7	(3.2%)	OR=1.245 (CI: 0.314, 4.940)
Dizziness – 84d	Dichotomous	77	2[c]	2 (2.6%)	222	10	(4.5%)	OR=0.565 (CI: 0.121, 2.639)
GI disorders – 84d[d]	Dichotomous	77	13	(16.9%)	222	32	(14.4%)	OR=1.206 (CI: 0.596, 2.439)
headache – 84d	Dichotomous	77	2	(2.6%)	222	7	(3.2%)	OR=0.819 (CI: 0.166, 4.030)
Infection – 84d	Dichotomous	77	13[e]	(16.9%)	222	44	(19.8%)	OR=0.822 (CI: 0.416, 1.624)
site pain – 84d	Dichotomous	77	2	(2.6%)	222	1	(0.5%)	OR=5.893 (CI: 0.527, 65.925)
site papules – 84d	Dichotomous	77	2	(2.6%)	222	3	(1.4%)	OR=1.947 (CI: 0.319, 11.875)
Vomiting – 84d	Dichotomous	77	1	(1.3%)	222	9	(4.1%)	OR=0.311 (CI: 0.039, 2.499)

treatment withdrawal: due to lack of efficacy – 84d	Dichotomous	77	0	(0.0%)	222	4	(1.8%)	OR=0.313 (CI: 0.017, 5.886)
lost to follow-up – 84d	Dichotomous	77	1	(1.3%)	222	7	(3.2%)	OR=0.404 (CI: 0.049, 3.339)
poor compliance – 84d	Dichotomous	77	1	(1.3%)	222	4	(1.8%)	OR=0.717 (CI: 0.079, 6.516)
Death unrelated to treatment – 84d	Dichotomous	77	1	(1.3%)	222	0	(0.0%)	OR=8.725 (CI: 0.352, 216.455)

[a] includes those considered 'very much', 'much', or 'slightly' improved; numerators estimated from percentages; approximated to nearest integer (percentages only presented in text)
[b] includes those considered 'very much', 'much', or 'slightly' improved; numerators estimated from percentages
[c] cant remove value in mean field
[d] includes abdominal pain, diarrhoea, nausea and vomiting
[e] includes gastroenteritis (viral, nasopharyngitis, pneumonia, upper respiratory tract infection

Comments	BPI and SFMPQ were measured but actual results not reported in study

Definitions of abbreviations are given at the end of this document.

Study	Wernicke et al. (2006)
Pain category	Peripheral pain
Study design	Country: Canada Design: Parallel Inclusion criteria: PDN for at least 6 months, with a pain score of at least 4 on the NRS (11 point) Exclusion criteria: pregnancy,breastfeeding, renal transplant or current dialysis, unstable cardiovascular, hepatic, renal respiratory, or hematological illness, medical or psychological conditions that might compromise participation in the study, diagnosis of psychological disorder or previous diagnosis of mania, bipolar, psychosis, historical exposure to drugs known to cause neuropathy, history of substance abuse or dependence, treatment with MAOI or fluoxetine within 30 days, chronic use of anti-depressants, anti-emetics, anglesics, anti-manics, anti-migraines, anti-psychotics, benzodiazepines, capsaicin, chlorial hydrate, guanethidine, topical lidocaine, MAOIs, narcotics, psycho-stimulatns, oral and injectable steroids, and anti-convulsants Study length (days): 84 Intention-to-treat analysis? No
Participants	Total number of patients: 334 Number of males: 204 (61.1%) Underlying cause of neuropathic pain: Painful diabetic neuropathy Mean duration of NP (in months): 45.6 Baseline pain severity: 6.1 (24-hour average pain intensity on NRS) Mean age: 60.7 (SD: 10.6)
Intervention(s)	(1) Duloxetine 60mg/d Intervention: duloxetine Length of treatment (weeks): 12 Fixed/flexible dose regimen: Fixed dose

Set dose: 60mg/d
Notes: no titration

(2) Duloxetine 120mg/d

Intervention: duloxetine
Length of treatment (weeks): 12
Fixed/flexible dose regimen: Fixed dose
Set dose: 120mg/d
Notes: patients received 60 mg/d for 3 days and then increased to 600 mg/d

(3) Placebo

Intervention: placebo
Length of treatment (weeks): 12
Fixed/flexible dose regimen: Fixed dose

Concomitant treatments

Drug free baseline period? Unclear

Concomitant pain treatment allowed? No (anti-depressants, anti-emetics, analgesics, anti-manics, anti-migraines, anti-psychotics, benzodiazepines, capsaicin, chlorial hydrate, guanethidine, topical lidocaine, MAOIs, narcotics, psycho-stimulants, oral and injectable steroids, and anti-convulsants not permitted; paracetamol (up to 4g/d) an aspirin up to 325 mg/d permited)

Outcomes measures and effect sizes

		DULOXETINE 60MG/D			DULOXETINE 120MG/D			
		N	k	mean	N	k	mean	Δ
pain score:								
NRS/NRS Pain – 0d	Continuous	114		6.1 (SD 1.6)	112		6.2 (SD 1.5)	
NRS/NRS Pain – 84d	Mean change	110		-2.72 (SD 2.31)	111		-2.84 (SD 2.42)	MD=0.120 (CI: -0.504, 0.744)
at least 30% pain reduction (NRS) – 84d[a]	Dichotomous	114	69	(60.5%)	112	77	(68.8%)	OR=0.697 (CI: 0.403, 1.206)
at least 50% pain reduction (NRS) – 84d[a]	Dichotomous	114	47	(41.2%)	112	59	(52.7%)	OR=0.630 (CI: 0.372, 1.066)
BPI (severity) – 84d	Mean change	112		-2.66 (SD 2.43)	107		-3.05 (SD 2.48)	MD=0.390 (CI: -0.262, 1.042)
SF McGill – 0d	Continuous	114		15.9 (SD 7.7)	112		16.8 (SD 6.7)	
SF McGill – 84d	Mean change	97		-7.23 (SD 6.89)	100		-7.98 (SD 7.1)	MD=0.750 (CI: -1.204, 2.704)
patient-reported global improvement:								
PGI-I – 84d	Continuous	112		2.61 (SD 15.2)	107		2.4 (SD 13.3)	MD=0.210 (CI: -3.579, 3.999)
patient-reported improvement in daily physical and emotional functioning, including sleep:								
Normalised (10-pt) sleep interference measure – 84d[b]	Mean change	111		-3.02 (SD 2.74)	107		-3.17 (SD 2.69)	MD=0.150 (CI: -0.571, 0.871)
BPI – 0d	Continuous	114		4.7 (SD 2.5)	112		5 (SD 2.4)	
BPI – 84d	Mean change	111		-2.36 (SD 2)	107		-2.79 (SD 1.97)	MD=0.430 (CI: -0.097, 0.957)
BPI Mood – 84d	Mean change	111		-1.95 (SD 2.21)	107		-2.48 (SD 2.17)	MD=0.530 (CI: -0.052, 1.112)
BPI Sleep – 84d	Mean change	111		-3.02 (SD 2.74)	107		-3.17 (SD 2.69)	MD=0.150 (CI: -0.571, 0.871)
HAMD – 0d	Continuous	114		3.3 (SD 3.4)	112		3.6 (SD 3)	
HAMD – 84d	Mean change	97		-0.65 (SD 2.56)	101		0.19 (SD 2.61)	MD=-0.840 (CI: -1.561, -0.119)
BPI general activity – 84d	Mean change	111		-2.4 (SD 2.42)	107		-2.57 (SD 2.38)	MD=0.170 (CI: -0.468, 0.808)
BPI walking ability – 84d	Mean change	111		-2.5 (SD 2.53)	107		-2.96 (SD 2.59)	MD=0.460 (CI: -0.219, 1.139)
BPI normal work – 84d	Mean change	111		-2.49 (SD 2.42)	107		-2.93 (SD 2.48)	MD=0.440 (CI: -0.212, 1.092)
BPI relationship with other people – 84d	Mean change	111		-1.44 (SD 1.9)	107		-1.81 (SD 1.97)	MD=0.370 (CI: -0.143, 0.883)
BPI enjoyment of life – 84d	Mean change	111		-2.58 (SD 2.42)	107		-3.42 (SD 2.38)	MD=0.840 (CI: 0.202, 1.478)
major adverse events (defined as leading to withdrawal):								
any major adverse event – 84d	Dichotomous	114	17	(14.9%)	112	20	(17.9%)	OR=0.806 (CI: 0.398, 1.634)

adverse events:								
Constipation – 84d	Dichotomous	114	8	(7.0%)	112	21	(18.8%)	OR=0.327 (CI: 0.138, 0.774)
Diarrhoea – 84d	Dichotomous	114	13	(11.4%)	112	5	(4.5%)	OR=2.754 (CI: 0.948, 8.003)
Dizziness – 84d	Dichotomous	114	18	(15.8%)	112	12	(10.7%)	OR=1.563 (CI: 0.715, 3.416)
Fatigue – 84d	Dichotomous	114	14	(12.3%)	112	14	(12.5%)	OR=0.980 (CI: 0.444, 2.162)
headache – 84d	Dichotomous	114	12	(10.5%)	112	15	(13.4%)	OR=0.761 (CI: 0.339, 1.707)
Nausea – 84d	Dichotomous	114	32	(28.1%)	112	36	(32.1%)	OR=0.824 (CI: 0.466, 1.456)
Somnolence – 84d	Dichotomous	114	9	(7.9%)	112	17	(15.2%)	OR=0.479 (CI: 0.204, 1.125)
overall improvement in quality of life:								
SF36 Mental – 84d	Mean change	108		1.63 (SD 15.4)	108		3.82 (SD 15.5)	MD=-2.190 (CI: -6.306, 1.926)
SF36 Physical – 84d	Mean change	109		12 (SD 18.9)	108		11.2 (SD 19.3)	MD=0.760 (CI: -4.327, 5.847)
EQ-5D - health status index – 84d	Mean change	108		0.15 (SD 0.208)	105		0.15 (SD 0.205)	MD=0.000 (CI: -0.055, 0.055)
treatment withdrawal:								
due to lack of efficacy – 84d	Dichotomous	114	1	(0.9%)	112	3	(2.7%)	OR=0.322 (CI: 0.033, 3.139)
unspecified/other reason – 84d	Dichotomous	114	4	(3.5%)	112	7	(6.3%)	OR=0.545 (CI: 0.155, 1.918)
withdrawal of consent – 84d	Dichotomous	114	3	(2.6%)	112	1	(0.9%)	OR=3.000 (CI: 0.307, 29.283)
protocol deviation – 84d	Dichotomous	114	2	(1.8%)	112	3	(2.7%)	OR=0.649 (CI: 0.106, 3.959)
lost to follow-up – 84d	Dichotomous	114	2	(1.8%)	112	0	(0.0%)	OR=5.000 (CI: 0.237, 105.322)

[a] numbers estimated from percentages (assuming the same denominator for other outcomes reported at this time)
[b] based on BPI Sleep

