Drug Class Review

Neuropathic Pain

Final Update 1 Evidence Tables

June 2011

The Agency for Healthcare Research and
Quality has not yet seen or approved this report

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The medical literature relating to this topic is scanned periodically. (See http://www.ohsu.edu/xd/research/centers-institutes/evidence-based-policy-center/derp/documents/methods.cfm for description of scanning process). Prior versions of this report can be accessed at the DERP website.

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Abbreviations used in evidence tables

Abbreviation	Term
ACT	Active-control trial
AE	Adverse event
AED	Anti-epileptic drugs
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
bid	Twice daily
BMI	Body mass index
BPI	Brief Pain Inventory
CCT	Controlled clinical trial
CES-D	Center for Epidemiologic Studies-Depression Scale
CESD-SF	The Center for Epidemiologic Studies Depression Scale-Short Form
CGIC	Clinical Global Impression of Change
CI	Confidence interval
CL_{cr}	Creatinine clearance rates
CNS	Central nervous system
COX-2	Cyclooxygenase-2 inhibitor
CPSP	Central post-stroke pain
CR	Controlled release
CRPS	Complex regional pain syndrome
CV	Cardiovascular
CVS	Cardiovascular system
d	Day
DAAC	Duration Adjusted Average Change
DB	Double-blind
dL	Deciliter
DM	Diabetes Mellitus
DPN	Diabetic peripheral neuropathic pain
DPRS	Daily Pain Rating Scale
ECG	Electrocardiogram
EEG	Electroencephalogram
EF	Ejection fraction
EQ-5D	European Quality of Life-5 Dimensions
ER	Extended release
FDA	US Food and Drug Administration
FU	Follow-up
g	Gram
GATE	Global Assessment of Therapeutic Effect
GI	Gastrointestinal
GP	General practitioner

Abbreviation	Term
h	Hour
HADS	Hospital Anxiety and Depression Scale
HbA1c	Hemoglobin A1c
HDL-C	High density lipoprotein cholesterol
HIV-DSP	HIV associated distal sensory polyneuropathy
HMO	Health maintenance organization
HR	Hazard ratio
HRQOL	Health-related quality of life
ICD-10	International Classification of Diseases, Tenth Revision
ICD-9	International Classification of Diseases, Ninth Revision
IR	Immediate release
ITT	Intent-to-treat
L	Liter
LA	Long acting
LANSS	Leeds assessment of neuropathic symptoms and signs questionnaire
LDL-C	Low-density lipoprotein cholesterol
LOCF	Last Observation Carried Forward
LS means	Least squares means
MANCOVA	Multivariate analysis of covariance
mcg	Microgram
MDD	Major depressive disorder
mg	Milligram
min	Minute
mL	Milliliter
MMRM	Mixed-model repeated measures model
MNSI	Michigan Neuropathy Screening Instrument
mo	Month
MOS-Sleep	Medical Outcome Study Sleep Scale
MPQ	McGill Pain Questionnaire
MS	Multiple sclerosis
MSQOL-54	54-item Multiple Sclerosis Quality-of-Life Questionnaire
N	Sample size (entire sample)
n	Subgroup sample size
NA	Not applicable
NCI-CTC	National Cancer Institute-Common Toxicity Criteria
NP	Neuropathic pain
NPRS	Numeric Pain Rating Scale
NPS	Neuropathic Pain Scale
NPSI	Neuropathic Pain Symptom Inventory
NR	Not reported

Abbreviation	Term
NS	Not significant
NSD	No significant difference
OR	Odds ratio
P	*P* value
P	Placebo
PCT	Placebo-controlled trial
PGIC	Patient Global Impression of Change
PHN	postherpetic neuralgia
PMPS	postmastectomy pain syndrome
POMS	Profile of Mood State
PP	Primary Progressive
PPI	Present Pain Intensity index
PPY	Per person year
QANeP	Quantitative Assessments of Neuropathic Pain
qd	Once daily
QOL	Quality of life
RCT	Randomized controlled trial
RR	Relapse-remitting
RR	Relative risk
SB	Single-blind
SCI	Spinal cord injury
SD	Standard deviation
SDLP	Standard deviation of lateral position
SE	Standard error
SF-MPQ	Short Form McGill Pain Questionnaire
SP	Secondary Progressive
SR	Sustained release
STAI	Spielberger State-Trait Anxiety Scales
tid	Three times daily
URTI	Upper respiratory tract infection
VAS	Visual analog scale
vs.	Compared with (versus)
WD	Withdrawal
XR	Extended release
y	Year

Evidence Table 1. Update 1: Data abstraction of head-to-head trials

Author Year Country Trial name (Quality rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics
Arai, 2010 Japan Fair	Cancer patients diagnosed as having neuropathic pain (both sharp pain and burning or shooting pain, with or without allodynia) that was not completely controlled with opioids analgesics and NSAIDs.	A: Gabapentin 200 mg + imipramine 10 mg every 12 hours B: Gabapentin 200 mg every 12 hours C: Gabapentin 400 mg every 12 hours D: Imipramine 10 mg every 12 hours	Opioids ("rescue" doses), and NSAIDs already administered remained unchanged.	66.6 years 65.4% male Ethnicity NR	Weight: 53 kg Daily opioid dose at baseline/day 7: 47.7 mg/d Karnofsky performance score: 61.1

Evidence Table 1. Update 1: Data abstraction of head-to-head trials

Author Year Country Trial name (Quality rating-optional)	N	Number withdrawn/ lost to follow-up/analyzed	Results
Arai, 2010 Japan Fair	52	3/0/52	Gabapentin 200 mg + Imipramine 10 mg BID vs Gabapentin 200 mg BID vs Gabapentin 400 mg BID vs Imipramine 10 mg BID Total pain score: Baseline: 7.0 vs 7.0 vs 6.5 vs 7.0; P=0.970 Day 7: 2.0 vs 4.5 vs 4.0 vs 5.0; P=0.005 Change, from baseline to day 7: -5.0 vs -2.5 vs -2.5 vs -2.0 Pain episodes: Baseline: 4.5 vs 4.0 vs 5.0 vs 4.0; P=0.749 Day 7: 1.0 vs 3.0 vs 3.5 vs 4.0; P<0.001 Change, from baseline to day 7: -3.5 vs -1.0 vs -1.5 vs 0 Opioid rescue dose at day 7: 8 vs 30 vs 25 vs 25; P=0.008

Evidence Table 1. Update 1: Data abstraction of head-to-head trials

Author Year Country Trial name (Quality rating-optional)	Adverse events reported	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Arai, 2010 Japan Fair	Gabapentin 200 mg + Imipramine 10 mg BID vs Gabapentin 200 mg BID vs Gabapentin 400 mg BID vs Imipramine 10 mg BID Mild drowsiness: 5 (35.7%) vs 5 (35.7%) vs 7 (58.3%) vs 4 (33.3%); P=0.559 Mild dizziness: 0 (0%) vs 0 (0%) vs 4 (33.3%) vs 1 (8.3%); P=0.014 Severe dizziness: 0 (0%) vs 0 (0%) vs 3 (25%) vs 0 (0%); P=0.015 Nausea: 1 (7.1%) vs 1 (7.1%) vs 1 (8.3%) vs 1 (8.3%); P=0.999	Gabapentin 200 mg + Imipramine 10 mg BID vs Gabapentin 200 mg BID vs Gabapentin 400 mg BID vs Imipramine 10 mg BID Total withdrawals: 0 (0%) vs 0 (0%) vs 3 (25%) vs 0 (0%) Due to AE: 0 (0%) vs 0 (0%) vs 3 (25%) vs 0 (0%)	NR	As pain control was not sufficient in the gabapentin 200 BID, gabapentin 400 BID, and Imipramine 10 mg groups, imipramine or gabapentin was prescribed at the second visit in order for the patients to take gabapentin 200 or 400 mg, and imipramine 10 mg every 12 hours orally. At 7 days after the second visit, the median (interquartile range) of the total pain score and paroxysmal pain episodes was 2 (1–3) and 1 (0–1), respectively.

Evidence Table 1. Update 1: Data abstraction of head-to-head trials

Author Year Country Trial name (Quality rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics
Bansal, 2009 India Fair	Males and Females 18-75 years old with painful diabetic neuropathy attending the endocrinology outpatient department of a tertiary-care hospital	Dose titrating study: A: Pregabalin 75mg, 150, 300mg twice daily B: Amitriptyline 10mg, 25mg, 50mg at bedtime	Paracetamol up to 3g per day	54.5 years Unclear Ethnicity NR	Duration of diabetes: 5 years Hypertensives 34 (77%)

Evidence Table 1. Update 1: Data abstraction of head-to-head trials

Author Year Country Trial name (Quality rating-optional)	N	Number withdrawn/ lost to follow-up/analyzed	Results
Bansal, 2009 India Fair	44	7/7/1944	Lamotrigine vs Amitriptyline Baseline: 72.5 vs 70.0; P=0.95 Week 2: 50.0 vs 60.0; P=0.17 Week 4: 50.0 vs 52.5; P=0.30 Week 6: 50.0 vs 52.5; P=0.23 Physician VAS: Baseline: 70.0 vs 70.0; P=0.31 Week 2: 55.0 vs 70.0; P=0.36 Week 4: 50.0 vs 60.0; P=0.38 Week 6: 50.0 vs 60.0; P=0.33 Likert pain Scale: Baseline: 3 vs 3; P=0.67 Week 2: 2 vs 2; P=0.47 Week 4: 2 vs 2; P=0.53 Week 6: 2 vs 2; P=0.38 McGill Pain Questionnaire: Baseline: 9 vs 8; P=0.13 Week 2: 6 vs 6; P=0.65 Week 4: 6 vs 6; P=0.55 Week 6: 6 vs 6; P=0.39

Evidence Table 1. Update 1: Data abstraction of head-to-head trials

Author Year Country Trial name (Quality rating-optional)	Adverse events reported	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Bansal, 2009 India Fair	Amitriptyline vs Pregabalin Increase in sleep: 18 (41%) vs 6 (14); P=0.008 Tiredness: 5 (11%) vs 0 (0%); P=0.07 Dizziness: 2 (5%) vs 3 (7%); P=0.61 Peripheral edema: 0 (0%) vs 2 (4%); P=0.49 Daytime somnolence: 2 (4%) vs 3 (7%); P=1.0 Postural hypotension: Amitriptyline:12 (2%) vs 0 (0%); P=1.0 Flu-like symptoms: 0 (0%) vs 1 (2%); P=1.0 Difficulty in urination: 2 (4%) vs 0 (0%); P=0.49 Dry Mouth: 2 (9%) vs 0 (0%); P=0.49 Constipation: 2 (7%),Pregabalin: 3 (7%); P=0.61 Headache: 0 (0%) vs 1 (2%); P=1.0 Confusion: 0 (0%) vs 1 (2%); P=1.0 Total: 34 (77%) vs 18 (41%); P<0.0001	7/23: 7 study participants randomized but not analyzed while 23 discontinued due to AE but were still analyzed	Pharmaceutical companies provided medications	

Evidence Table 1. Update 1: Data abstraction of head-to-head trials

Author Year Country Trial name (Quality rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics
Baron, 2009a/Baron 2009b (4 weeks non inferiority study + 8 weeks combination therapy study) 14 European countries	Male and female patients≥18 years with PHN or painful DPN, experiencing average pain intensity of >4 in the 4 week comparative phase study and at least 4 on 11 point NPRS during the last 3 days of the combination therapy phase. Patients with PHN included if neuropathic pain was present for ≥3 mo after healing of herpes zoster skin rash. Patients with painful DPN were required to have controlled, treated type 1 or 2 DM with glycosylated hemoglobin ≤11%	4 week comparative study A: 5% Lidocaine medicated plaster B: Pregabalin 8 week combination phase A: 5% lidocaine plaster monotherapy (if they reported NRS -3 ≤4) B: Lidocaine + Pregabalin (up to 600mg/d if NRS-3>4) C: Pregabalin up to 600mg/d D: Pregabalin + 5% lidocaine plaster for 8 weeks	NR	62.2 years Male: 48% Ethnicity: NR (Ethnicity reported as 100% Caucasian in the combination phase)	BMI: 29.7 (5.1) Duration of pain, mean no. of mo: 50.8 (55.2)

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Author Year Country Trial name (Quality rating-optional)	N	Number withdrawn/ lost to follow-up/analyzed	Results
Baron, 2009a/Baron 2009b (4 weeks non inferiority study + 8 weeks combination therapy study) 14 European countries	311	4 week comparative phase: 48/NR/281	*4 week comparative study phase* Lidocaine vs Pregabalin Mean (SD) change in NRS-3 score from baseline: -2.5(2.01) vs -2.3 (1.95), P=NR % of patients with NRS-3 score of ≥30% : 59% vs 54%, P=NR % of patients with NRS-3 score of ≥50%: 38.9% vs 32.1%, P=NR % of patients change from baseline in 'painful' and 'extremely painful' on allodynia severity rating scale: 12.9% vs 17.0%,P=NR Mean change(SD)for EQ-5D estimated scale state from baseline: 0.12 (0.240) vs 0.04 (0.235), P=NR PGIC % of patients very much or much improved: 50.0% vs 47.5%, P=NR PGIC % of patients with minimally improved or no change: 44.4% vs 46.0%, P=NR CGIC % of patients with very much or much improved: 46.5% vs 46.0%, P=NR CGIC % of patients with minimally improved or no change: 49.3% vs 46.0%, P=NR Patients satisfaction with treatment Excellent: 7.6% vs 5.1% Very good: 22.9% vs 24.8% Good: 45.1% vs 38.0% Fair: 14.6% vs 17.5% *8 week combination therapy phase* Lidocaine vs Pregabalin + Lidocaine + Pregabalin vs Pregabalin + Lidocaine Mean (SD)change in NRS -3 score from baseline : -0.7 (1.2) vs -0.6 (1.3) vs -2.5 (1.6) vs -1.7 (1.8), P=NR % patients with PGIC much or very much improved at endpoint: 88.6% vs 87.5% vs 64.9% vs 65.1%, P=NR % patients with CGIC much or very much improved at endpoint: 90% vs 87.5% vs 66.6% vs 62.8%, P=NR % patients reporting satisfaction excellent, very good or good at endpoint: 94.2% vs 91.1% vs 87.7% vs 86.0%, P=NR

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Author Year Country Trial name (Quality rating-optional)	Adverse events reported	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Baron, 2009a/Baron 2009b (4 weeks non inferiority study + 8 weeks combination therapy study) 14 European countries	*4 week comparative treatment phase* Lidocaine vs Placebo % of patients with any AE: 18.7% vs 46.4% 5 of patients with drug related AE Dizziness: 0% vs 11.8% Fatigue: 0% vs 8.5% Vertigo: 0% vs 7.8% Somnolence: 0% vs 5.2% Headache: 1.3% vs 4.6% Application site irritation: 1.3% vs 0% *8 week combination therapy phase* Lidocaine vs Pregabalin + Lidocaine + Pregabalin vs Pregabalin + Lidocaine % of patients with any AE: 19.0% vs 28.6% vs 41.7% vs 25.0% % of patients with drug related AE: 5.1% vs 7.9% vs 26.7% vs 6.3% % of patients with SAE: 0% vs 0% vs 0% vs 0%	Lidocaine vs Pregabalin + Lidocaine + Pregabalin vs Pregabalin + Lidocaine Total withdrawals: NR Withdrawals due to AE: 1.3% vs 1.6% vs 11.7% vs 10.4%	Grunenthal GmBh	Reports results from the 2nd part of the phase III study. Baseline characteristics and effectiveness outcomes reported on per protocol population

Evidence Table 1. Update 1: Data abstraction of head-to-head trials

Author Year Country Trial name (Quality rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics
Chandra, 2006 India GONIP Fair	Post-herpetic Neuralgia patients 18 years of age or older with > 8 weeks of PHN pain	A: Gabapentin 900-2700mg daily B: Nortriptyline: 50-150mg daily	Non-opioid analgesics	54 years Male: 48.6% Ethnicity NR	Time since rash in months: Gaba: 4.9 Nortrip: 4.7 P=0.810 Mean Daily Pain Score: Gaba: 5.6 Nortrip: 5.8 P=0.477 Mean Pain VAS Score: Gaba: 4.8 Nortrip: 5.3 P=0.452 Mean SF-MPQ score: Gaba: 10.4 Nortrip: 10.8 P=0.639 Mean SAS Score: Gaba 2.5 Nortrip: 3.0 P=0.378

Evidence Table 1. Update 1: Data abstraction of head-to-head trials

Author Year Country Trial name (Quality rating-optional)	N	Number withdrawn/ lost to follow-up/analyzed	Results
Chandra, 2006 India GONIP Fair	76	6/5/70	Gabapentin vs Nortriptyline Difference in Scores: Pain (Likert): -1.97 vs -2.18; P=0.62 Pain (VAS): -2.00 vs -2.37; P=0.47 SF-MPQ: -3.44 vs -3.80; P=0.64 Sleep (SAS): -1.45 vs -2.02; P=0.50

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Author Year Country Trial name (Quality rating-optional)	Adverse events reported	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Chandra, 2006 India GONIP Fair	Gabapentin vs Nortriptyline Dry Mouth: 0 (0%) vs 18 (50%); P=0.000 Constipation: 0 (0%) vs 8 (22.2%); P=0.003 Cough: 1 (2.9%) vs 2 (5.6%); P=0.589 Postural: 0 (0%) vs 12 (33.3%); P=0.000 Sleepiness: 4 (11.8%) vs 6 (16.7); P=0.558 Urinary retention: 0 (0%) vs 1 (2.8%); P=0.528 Urticaria: 2 (5.9%) vs 0 (0%); P=0.140 Giddiness: 1 (2.9%) vs 0 (0%); P=0.300 Fatigue: 1 (2.9%) vs 0 (0%); P=0.300	7; 0	Pfizer partly funded but had no role in protocol design, data analysis, or manuscript preparation	

Evidence Table 1. Update 1: Data abstraction of head-to-head trials

Author Year Country Trial name (Quality rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics
Dallocchio, 2000 Italy Fair	Males/Females greater than or equal to 60 years with type II diabetes and lower limb polyneuropathy	A: Gabapentin 400mg-2400mg daily, titrated upward for pain control B: Amitriptyline 10-90mg daily, titrated upward for pain control	Benzodiazepines allowed if on stable dose	71.0 (SD 7) years 40% male	Duration of Diabetes in yrs: Gaba: 12±4 Amitrip: 9±7 Pain Score: Gaba: 2.9±0.8 Amitrip: 2.8±0.8 Paresthesia Score: Gaba: 3.0±0.7 Amitrip: 2.5±0.7 Duration of Pain in months: Gaba: 34±11 Amitrip: 22±12 On insulin: Gaba: 5/13=38.5% Amitrip: 5/12=41.7% Type of Paresthesia: Gaba: 38.5% painful, 61.5% tingling Amitrip: 41.7% painful, 58.3% tingling

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Author Year Country Trial name (Quality rating-optional)	N	Number withdrawn/ lost to follow-up/analyzed	Results
Dallocchio, 2000 Italy Fair	25	0/0/25	Gabapentin vs Amitriptyline Change from baseline Pain Scores: -1.9 vs -1.3, P=0.026 Change in baseline Paresthesia Scores: -1.8 vs 0.9, P=0.004

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Author Year Country Trial name (Quality rating-optional)	Adverse events reported	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Dallocchio, 2000 Italy Fair	Gabapentin: 4 (2 dizziness, 1 somnolence, 1 ataxia) Amitriptyline: 11 (somnolence, dizziness, dry mouth most common) P=0.003	0; 0	NR	

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Author Year Country Trial name (Quality rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics
Gilron, 2009 Canada Fair	Diabetic Polyneuropathy or Postherpetic Neuralgia Pain score >=4 on scale of 1-10 for at least 6 months preceding trial	1:1:1 Latin Square Design A: Gabapentin 400mg Placebo Nortriptyline B: Nortriptyline 10mg Placebo Gabapentin C: Gabapentin 400mg Nortriptyline 10mg Target daily dose Gaba =3600mg Target daily dose Nortrip =100mg	Patients already on opioids, NSAIDS and paracetamol were allowed to be continued on these drugs at a steady dose for the entire study	DPN: 61 years PHN: 68 years DPN: 65% male PHN: 56% male White: 00%	PHN: 19% Trigeminal; 25% Cervical; 56% Thoracic Concomitant drugs: DPN: None 55%, Opioids 20%, Acetaminophen or NSAIDS 35% PHN: None 38%, Opioids 25%, Acetaminophen or NSAIDS 38%

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Author Year Country Trial name (Quality rating-optional)	N	Number withdrawn/ lost to follow-up/analyzed	Results
Gilron, 2009 Canada Fair	56	11/0/47	Baseline vs Gabapentin vs Nortriptyline vs Combined treatment Test NRS 0-10 (Higher scores mean greater pain): Daily Pain Intensity: 5.4 vs 3.2 vs 2.9 vs 2.3 Worst Pain past 24hr: 6.3 vs 4.3 vs 4.1 vs 3.2 Least Pain past 24hr: 3.1 vs 2.6 vs 2.1 vs 1.8 Average Pain: 4.9 vs 3.3 vs 3.1 vs 2.5 Pain at Present: 3.9 vs 2.7 vs 2.8 vs 2.1 Percent Pain Relief: NA vs 48.1 vs 45.7 vs 63.4 Pain Interferes with: General Activity: 3.9 vs 2.1 vs 2.2 vs 1.8 Mood: 3.8 vs 1.5 vs 2.1 vs 1.3 Walking: 3.9 vs 2.2 vs 2.0 vs 2.1 Normal Work: 4.0 vs 2.2 vs 2.3 vs 2.1 Social Relations: 2.8 vs 1.4 vs 1.4 vs 1.1 Sleep: 5.1 vs 2.2 vs 2.3 vs 1.0 Enjoyment of Life: 4.8 vs 2.1 vs 2.7 vs 1.5 Beck Depression Inventory (higher scores mean greater depression): 8.3 vs 5.8 vs 6.8 vs 5.4 SF-MPQ Sensory: 14.5 vs 6.7 vs 7.4 vs 5.3 SF-MPQ Affective: 4.3 vs 1.6 vs 2.0 vs 1.4 SF-MPQ Total: 18.8 vs 8.3 vs 9.4 vs 6.7 VAS(0-10cm): 4.3 vs 2.4 vs 2.5 vs 2.0 Present Pain Intensity Score: 2.0 vs 1.5 vs 1.6 vs 1.3 (NOTE: Not all secondary outcomes listed)

Evidence Table 1. Update 1: Data abstraction of head-to-head trials

Author Year Country Trial name (Quality rating-optional)	Adverse events reported	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Gilron, 2009 Canada Fair	Gabapentin vs Nortriptyline vs Combined treatment During dose titration: Dry mouth: 11 (20%) vs 29 (56%) vs 27 (52%) Fatigue: 7 (13%) vs 9 (17%) vs 6 (12%) Somnolence: 9 (17%) vs 8 (15%) vs 9 (17%) Insomnia: 3 (6%) vs 9 (17%) vs 6 (12%) Dizziness: 7 (13%) vs 6 (12%) vs 6 (12%) Headache: 7 (13%) vs 5 (10%) vs 2 (4%) Constipation: 4 (7%) vs 6 (12%) vs 5 (10%) Ataxia: 5 (9%) vs 1 (2%) vs 5 (10%) Feeling Intoxicated: 6 (11%) vs 1 (2%) vs 4 (8%) Inability to Concentrate: 6 (11%) vs 0 (0%) vs 3 (6%) High Blood Sugar: 4 (7%) vs 3 (6%) vs 4 (8%) Edema: 5 (9%) vs 2 (4%) vs 3 (6%) Abdominal Cramping: 5 (9%) vs 3 (6%) vs 3 (6%) Urinary Retention: 2 (4%) vs 4 (8%) vs 3 (6%) Emotional Lability: 1 (2%) vs 4 (8%) vs 1 (2%) Difficulty Swallowing: 0 (0%) vs 1 (2%) vs 0 (0%) Pruritus: 0 (0%) vs 3 (6%) vs 0 (0%) Excessive Sweating: 1 (2%) vs 3 (6%) vs 0 (0%) Weight Gain: 3 (6%) vs 1 (2%) vs 3 (6%) Blurry Vision: 3 (6%) vs 0 (0%) vs 0 (0%) During max tolerated dose: Dry mouth: 8 (17%) vs 29 (58%) 30 (60%) vs Fatigue: 2 (4%) vs 6 (12%) 4 (8%) Somnolence: 1 (2%) vs 1 (2%) 4 (8%) Insomnia: 0 (0%) vs 2 (4%) 2 (4%) Dizziness: 4 (9%) vs 2 (4%) 4 (8%) Headache: 2 (4%) vs 2 (4%) 1 (2%) Constipation: 1 (2%) vs 1 (2%) vs 1 (2%) Ataxia: 3 (7%) vs 1 (2%) vs 5 (10%) Feeling Intoxicated: 1 (2%) vs 0 (0%) vs 2 (4%) Inability to Concentrate: 2 (4%) vs 0 (0%) vs 2 (4%) High Blood Sugar: 5 (11%) vs 2 (4%) vs 3 (6%) Edema: 4 (9%) vs 2 (4%) 4 (8%) Abdominal Cramping: 0 (0%) vs 0 (0%) vs 1 (2%) Urinary Retention: 1 (2%) vs 3 (6%) 2 (4%) Emotional Lability: 1 (2%) vs 3 (6%) vs 0 (0%) Difficulty Swallowing: 0 (0%) vs 3 (6%) 1 (2%)	11; 9	Canadian Institutes of Health Research	Cross-over design: no significant effects of treatment sequence, treatment period, or carryover were recorded in the main analysis of "mean daily pain" but there was a statistically significant effect of drug treatment.

Evidence Table 1. Update 1: Data abstraction of head-to-head trials

Author Year Country Trial name (Quality rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics
Jia, 2006 China Fair	Painful diabetic neuropathy patients from 3 clinical centers aged 18-65 years	Parallel-group, double-blind, double-dummy, RCT: A: Venlafaxine 25mg daily Dummy Carbamazepine B: Carbamazepine 0.1g daily Dummy Venlafaxine	Hypoglycemic agents and antihypertensives	55 years Male: 60% Ethnicity NR	20/132=15% using other assistant drugs

Evidence Table 1. Update 1: Data abstraction of head-to-head trials

Author Year Country Trial name (Quality rating-optional)	N	Number withdrawn/ lost to follow-up/analyzed	Results
Jia, 2006 China Fair	Total: 132 A: 66 B: 66	13/4/129	Per Protocol: Mean Score of Pain Intensity (11-point Likert scale): Mean Pain Intensity Score: Decreased over time for both groups; In PP group, Venlafaxine had lower Pain Intensity scores at days 5, 7, 10, and 14 (P=0.02, 0.03, 0.003, 0.001, respectively); Assume that it is NS for ITT analysis Duration of Pain: Significant difference at 7 and 14 days favoring Venlafaxine: P=0.02 and 0.003, respectively, ITT. Quality of Life: (summation of "interferes with activities of daily living:, :interference with routine work", "sleep interference" and "mood interference"): favors Venlafaxine at days 10 and 14 P=.02 and .003, respectively. At the end of the trial Venlafaxine reduced sleep interference due to pain, P=0.02; Mood interference was improved at days 10 and 14 in the Venlafaxine group, P=0.02 and 0.01, respectively; Interference with routine work was improved on days 10 and 14 in favor of the Venlafaxine group, P=0.02 and 0.01, respectively.

Evidence Table 1. Update 1: Data abstraction of head-to-head trials

Author Year Country Trial name (Quality rating-optional)	Adverse events reported	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Jia, 2006 China Fair	Total: 46 AEs Venlafaxine: 43.9% Carbamazepine: 25.76% This difference not significant. AEs >10%: GI discomfort: 18.18% Dizziness: 13.64% Somnolence 12.12% Severe Adverse Events: Venlafaxine: 1 patient with severe GI discomfort Carbamazepine: 1 patient with severe dizziness and somnolence	13; 6	NR	In the Venlafaxine group it appears that the participant who "failed to return" was excluded from ITT analysis while the 3 participants who failed to return were included in the ITT analysis in the Carbamazepine group. See Fig 1.

Evidence Table 1. Update 1: Data abstraction of head-to-head trials

Author Year Country Trial name (Quality rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics
Jose, 2007 India Fair	18-75 yo Males and Females with painful diabetic neuropathy attending the endocrinology outpatient department of a tertiary-care hospital	Dose titrating study: A: Lamotrigine 25mg, 50mg, 100mg twice daily B: Amitriptyline 10mg, 25mg, 50mg at bedtime	Paracetamol up to 3g per day	56 years Male: 35% Ethnicity NR	Duration of diabetes: 48 months Hypertensive: 35/46= 76%

Evidence Table 1. Update 1: Data abstraction of head-to-head trials

Author Year Country Trial name (Quality rating-optional)	N	Number withdrawn/ lost to follow-up/analyzed	Results
Jose, 2007 India Fair	46	29/22/46	Lamotrigine vs Amitriptyline Baseline: 72.5 vs 70.0; P=0.95 Week 2: 50.0 vs 60.0; P=0.17 Week 4: 50.0 vs 52.5; P=0.30 Week 6: 50.0 vs 52.5; P=0.23 Physician VAS: Baseline: 70.0 vs 70.0; P=0.31 Week 2: 55.0 vs 70.0; P=0.36 Week 4: 50.0 vs 60.0; P=0.38 Week 6: 50.0 vs 60.0; P=0.33 Likert pain Scale: Baseline: 3 vs 3; P=0.67 Week 2: 2 vs 2; P=0.47 Week 4: 2 vs 2; P=0.53 Week 6: 2 vs 2; P=0.38 McGill Pain Questionnaire: Baseline: 9 vs 8; P=0.13 Week 2: 6 vs 6; P=0.65 Week 4: 6 vs 6; P=0.55 Week 6: 6 vs 6; P=0.39

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Author Year Country Trial name (Quality rating-optional)	Adverse events reported	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Jose, 2007 India Fair	Lamotrigine vs Amitriptyline Increase in sleep: 19 (43%) vs 0 (0%); P<0.001 Tiredness: 5 (11%) vs 0 (0%); P=0.07 Dizziness: 4 (9%) vs 0 (0%); P=0.12 Rash: 0 (0%) vs 3 (7%); P=0.24 Postural hypotension: 2 (5%) vs 0 (0%); P=0.49 Itching: 0 (0%) vs 2 (5%); P=0.49 Difficulty in urination: 1 (2%) vs 0 (0%); P=0.49 Dry Mouth: 1 (2%) vs 0 (0%); P=0.49 Constipation: 1 (2%) vs 0 (0%); P=0.49 Abdominal pain: 0 (0%) vs 1 (2%); P=0.49 Decreased sleep: 0 (0%) vs 1 (2%); P=0.49 Elevation of creatinine by>25%: 0 (0%) vs 4 (9%); P=0.12 Total: 33 (74%) vs 11 (25%); P<0.001	29; 27	Pharmaceutical companies provided medications	

Evidence Table 1. Update 1: Data abstraction of head-to-head trials

Author Year Country Trial name (Quality rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics
Morello, 1999 United States Fair	Veterans at least 18 years of age with diabetes mellitus with stable glycemic control who experienced chronic pain daily	A: Gabapentin 900-1800mg daily (mean daily dose= 1565mg B: Amitriptyline 25-75mg daily, mean daily dose= 59mg	4 doses of acetaminophen 325mg allowed daily	60.4 years 96% male White: 92% African American: 8%	Duration of Diabetes: 13.4 years On Insulin: 64%

Evidence Table 1. Update 1: Data abstraction of head-to-head trials

Author Year Country Trial name (Quality rating-optional)	N	Number withdrawn/ lost to follow-up/analyzed	Results
Morello, 1999 United States Fair	25	4/0/19	Gabapentin vs Amitriptyline Change from baseline Pain Diary Scores: -0.31±0.064 vs -0.44±0.089, P=0.3

Evidence Table 1. Update 1: Data abstraction of head-to-head trials

Author Year Country Trial name (Quality rating-optional)	Adverse events reported	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Morello, 1999 United States Fair	Gabapentin vs Amitriptyline Any Adverse Effect: 18 vs 17 Sedation: 12 vs 8 Dry mouth: 4 vs 8 Dizziness: 7 vs 2 Postural hypotension: 6 vs 5 Weight Gain: 0 vs 6; P=0.01 Ataxia: 5 vs 2 Constipation: 5 vs 3 Lethargy: 4 vs 5 Edema: 3 vs 2 Headache: 2 vs 3 Pruritus: 1 vs 3 Unpleasant taste: 2 vs 1 Nausea/dyspepsia: 2 vs 1 Diarrhea: 2 vs 1 Blurred Vision: 1 vs 2 Other: 3 vs 4	4; 3	NR	

Evidence Table 1. Update 1: Data abstraction of head-to-head trials

Author Year Country Trial name (Quality rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics
Pfizer unpublished study, 2007 Multiple European Countries Protocol no. 1008-040 Fair	Men and women at least 18 years of age with a diagnosis of type 1 or 2 DM for at least 1 yr prior to screening, HbA1C levels of ≤11% and a diagnosis of painful, distal, symmetrical, sensorimotor polyneuropathy due to diabetes for at least 1 year prior to screening. Patients must have had VAS scores of ≥40 at baseline and randomization and completed at least 4 daily pain dairies and have had an average pain score of ≥4 over the last 7 days on an 11 point pain rating scale at randomization	A: Pregabalin 600mg QD B: Amitriptyline 75 mg QD C: Placebo for 9 weeks		60 years (range 22 to 80) Male: 57% White: 93%	Type 2 diabetes: 86% Lower extremity neuropathic pain: 100% Upper extremity neuropathic pain: 24% Mean pain score at baseline: 6.5

Evidence Table 1. Update 1: Data abstraction of head-to-head trials

Author Year Country Trial name (Quality rating-optional)	N	Number withdrawn/ lost to follow-up/analyzed	Results
Pfizer unpublished study, 2007 Multiple European Countries Protocol no. 1008-040 Fair	256	66/NR/254	Placebo vs Pregabalin vs Amitriptyline Mean (SD) change from baseline in mean pain scores: -1.8 (2.5) vs -2.8 (2.5) vs -2.8 (2.6) point estimate of the difference between pregabalin and amitriptyline =0.29, 95% CI (-0.42 to 0.99), pregabalin vs placebo P=0.045, amitriptyline vs placebo P=0.006 Patients with ≥50% decrease in mean pain score from baseline: 30% vs 40% vs 46%, pregabalin vs placebo P=0.239, amitriptyline vs placebo P=0.034 SFMPQ endpoint analysis of VAS score, LSM (SE): 49.26 (3.02) vs 38.37 (2.93) vs 37.55 (2.91) treatment difference pregabalin vs placebo -10.39, 95% CI (-18.68 to -2.11), P=0.0142, treatment difference amitriptyline vs placebo -11.71 (-19.95 to -3.47), P=0.0055, point estimate of the difference between pregabalin and amitriptyline 1.32, 95% CI (-6.81 to 9.45) Endpoint analysis of PPI score, LSM (SE): 1.95 (0.14) vs 1.63 (0.14) vs 1.42 (0.14), treatment difference pregabalin vs placebo -0.32, 95% CI (-0.66 to 0.01), P=0.0591. Treatment difference amitriptyline vs placebo -0.54, 95% CI -0.87 to -0.20), P=0.0019, point estimate of the difference between pregabalin and amitriptyline groups 0.21, 95% CI (-0.21 to 0.54) Endpoint mean sleep interference scores, LSM (SE)3.96 (0.25) vs 2.89 (0.24) vs 2.69 (0.24)treatment difference pregabalin vs placebo -1.07, 95% CI (-1.75 to -0.39), P=0.0023, treatment difference amitriptyline vs placebo-1.27, 95% CI (-1.95 to -0.59), P=0.0003. Point estimate difference between pregabalin and amitriptyline 0.20, 95% CI (-0.47 to 0.87) HADS (anxiety) scores LSM (SE): 7.25 (0.34) vs 5.72 (0.34) vs 5.72 (0.33), treatment difference pregabalin vs placebo -1.53 , 95% CI (-2.47 to -0.58), P=0.0016. Treatment difference amitriptyline vs placebo -1.53, 95% CI (-2.46 to -0.59), P=0.0015 HADS (depression) scores, LSM (SE): 5.88 (0.35) vs 5.64 (0.35) vs 5.07 (0.34), treatment difference pregabalin vs placebo -0.24, 95% CI (-1.21 to 0.73), P=0.6302, treatment difference amitriptyline vs placebo -0.81, 95% CI (-1.77 to 0.15), P=0.0989

Evidence Table 1. Update 1: Data abstraction of head-to-head trials

Author Year Country Trial name (Quality rating-optional)	Adverse events reported	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Pfizer unpublished study, 2007 Multiple European Countries Protocol no. 1008-040 Fair	Placebo vs Pregabalin vs Amitriptyline Proportion of patients with any AE: 46.95 vs 66.3% vs 67.8% Proportion of patients with SAE: 2.5% vs 4.7% vs 5.7% AE experienced by at least 2 pregabalin treated patients Dizziness: 1.2% vs 20.9% vs 4.6% Neuropathy: 2.5% vs 10.5% vs 4.6% Asthenia: 3.7% vs 7.0% vs 9.2% Accidental injury: 1.2% vs 5.8% vs 4.6% Infection: 6.2% vs 5.8% 6.9% Peripheral edema: 0.0% vs 5.8% vs 1.1% Ataxia: 1.2% vs 4.7% vs 0 Constipation: 0 vs 4.7% vs 2.3% Creatinine clearance: 1.2% vs 4.7% vs 3.4% Dry mouth: 2.5% vs 4.7% vs 25.3% Headache: 4.9% vs 4.7% vs 1.1% Somnolence: 1.2% vs 4.7% vs 12.6% Diarrhea: 3.7% vs 3.5% vs 3.1% UTI: 1.2% vs 3.5% vs 0 Weight gain: 2.55 vs 3.5% vs 2.3% Abnormal vision: 1.2% vs 2.3% vs 1.1% Amblyopia: 0 vs 2.3% vs 1.1% Edema: 0 vs 2.3% vs 0 Flatulence: 1.2% vs 2.3% vs 0 Reflexes decreased: 1.2% vs 2.3% vs 1.1% Tremor: 0 vs 2.3% vs 0 Vertigo: 2.5% vs 2.3% vs 6.9%	Placebo vs Pregabalin vs Amitriptyline Total withdrawals: 23.5% vs 27.9% vs 26.4% Withdrawals due to AE: 6.2% vs 12.8% vs 18.4%	Pfizer Inc.	

Evidence Table 1. Update 1: Data abstraction of head-to-head trials

Author Year Country Trial name (Quality rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics
Rintala, 2007 U.S. Poor	Patients 18-70 years of age with SCI at any level and any degree of completeness , the SCI occurred at least 12 mo before entering the study, at least 1 chronic (>6 mo) pain component characteristic of neuropathic pain, at least 1 neuropathic pain component rated as at least 5 on 0 to 10 scale when initially contacted about participating and lived 160 Km of the Michael E. DeBakey Veterans Affairs Medical Center	A: Gabapentin-amitriptyline-diphenhydramine B: Gabapentin-Diphenhydramine-Amitriptyline C: Amitriptyline-Gabapentin-Diphenhydramine D: Amitriptyline-Diphenhydramine-Gabapentin E: Diphenhydramine-Gabapentin-Amitriptyline F: Diphenhydramine-Amitriptyline-Gabapentin For 8 weeks Gabapentin max dose: 1200mg TID Amitriptyline max dose: 50mg TID Diphenhydramine 25 mg TID	5 mg Oxycodone and 325mg acetaminophen	41 years Male: 94.7% White: 44.7% Black: 18.4% Hispanic: 36.8%	Time since onset: 15.5 years Duration of pain: 7.8 years Mean pain intensity at it's worst: 8.3 Pain intensity on average baseline week: 6.0 Pain intensity at its worst baseline week: 8.0 Baseline CESD-SF: 7.5 Level of completeness of SCI Tetraplegia(AIS grade A, B or C): 52.6% Paraplegia (AIS Grade A, B or C): 31.6% Any level (AIS Grade D): 15.8% Baseline depressive symptomatology CESD-SF score ≥10: 31.6 %(CESD-SF scores not available for 2 non-completers) CESD-SF score<10: 63.2% (CESD-SF scores not available for 2 non completers)

Evidence Table 1. Update 1: Data abstraction of head-to-head trials

Author Year Country Trial name (Quality rating-optional)	N	Number withdrawn/ lost to follow-up/analyzed	Results
Rintala, 2007 U.S. Poor	38	16/0/22	Mean (SD) VAS ratings at week 8 (completers): 3.46 (2.09) vs 4.85 (2.86) vs 5.11 (2.54), F=4.61, P=0.016 Mean Pain intensity in High CESD-SF group at endpoint: amitriptyline 4.21 (SD 1.95) vs diphenhydramine 6.68 (SD 1.88), t=2.61, P=0.035; amitriptyline vs gabapentin: trend towards lower pain intensity during amitriptyline therapy, t=2.23, P=0.061. Decrease from baseline in pain intensity among 3 medications significant in high CESD-SF group(F=4.02, P=0.042) <u>Amitriptyline vs Gabapentin vs Diphenhydramine</u> Change from baseline in mean pain intensity rating at 8 weeks in high CESD-SF group: -3.21 vs -0.70 vs -0.74, differences between groups F=4.02, P=0.042 Change from baseline in mean pain intensity rating at 8 weeks in low CESD-SF group: -1.58 vs -0.84 vs -0.40, P=NS Proportion of patients with at least 30% decrease from baseline in pain intensity in low CESD-SF group: 50% vs 42.9% vs 35.7% Proportion of patients with at least 30% decrease from baseline in pain intensity in high CESD-SF group: 62.5% vs 12.5% vs 25% Mean (SD) Pain intensity at its worst at week 8 for completers: 5.68 (2.39) vs 7.22 (2.38) vs 7.05 (2.09) For all 3 medications, regardless of the CESD-SF group, at least 50% of the participants who completed the study received no breakthrough medication At week 8, patients received a mean of 94% max dose of amitriptyline, 91% max dose of gabapentin and 91% max dose of diphenhydramine

Evidence Table 1. Update 1: Data abstraction of head-to-head trials

Author Year Country Trial name (Quality rating-optional)	Adverse events reported	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Rintala, 2007 U.S. Poor	Amitriptyline vs Gabapentin Dry mouth: 63.85 vs 38.8% Drowsiness: 27.1% vs 22.9% Fatigue: 20.5% vs 22.4% Constipation: 29.2% vs 10.9% Increased spasticity: 11.0% vs 6.0% Dizziness: 8.1% vs 11.5% Difficulty emptying bowel: 11.4% vs 5.0% Nausea: 9.0% vs 6.5% Edema: 5.7% vs 5.5% Itching: 5.7% vs 3.5% Difficulty emptying bladder: 5.2% vs 1.0% Nausea: 9.0% vs 6.5% Edema: 5.7% vs 5.5% Itching: 5.7% vs 3.5% Difficulty emptying bladder: 5.2% vs 1.0% Low blood pressure: 2.4% vs 3.0% Uncoordinated muscles: 2.9% vs 3.0% Vomiting: 2.9% vs 1.5% Abnormal heart rhythms: 1.4% vs 0.5% Skin rash: 0.0% vs 1.5% Weight gain: 0.5% vs 0.5%	Amitriptyline vs Gabapentin Total withdrawals: 7 vs 6 Withdrawals due to AE: 4 vs 4	Department of Veterans Affairs, Veterans Health Administration, Rehabilitation Research and Development Service (Grant no. B2573R)	Outcomes reported separately for completers and non completers Harms checklist completed by 210, 201 and 205 patients in amitriptyline, gabapentin group. Harms and withdrawals from Diphenhydramine arm not abstracted. Those who crossed over early due to adverse events were also considered withdrawals

Evidence Table 1. Update 1: Data abstraction of head-to-head trials

Author Year Country Trial name (Quality rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity	Other population characteristics
Tanenberg, 2010 United States Poor	Diabetic patients 18-65 years of age with DPN, who had been treated with a stable dose of gabapentin (at least 900 mg/d) and had an inadequate response (defined as having a baseline pain severity score ≥4).	A: Duloxetine: 60 mg qd B: Pregabalin: 300 mg/d C: Duloxetine 60 mg qd + Gabapentin Dosing schedule: Duloxetine: Weeks 1-2: 30 mg qd Weeks 2-12: 60 mg qd Pregabalin: Weeks 1-2: 50 mg tid (Germany, US) or 75 mg bid (Canada) Weeks 2-12: 100 mg tid (Germany, US) or 150 mg bid (Canada) For patients in duloxetine or pregabalin monotherapy, gabapentin was tapered over 1-2 weeks depending on dose at randomization.	NR	61.6 years (SD 10.6) 59.5% male Caucasian: 81.8%	Type 2 diabetes: 92.4% Duration of diabetes: 11.6 years (SD 4.5) DPN duration: 4.4 years (SD 3.9) Comorbid MDD: 2.7% Comorbid generalized anxiety disorder: 1% Mean gabapentin dose at baseline: 1226 mg/d (SD 670.6)

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Author Year Country Trial name (Quality rating-optional)	N	Number withdrawn/ lost to follow-up/analyzed	Results
Tanenberg, 2010 United States Poor	407	125/17/NR	Pregabalin vs Duloxetine vs Duloxetine + Gabapentin MMRM intent-to-treat analysis of the non-inferiority of duloxetine to pregabalin: Margin of non-inferiority: -0.80 97.5% lower confidence bound: -0.05 (non-inferior) Mean difference: 0.49 MMRM intent-to-treat analysis of the non-inferiority of duloxetine to duloxetine + pregabalin: Margin of non-inferiority: -0.80 97.5% lower confidence bound: -0.32 (non-inferior) Mean difference: 0.23 Estimated mean improvement (decrease in pain score) at 12 weeks: 2.12 vs 2.62 vs 2.39 Completion rate: 71.6% vs 63% vs 73.3%

Evidence Table 1. Update 1: Data abstraction of head-to-head trials

Author Year Country Trial name (Quality rating-optional)	Adverse events reported	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Tanenberg, 2010 United States Poor	Pregabalin vs Duloxetine vs Duloxetine + Gabapentin Nausea: 1.5% vs 13.8% vs 13.3%; P<0.001 Insomnia: 1.5% vs 12.3% vs 3.6%; P<0.001 pregabalin vs duloxetine Peripheral edema: 13.4% vs 1.4% vs 0%; P<0.001 Hyperhidrosis: 0% vs 8% vs 4.4%; P<0.05 Decreased appetite: 0% vs 6.5% vs 4.4%; P<0.05 Vomiting: 0% vs 3.6% vs 4.4%; P<0.05 pregabalin vs duloxetine + gabapentin	Pregabalin vs Duloxetine vs Duloxetine + Gabapentin Total withdrawals: 38 (28.4%) vs 51 (36.9%) vs 36 (26.7%) Due to AE: 14 (10.4%) vs 27 (19.6%) vs 18 (13.3%); P<0.05 for duloxetine vs pregabalin	Lilly USA	Open-label study

Evidence Table 2. Update 1: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity
Arezzo, 2008 United States Fair	Men and women ≥18 years of age with type 1 or type 2 diabetes with HbA1C ≤11%, and had painful DPN for ≥3 months and scored ≥40 mm on SF-MPQ VAS.	A: Pregabalin 300 mg BID (after one week dosage escalation period) B: Placebo For 12 weeks	Aspirin (up to 325 mg/d for cardiac and stroke prophylaxis), acetaminophen (up to 4 g/d), SSRIs (stable [>30 days] regimens for treatment of anxiety or depression), and benzodiazepines such as lorazepam (dosed at bedtime with stable [>30 days] regimen for sleep problems). If on antidiabetic medication, must have been on a stable antidiabetic medication regimen for 30 days prior to randomization.	58.3 years (SD 10.3) 61.6% male White: 73.7% Black: 12.6% Hispanic: 12.6% Others: 1.2%
Argyriou 2006 Greece Fair	Chemotherapy-naïve adults with a diagnosis of advanced colon cancer scheduled to receive 12 courses of cumulative oxaliplatin-based regimen.	A: Chemotherapy with oxcarbazepine (target dose 1200 mg) B: Chemotherapy without oxcarbazepine 24 weeks Parallel group design	None reported	63.8 years 55% male Ethnicity: NR

Evidence Table 2. Update 1: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed	Efficacy/Effectiveness
Arezzo, 2008 United States Fair	Mean BMI: 36.2 (SD 8.4) Mean weight: 106 kg (SD 24) Diabetes Type 1: 8% Diabetes Type 2: 92% Duration of diabetes: 10.3 years (SD 8.4) Duration of painful DPN: 4.6 years (SD 3.6) Baseline mean pain score: 6.43 (SD 1.53) Distribution of pain: Lower extremities: 100% Upper extremities: 41.5%	167	52/4/167	Placebo vs Pregabalin Endpoint mean pain score: 4.82 vs 3.54; Treatment difference -1.28 (95% CI, -1.96 to -0.60), P=0.0003 50% responders (≥50% reduction in mean pain score from baseline to endpoint): 23% vs 49%; P<0.001 Mean sleep interference scores at endpoint: 3.72 vs 2.64; Treatment difference: -1.08 (95% CI, -1.75 to -0.41), P=0.0019 Mean pain score as recorded on the 11- point NRS (patient diary), treatment difference: 11.06 (95% CI, -18.89 to -3.22), P=0.0060 PPI at endpoint, treatment difference: -0.34 (95% CI, -0.65 to -0.03), P=0.0311 CGIC: Much worse: 1.1% vs 0% Minimally worse: 9.6% vs 5.7% No change: 41.6% vs 22.8% Minimally improved: 11% vs 21.4% Much improved: 21.4% vs 35.9% Very much improved: 16% vs 14.6% P=0.0294 vs placebo PGIC: Much worse: 2.8% vs 0% Minimally worse: 10.7% vs 7.1% No change: 33.8% vs 13.9% Minimally improved: 12.5% vs 17.4% Much improved: 24.2% vs 34.2% Very much improved: 16.4% vs 28.5% P=0.0020 vs placebo
Argyriou 2006 Greece Fair	100% on oxaliplatin-based regimen FOLFAX 100% colon cancer	40	8/0/40	Oxcarbazepine vs control Incidence of Oxaliplatin-induced peripheral neuropathy: 31.2% vs 75%, P=0.033 (analysis on completer population) similar patters in ITT population, P=0.050 (Data NR) Mean(SD) Total Neuropathy Score at endpoint: 4.1 (6.5) range (0-17) vs 11.2 (9.05) range (0-28), P=0.016

Evidence Table 2. Update 1: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Arezzo, 2008 United States Fair	<u>Placebo vs Pregabalin</u> Peripheral edema: 27 (31.8%) vs 30 (36.6%) Dizziness: 5 (5.9%) vs 27 (32.9%) Weight gain: 1 (1.2%) vs 12 (14.6%) Somnolence: 5 (5.9%) vs 11 (13.4%) Asthenia: 1 (1.2%) vs 8 (9.8%) Ataxia: 0 (0%) vs 4 (4.9%) Dry mouth: 1 (1.2%) vs 4 (4.9%) Abdomen enlarged: 4 (4.7%) vs 3 (3.7%) Edema: 0 (0%) vs 3 (3.7%) Euphoria: 0 (0%) vs 3 (3.7%) Thinking abnormal: 0 (0%) vs 3 (3.7%)	<u>Placebo vs Pregabalin</u> Total withdrawals: 37 (43.5%) vs 43 (52.4%) Due to AE: 15 (17.6%) vs 21 (25.6%)	Pfizer	In pregabalin group, daily dosage was escalated over a 1-week period beginning with a single dose of 150 mg pregabalin on day 1, followed by two doses of 150 mg pregabalin on days 2–6 and two doses of 300 mg pregabalin on day 7 (end of titration), which were continued for 12 weeks (visits 4–7). No dosage changes were allowed during the study.
Argyriou 2006 Greece Fair	Commonly observed AE: similar incidence of diarrhea, myelosuppression, dizziness, nausea, vomiting and headache, P=0.657 between groups Data NR for each group	<u>Oxcarbazepine vs placebo</u> Total withdrawals:20% vs 20% Withdrawals due to AE: 10% vs 0%	NR	

Evidence Table 2. Update 1: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity
Binder, 2009 Europe Fair	Male and female patients ≥50 years, had suffered from PHN for at least 3 months after rash healing and had a mean pain intensity of ≥4 on the 11 point NRS scale.	A: Up to three 5% lidocaine plasters up to 12 h per day for 2 weeks B: Placebo for 2 weeks	stable analgesics permitted except topical analgesics or any additional lidocaine therapy	DB phase (full analysis set) 72.5 years 57.4% female Ethnicity: NR

Evidence Table 2. Update 1: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed	Efficacy/Effectiveness
Binder, 2009 Europe Fair	DB phase-full analysis set BMI: 25.8 kg/m2 Duration of PHN: 35.8 mo Pain intensity at randomization: 3.7 Allodynia severity rating: no pain: 12.7% uncomfortable but tolerable to touch: 71.8% painful: 12.7% extremely painful: 2.8% SF-MPQ total score: 11.7 SF-MPQ sensory subscore: 9.9	71	32/NR/71	Lidocaine plaster vs placebo (randomized full analysis set) Median time to exit: 13.5 days (range 2-14) vs 9.0 days (1-14) , P=0.1510 HR>1 (1.86, 95%CI (0.788 to 4.376) Patients switching to placebo from Lidocaine plaster experienced worsening in : daily pain intensity after plaster removal (P=0.0289), daily pain relief (P=0.0040), daily pain reduction (P=0.0007), mean pain relief in last week (P=0.0012), SF MPQ total score: (P=0.0254) and SF sensory sub-score (P=0.0180)

Evidence Table 2. Update 1: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Binder, 2009 Europe Fair	Lidocaine plaster vs placebo (randomized full analysis set) total AE: 5.6% vs 2.9% drug related AE: 1.45 vs 1.4%	Lidocaine plaster vs placebo (randomized full analysis set) total withdrawals: 30.6% vs 60% withdrawals due to AE: 0% vs 2.9%	Grunenthal GmbH	Data from 8 weeks run-in phase not reported here

Evidence Table 2. Update 1: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity
Breuer, 2007 United States Poor	Male and female patients ≥18 years of age, had a diagnosis of probable or definite MS, and reported pain with neuropathic features for at least 3 months.	A: Lamotrigine 50-400 mg/d B: Placebo Each treatment period began with an 8-week titration period during which the dose was increased from 25 mg to a maximum of 400 mg, until 1 of 3 potential end points was attained: (1) the patient reported total pain relief; (2) 1 or more unmanageable adverse events were reported; or (3) a maximum dose of 400 mg. There was a 3-week maintenance period after each titration period during which time patients continued to use the final dose attained during titration.	Patients receiving a stable dose of opioids (e.g., hydromorphone), nonopioid analgesics (e.g., NSAIDs, acetaminophen, or lidocaine dermal patch), or gabapentin as an adjuvant analgesic for ≥2 weeks prior to study enrollment were expected to maintain stable dose throughout study.	49.3 years (SD 11.7) 83.3% female White: 66.7% Black: 33.3%

Evidence Table 2. Update 1: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed	Efficacy/Effectiveness
Breuer, 2007 United States Poor	Mean weight: 76.5 kg (SD 19.9)	15	4/1/12 for efficacy, 15 for tolerability	Effect of study drug (lamotrigine or placebo) on study outcomes: BPI Pain Scores, β (placebo is reference), mean (SE) (lower estimates represent better outcome for lamotrigine): Average: 0.8 (1.2); P=0.5 Worst: -1.0 (0.8); P=0.3 Least: -0.8 (0.6); P=0.3 Pain interference with sleep: -0.02 (0.9); P=0.4 Pain interference with activity: -0.6 (0.6); P=0.4 Pain interference with mood: -1.4 (0.7); P=0.07 Pain interference with walking ability: -1.3 (1.1); P=0.3 Pain interference with relations with others: -0.5 (0.8); P=0.6 Pain interference with enjoyment of life: -0.5 (0.8); P=0.5 Weekly score, Average: 0.02 (1.0); P=0.1 Weekly score, Worst: -0.4 (1.3); P=0.8 Weekly score, Least: -0.4 (0.9); P=0.7 NPS: Intense: 0.8 (0.9); P=0.4 Sharp: 0.2 (1.2); P=0.9 Hot: -0.7 (0.9); P=0.4 Dull: -0.6 (1.0); P=0.5 Itchy: -0.4 (0.5); P=0.4 Unpleasant: -0.6 (0.6); P=0.3 Deep: -0.5 (0.8); P-0.6 Surface: 0.1 (1.4); P=0.9 MSQOL-54 end-of-period scores: Extent that physical health or emotional problems interfered with social activities: -0.3 (0.3); P=0.5 Overall rating of quality of life: 0.05 (0.5); P=0.9 (higher estimates signify better results with lamotrigine) Feeling about life as a whole: -0.4 (0.5); P=0.4 Lamotrigine vs Placebo Rate of responders: 5 (45.4%) vs 2 (18.2%); P=NS

Evidence Table 2. Update 1: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Breuer, 2007 United States Poor	Lamotrigine vs Placebo Headache: 3 (20%) vs 3 (20%) Increased fatigue/sleepiness: 3 (20%) vs 2 (13.3%) Nausea: 3 (20%) vs 0 (0%) Worsening pain: 2 (13.3%) vs 4 Cold/cough/sore throat: 2 (13.3%) vs 2 (13.3%) Numbness/"pins and needles" sensation: 2 (13.3%) vs 1 (6.7%) Body stiffness: 2 (13.3%) vs 0 (0%) Edema: 1 (6.7%) vs 3 (20%) Decreased motor ability: 1 (6.7%) vs 1 (6.7%) Increased muscle weakness: 1 (6.7%) vs 1 (6.7%) Note: More AEs (reported by a single participant) are also reported in article.	Lamotrigine vs Placebo Total withdrawals: 1 (6.7%) vs 2 (13.3%), plus 2 who withdrew prior to taking study medication (groups NR) Due to AE: 1 (6.7%) vs 1 (6.7%)	GlaxoSmithKline	

Evidence Table 2. Update 1: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity
Finnerup, 2009 Denmark Poor	Patients ≥18 years with at and/or below level NP for at least 3 mo due to trauma or spinal cord disease or cauda equina with a median pain intensity ≥4 on a 0-10 point NRS during 1 wk baseline period.	A: Levetiracetam (target dose 300mg/d) B: Placebo 5 weeks Crossover design	Paracetamol up to 6 tablets of 500mg daily was used as escape medication Concomitant pain medications Gabapentin: 25% Pregabalin: 25% Opioids, tramadol: 36.1% Simple analgesics, NSAIDs 27.8%	52.8 (SD 11.0) years 80.6% male Ethnicity: NR

Evidence Table 2. Update 1: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed	Efficacy/Effectiveness
Finnerup, 2009 Denmark Poor	Mechanism of spinal cord injury Transport: 25% Fall: 27.8% Sports: 5.6% Transversal myelitis: 16.7% Hemorrhage5.6% Prolapsed disk/stenosis: 13.9% Tumor: 2.8% Operation: 5.6% Neurological level Cervical: 36.1% Thoracic: 52.8% Lumbosacral: 11.1% Location of pain At level pain: 47.2% Below level pain: 86.1%	36	12/0/24	<u>Levetiracetam vs placebo</u> Pain intensity as measured by NRS 0-10: Median 6 (range 3 to 9.5) vs Median 7 (range 3-9), P=0.46 Sleep interference (NRS 0-10): Median 3 (range 0-9) vs median 3.5 (range 0 to 9) Proportion of patients with 33% pain relief: 23.1% vs 36.4%, P=NS NPSI (P=NS for all) Burning NRS: median 6 (0-10) vs median 7 (0 to 9) Pressing, median (range): 2.25 (0 to 7) vs 1.8 (0 to 6) Evoked pain, median (range): 0 (0 to 8) vs 2 (0 to 8) Paresthesia, median (range) 5 (0 to 10) vs 5 (0 to 10) Spasticity/spasms (P=NS for all) Spasms intensity (NRS 0 to 10) median, (range): 2 (0 to 8) vs 2 90 to 8) Penn spasm frequency: 1 (0 to 4) vs 1 (0 to 3) Modified Ashworth scale: Extensor, median (range): 1 (0 to 4) vs 0 (0 to 4), P=NS Flexor, median (range): 0 (0 to 3) vs 0 (0 to 3), P=NS

Evidence Table 2. Update 1: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Finnerup, 2009 Denmark Poor	Levetiracetam vs placebo % of patients with any AE: 41.2% vs 34.4% % of patients with moderate to severe AE: 26.5% vs 12.5% Incoordination: 14.7% vs 34.4% Dizziness:17.6% vs 6.3% Somnolence:32.4% vs 12.5% Constipation/nausea: 20.6% v15.6%s Headache:0% vs 3.1% Other (Rash, itch, blurred vision, increased pain, increased spasms, confusion): 23.5% vs 18.8%	Levetiracetam vs placebo Total Withdrawals:50% vs 16.7% Withdrawals due to AE:38.9% vs 11.1%	UCB Pharma, The Danish Medical Research Council (no. 22040561)	

Evidence Table 2. Update 1: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity
GlaxoSmithKline, 2005a Study no. NPP30004/Vinik 2007 Fair	Male or female subjects ≥18 years of age with type 1 or type 2 DM with diabetic neuropathy (defined by bilateral decreased or absent reflexes at the ankles or bilateral decreased vibration, pinprick, fine touch or temperature perception in the distal lower extremities) for ≥6 months, but ≤5 years; had mean pain score ≥4 during Baseline Phase using an 11-point numerical rating scale.	A: Lamotrigine 100 mg/d BID (total of 200 mg/d) B: Lamotrigine 150 mg/d BID (total of 300 mg/d) C: Lamotrigine 200mg/d BID (total of 400 mg/d) D: Placebo For 19 weeks (7 weeks dose-escalation phase plus a 12-week fixed-dose maintenance phase)	Acetaminophen as rescue medication (instructed to take 1000 mg every 4-6 hours as needed but to take no more than 4000 mg in 24 hours). Concomitant medications including gabapentin and tricyclic antidepressants were permitted. (Actual use listed in Vinik 2007)	59.9 years (SD 11.8) 54.3% male White: 80.8% Black: 9% Hispanic: 7.8% Other: 2.5%

Evidence Table 2. Update 1: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed	Efficacy/Effectiveness
GlaxoSmithKline, 2005a Study no. NPP30004/Vinik 2007 Fair	DM Type 1: 6.5% DM Type 2: 93.5% Mean duration of diabetes: 124.2 months Mean duration of NP: 31.6 months	360	138/10/340 for efficacy, 355 for safety	Placebo vs Lamotrigine 200 mg/d vs Lamotrigine 300 mg/d vs Lamotrigine 400 mg/d SF-MPQ total pain score, Adjusted mean change from Baseline at Week 19 (SE): -5.01 (1.408) vs -4.81 (1.319; 95% CI of adjusted difference vs placebo, -3.38 to 2.98) vs -6.35 (1.400; 95% CI of adjusted difference vs placebo, -1.86 to 4.55) vs -4.67 (1.549; 95% CI of adjusted difference vs placebo, -3.71 to 3.03) Proportion of subjects with a ≥30% reduction in pain intensity scores at week 19: 32 (38%) vs 25 (30%) vs 37 (44%) vs 25 (29%) Difference from placebo: N/A vs 7.2 vs -5.4 vs 8.9 Proportion of subjects with a ≥50% reduction in pain intensity scores at week 19: 23 (27%) vs 19 (23%) vs 28 (33%) vs 16 (18%) Difference from placebo: N/A vs 3.9 vs -5.5 vs 8.7

Evidence Table 2. Update 1: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
GlaxoSmithKline, 2005a Study no. NPP30004/Vinik 2007 Fair	Placebo vs Lamotrigine 200 mg/d vs Lamotrigine 300 mg/d vs Lamotrigine 400 mg/d Any adverse event: 62 (70%) vs 65 (74%) vs 74 (82%) vs 67 (75%) Subjects with any serious AEs: 6 (7%) vs 6 (7%) vs 6 (7%) vs 8 (9) Most common adverse events (reported more often in any lamotrigine group than in the placebo group and were reported in >8% of patients in any treatment group): Headache: 3 (3%) vs 7 (8%) vs 19 (21%) vs 14 (16%) Rash (serious or non-serious): 8 (9%) vs 13 (15%) vs 7 (8%) vs 11 (12%) Nausea: 4 (5%) vs 10 (11%) vs 4 (4%) vs 9 (10%) Dizziness: 2 (2%) vs 3 (3%) vs 8 (9%) vs 10 (11%)	Placebo vs Lamotrigine 200 mg/d vs Lamotrigine 300 mg/d vs Lamotrigine 400 mg/d Total withdrawals: 28 (31.1%) vs 31 (34.4%) vs 34 (37.8%) vs 45 (50%) Due to AE: 9 (10%) vs 12 (13.3%) vs 12 (13.3%) vs 19 (21.1%)	GlaxoSmithKline	

Evidence Table 2. Update 1: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity
GlaxoSmithKline, 2005b Study no. NPP30005/Vinik 2007 Fair	Male or female subjects ≥18 years of age with type 1 or type 2 DM with diabetic neuropathy (defined by bilateral decreased or absent reflexes at the ankles or bilateral decreased vibration, pinprick, fine touch or temperature perception in the distal lower extremities) for ≥6 months, but ≤5 years; had mean pain score ≥4 during Baseline Phase using an 11-point numerical rating scale.	A: Lamotrigine 100 mg/d BID (total of 200 mg/d) B: Lamotrigine 150 mg/d BID (total of 300 mg/d) C: Lamotrigine 200mg/d BID (total of 400 mg/d) D: Placebo For 19 weeks (7 weeks dose-escalation phase plus a 12-week fixed-dose maintenance phase)	Acetaminophen as rescue medication (instructed to take 1000 mg every 4-6 hours as needed but to take no more than 4000 mg in 24 hours). Concomitant medications including gabapentin and tricyclic antidepressants were permitted. (Actual use listed in Vinik 2007)	60.3 years (SD 11.8) 53.3% male White: 87% Black: 8.5% Hispanic: 2.8% Other: 1.5%

Evidence Table 2. Update 1: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed	Efficacy/Effectiveness
GlaxoSmithKline, 2005b Study no. NPP30005/Vinik 2007 Fair	DM Type 1: 8.3% DM Type 2: 91.7% Mean duration of diabetes: 116.3 months Mean duration of NP: 34.4 months	360	138/12/339 for efficacy, 351 for safety	Placebo vs Lamotrigine 200 mg/d vs Lamotrigine 300 mg/d vs Lamotrigine 400 mg/d SF-MPQ total pain score, Adjusted mean change from Baseline at Week 19 (SE): -4.81 (1.366) vs -4.86 (1.310; 95% CI of adjusted difference vs placebo, -2.99 to 3.09) vs -5.99 (1.331; 95% CI of adjusted difference vs placebo, -1.89 to 4.24) vs -4.53 (1.424; 95% CI of adjusted difference vs placebo, -3.48 to 2.91) Proportion of subjects with a ≥30% reduction in pain intensity scores at week 19: 25 (30%) vs 32 (37%) vs 28 (33%) vs 27 (32%) Difference from placebo: N/A vs -7.4 vs -3.2 vs -2.4 Proportion of subjects with a ≥50% reduction in pain intensity scores at week 19: 19 (23%) vs 21 (24%) vs 20 (24%) vs 20 (24%) Difference from placebo: N/A vs -1.8 vs -0.9 vs -1.2

Evidence Table 2. Update 1: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
GlaxoSmithKline, 2005b Study no. NPP30005/Vinik 2007 Fair	Placebo vs Lamotrigine 200 mg/d vs Lamotrigine 300 mg/d vs Lamotrigine 400 mg/d Any adverse event: 54 (63%) vs 63 (71%) vs 65 (73%) vs 64 (74%) Subjects with any serious AEs: 5 (6%) vs 8 (9%) vs 4 (4%) vs 4 (5%) Most common adverse events (reported more often in any lamotrigine group than in the placebo group and were reported in >8% of patients in any treatment group): Headache: 6 (7%) vs 14 (16%) vs 15 (17%) vs 18 (21%) Rash (serious or non-serious): 8 (9%) vs 9 (10%) vs 10 (11%) vs 14 (16%) Nausea: 7 (8%) vs 11 (12%) vs 5 (6%) vs 5 (6%) Dizziness: 6 (7%) vs 4 (4%) vs 6 (7%) vs 9 (10%) Arthralgia: 8 (9%) vs 9 (10%) vs 3 (3%) vs 2 (2%)	Placebo vs Lamotrigine 200 mg/d vs Lamotrigine 300 mg/d vs Lamotrigine 400 mg/d Total withdrawals: 32 (35.6%) vs 32 (35.6%) vs 32 (35.6%) vs 42 (46.7%) Due to AE: 11 (12.2%) vs 13 (14.4%) vs 16 (17.8%) vs 21 (23.3%)	GlaxoSmithKline	

Evidence Table 2. Update 1: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity
Gordh, 2008 Denmark, Finland, Norway and Sweden Fair	Patients ≥18 years with NP due to peripheral nerve injury caused by surgery or trauma, with the NP having lasted for ≥6 months and a pain intensity of ≥30 on a 0–100 VAS. They also had to show hyper- or hypo-phenomena in sensibility tests within a neuroanatomically relevant distribution area.	A: Gabapentin 300-2400 mg/d (mean 2243mg ± 402) B: Placebo This cross-over study comprised a run-in period of 2 weeks, two treatment periods of 5 weeks separated by a 3 weeks' washout period. Titration started with 300 mg and the dose was increased until maximum pain relief at a tolerable dose was achieved (max daily dose was 2400 mg).	Occasional use of NSAIDs for other types of pain and the use of benzodiazepines, zolpidem or zopiclone, for insomnia were allowed if they had been prescribed before screening. Paracetamol with/without codeine and dextropropoxyphene were allowed as rescue medication. During the study, 23% of the patients used analgesics and 27% NSAIDs.	48.8 years 52.2% female Ethnicity NR

Evidence Table 2. Update 1: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed	Efficacy/Effectiveness
Gordh, 2008 Denmark, Finland, Norway and Sweden Fair	Weight: 77.1 kg Height: 171.1 cm Injured nerves, % of patients: Ulnar nerve: 13.3% Median nerve: 10.8% Intercostal nerve: 10.8% Duration of pain, number of patients: 6-12 months: 13 1-5 years: 94 ≥5 years: 13	120	22/NR/98 ITT, 120 for safety	<u>Gabapentin vs Placebo</u> Mean change (SD) VAS pain intensity score from beginning to end of treatment arm, ITT-population: Gabapentin-placebo group: -7.2 (17.8) vs -0.5 (9.7) Placebo-gabapentin group: -5.1 (11.6) vs -6.9 (15.5) Pain relief during gabapentin treatment and placebo treatment, ITT-population, randomization groups combined, number of patients: Marked: 18 vs 5 Moderate: 13 vs 9 Some: 13 vs 13 No: 54 vs 70 Response to treatment, ITT-population, randomization arms combined, number of patients: ≥50% reduction in weekly pain intensity: 11 vs 7 ≥30% reduction in weekly pain intensity: 20 vs 10 At least marked pain relief: 17 vs 4 At least moderate pain relief: 26 vs 9 Mean change (SD) sleep interference score from beginning to end of treatment arm, ITT-population: Gabapentin-placebo group: -10.2 (15.6) vs -0.5 (10.5); P=0.0016 Placebo-gabapentin group: -3.8 (9.3) vs -6.3 (12.5) CGIC, ITT-population, randomization arms combined, number of patients: Much improved: 7 vs 2 Moderately improved: 22 vs 11 Minimally improved: 19 vs 14 No change: 38 vs 58 Minimally worse: 8 vs 12 Moderately worse: 4 vs 1 Statistically significantly more patients had improved more during gabapentin treatment compared with placebo treatment (P=0.037).