		DULOXETINE 60MG/D			PLACEBO			
		N	k	mean	N	k	mean	Δ
pain score:								
NRS/NRS Pain – 0d	Continuous	114		6.1 (SD 1.6)	108		5.9 (SD 1.4)	
NRS/NRS Pain – 84d	Mean change	110		-2.72 (SD 2.31)	106		-1.39 (SD 2.37)	MD=-1.330 (CI: -1.954, -0.706)
at least 30% pain reduction (NRS) – 84d[a]	Dichotomous	114	69	(60.5%)	108	45	(41.7%)	OR=2.147 (CI: 1.256, 3.669)
at least 50% pain reduction (NRS) – 84d[a]	Dichotomous	114	47	(41.2%)	108	29	(26.9%)	OR=1.911 (CI: 1.085, 3.365)
BPI (severity) – 84d	Mean change	112		-2.66 (SD 2.43)	104		-1.48 (SD 2.35)	MD=-1.180 (CI: -1.818, -0.542)
SF McGill – 0d	Continuous	114		15.9 (SD 7.7)	108		16.2 (SD 7.5)	
SF McGill – 84d	Mean change	97		-7.23 (SD 6.89)	91		-4.18 (SD 6.96)	MD=-3.050 (CI: -5.032, -1.068)
patient-reported global improvement:								
PGI-I – 84d	Continuous	112		2.61 (SD 15.2)	105		3.17 (SD 14.8)	MD=-0.560 (CI: -4.551, 3.431)
patient-reported improvement in daily physical and emotional functioning, including sleep:								
Normalised (10-pt) sleep interference measure – 84d[b]	Mean change	111		-3.02 (SD 2.74)	104		-2.34 (SD 2.65)	MD=-0.680 (CI: -1.401, 0.041)
BPI – 0d	Continuous	114		4.7 (SD 2.5)	108		4.2 (SD 2.2)	
BPI – 84d	Mean change	111		-2.36 (SD 2)	104		-1.72 (SD 1.94)	MD=-0.640 (CI: -1.167, -0.113)
BPI Mood – 84d	Mean change	111		-1.95 (SD 2.21)	104		-1.37 (SD 2.14)	MD=-0.580 (CI: -1.162, 0.002)
BPI Sleep – 84d	Mean change	111		-3.02 (SD 2.74)	104		-2.34 (SD 2.65)	MD=-0.680 (CI: -1.401, 0.041)
HAMD – 0d	Continuous	114		3.3 (SD 3.4)	108		3.4 (SD 2.7)	
HAMD – 84d	Mean change	97		-0.65 (SD 2.56)	95		-0.64 (SD 2.53)	MD=-0.010 (CI: -0.731, 0.711)
BPI general activity – 84d	Mean change	111		-2.4 (SD 2.42)	104		-1.79 (SD 2.35)	MD=-0.610 (CI: -1.248, 0.028)
BPI walking ability – 84d	Mean change	111		-2.5 (SD 2.53)	104		-1.74 (SD 2.55)	MD=-0.760 (CI: -1.439, -0.081)
BPI normal work – 84d	Mean change	111		-2.49 (SD 2.42)	104		-2.03 (SD 2.45)	MD=-0.460 (CI: -1.112, 0.192)
BPI relationship with other people – 84d	Mean change	111		-1.44 (SD 1.9)	104		-0.88 (SD 1.94)	MD=-0.560 (CI: -1.073, -0.047)
BPI enjoyment of life – 84d	Mean change	111		-2.58 (SD 2.42)	104		-2.24 (SD 2.35)	MD=-0.340 (CI: -0.978, 0.298)

major adverse events (defined as leading to withdrawal):								
any major adverse event – 84d	Dichotomous	114	17	(14.9%)	108	8	(7.4%)	OR=2.191 (CI: 0.904, 5.311)
adverse events:								
Constipation – 84d	Dichotomous	114	8	(7.0%)	108	2	(1.9%)	OR=4.000 (CI: 0.830, 19.279)
Diarrhoea – 84d	Dichotomous	114	13	(11.4%)	108	2	(1.9%)	OR=6.822 (CI: 1.502, 30.987)
Dizziness – 84d	Dichotomous	114	18	(15.8%)	108	6	(5.6%)	OR=3.188 (CI: 1.214, 8.367)
Fatigue – 84d	Dichotomous	114	14	(12.3%)	108	3	(2.8%)	OR=4.900 (CI: 1.367, 17.565)
headache – 84d	Dichotomous	114	12	(10.5%)	108	7	(6.5%)	OR=1.697 (CI: 0.642, 4.486)
Nausea – 84d	Dichotomous	114	32	(28.1%)	108	7	(6.5%)	OR=5.631 (CI: 2.363, 13.415)
Somnolence – 84d	Dichotomous	114	9	(7.9%)	108	1	(0.9%)	OR=9.171 (CI: 1.142, 73.666)
overall improvement in quality of life:								
SF36 Mental – 84d	Mean change	108		1.63 (SD 15.4)	101		-0.31 (SD 15.3)	MD=1.940 (CI: -2.218, 6.098)
SF36 Physical – 84d	Mean change	109		12 (SD 18.9)	101		3.64 (SD 19.1)	MD=8.320 (CI: 3.177, 13.463)
EQ-5D - health status index – 84d	Mean change	108		0.15 (SD 0.208)	99		0.08 (SD 0.199)	MD=0.070 (CI: 0.015, 0.125)
treatment withdrawal:								
due to lack of efficacy – 84d	Dichotomous	114	1	(0.9%)	108	5	(4.6%)	OR=0.182 (CI: 0.021, 1.586)
unspecified/other reason – 84d	Dichotomous	114	4	(3.5%)	108	3	(2.8%)	OR=1.273 (CI: 0.278, 5.823)
withdrawal of consent – 84d	Dichotomous	114	3	(2.6%)	108	3	(2.8%)	OR=0.946 (CI: 0.187, 4.791)
protocol deviation – 84d	Dichotomous	114	2	(1.8%)	108	1	(0.9%)	OR=1.911 (CI: 0.171, 21.381)
lost to follow-up – 84d	Dichotomous	114	2	(1.8%)	108	3	(2.8%)	OR=0.625 (CI: 0.102, 3.815)

[a] numbers estimated from percentages (assuming the same denominator for other outcomes reported at this time)
[b] based on BPI Sleep

		DULOXETINE 120MG/D			PLACEBO			
		N	k	mean	N	k	mean	Δ
pain score:								
NRS/NRS Pain – 0d	Continuous	112		6.2 (SD 1.5)	108		5.9 (SD 1.4)	
NRS/NRS Pain – 84d	Mean change	111		-2.84 (SD 2.42)	106		-1.39 (SD 2.37)	MD=-1.450 (CI: -2.088, -0.812)
at least 30% pain reduction (NRS) – 84d[a]	Dichotomous	112	77	(68.8%)	108	45	(41.7%)	OR=3.080 (CI: 1.771, 5.355)
at least 50% pain reduction (NRS) – 84d[a]	Dichotomous	112	59	(52.7%)	108	29	(26.9%)	OR=3.033 (CI: 1.724, 5.333)
BPI (severity) – 84d	Mean change	107		-3.05 (SD 2.48)	104		-1.48 (SD 2.35)	MD=-1.570 (CI: -2.222, -0.918)
SF McGill – 0d	Continuous	112		16.8 (SD 6.7)	108		16.2 (SD 7.5)	
SF McGill – 84d	Mean change	100		-7.98 (SD 7.1)	91		-4.18 (SD 6.96)	MD=-3.800 (CI: -5.796, -1.804)
patient-reported global improvement:								
PGI-I – 84d	Continuous	107		2.4 (SD 13.3)	105		3.17 (SD 14.8)	MD=-0.770 (CI: -4.559, 3.019)
patient-reported improvement in daily physical and emotional functioning, including sleep:								
Normalised (10-pt) sleep interference measure – 84d[b]	Mean change	107		-3.17 (SD 2.69)	104		-2.34 (SD 2.65)	MD=-0.830 (CI: -1.551, -0.109)
BPI – 0d	Continuous	112		5 (SD 2.4)	108		4.2 (SD 2.2)	
BPI – 84d	Mean change	107		-2.79 (SD 1.97)	104		-1.72 (SD 1.94)	MD=-1.070 (CI: -1.597, -0.543)
BPI Mood – 84d	Mean change	107		-2.48 (SD 2.17)	104		-1.37 (SD 2.14)	MD=-1.110 (CI: -1.692, -0.528)
BPI Sleep – 84d	Mean change	107		-3.17 (SD 2.69)	104		-2.34 (SD 2.65)	MD=-0.830 (CI: -1.551, -0.109)
HAMD – 0d	Continuous	112		3.6 (SD 3)	108		3.4 (SD 2.7)	
HAMD – 84d	Mean change	101		0.19 (SD 2.61)	95		-0.64 (SD 2.53)	MD=0.830 (CI: 0.109, 1.551)
BPI general activity – 84d	Mean change	107		-2.57 (SD 2.38)	104		-1.79 (SD 2.35)	MD=-0.780 (CI: -1.418, -0.142)
BPI walking ability – 84d	Mean change	107		-2.96 (SD 2.59)	104		-1.74 (SD 2.55)	MD=-1.220 (CI: -1.913, -0.527)
BPI normal work – 84d	Mean change	107		-2.93 (SD 2.48)	104		-2.03 (SD 2.45)	MD=-0.900 (CI: -1.565, -0.235)
BPI relationship with other people – 84d	Mean change	107		-1.81 (SD 1.97)	104		-0.88 (SD 1.94)	MD=-0.930 (CI: -1.457, -0.403)

	BPI enjoyment of life – 84d	Mean change	107		-3.42 (SD 2.38)	104	-2.24 (SD 2.35)	MD=-1.180 (CI: -1.818, -0.542)
	major adverse events (defined as leading to withdrawal):							
	any major adverse event – 84d	Dichotomous	112	20	(17.9%)	108	8 (7.4%)	OR=2.717 (CI: 1.141, 6.469)
	adverse events:							
	Constipation – 84d	Dichotomous	112	21	(18.8%)	108	2 (1.9%)	OR=12.231 (CI: 2.792, 53.579)
	Diarrhoea – 84d	Dichotomous	112	5	(4.5%)	108	2 (1.9%)	OR=2.477 (CI: 0.470, 13.047)
	Dizziness – 84d	Dichotomous	112	12	(10.7%)	108	6 (5.6%)	OR=2.040 (CI: 0.737, 5.646)
	Fatigue – 84d	Dichotomous	112	14	(12.5%)	108	3 (2.8%)	OR=5.000 (CI: 1.394, 17.929)
	headache – 84d	Dichotomous	112	15	(13.4%)	108	7 (6.5%)	OR=2.231 (CI: 0.872, 5.709)
	Nausea – 84d	Dichotomous	112	36	(32.1%)	108	7 (6.5%)	OR=6.835 (CI: 2.885, 16.193)
	Somnolence – 84d	Dichotomous	112	17	(15.2%)	108	1 (0.9%)	OR=19.147 (CI: 2.501, 146.612)
	overall improvement in quality of life:							
	SF36 Mental – 84d	Mean change	108		3.82 (SD 15.5)	101	-0.31 (SD 15.3)	MD=4.130 (CI: -0.042, 8.302)
	SF36 Physical – 84d	Mean change	108		11.2 (SD 19.3)	101	3.64 (SD 19.1)	MD=7.560 (CI: 2.349, 12.771)
	EQ-5D - health status index – 84d	Mean change	105		0.15 (SD 0.205)	99	0.08 (SD 0.199)	MD=0.070 (CI: 0.015, 0.125)
	treatment withdrawal:							
	due to lack of efficacy – 84d	Dichotomous	112	3	(2.7%)	108	5 (4.6%)	OR=0.567 (CI: 0.132, 2.433)
	unspecified/other reason – 84d	Dichotomous	112	7	(6.3%)	108	3 (2.8%)	OR=2.333 (CI: 0.587, 9.268)
	withdrawal of consent – 84d	Dichotomous	112	1	(0.9%)	108	3 (2.8%)	OR=0.315 (CI: 0.032, 3.079)
	protocol deviation – 84d	Dichotomous	112	3	(2.7%)	108	1 (0.9%)	OR=2.945 (CI: 0.302, 28.758)
	lost to follow-up – 84d	Dichotomous	112	0	(0.0%)	108	3 (2.8%)	OR=0.134 (CI: 0.007, 2.625)
	[a] numbers estimated from percentages (assuming the same denominator for other outcomes reported at this time) [b] based on BPI Sleep							
Comments	3-week assessment and screening period - not clear if any of this was a drug-free period							

Definitions of abbreviations are given at the end of this document.

Study	Wu et al. (2008)
Pain category	Mixed (central and peripheral) or unclear if mixed
Study design	Country: USA Design: Crossover Inclusion criteria: Adults aged 18 years and older with the presence of persistent post amputation pain rated as greater than 3 on a 0-10 NRS for a period of 6 months or longer. Exclusion criteria: History of allergic reaction to any of the study drugs, cardiac condution defects, myocardial infarction within 3 months of evaluation, severe pulmonary disease, current history of alcohol or substance abuse, seizures, dementia, encephalopathy, pregnant or breast feeding, chronic hepatic diseae, hepatic or renal failure, any haematologic disease associated with leukopenia or thrombocytopenia, or the presence of any terminal disease with a life expectancy of less than 6 months Study length (days): 182 Intention-to-treat analysis? No
Participants	Total number of patients: 60 Number of males: 47 (78.3%) Underlying cause of neuropathic pain: Phantomb limb pain Mean duration of NP (in months): 51.3

	Baseline pain severity: 6.85 (NRS (average of arm means)) Mean age: 63.4 (SD: 16.4)
Intervention(s)	(1) Morphine sustained-release flexible dose Intervention: morphine Length of treatment (weeks): 6 Fixed/flexible dose regimen: Flexible dose Mean dose: 112mg/d (SD: 62.7) Range: 15–180 Notes: treatment consited of 4 weeks titration, 2 weeks maintenance, and 2 weeks taper phases, followed by 1 week drug free; each capsule had 15 mg sustained-release morphine; titration period started with 1 capsule every morning to 1 capsule 2x per day and, if no significant side effects, subsequent increments were made at 3 to 4 day intervals (increases of 2 capsules/day - 1 in the morning and one in the evening) up to a maximum of 16 capsules (180 mg) - aim was maximum tolerated dosage (2) Placebo Intervention: placebo Length of treatment (weeks): 6 Fixed/flexible dose regimen: Flexible dose
Concomitant treatments	Drug free baseline period? Yes (duration: 14d) Concomitant pain treatment allowed? Unclear (patients withdrawn from opioids, benzodiazepines, antiepileptics, mexiletine, baclofen or other neuroleptic drugs precribed for pain (but unclear about anti-depressant usage); paracetamol (up to 4 g/d) and NSAIDs allowed as needed during the study as rescue medications)
Outcomes measures and effect sizes	

		MORPHINE SUSTAINED-RELEASE FLEXIBLE DOSE			PLACEBO			
		N	k	mean	N	k	mean	Δ
pain score:								
NRS/NRS Pain – 0d[a]	Continuous	50		6.8 (SD 1)	43		6.9 (SD 0.85)	
NRS/NRS Pain – 42d[a]	Continuous	50		3.7 (SD 0.85)	43		4.5 (SD 1)	MD=-0.800 (CI: -1.181, -0.419)
NRS/NRS Pain – 42d	Percentage change from baseline	50		53	43		19	MD=34.000
NRS/NRS Pain – 42d	Mean change	50		-2.8 (SD 2.16)	43		-1.4 (SD 2.68)	MD=-1.400 (CI: -2.430, -0.370)
at least 30% pain reduction (NRS) – 42d	Dichotomous	56	33	(58.9%)	56	19	(33.9%)	OR=2.794 (CI: 1.297, 6.021)
at least 50% pain reduction (NRS) – 42d	Dichotomous	56	23	(41.1%)	56	13	(23.2%)	OR=2.305 (CI: 1.018, 5.221)
adverse events:								
any adverse event – 42d	Dichotomous	56	27	(48.2%)	56	7	(12.5%)	OR=6.517 (CI: 2.521, 16.847)
Constipation – 42d	Dichotomous	56	17	(30.4%)	56	2	(3.6%)	OR=11.769 (CI: 2.569, 53.917)
Dizziness – 42d	Dichotomous	56	2	(3.6%)	56	2	(3.6%)	OR=1.000 (CI: 0.136, 7.359)
Drowsiness – 42d	Dichotomous	56	9	(16.1%)	56	3	(5.4%)	OR=3.383 (CI: 0.864, 13.239)

	Nausea – 42d	Dichotomous	56	4	(7.1%)	56	1	(1.8%)	OR=4.231 (CI: 0.458, 39.105)
	treatment withdrawal: unspecified/other reason – 42d[b]	Dichotomous	56	10	(17.9%)	56	5	(8.9%)	OR=2.217 (CI: 0.706, 6.969)
	[a] estimated from graph [b] reasons for these patients not reported								
Comments	study compared morphine to mexiletine and placebo (results from mexiletine not reported here as drug was not in scope); of 60 patients randomised, 4 dropped out before participation in the treatment periods, and only 42 had data from both treatment periods								

Definitions of abbreviations are given at the end of this document.

Study	Wymer et al. (2009)
Pain category	Peripheral pain
Study design	Country: USA Design: Parallel Inclusion criteria: at least 18 years with diagnosed diabetes mellitus type 1 or 2 and painful diabetic neuropathy for 6 months to 5 years, HbA1c < 12% for at least 3 months prior to enrollment, moderate severity of pain intensity =on 11-point Likert scale in 7 days prior to randomisation Exclusion criteria: pregnant women, those breastfeeding or trying to have children, participation in investigational trial in last 30 days, any other condition to interfer with assessment of NP, major skin ulcers, clinically significant ECG abnormalities, any cardiac disorder putting the patient at risk of arrhythmia and MI, history of alcohol or drug abuse in last year, those taking any drugs that may interfer with results of trial (including anti-convulsants) Study length (days): 140 Intention-to-treat analysis? Yes
Participants	Total number of patients: 370 Number of males: 202 (54.6%) Underlying cause of neuropathic pain: Painful diabetic neuropathy Mean duration of NP (in months): 39.6 Baseline pain severity: 6.55 (NRS (average of scores for the 2 arms that baseline values were given for [400 mg/d and placebo]; paper says the average baseline value ranges from 6.4 to 6.6 across the arms so 6.55 may be a reasonable estimate)) Mean age: 58.2 (SD: 9.6)
Intervention(s)	(1) Lacosamide 600 mg/d Intervention: lacosamide Length of treatment (weeks): 18 Fixed/flexible dose regimen: Fixed dose Set dose: 600mg/d Notes: 6 week titration, 12 week maintenance (2) Lacosamide 400 mg/d Intervention: lacosamide Length of treatment (weeks): 18 Fixed/flexible dose regimen: Fixed dose Set dose: 400mg/d

Notes: 6 week titration, 12 week maintenance

(3) Lacosamide 200 mg/d

Intervention: lacosamide
Length of treatment (weeks): 18
Fixed/flexible dose regimen: Fixed dose
Set dose: 200mg/d
Notes: 6 week titration, 12 week maintenance

(4) Placebo

Intervention: placebo
Length of treatment (weeks): 18
Fixed/flexible dose regimen: Fixed dose

(5) All lacosamide dosages

Intervention: lacosamide
Length of treatment (weeks): 18
Fixed/flexible dose regimen: Fixed dose

Concomitant treatments

Drug free baseline period? Yes (duration: 14d)

Concomitant pain treatment allowed? Yes (concomitant treatment for depression, anxiety or sleep disorder (including tricyclics) were allowed if the patient was on a stable dose not likely to change during trial; paracetamol up to 2g/d as rescue medication)

Outcomes measures and effect sizes

		LACOSAMIDE 600 MG/D			PLACEBO			
		N	k	mean	N	k	mean	Δ
pain score:								
NRS/NRS Pain – 84d[a]	Mean difference from baseline to average f-u	54		-2.55	73		-1.65	MD=-0.900
NRS/NRS Pain – 112d[b]	Mean difference from baseline to average f-u	92		-2.02	90		-1.6	MD=-0.420
patient-reported global improvement:								
PGIC - worse (all grades) or no change – 126d[c]	Dichotomous	93	11	(11.8%)	93	29	(31.2%)	OR=0.296 (CI: 0.137, 0.638)
PGIC - better (all grades) – 126d[c]	Dichotomous	93	81	(87.1%)	93	61	(65.6%)	OR=3.541 (CI: 1.686, 7.437)
major adverse events (defined as leading to withdrawal):								
any major adverse event – 126d	Dichotomous	93	37	(39.8%)	93	8	(8.6%)	OR=7.020 (CI: 3.045, 16.186)
adverse events:								
asthenia – 126d	Dichotomous	93	5	(5.4%)	93	2	(2.2%)	OR=2.585 (CI: 0.489, 13.676)
balance disorder – 126d	Dichotomous	93	6	(6.5%)	93	0	(0.0%)	OR=13.891 (CI: 0.771, 250.247)
Diarrhoea – 126d	Dichotomous	93	3	(3.2%)	93	4	(4.3%)	OR=0.742 (CI: 0.161, 3.409)
Dizziness – 126d	Dichotomous	93	27	(29.0%)	93	5	(5.4%)	OR=7.200 (CI: 2.632, 19.693)
Fatigue – 126d	Dichotomous	93	9	(9.7%)	93	3	(3.2%)	OR=3.214 (CI: 0.842, 12.276)
headache – 126d	Dichotomous	93	9	(9.7%)	93	6	(6.5%)	OR=1.554 (CI: 0.530, 4.555)
Nausea – 126d	Dichotomous	93	14	(15.1%)	93	8	(8.6%)	OR=1.883 (CI: 0.750, 4.730)
vertigo – 126d	Dichotomous	93	6	(6.5%)	93	1	(1.1%)	OR=6.345 (CI: 0.749, 53.777)
treatment withdrawal:								
due to lack of efficacy – 126d	Dichotomous	93	3	(3.2%)	93	2	(2.2%)	OR=1.517 (CI: 0.248, 9.293)
unspecified/other reason – 126d	Dichotomous	93	1	(1.1%)	93	3	(3.2%)	OR=0.326 (CI: 0.033, 3.194)

withdrawal of consent – 126d	Dichotomous	93	6	(6.5%)	93	7	(7.5%)	OR=0.847 (CI: 0.274, 2.624)
protocol deviation – 126d	Dichotomous	93	1	(1.1%)	93	1	(1.1%)	OR=1.000 (CI: 0.062, 16.230)
lost to follow-up – 126d	Dichotomous	93	3	(3.2%)	93	5	(5.4%)	OR=0.587 (CI: 0.136, 2.529)

[a] least squares mean; outcome from weeks 6 to 18
[b] least squares mean; outcome from weeks 14 to 18
[c] approximated to nearest integer (percentages only presented in text)

		LACOSAMIDE 400 MG/D			PLACEBO			
		N	k	mean	N	k	mean	Δ
pain score:								
NRS/NRS Pain – 0d	Continuous	91		6.5	93		6.6	
NRS/NRS Pain – 84d[a]	Mean difference from baseline to average f-u	72		-2.39	73		-1.65	MD=-0.740
NRS/NRS Pain – 112d[b]	Mean difference from baseline to average f-u	91		-2.34	90		-1.6	MD=-0.740
NRS/NRS Pain – 126d	Mean change	91		2.5	93		1.8	MD=0.700
NRS/NRS Pain – 126d	Continuous	91		4	93		4.8	MD=-0.800
at least 30% pain reduction (NRS) – 126d[c]	Dichotomous from baseline to average f-u	91	53		93	41		OR=1.769 (CI: 0.986, 3.172)
patient-reported global improvement:								
PGIC - worse (all grades) – 126d[d]	Dichotomous	91	5	(5.5%)	93	15	(16.1%)	OR=0.302 (CI: 0.105, 0.870)
PGIC - worse (all grades) or no change – 126d[d]	Dichotomous	91	17	(18.7%)	93	29	(31.2%)	OR=0.507 (CI: 0.255, 1.007)
PGIC - no change – 126d[d]	Dichotomous	91	12	(13.2%)	93	14	(15.1%)	OR=0.857 (CI: 0.373, 1.969)
PGIC - minimally or moderately better – 126d[d]	Dichotomous	91	40	(44.0%)	93	42	(45.2%)	OR=0.952 (CI: 0.532, 1.704)
PGIC - better (all grades) – 126d[d]	Dichotomous	91	74	(81.3%)	93	61	(65.6%)	OR=2.284 (CI: 1.158, 4.502)
PGIC - much better – 126d[d]	Dichotomous	91	34	(37.4%)	93	19	(20.4%)	OR=2.323 (CI: 1.202, 4.491)
patient-reported improvement in daily physical and emotional functioning, including sleep:								
NRS Sleep – 112d[b]	Mean difference from baseline to average f-u	91		-2.3	90		-1.8	MD=-0.500
major adverse events (defined as leading to withdrawal):								
any major adverse event – 126d	Dichotomous	91	21	(23.1%)	93	8	(8.6%)	OR=3.188 (CI: 1.331, 7.636)
adverse events:								
asthenia – 126d	Dichotomous	91	3	(3.3%)	93	2	(2.2%)	OR=1.551 (CI: 0.253, 9.507)
balance disorder – 126d	Dichotomous	91	1	(1.1%)	93	0	(0.0%)	OR=3.099 (CI: 0.125, 77.081)
Diarrhoea – 126d	Dichotomous	91	5	(5.5%)	93	4	(4.3%)	OR=1.294 (CI: 0.336, 4.979)
Dizziness – 126d	Dichotomous	91	12	(13.2%)	93	5	(5.4%)	OR=2.673 (CI: 0.902, 7.924)
Fatigue – 126d	Dichotomous	91	6	(6.6%)	93	3	(3.2%)	OR=2.118 (CI: 0.513, 8.737)