Evidence Table 2. Update 1: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Gordh, 2008 Denmark, Finland, Norway and Sweden Fair	<u>Gabapentin vs Placebo</u> Total events reported: 241 vs 168 Dizziness and vertigo: 39 (32.5%) vs 9 (7.5%) Malaise and tiredness: 31 (25.8%) vs 17 (14.2%) Headache including migraine: 18 (15%) vs 20 (16.7) Nausea and vomiting: 8 (6.7%) vs 10 (8.3%) Infections: 10 (8.3%) vs 15 (12.5%) Skin disorders: 10 (8.3%) vs 5 (4.2%) Confusion: 16 (13.3%) vs 2 (1.7%) Dry mouth: 9 (7.5%) vs 3 (2.5%)	<u>Gabapentin vs Placebo</u> Total withdrawals: 11 (9.2%) vs 9 (7.5%), plus 2 withdrawn during washout between placebo and gabapentin treatment; 13 in gabapentin-placebo group and 9 in placebo-gabapentin group Due to AE: 7 (5.8%) vs 4 (3.3%)	Parke-Davis AB, Pfizer AB	In case of adverse effects the dose could be decreased at any time during the titration period, but after titration the dose was fixed for 3 weeks and no dose adjustments were allowed. On the average the patients were treated with gabapentin and placebo for 31 days each.

Evidence Table 2. Update 1: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity
Grosskopf, 2006 U.S., Germany, U.K. Poor	Patients ≥18 years of age with NP of diabetic origin, a history of NP for 6 months to 5 years, stable diabetic control, a pain rating ≥50 on the 100-unit VAS, and a mean VAS score ≥40 units over 4 of the last 7 days prior to randomization.	A: Oxcarbazepine 1200 mg/day (600 mg BID) or tolerable dose B: Placebo	Acetaminophen (as rescue medication) up to 4 g/day	61.1 years (SD 10.6) 55% male Ethnicity NR

Evidence Table 2. Update 1: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed	Efficacy/Effectiveness
Grosskopf, 2006 U.S., Germany, U.K. Poor	History of diabetes: 10.8 years (SD 9.0) HbA1c ≤8: 79% HbA1c >8: 21% History of NP: 2.9 years (SD 1.9) Baseline VAS score: 71.4 (SD 13.9)	141	46/NR/NR	<u>Oxcarbazepine vs Placebo</u> Average reduction in VAS scores, from baseline to endpoint: 27.9% vs 31.1% (NSD) NSD between groups in the GATE, onset of therapeutic effect, sleep questionnaire and quality of life.

Evidence Table 2. Update 1: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Grosskopf, 2006 U.S., Germany, U.K. Poor	<u>Oxcarbazepine vs Placebo</u> During titration phase: Dizziness: 14 (19.7%) vs 4 (5.7%) Nausea: 12 (16.9%) vs 1 (1.4%) Headache: 7 (9.9%) vs 3 (4.3%) During maintenance phase: Dizziness: 7.6% vs 1.7% Nausea: 5.5% vs 0% Headache: 3.7% vs 1.1% Clinically notable hyponatremia: 1 (1.4%) vs 0 (0%)	<u>Oxcarbazepine vs Placebo</u> Total withdrawals: 29 (40.8%) vs 17 (24.3%) Due to AE: 18 (25.4%) vs 4 (5.7%)	Novartis	Oxcarbazepine was initiated at 300 mg/day and titrated over 4 weeks to tolerability or a max dose of 600 mg twice a day (1200 mg). The dose remained unchanged throughout the maintenance period, except for dose reductions in the event of poor tolerability. Mean oxcarbazepine dose during the maintenance period was 1091 mg/day (SD 222 mg/day).

Evidence Table 2. Update 1: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity
Holbech 2010 (In Press) Denmark Fair	Patients aged 20-80 years with painful polyneuropathy for more than 6 mo (distal symmetric pain localization)plus sensory disturbance in area of pain. Median total pain rating of at least 4 on a 11 point scale during week 1 off pain medication before being finally included and randomized. Patients with polyneuropathy due to diabetes, hyperthyroidism etc, the causative condition had to be stable for at least 3 mo before inclusion in the trial, i.e. for diabetes e.g. glycosylated hemoglobin levels had to be stable.	A: Levetiracetam: Max dose 3000mg/day B: Placebo 1 wk baseline observation, 2 treatment period of 6 weeks (DB),	Up to 6 tablets of 500mg paracetamol and 1 tablet for 50mg tramadol used as escape medication	Median: 57 years (range 21-74) 56.4% male Ethnicity: NR
Kautio 2008 Finland Fair	Adults aged 20 to 65 years with chemotherapy-induced neuropathy manifesting as numbness, tingling, or pain of at least moderate severity, duration of at least 2 months.	A: Amitriptyline (target dose 50 mg) B: Placebo 8 weeks Parallel group design	Patients excluded if using concomitant medications for neuropathic symptoms	54 years (range 35-69) 73% female Ethnicity: NR

Evidence Table 2. Update 1: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed	Efficacy/Effectiveness
Holbech 2010 (In Press) Denmark Fair	Etiology of polyneuropathy Diabetic: 51.4% Idiopathic: 14.2% Monoclonal gammopathy of unspecific evidence: 8.5% Hypothyroidism: 8.5% Alcohol: 2.9% Drug-induced: 2.9% Vasculitis: 2.9% Guillain-Barre syndrome sequelae: 2.9% Hereditary: 2.9% Critical illness polyneuropathy sequelae: 2.9% Duration of pain. mo: Median 49 (range 6-120) Total pain at baseline: Median 5.7 (range 4-9)	39	13/NR/35	<u>Levetiracetam vs placebo (p-values are vs placebo)</u> Mean(SD) pain relief at endpoint: 2.29 (1.13) vs 2.28 (1.19), P=0.979 Change from baseline in total pain: -0.2 vs -0.4, P=0.293 Change from baseline in deep aching pain: -0.3 vs -0.4, P=0.609 Burning pain: -0.3 vs -0.3 Pressure-evoked pain: 0.1 vs 0.2, P=0.392 Touch-evoked pain: 0.6 vs 0.3 , P=0.263 Sleep disturbances: -1.0 vs -0.8, P=0.648 Change in QOL-SF 36 (vitality) P=0.0005 (in favor of placebo) Change in QOL-social functioning: P=0.028 (in favor of placebo)
Kautio 2008 Finland Fair	Chemotherapy regimens: Vinca alkaloids: 34% Platinum derivatives: 32% Taxanes: 30% Combination: 4%	44	9/0/33	<u>Amitriptyline vs placebo</u> Global improvement mean (SD): 3.4 (3.6) vs 1.9 (3.1), P=NS % of patients with some relief from NP: 47% vs 31%, P=NS % of patients with complete relief from NP: 11.8% vs 0% % patients with major relief from NP: 5.9% vs 6.3% No statistically significant differences in the severity of NP symptoms between amitriptyline and placebo (data NR by treatment arm) Amitriptyline improved QOL as measured with EORTC QKQ-C30 statistically significantly compared to placebo (P=0.038) % of patients with improved global health score: 41.2% vs 12.5%, P=NR No significant changes in depression scale in either group, no differences between group (data NR) % less of nightly awakenings:52.9% vs 31.2%, P=NR % of no change in nightly awakenings: 47.1% vs 68.8%, change in sleep duration between 2 groups=NS

Evidence Table 2. Update 1: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Holbech 2010 (In Press) Denmark Fair	Levetiracetam vs placebo Overall AE: 22 (59.5%)vs 17 (45.9%) Tiredness: 14 (37.8%)vs 4 (10.8%) Dizziness: 5 (13.5%) vs 1 (2.7%) Nausea: 3 (8.1%)vs 2 (5.4%) Constipation: 4 (10.8%)vs 2 (5.4%) Headache: 2 (5.4%)vs 3 (8.1%) Dry mouth: 0 vs 1 (2.7%) Edema: 1 (2.7%) vs 1 (2.7%) Sleep disturbance: 1 vs 0	Levetiracetam vs placebo Total withdrawals: 20.5% vs 12.8% Withdrawals due to AE: 5.1% vs 0%	UCB-Pharma sponsored GCP-monitor unit throughout the trial	
Kautio 2008 Finland Fair	NR	Total withdrawals: 9 (Data NR by treatment arm) Withdrawals due to AE: 3 (Data NR by treatment arm)	Grant from Finnish Cancer Society and Research Funds University Central Hospital T10200066)	

Evidence Table 2. Update 1: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity
Kautio, 2009 Finland Fair	Cancer patients aged 20-75 years starting their first neurotoxic chemotherapy with vinca alkaloids, platinum derivatives or taxanes	A: Amitriptyline (target dose 100mg/d) B: Placebo Parallel group design Median follow up time 21 weeks for amitriptyline and 19 weeks for placebo	NR	56 years (range 25-75) 72% female Ethnicity: NR
Keskinbora, 2007 Turkey Poor	Patients having sufficient relief of nociceptive but not the neuropathic component of the cancer pain while receiving ongoing opioid treatment without significant opioid-related side-effects; pain intensity ≥4 on a NRS ranging from 0-10 and a Karnofsky score of 0-10	A: Gabapentin (target dose 3600mg/d adjuvant to opioid B: Opioid opioids included oral tramadol/transdermal fentanyl/SR morphine) 13 days	NR	54.9 years 66.7% male Ethnicity: NR

Evidence Table 2. Update 1: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed	Efficacy/Effectiveness
Kautio, 2009 Finland Fair	Diagnosis Ovarian cancer: 44% Lymphoma: 16% Colorectal cancer: 13% Breast cancer: 7% Uterine cancer: 6% Chemotherapy regimens Vinca alkaloids: 21% Platinum derivatives: 23% Taxanes: 6% Combination: 50% Current Chemotherapy 1st line 47% 2nd line: 9%	114	32/0/99	Amitriptyline vs Placebo Neuropathy score at endpoint: P=NS between 2 groups, intensity generally mild NCI-CTC score: P=NS between two groups Intensity of neuropathy as measured by NCI-CTC grading system at visit 4 Sensory Grade 0 at visit 4: 13.7% vs 7.3% Grade 1 at visit 4: 11.8% vs 24.4% Grade 2 at visit 4: 9.8% vs 7.3% Grade 3 at visit 4: 5.9% vs 9.8% Motor Grade 0 at visit 4: 38.3% vs 33.3% Grade 1 at visit 4: 4.3% vs 11.9% Grade 2 at visit 4: 0% vs 2.4% Grade 3 at visit 4: 2.1%vs 0% No significant difference in EORTC-C30 results between amitriptyline and placebo at follow-up visits. (Data NR)
Keskinbora, 2007 Turkey Poor	Tumor related NP Cranial neuralgia: 15.9% Cervical plexopathy: 1.6% Brachial plexopathy: 20.6% Radiculopathy: 4.8% Lumbosacral plexopathy: 11.1% Sacral plexopathy: 23.8% Mononeuropathy: 3.2% Central neuropathy:3.2% NP related to cancer therapy Mononeuropathy: 7.9% Phantom pain: 1.6% Post-thoracotomy pain: 3.2% Acute herpes zoster: 3.2%	75	12/6/1963	Gabapentin + Opioid vs Opioid Change from baseline in burning pain at endpoint: -7.39 (± 2.86) vs -5.78 (± 2.35), p<0.001 vs baseline, P=0.018 between 2 groups Change from baseline in shooting pain at endpoint: -6.77 (± 3.37) vs -4.66 (± 2.80), p<0.001 vs baseline, P=0.009 between 2 groups Mean NRS score for burning and shooting pain was stable after the fourth day in Gabapentin and Opioid group, but continued to decrease in the opioid group. Frequency of Allodynia at endpoint: 0.0 vs 6.3%, P=0.0001 vs baseline and P=0.157 between 2 groups

Evidence Table 2. Update 1: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Kautio, 2009 Finland Fair	Amitriptyline vs placebo Tiredness: 19% vs 1.8% Dry mouth: 1.7% vs 1.8% (titration phase and stable dose phase: p<0.001) Visual disturbance and constipation: 1.7% in amitriptyline group Palpitation and dizziness: 1.8% in placebo group	Amitriptyline vs placebo Total withdrawals: 12.1% vs 26.8% Withdrawals due to AE: 3.4% vs 0%	Finnish Cancer Society and research funds of the Helsinki University Central Hospital TIO200066	
Keskinbora, 2007 Turkey Poor	Gabapentin + Opioid vs Opioid % of patients reporting any AE: 29% vs 59.4%, P=0.015 Constipation: 0 vs 21.8% Dizziness: 12.9% vs 12.5% Nausea/vomiting: 3.2% vs 18.7% Sedation: 12.9% vs 6.2%	Gabapentin + Opioid vs Opioid Total withdrawals: 18.4% vs 13.5% Withdrawals due to AE: 2.6% vs 0%	NR	Baseline characteristics reported on completer population

Evidence Table 2. Update 1: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity
Khoromi, 2007 U.S. Fair	Patients aged 18-65 years with chronic sciatica, evidence of 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 features on the side corresponding to leg pain, and an average leg pain of at least 4/10 for the past month.	A: Sustained-release morphine 15-90 mg (mean 62 mg/d) B: Nortriptyline 25-100 mg (mean 84 mg/d) C: Morphine 15-90 mg (mean 49 mg/d) + nortriptyline 25-100 mg (mean 55 mg/d) D: Benztropine (active placebo) 0.25-1 mg For 4 periods of 9 weeks (5 weeks dose escalation, 2 weeks maintenance at highest tolerated dose, and 2 weeks of dose tapering)	Anti-inflammatory medications and acetaminophen as rescue medications.	53 years 45% female Ethnicity NR

Evidence Table 2. Update 1: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed	Efficacy/Effectiveness
Khoromi, 2007 U.S. Fair	Median pain duration: 5 years	55	27/NR/28	<u>Placebo vs Morphine vs Nortriptyline vs Combination (Morphine + Nortriptyline)</u> Pain scores in 28 study completers, mean (SD): Average leg: 3.7 (2.7) vs 3.4 (2.8) vs 3.0 (2.7) vs 3.4 (2.5) Pain reduction below placebo: NA vs 0.3 (7% reduced; 95% CI, -8% to 22%) vs 0.5 (14% reduced; 95% CI, -2% to 30%) vs 0.3 (7% reduced; 95% CI, -4% to 18%) Average back: 3.8 (2.5) vs 3.4 (2.5) vs 2.9 (2.4) vs 3.2 (2.4) Pain reduction below placebo: NA vs 0.2 (5% reduced, 95% CI -5% to 14%) vs 0.4 (10% reduced; 95% CI, -4% to 25%) vs 0.2 (7% reduced; 95% CI, -5% to 19%) Average overall: 3.9 (2.4) vs 3.8 (2.5) vs 3.2 (2.4) vs 3.4 (2.5) Pain reduction below placebo: NA vs 0.04 (1% reduction; 95% CI, -16% to 18%) vs 0.5 (14% reduction; 95% CI, -2% to 30%) vs 0.4 (11% reduction; 95% CI 2% to 20%) Worst leg: 4.6 (2.8) vs 4.5 (3.1) vs 3.8 (3.0) vs 3.8 (2.4) Pain reduction below placebo: NA vs 0.04 (1% reduction; 95% CI, -18% to 20%) vs 0.6 (13% reduction; 95% CI, -5% to 31%) vs 0.6 (12% reduction; 95% CI, -1% to 26%) Worst back: 4.4 (2.6) vs 4.2 (3.0) vs 3.8 (2.9) vs 4.0 (2.6) Pain reduction below placebo: NA vs 0.03 (1% reduction; 95% CI, -15% to 16%) vs 0.4 (9% reduction; 95% CI, -5% to 23%) vs 0.2 (6% reduction; 95% CI, -8% to 20%) Worst overall: 4.8 (2.5) vs 4.5 (2.8) vs 3.8 (2.9) vs 4.0 (2.4) Pain reduction below placebo: NA vs 0.2 (4% reduction; 95% CI, -14% to 21%) vs 0.6 (13% reduction; 95% CI, -3% to 30%) vs 0.7 (15% reduction; 95% CI, 3% to 27%)

Evidence Table 2. Update 1: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Khoromi, 2007 U.S. Fair	Morphine vs Nortriptyline vs Combination vs Placebo Any side effect: 93% vs 68% vs 89% vs 50% Constipation: 64% vs 25% vs 71% vs 7% Dry Mouth: 21% vs 36% vs 29% vs 21% Headache: 14% vs 7% vs 14% vs 14% Drowsiness: 25% vs 7% vs 11% vs 4% Tired/fatigue: 7% vs 11% vs 14% vs 18% Dizziness: 14% vs 7% vs 4% vs 4% Insomnia: 7% vs 11% vs 11% vs 0% Nausea: 7% vs 0% vs 4% vs 0% Difficulty urinating: 4% vs 4% vs 7% vs 0% Sexual dysfunction: 11% vs 0% vs 4% vs 0% Abdominal pain: 4% vs 4% vs 7% vs 0% Weakness: 0% vs 0% vs 7% vs 7% Decreased appetite: 7% vs 0% vs 4% vs 0% Heartburn: 4% vs 7% vs 0% vs 4% Blurred vision: 7% vs 0% vs 4% vs 11% Thirsty/dehydrated: 0% vs 7% vs 0% vs 0% Weight gain: 0% vs 7% vs 0% vs 0%	Morphine vs Nortriptyline vs Combination vs Placebo Total withdrawals: 9 (16.4%) vs 3 (5.5%) vs 6 (10.9%) vs 9 (16.4%) Due to AE: 3 (5.5%) vs 2 (3.6%) vs 4 (7.3%) vs 1 (1.8%)	National Institute of Dental and Craniofacial Research	

Evidence Table 2. Update 1: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity
Pfizer unpublished study, 2007 Protocol no. A0081030 Asia, U.S., Middle East Fair	Male and female subjects ≥ 18 years with a diagnosis of painful symmetrical sensorimotor DPN for ≥12 mo and <5 years, type 1 and type 2 DM, and a pain score of at least 40mm on a 100mm VAS of the SF MPQ both at screening and randomization.	A: Pregabalin 150-600mg/d B: Placebo Parallel design 14 weeks (1 wk screening phase, 12 wks DB treatment phase, 1 wk taper period)	NR	57.2 years 39.2% male White: 29.6% Black: 3% Asian: 51.7% Other: 15.8%

Evidence Table 2. Update 1: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed	Efficacy/Effectiveness
Pfizer unpublished study, 2007 Protocol no. A0081030 Asia, U.S., Middle East Fair	Mean weight: 72.2 kg BMI: 28.1 kg/m2 Height: 160.3 cm	412	64/0/401	Pregabalin vs placebo Change from baseline in mean pain score as measured by daily pain rating scale at 12 weeks: -2.7 vs -2.4, LS Mean difference between groups -0.3, (95% CI -0.7 to 0.1), P=0.17. Significant differences between groups at Week 1, 4, 5 and 6. Mean pain score on the daily pain rating scale by subgroup Depressed: LS mean at 12 weeks 3.7 vs 3.8, difference between 2 groups -0.1, P=0.718, 95% CI (-0.7 to 0.5) Anxious: LS mean at 12 weeks 3.6 vs 3.8, difference between 2 groups -0.2, P=0.534, 95% CI (-0.8 to 0.4) Poor sleep: LS mean at 12 weeks 3.7 vs 3.9, difference between 2 groups -0.3, P=0.408, 95% CI (-0.9 to 0.4) Proportion of patients with ≥30% reduction in pain at 12 weeks: 64.4% vs 54.5%, P=0.045 Proportion of patients with ≥50% reduction in pain at 12 weeks: 42.7% vs 39.6%, P=0.509 Change from baseline in daily sleep interference at 12 weeks: -2.4 vs -2.1 , difference between LSM Mean -0.3, 95% CI (-0.7 to 0.1), P=0.174 VAS pain change from baseline in 12 weeks: -36.8 vs -36, difference between LS mean -2.4, 95% CI -7.5 to 2.6, P=0.338 Modified BPI Pain Severity Index change from baseline in 12 weeks: -3.6 vs -3.1, difference between LS mean -0.5, 95% CI(-1.0 to 0.1), P=0.148 Pain inference index change from baseline at 12 weeks: -3.1 vs -2.5, difference between LS mean -0.3, 95% CI -0.8 to 0.1, P=0.148 Pain treatment satisfaction impact of pain medication change from baseline at 12 weeks: 11.7 vs 8.4 , difference between LS means 8.1, 95% CI (2.5 to 13.7), P=0.005 Satisfaction with pain medication/care change from baseline at 12 weeks: 19.6 vs 15, difference between LS means 3.6, 95% CI (-0.7 to 7.9), P=0.097 VAS-Anxiety change from baseline at 12 weeks: -26.6 vs -21.4, difference between LS mean -5.4, 95% CI (-10.5 to -0.4), P=0.036 HADS-Anxiety change from baseline at 12 weeks: -3.0 vs -2.3, difference between LS mean -0.9, 95% CI (-1.7 to -0.1), P=0.022 HADS-Depression change from baseline at 12 weeks: -2.2 vs -2.0, difference between LS means -0.4, 95% CI (-1.1 to 0.3), P=0.225 EQ-5D health state profile change from baseline at 12 weeks: -0.28 vs -0.20, difference between LS means 0.06, 95% CI (0.01 to 0.12), P=0.027 EQ-5D VAS change from baseline at 12 weeks: -14.8 vs -15.5, difference between LS means 2.5, 95% CI (-1.8 to 6.9), P=0.253 Mean (SD) PGIC at 12 weeks: 2.4 (1.06) vs 2.7 (1.31), difference between LS means -0.3, 95% CI (-0.5 to 0.0), P=0.033 Mean (SD) CGIC at 12 weeks: 2.2(1.11) vs 2.5(1.22), -0.3, 95% CI -0.5 to 0.0, P=0.028

Evidence Table 2. Update 1: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Pfizer unpublished study, 2007 Protocol no. A0081030 Asia, U.S., Middle East Fair	<u>Pregabalin vs placebo</u> Serious AE: 4.1% vs 3.0% Dizziness: 20.3% vs 9.6% Somnolence: 18.5% vs 6.7% Edema peripheral: 10.7% vs 6.7% Weight increase: 10.0% vs 0.7% Headache: 4.4% vs 6.7% Nasopharyngitis: 4.4% vs 2.2% Constipation: 3.3% vs 1.5% Constipation: 3.3% vs 1.5% Diarrhea: 3.0% vs 3.0% Insomnia: 3.0% vs 2.2% Nausea: 3.0% vs 0.7% Dry mouth: 2.2% vs 0.7% Edema: 2.2% vs 0 Back pain: 1.8% vs 2.2% Vomiting and blood glucose increase: 1.8% vs 0.7% Hypoesthesia: 1.8% vs 0% Influenza: 1.5% vs 4.4%	<u>Pregabalin vs placebo</u> Total withdrawals: 16.2% vs 17.8% Withdrawals due to AE: 5.5% vs 3.0%	Pfizer Inc.	

Evidence Table 2. Update 1: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity
Pfizer unpublished study, 2008 Protocol no. A0081081 China Fair	Male and female Chinese outpatients ≥18 years and ≤75 years with a diagnosis of neuropathic pain associated with either DPN or PHN and a pain score of at least 40mm on a 100mm VAS of the SF-MPQ, both at screening and randomization	A: Pregabalin 150-600mg QD B: Placebo Parallel design 1 wk run-in, 8 weeks D treatment and 1 wk drug taper off phase	NR	60 years Gender: NR Asian (Chinese): 100%

Evidence Table 2. Update 1: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed	Efficacy/Effectiveness
Pfizer unpublished study, 2008 Protocol no. A0081081 China Fair	Diabetic neuropathy: 69.8% PHN: 30.2%	309	41/NR/308	<u>Pregabalin vs placebo</u> Change from baseline in mean pain score -2.7 vs -2.0 Endpoint score LS mean (SE) 3.7 (0.14), 95% CI (3.4 to 4.0) vs 4.3 (0.19), 95% CI (4.0 to 4.7) treatment difference -0.6 (favoring pregabalin), 95% CI (-1.1 to -0.2), P=0.005 Proportion of patients with ≥30% reduction in mean pain score at endpoint: 64.0% vs 52%, P=0.041 Mean (SD) DAAC scores: -1.9 (1.51) vs -1.3 (1.38), treatment difference in LS means -0.57, 95% CI(-0.92 to -0.23), P=0.001 favoring pregabalin Endpoint sleep interference scores, difference in LS mean -0.5, 95% CI (-0.93 to -0.07), P=0.023 VAS score at wk 8: difference in LS means -6.56, 95% CI (-11.65 to -1.47), P=0.012 PPI score at wk 8: difference in LS means -0.35, 95% CI (-0.58 to -0.12), P=0.003 PGIC score at wk 8: difference in LS means -0.33, 95% CI -0.55 to -0.11, P=0.004 CGIC score at wk 8: difference in LS means -0.39, 95% CI (-0.63 to -0.16), P=0.001

Evidence Table 2. Update 1: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Pfizer unpublished study, 2008 Protocol no. A0081081 China Fair	Pregabalin vs placebo % of patients with any AE: 50% vs 40.2% % of patients with serious AE: 1.5% vs 2% Dizziness:10.7% vs 6.9% Lethargy:7.8% vs 2.9% Somnolence:4.9% vs 1.0% Peripheral edema:4.9% vs 2.0% Eye disorder: 10.7% vs 8.8%	Pregabalin vs placebo Total withdrawals: 11.7% vs 16.7% Withdrawals due to AE: 5% vs 4%	Pfizer Inc.	

Evidence Table 2. Update 1: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity
Pfizer unpublished study, 2009 Protocol no. A0081063 11 countries in the Asia Pacific region Fair	Adult subjects ≥18 years of age with a positive history of clinical stroke for ≥4 months and CPSP for ≥3 months, with a score of ≥40 mm the VAS of the SF-MPQ, and an average pain score of ≥4 and had completed ≥4 daily pain diaries during the 7 days prior to randomization.	A: Pregabalin 75 to 300 BID B: Placebo	NR	58 years 62.6% male Asian: 91.3%

Evidence Table 2. Update 1: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed	Efficacy/Effectiveness
Pfizer unpublished study, 2009 Protocol no. A0081063 11 countries in the Asia Pacific region Fair	Mean weight: 67.2 kg Mean height: 162.8 cm Mean duration since first diagnosis: 2.3 years	220	36/7/NR	Pregabalin vs Placebo: Mean change in DPRS: -1.6 vs -1.5 (P=0.578) Subjects with ≥30% reduction in mean pain score: 44.4% vs 32.4% (P=0.087) Subjects with ≥50% reduction in mean pain score: 24.1% vs 20.4% (P=0.622) Mean DAAC from baseline (SD): -1.3 (1.78) vs -0.8 (1.53) Mean change in sleep interference: -1.4 vs -1.1 (P=0.627) Mean change in SF-MPQ VAS score: -17.7 vs -17 (P=0.741) Mean change in NPSI: -11.3 vs -9.1 (P=0.138) MOS-Sleep, mean change: Sleep disturbance: -14.5 vs -10.3; Difference between LS means at wk 12: -4.8 (95% CI, -10.3 to 0.7), P=0.086 Snoring: 1.9 vs -6.2; Difference between LS means at wk 12: 7.7 (95% CI, 0.4 to 15.1), P=0.039 Short of breath/headache: -6.2 vs -4.4; Difference between LS means at wk 12: -3.7 (95% CI, -9.1 to 1.6); P=0.169 Sleep quantity: 0.7 vs 0.1; Difference between LS means at wk 12: 0.4 (95% CI, 0.0 to 0.7); P=0.030 Sleep adequacy: 13 vs -2.1; Difference between LS means at wk 12: 8.6 (95% CI, 1.8 to 15.4); P=0.013 Sleep somnolence: -1.3 vs -0.2; Difference between LS means at wk 12: 2.1 (95% CI, -2.8 to 7.1); P=0.399 Sleep problems index: -10.4 vs -4.8; Difference between LS means at wk 12: -4.2 (95% CI, -8.4 to -0.0); P=0.049 HADS, mean change: Anxiety subscale: -2.2 vs -1.0; Difference between LS means at wk 12: -1.0 (95% CI, -1.8 to -0.2), P=0.015 Depression subscale: -1.6 vs -1.1; Difference between LS means at wk 12: 0.2 (95% CI, -0.6 to 1.0), P=0.600 Euro QOL (Health State Profile, VAS), mean change: EQ-5D utility score: 0.2 vs 0.1 EQ-5D VAS: 7.2 vs 2.6; P=0.220 PGIC, wk 12 LS mean: 2.9 vs 3.1; Difference between LS means at wk 12: -0.2 (95% CI, -0.5 to 0.1), P=0.144 CGIC, wk 12 LS mean: 2.8 vs 3.1; Difference between LS means at wk 12: -0.3 (95% CI, -0.6 to 0.0), P=0.049 QANeP: Mechanical allodynia: -0.7 vs -0.5 Dynamic mechanical allodynia: -0.8 vs -0.6 Punctate hyperalgesia test area: -0.7 vs -0.0 Cold allodynia: -1.1 vs -0.3 Temporal summation to tactile stimuli: -1.0 vs -0.5

Evidence Table 2. Update 1: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Pfizer unpublished study, 2009 Protocol no. A0081063 11 countries in the Asia Pacific region Fair	<u>Pregabalin vs Placebo, all causality (treatment-related):</u> Dizziness: 31 (26) vs 8 (7) Somnolence: 24 (23) vs 5 (4) Edema peripheral: 11 (9) vs 3 (2) Headache: 7 (3) vs 8 (2) Diarrhea: 6 (2) vs 2 (0) Edema: 6 (5) vs 0 Weight increased: 6 (6) vs 2 (2) Upper respiratory tract infection: 3 (0) vs 6 (0) Treatment-related serious AEs: Edema peripheral: 1 (0.9%) vs 0	<u>Pregabalin vs Placebo</u> Total withdrawals: 17 (15.5%) vs 19 (17.4%) Due to AE, total: 9 (8.1%) vs 4 (3.7%) Due to AE related to study drug: 5 (4.5%) vs 3 (2.8%) Due to AE not related to study drug: 4 (3.6%) vs 1 (0.9%)	Pfizer	The study consisted of 4 phases: (1) 2-week screening and washout phase; (2) 4-week randomized, double-blind, placebo-controlled flexible-dose adjustment phase, during which subjects started on 150 mg/day pregabalin (or matching placebo) and could have increased to a maximum of 600 mg/day pregabalin (or matching placebo); (3) 8-week randomized, double-blind, placebo-controlled treatment maintenance phase (dose of pregabalin remained constant at 150 mg/day, 300 mg/day, or 600 mg/day or matching placebo); and (4) 1-week taper double-blind, placebo-controlled treatment phase (either pregabalin 150 mg/day or matching placebo).