headache – 126d	Dichotomous	91	7	(7.7%)	93	6	(6.5%)	OR=1.208 (CI: 0.390, 3.744)
Nausea – 126d	Dichotomous	91	7	(7.7%)	93	8	(8.6%)	OR=0.885 (CI: 0.307, 2.551)
vertigo – 126d	Dichotomous	91	2	(2.2%)	93	1	(1.1%)	OR=2.067 (CI: 0.184, 23.205)
treatment withdrawal:								
due to lack of efficacy – 126d	Dichotomous	91	1	(1.1%)	93	2	(2.2%)	OR=0.506 (CI: 0.045, 5.674)
unspecified/other reason – 126d	Dichotomous	91	4	(4.4%)	93	3	(3.2%)	OR=1.379 (CI: 0.300, 6.342)
withdrawal of consent – 126d	Dichotomous	91	6	(6.6%)	93	7	(7.5%)	OR=0.867 (CI: 0.280, 2.687)
protocol deviation – 126d	Dichotomous	91	1	(1.1%)	93	1	(1.1%)	OR=1.022 (CI: 0.063, 16.593)
lost to follow-up – 126d	Dichotomous	91	2	(2.2%)	93	5	(5.4%)	OR=0.396 (CI: 0.075, 2.093)

[a] least squares mean; outcome from weeks 6 to 18
[b] least squares mean; outcome from weeks 14 to 18
[c] OR ≥2 point reduction in NRS; numbers estimated from percentages so may not be absolutely accurate; outcome from weeks 14 to 18
[d] approximated to nearest integer (percentages only presented in text)

		LACOSAMIDE 200 MG/D			PLACEBO			
		N	k	mean	N	k	mean	Δ
pain score:								
NRS/NRS Pain – 84d[a]	Mean difference from baseline to average f-u	79		-1.93	73		-1.65	MD=-0.280
NRS/NRS Pain – 112d[b]	Mean difference from baseline to average f-u	92		-1.99	90		-1.6	MD=-0.390
patient-reported global improvement:								
PGIC - worse (all grades) or no change – 126d[c]	Dichotomous	93	29	(31.2%)	93	29	(31.2%)	OR=1.000 (CI: 0.538, 1.860)
PGIC - better (all grades) – 126d[c]	Dichotomous	93	63	(67.7%)	93	61	(65.6%)	OR=1.102 (CI: 0.599, 2.027)
major adverse events (defined as leading to withdrawal):								
any major adverse event – 126d	Dichotomous	93	8	(8.6%)	93	8	(8.6%)	OR=1.000 (CI: 0.359, 2.787)
adverse events:								
asthenia – 126d	Dichotomous	93	0	(0.0%)	93	2	(2.2%)	OR=0.196 (CI: 0.009, 4.133)
balance disorder – 126d	Dichotomous	93	0	(0.0%)	93	0	(0.0%)	OR=1.000 (CI: 0.020, 50.927)
Diarrhoea – 126d	Dichotomous	93	1	(1.1%)	93	4	(4.3%)	OR=0.242 (CI: 0.027, 2.206)
Dizziness – 126d	Dichotomous	93	9	(9.7%)	93	5	(5.4%)	OR=1.886 (CI: 0.607, 5.857)
Fatigue – 126d	Dichotomous	93	3	(3.2%)	93	3	(3.2%)	OR=1.000 (CI: 0.197, 5.087)
headache – 126d	Dichotomous	93	6	(6.5%)	93	6	(6.5%)	OR=1.000 (CI: 0.310, 3.222)
Nausea – 126d	Dichotomous	93	8	(8.6%)	93	8	(8.6%)	OR=1.000 (CI: 0.359, 2.787)

vertigo – 126d	Dichotomous	93	1	(1.1%)	93	1	(1.1%)	OR=1.000 (CI: 0.062, 16.230)
treatment withdrawal:									
due to lack of efficacy – 126d	Dichotomous	93	3	(3.2%)	93	2	(2.2%)	OR=1.517 (CI: 0.248, 9.293)
unspecified/other reason – 126d	Dichotomous	93	3	(3.2%)	93	3	(3.2%)	OR=1.000 (CI: 0.197, 5.087)
withdrawal of consent – 126d	Dichotomous	93	6	(6.5%)	93	7	(7.5%)	OR=0.847 (CI: 0.274, 2.624)
protocol deviation – 126d	Dichotomous	93	1	(1.1%)	93	1	(1.1%)	OR=1.000 (CI: 0.062, 16.230)
lost to follow-up – 126d	Dichotomous	93	3	(3.2%)	93	5	(5.4%)	OR=0.587 (CI: 0.136, 2.529)

[a] least squares mean; outcome from weeks 6 to 18
[b] least squares mean; outcome from weeks 14 to 18
[c] approximated to nearest integer (percentages only presented in text)

		PLACEBO			ALL LACOSAMIDE DOSAGES			
		N	k	mean	N	k	mean	Δ
patient-reported global improvement:								
PGIC - worse (all grades) or no change – 126d[a]	Dichotomous	93	29	(31.2%)	277	57	(20.6%)	OR=1.749 (CI: 1.033, 2.961)
PGIC - better (all grades) – 126d[a]	Dichotomous	93	61	(65.6%)	277	218	(78.7%)	OR=0.516 (CI: 0.308, 0.864)
major adverse events (defined as leading to withdrawal):								
any major adverse event – 126d	Dichotomous	93	8	(8.6%)	277	66	(23.8%)	OR=0.301 (CI: 0.139, 0.654)
adverse events:								
asthenia – 126d	Dichotomous	93	2	(2.2%)	277	8	(2.9%)	OR=0.739 (CI: 0.154, 3.544)
balance disorder – 126d	Dichotomous	93	0	(0.0%)	277	7	(2.5%)	OR=0.193 (CI: 0.011, 3.410)
Diarrhoea – 126d	Dichotomous	93	4	(4.3%)	277	9	(3.2%)	OR=1.338 (CI: 0.402, 4.452)
Dizziness – 126d	Dichotomous	93	5	(5.4%)	277	48	(17.3%)	OR=0.271 (CI: 0.104, 0.703)
Fatigue – 126d	Dichotomous	93	3	(3.2%)	277	18	(6.5%)	OR=0.480 (CI: 0.138, 1.667)
headache – 126d	Dichotomous	93	6	(6.5%)	277	22	(7.9%)	OR=0.799 (CI: 0.314, 2.036)
Nausea – 126d	Dichotomous	93	8	(8.6%)	277	29	(10.5%)	OR=0.805 (CI: 0.354, 1.828)
oedema – 126d	Dichotomous	93	4	(4.3%)	277	9	(3.2%)	OR=1.338 (CI: 0.402, 4.452)
vertigo – 126d	Dichotomous	93	1	(1.1%)	277	9	(3.2%)	OR=0.324 (CI: 0.040, 2.590)
treatment withdrawal:								
due to lack of efficacy – 126d	Dichotomous	93	2	(2.2%)	277	7	(2.5%)	OR=0.848 (CI: 0.173, 4.154)
unspecified/other reason – 126d	Dichotomous	93	3	(3.2%)	277	8	(2.9%)	OR=1.121 (CI: 0.291, 4.316)
withdrawal of consent – 126d	Dichotomous	93	7	(7.5%)	277	18	(6.5%)	OR=1.171 (CI: 0.473, 2.899)
protocol deviation – 126d	Dichotomous	93	1	(1.1%)	277	3	(1.1%)	OR=0.993 (CI: 0.102, 9.662)
lost to follow-up – 126d	Dichotomous	93	5	(5.4%)	277	8	(2.9%)	OR=1.911 (CI: 0.609, 5.992)

[a] approximated to nearest integer (percentages only presented in text)

Comments	ITT population was defined as any patients who received at least 1 dose of study medication and had at least 1 postbaseline pain score entry; most patients had previously failed on other medications for NP; baseline scores were given as a range or dichotomised into categories (ie. <4, 4-6, 6-8, 8-10); concomittant tricyclic antidepressants in 9.6% (placebo), 7.6% (200 mg/d), 1.4% (400 mg/d), 7.4% (600 mg/d) but there were no apparent differences in pain reduction in those with and those without

Definitions of abbreviations are given at the end of this document.

Study	Yasuda et al. (2011)
Pain category	Peripheral pain
Study design	Country: Japan Design: Parallel Inclusion criteria: 20-80 years, sustained pain for =6 months from distal symmetric polyneuropathy from type 1 or 2 diabetes, =4 NRS weekly mean 24 hour average, HBA1c =9.4% at screening, fluctuation of HbA1c =1% at 42-70 days before screening Exclusion criteria: psychiatric disease or with history of these diseases in past year requiring pharmacotherapy, any disorders that might affect assessment of PDN, such as neurological disorders Study length (days): 91 Intention-to-treat analysis? Yes
Participants	Total number of patients: 339 Number of males: 256 (75.5%) Underlying cause of neuropathic pain: Painful diabetic neuropathy Mean duration of NP (in months): 54 Baseline pain severity: 5.78 (weekly mean 24 hour average on NRS) Mean age: 60.8
Intervention(s)	(1) Duloxetine 40 mg/d Intervention: duloxetine Length of treatment (weeks): 12 Fixed/flexible dose regimen: Fixed dose Set dose: 40mg/d Notes: first 1-2 week titration, starting with 20 mg/d and increasing the dose at 20 mg weekly increments (2) Duloxetine 60 mg/d Intervention: duloxetine Length of treatment (weeks): 12 Fixed/flexible dose regimen: Fixed dose Set dose: 60mg/d Notes: first 1-2 week titration, starting with 20 mg/d and increasing the dose at 20 mg weekly increments (3) Placebo Intervention: placebo Length of treatment (weeks): 12 Fixed/flexible dose regimen: Fixed dose (4) Pooled duloxetine Intervention: duloxetine Length of treatment (weeks): 12 Fixed/flexible dose regimen: Fixed dose Notes: Arms 1 & 2 combined
Concomitant	Drug free baseline period? Yes (duration: 7d)

treatments	Concomitant pain treatment allowed? No (paracetamol (max daily dose of 1.5g) (but none other))
Outcomes measures and effect sizes	

		DULOXETINE 40 MG/D			DULOXETINE 60 MG/D			
		N	k	mean	N	k	mean	Δ
pain score:								
NRS/NRS Pain – 0d	Continuous	85		5.79 (SD 1.23)	86		5.76 (SD 1.17)	
NRS/NRS Pain – 84d	Mean change	85		-2.41 (SD 1.94)	86		-2.53 (SD 1.95)	MD=0.120 (CI: -0.462, 0.702)
NRS/NRS Pain – 84d	Continuous	85		3.38	86		3.23	MD=0.150
at least 30% pain reduction (NRS) – 84d	Dichotomous	85	47	(55.3%)	86	51	(59.3%)	OR=0.849 (CI: 0.463, 1.557)
at least 50% pain reduction (NRS) – 84d	Dichotomous	85	32	(37.6%)	86	35	(40.7%)	OR=0.880 (CI: 0.476, 1.626)
patient-reported global improvement:								
PGI-I – 84d[a]	Continuous	85		2.53 (SD 1.29)	86		2.52 (SD 1.3)	MD=0.010 (CI: -0.378, 0.398)
patient-reported improvement in daily physical and emotional functioning, including sleep:								
Normalised (10-pt) sleep interference measure – 0d[b]	Continuous	85		4 (SD 2.8)	86		4.3 (SD 2.7)	
Normalised (10-pt) sleep interference measure – 84d[b]	Mean change	85		-2.26 (SD 2.67)	86		-2.05 (SD 2.69)	
BPI – 0d[c]	Continuous	85		3.88 (SD 2.25)	86		4.09 (SD 2.13)	
BPI – 84d[c]	Mean change	85		-2 (SD 2.21)	86		-2.08 (SD 2.23)	MD=0.080 (CI: -0.585, 0.745)
BPI Mood – 0d	Continuous	85		3.9 (SD 2.5)	86		4.2 (SD 2.5)	
BPI Mood – 84d	Mean change	85		-2.18 (SD 2.67)	86		-2.39 (SD 2.69)	MD=0.210 (CI: -0.594, 1.014)
BPI Sleep – 0d	Continuous	85		4 (SD 2.8)	86		4.3 (SD 2.7)	
BPI Sleep – 84d	Mean change	85		-2.26 (SD 2.67)	86		-2.05 (SD 2.69)	MD=-0.210 (CI: -1.014, 0.594)
BPI general activity – 0d	Continuous	85		4.5 (SD 2.7)	86		4.5 (SD 2.4)	
BPI general activity – 84d	Mean change	85		-2.48 (SD 2.67)	86		-2.1 (SD 2.69)	MD=-0.380 (CI: -1.184, 0.424)
BPI walking ability – 0d	Continuous	85		4.4 (SD 2.8)	86		4.3 (SD 2.5)	
BPI walking ability – 84d	Mean change	85		-2.32 (SD 2.58)	86		-2.31 (SD 2.6)	MD=-0.010 (CI: -0.786, 0.766)
BPI normal work – 0d	Continuous	85		3.9 (SD 2.6)	86		4.3 (SD 2.5)	
BPI normal work – 84d	Mean change	85		-1.84 (SD 2.58)	86		-1.9 (SD 2.6)	MD=0.060 (CI: -0.716, 0.836)
BPI relationship with other people – 0d	Continuous	85		2.7 (SD 2.7)	86		2.9 (SD 2.4)	
BPI relationship with other people – 84d	Mean change	85		-1.16 (SD 2.49)	86		-1.49 (SD 2.5)	MD=0.330 (CI: -0.418, 1.078)
BPI enjoyment of life – 0d	Continuous	85		3.7 (SD 2.7)	86		4.2 (SD 2.5)	
BPI enjoyment of life – 84d	Mean change	85		-1.96 (SD 2.58)	86		-2.35 (SD 2.6)	MD=0.390 (CI: -0.386, 1.166)
major adverse events (defined as leading to withdrawal):								
any major adverse event – 84d	Dichotomous	85	9	(10.6%)	86	12	(14.0%)	OR=0.730 (CI: 0.291, 1.835)
adverse events:								
any adverse event – 84d	Dichotomous	85	72	(84.7%)	86	73	(84.9%)	OR=0.986 (CI: 0.428, 2.273)
Constipation	Dichotomous	85	6	(7.1%)	86	5	(5.8%)	OR=1.230 (CI: 0.361, 4.195)
Diarrhoea	Dichotomous	85	4	(4.7%)	86	7	(8.1%)	OR=0.557 (CI: 0.157, 1.979)
Dizziness – 84d	Dichotomous	85	6	(7.1%)	86	4	(4.7%)	OR=1.557 (CI: 0.423, 5.726)
Nausea	Dichotomous	85	10	(11.8%)	86	14	(16.3%)	OR=0.686 (CI: 0.286, 1.643)
Somnolence – 84d	Dichotomous	85	16	(18.8%)	86	21	(24.4%)	OR=0.718 (CI: 0.345, 1.494)
Vomiting	Dichotomous	85	4	(4.7%)	86	5	(5.8%)	OR=0.800 (CI: 0.207, 3.087)
treatment withdrawal:								
unspecified/other reason – 84d	Dichotomous	85	4	(4.7%)	86	4	(4.7%)	OR=1.012 (CI: 0.245, 4.186)

[a] Table says this is a mean difference but text says it is the figures at week 12. As no baseline given, assumed it was the value at 12 weeks
[b] based on BPI Sleep
[c] average of all 7 inference scores

		DULOXETINE 40 MG/D			PLACEBO			
		N	k	mean	N	k	mean	Δ
pain score:								
NRS/NRS Pain – 0d	Continuous	85		5.79 (SD 1.23)	167		5.78 (SD 1.17)	
NRS/NRS Pain – 84d	Mean change	85		-2.41 (SD 1.94)	167		-1.61 (SD 2.33)	MD=-0.800 (CI: -1.342, -0.258)
NRS/NRS Pain – 84d	Continuous	85		3.38	167		4.17	MD=-0.790
at least 30% pain reduction (NRS) – 84d	Dichotomous	85	47	(55.3%)	167	59	(35.3%)	OR=2.264 (CI: 1.329, 3.856)
at least 50% pain reduction (NRS) – 84d	Dichotomous	85	32	(37.6%)	167	33	(19.8%)	OR=2.452 (CI: 1.371, 4.383)
patient-reported global improvement:								
PGI-I – 84d[a]	Continuous	85		2.53 (SD 1.29)	167		3.18 (SD 1.55)	MD=-0.650 (CI: -1.011, -0.289)
patient-reported improvement in daily physical and emotional functioning, including sleep:								
Normalised (10-pt) sleep interference measure – 0d[b]	Continuous	85		4 (SD 2.8)	167		3.9 (SD 2.7)	
Normalised (10-pt) sleep interference measure – 84d[b]	Mean change	85		-2.26 (SD 2.67)	167		-1.69 (SD 3.1)	
BPI – 0d[c]	Continuous	85		3.88 (SD 2.25)	167		3.75 (SD 2.15)	
BPI – 84d[c]	Mean change	85		-2 (SD 2.21)	167		-1.56 (SD 2.58)	MD=-0.440 (CI: -1.052, 0.172)
BPI Mood – 0d	Continuous	85		3.9 (SD 2.5)	167		4.2 (SD 2.4)	
BPI Mood – 84d	Mean change	85		-2.18 (SD 2.67)	167		-1.91 (SD 3.1)	MD=-0.270 (CI: -1.008, 0.468)
BPI Sleep – 0d	Continuous	85		4 (SD 2.8)	167		3.9 (SD 2.7)	
BPI Sleep – 84d	Mean change	85		-2.26 (SD 2.67)	167		-1.69 (SD 3.1)	MD=-0.570 (CI: -1.308, 0.168)
BPI general activity – 0d	Continuous	85		4.5 (SD 2.7)	167		4.4 (SD 2.4)	
BPI general activity – 84d	Mean change	85		-2.48 (SD 2.67)	167		-1.88 (SD 3.1)	MD=-0.600 (CI: -1.338, 0.138)
BPI walking ability – 0d	Continuous	85		4.4 (SD 2.8)	167		4 (SD 2.6)	
BPI walking ability – 84d	Mean change	85		-2.32 (SD 2.58)	167		-1.82 (SD 2.97)	MD=-0.500 (CI: -1.210, 0.210)
BPI normal work – 0d	Continuous	85		3.9 (SD 2.6)	167		3.7 (SD 2.7)	
BPI normal work – 84d	Mean change	85		-1.84 (SD 2.58)	167		-1.49 (SD 2.97)	MD=-0.350 (CI: -1.060, 0.360)
BPI relationship with other people – 0d	Continuous	85		2.7 (SD 2.7)	167		2.6 (SD 2.5)	
BPI relationship with other people – 84d	Mean change	85		-1.16 (SD 2.49)	167		-0.77 (SD 2.97)	MD=-0.390 (CI: -1.085, 0.305)
BPI enjoyment of life – 0d	Continuous	85		3.7 (SD 2.7)	167		3.5 (SD 2.5)	
BPI enjoyment of life – 84d	Mean change	85		-1.96 (SD 2.58)	167		-1.59 (SD 2.97)	MD=-0.370 (CI: -1.080, 0.340)
major adverse events (defined as leading to withdrawal):								
any major adverse event – 84d	Dichotomous	85	9	(10.6%)	167	9	(5.4%)	OR=2.079 (CI: 0.793, 5.449)
adverse events:								
any adverse event – 84d	Dichotomous	85	72	(84.7%)	167	123	(73.7%)	OR=1.981 (CI: 1.000, 3.925)
Constipation	Dichotomous	85	6	(7.1%)	167	9	(5.4%)	OR=1.333 (CI: 0.458, 3.878)
Diarrhoea	Dichotomous	85	4	(4.7%)	167	6	(3.6%)	OR=1.325 (CI: 0.364, 4.828)
Dizziness – 84d	Dichotomous	85	6	(7.1%)	167	2	(1.2%)	OR=6.266 (CI: 1.237, 31.745)
Nausea	Dichotomous	85	10	(11.8%)	167	3	(1.8%)	OR=7.289 (CI: 1.949, 27.253)
Somnolence – 84d	Dichotomous	85	16	(18.8%)	167	14	(8.4%)	OR=2.534 (CI: 1.172, 5.482)
Vomiting	Dichotomous	85	4	(4.7%)	167	2	(1.2%)	OR=4.074 (CI: 0.731, 22.708)
treatment withdrawal:								
unspecified/other reason – 84d	Dichotomous	85	4	(4.7%)	167	8	(4.8%)	OR=0.981 (CI: 0.287, 3.357)

[a] Table says this is a mean difference but text says it is the figures at week 12. As no baseline given, assumed it was the value at 12 weeks
[b] based on BPI Sleep
[c] average of all 7 inference scores

		DULOXETINE 60 MG/D	PLACEBO

		N	k	mean	N	k	mean	Δ
pain score:								
NRS/NRS Pain – 0d	Continuous	86		5.76 (SD 1.17)	167		5.78 (SD 1.17)	
NRS/NRS Pain – 84d	Mean change	86		-2.53 (SD 1.95)	167		-1.61 (SD 2.33)	MD=-0.920 (CI: -1.462, -0.378)
NRS/NRS Pain – 84d	Continuous	86		3.23	167		4.17	MD=-0.940
at least 30% pain reduction (NRS) – 84d	Dichotomous	86	51	(59.3%)	167	59	(35.3%)	OR=2.667 (CI: 1.563, 4.552)
at least 50% pain reduction (NRS) – 84d	Dichotomous	86	35	(40.7%)	167	33	(19.8%)	OR=2.787 (CI: 1.569, 4.950)
patient-reported global improvement:								
PGI-I – 84d[a]	Continuous	86		2.52 (SD 1.3)	167		3.18 (SD 1.55)	MD=-0.660 (CI: -1.021, -0.299)
patient-reported improvement in daily physical and emotional functioning, including sleep:								
Normalised (10-pt) sleep interference measure – 0d[b]	Continuous	86		4.3 (SD 2.7)	167		3.9 (SD 2.7)	
Normalised (10-pt) sleep interference measure – 84d[b]	Mean change	86		-2.05 (SD 2.69)	167		-1.69 (SD 3.1)	
BPI – 0d[c]	Continuous	86		4.09 (SD 2.13)	167		3.75 (SD 2.15)	
BPI – 84d[c]	Mean change	86		-2.08 (SD 2.23)	167		-1.56 (SD 2.58)	MD=-0.520 (CI: -1.132, 0.092)
BPI Mood – 0d	Continuous	86		4.2 (SD 2.5)	167		4.2 (SD 2.4)	
BPI Mood – 84d	Mean change	86		-2.39 (SD 2.69)	167		-1.91 (SD 3.1)	MD=-0.480 (CI: -1.218, 0.258)
BPI Sleep – 0d	Continuous	86		4.3 (SD 2.7)	167		3.9 (SD 2.7)	
BPI Sleep – 84d	Mean change	86		-2.05 (SD 2.69)	167		-1.69 (SD 3.1)	MD=-0.360 (CI: -1.098, 0.378)
BPI general activity – 0d	Continuous	86		4.5 (SD 2.4)	167		4.4 (SD 2.4)	
BPI general activity – 84d	Mean change	86		-2.1 (SD 2.69)	167		-1.88 (SD 3.1)	MD=-0.220 (CI: -0.958, 0.518)
BPI walking ability – 0d	Continuous	86		4.3 (SD 2.5)	167		4 (SD 2.6)	
BPI walking ability – 84d	Mean change	86		-2.31 (SD 2.6)	167		-1.82 (SD 2.97)	MD=-0.490 (CI: -1.200, 0.220)
BPI normal work – 0d	Continuous	86		4.3 (SD 2.5)	167		3.7 (SD 2.7)	
BPI normal work – 84d	Mean change	86		-1.9 (SD 2.6)	167		-1.49 (SD 2.97)	MD=-0.410 (CI: -1.120, 0.300)
BPI relationship with other people – 0d	Continuous	86		2.9 (SD 2.4)	167		2.6 (SD 2.5)	
BPI relationship with other people – 84d	Mean change	86		-1.49 (SD 2.5)	167		-0.77 (SD 2.97)	MD=-0.720 (CI: -1.415, -0.025)
BPI enjoyment of life – 0d	Continuous	86		4.2 (SD 2.5)	167		3.5 (SD 2.5)	
BPI enjoyment of life – 84d	Mean change	86		-2.35 (SD 2.6)	167		-1.59 (SD 2.97)	MD=-0.760 (CI: -1.470, -0.050)
major adverse events (defined as leading to withdrawal):								
any major adverse event – 84d	Dichotomous	86	12	(14.0%)	167	9	(5.4%)	OR=2.847 (CI: 1.149, 7.053)
adverse events:								
any adverse event – 84d	Dichotomous	86	73	(84.9%)	167	123	(73.7%)	OR=2.009 (CI: 1.014, 3.977)
Constipation	Dichotomous	86	5	(5.8%)	167	9	(5.4%)	OR=1.084 (CI: 0.352, 3.340)
Diarrhoea	Dichotomous	86	7	(8.1%)	167	6	(3.6%)	OR=2.378 (CI: 0.773, 7.310)
Dizziness – 84d	Dichotomous	86	4	(4.7%)	167	2	(1.2%)	OR=4.024 (CI: 0.722, 22.427)
Nausea	Dichotomous	86	14	(16.3%)	167	3	(1.8%)	OR=10.630 (CI: 2.963, 38.130)
Somnolence – 84d	Dichotomous	86	21	(24.4%)	167	14	(8.4%)	OR=3.531 (CI: 1.692, 7.370)
Vomiting	Dichotomous	86	5	(5.8%)	167	2	(1.2%)	OR=5.093 (CI: 0.967, 26.817)
treatment withdrawal:								
unspecified/other reason – 84d	Dichotomous	86	4	(4.7%)	167	8	(4.8%)	OR=0.970 (CI: 0.284, 3.315)