Evidence Table 2. Update 1: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity
Pfizer unpublished study, 2009 Protocol no. A0081120 Japan Fair	Male and female 18 years or older with pain persisting for at least 3 mo after healing of herpes zoster skin rash and a score ≥ 40mm on the VAS-SF-MPQ at baseline and randomization	Doses administered BID A: Pregabalin 75mg B: Pregabalin 150mg C: Pregabalin 300mg D: Placebo Time period: 13 weeks Parallel design	NR	70.1 years (range 24-92) 53.4% male Ethnicity : NR (possibly 100% Japanese as the study was conducted in Japan)

Evidence Table 2. Update 1: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed	Efficacy/Effectiveness
Pfizer unpublished study, 2009 Protocol no. A0081120 Japan Fair	Creatinine clearance: 74.0mL/min (range 31.0mL/min to 183.0ml/min)	372	74/1/369	<u>Placebo vs Pregabalin 150mg vs Pregabalin 300mg vs Pregabalin 600mg</u> LSM (SE), pain scores : 5.12 (0.19) vs 4.81 (0.20) vs 4.26(0.20) vs 4.49 (0.19) mean change in pain scores, difference from placebo: 150mg pregabalin -0.31 (95% CI-0.85 to 0.23),P=0.262 vs 300mg pregabalin -0.86 (95% CI -1.39 to -0.32), P=0.002, vs 600mg pregabalin -0.63 (-1.15 to -0.10), P=0.019 Proportion of responders (p-values vs placebo): 15.5% vs 24.4%, P=0.1160 vs 36.0%, P=0.0015 vs 30.9%, P=0.0107 SF-MPQ total, LSM (SE), : 11.39(0.75) vs 10.56 (0.79) vs 8.84 (0.79) vs 8.78 (0.75) Difference with placebo , 95% CI: -0.83 (-2.93 to 1.28), P=0.441 vs -2.55 (-4.64 to -0.46), P=0.017 vs -2.61 (-4.65 to -0.56), P=0.012 VAS score LSM (SE): 50.02 (2.15) vs 47.80 (2.28) vs 41.99 (2.25) vs 42.59 (2.14) Difference with placebo, 95% CI: -2.23 (-8.28 to 3.83), P=0.470 vs -8.04 (-14.0 to -2.06), P=0.008 PPI score, LSM (SE): 2.21 (0.10) vs 2.01 (0.11) vs 1.78 (0.11) vs 1.90 (0.10) Difference with placebo: -0.20 (-0.48 to 0.09) P=0.178 vs -0.43 (-0.72 to -0.15), P=0.003 vs -0.31 (-0.59 to -0.03), P=0.030 LSM (SE)sleep interference score: 3.20 (0.17) vs 2.44 (0.18) vs 2.39 (0.17) vs 2.26 (0.17) Difference with placebo: -0.76 (-1.23 to -0.30), P=0.001 vs -0.81 (-1.27 to -0.34), P=0.001 vs -0.94 (-1.40 to -0.49), p<0.001 Proportion of patients reporting "very much improved", "much improved" and "minimally improved" on PGIC :57.3% Pregabalin 150mg vs 72.4 Pregabalin 300mg and 71.0% for Pregabalin 600mg Difference from placebo: P=0.0466 vs p<0.001 vs p<0.001 Proportion of patients reporting "very much improved", "much improved" and "minimally improved" on CGIC: 55.4% for 150mg vs 73.6% for 300mg vs 74.2% for 600mg Difference from placebo: 300mg and 600mg p<0.001

Evidence Table 2. Update 1: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Pfizer unpublished study, 2009 Protocol no. A0081120 Japan Fair	Placebo vs Pregabalin 150mg vs Pregabalin 300mg vs Pregabalin 600mg % of patients with any AE: 63.3% vs 74.7% vs 87.6% vs 92.8% % of patients with treatment-emergent AE: 43.9% vs 57.5% vs 73.0% vs 82.5% % of patients with serious AE (treatment related): 2.0% vs 1.1% vs 1.1% vs 0% Constipation: 6.1% vs 13.8% vs 12.4% vs 14.4% Nausea: 5.1% vs 2.3% vs 6.7% vs 7.2% Face edema: 0% vs 4.6% vs 1.1% vs 6.2% Peripheral edema: 1.0% vs 4.6% vs 13.5% vs 18.6% Dizziness: 7.1% vs 11.5% vs 30.3% vs 49.5% Headache: 1.0% vs 2.3% vs 1.1% vs 5.2% Somnolence: 9.2% vs 21.8% vs 24.7% vs 38.1% Eczema: 2.0% vs 3.4% vs 0 vs 6.2%	Placebo vs Pregabalin 150mg vs Pregabalin 300mg vs Pregabalin 600mg Total withdrawals: 15.3% vs 16.1% vs 20.2% vs 27.8% Withdrawals due to AE: 5.1% vs 8.0% vs 18.0% vs 20.6%	Pfizer Inc	

Evidence Table 2. Update 1: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity
Pfizer unpublished study, 2007 Protocol no. A0081071 U.S. Fair	Male and non pregnant non lactating, post menopausal or surgically sterilized female subjects at least 18 years of age with a documented diagnosis of type 1 or type 2 DM for at least 1 year, with a stable glycemic control and painful distal, symmetrical, sensorimotor polyneuropathy, due to diabetes at least 3 months prior to screening with a pain score ≥4 on a 11 point NRS.	Doses administered BID A: Pregabalin 300mg B: Pregabalin 600mg C: Placebo Time period: 14 weeks Parallel design	NR	59 years 56.4% male Ethnicity: NR (stated as majority white)

Evidence Table 2. Update 1: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed	Efficacy/Effectiveness
Pfizer unpublished study, 2007 Protocol no. A0081071 U.S. Fair	NR	462	147/NR/451	Change from baseline in mean daily pain diary (NRS pain): Pregabalin 300mg vs placebo P=0.4744 (LOCF adjusted), 600mg vs placebo P=0.4530 (LOCF adjusted) <u>Pregabalin 300mg vs Pregabalin 600mg vs placebo</u> % of patients with ≥50% reduction in pain: 40.4% vs 36.2% vs 34.9% % of patients with ≥30% reduction in pain: 58.3% vs 61.7% vs 52.3% % of patients with meaningful pain relief (defined as 1-point relief in their pain scores): 58.3% vs 61.7% vs 52.3% Median time to onset of pain relief (days): 5 vs 14 vs 12 days, HR pregabalin 300mg vs placebo 1.211 (adjusted P=0.2287), HR pregabalin 600mg vs placebo 1.393 (adjusted P=0.0677) Sleep interference scores: Pregabalin 300mg vs placebo -0.51, adjusted P=0.0461 Pregabalin 600mg vs placebo:-0.79, adjusted P=0.0047 Change from baseline in HADS-A anxiety subscale: -1.81 vs -1.93 vs -1.36, P=NS for any treatment group vs placebo Change from baseline in HADS-D Depression subscale: -1.20 vs -1.54 vs -0.88, P=NS for any treatment group vs placebo

Evidence Table 2. Update 1: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Pfizer unpublished study, 2007 Protocol no. A0081071 U.S. Fair	Pregabalin 300mg vs Pregabalin 600mg vs placebo Proportion of patients with all any AE: 81% vs 80.9% vs 64.9% Proportion of patients with treatment-emergent AE: 59.5% vs 64.5% vs 36.4% Proportion of patients with severe AE: 13.1% vs 16.4% vs 12.6%	Pregabalin 300mg vs Pregabalin 600mg vs placebo Total withdrawals: 32% vs 42.1% vs 22.5% Withdrawals due to AE: 15.7% vs 24.3% vs 7.9%	Pfizer	Denominator for % male was no. treated and not no. randomized as it was unclear how many patients were randomized to each group

Evidence Table 2. Update 1: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity
Rao 2007 U.S. Fair	Adults with symptomatic chemotherapy-induced peripheral neuropathy for greater than 1 month.	A: Gabapentin (target dose 2700 mg) B: Placebo 6 weeks Crossover design	Permitted opioid and non-opioid analgesics	59 years (range 25-84) 73% female White: 95% Black: 5% Asian: 1%

Evidence Table 2. Update 1: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed	Efficacy/Effectiveness
Rao 2007 U.S. Fair	Chemotherapy active: 50% Chemotherapy discontinued: 50% Neurotoxic chemotherapy regimens: Vinca alkaloids: 10% Taxanes: 44% Platinum based compounds: 20% Combination: 27%	115	47/0/115	<u>Gabapentin vs placebo</u> NRS average pain score change from baseline at 6 weeks (before crossover): -1.0 vs -0.6, P=0.8 NRS average pain score change from baseline at 14 weeks (after crossover): -0.5 vs -0.2, P=0.2 NRS "worst" pain score change from baseline at 6 weeks (before crossover): 0.6 vs 0.7, P=0.8 NRS "worst" pain score change from baseline at 14 weeks (after crossover): 0.8 vs 0.2, P=0.05 Change from baseline in mean BPI score at 6 weeks (before crossover): -1.1 vs -0.4, P=0.2 Change from baseline in mean BPI score at 14 weeks (after crossover): -0.3 vs 0, P=0.6 Change from baseline in mean McGill pain rating index at 6 weeks(before crossover): -12.0 vs -3.5, P=0.03 Change from baseline in mean McGill pain rating index at 14 weeks (after crossover): +4.1 vs -2.5, P=0.97 QOL uniscale change from baseline at 6 weeks (before crossover): +2.5 vs -2.1, P=0.8 QOL uniscale change from baseline at 14 weeks (after crossover): -2.5 vs-0.6, P=0.7 Subject global impression of change at 6 weeks (before crossover): 0.3 vs 0.2, P=0.7 Subject global impression of change at 14 weeks (after crossover): 0.1 vs 0.5, P=0.3 WHO neuropathy score change from baseline at 6 weeks (before crossover): 0 vs 0.1, P=0.7 WHO neuropathy score change from baseline at 14 weeks (after crossover): 0.1 vs 0.1, P=0.3

Evidence Table 2. Update 1: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Rao 2007 U.S. Fair	Gabapentin vs placebo Dehydration - Grade 3: 0 vs 1% Diarrhea - Grade 2: 3% vs 1% Dizziness - Grade 2: 7% vs 3% Dizziness - Grade 3: 2% s 1% Dyspepsia - Grade 2: 0 vs 3% Fatigue - Grade 2: 4% vs 6% Fatigue - Grade 3: 1% vs 2% Flatulence - Grade 2: 0% vs 2% Flatulence - Grade 3: 2% vs 0% Myalgia - Grade 2: 2% vs 2% Vomiting - Grade 2: 2% vs 2%	Gabapentin vs placebo Total Withdrawals: 36.8% vs 34.5% (5.2% withdrew during washout) Withdrawals due to AE: NR	Public Health Service Grants CA25224, CA 37404, CA 35103, CA-63849, CA 63848, CA 35195, CA 35272, CA 37417, CA 35448	

Evidence Table 2. Update 1: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity
Rao, 2008 U.S. Fair	Adults with symptomatic chemotherapy-induced peripheral neuropathy for greater than 1 month.	A: Lamotrigine (target dose 300mg B: Placebo 10 weeks Parallel design	Antidepressants, opioids, adjuvant analgesic agents (e.g. anticonvulsants, clonazepam or mexiletine), topical analgesics, and amifostine could be initiated after study entry. NSAIDs were also allowed.	61 years (range 29-84) 59% female White: 93% Black: 6% Asian: 0.8%

Evidence Table 2. Update 1: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed	Efficacy/Effectiveness
Rao, 2008 U.S. Fair	Chemotherapy Active: 42% Discontinued or completed : 58% Chemotherapy regimens Vinca alkaloids: 35% Taxanes: 27% Platinum-based compounds: 7% Combination: 28%	131	51/0/125	Lamotrigine vs placebo Change from baseline in mean pain score using NRS at 10 weeks -0.3 vs -0.5, P=0.56 Change from baseline in Symptom severity as measured by ENS at 10 weeks: -0.4 vs -0.3 P=0.36 Change from baseline in worst pain scores by NRS at 10 weeks: -0.2 vs -0.8, P=0.5 Change from baseline in mean total SDS score at 10 weeks: 4.4 vs 4.0, P=1.0 BPI average score change from baseline at 10 weeks: -0.1 vs -0.8, P=0.2 Change from baseline in McGill pain rating index at 10 weeks -12.3 vs -4.0, P=0.3 QOL uniscale change from baseline at 10 weeks: -4.3 vs 0.3, P=0.3

Evidence Table 2. Update 1: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Rao, 2008 U.S. Fair	Lamotrigine vs placebo (P=NS between groups) AE (grade ≥2):26(36.5%) vs28(45.2%) Dehydration: Grade 3: 0vs 1% Diarrhea: Grade 2: 3% vs 1% Dizziness: Grade 2: 7% vs 3%, Grade 3: 2% vs 1% Dyspepsia: Grade: 2:0% vs 3% Fatigue-grade 2: 4% vs 6%, grade 3: 1% vs 2% Flatulence-Grade 2: 0% vs 2%Grade 3: 1% vs 0% Nausea: Grade2: 2% vs 6% Rash: Grade 2: 1% vs0%, Grade 3: 2% vs 0% Myalgia: Grade 2 2% vs 2% Vomiting Grade 2: 2% vs 3%	Lamotrigine vs placebo Total withdrawals: 61.9% vs 25.8% Withdrawals due to AE: 11.1% vs 1.6%	Public Health Service Grants CA25224, CA 35431, CA 35090, CA-63849, CA-63848, CA 35267, CA-45450, CA 35195, CA-52352, CA-35269, CA-35448, CA-52654, CA-63844, CA-35113, CA-60276, CA-35103, CA-35415	Total withdrawals for the whole group includes those who were excluded for cancellations and those considered ineligible (total 6)

Evidence Table 2. Update 1: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity
Rauck, 2007 U.S. Fair	Patients 18 years or older with a diagnosis of Type 1 or 2 DM and painful DPN, HbA1C level of 10% or less for at least past 3 mo, a 1-5 year history of moderate to severe intensity of NP and a score of 4 on the 11 point numeric Likert scale	A: 100 mg/day, max dose 400mg/day B: Placebo 4 weeks run in, 100mg/day for 3 weeks, titration phase 3 weeks, 4 week maintenance period, 1 week taper period	acetylsalicyclic acid, serotonin uptake inhibitors and acetaminophen	55 years Male: 47.1% White: 86% African American: 9.2% Asian: 0.8% Others: 4.2%

Evidence Table 2. Update 1: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed	Efficacy/Effectiveness
Rauck, 2007 U.S. Fair	Mean duration of painful diabetic polyneuropathy: 3.8 years Duration of DM: 10.4 years % of patients with previous treatment for NP: 39.5% Mean duration of NP treatment: 3.4 years Previous surgical or invasive intervention for diabetes: 5%	119	25/2/119	<u>Placebo vs Lacosamide</u> Mean (SD) Likert pain score at endpoint (LOCF analysis): 4.5 (2.6) vs 3.0 (2.4), endpoint LS mean -2.21 vs -3.31, treatment difference 0.9 (95% CI 0.0 to 1.8), P=0.039 % of patients with a minimum of 2 point reduction in Likert pain score: 60% vs 50.8% Sleep interference: change from baseline: -2.06 vs -3.10, difference 1.0, 95% CI 0.2 to 1.9), P=0.013 Interference with general activity, change from baseline: -2.00 vs -2.96, difference 1.0, 95% CI 0.2 to 1.7), P=0.184 SF-MPQ (overall pain-VAS) change from baseline: -26.0 vs -36.1, difference 10.2, (95% CI 0.1 to 20.3), P=0.0477 Present pain intensity: -0.71 vs -1.11, difference 0.4, 95% CI 0.1 to 0.7, P=0.0101 % of pain free days: 7.5% vs 18.1% SF-36 bodily pain improved with lacosamide compared to placebo P=0.022, data NR, SF-36 vitality improved with lacosamide compared to placebo, P=0.024, data NR Use of rescue analgesics: 67% vs 59% No reduction in Likert scale: 16.9% vs 8.3% PGIC worse: 10.5% vs 1.8% CGIC worse: 7.0% vs 1.9% Reduction in Likert score<1: 20.3% vs 15% PGIC no change: 21% vs 16.1% CGIC no change: 24.6% vs 22.2% Reduction in Likert scale< 2: 11.9% vs 16.7% PGIC mildly better: 22.8% vs 16.1% CGIC mildly better: 31.6% vs 48.1% Reduction in Likert score<3: 16.9% vs 15% PGIC moderately better: 14% vs 23.2% CGIC moderately better: 19.3% vs 16.7% Reduction in Likert score ≥3: 33.8% vs 45% PGIC much better: 31.6% vs 42.9% CGIC much better: 31.6% vs 48.1%

Evidence Table 2. Update 1: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Rauck, 2007 U.S. Fair	Placebo vs lacosamide Patients with at least 1 treatment-emergent AE: 75% vs 87% Patients with severe AE: 12% vs 7% Tachycardia: 0% vs 5% Headache: 22% vs 18% Dizziness: 8% vs 15% Tremor: 3% vs 5% Paresthesia: 5% vs 2% Nausea: 7% vs 12% Constipation: 0% vs 5% Diarrhea: 12% vs 5% Abdominal pain: 7% vs 0% Hypoglycemia: 7% vs 5% Myalgia: 8% vs 3% Back pain: 8% vs 3% Anxiety: 0% vs 5% Nervousness: 0% vs 5% Somnolence: 5% vs 5% Upper respiratory tract symptoms: 27% vs 25% Erythematous rash: 5% vs 2%	Placebo vs lacosamide Total withdrawals: 18.6% vs 23.3% Withdrawals due to AE:5.1% vs 8.3%	Schwarz Pharma, AG, Germany	

Evidence Table 2. Update 1: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity
Rossi, 2009 Italy Fair	Patients 18-60 years old with a MS diagnosis, normal hematologic exams, and chronic NP defined as a constant or intermittent sensory symptom with unpleasant feelings or pain lasting more than 1 month and having a stereotyped neurological distribution and superficial localization.	A: Levetiracetam 3000 mg B: Placebo For 3 months	Immunomodulatory (interferon beta 1a and 1b, glatiramer acetate) or immunosuppressant agents (mitoxantrone, azathioprine) were not modified during the study nor during the previous 2 months.	37.5 years (SD 7.5) 74.4% female Ethnicity NR

Evidence Table 2. Update 1: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed	Efficacy/Effectiveness
Rossi, 2009 Italy Fair	EDSS: 2.5 (SD 1.3) Disease duration: 7.2 years (SD 5.7) Baseline pain level: 70.5 (SD 18.8) Pain duration: 8.1 months (SD 5.8) Disease type: RR: 85.4% PP: 4.8% SP: 9.8% Pain type: Constant: 64.6% Intermittent: 25.2% Constant/Intermittent: 10.2%	20	3/NR/NR	Levetiracetam vs Placebo Mean pain VAS score, mm: T0: 75 vs 65 T1: 57 vs 63 T2: 41 (P>0.05 vs T0 value) vs 58 T3: 29 (P>0.05 vs T0 value) vs 51 The mean difference in pain intensity (VAS reduction) between the two treatments was significantly different at T2 and T3 (P < 0.05 for both time-points). Rate of responders (patients showing >20 mm reduction in VAS): T1: 18.2% vs 12.5% T2: 72.7% vs 12.5%; P<0.05 T3: 81.8% vs 14.3%; P<0.05 Overall rating of quality of life item on MSQoL-54: T0: 32 vs 33 T3: 67 (P<0.05 vs T0 value) vs 37 EDSS and HDS scores failed to show any significant effect between groups over time nor a significant correlation with VAS reduction (r squared = 0.1 and P > 0.05 for delta EDSS score; r squared = 0.06 and P > 0.05 for delta HDS score).

Evidence Table 2. Update 1: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Rossi, 2009 Italy Fair	Levetiracetam vs Placebo Somnolence: 3 (25%) vs 0 (0%) Dizziness: 1 (8.3%) vs 0 (0%) Nausea: 1 (8.3%) vs 1 (12.5%) Insomnia: 0 (0%) vs 1 (12.5%) Flu: 2 (16.7%) vs 3 (37.5%) Cough: 2 (16.7%) vs 2 (25%) Sore throat: 2 (16.7%) vs 3 (37.5%)	Levetiracetam vs Placebo Total withdrawals: 2 (16.7%) vs 1 (12.5%) Due to AE: 1 (8.3%) vs 0 (0%)	Grants from Fonazine Italiana Sclerosi Multipla, Italian Ministero della Salute, Italian Ministero della Universita e della Ricerca, and from UCB Pharma to DC	Single-blind study design. Two patients did not tolerate the maximum dosage of 3000 mg levetiracetam because of dizziness and somnolence (non severe) and completed the study assuming 2000 mg levetiracetam.

Evidence Table 2. Update 1: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity
Shaibani, 2009 U.S., Germany Fair	Men and women at least 18 years of age with Type 1 or 2 DM and had symptoms of painful distal diabetic neuropathy for 6 mo to 5 years, NP of at least moderate intensity defined as an average pain intensity of ≥4 on an 11 point NRS, HbA1C levels <12% with a clinically determined optimized blood control for at least 3 mo before randomization	A: Lacosamide 200mg/d B: Lacosamide 400mg/d C: Lacosamide 600mg/d for 18 weeks	Tricyclic antidepressants	59.8 (SD 10.0) years 56.5% male White: 80.4% Black:11.9% Asian: 0.4% Other: 7.2%

Evidence Table 2. Update 1: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed	Efficacy/Effectiveness
Shaibani, 2009 U.S., Germany Fair	Diabetic neuropathy duration, years, mean (SD): 3.0 (1.5) Patients on stable doses of antidepressants: 5.1% (dose 10-75 mg)	469	212/17/453	<u>Placebo vs lacosamide 200mg vs lacosamide 400mg vs lacosamide 600mg</u> *Change from baseline in mean pain scale score:* 400mg vs placebo: -1.8 (29%) vs -2.5 (39%) *Treatment difference in LS means, last 4 weeks of maintenance period:* 200mg vs placebo: -0.33 (95% CI -0.94 to 0.27), P=0.28 400mg vs placebo: -0.61 (95% CI; -1.23 to 0.00), P=0.0507 600mg vs placebo: -0.56 (95% CI -1.17 to 0.05), P=0.07 *Treatment difference in LS means, entire treatment period:* Endpoint LSM: -1.27 vs -1.73 vs -1.89 vs -1.85 200mg vs placebo: -0.45, (95% CI-0.97 to 0.06), P=0.09 400mg vs placebo: -0.62 (95% CI -1.15 to -0.09), P=0.02 600mg vs placebo: -0.57 (95% CI -1.10 to -0.05), P=0.03 % of patients feeling better at the end of maintenance period in PGIC: 71% vs 65% vs 82% vs 79%, P=.05 for 400mg vs placebo Mean (SD) change from baseline to last 4 weeks of maintenance period of pain interference with sleep:-1.9 (2.13) vs NR vs -2.1 (2.07) vs 2.8 (2.09), P=NS for 400mg vs placebo, P=0.04 for 600mg vs placebo, Mean (SD) change from baseline to last 4 weeks of maintenance period of pain interference with general activity:-1.8 (1.99) vs NR vs -2.2 (2.3) vs -2.7 (2.36), P=0.04 for 400mg vs placebo, P=0.02 for 600mg vs placebo % of pain free days during maintenance period: 2.5% vs 5.7% vs 10.9% vs 9.4% % of patients experiencing 30% or greater risk reduction: Lacosamide 600mg vs 200mg 58% vs 54%

Evidence Table 2. Update 1: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Shaibani, 2009 U.S., Germany Fair	Placebo vs lacosamide 200mg vs lacosamide 400mg vs lacosamide 600mg Any AE: 84.6% vs 80.1% vs 79.2% vs 86.9% Dizziness: 4.6% vs 5.7% vs 21.6% vs 28.5% Headache: 12.3% vs 9.9% vs 8.0% vs 13.1% Tremor: 0% vs 4.3% vs 9.6% vs 14.6% Somnolence: 0% vs 5.0% vs 8.0% vs 8.8% Balance disorder: 0% vs 2.8% vs 4.8% vs 9.5% Hypoesthesia: 0% vs 0% vs 0% vs 5.1% Nausea: 6.2% vs 9.9% vs 7.2% vs 18.2% Diarrhea: 7.7% vs 6.4% vs 4.8% vs 8.0% Vomiting: 0% vs 4.3% vs 1.6% vs 6.6% Flatulence: 0% vs 3.5% vs 0% vs 6.6% Pruritus: 1.5% vs 4.3% vs 7.2% vs 5.1% Vertigo: 1.5% vs 0.7% vs 0.8% vs 5.8% Vision blurred: 0% vs 1.4% vs 2.4% vs 5.1% Fatigue: 3.1% vs 3.5% vs 5.6% vs 4.4% Sinusitis: 3.1% vs 5.7% vs 3.2% vs 3.6% Back pain: 3.1% vs 5.7% vs 3.2% vs 3.6%	Placebo vs lacosamide 200mg vs lacosamide 400mg vs lacosamide 600mg Total withdrawals: 32.3% vs 32.6% vs 43.2% vs 66.4% Withdrawals due to AE: 13.8% vs 12.1% vs 24% vs 42.3%	Schwarz Biosciences Inc, UCB Group	

Evidence Table 2. Update 1: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity
Silver, 2007 United States Fair	Outpatients ≥12 years of age with a diagnosis of NP arising from diabetic peripheral neuropathy, postherpetic neuralgia, traumatic/surgical nerve injury, incomplete spinal cord injury, trigeminal neuralgia, MS, or HIV-associated peripheral neuropathy. Patients had to have received one of the following treatments for NP at a stable dose for ≥4 weeks before the start of the baseline period: gabapentin 900 to 3,600 mg/day, a single tricyclic antidepressant 25 to 100 mg/day, or a single nonopioid analgesic at or below the maximum labeled dose.	A: Lamotrigine 200-400 mg/day (mean maintenance dose was 360 mg [SD 70 mg]) B: Placebo Study comprised of a 2-4 week washout phase, a 1 week baseline phase, and a 14 week treatment phase that included an 8 week dose-escalation/-adjustment phase and a 6 week fixed-dose maintenance phase.	Acetaminophen (1,000 mg every four to six hours as needed, but no more than 3,000 mg in 24 hours)	60.3 years 53.6% male White: 82.7% Black: 10% Hispanic: 6.4% Other: 0.9%
Simpson, 2010 U.S. and Puerto Rico Good	Patients with HIV-DSP for ≥3 mo and a Karnofsky performance score of ≥60 at screening. Patients receiving neurotoxic antiretroviral drugs known to cause sensory neuropathy clinically similar to HIV-DSP must have been on stable doses for ≥30 days before screening and throughout the study,	A: Pregabalin 150-600mg/d, mean daily dose 385.7 (SD 160.3)mg/d B: Placebo 2 week DB dose adjustment phase and 12 wk DB maintenance phase and 3 mo optional open label extension phase	NSAIDs and other	47 years 18.9% female White: 56.6% Black: 34.8% Asian: 0.3% Other: 8.3%

Evidence Table 2. Update 1: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed	Efficacy/Effectiveness
Silver, 2007 United States Fair	Mean duration of NP: 58.5 months NP etiology: Diabetic neuropathy: 65.3% Postherpetic neuralgia: 18.3% Traumatic/surgical nerve injury: 5.5% Spinal cord injury: 1.4% Trigeminal neuralgia: 5.1% MS: 4.2% HIV-associated peripheral neuropathy: 0.5% Concomitant medication for NP: Gabapentin: 44.5% Tricyclic antidepressant: 11.5% Nonopioid analgesic: 26% Other: 18%	223	78/6/213	<u>Placebo vs Lamotrigine:</u> Pain-intensity score, mean change at week 14 (SE): -2.1 (0.21) vs -2.1 (0.23) McGill Pain, mean change at week 14 (SE): -4.2 (0.98) vs -4.2 (1.06) Neuropathy Pain Scale, mean change at week 14 (SE): -15.5 (2.13) vs -15.1 (2.06) Sleep Interference Score, mean change at week 14 (SE): -1.7 (0.25) vs -1.6 (0.24) Rescue medication use, mean change at week 14 (SE): -1.6 mg (1.20) vs -3.2 mg (1.40) Patient Global Impression of Change, n (%) much or very much improved at week 14: 29 (27%) vs 29 (27%) Clinician Global Impression of Change, n (%) much or very much improved at week 14: 28 (26%) vs 28 (26%) 30% responders, proportion (%) at week 14: 45/74 (61%) vs 37/63 (59%) 50% responders, proportion (%) at week 14: 27/74 (36%) vs 26/63 (41%)
Simpson, 2010 U.S. and Puerto Rico Good	Mean numeric pain rating scale score: 6.8 Mean disease duration Polyneuropathy: 5.2 years NP symptoms: 6.1 years Pain medication prior to initiation of treatment: Antiepileptics: 20.2% Tricyclic antidepressants: 5.6% Opioids: 31.5% NSAIDs: 24.8% Other: 14.6%	302	61/15/299	<u>Pregabalin vs placebo:</u> Mean decrease from baseline in NPRS at endpoint: 2.88 vs 2.63, difference between 2 groups 0.25, P=0.3914 Mean change(decrease) from baseline to endpoint at week 1: 1.14 vs 0.69, P=0.0131, at week 2 (decrease) 1.92 vs 1.43, P=0.0393, at week 7 (decrease) 3.22 vs 2.53 , P=0.0307 and week 8 (decrease) 3.33 vs 2.53, P=0.0156 No difference observed at weeks 6 (P=0.0879), 10 (P=0.3060)and 14(P=0.1856) 50% responder rate: 38.9% vs 42.8% , P=0.5003 30% responder rate: 56.3% vs 55.9%, P=0.9061 Sleep interference score at endpoint =NS between 2 groups PGIC score of "Improved" : 82.8% vs 66.7% PGIC -no change: 13.3% vs 25.4% PGIC "worsened": 3.9% vs 7.9%,P=0.008

Evidence Table 2. Update 1: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Silver, 2007 United States Fair	<u>Placebo vs Lamotrigine</u> Any adverse event leading to premature withdrawal from study: 12 (11%) vs 27 (24%) Rash: 7 (6%) vs 11 (10%) Pruritus 3 (3%) vs 6 (5%) Dizziness 1 (<1%) vs 2 (2%) Paresthesia 1 (<1%) vs 2 (2%) Swelling face 0 (0%) vs 2 (2%) Diabetic neuropathy 0 (0%) vs 2 (2%) Fatigue 0 (0%) vs 2 (2%) Nausea 0 (0%) vs 2 (2%) Vomiting 0 (0%) vs 2 (2%) Dyspnea 0 (0%) vs 2 (2%) Most common adverse events: Dizziness 11 (10%) vs 10 (9%) Rash 14 (13%) vs 20 (18%) Somnolence 2 (2%) vs 7 (6%)	<u>Placebo vs Lamotrigine</u> Total withdrawals: 31 (28.4%) vs 47 (42.3%) Due to AE: 11 (10.1%) vs 28 (25.2%)	GlaxoSmithKline	
Simpson, 2010 U.S. and Puerto Rico Good	<u>Pregabalin vs Placebo</u> % patients with any AE: 81.5% vs 70.2% Somnolence: 23.2% vs 8.6% Dizziness: 19.2% vs 10.6% Euphoric mood: 9.9% vs 0.7% Dry mouth: 9.3% vs 0.7% Peripheral edema: 6.0% vs 4.6%	<u>Pregabalin vs Placebo</u> Total Withdrawals: 21.2% vs 19.2% Discontinuations due to AE: 6.0% vs 2.6%	Pfizer Inc.	

Evidence Table 2. Update 1: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity
Stacey, 2008 US Fair	Men and women at least 18 years of age with PHN, defined as pain present for at least 3 months after the healing of the herpes zoster skin rash, pain score of 40mm on the 100 mm VAS of the SF-MPQ at both screening and randomization visits.	A: Pregabalin 150-600mg/d B: Pregabalin 300mg/d C: Placebo for 1 week baseline, 4 weeks of DB treatment phase, 1 week of medication tapering phase	Gabapentin, acetylsalicyclic acid, paracetamol, Tramadol and Tramadol hydrochloride were allowed.	67.4 years 55.8% male White: 95.2% Other: 4.8%

Evidence Table 2. Update 1: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed	Efficacy/Effectiveness
Stacey, 2008 US Fair	Mean duration of PHN: 2.5 years Mean no. of patients with allodynia at baseline: 84.7 % of patients with Allodynia ≥40 mm: 68%	270	DB phase: 38/NR/269	<u>Pregabalin fixed dose vs Pregabalin flexible vs placebo</u> Median time to onset of pain relief: 1.5 days vs 3.5 days vs NR , difference between pregabalin groups vs placebo p<0.0001. Difference between 2 pregabalin fixed dose and flexible dose=NS, HR 1.112, 95% CI (0.75 to 1.64) % patients with ≥30% reduction in pain: 58% vs 70% vs 31% (fixed dose: P=0.0003 vs placebo, flexible dose: p<0.0001 vs placebo) % patients with ≥50% reduction in pain: 39.8% vs 46.7% vs 18.4% (fixed dose: P=0.0020 vs placebo, flexible dose: P=0.0001 vs placebo) OR flexible vs fixed ≥30% improvement in pain: 1.69 (95% CI, 0.92 to 3.12) OR flexible vs fixed ≥50% improvement in pain: 1.30 (95% CI, 0.71 to 2.36) Change in VAS allodynia scores vs baseline: fixed dose -20.81mm, P=0.0075 vs placebo, flexible dose -26.23 mm, p<0.0001 vs placebo, placebo: -11.83mm Improvement in VAS pain portion of the SF-MPQ at endpoint: fixed dose -33.19mm P=0.0008 vs placebo, flexible dose -37.55mm P=p<0.0001, placebo: -21.22mm Improvement in VAS anxiety score vs placebo: fixed dose -19.95, P=0.025, flexible dose: -17.81 , P=0.024

Evidence Table 2. Update 1: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Stacey, 2008 US Fair	<u>Pregabalin fixed dose vs Pregabalin flexible vs placebo</u> % patients ≥AE: 62.5% vs 72.5% vs 43.3% % patients with severe AE: 9.1% vs 6.6% vs 7.8% % patients with serious AE: 1.1% vs 1.1% vs 1.1% *Nervous system disorders* Dizziness: 30.7% vs 24.2% vs 6.7% Somnolence: 19.3% vs 11.0% vs 2.2% Balance disorder: 4.5% vs 3.3% vs 0% Tremor: 1.15 vs 3.3% vs 0% Memory impairment: 0% s 3.3% vs 0% Depressed level of consciousness: 1.1% vs 2.2% vs 1.1% Coordination abnormal, amnesia and lethargy: 2.3% vs 0% vs 0% *Skin and subcutaneous tissue disorders* Hyperhidrosis: 2.3% vs 0% vs 1.1%	<u>Pregabalin fixed dose vs Pregabalin flexible vs placebo</u> Total withdrawals: 20% vs 5.5% vs 16.7% Withdrawals due to AE: 18.2% vs 4.4% vs 4.4%	Pfizer Inc.	Median time to onset of pain relief could not be calculated for placebo as only 31% of placebo treated patients met the predefined pain relief criteria in the study period.

Evidence Table 2. Update 1: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity
Tolle, 2008 Europe, Australia, South Africa Fair	Men and women ≥18 years of age with type 1 or type 2 DM for ≥1 yr, HbA1c≤11% and painful, distal, symmetrical sensorimotor polyneuropathy due to diabetes for ≥1 yr. All patients had scores ≥40mm on a VAS-MPQ at baseline and at randomization and an average daily pain score of ≥4 on a numeric rating scale during the 1 week baseline period.	A: 150mg/d Pregabalin B: 300mg/d Pregabalin C: 150 or 300mg/day Pregabalin D: Placebo for 12 weeks	NR	58.61 (SD 11.5) years 55.4% male White: 96.2% Black: 0.5% Asian or Pacific Islander: 1.8% Other: 1.5%

Evidence Table 2. Update 1: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed	Efficacy/Effectiveness
Tolle, 2008 Europe, Australia, South Africa Fair	Weight, Kg mean (SD): 85.75 (15.3) Estimated baseline CL_{cr} (mL/min) Mean (SD) 93.48 (29.0) CL_{cr} status Normal (>60mL/min): 88.1% Low (30-60mL/min): 11.9%	396	77/NR/395	<u>Placebo vs pregabalin 150 mg vs pregabalin 300 mg vs pregabalin 600 mg</u> Mean change from baseline in numeric rating scale: -1.9 vs -2.1 vs -2.1 vs -3.0 Difference vs placebo in endpoint mean score 150mg /day: -0.27 (95% CI -0.87 to 0.34), P=0.7481 300mg/day: -0.10(95% CI -0.70 to 0.50), P=0.7481 600mg/day: -0.91 (95% CI -1.51 to -0.31), P=0.0093 % Treatment responders (≥50% reduction in mean pain score from baseline): 30.1% vs 34.4% vs 33.3% vs 45.9%, pregabalin 600mg/day vs placebo P=0.036 NNT for 600mg/day pregabalin to achieve ≥50% improvement in endpoint mean pain score 6.3 (95% CI 3.4 to 44.7) NNH for 1 discontinuation due to AE was 10.3 (95% CI 5.8 to 42.6) Pain related sleep interference scores vs placebo: 150 mg pregabalin -0.45 (95% CI -1.05 to 0.15) vs 300mg pregabalin -0.62 (95% CI,-1.22 to -0.02) vs 600mg pregabalin-1.01 (95% CI -1.60 to -0.41), P=0.003 pregabalin 600mg/day vs placebo, p for 150mg or 300 mg vs placebo=NS PGIC reporting of "very much" or "much improved": 33.3% vs 45.8% vs 42.5% vs 50.5%, P=0.021 for 600mg/day pregabalin vs placebo CGIC reporting of "very much" or "much improved": 34.5% vs 47.9% s 40.4% vs 53.7%, P=0.009 for pregabalin 600mg/day vs placebo EQ-5D score vs placebo: 0.10 (95% CI 0.03 to 0.16) vs 300mg 0.08 (0.01 to 0.14) or pregabalin 600 mg 0.14 (95% CI 0.07 to 0.20), P=0.0092 , P=0.2363 and P=0.003 for pregabalin 150mg/day, 300 mg/day and 600mg/day vs placebo respectively.

Evidence Table 2. Update 1: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Tolle, 2008 Europe, Australia, South Africa Fair	Placebo vs pregabalin 150 mg vs pregabalin 300 mg vs pregabalin 600 mg Severe treatment associated AE: 1% vs 2% vs 4% vs 4% Serious non-fatal AE: 2.1% vs 4.0% vs 3.0% vs 5.9% Treatment associated serious non fatal AE: 05 vs 1% vs 2% vs 0% Dizziness: 2.1% vs 3.0% vs 9.1% vs 13.9% Peripheral edema: 2.1% vs 5.1% 9.1% vs 9.9% Somnolence: 1.0% vs 5.1% vs 4.0% vs 7.9% Dry mouth: 0.0% vs 3.0% vs 5.1% vs 6.9% Weight change: 0.05 vs 6.1% vs 6.1% vs 6.9% Asthenia: 0.0% vs 1.0% vs 4.0% vs 5.0% Vertigo: 0.0% vs 2.0% vs 6.1% vs 5.0% Edema: 0.0% vs 4.0% vs 12.1% vs 4.0% Headache: 5.1% vs 5.1% vs 3.0% vs 1.0% 2 deaths in 150mg and 300mg/day pregabalin group not related to study drug	Placebo vs pregabalin 150 mg vs pregabalin 300 mg vs pregabalin 600 mg Total withdrawals: 17.7% vs 17.2% vs 20.2% vs 22.8% Withdrawals due to AE: 3.1% vs 5.1% vs 11.1% vs 12.9% Withdrawals due to treatment associated AE: 2.1% vs 3.0% vs 10.1% vs 10.9%	Pfizer Inc.	

Evidence Table 2. Update 1: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity
Van de Vusse, 2004 The Netherlands Fair	Patients recruited from a database fulfilling IASP criteria for the diagnosis of CRPS type 1, between 18-75 years old with a score for pain>3 as rated on a VAS. All patients had functional loss and pain outside the original traumatized area.	A: Gabapentin titrated to 600mg TID on day 5-21-washout-placebo B: Placebo-washout-Gabapentin Cross over study, 3 weeks of medication separated by 2 weeks of washout, total 8 weeks	Analgesics	44.0 years (range 24-75) 82.8% female Ethnicity: NR

Evidence Table 2. Update 1: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed	Efficacy/Effectiveness
Van de Vusse, 2004 The Netherlands Fair	Duration of illness in months: 47.1 Upper extremity in pain: 72.4% Lower extremity in pain: 43.1%	58	12/2/46	Gabapentin vs placebo % patients with global perceived pain relief (total): 43% vs 17%, P=0.002 5 of patients with aggravation of pain: 13% vs 9% VAS pain score at 8 weeks: data interpreted from graph 70 vs 65, P=NS between groups Limb dysfunction and quality of life function improvement: 10 vs 7, P=NS

Evidence Table 2. Update 1: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Van de Vusse, 2004 The Netherlands Fair	<u>Gabapentin vs placebo</u> Improvement in relative skin temperature: 10 vs 45, P=0.096 Dizziness: 37.3% vs 3.9%, P=0.0000 Somnolence: 27.8 vs 5.9%, P=0.003 Lethargy: 20.4% vs 2.0 % (0.003 Nausea: 18.5% vs 9.8%, P=NS Headache: 14.8% vs 5.9%, P=NS Stomach problems: 7.4% vs 5.9%, P=NS Drunken: 7.4% vs 0%, P=NS Disturbed gait: 7.4% vs 0%, P=NS Water retention: 1.9% vs 5.9%, P=NS	<u>Gabapentin vs placebo</u> Total withdrawals: 6.9% vs 10.3% Withdrawals due to AE: 6.9% vs 0%	NR. Parke Davis supplied gabapentin and placebo capsules.	2 patients withdrew during washout

Evidence Table 2. Update 1: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity
van Seventer, 2010 10 European countries and Canada Fair	Men or women aged 18-80 with post-traumatic peripheral NP confirmed by a pain specialist, which had persisted for ≥3 months following the traumatic event, and a score >40 mm on the 100 mm VAS of the SF-MPQ.	A: Pregabalin flexible dose, 150-600 mg/d taken BID B: Placebo For 8 weeks Dosing schedule: Week 1: 150 mg/d Week 2: 300 mg/d Week 3-8: 600 mg/d if needed for efficacy. Investigators were encouraged to have patients take their first dose in the morning. Only one dose reduction was allowed.	NSAIDs including cyclooxygenase-2 inhibitors, opioid and non-opioid analgesics, AEDs (excluding gabapentin), and antidepressant medications if they had been stable for at least 1 month before the study and would remain so during the study. Concomitant pain medications: 79.9% NSAIDs/Cox-2s: 40.6% TCAs: 31.5% SNRIs: 3.6% Opioids: 13.8% Tramadol: 32.7% AEDs: 34.3%	51.5 years (SD 13.5) 50.8% female White: 96%

Evidence Table 2. Update 1: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed	Efficacy/Effectiveness
van Seventer, 2010 10 European countries and Canada Fair	Aged ≥65-80 years: 21.3% Weight: 79.5 kg Mean duration of NP: 4.4 years	254	60/1/252	Placebo vs Pregabalin Change from baseline: Pain (based on the average of each patient's last 7 daily diary entries): -0.8 vs -1.4 Sleep interference: -0.67 vs -1.37 MOS sleep scale problems index: -1.3 vs -7.5 HADS anxiety score all patients: -0.9 vs -1.4 Patients with baseline HADS anxiety subscale >10: -2.2 vs -3.4 HADS depression score: -0.3 vs -1.2 Patients with baseline HADS depression subscale >10: -1.6 vs -1.8 End-point comparison placebo - pregabalin, adjusted difference: Pain (based on the average of each patient's last 7 daily diary entries): -0.62; 95% CI, -1.09 to -0.15; P=0.01 Sleep interference: -0.79; 95% CI, -1.25 to -0.34; P=0.001 MOS sleep scale problems index: -7.54; 95% CI, --11.52 to -3.56; P<0.001 HADS anxiety score all patients: -0.84; 95% CI, -1.6 to -0.08; P=0.031 Patients with baseline HADS anxiety subscale >10: -1.68; 95% CI, -3.69 to 0.32; P=0.099 HADS depression score: -0.97; 95% CI, -1.67 to -0.33; P=0.003 Patients with baseline HADS depression subscale >10: 0.24; 95% CI, -1.87 to 2.34; P=0.819 PGIC: Worse: 14.9% vs 7.4%; P=0.006 No change: 40.5% vs 23.6%; P=0.006 Improved: 42.6% vs 67.6%; P=0.006

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Author Year Country Trial name (Quality rating-optional)	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
van Seventer, 2010 10 European countries and Canada Fair	Placebo vs Pregabalin Any treatment-emergent AE: 58.3% vs 85.8% AEs rated severe in intensity: 9% vs 10% Dizziness: 12 (9.4%) vs 55 (43.3%) Somnolence: 8 (6.3%) vs 20 (15.7%) Headache: 14 (11.0%) vs 15 (11.8%) Fatigue: 10 (7.9%) vs 15 (11.8%) Dry mouth: 6 (4.7%) vs 14 (11.0%) Nausea: 8 (6.3%) vs 12 (9.4%) Constipation: 4 (3.1%) vs 9 (7.1%) Peripheral edema: 3 (2.4%) vs 9 (7.1%) Disturbance in attention: 4 (3.1%) vs 9 (7.1%) Blurred vision: 3 (2.4%) vs 8 (6.3%) Weight gain: 2 (1.6%) vs 5 (3.9%) *Serious AEs* : Serious AEs were reported in 4 patients in the pregabalin group, one of which was considered related to treatment, and two in the placebo group. The event considered related to pregabalin was a patient with tremor and dyspnea who was on 600 mg/day who discontinued and recovered.	Placebo vs Pregabalin Total withdrawals (post-randomization): 29 (22.8%) vs 31 (24.4%) Due to AE (post-randomization): 9 (7.1%) vs 25 (19.7%)	Pfizer Inc.	Randomization was preceded by a 2-week, single-blind, placebo run-in period. Patients who did not meet both pain entry criteria at randomization (i.e. NRS and VAS assessments) were not randomized. A total of 113 patients were not randomized (28 for not meeting pain entry criteria, 14 for adverse event, 25 for lab abnormality, 16 for positive for illicit substances, 12 for not willing to participate, 2 for lack of efficacy, 3 lost to follow-up, and 13 for other protocol violations).

Evidence Table 2. Update 1: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity
Vilholm, 2008 Denmark Fair	Women >18 years old with symptoms corresponding to PMPS, pain located in the breast, axilla and/or arm, at least 6 months after surgery for breast cancer, pain of more than 3 months duration present at least 4 days a week, peripheral nerve lesion confirmed by abnormal neurological examination and/or quantitative sensory tests.	A: Levetiracetam 1500 mg bid B: Placebo Crossover study with 4 weeks per treatment, separated by a 1 week washout period Dosing schedule: Starting dose of levetiracetam was 500 mg/day and the dose was increased with 500 mg every other day to six tablets of 500 mg, divided into two doses daily corresponding to 3000 mg/day. The dose was kept at this level throughout the remaining treatment period.	Up to eight tablets of paracetamol 500 mg and one capsule tramadol 50 mg could be used daily as escape medication. <u>Levetiracetam vs Placebo</u> Paracetamol tablets/week: 14.9 vs 13.9; P=NS Tramadol tablets/week: 0.4 vs 0.3; P=NS	60 years (median) 100% female Ethnicity NR
von Delius, 2007 Germany Fair	Histologically or cytologically advanced colorectal cancer, at least 18 years of age with a performance status (WHO) of 0 or 1 and an anticipated life expectancy of at least 3 mo.	A: Folinic acid 5-FU and Oxaliplatin +Carbamazepine start dose 200mg, stepwise elevated by 200mg until targeted plasma levels of4-6mg/L B: Folinic acid and Oxaliplatin 85mg/m2 biweekly as a 2 hr infusion of 5FU 2000mg/m2 Study duration depended on response to therapy	NR	63 years 50% male Ethnicity: NR

Evidence Table 2. Update 1: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed	Efficacy/Effectiveness
Vilholm, 2008 Denmark Fair	Median height: 168 cm Median weight: 73 kg Median number of children: 2 Married: 76% Smoking: 16% Diabetes: 8% School >12 years: 52% Operation: Mastectomy: 76% Lumpectomy: 24% Post-operative radiation therapy: 68% Post-operative chemotherapy: 60%	27	2/0/25	<u>Levetiracetam vs Placebo</u> Median pain relief: 0 vs 2; P=0.83 Pain relief in subgroups: Mechanical allodynia (n = 3): 2.7 vs 5.0; P=NS Cold allodynia (n = 8): 2.4 vs 4.0; P=NS Temporal summation (n = 12): 2.3 vs 3.8; P=NS NRS, mean change from baseline to 4th week of treatment: Total pain: -1.8 vs -1.8; P=NS Deep aching pain: -2.1 vs -1.7; P=NS Burning pain: -1.1 vs -1.2; P=NS Lancinating pain: -1.3 vs -1.5; P=NS Touch-evoked pain: -0.7 vs -0.9; P=NS Pressure-evoked pain: -1.4 vs -1.7; P=NS Responders (pain relief of ≥50% corresponding to a score of ≥5 on the 11-point numeric rating scale): 8 vs 8
von Delius, 2007 Germany Fair	Performance status: WHO-0: 61.1% WHO-1: 38.9% Primary site: Colon 69.4% Rectum: 30.6% Metastases: 80.6% Previous chemotherapy: 72.2% Previous radiotherapy: 16.7%	36	9/0/36	<u>Carbamazepine vs control</u> Complete response, 95% CI: 0 (0-0.16) vs 0 (0 to 0.16), P=1.00 Partial response (95% CI): 16% (0.04 to 0.38) vs 24% (0.08 to 0.49), P=0.68 Overall response , complete and partial (95% CI): 16% (0.04 to 0.38) vs 24% (0.08 to 0.49), P=0.68 Median progression free survival (95% CI), mo: 6.0 (3.2 to 8.9) vs 7.2 (5.4 to 9.0), P=0.40 Median Overall Survival (95% CI), mo: 15.1 (10.9 to 19.4) vs 17.4 (4.8 to 30.0), P=0.78 No difference between carbamazepine and placebo on worst neurotoxicity according to Levi's scale: P=0.46 No difference between carbamazepine and placebo when comparing Grade 3 and 4 neurotoxicity: 21.1% vs 35.3%, P=0.72

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Author Year Country Trial name (Quality rating-optional)	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Vilholm, 2008 Denmark Fair	<u>Levetiracetam vs Placebo</u> Tiredness: 10 (40%) vs 2 (8%) Dizziness: 3 (12%) vs 3 (12%) Headache: 3 (12%) vs 6 (24%) Gastric upset: 3 (12%) vs 5 (20%) Constipation: 0 (0%) vs 1 (4%) Irritability: 1 (4%) vs 2 (8%) Sweating: 0 (0%) vs 1 (4%) Paraesthesia: 1 (4%) vs 0 (0%) Fall incidence: 1 (4%) vs 0 (0%) Itching: 1 (4%) vs 0 (0%) Neck pain: 1 (4%) vs 0 (0%)	<u>Levetiracetam vs Placebo</u> Total withdrawals: 1 (4%) vs 1 (4%) Due to AE: 0 (0%) vs 1 (4%)	UCB Pharma	
von Delius, 2007 Germany Fair	<u>Carbamazepine vs control</u> 2 patients (10.5%) vs 0 reported dizziness, headache, mnemonic problems and optical hallucinations Harms associated with chemotherapy Carbamazepine vs control Diarrhea: 10.5% vs 5.9% Thrombocytopenia: 5.3% vs 0% Neurotoxicity: 0% vs 5.9%	<u>Carbamazepine vs control</u> Total withdrawals: 31.6%% vs 17.6% Withdrawals due to AE: 10.5% vs 0%	Sanofi Aventis	

Evidence Table 2. Update 1: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity
Vranken, 2008 The Netherlands Fair	Age 18 years or older, suffering from severe NP, VAS score of >6 caused by lesion or dysfunction in the central nervous system, score>12 on the LANSS	A: Flexible dose Pregabalin 150mg/d to 600mg/d B: Placebo for 4 weeks	Opioids, anti-inflammatories, antidepressants, carbamazepine and baclofen	54.5 years 52.5% male Ethnicity: NR
Wernicke 2006 Canada Fair	(Acute phase)Pain due to bilateral peripheral neuropathy caused by type 1 or type 2 diabetes and ≥18 years, pain had to initiate in the feet with symmetric onset, and pain for a minimum of 6 months, score of ≥3 on the physical examination of the MNSI	A: Duloxetine 60 mg BID B: Routine care for 52 weeks	Rescue analgesics in duloxetine group: oral hypoglycemics (75.2%, NSAIDs 64.4%, antihypertensives 63.5% Routine care group: oral hypoglycemics 76.5%, NSAIDs 68.7%, antihypertensive agents 63.5% , diet supplements 55.7%	59.8 years 39.2% female White: 77.2% Hispanic: 11% Black: 8.3% East/South East Asian: 1.5% Western Asian: 1.2% Other: 0.9%

Evidence Table 2. Update 1: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed	Efficacy/Effectiveness
Vranken, 2008 The Netherlands Fair	Calculated CL_{cr} mean (SD): 130.5 % patients with stroke: 30% % patients with thalamus lesion: 10% % patients with brainstem pathology:7.5% % of patients with Spinal Cord (complete) lesion: 27.5% % of patients with Spinal cord (incomplete) lesion: 25% Presence of allodynia: 85%	41	8/0/40	<u>Placebo vs Pregabalin</u> Change from baseline in VAS intensity score: -0.1 vs -2.5, difference between pregabalin vs placebo 2.18 in favor of pregabalin, P=0.01, 95% CI 0.57 to 3.80 Change in pain disability index score from baseline: 1.7 (deterioration) vs -4.2 (improvement), P=0.111 for pregabalin vs placebo EQ-5D utility score change from baseline: -0.1 (deterioration)vs 0.31(improvement), p<0.001 for pregabalin vs placebo EQ-5D VAS score change from baseline: -12.3 (deterioration) vs 5.3 (improvement), p<0.001 for pregabalin vs placebo Change from baseline SF 36 QOL-bodily pain domain: 1.6 (improvement) vs 15.6 (improvement) p<0.009 for pregabalin vs placebo
Wernicke 2006 Canada Fair	Height: 171.4 cm Weight: 95.3cm DM type 1: 11.6% DM type 2: 88.4% Duration of diabetes: 11.6 years Duration of diabetic neuropathy: 3.7 years MNSI score, mean: 5.2 24 hour average pain score, mean: 5.9	337	85/7/337	<u>Duloxetine vs routine care</u> % of patients with ≥1 significant hypoglycemic episode at week 52: 16.5% vs 15.1%, P=0.020 Difference in mean change in MNSI score from baseline: -0.20 (95% CI, -0.57 to 0.16) % of patients with worsening of visual activity in right eye: 5.7% vs 7.4% , P=NS % of patients with worsening of visual activity in left eye: 4.4% vs 2.4% , P=NS % of patients with changes in retinopathy, right eye: 11.0% vs 6.5%, P=NS % of patients with changes in retinopathy, left eye: 10.0% vs 8.7%, P=NS Mean (SD) change from baseline in SF 36 bodily pain: 1.5 (1.6) vs -4.1 (2.1), between group difference 5.6 (0.8 to 10.4), P=0.021 change from baseline in European quality of life measures: -0.00 (0.1) vs -0.1 (0.02), between group difference 0.1 (0.03 to 0.1), P=0.001

Evidence Table 2. Update 1: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Vranken, 2008 The Netherlands Fair	<u>Placebo vs Pregabalin</u> Nausea: 20% vs 30%, P=0.507 Cognitive performance: 20% vs 30%, P=0.507 Somnolence: 45% vs 45%, P=1.0 Dizziness: 30% vs 35%, P=0.736 Confusion: 20% vs 35%, P=0.288 Peripheral edema: 20% vs 5%, P=0.342	<u>Placebo vs Pregabalin</u> Total withdrawals: 20% vs 15% Withdrawals due to AE: 15% vs 15%	NR	1 person withdrew after being randomized but before taking any study medication
Wernicke 2006 Canada Fair	<u>Duloxetine vs routine care</u> Treatment-emergent AE: 85.6% vs 92.2%, P=NS Dizziness: 9.0% vs 11.3% Fatigue: 9.0% vs 9.6% Headache: 7.7%vs 10.4% Nausea: 7.7% vs 9.6% Somnolence 6.8% vs 13.0% Increased sweating: 5.9% Upper RTI: 5.4% vs 9.6% Constipation: 5.4% Arthralgia: 5.0% vs 8.7% *Serious AEs:* Myocardial infarction: 2.7% vs 4.3% Cellulitis: 1.4% vs 1.7%	<u>Duloxetine vs routine treatment</u> Withdrawals: 63(28.4%) vs 22 (19.1%), P=NS Withdrawal due to AE: 31 (14.0% vs 11 (9.6), P=NS	Eli Lilly and Company and Boehringer Ingelheim GmbH, Ingelheim, Germany	

Evidence Table 2. Update 1: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity
Wernicke, 2007 Canada, Croatia, Hungary, Poland, Germany, and the Russian Federation Fair	Patients ≥18 years old who presented with pain due to bilateral peripheral neuropathy caused by type 1 or type 2 DM. The pain had to begin in the feet and with relatively symmetrical onset; daily pain must have been present for at least 6 months, and neuropathy was confirmed by a score of ≥3 on the MNSI.	A: Duloxetine 60 mg BID B: Routine care (therapies that the investigator and the patient believed gave the optimal benefit to the patient) For 52 weeks (open-label extension therapy phase) Patients who completed the 13 week acute phase (12 weeks with an additional 1-week drug-tapering phase) were re-randomized to this open-label extension study. Medications used by >5% of patients in routine care group: Thioctic acid: 46 (47.9%) Cyanocobalamin/benfotiamine: 18 (18.8%) Paracetamol: 16 (16.7%) Amitriptyline: 14 (14.6%) Benfotiamine: 13 (13.5%) Carbamazepine: 9 (9.4%) Pentoxifylline: 9 (9.4%) Diclofenac sodium: 7 (7.3%) Meloxicam: 6 (6.3%) Diclofenac diethylamine: 5 (5.2%)	The duloxetine-treated patients were allowed most therapies, including non-medicinal therapy offered to the routine care group, with the exception of antidepressants, anticonvulsants, and antipsychotics. Patients in both treatment groups were permitted to supplement their analgesia with acetaminophen, NSAIDs, or opioid analgesics. (Extensive list and usage data in article.)	58.2 years (SD 10.1) 53.9% female Caucasian: 99.7% East/Southeast Asian: 0.3%

Evidence Table 2. Update 1: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed	Efficacy/Effectiveness
Wernicke, 2007 Canada, Croatia, Hungary, Poland, Germany, and the Russian Federation Fair	Mean weight: 85.1 kg (SD 17.6) Mean duration of diabetes: 13.8 years (SD 9.1) Mean duration of diabetic neuropathy: 4.4 years (SD 4.1) Type of DM: Type 1: 15.7% Type 2: 84.3%	293	34/6/293	<u>Duloxetine vs Routine care</u> Short Form 36 Health Status Survey, mean change (SE); LS means reported as Duloxetine-Routine: Mental health: -2.11 (1.07) vs -6.15 (1.63); LS Means: 4.04 (95% CI, 0.26 to 7.81); P<0.05; Significant therapy-by-investigator interaction at a significance level of 0.1 General health perceptions: 0.38 (1.07) vs -2.40 (1.60); LS Means: 2.78 (95% CI, -0.92 to 6.47); Significant therapy-by-investigator interaction at a significance level of 0.1 Bodily pain: 3.27 (1.50) vs -3.85 (2.27); LS Means: 7.12 (95% CI, 1.88 to 12.36); P<0.01 Mental component summary: -0.89 (0.65) vs -3.08 (0.98); LS Means: 2.19 (95% CI, -0.07 to 4.45) Physical component summary: 1.20 (0.63) vs -1.26 (0.94); LS Means: 2.47 (95% CI, 0.29 to 4.65); P<0.05 Vitality: -1.03 (1.08) vs -6.86 (1.63); LS Means: 5.83 (95% CI, 2.06 to 9.61); P<0.01 Social functions: -0.03 (1.57) vs -4.71 (2.37); LS Means: 4.69 (95% CI, -0.79 to 10.17); Significant therapy-by-investigator interaction at a significance level of 0.1 Physical role limit: 2.46 (2.90) vs -6.13 (4.37); LS Means: 8.59 (95% CI, -1.52 to 18.69) Emotional role limit: 0.46 (3.03) vs -8.37 (4.56); LS Means: 8.83 (95% CI, -1.73 to 19.39) Physical functioning: 0.87 (1.51) vs -4.84 (2.27); LS Means: 5.71 (95% CI, 0.45 to 10.96); P<0.05 EQ-5D, mean change (SE); LS means reported as Duloxetine-Routine: 0.00 (0.01) vs -0.04 (0.02); LS Means: 0.04 (95% CI, -0.01 to 0.09) Duration of exposure, mean days (SD): 340.2 (82.9) vs 349.4 (68.1); P=0.433 ≥180 days of drug exposure: 181 (91.9%) vs 92 (95.8%) ≥360 days of drug exposure: 148 (75.1%) vs 77 (80.2%)

Evidence Table 2. Update 1: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Wernicke, 2007 Canada, Croatia, Hungary, Poland, Germany, and the Russian Federation Fair	<u>Duloxetine vs Routine care:</u> Serious AEs: 22 (11.2%) vs 16 (16.7%); specific AEs not reported by group, because not considered to be drug-related One duloxetine- treated patient completed the trial, but did not complete the taper period and experienced the serious AEs of anxiety and depression that were considered to be possibly related to the study drug. Treatment-emergent AEs with significant therapy-group difference: Asthenia: 11 (5.6%) vs 0 (0%); P=0.018 Reported other treatment-emergent AEs only when 5% or more of patients reported them, so between-group comparisons were not possible because data was not reported for each group. Incidence of treatment-emergent AEs by severity: Mild: 16.8% vs 8.3% Moderate: 23.4% vs 22.9% Severe: 15.7% vs 17.7% During the trial, four deaths occurred, 1 (0.05%) duloxetine-treated patient (cause: myocardial infarction), and 3 (3.1%) routine care-treated patients (cause: cardiac arrest, cerebrovascular accident [stroke], and diabetic coma). These deaths were considered by the principal investigators to be unrelated to the study drug or protocol procedures.	<u>Duloxetine vs Routine care:</u> Total withdrawals: 22 (11.2%) vs 12 (12.5%) Due to AE: 11 (5.6%) vs 2 (3.1%)	NR	Only those patients who completed the acute period (12 weeks in duration, with an additional 1-week drug-tapering phase) of the trial, independent of treatment assignment, were allowed to continue into the extension phase of the trial. Of the 197 duloxetine-treated patients entering the extension phase, 66 were in the placebo therapy group during the acute phase. Of the 96 routine care-treated patients in the extension phase, 34 were in the placebo therapy group during the acute phase.