[a] Table says this is a mean difference but text says it is the figures at week 12. As no baseline given, assumed it was the value at 12 weeks
[b] based on BPI Sleep
[c] average of all 7 inference scores

	PLACEBO			POOLED DULOXETINE			
	N	k	mean	N	k	mean	Δ

pain score:								
NRS/NRS Pain – 0d	Continuous	167		5.78 (SD 1.17)	171		5.77 (SD 1.2)	
NRS/NRS Pain – 28d[a]	Mean change	167		-1.05	171		-1.75	MD=0.700
NRS/NRS Pain – 56d[a]	Mean change	167		-1.48	171		-2.25	MD=0.770
NRS/NRS Pain – 84d	Mean change	167		-1.61 (SD 2.33)	171		-2.47 (SD 2.35)	MD=0.870 (CI: 0.576, 1.164)
NRS/NRS Pain – 84d	Continuous	167		4.17	171		3.3	MD=0.870
at least 30% pain reduction (NRS) – 84d	Dichotomous	167	59	(35.3%)	171	98	(57.3%)	OR=0.407 (CI: 0.262, 0.631)
at least 50% pain reduction (NRS) – 84d	Dichotomous	167	33	(19.8%)	171	67	(39.2%)	OR=0.382 (CI: 0.234, 0.624)
patient-reported global improvement:								
PGI-I – 84d	Continuous	167		3.18 (SD 1.55)[b]	171		2.53 (SD 1.57)	MD=0.650 (CI: 0.317, 0.983)
patient-reported improvement in daily physical and emotional functioning, including sleep:								
Normalised (10-pt) sleep interference measure – 0d[c]	Continuous	167		3.9 (SD 2.7)	171		4.2 (SD 2.8)	
Normalised (10-pt) sleep interference measure – 84d[c]	Mean change	167		-1.69 (SD 3.1)	171		-2.15 (SD 3.14)	
BPI – 0d[d]	Continuous	167		3.75 (SD 2.15)	171		3.99 (SD 2.18)	
BPI – 84d[d]	Mean change	167		-1.56 (SD 2.58)	171		-2.04 (SD 2.62)	MD=0.480 (CI: -0.074, 1.034)
BPI Mood – 0d	Continuous	167		4.2 (SD 2.4)	171		4.1 (SD 2.5)	
BPI Mood – 84d	Mean change	167		-1.91 (SD 3.1)	171		-2.28 (SD 3.14)	MD=0.370 (CI: -0.295, 1.035)
BPI Sleep – 0d	Continuous	167		3.9 (SD 2.7)	171		4.2 (SD 2.8)	
BPI Sleep – 84d	Mean change	167		-1.69 (SD 3.1)	171		-2.15 (SD 3.14)	MD=0.460 (CI: -0.205, 1.125)
BPI general activity – 0d	Continuous	167		4.4 (SD 2.4)	171		4.5 (SD 2.5)	
BPI general activity – 84d	Mean change	167		-1.88 (SD 3.1)	171		-2.29 (SD 3.14)	MD=0.410 (CI: -0.255, 1.075)
BPI walking ability – 0d	Continuous	167		4 (SD 2.6)	171		4.4 (SD 2.6)	
BPI walking ability – 84d	Mean change	167		-1.82 (SD 2.97)	171		-2.31 (SD 3.01)	MD=0.490 (CI: -0.148, 1.128)
BPI normal work – 0d	Continuous	167		3.7 (SD 2.7)	171		4.1 (SD 2.5)	
BPI normal work – 84d	Mean change	167		-1.49 (SD 2.97)	171		-1.86 (SD 3.01)	MD=0.370 (CI: -0.268, 1.008)
BPI relationship with other people – 0d	Continuous	167		2.6 (SD 2.5)	171		2.8 (SD 2.5)	
BPI relationship with other people – 84d	Mean change	167		-0.77 (SD 2.97)	171		-1.32 (SD 3.01)	MD=0.550 (CI: -0.088, 1.188)
BPI enjoyment of life – 0d	Continuous	167		3.5 (SD 2.5)	171		3.9 (SD 2.6)	
BPI enjoyment of life – 84d	Mean change	167		-1.59 (SD 2.97)	171		-2.15 (SD 3.01)	MD=0.560 (CI: -0.078, 1.198)
major adverse events (defined as leading to withdrawal):								
any major adverse event – 84d	Dichotomous	167	9	(5.4%)	171	21	(12.3%)	OR=0.407 (CI: 0.181, 0.917)
adverse events:								
any adverse event – 84d	Dichotomous	167	123	(73.7%)	171	145	(84.8%)	OR=0.501 (CI: 0.292, 0.861)
Constipation	Dichotomous	167	9	(5.4%)	171	11	(6.4%)	OR=0.829 (CI: 0.334, 2.054)
Diarrhoea	Dichotomous	167	6	(3.6%)	171	11	(6.4%)	OR=0.542 (CI: 0.196, 1.501)
Dizziness – 84d	Dichotomous	167	2	(1.2%)	171	10	(5.8%)	OR=0.195 (CI: 0.042, 0.905)
Nausea	Dichotomous	167	3	(1.8%)	171	24	(14.0%)	OR=0.112 (CI: 0.033, 0.380)
Somnolence – 84d	Dichotomous	167	14	(8.4%)	171	37	(21.6%)	OR=0.331 (CI: 0.172, 0.639)
Vomiting	Dichotomous	167	2	(1.2%)	171	9	(5.3%)	OR=0.218 (CI: 0.046, 1.025)
treatment withdrawal:								
unspecified/other reason – 84d	Dichotomous	167	8	(4.8%)	171	8	(4.7%)	OR=1.025 (CI: 0.376, 2.798)

[a] estimated from graph using ruler
[b] Table says this is a mean difference but text says it is the figures at week 12. As no baseline given, assumed it was the value at 12 weeks
[c] based on BPI Sleep
[d] average of all 7 inference scores

Comments	1 patient in 40mg group did not receive drug and was not assessed

Definitions of abbreviations are given at the end of this document.

Study	Yucel et al. (2005)
Pain category	Mixed (central and peripheral) or unclear if mixed
Study design	Country: Turkey Design: Parallel Inclusion criteria: Neuropathic pain for longer than 6 months with at least 4cm on 10cm VASpi- patients were subjected to experimentally induced pain but this data was not used in this review Exclusion criteria: pain other than neuropathic pain, pain of mixed origin, previous hypersensitivity to venlafaxine, experience of MI in last 6 months or current being treated for angina pectoris, alcohol or drug addiction, bipolar depression, psychotic disorder, major depressive treatment with monoamine oxidase inhibitors Study length (days): 56 Intention-to-treat analysis? No
Participants	Total number of patients: 60 Number of males: 24 (40.0%) Underlying cause of neuropathic pain: Mixed neuropathic pain Mean duration of NP (in months): not reported Baseline pain severity: 7.7 (VAS (average of arm medians)) Mean age: 50.2066666666667
Intervention(s)	(1) Venlafaxine 75 mg/d Intervention: venlafaxine Length of treatment (weeks): 8 Fixed/flexible dose regimen: Fixed dose Set dose: 75mg/d (2) Venlafaxine 150mg/d Intervention: venlafaxine Length of treatment (weeks): 8 Fixed/flexible dose regimen: Fixed dose Set dose: 150mg/d (3) Placebo Intervention: placebo Length of treatment (weeks): 8 Fixed/flexible dose regimen: Fixed dose
Concomitant treatments	Drug free baseline period? No Concomitant pain treatment allowed? Unclear (no anti-depressants or anti-convulsants were permitted but not clear if opioids were allowed; 500mg paracetamol (3-4 tablets per day) was permitted as rescue analgesia)
Outcomes measures and effect sizes	**VENLAFAXINE 75 MG/D** — **N k mean**; **VENLAFAXINE 150MG/D** — **N k mean**; **Δ**

pain score:								
VAS – 0d[a]	Continuous	17		med: 7 [rng 5–10]	17		med: 8 [rng 5–10]	
VAS – 56d[a]	Mean change	17		med: 4 [rng 0–8]	17		med: 4 [rng -3–7]	
VAS – 56d[a]	Continuous	17		med: 4 [rng 0–6]	17		med: 4 [rng 0–8]	
major adverse events (defined as leading to withdrawal):								
any major adverse event – 56d	Dichotomous	20	1	(5.0%)	20	3	(15.0%)	OR=0.298 (CI: 0.028, 3.146)
adverse events:								
any adverse event – 56d[b]	Dichotomous	20	9	(45.0%)	20	14	(70.0%)	OR=0.351 (CI: 0.096, 1.287)

[a] only medians reported
[b] rate of each side effect not given but included nausea-vomiting, dizziness and somnolence

		VENLAFAXINE 75 MG/D			PLACEBO			
		N	k	mean	N	k	mean	Δ
pain score:								
VAS – 0d[a]	Continuous	17		med: 7 [rng 5–10]	18		med: 8 [rng 6–10]	
VAS – 56d[a]	Mean change	17		med: 4 [rng 0–8]	18		med: 1 [rng -1–6]	
VAS – 56d[a]	Continuous	17		med: 4 [rng 0–6]	18		med: 7 [rng 0–10]	
major adverse events (defined as leading to withdrawal):								
any major adverse event – 56d	Dichotomous	20	1	(5.0%)	20	1	(5.0%)	OR=1.000 (CI: 0.058, 17.181)
adverse events:								
any adverse event – 56d[b]	Dichotomous	20	9	(45.0%)	20	11	(55.0%)	OR=0.669 (CI: 0.193, 2.327)

[a] only medians reported
[b] rate of each side effect not given but included nausea-vomiting, dizziness and somnolence

		VENLAFAXINE 150MG/D			PLACEBO			
		N	k	mean	N	k	mean	Δ
pain score:								
VAS – 0d[a]	Continuous	17		med: 8 [rng 5–10]	18		med: 8 [rng 6–10]	
VAS – 56d[a]	Continuous	17		med: 4 [rng 0–8]	18		med: 7 [rng 0–10]	
VAS – 56d[a]	Mean change	17		med: 4 [rng -3–7]	18		med: 1 [rng -1–6]	
major adverse events (defined as leading to withdrawal):								
any major adverse event – 56d	Dichotomous	20	3	(15.0%)	20	1	(5.0%)	OR=3.353 (CI: 0.318, 35.364)
adverse events:								
any adverse event – 56d[b]	Dichotomous	20	14	(70.0%)	20	11	(55.0%)	OR=1.909 (CI: 0.520, 7.007)

[a] only medians reported
[b] rate of each side effect not given but included nausea-vomiting, dizziness and somnolence

Comments	global effficacy and affect on daily activities were reported in the study but not extracted as they did not use measurement tools where the results would be combinable with the results from other studies

Definitions of abbreviations are given at the end of this document.

Study	Ziegler et al. (2010)
Pain category	Peripheral pain
Study design	Country: Europe Design: Parallel Inclusion criteria: =18 years with type1 or type 2 diabetes, symptoms for 6 months to 5 years (=4 on NRS), A1C < 12% Exclusion criteria: other conditions contributing to chronic pain, MI or clinically relevant cardiac dysfunction in last year, chronic alcohol or drug abuse in last year or any drug use that might interfere with trial results, 2nd or 3rd degree atrioventricular block Study length (days): 140 Intention-to-treat analysis? Yes
Participants	Total number of patients: 357 Number of males: 184 (51.5%) Underlying cause of neuropathic pain: Painful diabetic neuropathy Mean duration of NP (in months): 38.4 Baseline pain severity: 6.46666666666667 (NRS (average of arm means)) Mean age: 57.9 (SD: 10.6)
Intervention(s)	(1) Lacosamide 600 mg/d Intervention: lacosamide Length of treatment (weeks): 18 Fixed/flexible dose regimen: Fixed dose Set dose: 600mg/d Notes: 6 week titration, 12 week maintenance; titration period was standard: 100 mg/d with weekly increases of 100 mg/d to 600 mg/d target dosage (2) Lacosamide 400 mg/d Intervention: lacosamide Length of treatment (weeks): 18 Fixed/flexible dose regimen: Fixed dose Set dose: 400mg/d Notes: this group was further randomised to slow titration (100 mg/d for 3 weeks, then weekly increases of 100 mg/d, to 400 mg/d target dose at week 6) and standard titration (100 mg/d with weekly increases of 100 mg/d to 400 mg/d target dosage) (3) Placebo Intervention: placebo Length of treatment (weeks): 18 Fixed/flexible dose regimen: Fixed dose
Concomitant treatments	Drug free baseline period? Yes (duration: 7d) Concomitant pain treatment allowed? No (paracetamol =2 g/day as rescue medication (no others allowed))
Outcomes measures and effect sizes	

	LACOSAMIDE 600 MG/D			LACOSAMIDE 400 MG/D			
	N	k	mean	N	k	mean	Δ

adverse events:									
any adverse event – 126d	Dichotomous	133	86	(64.7%)	150	88	(58.7%)	OR=0.893 (CI: 0.402, 1.982)
Fatigue – 126d	Dichotomous	133			150			OR=0.870 (CI: 0.315, 2.405)
headache – 126d	Dichotomous	133			150			OR=3.051 (CI: 1.148, 8.109)
Nausea – 126d	Dichotomous	133			150			OR=1.554 (CI: 0.633, 3.813)
vertigo – 126d	Dichotomous	133			150			OR=4.111 (CI: 0.839, 20.146)
Vomiting – 126d	Dichotomous	133			150			
ITT/LOCF (last-observation carried forward)								
pain score:								
NRS/NRS Pain – 0d	Continuous	133		6.4 (SD 1.4)	150		6.4 (SD 1.3)	
NRS/NRS Pain – 126d	Mean difference from baseline to average f-u	132		-1.86	149		-1.9	MD=0.040
VAS – 63d[a]	Mean difference from baseline to average f-u	131		-18.8	149		-18.1	MD=-0.700
at least 30% pain reduction (NRS) – 126d[b]	Dichotomous from baseline to average f-u	132	66		149	64		OR=1.328 (CI: 0.829, 2.127)
at least 50% pain reduction (NRS) – 105d[c]	Dichotomous	132	39	(29.5%)	149	42	(28.2%)	OR=1.068 (CI: 0.637, 1.791)
at least 50% pain reduction (NRS) – 126d[c]	Dichotomous	132	35	(26.5%)	149	43	(28.9%)	
patient-reported global improvement:								
PGIC - much worse – 126d	Dichotomous	132	2	(1.5%)	149	1	(0.7%)	OR=2.277 (CI: 0.204, 25.402)
PGIC - moderately worse – 126d	Dichotomous	132	1	(0.8%)	149	1	(0.7%)	OR=1.130 (CI: 0.070, 18.243)
PGIC - minimally worse – 126d	Dichotomous	132	1	(0.8%)	149	2	(1.3%)	OR=0.561 (CI: 0.050, 6.259)
PGIC - no change – 126d	Dichotomous	132	16	(12.1%)	149	16	(10.7%)	OR=1.147 (CI: 0.549, 2.394)
PGIC - minimally better – 126d	Dichotomous	132	21	(15.9%)	149	36	(24.2%)	OR=0.594 (CI: 0.326, 1.080)
PGIC - moderately better – 126d	Dichotomous	132	19	(14.4%)	149	20	(13.4%)	OR=1.085 (CI: 0.551, 2.134)
PGIC - much better – 126d	Dichotomous	132	17	(12.9%)	149	20	(13.4%)	OR=0.953 (CI: 0.476, 1.908)
patient-reported improvement in daily physical and emotional functioning, including sleep:								
NRS Sleep – 84d[d]	Mean difference from baseline to average f-u	96		-2.29	122		-1.92	MD=-0.370
major adverse events (defined as leading to withdrawal):								
any major adverse event – 126d	Dichotomous	133	31	(23.3%)	150	17	(11.3%)	OR=0.447 (CI: 0.145, 1.380)
any major adverse event – 126d	Dichotomous	74	31	(23.3%)	150	17	(11.3%)	OR=0.447 (CI: 0.145, 1.380)
adverse events:								
Dizziness – 126d	Dichotomous	133	26	(19.5%)	150	11	(7.3%)	OR=1.370 (CI: 0.633, 2.962)

Dizziness – 126d	Dichotomous	133	26	(19.5%)	73	11	(7.3%)	OR=1.370 (CI: 0.633, 2.962)
Fatigue – 126d	Dichotomous	133	12	(9.0%)	150	15	(10.0%)	
headache – 126d	Dichotomous	133	7	(5.3%)	150	9	(6.0%)	
Nausea – 126d	Dichotomous	133	15	(11.3%)	150	6	(4.0%)	
vertigo – 126d	Dichotomous	133	12	(9.0%)	150	9	(6.0%)	
Vomiting – 126d	Dichotomous	133	7	(5.3%)	150	2	(1.3%)	
treatment withdrawal:								
due to lack of efficacy – 126d	Dichotomous	133	6	(4.5%)	150	4	(2.7%)	OR=1.542 (CI: 0.336, 7.077)
due to lack of efficacy – 126d	Dichotomous	74	6	(4.5%)	150	4	(2.7%)	OR=1.542 (CI: 0.336, 7.077)
unspecified/other reason – 126d	Dichotomous	74	5	(3.8%)	150	4	(2.7%)	OR=0.500 (CI: 0.055, 4.554)
unspecified/other reason – 126d	Dichotomous	133	5	(3.8%)	150	4	(2.7%)	OR=0.500 (CI: 0.055, 4.554)
withdrawal of consent – 126d	Dichotomous	74	14	(10.5%)	150	10	(6.7%)	OR=1.014 (CI: 0.334, 3.083)
withdrawal of consent – 126d	Dichotomous	133	14	(10.5%)	150	10	(6.7%)	OR=1.014 (CI: 0.334, 3.083)
protocol deviation – 126d	Dichotomous	74	1	(0.8%)	150	1	(0.7%)	OR=2.041 (CI: 0.126, 33.096)
protocol deviation – 126d	Dichotomous	133	1	(0.8%)	150	1	(0.7%)	OR=2.041 (CI: 0.126, 33.096)
poor compliance – 126d	Dichotomous	74	2	(1.5%)	150	1	(0.7%)	OR=2.041 (CI: 0.126, 33.096)
poor compliance – 126d	Dichotomous	133	2	(1.5%)	150	1	(0.7%)	OR=2.041 (CI: 0.126, 33.096)

[a] least squares mean; outcome from baseline to entire treatment period (weeks 1 to 18)
[b] OR ≥2 point reduction in NRS; outcome from baseline to weeks 14 to 18
[c] OR ≥2 point reduction in NRS; numbers estimated from percentages so may not be absolutely accurate
[d] least squares mean; outcome from baseline to entire maintenance period (weeks 6 to 18)

		LACOSAMIDE 600 MG/D			**PLACEBO**			
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**
adverse events:								
any adverse event – 126d	Dichotomous	133	86	(64.7%)	74	40	(54.1%)	
Fatigue – 126d	Dichotomous	133			74			OR=1.369 (CI: 0.463, 4.048)
headache – 126d	Dichotomous	133			74			OR=2.000 (CI: 0.405, 9.885)
Nausea – 126d	Dichotomous	133			74			OR=4.576 (CI: 1.017, 20.597)
vertigo – 126d	Dichotomous	133			74			OR=3.570 (CI: 0.777, 16.408)
Vomiting – 126d	Dichotomous	133			74			OR=8.834 (CI: 0.497, 156.897)
ITT/LOCF (last-observation carried forward)								
pain score:								
NRS/NRS Pain – 0d	Continuous	133		6.4 (SD 1.4)	74		6.6 (SD 15)	