Evidence Table 2. Update 1: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity
Wymer, 2009 Lacosamide SP742 Study group U.S. and Germany Fair	Men and women at least 18 years with a diagnosis of DM (type 1 or 2) with symptoms of painful distal diabetic neuropathy for 6 months to 5 years. Glycosylated hemoglobin below 12%, optimized diabetic control for at least 3 months before enrolment and pain intensity of ≥4 on 11 point Likert scale	A: Lacosamide 200mg B: Lacosamide 400mg C: Lacosamide 600mg D: Placebo for 18 weeks	Concomitant medications including tricyclic antidepressants for depression, anxiety or sleep disorder and acetaminophen up to 2g/day as rescue medication for pain . Tricyclic antidepressants used by 9.6% in placebo, 7.6 in lacosamide 200 mg, 1.4% in 400mg and 7.4% in 600mg groups	58.2 years (SD 9.6) 45% female White: 81% Black: 7% Asian: 1% Other: 11%

Evidence Table 2. Update 1: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed	Efficacy/Effectiveness
Wymer, 2009 Lacosamide SP742 Study group U.S. and Germany Fair	BMI: 34.7 (SD 7.9) duration of diabetic neuropathy, years: 3.3 (SD 1.6) Previous intake of NP medication: 67%	370	136/13/365	Change from baseline in mean daily pain score in Lacosamide 400mg vs placebo: 2.5 (38.5%) vs 1.8 (27.3%) *Changes from baseline in pain score in last 4 weeks of maintenance phase (all treatment differences are versus placebo):* Lacosamide 200mg vs placebo: Endpoint LS mean: -1.99 vs -1.60, treatment difference -0.39, P=0.19 (95% CI, -0.97 to 0.19) Lacosamide 400mg: Endpoint LS mean -2.34, treatment difference -0.74, P=0.01 (95% CI, -1.32 to -0.16) Lacosamide 600 mg: Endpoint LS mean -2.02, treatment difference -0.42, P=0.16 (95% CI, -1.00 to 0.16) *Changes from baseline in pain score in the 12 week maintenance phase (all differences are vs placebo):* Lacosamide 200mg vs placebo: endpoint LS mean -1.99 vs -1.65, treatment difference -0.39, P=0.19 (95% CI, -0.97 to 0.19) Lacosamide 400mg: Endpoint LS mean -2.39, treatment difference -0.74, P=0.02 (95% CI, -1.36 to -0.12) Lacosamide 600mg: endpoint LS mean -2.55, treatment difference -0.90, p<0.01 (95% CI, -1.57 to -0.23) Lacosamide 400mg significantly better than placebo in overall 18 weeks, p<0.01, titration phase: P=0.01 <u>Lacosamide 400mg vs Lacosamide 600mg vs Lacosamide 200mg vs placebo</u> Patient reported PGIC "feeling better": 81% (P=<0.02 vs placebo)vs 83% (p<0.02 s placebo) vs 69%(p>0.05 vs placebo) vs 68% Patient reported PGIC "feeling worse": 400mg vs placebo 6% vs 17% Change from baseline in patient perception of pain interference with sleep: 400mg vs placebo -2.3 vs -1.8, P=NS Change from baseline in patient perception of pain interference with general activity 400mg vs placebo: -2.1 vs -1.6, P=NS

Evidence Table 2. Update 1: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Wymer, 2009 Lacosamide SP742 Study group U.S. and Germany Fair	Placebo vs lacosamide 200mg vs lacosamide 400mg vs lacosamide 600mg Any AE: 78.5% vs 75.3% vs 78.0% vs 89.2% Serious AE: 7% vs 3% vs 10% vs 10% Dizziness: 5.4% vs 9.7% vs 13.2% vs 29% Nausea: 8.6% vs 8.6% vs 7.7% vs 15.1% Fatigue: 3.2% vs 3.2% vs 6.6% vs 9.7% Headache: 6.5% vs 6.5% vs 7.7% vs 9.7% Diarrhea: 4.3% vs 0% vs 5.5% vs 3.2% Nasopharyngitis: 7.5% vs 9.7% vs 3.3% vs 3.2% Back pain: 2.2% vs 1.1% vs 5.5% vs 2.2% URTI: 5.4% vs 4.3% vs 5.5% vs 6.5%	Placebo vs lacosamide 200mg vs lacosamide 400mg vs lacosamide 600mg Total withdrawals: 26(28%) vs 24(25.8%) vs 35 (38.5%) vs 51(54.8%) Withdrawals due to adverse events: 8 (30.8%) vs 8(33.3%) vs 21(60%) vs 37(72.5%)	Schwarz Biosciences, Germany	

Evidence Table 2. Update 1: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Population	Interventions	Allowed other medications/ interventions	Age Gender Ethnicity
Ziegler, 2010 Europe Fair	Patients18 years or older with type 1 or type 2 diabetes, symptomatic DPN for 6 months to 5 years (score ≥4 on an 11-point NPRS), and A1C <12%.	A: Oral lacosamide 400 mg/d B: Oral lacosamide 600 mg/d C: Placebo For 18 weeks (6-week titration period and 12-week maintenance period) Dosing schedule: The 400 mg/d group was further randomized to receive slow titration (100 mg/d for 3 weeks, followed by weekly increases of 100 mg/d, to 400 mg/d target dose at week 6) or a standard titration (100 mg/d, with weekly increases of 100 mg/d, to 400 mg/d target dose for titration weeks 4–6). The 600 mg/d group followed standard titration increasing by 100 mg/d each week. No back titration was allowed.	Acetaminophen 2 g/d as rescue medication	57.9 years (SD 10.6) 51.5% male Caucasian: 99.6% Other: 0.3%

Evidence Table 2. Update 1: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Other population characteristics	N	Number withdrawn/ lost to follow-up/analyzed	Efficacy/Effectiveness
Ziegler, 2010 Europe Fair	Mean BMI: 30.7 kg/m2 (SD 5.3) Duration of diabetic neuropathy: 3.2 years (SD 2.6) Prior medication for DPN: 63%	357	111/0/355	<u>Placebo vs Lacosamide 400 mg/d vs Lacosamide 600 mg/d</u> Change from baseline in Numeric Pain Rating Scale Scores, endpoint LS mean: Titration period (6 weeks): -0.61 vs -0.95 (P=0.03) vs -1.07 (P<0.01) Maintenance period (12 weeks): -1.40 vs -2.05 (P=0.01) vs -2.19 (P<0.01) Entire treatment period (18 weeks): -1.05 vs -1.50 (P=0.03) vs -1.52 (P=0.02) Primary endpoint (last 4 weeks of maintenance period): -1.50 vs -1.90 (P=0.12) vs -1.86 (P=0.18) Percent of subjects with ≥30% or ≥2-point reduction on NPRS from Baseline to last 4 weeks of the maintenance period (ITT[LOCF]): 35.1% vs 43% (OR 1.4; P=0.26) vs 50% (OR 1.8; P=0.04) Change in VAS score from baseline to the entire treatment phase (ITT [LOCF]), endpoint LS mean: -12.8 vs -18.1 (P=0.04) vs -18.8 (P=0.02) PGIC in Pain (ITT): Much better: 10.9% vs 20.8% vs 22.1% Moderately better: 21.8% vs 20.8% vs 24.7% Mildly better: 29.1% vs 37.5% vs 27.3% No change: 29.1% vs 16.7% vs 20.8% Mildly worse: 0% vs 2.1% vs 1.3% Moderately worse: 7.3% vs 1.0% vs 1.3% Much worse: 1.8% vs 1.0% vs 2.6% Lacosamide 400 mg/d vs placebo P=0.0181; Lacosamide 600 mg/d vs placebo P=0.0641 Change in subject's perception of pain interference with sleep from baseline to the maintenance phase (ITT[LOCF]): -1.28 vs -1.92 (P=0.02) vs -2.29 (P=0.0004) Change in subject's perception of pain interference with activity from baseline to the maintenance phase (ITT[LOCF]): -1.38 vs -1.95 (P=0.03) vs -2.10 (P=0.01)

Evidence Table 2. Update 1: Data abstraction of placebo-controlled trials

Author Year Country Trial name (Quality rating-optional)	Harms	Total withdrawals; withdrawals due to adverse events	Funding	Comments
Ziegler, 2010 Europe Fair	Placebo vs Lacosamide 400 mg/d vs Lacosamide 600 mg/d Patients with one or more treatment-emergent AE: 40 (54.1%) vs 88 (58.7%) vs 86 (64.7%) Patients with one or more treatment-emergent serious AE: 3 (4.1%) vs 11 (7.3%) vs 11 (8.3%) Dizziness: 2 (2.7%) vs 11 (7.3%) vs 26 (19.5%) Fatigue: 5 (6.8%) vs 15 (10.0%) vs 12 (9.0%) Nausea: 2 (2.7%) vs 6 (4.0%) vs 15 (11.3%) Vertigo: 2 (2.7%) vs 9 (6.0%) vs 12 (9.0%) Headache: 2 (2.7%) vs 9 (6.0%) vs 11 (8.3%) Vomiting: 0 (0%) vs 2 (1.3%) vs 7 (5.3%)	Placebo vs Lacosamide 400 mg/d vs Lacosamide 600 mg/d Total withdrawals: 15 (20%) vs 37 (25%) vs 59 (44%) Due to AE: 4 (5.4%) vs 17 (11.3%) vs 31 (23.3%)	Schwarz Biosciences, UCB Group, Monheim, Germany, sponsored and funded the trial	

Evidence Table 3. Update 1: Quality assessment of trials

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Arai 2010 Japan	Yes	Unclear	Yes	Yes	Not reported	Not reported	Not reported
Arezzo 2008 US	Yes	Yes	No, (71% vs 53% male)	Yes	Yes	Yes	Yes
Argyriou 2006	Unclear	No	Yes	Yes	No - open label	No	No
Bansal 2009 India	Yes	Yes	Unclear	Yes	Unclear	Yes	Yes
Baron, 2009; phase I	Yes	Yes, centralized	Some differences in duration of pain in PHN patients but not overall	Yes	No- open label	No- open label	No- open label
Binder 2009	Unclear	Unclear	Differences between groups at baseline in duration of PHN and allodynia severity score; analysis found that this had the effect of reducing the difference between groups on the primary endpoint, however.	Yes	Unclear, described as double-blind	Unclear, reported as double-blind	Unclear, described as double-blind; all patients had used lidocaine plaster previously

Evidence Table 3. Update 1: Quality assessment of trials

Author, Year Country	Intent-to-treat analysis	Maintenance of comparable groups	Acceptable levels of crossovers, adherence, and contamination?	Acceptable levels of overall attrition and between-group differences in attrition?	Quality rating
Arai 2010 Japan	Yes	Yes	Unclear/unclear/unclear	Yes	Fair
Arezzo 2008 US	Yes (LOCF, BOCF)	Unclear	Unclear/Yes/Unclear	Overall Yes: 69% discontinued treatment, but 83% returned for followup assessment even though some had dropped treatment. Not differential: 15% and 18%	Fair
Argyriou 2006	Yes	Unclear	Yes, Yes, Yes	20% in each arm, 2 withdrawals due to AE in treatment group, none in control	Fair
Bansal 2009 India	No, 7/51 (13.7%) randomized but not analyzed	Unclear	Unclear	Yes overall; 7 of 51 withdrew (14%); but reasons for attrition differed between groups	Fair
Baron, 2009; phase I	Yes for primary outcome, no for secondary outcomes	Unable to determine	Unclear/no(6%)/unclear	Yes - 9.6%; 8% vs 11%	Fair
Binder 2009	Yes all 71 randomized were analyzed.	Unclear	Unclear/5.6%/unclear	No - 45%; 31% vs 60%	Fair

Evidence Table 3. Update 1: Quality assessment of trials

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Breuer 2007 US	Yes	Unclear	Unclear - not reported	Yes	Unclear - research coordinator blinded	Unclear, described as double-blind	Unclear, described as double-blind
Finnerup 2009	Yes	No (sealed envelopes)	Unclear, not reported by order of randomization	Yes	Unclear, described as double-blind	Yes	Yes
Gilron 2009 Canada	Yes	Yes	Unclear	Yes	Yes	Yes	Yes
Gordh 2008 Scandinavia	Unclear	Unclear	Pain intensity score slightly higher in placebo-gabapentin arm	Yes	Unclear, described as double-blind	Yes	Yes
Grosskopf 2006 International	Unclear	Unclear	Yes	Yes	Unclear, described as double-blind	Unclear, described as double-blind	Unclear, described as double-blind

Evidence Table 3. Update 1: Quality assessment of trials

Author, Year Country	Intent-to-treat analysis	Maintenance of comparable groups	Acceptable levels of crossovers, adherence, and contamination?	Acceptable levels of overall attrition and between-group differences in attrition?	Quality rating
Breuer 2007 US	No 12/15 analyzed (80%)	Unable to determine	Unclear/5.5%/Unclear	No - 27%; not clear how many patients in each group	Poor
Finnerup 2009	No 24/36 (67% analyzed)	Withdrawn patients more often treated with concomitant pain medication; otherwise similar.	Unclear/yes/unclear	No (33% withdrew before 2 weeks, an additional 4 patients withdrew after 4 weeks of treatment); more withdrew during treatment (9 vs 3 during placebo)	Poor
Gilron 2009 Canada	No	Unclear	Unclear/Yes/Unclear (reported 1 patient withdrawn for nonadherence to protocol)	Yes - Overall: 11/56=19.6% Sequence: GCN: 4/19=21.1% NGC: 3/18=16.7% CNG: 4/19=21.1% where: G=Gabapentin N=Nortriptyline C=Combined Treatment	Fair
Gordh 2008 Scandinavia	No - 98/120	Unable to determine	Unclear/Yes/Unclear	Yes: 18% overall; differential- 21% gaba-placebo arm vs 15% placebo-gabapentin arm; reasons differed	Fair
Grosskopf 2006 International	Unclear, number analyzed is not reported	Unclear	Unclear/Yes/Unclear	No: Overall 41% treatment vs 24% placebo; more withdrew for adverse events in treatment group;	Poor

Evidence Table 3. Update 1: Quality assessment of trials

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
GSK NPP30004	Yes	Yes	Yes	Yes	Unclear, reported as double-blind (yes for patient-reported outcomes)	Yes	Yes
GSK NPP30005	Yes	Yes	Yes	Yes	Unclear, reported as double-blind (yes for patient-reported outcomes)	Yes	Yes
Jia 2006 China	Yes	No	Yes	Yes	Unclear (probably yes)	Yes	Yes
Jose 2007 India	Yes	Yes	Unclear	Yes	Unclear Yes		Yes
Kautio 2008	Yes	Yes	Yes	Yes	Yes for efficacy (patients), unclear for adverse events	Yes	Yes
Kautio 2009	Yes	Yes	Yes (but excluded 9 post-randomization)	Yes	Unclear, reported as double-blind	Unclear, reported as double-blind	Yes

Evidence Table 3. Update 1: Quality assessment of trials

Author, Year Country	Intent-to-treat analysis	Maintenance of comparable groups	Acceptable levels of crossovers, adherence, and contamination?	Acceptable levels of overall attrition and between-group differences in attrition?	Quality rating
GSK NPP30004	340/360 analyzed (94.4%)	Unable to determine	Unclear/Unclear/Unclear	No 38% total and differential 31% vs 34% vs 38% vs 50%	Fair
GSK NPP30005	Yes	Unclear	Unclear/Unclear/Unclear	No 38% total and differential, 35% vs 35% vs 35% vs 47%	Fair
Jia 2006 China	Yes, but not clear on which 3 participants not included in ITT (2.3%)	Unclear	Unclear/Yes/Unclear (2 patients withdrawn due to protocol violation)	Yes: 9.8% overall; Venlafaxine: 6/66=9.1% for Per Protocol Carbamazepine: 59/66=10.6%	Fair
Jose 2007 India	No, 29/75 (38.7%) randomized and not included in analysis	Unclear, 7 additional dropouts in the amitriptyline group just prior to wash-out period (compared to 0 in the lamotrigine group)	Unclear/Yes/Unclear (5 of 53 withdrawn due to noncompliance)	No	Fair
Kautio 2008	States LOCF was used for missing data, but results for only completers are reported	Unclear	Unclear	No - 9/42 withdrew (21%); not differential	Fair
Kautio 2009	No - analyzed those who returned diaries; excluded 15 who did not (13%)	Unable to determine	Unclear	No: high and differential: 20% withdrawn after randomization; 93% amitriptyline and 80% of placebo completed.	Fair

Evidence Table 3. Update 1: Quality assessment of trials

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Keskinbora 2007	Unclear	Unclear	Unclear - differences between groups in types of pain; also report only baseline characteristics on completers	Yes	No - open label	No - open label	No - open label
Khoromi 2007	Yes (random numbers)	Unclear	Unclear- not reported by order of randomization	Yes	Unclear	Yes	Yes
Pfizer unpublished study, 2007 Multiple European Countries Protocol no. 1008-040	Unclear	Unclear	No: least even gender distribution in amitriptyline group, baseline pain score higher in pregabalin group than amitriptyline or placebo	Yes	Unclear, described as double-blind	Yes	Yes
Pfizer unpublished study, 2007 Protocol no. A0081030 Asia, U.S., Middle East	Unclear	Unclear	Yes	Yes	Unclear, described as double-blind	Unclear	Unclear
Pfizer unpublished study, 2008 Protocol no. A0081081 China	Unclear	Unclear	Unclear (no data but states well matched on weight height and diagnosis, baseline pain scores similar)	Yes	Unclear, described as double-blind	Yes	Yes

Evidence Table 3. Update 1: Quality assessment of trials

Author, Year Country	Intent-to-treat analysis	Maintenance of comparable groups	Acceptable levels of crossovers, adherence, and contamination?	Acceptable levels of overall attrition and between-group differences in attrition?	Quality rating
Keskinbora 2007	No- per protocol only	Unable to determine	Unclear	16% withdrew; not differential	Poor
Khoromi 2007	No- only included those who completed 2 or more treatment periods (34/55, 62%)	Unable to determine	Yes (1)/yes/unclear	No: 28/55 completed (51%);	Fair
Pfizer unpublished study, 2007 Multiple European Countries Protocol no. 1008-040	Yes (254/256 analyzed)	Unable to determine	Unclear, Yes, Unclear	No: overall 66/256 (26%); 23.5% placebo, 27.9% pregabalin, 26.4% amitriptyline; more withdrawals due to adverse events in amitriptyline (18.4%) and pregabalin (12.8%) groups than placebo (4.9%)	Fair
Pfizer unpublished study, 2007 Protocol no. A0081030 Asia, U.S., Middle East	Yes	Unable to determine	Unclear/unclear/unclear	Yes (16% overall); 16% treatment vs 18% placebo. 6 additional patients randomized but did not receive any medication; not reported by group.	Fair
Pfizer unpublished study, 2008 Protocol no. A0081081 China	Yes (308/308 analyzed)	Unable to determine	Unclear, Unclear, Unclear	Yes 42/309 (14%); 12% treatment vs 17% placebo	Fair

Evidence Table 3. Update 1: Quality assessment of trials

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Pfizer unpublished study, 2009 Protocol no. A0081063 Asia Pacific region	Unclear	Unclear	Yes	Yes	Unclear, reported as double-blind	Yes (matching placebo)	Yes (matching placebo)
Pfizer unpublished study, 2009 Protocol no. A0081120 Japan	Unclear	Unclear	Unclear (no data presented but states treatment groups well balanced with respect to sex, age, height, body weight	Yes	Unclear, described as double blind	Unclear, described as double blind	Unclear, described as double blind
Pfizer unpublished study 2007 Protocol no. A0081071 U.S.	Unclear	Unclear	Unclear. Only gender and mean age were reported per group. Majority of subjects in the three treatment groups were white.	Yes	Unclear, described as double blind	Yes (matching placebo)	Yes (matching placebo)
Rao 2007	Unclear	Unclear	Yes	Yes	Yes for efficacy (patients), unclear for adverse events	Yes	Yes
Rao 2008	Unclear	Unclear	Yes	Yes	Yes	Unclear, reported as double-blind	Yes

Evidence Table 3. Update 1: Quality assessment of trials

Author, Year Country	Intent-to-treat analysis	Maintenance of comparable groups	Acceptable levels of crossovers, adherence, and contamination?	Acceptable levels of overall attrition and between-group differences in attrition?	Quality rating
Pfizer unpublished study, 2009 Protocol no. A0081063 Asia Pacific region	Yes	Unclear	Unclear/Unclear/Unclear	Yes; 15% vs 17%	Fair
Pfizer unpublished study, 2009 Protocol no. A0081120 Japan	Yes	Unclear	Unclear, Unclear, Unclear	Yes 74/372 (19.9%) Overall Differential: No for placebo vs 600mg pregabalin(>10%) Placebo 15.3% vs 150mg 16.1% vs 300mg 20.2% vs 600mg 27.8%	Fair
Pfizer unpublished study 2007 Protocol no. A0081071 U.S.	Yes	Unclear	Unclear, unclear, unclear	No. 147/462 (31.8%) discontinued overall Differential: No, for 300mg vs 600mg and 600 mg vs placebo. 300mg 32% vs 600mg 42.1% vs placebo 22.5%	Fair
Rao 2007	Yes - gives only results without imputation, but says no difference based on method of handling missing data	Unclear	Unclear	No - 73% entered 2nd crossover phase; not differential	Fair
Rao 2008	Yes	Unable to determine	Unclear	No- 56% of treatment and 74% of placebo group stopped treatment; also excluded 6 post-randomization (groups not clear)	Fair

Evidence Table 3. Update 1: Quality assessment of trials

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Rauck 2007 US	Yes	Unclear	Yes	Yes	Unclear, described as double-blind	Yes	Yes
Rintala 2007	Yes	Unclear	Unable to determine, crossover and reported for whole group	Yes	Unclear, described as double-blind	Yes	Yes
Rossi 2009 Italy	Yes	Unclear	Yes	Yes	No (single-blind)	Unclear, described as single-blind	Yes
Shaibani 2009 US	Yes	Unclear	Yes	Yes	Unclear	Yes	Yes
Silver 2007 US	Unclear	Unclear	Yes	Yes	Unclear, described as double-blind	Unclear, described as double-blind	Unclear, described as double-blind
Simpson 2010 US and Puerto Rico	Yes	Yes	Yes	Yes	Unclear, described as double-blind	Yes	Yes

Evidence Table 3. Update 1: Quality assessment of trials

Author, Year Country	Intent-to-treat analysis	Maintenance of comparable groups	Acceptable levels of crossovers, adherence, and contamination?	Acceptable levels of overall attrition and between-group differences in attrition?	Quality rating
Rauck 2007 US	Yes (LOCF)	Unclear	Unclear/Yes/Unclear	Overall high (21%); but not differential.	Fair
Rintala 2007	No, but compared completers vs non-completers (using available data)	Unable to determine	7 early crossovers/yes/unclear	No - 42%; no - 57% vs 33% vs 50% vs 33% vs 57% vs 17% (small numbers randomized in each group: 6 or 7)	Poor
Rossi 2009 Italy	No	Unable to determine	Unclear, unclear, unclear	Yes - 15%; yes - 17% vs 13%	Fair
Shaibani 2009 US	No for efficacy (ITT defined as those with one post-baseline measurement), yes for safety	Unclear	Unclear/yes/unclear	No-45%; No-31% vs 33% vs 43% vs 66%	Fair
Silver 2007 US	Yes (95% analyzed); LOCF used	Unable to determine	Unclear/6.3%/unclear	No: 35% overall withdrew; more for adverse events in lamotrigine group; 28% placebo and 42% lamotrigine withdrew	Fair
Simpson 2010 US and Puerto Rico	Yes; 299/302 analyzed (99%, used LOCF)	Yes	Unclear/unclear/unclear	Yes: 20% withdrew overall; not differential	Good

Evidence Table 3. Update 1: Quality assessment of trials

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
Stacey 2008	Unclear	Unclear	Yes	Yes	Unclear, described as double-blind	Yes	Yes
Tanenberg 2010	Unclear	Unclear	Yes	Yes	No: open-label	No: open-label	No: open-label
Tolle 2008 International	Unclear	Unclear	Yes	Yes	Unclear, described as double-blind	Unclear, described as double-blind	Unclear, described as double-blind
Van de Vusse 2004	Yes	Yes	Yes	Yes	Unclear, described as double-blind	Not successful	Successful only in first phase
Van Seventer 2010	Unclear	Unclear	More women in pregabalin group (61% vs 41%); otherwise similar	Yes	Unclear, reported as double-blind (yes for patient-reported outcomes)	Yes (identical placebo)	Yes (identical placebo)
Vilholm 2008 Denmark	Yes	Yes	Unable to determine, crossover and reported for whole group	Yes	Yes	Yes	Yes

Evidence Table 3. Update 1: Quality assessment of trials

Author, Year Country	Intent-to-treat analysis	Maintenance of comparable groups	Acceptable levels of crossovers, adherence, and contamination?	Acceptable levels of overall attrition and between-group differences in attrition?	Quality rating
Stacey 2008	5.9% missing from last observation	Unclear	Unclear/unclear/unclear	Yes, (14% overall); no (94.5% vs 79.5% vs 83.3% completed in flex, fixed, and placebo groups; more discontinued for adverse events in fixed-dose group)	Fair
Tanenberg 2010	Used LOCF but unclear how many included in ITT analysis	Unable to determine	Unclear, yes, unclear	No: Overall 125/407 withdrew (31%); reasons differed	Poor
Tolle 2008 International	Yes (294 of 395 analyzed)	Unclear	Unclear/Yes/Unclear	Yes-19%; yes-18% vs 17% vs 20% vs 23%	Fair
Van de Vusse 2004	No; 46/58 analyzed (79%)	Yes except that those who started in the placebo group and discontinued had pain twice as long as long as all others	Unclear/unclear/unclear	No - 21%; no - 21% vs 32%	Fair
Van Seventer 2010	Yes; 252 of 254 analyzed (99%)	Unable to determine	Unclear/Unclear/Unclear	No 35% overall; Yes 37% vs 30% vs 37% vs 37%	Fair
Vilholm 2008 Denmark	No: 25/27 analyzed (93%)	Unable to determine	Unclear/Yes/Unclear	Yes; 2/27 withdrew (7%); not differential	Fair

Evidence Table 3. Update 1: Quality assessment of trials

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?
von Delius 2007	Unclear	Unclear	Yes	Yes	Not reported	Not reported	Unclear
Vranken 2008	Unclear	Yes	Yes	Yes	Yes (patient reported)	Yes	Yes
Wernicke 2006 US?	Unclear	Unclear	Yes	Yes	No	No	No
Wernicke 2007	Unclear	Unclear	Yes	Yes	No	No	No
Wymer 2009 US	Yes	Unclear	More women in placebo group	Yes	Probably yes	Yes	Yes
Ziegler 2010 US	Unclear	Unclear	More women in placebo group	Yes	Unclear, described as double-blind	Yes	Yes

Evidence Table 3. Update 1: Quality assessment of trials

Author, Year Country	Intent-to-treat analysis	Maintenance of comparable groups	Acceptable levels of crossovers, adherence, and contamination?	Acceptable levels of overall attrition and between-group differences in attrition?	Quality rating
von Delius 2007	Yes	Yes	Unclear	2 patients (11%) prematurely discontinued carbamazepine 21% treatment and 18% control discontinued chemotherapy early	Fair
Vranken 2008	Yes (1/40 excluded, 3%)	Unclear	Unclear/unclear/unclear	Yes 17.5%; yes-20% vs 15%	Fair
Wernicke 2006 US?	No	Unclear	Unclear/Yes/Unclear	25% for 52 week study; differential: 28% vs 19%	Fair
Wernicke 2007	No	Unclear	Unclear/Yes/Unclear	25% for 52 week study; differential: 28% vs 19%	Fair
Wymer 2009 US	Yes for last 4 weeks of maintenance phase (365/370 analyzed; 98.6%), no for 12-week maintenance phase	Unclear	Unclear/Yes/Unclear	No: Overall 36.8% withdrew; differential in reasons (more withdrew for adverse events in treatment groups)	Fair
Ziegler 2010 US	Yes (LOCF, 355/357 analyzed)	Unclear	Unclear, yes, unclear	No - 31%; no - 20% vs 25% vs 44% vs 31%	Fair

Evidence Table 4. Update 1: Quality assessment of observational studies

Author Year Country	Non-biased selection?	High overall loss to follow-up or differential loss to follow-up?	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall quality rating
Hans 2009	Unclear; while eligibility criteria are clear and unbiased, the source of subjects is not described.	39% attrition	Yes	No	Unclear	No; no analysis conducted on adverse events	Yes	Poor
NCT00220337 UCB Dossier 2008	Unclear; while eligibility criteria are clear and unbiased, the source of subjects is not described.	52% attrition	Unclear; Sponsor study summary not clear on whether these were chosen a priori, and did not provide definitions	No	Unclear	No; no analysis conducted on adverse events	Yes	Poor

Evidence Table 5. Update 1: Data abstraction of systematic reviews

Author Year Country	Aims	Time period covered	Eligibility criteria	Number of patients	Characteristics of identified articles: study designs	Characteristics of identified articles: populations
Teasell, 2010 Canada	Conduct systematic review of published research on the pharmacologic treatment of pain after SCI	1980 to June 2009	50% of subjects had SCI, there were at least 3 subjects with an SCI, and there was a definable intervention being studied.	791	21 RCTs and 7 non-RCT	Patients with all types of pain after SCI: nociceptive, neuropathic and mixed
Wolff, 2010	Compare 5% lidocaine medicated plaster for the relief of DPN with other relevant interventions or placebo	1950 to June 2009	RCTs on adult patients with neuropathic pain associated with painful DPN and PHN	NR	RCTs	PHN and DPN

Evidence Table 5. Update 1: Data abstraction of systematic reviews

Author Year Country	Characteristics of identified articles: interventions	Main results
Teasell, 2010 Canada	Anticonvulsants: Gabapentin, Lamotrigine, Valproate Antidepressants: Amitriptyline	**Anticonvulsants**: Level 1 evidence that gabapentin and pregabalin improve neuropathic pain with SCI. level 4 evidence gabapentin more effective when SCI pain present<6 mos vs > 6 mo, Level 2 evidence that lamotrigine is effective in reducing neuropathic pain in persons with incomplete SCI. Level 1 evidence that valproic acid does not significantly relieve neuropathic pain after SCI, however a non significant trend towards improvement is seen. **Antidepressants:** Level 1 evidence that amitriptyline is effective in the treatment of post SCI pain but only in depressed persons
Wolff, 2010	5% lidocaine plaster (4 plasters for up to 12 hours) vs pregabalin 150 to 600mg/d Amitriptyline vs capsaicin Amitriptyline vs gabapentin Amitriptyline vs placebo Amitriptyline vs pregabalin Capsaicin vs placebo Pregabalin vs placebo	Results from Network meta analysis Pain change from baseline Amitriptyline vs placebo -12.58, 95% CI (-16.66 to -8.51) Gabapentin vs placebo -9.38, 95% CI (-13.93 to -4.84) Pregabalin vs placebo: -12.10, 95% CI(-17.12 to -7.08) Gabapentin vs amitriptyline: 3.20, 95% CI (-3.99 to 4.96) Pregabalin vs amitriptyline: 0.49, 95% CI (-3.99 to 4.96) 5% lidocaine plaster vs placebo: -9.10, 95% CI (-13.93 to -4.27) 5% lidocaine plaster vs amitriptyline: 3.48, 95% CI (-0.77 to 7.74) 5% lidocaine plaster vs gabapentin: 1.12 (-6.02 to 8.27) 5% lidocaine plaster vs pregabalin: 1.43, 95% CI (-2.96 to 5.83) Pregabalin vs gabapentin: -0.31, 95% CI (-7.05 to 6.43)

Evidence Table 5. Update 1: Data abstraction of systematic reviews

Author Year Country	Subgroups	Adverse events	Comments
Teasell, 2010 Canada	Level 1 evidence that amitriptyline is effective in the treatment of post SCI pain but only in depressed persons	NR	PEDro Scoring system on study quality: 9-10 excellent, 6 to 8 good, 4 to 5 fair, <4 poor Modified Sackett's Level of Evidence Level 1 RCTs with a PEDro score ≥6 Level 2 RCTs with a PEDro score <6, cohort and non RCTs Level 3 Case Control Studies Level 4 Pre-post or post interventions and case series Level 5 Case reports, clinical consensus or observational studies
Wolff, 2010	NR	Reports only results from 1 study comparing lidocaine to placebo Most common AE: Pregabalin: Dizziness, fatigue, vertigo, somnolence Lidocaine: Headache, application site reactions.	

Evidence Table 6. Update 1: Quality assessment of systematic reviews

Author Year	Report clear review question, state inclusion and exclusion criteria of primary studies?	Substantial effort to find relevant research?	Adequate assessment of validity of included studies?	Sufficient detail of individual studies presented?	Primary studies summarized appropriately?	Quality rating
Teasell 2010	Yes	Yes	Yes	Yes	Yes	Good
Wolff 2010	Yes	Yes	Yes	Yes	Yes	Fair

Evidence Table 7. Original report: Data abstraction of pregabalin, gabapentin, serotonin-norepinephrine reuptake inhibitors, and topical lidocaine (patch or gel)

Study	Design	Type of pain/ Sample size and characteristics	Intervention	Eligibility	Exclusion
Backonja 1998 US Efficacy quality: Fair	RCT Parallel Multicenter	Painful diabetic neuropathy N=165 Mean Age (SD): 53.0 Male: 60% Female: 40% White: 81.2% Black: 6.7% Other: 12.1%	Gabapentin 3600 mg N=84 Placebo N=81	At screening, pain attributed to diabetic neuropathy for 1 to 5 years, a diagnosis of diabetes mellitus (type 1 or 2), and a pain rating score of at least 40 mm on the 100-mm VAS of the Short-Form McGill Pain Questionnaire. Patients with an average pain score of at least 4 on an 11-point Likert scale and at least 4 observations recorded in daily pain diaries over the next week were randomized. Only patients with a hemoglobin A1c level of 0.11 or less were randomized.	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, and amputations other than toes. Creatinine clearance of less than 60 mL/min.
Bone 2002 UK and Ireland Efficacy quality: Fair	RCT Crossover Single Center	Phantom limb pain N=19 Mean Age (SD): 56.25 (17.5); Range: 24-68 Male: 78.95% Female: 21.05% White: 68.4% Asian: 21.1% Other: 10.5%	Gabapentin 2400 mg N=10 Placebo N=9	Patients attending a Disablement Services Clinic, with established phantom limb pain of a minimum of 6 months duration after a previous surgical amputation, between age 18 and 75 years, and had a pain score of at least 40 mm on a 100-mm VAS.	Coexisting epilepsy or a known allergy to gabapentin, significant hepatic or renal insufficiency, severe hematologic disease, a history of illicit drug or alcohol abuse, any serious psychiatric condition, and other severe pain that could confound the assessment.
Dworkin 2003 US Efficacy quality: Fair	RCT Parallel Multicenter	Post-herpetic neuralgia N=173 Mean Age (SD): 71.5 (10.9) Male: 46.82% Female: 53.18% White: 94.8% Asian: 1.2% Hispanic: 4%	Pregabalin 300-600 mg N=89 Placebo N=84	Men and women of any race who were at least 18 years of age and had postherpetic neuralgia defined as pain present for more than 3 months after healing of a herpes zoster skin rash. Pain at least 40 mm on the 100 mm VAS of the Short-Form McGill Pain Questionnaire at baseline and randomization visits, completed at least 4 daily pain diaries and had a minimum mean daily pain rating of 4 on an 11-point numerical pain rating scale during the baseline week preceding randomization; women had to practice an appropriate method of contraception throughout the study, normal chest X-ray within the preceding 2 years.	Pregnant or lactating women, serious or unstable medical conditions, other severe pain that might confound assessment or self-evaluation of pain due to post-herpetic neuralgia, or previous neurolytic or neurosurgical therapy for postherpetic neuralgia; patients who had failed to respond to previous postherpetic neuralgia treatment with gabapentin at dosages ≥1200 mg/day; baseline serum creatinine clearance ≤30 ml/min, white blood cell count <2500/mm3, neutrophil count <1500/mm3, or platelet count <100X103/mm3; participation in any other clinical trial of an investigational drug within 30 days before screening.

Evidence Table 7. Original report: Data abstraction of pregabalin, gabapentin, serotonin-norepinephrine reuptake inhibitors, and topical lidocaine (patch or gel)

Study	Patient-reported pain	Observer-reported pain	Functional capacity
Backonja 1998 US Efficacy quality: Fair	Gabapentin vs Placebo Average pain, 11-point Likert scale (0-10) Mean score: 3.9 vs 5.1 at 8 weeks (p<0.001) Average pain, SF-MPQ VAS (0-100) Mean score: 36.9 vs 53.8 at 8 weeks (p<0.001) Average pain, Total SF McGill Pain Questionnaire (SF-MPQ) Mean score: 10.9 vs 16.8 at 8 weeks (p<0.001) Pain intensity, SF-MPQ Present Pain Intensity (0-5) Mean score: 1.2 vs 1.8 at 8 weeks (p<0.001)	NR	Gabapentin vs Placebo QOL, SF-36 Bodily Pain Mean score: 55.2 (p=0.01) vs 47.4 at 8 weeks QOL, SF-36 Mental Health Mean score: 75.7 (p=0.03) vs 70.4 at 8 weeks QOL, SF-36 Vitality Mean score: 53.5 (p=0.001) vs 43.7 at 8 weeks
Bone 2002 UK and Ireland Efficacy quality: Fair	Gabapentin vs Placebo Pain intensity, Categorical (0-3; none, mild, moderate, severe) Mean score: 1.45 (95% CI, 0.83 to 2.07) vs 1.6 (95% CI, 0.82 to 2.38) at 6 weeks (p=0.80) Pain intensity, VAS (0-100) Mean score: 2.9 (95% CI, 1.54 to 4.26) vs 5.1 (95% CI, 3.66 to 6.54) at 6 weeks (p=0.025)	NR	Gabapentin vs Placebo Activities of Daily Living, Barthel Index Median score: 85 (IQR: 70-105) vs 87 (IQR: 65-105) at 6 weeks
Dworkin 2003 US Efficacy quality: Fair	Pregabalin vs Placebo Average pain intensity (0-10), SF-MPQ Present Pain Intensity (0-5) LS mean: 1.58 (95% CI: 1.34, 1.82) vs 1.98 (95% CI: 1.74, 2.22) at 8 weeks (p=0.127) Average pain, 11-point scale (0-10) LS mean: 3.60 (95% CI: 3.13, 4.07) vs 5.29 (95% CI: 4.82, 5.76) at 8 weeks (p=0.0001) Average pain, SF-MPQ Total (0-45) LS mean: 9.85 (95% CI: 7.99, 11.71) vs 14.72 (95% CI: 12.84, 16.60) at 8 weeks (p=0.0002) Average pain, SF-MPQ VAS (100 mm) LS mean: 38.68 (95% CI: 33.00, 44.36) vs 56.30 (95% CI: 50.56, 62.04) at 8 weeks (p=0.0001) Response, ≥30% decrease in pain % of patients: 63% vs 25% at 8 weeks (p=0.001) Response, ≥50% decrease in pain % of patients: 50% vs 20% at 8 weeks (p-value NR)	NR	Pregabalin vs Placebo QOL, SF-36 Bodily Pain, LS mean: 55.14 (p=0.0021; 95% CI: 50.97, 59.31) vs 46.14 (95% CI: 41.97, 50.31) at 8 weeks QOL, SF-36 General Health Perception, LS mean: 67.61 (p=0.0488; 95% CI: 64.51, 70.71) vs 63.40 (95% CI: 60.30, 66.50) at 8 weeks QOL, SF-36 Mental Health, LS mean: 77.53 (p=0.0676; 95% CI: 74.51, 80.55) vs 73.73 (95% CI: 70.71, 76.75) at 8 weeks QOL, SF-36 Physical Functioning, LS mean: 62.25 (p=0.7449; 95% CI: 58.41, 66.09) vs 61.41 (95% CI: 57.69, 65.13) at 8 weeks QOL, SF-36 Vitality, LS mean: 49.99 (p=0.6798; 95% CI: 46.29, 53.69) vs 48.94 (95% CI: 45.26, 52.62) at 8 weeks

Evidence Table 7. Original report: Data abstraction of pregabalin, gabapentin, serotonin-norepinephrine reuptake inhibitors, and topical lidocaine (patch or gel)

Study	Other outcomes	Withdrawals/ Withdrawals due to AEs	Specific adverse events
Backonja 1998 US Efficacy quality: Fair	Gabapentin vs Placebo Interference with sleep, 11-point Likert scale (0-10) Mean score: 2.3 vs 3.8 at 8 weeks (p<0.001)	Gabapentin vs Placebo Total: 14 (16.67%) vs 16 (19.75%) AE: 7 (8.33%) vs 5 (6.17%)	Gabapentin vs Placebo Confusion: 8.3% (7/84) vs 1.2% (1/81) Diarrhea: 10.7% (9/84) vs 8.6% (7/81) Dizziness: 23.8% (20/84) vs 4.9% (4/81) Headache: 10.7% (9/84) vs 3.7% (3/81) Nausea: 8.3% (7/84) vs 4.9% (4/81) Somnolence: 22.6% (19/84) vs 6.2% (5/81)
Bone 2002 UK and Ireland Efficacy quality: Fair	Gabapentin vs Placebo Depression, Hospital Anxiety & Depression Scale (higher worse) Median score: 12 (IQR: 4-22) vs 14 (IQR: 5-25) at 6 weeks Interference with sleep, 11-point scale (0-10) Median score: 3 (IQR: 1-5) vs 4 (IQR: 1-5) at 6 weeks	Gabapentin vs Placebo Total: 2 (20%) vs 3 (33.33%) AE: NR	Gabapentin vs Placebo Dizziness: 20.0% (2/10) vs 11.1% (1/9) Headache: 20.0% (2/10) vs 11.1% (1/9) Nausea: 10.0% (1/10) vs 11.1% (1/9) Somnolence: 70.0% (7/10) vs 22.2% (2/9)
Dworkin 2003 US Efficacy quality: Fair	Pregabalin vs Placebo Interference with sleep, 11-point numeric scale (0-10) Least squares mean: 1.93 (p=0.0001; 95% CI: 1.48, 2.38) vs 3.51 (95% CI: 3.06, 3.96) at 8 weeks Interference with sleep, Medical Outcomes Study Sleep Scale (higher=worse) Least squares mean: 26.63 (p=0.0001; 95% CI: 23.16, 30.10) vs 36.43 (95% CI: 33.00, 39.86) at 8 weeks	Pregabalin vs Placebo Total: 31 (34.83%) vs 10 (11.9%) AE: 28 (31.46%) vs 4 (4.76%)	Pregabalin vs Placebo Amblyopia: 11.2% (10/89) vs 1.2% (1/84) Ataxia: 6.7% (6/89) vs 0.0% (0/84) Confusion: 6.7% (6/89) vs 0.0% (0/84) Diarrhea: 6.7% (6/89) vs 4.8% (4/84) Dizziness: 28.1% (25/89) vs 11.9% (10/84) Dry mouth: 11.2% (10/89) vs 2.4% (2/84) Edema, peripheral: 19.1% (17/89) vs 2.4% (2/84) Gait abnormal: 7.9% (7/89) vs 1.2% (1/84) Headache: 7.9% (7/89) vs 8.3% (7/84) Somnolence: 24.7% (22/89) vs 7.1% (6/84) Speech disorder: 5.6% (5/89) vs 0.0% (0/84)

Evidence Table 7. Original report: Data abstraction of pregabalin, gabapentin, serotonin-norepinephrine reuptake inhibitors, and topical lidocaine (patch or gel)

Study	Design	Type of pain/ Sample size and characteristics	Intervention	Eligibility	Exclusion
Freynhagen 2005 Multiple European Efficacy quality: Fair	RCT Parallel Multicenter	Mixed N=338 Mean Age (SD): 62.2 (11.1); Range: 26-87 Male: 54.14% Female: 45.86% White: 97.6% Black: 0.3% Asian: 0.6% Hispanic: 1.5%	Pregabalin 150-600 mg N=141 Pregabalin 600 mg N=132 Placebo N=65	Men and non-pregnant, non-lactating women ≥18 years of age with a primary diagnosis of painful diabetic peripheral neuropathy (type 1 or 2 diabetes mellitus with HbA1c ≤11% and painful, distal, symmetrical, sensorimotor polyneuropathy for ≥6 months) or postherpetic neuralgia (pain present for ≥3 months after healing of the herpes zoster skin rash). Also required to have a score of ≥40 mm (0 mm=no pain, 100 mm=worst possible pain) on the VAS of the Short Form McGill Pain Questionnaire at baseline and randomization.	Any clinically significant or unstable medical or psychiatric condition. Malignancy within the past 2 years (with the exception of basal cell carcinoma) or an anticipated need for surgery during the study; patients with an abnormal ECG, creatinine clearance <60 mL/min, or abnormal hematology; patients who had abused illicit drugs or alcohol within the last 2 years; participated in a previous clinical trial for pregabalin or had taken any investigational drug or agent within 30 days prior to screening. History of hepatitis B or C or HIV infection, neurologic disorders, severe pain unrelated to primary diagnosis of postherpetic neuralgia or diabetic neuropathy, or any potentially sensation-altering skin conditions in the affected dermatome or area of neuropathic involvement that could confound their assessment of neuropathic pain. Patients with diabetic neuropathy and a history of pernicious anemia, untreated hypothyroidism, or amputations other than toes, patients with postherpetic neuralgia who had undergone neurolytic or neurosurgical therapy for their condition.
Galer (A) 2002 US Efficacy quality: Poor	RCT Parallel Multicenter	Post-herpetic neuralgia N=96 Mean Age (SD): 74 Male: 37.5% Female: 62.5% White: 87.5% Black: 1% Asian: 10.4% Hispanic: 1%	Lidocaine transdermal patch N=67 Placebo N=29	Established torso postherpetic neuralgia for at least 1 month and the presence of allodynia on physical examination.	Not reported.

Evidence Table 7. Original report: Data abstraction of pregabalin, gabapentin, serotonin-norepinephrine reuptake inhibitors, and topical lidocaine (patch or gel)

Study	Patient-reported pain	Observer-reported pain	Functional capacity
Freynhagen 2005 Multiple European Efficacy quality: Fair	Pregabalin 150-600 mg vs Pregabalin 600 mg vs Placebo Average pain, 11-point scale (0-10) Mean score: Reported graphically only at 12 weeks (p=NR) Global Impression of Improvement, "much improved" or "very much improved" % of patients: 52.0% (p<0.01) vs 53.6% (p<0.01) vs 30.5% at 12 weeks Response, ≥30% reduction in pain % of patients: 59.0% (p=0.003) vs 66.4% (p<0.001) vs 37.1% at 12 weeks Response, ≥50% reduction in pain % of patients: 48.2% (p<0.001) vs 52.3% (p<0.001) vs 24.2% at 12 weeks	NR	NR
Galer (A) 2002 US Efficacy quality: Poor	Lidocaine patch vs Placebo Pain, NPS 4 Score (0-100) Mean change from baseline: 18.0 (p=0.013) vs 6.6 at 3 weeks Pain, NPS Composite Score (0-100) Mean change from baseline: 15.3 (p=0.043) vs 7.7 at 3 weeks Pain, NPS Non-allodynic Score (0-100) Mean change from baseline: 15.1 (p=0.022) vs 6.8 at 3 weeks Pain, NPS Total Descriptor Score (0-100) Mean change from baseline: 14.1 (p=0.042) vs 6.6 at 3 weeks	NR	NR

Evidence Table 7. Original report: Data abstraction of pregabalin, gabapentin, serotonin-norepinephrine reuptake inhibitors, and topical lidocaine (patch or gel)

Study	Other outcomes	Withdrawals/ Withdrawals due to AEs	Specific adverse events
Freynhagen 2005 Multiple European Efficacy quality: Fair	Interference with sleep, Medical Outcomes Study Sleep Scale reported graphically only at 12 weeks (p<0.001)	Pregabalin 150-600 mg vs Pregabalin 600 mg vs Placebo Total: 49 (34.75%) vs 50 (37.88%) vs 30 (46.15%) AE: 24 (17.02%) vs 33 (25%) vs 5 (7.69%)	Pregabalin 150-600 mg vs Pregabalin 600 mg vs Placebo Asthenia: 6.4% (9/141) vs 9.1% (12/132) vs 0.0% (0/65) Dizziness: 2.1% (3/141) vs 28.8% (38/132) vs 4.6% (3/65) Dry mouth: 2.8% (4/141) vs 6.1% (8/132) vs 4.6% (3/65) Edema, peripheral: 2.1% (3/141) vs 7.6% (10/132) vs 3.1% (2/65) Headache: 5.0% (7/141) vs 2.3% (3/132) vs 3.1% (2/65) Nausea: 5.0% (7/141) vs 10.6% (14/132) vs 1.5% (1/65) Somnolence: 10.6% (15/141) vs 12.9% (17/132) vs 0.0% (0/65) Vertigo: 7.8% (11/141) vs 9.8% (13/132) vs 1.5% (1/65) Weight gain: 0.7% (1/141) vs 13.6% (18/132) vs 3.1% (2/65)
Galer (A) 2002 US Efficacy quality: Poor	NR	NR	NR

Evidence Table 7. Original report: Data abstraction of pregabalin, gabapentin, serotonin-norepinephrine reuptake inhibitors, and topical lidocaine (patch or gel)

Study	Design	Type of pain/ Sample size and characteristics	Intervention	Eligibility	Exclusion
Galer (B) 1999 US Efficacy quality: Fair	RCT Crossover Multicenter	Post-herpetic neuralgia N=32 Mean Age (SD): 77.4; Range: 62.1-96.6 Male: 43.75% Female: 56.25%	Lidocaine transdermal patch N=32 Placebo N=32	All patients had been successfully treated with lidocaine patches on a regular basis for at least 1 month. Subjects were recruited from postherpetic neuralgia patients who were enrolled in the open-label compassionate use protocol and using lidocaine patches on a regular basis for at least 1 month. Patients were either participants in prior studies of the lidocaine patch, who had requested open-label use, or were refractory postherpetic neuralgia patients whose physicians obtained the lidocaine patch for clinical use. Subjects must have rated their current pain relief from the lidocaine patches as "moderate relief", "a lot of relief", or "complete pain relief" using the 6-item pain relief scale.	Patients who reported they did not experience pain before patch application.
Gilron (A) 2005 Canada Efficacy quality: Fair	RCT Crossover Single Center	Mixed N=57 Mean Age (SD): 60 (pts PDN), 68 (pts PHN); Range: 40-81 Male: 56.14% Female: 43.86% White: 97% Other: 3%	Gabapentin 3200 mg N=48 Lorazepam 1.6 mg N=44	Diabetic nephropathy or postherpetic neuralgia. Patients with diabetic nephropathy had distal, symmetric, sensory diabetic polyneuropathy as determined on the basis of their medical history and either an unequivocal decrease in response to pinprick, temperature, or vibration in both feet or bilaterally decreased or absent ankle-jerk reflexes. Patients with post-herpetic neuralgia had an eruption of herpes zoster rash not more recently than 6 months before enrollment. General criteria for inclusion were daily moderate pain for 3 months or more, age 18 to 89 years, serum alanine aminotransferase or aspartate aminotransferase level less than 1.2 times the normal level, creatinine level less than 1.5 times the upper limit of normal, and sufficient language skills to communicate with research staff.	Hypersensitivity to study medications, another painful condition as severe as the diabetic neuropathy or postherpetic neuralgia, recent MI, unstable angina or congestive heart failure, any central neurologic disorder (including seizures), a serious mood disorder, a history of serious drug or alcohol abuse, pregnancy, lactation, and lack of a primary care physician.

Evidence Table 7. Original report: Data abstraction of pregabalin, gabapentin, serotonin-norepinephrine reuptake inhibitors, and topical lidocaine (patch or gel)

Study	Patient-reported pain	Observer-reported pain	Functional capacity
Galer (B) 1999 US Efficacy quality: Fair	Lidocaine patch vs Placebo Pain relief, Verbal pain relief scale (0- 5) % of patients: 90.6% vs 40.6% at 2-14 day Pain relief, Verbal pain relief scale (0- 5) Median "time to exit": >14 days (p<0.001) vs 3.8 days at 2-14 days	NR	NR
Gilron (A) 2005 Canada Efficacy quality: Fair	Gabapentin vs Lorazepam Average pain intensity (0-10), 10- cm VAS Mean score: 3.5 (95% CI, 2.72 to 4.28) vs 3.9 (95% CI, 3.12 to 4.68) at 5 weeks (p=NS) Average pain, Short-Form McGill Pain Questionnaire Total (0-45) Mean score: 10.7 (95% CI, 8.15 to 13.25) vs 14.4 (95% CI, 11.85 to 16.95) at 5 weeks (p<0.05) Interference with activities, Brief Pain Inventory (General activity, 0-10) Mean score: 3.0 (95% CI, 2.22 to 3.78) vs 4.5 (95% CI, 3.72 to 5.28) at 5 weeks (p<0.05) Pain intensity, Present pain intensity (0-3) Mean score: 1.64 (95% CI, 1.33 to 1.95) vs 2.07 (95% CI, 1.76 to 2.38) at 5 weeks (p<0.05)	NR	Gabapentin vs Lorazepam QOL, SF-36 Bodily Pain (0-100) Mean score: 65.6 (p<0.05; 95% CI: 59.92, 71.28) vs 56.0 (95% CI: 50.12, 61.88) at 5 weeks QOL, SF-36 Mental Health (0-100) Mean score: 80.9 (p<0.05; 95% CI: 75.80, 86.00) vs 73.4 (95% CI: 68.30, 78.50) at 5 weeks QOL, SF-36 Physical Functioning (0-100) Mean score: 61.1 (p<0.05; 95% CI: 53.26, 68.94) vs 56.0 (95% CI: 48.16, 63.84) at 5 weeks

Evidence Table 7. Original report: Data abstraction of pregabalin, gabapentin, serotonin-norepinephrine reuptake inhibitors, and topical lidocaine (patch or gel)

Study	Other outcomes	Withdrawals/ Withdrawals due to AEs	Specific adverse events
Galer (B) 1999 US Efficacy quality: Fair	Lidocaine patch vs Placebo Use of rescue analgesics % of patients: 9.4% vs 12.5% at 2-14 days	NR	NR
Gilron (A) 2005 Canada Efficacy quality: Fair	Gabapentin vs Lorazepam Depression, Beck Depression Inventory (0-63) Mean score: 6.4 (p<0.05; 95% CI: 4.44, 8.36) vs 8.5 (95% CI: 6.54, 10.46) at 5 weeks Interference with sleep, Brief Pain Inventory (Sleep, 0-10) Mean score: 1.5 (p<0.05; 95% CI: 0.72, 2.28) vs 3.4 (95% CI: 2.62, 4.18) at 5 weeks	NR	NR

Evidence Table 7. Original report: Data abstraction of pregabalin, gabapentin, serotonin-norepinephrine reuptake inhibitors, and topical lidocaine (patch or gel)

Study	Design	Type of pain/ Sample size and characteristics	Intervention	Eligibility	Exclusion
Goldstein 2005 US Efficacy quality: Fair	RCT Parallel Multicenter	Painful diabetic neuropathy N=457 Mean Age (SD): 60.1 (10.9) Male: 61.49% Female: 38.51% White: 77.2% Black: 8.1% Hispanic: 11.2% Other: 3.5%	Duloxetine 20 mg daily N=115 Duloxetine 60 mg daily N=114 Duloxetine 60 mg BID Total daily dose: 120 mg/d N=113 Placebo N=115	Age 18+; daily pain due to polyneuropathy caused by Type 1 or Type 2 diabetes mellitus which was present for at least 6 months (pain had to begin in the feet with relatively symmetrical onset); minimum score of 4 on the 24-hour Average Pain Score (11-point Likert scale)	DSM-IV criteria for Axis I diagnosis of MDD, depression-partial remission, dysthymic disorder, generalized anxiety disorder, alcohol or eating disorders as determined by the Mini International Neuropsychiatric Interview (MINI); current or historical DSM-IV diagnosis of mania, bipolar disorder, or psychosis as determined by the MINI; pain that could not be clearly differentiated from, or conditions that might interfere with, the assessment of the DPNP, such as peripheral vascular disease (ischemic pain); neurological disorders unrelated to diabetic neuropathy (e.g. phantom limb pain from amputation); skin condition in the area of the neuropathy that could alter sensation; other painful conditions; history of substance abuse or dependence within the past year or had positive urine drug screen, or received treatment within last 30 days; had taken excluded medications within 7 days of baseline; received treatment with a MAOI or fluoxetine within 30 days of baseline, or used an opioid within 3 days of baseline
Gorson 1999 Efficacy quality: Fair	RCT Crossover	Painful diabetic neuropathy N=40 Mean Age (SD): 62 (10.9); Range: 43-82 Male: 77.5% Female: 22.5%	Gabapentin 900 mg N=19 Placebo N=21	Painful diabetic neuropathy and 1) diabetes for at least 6 months on a stable dosage of insulin or oral hypoglycemic agent, 2) distal symmetric sensorimotor neuropathy as shown by impaired pin prick, temperature, or vibration sensation in both feet and absent or reduced ankle reflexes, and 3) daily neuropathic pain in the acral extremities, of at least moderate severity, for over 3 months that interfered with daily activity or sleep.	Diabetes and chronic renal insufficiency, painful diabetic plexopathy, or lumbosacral polyradiculopathy, peripheral vascular disease, another painful condition, or other cause for neuropathy.

Evidence Table 7. Original report: Data abstraction of pregabalin, gabapentin, serotonin-norepinephrine reuptake inhibitors, and topical lidocaine (patch or gel)

Study	Patient-reported pain	Observer-reported pain	Functional capacity
Goldstein 2005 US Efficacy quality: Fair	Duloxetine 20 mg/d vs Duloxetine 60 mg/d vs Duloxetine 120 mg/d vs Placebo 24h worst pain score, 11-point Likert scale (0-10) Mean change from baseline: -2.78 (95% CI: -3.23, -2.33) vs -3.31 (p≤0.05; 95% CI: -3.78, -2.84) vs -3.72 (p≤0.001; 95% CI: -4.19, -3.25) vs -2.09 (95% CI: -2.56, -1.62) at 12 weeks 24-hour average pain score, 11-point Likert scale (0-10) Mean change from baseline: -2.36 (95% CI: -2.77, -1.95) vs -2.89 (95% CI: -3.32, -2.46) vs -3.24 (95% CI: -3.69, -2.79) vs -1.91 (95% CI: -2.34, -1.48) at 12 weeks Average pain severity, BPI Mean change from baseline: -2.25 (95% CI: -2.66, -1.84) vs -2.81 (p≤0.01; 95% CI: -3.22, -2.40) vs -3.07 at 12 weeks (p≤0.001; 95% CI: -3.50, -2.64) vs -2.04 (95% CI: -2.45, -1.63) at 12 weeks Improvement, PGI-Improvement Mean change from baseline: 2.68 (95% CI: 2.44, 2.92) vs 2.21 (p≤0.001; 95% CI: 1.97, 2.45) vs 2.24 (p≤0.01; 95% CI: 2.00, 2.48) vs 2.91 (95% CI: 2.67, 3.15) at 12 weeks Night pain score, 11-point Likert scale (0-10) Mean change from baseline: -2.48 (95% CI: -2.91, -2.05) vs -2.91 (p≤0.05; 95% CI: -3.36, -2.46) vs -3.45 (p≤0.001; 95% CI: -3.92, -2.98) vs -2.20 (95% CI: -2.65, -1.75) at 12 weeks Severity of pain, SF McGill Pain Questionnaire Mean change from baseline: -7.23 (p≤0.05; 95% CI: -8.54, -5.92) vs -8.25 (p≤0.001; 95% CI: -9.52, -6.98) vs -9.18 (p≤0.001; 95% CI: -10.43, -7.93) vs -5.39 (95% CI: -6.68, -4.10) at 12 weeks	Duloxetine 20 mg/d vs Duloxetine 60 mg/d vs Duloxetine 120 mg/d vs Placebo Severity, CGI-Severity Mean change from baseline: -1.28 (p≤0.05; 95% CI: -1.50, -1.06) vs -1.42 (p≤0.001; 95% CI: -1.66, -1.18) vs -1.70 (p≤0.001; 95% CI: -1.94, -1.46) vs -0.83 (95% CI: -1.07, -0.59) at 12 weeks	Duloxetine 20 mg/d vs Duloxetine 60 mg/d vs Duloxetine 120 mg/d vs Placebo Interference, BPI Interference- average of 7 questions) Mean change from baseline: -1.73 (95% CI: -2.06, -1.40) vs -2.33 (p≤0.01; 95% CI: -2.66, -2.00) vs -2.30 (p≤0.05; 95% CI: -2.65, -1.95) vs -1.73 (95% CI: -2.06, -1.40) at 12 weeks QOL, Euro QOL Mean change from baseline: 0.10 (95% CI: 0.06, 0.14) vs 0.13 (p≤0.05; 95% CI: 0.09, 0.17) vs 0.13 (p≤0.05; 95% CI: 0.09, 0.17) vs 0.08 (95% CI: 0.04, 0.12) at 12 weeks Quality of life, SF-36 bodily pain Mean change from baseline: 13.22 (95% CI: 9.48, 16.96) vs 18.00 (p≤0.01; 95% CI: 14.30, 21.70) vs 18.32 (p≤0.01; 95% CI: 14.64, 22.00) vs 0.32 (95% CI: 6.62, 14.02) at 12 weeks Quality of life, SF-36 Mental Health Mean change from baseline: 0.74 (95% CI: -2.55, 4.03) vs 2.99 (p<0.05; 95% CI: -0.24, 6.22) vs 5.14 (p<0.001; 95% CI: 1.96, 8.32) vs 2.63 (95% CI: -5.94, 0.68) at 12 weeks Quality of life, SF-36 physical Mean change from baseline: 3.67 (95% CI: 2.14, 5.20) vs 5.86 (95% CI: 4.35, 7.37) vs 5.85 (95% CI: 4.36, 7.34) vs 3.94 (95% CI: 2.43, 5.45) at 12 weeks
Gorson 1999 Efficacy quality: Fair	Gabapentin vs Placebo 24-hour average pain score, VAS (0-10) Mean score: 1.8 (95% CI, 1.58 to 2.02) vs 1.4 (95% CI, 1.27 to 1.53) at 6 weeks (p=0.42) Pain intensity, Present pain intensity (0-10) Mean score: 1.2 (95% CI, 1.02 to 1.38) vs 0.3 (95% CI, 0.09 to 0.51) at 6 weeks (p=0.20) Pain relief, Moderate or excellent vs none or mild % of patients: 89.5% vs 42.9% at 6 weeks (p=0.11) Pain, McGill Pain Questionnaire Mean score: 8.9 (95% CI, 7.87 to 9.93) vs 2.2 (95% CI, 1.26 to 3.14) at 6 weeks (p=0.03)	NR	NR

Evidence Table 7. Original report: Data abstraction of pregabalin, gabapentin, serotonin-norepinephrine reuptake inhibitors, and topical lidocaine (patch or gel)

Study	Other outcomes	Withdrawals/ Withdrawals due to AEs	Specific adverse events
Goldstein 2005 US Efficacy quality: Fair	Duloxetine 20 mg/d vs Duloxetine 60 mg/d vs Duloxetine 120 mg/d vs Placebo Depression, Beck Depression Inventory Mean change from baseline: -2.44 (95% CI: -3.38, -1.50) vs -2.71 (95% CI: -3.67, -1.75) vs -3.11 (p≤0.05; 95% CI: -4.09, -2.13) vs -1.74 (95% CI: -2.68, -0.80) at 12 weeks	Duloxetine 20 mg/d vs Duloxetine 60 mg/d vs Duloxetine 120 mg/d vs Placebo Total: 24 (20.87%) vs 28 (24.56%) vs 33 (29.2%) vs 28 (24.35%) AE: 5 (4.35%) vs 15 (13.16%) vs 22 (19.47%) vs 7 (6.09%)	Duloxetine 20 mg/d vs Duloxetine 60 mg/d vs Duloxetine 120 mg/d vs Placebo Anorexia: 2.6% (3/115) vs 2.6% (3/114) vs 8.0% (9/113) vs 0.9% (1/115) Appetite decreased: 2.6% (3/115) vs 2.6% (3/114) vs 12.4% (14/113) vs 0.0% (0/115) Constipation: 5.2% (6/115) vs 14.9% (17/114) vs 10.6% (12/113) vs 3.5% (4/115) Dizziness: 6.1% (7/115) vs 9.6% (11/114) vs 23.0% (26/113) vs 7.0% (8/115) Dry mouth: 5.2% (6/115) vs 7.0% (8/114) vs 15.0% (17/113) vs 6.1% (7/115) Nausea: 13.9% (16/115) vs 16.7% (19/114) vs 27.4% (31/113) vs 9.6% (11/115) Somnolence: 7.8% (9/115) vs 20.2% (23/114) vs 28.3% (32/113) vs 7.8% (9/115) Sweating increased: 6.1% (7/115) vs 3.5% (4/114) vs 8.8% (10/113) vs 2.6% (3/115) Weakness: 0.9% (1/115) vs 2.6% (3/114) vs 7.1% (8/113) vs 0.0% (0/115)
Gorson 1999 Efficacy quality: Fair	NR	NR	NR

Evidence Table 7. Original report: Data abstraction of pregabalin, gabapentin, serotonin-norepinephrine reuptake inhibitors, and topical lidocaine (patch or gel)

Study	Design	Type of pain/ Sample size and characteristics	Intervention	Eligibility	Exclusion
Hahn 2004 Germany Efficacy quality: Fair	RCT Parallel Multicenter	HIV-related neuropathic pain N=26 Mean Age (SD): 44-46; Range: 27-61 Male: 76.92% Female: 23.08%	Gabapentin 1200-2400 mg N=15 Placebo N=11	Symptoms of painful HIV-associated sensory neuropathy, diagnosed by a neurologist based on history, as well as clinical and neurophysiological examination, gave informed written consent, aged 18 years or over and completed a baseline pain diary over one week prior to randomization. HIV-associated sensory neuropathy was diagnosed according to the standard definition including sensory symptoms (paresthesia, dysesthesia, or pain), abnormal sensory signs (elevated vibratory threshold or pin hyperalgesia), decreased or absent ankle reflexes.	Pregnant or taking tricyclic or tetracyclic antidepressants, other anticonvulsants, topical capsaicin, mexiletine, alpha-lipoic acid, systemic corticosteroids or immune modulators, central analgesics or had received nerve blocks or acupuncture. Alternative causes for neuropathy (i.e., diabetes mellitus, alcohol and/or drug abuse, vitamin B12 deficiency), acute or chronic pancreatitis or chronic renal insufficiency and elevated parameters of lipase and/or amylase.
Lesser 2004 US Efficacy quality: Fair	RCT Parallel Multicenter	Painful diabetic neuropathy N=337 Mean Age: 59.9 (10.5); Range: 26-85 Male: 59.94% Female: 40.06% White: 94.4% Black: 3.6% Other: 2.1%	Pregabalin 75 mg N=77 Pregabalin 300 mg N=81 Pregabalin 600 mg N=82 Placebo N=97	Men and women 18 or older with a diagnosis of type 1 or type 2 diabetes mellitus and distal symmetric sensorimotor polyneuropathy for 1 to 5 years. Female patients were required to be nonpregnant, non-lactating, postmenopausal, or surgically sterilized; women at risk of pregnancy were required to be using an appropriate method of contraception. Antidiabetic medication was to be stabilized prior to initiation of the study and held constant throughout the study, provided adequate glucose control was maintained to ensure patient safety. Patients must have completed at least 4 daily pain diaries during the baseline phase, and had to have an average baseline daily pain score of ≥4 on a 0 to 10 scale. Score of ≥40mm on the VAS of the Short-Form McGill Pain Questionnaire at baseline and randomization visits.	HbA1c levels >11%, clinically significant or unstable hepatic, respiratory, or hematologic illnesses, unstable cardiovascular disease, or symptomatic peripheral vascular disease. Estimated creatinine clearance of ≤60 mL/minute; any conditions that might confound pain assessment (for example, other severe pain or a skin condition in the area affected by neuropathy), patients who had failed to respond to previous treatment with gabapentin at doses ≥1200 mg/day for treatment of pain associated with diabetic neuropathy.