NRS/NRS Pain – 126d	Mean difference from baseline to average f-u	132		-1.86	74		-1.5	MD=-0.360 (CI: -0.870, 0.150)
VAS – 63d[a]	Mean difference from baseline to average f-u	131		-18.8	74		-12.8	MD=-6.000
at least 30% pain reduction (NRS) – 126d[b]	Dichotomous from baseline to average f-u	132	66		74	26		OR=1.800 (CI: 5.162, 0.628)
at least 50% pain reduction (NRS) – 105d[c]	Dichotomous	132	39	(29.5%)	74	12	(16.2%)	OR=2.167 (CI: 1.052, 4.462)
at least 50% pain reduction (NRS) – 126d[c]	Dichotomous	132	35	(26.5%)	74	17	(23.0%)	
McGill VAS – 63d	Mean difference from baseline to average f-u	132			74			MD=-5.990 (CI: -11.184, -0.796)
patient-reported global improvement:								
PGIC - much worse – 126d	Dichotomous	132	2	(1.5%)	74	1	(1.4%)	OR=1.123 (CI: 0.100, 12.599)
PGIC - moderately worse – 126d	Dichotomous	132	1	(0.8%)	74	4	(5.4%)	OR=0.134 (CI: 0.015, 1.218)
PGIC - minimally worse – 126d	Dichotomous	132	1	(0.8%)	74	0	(0.0%)	OR=1.700 (CI: 0.068, 42.250)
PGIC - no change – 126d	Dichotomous	132	16	(12.1%)	74	16	(21.6%)	OR=0.500 (CI: 0.234, 1.070)
PGIC - minimally better – 126d	Dichotomous	132	21	(15.9%)	74	16	(21.6%)	OR=0.686 (CI: 0.333, 1.414)
PGIC - moderately better – 126d	Dichotomous	132	19	(14.4%)	74	12	(16.2%)	OR=0.869 (CI: 0.396, 1.907)
PGIC - much better – 126d	Dichotomous	132	17	(12.9%)	74	6	(8.1%)	OR=1.675 (CI: 0.630, 4.454)
patient-reported improvement in daily physical and emotional functioning, including sleep:								
NRS Sleep – 84d[d]	Mean difference from baseline to average f-u	96		-2.29	63		-1.28	MD=-0.640 (CI: -1.169, -0.111)
major adverse events (defined as leading to withdrawal):								
any major adverse event – 126d	Dichotomous	133	31	(23.3%)	74	4	(5.4%)	OR=0.188 (CI: 0.064, 0.556)
any major adverse event – 126d	Dichotomous	74	31	(23.3%)	133	4	(5.4%)	OR=0.188 (CI: 0.064, 0.556)
adverse events:								
Dizziness – 126d	Dichotomous	133	26	(19.5%)	77	2	(2.7%)	OR=9.112 (CI: 2.099, 39.559)
Dizziness – 126d	Dichotomous	133	26	(19.5%)	74	2	(2.7%)	OR=9.112 (CI: 2.099, 39.559)
Fatigue – 126d	Dichotomous	133	12	(9.0%)	74	5	(6.8%)	
headache – 126d	Dichotomous	133	7	(5.3%)	74	2	(2.7%)	
Nausea – 126d	Dichotomous	133	15	(11.3%)	74	2	(2.7%)	
vertigo – 126d	Dichotomous	133	12	(9.0%)	74	2	(2.7%)	
Vomiting – 126d	Dichotomous	133	7	(5.3%)	74	0	(0.0%)	
treatment withdrawal:								
due to lack of efficacy – 126d	Dichotomous	74	6	(4.5%)	133	3	(4.1%)	OR=0.894 (CI: 0.217, 3.685)
due to lack of efficacy – 126d	Dichotomous	133	6	(4.5%)	74	3	(4.1%)	OR=0.894 (CI: 0.217, 3.685)
unspecified/other reason – 126d	Dichotomous	74	5	(3.8%)	133	1	(1.4%)	OR=0.351 (CI: 0.040, 3.060)
unspecified/other reason – 126d	Dichotomous	133	5	(3.8%)	74	1	(1.4%)	OR=0.351 (CI: 0.040, 3.060)
withdrawal of consent – 126d	Dichotomous	74	14	(10.5%)	133	5	(6.8%)	OR=0.616 (CI: 0.213, 1.784)
withdrawal of consent – 126d	Dichotomous	133	14	(10.5%)	74	5	(6.8%)	OR=0.616 (CI: 0.213, 1.784)
protocol deviation – 126d	Dichotomous	74	1	(0.8%)	133	1	(1.4%)	OR=1.808 (CI: 0.111, 29.337)
protocol deviation – 126d	Dichotomous	133	1	(0.8%)	74	1	(1.4%)	OR=1.808 (CI: 0.111, 29.337)
poor compliance – 126d	Dichotomous	74	2	(1.5%)	133	1	(1.4%)	OR=0.897 (CI: 0.080, 10.065)

poor compliance – 126d	Dichotomous	133	2	(1.5%)	74	1	(1.4%)	OR=0.897 (CI: 0.080, 10.065)

[a] least squares mean; outcome from baseline to entire treatment period (weeks 1 to 18)
[b] OR ≥2 point reduction in NRS; outcome from baseline to weeks 14 to 18
[c] OR ≥2 point reduction in NRS; numbers estimated from percentages so may not be absolutely accurate
[d] least squares mean; outcome from baseline to entire maintenance period (weeks 6 to 18)

		LACOSAMIDE 400 MG/D			**PLACEBO**			
		N	**k**	**mean**	**N**	**k**	**mean**	**Δ**
adverse events:								
any adverse event – 126d	Dichotomous	150	88	(58.7%)	74	40	(54.1%)	
Fatigue – 126d	Dichotomous	150			74			OR=1.533 (CI: 0.535, 4.394)
headache – 126d	Dichotomous	150			74			OR=2.298 (CI: 0.484, 10.916)
Nausea – 126d	Dichotomous	150			74			OR=1.500 (CI: 0.295, 7.619)
vertigo – 126d	Dichotomous	150			74			OR=2.298 (CI: 0.484, 10.916)
Vomiting – 126d	Dichotomous	150			74			OR=2.508 (CI: 0.119, 52.918)
ITT/LOCF (last-observation carried forward)								
pain score:								
NRS/NRS Pain – 0d	Continuous	150		6.4 (SD 1.3)	74		6.6 (SD 15)	
NRS/NRS Pain – 126d	Mean difference from baseline to average f-u	149		-1.9	74		-1.5	MD=-0.400 (CI: -0.929, 0.129)
VAS – 63d[a]	Mean difference from baseline to average f-u	149		-18.1	74		-12.8	MD=-5.300
at least 30% pain reduction (NRS) – 126d[b]	Dichotomous from baseline to average f-u	149	64		74	26		OR=1.400 (CI: 7.199, 0.272)
at least 50% pain reduction (NRS) – 105d[c]	Dichotomous	149	42	(28.2%)	74	12	(16.2%)	OR=2.028 (CI: 0.993, 4.141)
at least 50% pain reduction (NRS) – 126d[c]	Dichotomous	149	43	(28.9%)	74	17	(23.0%)	
McGill VAS – 63d	Mean difference from baseline to average f-u	149			74			MD=-5.320 (CI: -10.396, -0.244)
patient-reported global improvement:								
PGIC - much worse – 126d	Dichotomous	149	1	(0.7%)	74	1	(1.4%)	OR=0.493 (CI: 0.030, 7.998)
PGIC - moderately worse – 126d	Dichotomous	149	1	(0.7%)	74	4	(5.4%)	OR=0.118 (CI: 0.013, 1.078)
PGIC - minimally worse – 126d	Dichotomous	149	2	(1.3%)	74	0	(0.0%)	OR=2.525 (CI: 0.120, 53.278)
PGIC - no change – 126d	Dichotomous	149	16	(10.7%)	74	16	(21.6%)	OR=0.436 (CI: 0.204, 0.931)
PGIC - minimally better – 126d	Dichotomous	149	36	(24.2%)	74	16	(21.6%)	OR=1.155 (CI: 0.592, 2.254)
PGIC - moderately better – 126d	Dichotomous	149	20	(13.4%)	74	12	(16.2%)	OR=0.801 (CI: 0.368, 1.742)
PGIC - much better – 126d	Dichotomous	149	20	(13.4%)	74	6	(8.1%)	OR=1.757 (CI: 0.674, 4.582)
patient-reported improvement in daily physical and emotional functioning, including sleep:								
NRS Sleep – 84d[d]	Mean difference from baseline to average f-u	122		-1.92	63		-1.28	MD=-1.000 (CI: -1.549, -0.451)

major adverse events (defined as leading to withdrawal):									
any major adverse event – 126d	Dichotomous	150	17	(11.3%)	133	4	(5.4%)	OR=0.421 (CI: 0.221, 0.802)	
any major adverse event – 126d	Dichotomous	150	17	(11.3%)	74	4	(5.4%)	OR=0.421 (CI: 0.221, 0.802)	
adverse events:									
Dizziness – 126d	Dichotomous	150	11	(7.3%)	74	2	(2.7%)	OR=6.653 (CI: 1.421, 31.151)	
Dizziness – 126d	Dichotomous	73	11	(7.3%)	77	2	(2.7%)	OR=6.653 (CI: 1.421, 31.151)	
Fatigue – 126d	Dichotomous	150	15	(10.0%)	74	5	(6.8%)		
headache – 126d	Dichotomous	150	9	(6.0%)	74	2	(2.7%)		
Nausea – 126d	Dichotomous	150	6	(4.0%)	74	2	(2.7%)		
vertigo – 126d	Dichotomous	150	9	(6.0%)	74	2	(2.7%)		
Vomiting – 126d	Dichotomous	150	2	(1.3%)	74	0	(0.0%)		
treatment withdrawal:									
due to lack of efficacy – 126d	Dichotomous	150	4	(2.7%)	74	3	(4.1%)	OR=0.580 (CI: 0.160, 2.101)	
due to lack of efficacy – 126d	Dichotomous	150	4	(2.7%)	133	3	(4.1%)	OR=0.580 (CI: 0.160, 2.101)	
unspecified/other reason – 126d	Dichotomous	150	4	(2.7%)	74	1	(1.4%)	OR=0.701 (CI: 0.184, 2.668)	
unspecified/other reason – 126d	Dichotomous	150	4	(2.7%)	133	1	(1.4%)	OR=0.701 (CI: 0.184, 2.668)	
withdrawal of consent – 126d	Dichotomous	150	10	(6.7%)	74	5	(6.8%)	OR=0.607 (CI: 0.260, 1.417)	
withdrawal of consent – 126d	Dichotomous	150	10	(6.7%)	133	5	(6.8%)	OR=0.607 (CI: 0.260, 1.417)	
protocol deviation – 126d	Dichotomous	150	1	(0.7%)	74	1	(1.4%)	OR=0.886 (CI: 0.055, 14.304)	
protocol deviation – 126d	Dichotomous	150	1	(0.7%)	133	1	(1.4%)	OR=0.886 (CI: 0.055, 14.304)	
poor compliance – 126d	Dichotomous	150	1	(0.7%)	74	1	(1.4%)	OR=0.440 (CI: 0.039, 4.904)	
poor compliance – 126d	Dichotomous	150	1	(0.7%)	133	1	(1.4%)	OR=0.440 (CI: 0.039, 4.904)	

[a] least squares mean; outcome from baseline to entire treatment period (weeks 1 to 18)
[b] OR ≥2 point reduction in NRS; outcome from baseline to weeks 14 to 18
[c] OR ≥2 point reduction in NRS; numbers estimated from percentages so may not be absolutely accurate
[d] least squares mean; outcome from baseline to entire maintenance period (weeks 6 to 18)

Comments	proportion with 50% response reported at 15 and 18 weeks but only percentages (not denominators) and unable to calculate correctly; bottom of the article (which is a 'brief report') states that the costs of publication were defrayed in part by the payment of page charges and, thus, this article must be marked 'advertisement'; ITT included those who received at least 1 dose of medication with at least one post-baseline efficacy assessment (2 patients randomised - 1 in 400 mg/d and 1 in 600 mg/d group - were not included in the ITT population) - LOCF was performed

Definitions of abbreviations are given at the end of this document.

Abbreviations

Abbreviation	Term
AEDs	anti-epileptic drugs
ART	anti-retroviral therapy
avg.	average
BOCF	baseline observation carried forward (a form of ITT)
BPI	Brief Pain Inventory
BDI	Beck's Depression Inventory
CBD	cannabidiol
CBME	cannabis based medicine extract
CI	confidence interval
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
CPSP	central post-stroke pain
DSM-IV	diagnostic and statistical manual of mental disorders
ECG	electrocardiogram
f-u	follow-up
GATE	global assessment of therapeutic effect
HADS	Hospital Anxiety and Depression Scale
HAMD	Hamilton Depression Rating Scale
HbA1c	glycated haemoglobin
HIV	human immunodeficiency virus
HIV DSP	human immunodeficiency virus distal sensory polyneuropathy
IQR	interquartile range
ITT	intention-to-treat
LOCF	last observation carried forward (a form of ITT)
LS	least squares
MAOI	monoamine oxidase inhibitor
MD	mean difference
MI	myocardial infarction
MOS	Medical Outcomes Study sleep scale
MPQ	McGill Pain Questionnaire
MS	multiple sclerosis
NCP	neuropathic cancer pain
NP	neuropathic pain
NRS	numerical rating scale
NPS/NPRS	numerical pain rating scale
NSAIDs	non-steroidal anti-inflammatory drugs

OR	odds ratio
OTC	over-the-counter
PDN	painful diabetic neuropathy
PGIC	patient reported global impression of change
PGI-I	patient reported global impression of improvement
PHN	post-herpetic neuralgia
PHQ-15	patient health questionnaire with 15 somatic symptoms
POMS	profile of mood states
PPI	present pain intensity
SCI	spinal cord injury
SD	standard deviation
SE	standard error
SF	short form
SNRI	serotonin–norepinephrine reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor
TAD	tricyclic anti-depressants
TB	tuberculosis
TENS	transcutaneous electrical nerve stimulation
THC	delta-9-tetrahydrocannabinol
TIA	transient ischaemic attack
VAS	visual analogue scale
VASpr	visual analogue scale for pain relief
VASpi	visual analogue scale for pain intensity
VRS	verbal rating scale
VRSpr	verbal rating scale for pain relief
VRSpi	verbal rating scale for pain intensity