Evidence Table 7. Original report: Data abstraction of pregabalin, gabapentin, serotonin-norepinephrine reuptake inhibitors, and topical lidocaine (patch or gel)

Study	Patient-reported pain	Observer-reported pain	Functional capacity
Hahn 2004 Germany Efficacy quality: Fair	Gabapentin vs Placebo Pain, VAS (0-10) % change from baseline: -44.1% vs -29.8% at 4 weeks (p=NS) Pain, VAS (0-10) Median score: 2.85 vs 3.3 at 4 weeks	NR	NR
Lesser 2004 US Efficacy quality: Fair	Pregabalin 75 mg vs Pregabalin 300 mg vs Pregabalin 600 mg vs Placebo Average pain intensity (0-10), SF-MPQ Present Pain Intensity (0-5) LS mean: 1.67 (p=0.4286; 95% CI: 1.45, 1.89) vs 1.20 (p=0.0001; 95% CI: 0.98, 1.42) vs 1.18 (p=0.0001; 95% CI: 0.96, 1.40) vs 1.79 (95% CI: 1.59, 1.99) at 5 weeks Average pain, SF-MPQ Total (0-45) LS mean: 15.06 (p=0.9966; 95% CI: 13.22, 16.90) vs 10.17 (p=0.0001; 95% CI: 8.37, 11.97) vs 9.88 (p=0.0001; 95% CI: 8.10, 11.66) vs 15.06 (95% CI: 13.41, 16.71) at 5 weeks Average pain, SF-MPQ VAS (0-40) LS mean: 49.70 (p=0.2947; 95% CI: 44.33, 55.07) vs 37.40 (p=0.0001; 95% CI: 32.13, 42.67) vs 34.48 (p=0.0001; 95% CI: 29.29, 39.67) vs 53.49 (95% CI: 48.67, 58.31) at 5 weeks Average pain, VAS (0-10) LS mean: 4.91 (p=0.6267; 95% CI: 4.44, 5.38) vs 3.80 (p=0.0001; 95% CI: 3.35, 4.25) vs 3.60 (p=0.0001; 95% CI: 3.15, 4.05) vs 5.06 (95% CI: 4.65, 5.47) at 5 weeks Global impression of improvement, "much improved" or "very much improved" % of patients: NR vs 55.7% (p=0.001) vs 69.2% (p=0.001) vs 24.2% at 5 weeks Response, ≥50% reduction in pain % of patients: NR vs 46% (p=NR(significant)) vs 48% (p=NR(significant)) vs 18% at 5 weeks	Pregabalin 75 mg vs Pregabalin 300 mg vs Pregabalin 600 mg vs Placebo Global impression of improvement, "much improved" or "very much improved" % of patients: NR vs 58.2% (p=0.001) vs 64.1% (p=0.001) vs 26.3% at 5 weeks	Pregabalin 75 mg vs Pregabalin 300 mg vs Pregabalin 600 mg vs Placebo QOL, SF-36 bodily pain: NR vs NR (p<0.005) vs NR (p<0.0005) vs NR at 5 weeks QOL, SF-36 vitality: data NR (p<0.05) vs NR (p<0.01) vs NR vs NR

Evidence Table 7. Original report: Data abstraction of pregabalin, gabapentin, serotonin-norepinephrine reuptake inhibitors, and topical lidocaine (patch or gel)

Study	Other outcomes	Withdrawals/ Withdrawals due to AEs	Specific adverse events
Hahn 2004 Germany Efficacy quality: Fair	Gabapentin vs Placebo Interference with sleep, VAS (0-10) % change from baseline: -48.9% vs -11.6% at 4 weeks (p=NS) Interference with sleep, VAS (0-10) Median score: 2.3 vs 4.95 at 4 weeks	Gabapentin vs Placebo Total: 2 (13.33%) vs 3 (27.27%) AE: 1 (6.67%) vs 0 (0%)	Gabapentin vs Placebo Dizziness: 60.0% (9/15) vs 45.5% (5/11) Gait abnormal: 46.7% (7/15) vs 27.3% (3/11) Headache: 6.7% (1/15) vs 9.1% (1/11) Nausea: 33.3% (5/15) vs 18.2% (2/11) Somnolence: 80.0% (12/15) vs 18.2% (2/11)
Lesser 2004 US Efficacy quality: Fair	Pregabalin 75 mg vs Pregabalin 300 mg vs Pregabalin 600 mg vs Placebo Interference with sleep, Sleep interference score Mean difference from placebo: NR vs 1.3 (p=0.0001) vs 1.6 (p=0.0001) vs NA at 5 weeks	Pregabalin 75 mg vs Pregabalin 300 mg vs Pregabalin 600 mg vs Placebo Total: 10 (12.99%) vs 5 (6.17%) vs 12 (14.63%) vs 8 (8.25%) AE: 2 (2.6%) vs 3 (3.7%) vs 10 (12.2%) vs 3 (3.09%)	Pregabalin 75 mg vs Pregabalin 300 mg vs Pregabalin 600 mg vs Placebo Accidental injury: 5.2% (4/77) vs 2.5% (2/81) vs 4.9% (4/82) vs 0.0% (0/97) Amblyopia: 2.6% (2/77) vs 4.9% (4/81) vs 8.5% (7/82) vs 1.0% (1/97) Amnesia: 2.6% (2/77) vs 0.0% (0/81) vs 6.1% (5/82) vs 1.0% (1/97) Asthenia: 3.9% (3/77) vs 4.9% (4/81) vs 7.3% (6/82) vs 3.1% (3/97) Ataxia: 6.5% (5/77) vs 3.7% (3/81) vs 8.5% (7/82) vs 2.1% (2/97) Confusion: 0.0% (0/77) vs 4.9% (4/81) vs 8.5% (7/82) vs 2.1% (2/97) Constipation: 0.0% (0/77) vs 3.7% (3/81) vs 8.5% (7/82) vs 1.0% (1/97) Diarrhea: 5.2% (4/77) vs 1.2% (1/81) vs 3.7% (3/82) vs 7.2% (7/97) Dizziness: 7.8% (6/77) vs 27.2% (22/81) vs 39.0% (32/82) vs 5.2% (5/97) Dry mouth: 2.6% (2/77) vs 7.4% (6/81) vs 4.9% (4/82) vs 0.0% (0/97) Edema, peripheral: 3.9% (3/77) vs 7.4% (6/81) vs 13.4% (11/82) vs 2.1% (2/97) Euphoria: 0.0% (0/77) vs 6.2% (5/81) vs 4.9% (4/82) vs 0.0% (0/97) Headache: 6.5% (5/77) vs 8.6% (7/81) vs 9.8% (8/82) vs 10.3% (10/97) Infection: 3.9% (3/77) vs 9.9% (8/81) vs 1.2% (1/82) vs 7.2% (7/97) Somnolence: 3.9% (3/77) vs 23.5% (19/81) vs 26.8% (22/82) vs 4.1% (4/97)

Evidence Table 7. Original report: Data abstraction of pregabalin, gabapentin, serotonin-norepinephrine reuptake inhibitors, and topical lidocaine (patch or gel)

Study	Design	Type of pain/ Sample size and characteristics	Intervention	Eligibility	Exclusion
Levendoglu 2004 Turkey Efficacy quality: Fair	RCT Crossover	Spinal cord injury-related pain N=20 Mean Age (SD): 35.9 (9.8) Male: 65% Female: 35%	Gabapentin 3600 mg N=20 Placebo N=20	Paraplegic patients with complete traumatic spinal cord injury at the thoracic and lumbar level, aged between 20 and 65 years, with neuropathic pain for more than 6 months confirmed by a physician.	Severe cognitive impairment, pregnancy, seizure disorder, use of anticonvulsants and antidepressants, major depression or a score above 16 on the Beck Depression Inventory, and hypersensitivity to gabapentin.
Meier 2003 Germany and Switzerland Efficacy quality: Poor	RCT Crossover Multicenter	Mixed N=58 Mean Age (SD): 63.4 (15.2) Male: 48.28% Female: 51.72%	Lidocaine transdermal patch 5% N=28 Placebo N=30	Outpatients suffering from chronic peripheral focal neuropathic pain syndromes, defined as damage to or dysfunction of the peripheral nervous system with positive spontaneous or evoked sensory signs with mechanical allodynia in the territories of peripheral nerves. Pain assessed by repetitive gentle movement of a cotton swab over the affected skin. Pain had to be superficial and localized to a limited skin zone. Over 21 years of age, average pain score above 40 on a 100 mm VAS. Patient's consumption of analgesic drugs, including antidepressants, had to be stable with no change in medication or dosage from 4 weeks before the beginning of the study.	Another form of pain with greater or similar intensity, previous nerve blockade or neurosurgery, or patients taking topical products for pain relief or with ascertained hypersensitivity to lidocaine or to amide-type anesthetics. Injuries, inflammation, or insufficient wound healing of the skin area to be treated; patients who were judged to be unreliable or unable to understand the protocol procedures.

Evidence Table 7. Original report: Data abstraction of pregabalin, gabapentin, serotonin-norepinephrine reuptake inhibitors, and topical lidocaine (patch or gel)

Study	Patient-reported pain	Observer-reported pain	Functional capacity
Levendoglu 2004 Turkey Efficacy quality: Fair	Gabapentin vs Placebo Pain intensity, Neuropathic Pain Scale (NPS) Pain intensity (0-10) Mean score at 4 weeks: 4.8 (95% CI: 4.32, 5.28) vs 7.8 (95% CI: 7.49, 8.11); (p=0.000) Mean score at 8 weeks: 3.2 (95% CI: 2.67, 3.73) vs 7.4 (95% CI: 7.09, 7.71); (p=0.000) Pain, NPS cold (0-10) Mean score at 4 weeks: 0.7 (95% CI: -0.13, 1.53) vs 0.9 (95% CI: -0.11, 1.91); (p=NS) Mean score at 8 weeks: 0.8 (95% CI: -0.03, 1.63) vs 0.8 (95% CI: -0.12, 1.72); (p=NS) Pain, NPS deep (0-10) Mean score at 4 weeks: 4.5 (95% CI: 3.71, 5.29) vs 6.3 (95% CI: 5.29, 7.31); (p=0.001) Mean score at 8 weeks: 3.5 (95% CI: 2.80, 4.20) vs 6.2 (95% CI: 5.19, 7.21); (p=0.000) Pain, NPS dull (0-10) Mean score at 4 weeks: 0.4 (95% CI: -0.13, 0.93) vs 0.6 (95% CI: -0.19, 1.39); (p=NS) Mean score at 8 weeks: 0.3 (95% CI: -0.23, 0.83) vs 0.6 (95% CI: -0.19, 1.39); (p=NS)	NR	NR
Meier 2003 Germany and Switzerland Efficacy quality: Poor	Lidocaine patch vs Placebo Allodynia, VAS (0-100) Mean change from baseline: Reported graphically only at 2 hours to 7 days Pain intensity, VAS (0-100) Mean change from baseline: Reported graphically only at 2 hours to 7 days	NR	NR

Evidence Table 7. Original report: Data abstraction of pregabalin, gabapentin, serotonin-norepinephrine reuptake inhibitors, and topical lidocaine (patch or gel)

Study	Other outcomes	Withdrawals/ Withdrawals due to AEs	Specific adverse events
Levendoglu 2004 Turkey Efficacy quality: Fair	NR	Gabapentin vs Placebo Total: 0 (0%) vs 0 (0%) AE: 0 (0%) vs 0 (0%)	Gabapentin vs Placebo Edema: 15.0% (3/20) vs 0.0% (0/20) Headache: 5.0% (1/20) vs 5.0% (1/20) Itching: 10.0% (2/20) vs 0.0% (0/20) Nausea: 0.0% (0/20) vs 5.0% (1/20) Somnolence: 15.0% (3/20) vs 0.0% (0/20) Vertigo: 15.0% (3/20) vs 5.0% (1/20) Vomiting: 0.0% (0/20) vs 5.0% (1/20) Weakness: 25.0% (5/20) vs 10.0% (2/20)
Meier 2003 Germany and Switzerland Efficacy quality: Poor	NR	NR	NR

Evidence Table 7. Original report: Data abstraction of pregabalin, gabapentin, serotonin-norepinephrine reuptake inhibitors, and topical lidocaine (patch or gel)

Study	Design	Type of pain/ Sample size and characteristics	Intervention	Eligibility	Exclusion
Raskin (B) 2005 and 2006 US Efficacy quality: Fair	RCT Parallel Multicenter	Painful diabetic neuropathy N=348 Mean Age (SD): 58.8 (10.1) Male: 46.55% Female: 53.45% White: 99.7% Asian: 0.3%	Duloxetine 60 mg once daily Total daily dose: 60 mg N=116 Duloxetine 60 mg twice daily Total daily dose: 120 mg N=116 Placebo N=116	Age 18 or older, presented with pain due to bilateral peripheral neuropathy caused by type 1 or type 2 diabetes. Pain had to begin in the feet and with relatively symmetrical onset.; Daily pain must have been present for at least 6 months, and diagnosis was to be confirmed by a score of at least 3 on the Michigan Neuropathy Screening Instrument. Mean score of 4 or greater when assessed for 24-hour average pain severity on the 11-point Likert scale from patient diary prior to randomization, and stable glycemic control.	Pregnant or breastfeeding, prior renal transplant or current renal dialysis, or a serious or unstable illness, symptomatic peripheral vascular disease, or other medical condition or psychological conditions that might compromise participation in the study. Current (within 1 year) DSM-IV Axis I diagnosis of major depressive disorder, dysthymia, generalized anxiety disorder, alcohol, or eating disorders, or diagnosis or previous diagnosis of mania, bipolar disorder, or psychosis. Historical exposure to drugs known to cause neuropathy, history of substance abuse or dependence within previous year, positive urine drug screen for any substances of abuse or excluded medication, or history of a medical condition including pernicious anemia and hypothyroidism that could have been responsible for neuropathy, and treatment with a MAO inhibitor or fluoxetine within 30 days of randomization. Severe allergic reactions to multiple medications, and prior participation in a study of duloxetine.
Rice 2001 UK Efficacy quality: Fair	RCT Parallel Multicenter	Post-herpetic neuralgia N=334 Mean Age (SD): 75.3; Range: 22.5-94.8 Male: 41.32% Female: 58.68%	Gabapentin 1800 mg N=115 Gabapentin 2400 mg N=108 Placebo N=111	Men and women aged at least 18 years, of any race. Nonpregnant (using barrier or hormonal contraception where appropriate), non-lactating, postmenopausal or surgically sterilized. Pain had to have been present for more than 3 months after the healing of the acute herpes zoster skin rash. Average pain scores of 4 or more, based on an 11-point Likert scale, on the week before commencing study medication.	Failure to respond to previous treatment with gabapentin at ≥1200 mg/day, failure to respond to gabapentin at any dose level due to side effects or contraindication to gabapentin treatment.

Evidence Table 7. Original report: Data abstraction of pregabalin, gabapentin, serotonin-norepinephrine reuptake inhibitors, and topical lidocaine (patch or gel)

Study	Patient-reported pain	Observer-reported pain	Functional capacity
Raskin (B) 2005 and 2006 US Efficacy quality: Fair	Duloxetine 60 mg/d vs Duloxetine 120 mg/d vs Placebo 24-hour average pain score, 11-point Likert scale Mean change from baseline: -2.50 (p≤0.001; 95% CI: -2.85, -2.15) vs -2.47 (p≤0.001; 95% CI: -2.82, -2.12) vs -1.60 (95% CI: -1.95, -1.25) at 12 weeks 24-hour worst pain score, Likert scale Mean change from baseline: -2.97 (p≤0.001; 95% CI: -3.36, -2.58) vs -2.84 (p≤0.01; 95% CI: -3.23, -2.45) vs -2.03 (95% CI: -2.42, -1.64) at 12 weeks Average pain, BPI Mean change from baseline: -2.65 (p≤0.01; 95% CI: -3.02, -2.28) vs -2.62 (p≤0.01; 95% CI: -2.99, -2.25) vs -1.82 (95% CI: -2.19, -1.45) at 12 weeks Average pain, SF-McGill Pain Questionnaire Mean change from baseline: -7.47 (p≤0.01; 95% CI: -8.67, -6.27) vs -7.82 (p≤0.001; 95% CI: -9.02, -6.62) vs -4.96 (95% CI: -6.14, -3.78) at 12 weeks Improvement, PGI-Improvement Mean change from baseline: 2.50 (p≤0.001; 95% CI: 2.30, 2.70) vs 2.54 (p≤0.001; 95% CI: 2.34, 2.74) vs 3.04 (95% CI: 2.84, 3.24) at 12 weeks Night pain score, Likert scale Mean change from baseline: -2.81 (p≤0.001; 95% CI: -3.18, -2.44) vs -2.78 (p≤0.001; 95% CI: -3.15, -2.41) vs -1.87 (95% CI: -2.24, -1.50) at 12 weeks	Duloxetine 60 mg/d vs Duloxetine 120 mg/d vs Placebo Severity, CGI-Severity Mean change from baseline: -1.42 (p≤0.001; 95% CI: -1.60, -1.24) vs -1.40 (p≤0.001; 95% CI: -1.60, -1.20) vs -0.93 (95% CI: -1.11, -0.75) at 12 weeks	Duloxetine 60 mg/d vs Duloxetine 120 mg/d vs Placebo Interference, BPI Interference (average of 7 questions) Mean change from baseline: -2.43 (p≤0.001; 95% CI: -2.78, -2.08) vs -2.54 (p≤0.001; 95% CI: -2.89, -2.19) vs -1.56 (95% CI: -1.91, -1.21) at 12 weeks
Rice 2001 UK Efficacy quality: Fair	Gabapentin 1800 mg vs Gabapentin 2400 mg vs Placebo 24-hour average pain score, Likert scale (0-10) Mean score: 4.3 (p<0.01) vs 4.2 (p<0.01) vs 5.3 at 7 weeks Improvement, Very much or much improved % of patients: 41% (p=0.003) vs 43% (p=0.005) vs 23% at 7 weeks Pain intensity, SF McGill Pain Present pain intensity (0-5) Mean score: 1.9 (95% CI: 1.70, 2.10) vs 1.9 (95% CI: 1.67, 2.13) vs 2.0 (95% CI: 1.76, 2.24) at 7 weeks Pain relief, 50% or greater reduction in mean pain score % of patients: 32% (p=0.001) vs 34% (p=0.001) vs 14% at 7 weeks Pain, SF McGill Pain Score Total (0-45) Mean score: 11.9 (95% CI: 10.29, 13.51; p<0.05) vs 12.5 (95% CI: 10.93, 14.07; p<0.05) vs 3.7 (95% CI: 11.93, 15.47) at 7 weeks Pain, SF McGill Pain VAS (0-100) Mean score: 47 (95% CI: 41.88, 52.12) vs 46 (95% CI: 41.28, 50.72; p<0.05) vs 54 (95% CI: 49.16, 58.84) at 7 weeks	Gabapentin 1800 mg vs Gabapentin 2400 mg vs Placebo Global impression of improvement, Very much or much improved % of patients: 44% (p=0.002) vs 44% (p=0.001) vs 19% at 7 weeks	QOL: Reported graphically only at 7 weeks

Evidence Table 7. Original report: Data abstraction of pregabalin, gabapentin, serotonin-norepinephrine reuptake inhibitors, and topical lidocaine (patch or gel)

Study	Other outcomes	Withdrawals/ Withdrawals due to AEs	Specific adverse events
Raskin (B) 2005 and 2006 US Efficacy quality: Fair	Duloxetine 60 mg/d vs Duloxetine 120 mg/d vs Placebo Depression, HAM-D Mean change from baseline: -1.17 (95% CI: -1.66, -0.68) vs -0.65 (95% CI: -1.14, -0.16) vs -0.55 (95% CI: -1.04, -0.06) at 12 weeks	Duloxetine 60 mg/d vs Duloxetine 120 mg/d vs Placebo Total: 15 (12.93%) vs 21 (18.1%) vs 16 (13.79%) AE: 5 (4.31%) vs 14 (12.07%) vs 3 (2.59%)	Duloxetine 60 mg/d vs Duloxetine 120 mg/d vs Placebo Any adverse event: 61.2% (71/116) vs 62.9% (73/116) vs 49.1% (57/116) Serious AEs: 3.4% (4/116) vs 1.7% (2/116) vs 3.4% (4/116)
Rice 2001 UK Efficacy quality: Fair	Gabapentin 1800 mg vs Gabapentin 2400 mg vs Placebo Interference with sleep, Likert scale (0-10) Difference from placebo: 0.9 (p<0.01; 95% CI: 0.4-1.4) vs 1.1 (p<0.01; 95% CI: 0.7-1.6) vs NA at 7 weeks	Gabapentin 1800 mg vs Gabapentin 2400 mg vs Placebo Total: 22 (19.13%) vs 23 (21.3%) vs 17 (15.32%) AE: 15 (13.04%) vs 19 (17.59%) vs 7 (6.31%)	Gabapentin 1800 mg vs Gabapentin 2400 mg vs Placebo Any adverse event: 70.4% (81/115) vs 75.0% (81/108) vs 49.5% (55/111) Serious AEs: 2.6% (3/115) vs 0.9% (1/108) vs 0.9% (1/111) Asthenia: 6.1% (7/115) vs 5.6% (6/108) vs 3.6% (4/111) Diarrhea: 6.1% (7/115) vs 4.6% (5/108) vs 0.9% (1/111) Dizziness: 31.3% (36/115) vs 33.3% (36/108) vs 9.9% (11/111) Dry mouth: 6.1% (7/115) vs 4.6% (5/108) vs 0.9% (1/111) Edema, peripheral: 5.2% (6/115) vs 11.1% (12/108) vs 0.0% (0/111) Somnolence: 17.4% (20/115) vs 20.4% (22/108) vs 6.3% (7/111)

Evidence Table 7. Original report: Data abstraction of pregabalin, gabapentin, serotonin-norepinephrine reuptake inhibitors, and topical lidocaine (patch or gel)

Study	Design	Type of pain/ Sample size and characteristics	Intervention	Eligibility	Exclusion
Richter 2005 US Efficacy quality: Fair	RCT Parallel Multicenter	Painful diabetic neuropathy N=246 Mean Age (SD): 57.1 Male: 60.57% Female: 39.43% White: 83.7% Black: 7.7% Hispanic: 7.3% Other: 1.2%	Pregabalin 150 mg N=79 Pregabalin 600 mg N=82 Placebo N=85	Diabetes and painful distal symmetrical sensorimotor polyneuropathy for 1 to 5 years. Neuropathy was confirmed by history and detailed neurologic examination. Age ≥18 years, HbA1c levels ≤11%, and the ongoing experience of moderate to severe pain. Poorly controlled pain, including a score of ≥40 mm on the VAS of the Short Form-McGill Pain Questionnaire and an average daily pain score of ≥4 for 4 or more days during baseline (1 week).	Neurologic disorders unrelated to diabetic neuropathy, any condition that could confound study assessments, recent treatment with any investigational drug, or serious medical problems. Women could not be lactating and were required to have a negative pregnancy test result and to use appropriate contraception if of childbearing potential.

Evidence Table 7. Original report: Data abstraction of pregabalin, gabapentin, serotonin-norepinephrine reuptake inhibitors, and topical lidocaine (patch or gel)

Study	Patient-reported pain	Observer-reported pain	Functional capacity
Richter 2005 US Efficacy quality: Fair	Pregabalin 150 mg vs Pregabalin 600 mg vs Placebo Average pain intensity (0-10), SF-MPQ Present Pain Intensity (0-5) LS mean: 1.78 (p=0.2836; 95% CI: 1.54, 2.02) vs 1.30 (p=0.0002; 95% CI: 1.06, 1.54) vs 1.96 (95% CI: 1.74, 2.18) at 6 weeks Average pain, 11-point numeric rating scale (0-10) LS mean: 5.11 (p=0.1763; 95% CI: 4.64, 5.58) vs 4.29 (p=0.0002; 95% CI: 3.78, 4.80) vs 5.55 (95% CI: 5.10, 6.00) at 6 weeks Average pain, SF-MPQ Total LS mean: 15.48 (p=0.0651; 95% CI: 13.54, 17.42) vs 12.14 (p=0.0002; 95% CI: 10.24, 14.04) vs 17.97 (95% CI: 16.09, 19.85) at 6 weeks Average pain, SF-MPQ VAS (100 mm) LS mean: 53.27 (p=0.2058; 95% CI: 47.88, 58.66) vs 43.38 (p=0.0002; 95% CI: 38.09, 48.67) vs 58.05 (95% CI: 52.80, 63.30) at 6 weeks Global impression of change, "much improved" or "very much improved" % of patients (reported graphically only at 6 weeks): p=NS vs p=0.002 vs p=NS	Pregabalin 150 mg vs Pregabalin 600 mg vs Placebo Global impression of change, "much improved" or "very much improved" % of patients (reported graphically only at 6 weeks): p=NS vs p=0.002 vs p=NS	Pregabalin 150 mg vs Pregabalin 600 mg vs Placebo QOL, SF-36 Bodily Pain LS mean: NR (p<0.016) vs NR (p<0.016) vs NR (p=NS) at 6 weeks QOL, SF-36 Other domains LS mean: NR (p=NS) vs NR (p=NS) vs NR (p=NS)

Evidence Table 7. Original report: Data abstraction of pregabalin, gabapentin, serotonin-norepinephrine reuptake inhibitors, and topical lidocaine (patch or gel)

Study	Other outcomes	Withdrawals/ Withdrawals due to AEs	Specific adverse events
Richter 2005 US Efficacy quality: Fair	Pregabalin 150 mg vs Pregabalin 600 mg vs Placebo Interference with sleep, 11-point numeric rating scale (0-10) LS mean difference: NR (p=NS) vs -1.152 (p=0.0004; 95% CI: -1.752 to -0.551) vs NR	Pregabalin 150 mg vs Pregabalin 600 mg vs Placebo Total: 4 (5.06%) vs 10 (12.2%) vs 13 (15.29%) AE: 2 (2.53%) vs 7 (8.54%) vs 4 (4.71%)	Pregabalin 150 mg vs Pregabalin 600 mg vs Placebo Accidental injury: 2.5% (2/79) vs 9.8% (8/82) vs 5.9% (5/85) Amblyopia: 2.5% (2/79) vs 8.5% (7/82) vs 5.9% (5/85) Asthenia: 3.8% (3/79) vs 12.2% (10/82) vs 3.5% (3/85) Constipation: 3.8% (3/79) vs 6.1% (5/82) vs 4.7% (4/85) Diarrhea: 5.1% (4/79) vs 2.4% (2/82) vs 3.5% (3/85) Dizziness: 10.1% (8/79) vs 37.8% (31/82) vs 2.4% (2/85) Dry mouth: 0.0% (0/79) vs 8.5% (7/82) vs 2.4% (2/85) Edema, peripheral: 3.8% (3/79) vs 17.1% (14/82) vs 4.7% (4/85) Headache: 7.6% (6/79) vs 15.9% (13/82) vs 10.6% (9/85) Infection: 12.7% (10/79) vs 6.1% (5/82) vs 9.4% (8/85) Somnolence: 5.1% (4/79) vs 22.0% (18/82) vs 3.5% (3/85) Weight gain: 1.3% (1/79) vs 9.8% (8/82) vs 0.0% (0/85)

Evidence Table 7. Original report: Data abstraction of pregabalin, gabapentin, serotonin-norepinephrine reuptake inhibitors, and topical lidocaine (patch or gel)

Study	Design	Type of pain/ Sample size and characteristics	Intervention	Eligibility	Exclusion
Rosenstock 2004 US Efficacy quality: Fair	RCT Parallel Multicenter	Painful diabetic neuropathy N=146 Mean Age: 59.7 (11.4) Male: 56.16% Female: 43.84% White: 87.7% Black: 6.2% Other: 6.2%	Pregabalin 300 mg N=76 Placebo N=70	Male or female patients of at least 18 years of age with type 1 or 2 diabetes mellitus who reported symmetrical painful symptoms in distal extremities for a period of 1-5 years prior to the study, and whose symptoms were attributable to sensorimotor diabetic peripheral neuropathy; a score of at least 40 mm on the 100-mm VAS of the Short-Form McGill Pain Questionnaire at baseline and randomization visits; completion of daily diaries (a minimum of four) during the week preceding randomization; and a minimum average daily pain score of 4 on an 11-point numerical pain rating scale during the baseline period. Female patients had to have a confirmed negative serum pregnancy test at baseline and practice appropriate methods of contraception throughout the study period; normal chest x-ray within the preceding 2 years and HbA1c levels ≤11% at baseline.	Pregnancy or lactation; serious or unstable medical conditions, including psychiatric disorders, certain conditions that cold confound evaluation of painful diabetic peripheral neuropathy, in particular, amputations other than toes, non-diabetic neurologic disorders and skin conditions affecting sensation in painful limbs. Baseline serum creatinine clearance ≤60 ml.min, or if baseline WBC count was <2500/mm3, neutrophil count was <1500/mm3, or platelet count was <100 x 103/mm3. Failure to respond to previous treatment with gabapentin at doses of ≥1200 mg/day for pain associated with diabetic peripheral neuropathy. Participation in any other clinical trial for an investigational drug within 30 days prior to screening.
Rowbotham (A) 1996 US Efficacy quality: Fair	RCT Crossover Single Center	Post-herpetic neuralgia N=35 Mean Age (SD): 75; Range: 50-90 Male: 57.14% Female: 42.86%	Lidocaine transdermal patch 5%; up to 3 patches to cover area N=40 Placebo N=35	Postherpetic neuralgia, defined as pain present more than 1 month after healing of the skin rash, and had a well-defined area of painfully sensitive (allodynic) skin on the torso or limbs; in stable health.	Medical contraindications to topical local anesthetic application, neurolytic or neurosurgical therapy for postherpetic neuralgia.
Rowbotham (B) 2004 US Efficacy quality: Fair	RCT Parallel Multicenter	Painful diabetic neuropathy N=244 Mean Age (SD): 59.0 Male: 59.43% Female: 40.57%	Venlafaxine 75 mg daily N=81 Venlafaxine 150-225 mg daily N=82 Placebo N=81	18 years or older with metabolically stable type 1 or 2 diabetes, with symptomatic peripheral neuropathy due only to diabetes and daily pain consistent with bilateral distal peripheral neuropathy of at least moderate severity for 3 months or longer. At screening and during the baseline period, patients had to have a score of more than 40 mm on the VAS-Pain Intensity (100-mm line scale, 0-100 mm).	Clinically significant psychiatric disorders or a history of recent drug or alcohol abuse, as defined by the DSM-IV; major depressive disorder within 6 months of study initiation; pre-study or baseline score of 13 or greater on the patient-rated Beck Depression Inventory; total score greater than 9 (or greater than 3 on any single item) on the clinician-administered Raskin Depression Scale; history of seizure disorders; clinically significant cardio vascular, renal or hepatic disease; or clinically significant abnormalities in physical examination results, vital signs, ECG , or laboratory test results at the pre-study evaluations. Use of investigational drugs or procedures, antipsychotics or ECT within 30 days of study initiation; and use of any anxiolytic, sedative hypnotic, anticonvulsant, or any other psychotropic drugs or capsaicin products 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 double-blind treatment were also excluded.

Evidence Table 7. Original report: Data abstraction of pregabalin, gabapentin, serotonin-norepinephrine reuptake inhibitors, and topical lidocaine (patch or gel)

Study	Patient-reported pain	Observer-reported pain	Functional capacity
Rosenstock 2004 US Efficacy quality: Fair	Pregabalin vs Placebo Average pain intensity (0-10), SF-MPQ Present Pain Intensify (0-5) LS mean: 1.42 (95% CI: 1.17, 1.67) vs 1.79 (95% CI: 1.54, 2.04) at 8 weeks (p=0.0364) Average pain, 11-point numeric rating scale (0-10) LS mean: 3.99 (95% CI: 3.48, 4.50) vs 5.46 (95% CI: 4.91, 6.01) at 8 weeks (p=0.0001) Average pain, SF-MPQ Total score LS mean: 10.51 (95% CI: 8.43, 12.59) vs 14.92 (95% CI: 12.71, 17.13) at 8 weeks (p=0.0033) Average pain, SF-MPQ VAS (100 mm) LS mean: 40.83 (95% CI: 34.87, 46.79) vs 57.02 (95% CI: 50.73, 63.31) at 8 weeks (p=0.0002) Global Impression of Change, Improved (items not specified) % of patients: 64.5% vs 38.6% at 8 weeks (p=0.001)	Pregabalin vs Placebo Global impression of change, Improved (items not specified) % of patients: 59.2% vs 38.6% at 8 weeks (p=0.004)	Pregabalin vs Placebo QOL, SF-36 Bodily Pain LS mean: 53.83 (95% CI: 49.44, 58.22) vs 46.96 (95% CI: 42.31, 51.61) at 8 weeks (p=0.0294) QOL, SF-36 Mental Health LS mean: 75.82 (95% CI: 72.10, 79.54) vs 72.36 (95% CI: 68.50, 76.22) at 8 weeks (p=0.1893) QOL, SF-36 Vitality LS mean: 46.82 (95% CI: 42.98, 50.66) vs 43.57 (95% CI: 39.55, 47.59) at 8 weeks (p=0.2343)
Rowbotham (A) 1996 US Efficacy quality: Fair	Lidocaine patch vs Placebo Pain intensity, VAS (0-100) Mean change from baseline: 10.2 mm (p≤0.001-p=0.038) vs reported graphically only at 30 min, 1, 2, 4, 6, 9, 12 hours Pain relief, Category scale (0-4; 0=worse, 4= "a lot" Mean score: 2.17 (p=0.033) vs reported graphically only at 30 min, 1, 2, 4, 6, 9, 12 hours	NR	NR
Rowbotham (B) 2004 US Efficacy quality: Fair	Venlafaxine 75 mg vs Venlafaxine 150-225 mg vs Placebo Pain intensity, VAS (0-100) Mean change from baseline (adjusted): 22.4 vs 33.8 (p<0.001) vs 18.7 at 6 weeks Pain relief, Global pain relief (0-5) Mean score: 2.8 vs 3.3 (p<0.01) vs 2.7 at 6 weeks Pain relief, VAS (0-100) Mean change from baseline (adjusted): 51.0 vs 59.9 (p<0.001) vs 43.6 at 6 weeks	Venlafaxine 75 mg vs Venlafaxine 150-225 mg vs Placebo Global impression of improvement, CGI-Improvement (1-7) Mean score: 2.5 vs 2.1 (p<0.001) vs 2.8 at 6 weeks Severity, CGI-Severity (1-7) Mean score: 3.2 vs 2.8 (p<0.001) vs 3.5 at 6 weeks	NR

Evidence Table 7. Original report: Data abstraction of pregabalin, gabapentin, serotonin-norepinephrine reuptake inhibitors, and topical lidocaine (patch or gel)

Study	Other outcomes	Withdrawals/ Withdrawals due to AEs	Specific adverse events
Rosenstock 2004 US Efficacy quality: Fair	Pregabalin vs Placebo Interference with sleep, 11-pont scale (0-10) LS mean: 2.78 (95% CI: 2.25, 3.31) vs 4.32 (95% CI: 3.75, 4.89) at 8 weeks (p=0.0001)	Pregabalin vs Placebo Total: 11 (14.47%) vs 8 (11.43%) AE: 8 (10.53%) vs 2 (2.86%)	Pregabalin vs Placebo Accidental injury: 3.9% (3/76) vs 5.7% (4/70) Amblyopia: 5.3% (4/76) vs 1.4% (1/70) Asthenia: 3.9% (3/76) vs 2.9% (2/70) Constipation: 5.3% (4/76) vs 0.0% (0/70) Diarrhea: 3.9% (3/76) vs 2.9% (2/70) Dizziness: 35.5% (27/76) vs 11.4% (8/70) Edema, peripheral: 10.5% (8/76) 1.4% (1/70) Euphoria: 5.3% (4/76) vs 0.0% (0/70) Flatulence: 3.9% (3/76) vs 1.4% (1/70) Flu syndrome: 3.9% (3/76) vs 4.3% (3/70) Headache: 6.6% (5/76) vs 10.0% (7/70) Hyperglycemia: 3.9% (3/76) vs 0.0% (0/70) Infection: 14.5% (11/76) vs 5.7% (4/70) Nausea: 7.9% (6/76) vs 8.6% (6/70) Somnolence: 19.7% (15/76) vs 2.9% (2/70) Vomiting: 3.9% (3/76) vs 1.4% (1/70)
Rowbotham (A) 1996 US Efficacy quality: Fair	NR	NR	NR
Rowbotham (B) 2004 US Efficacy quality: Fair	NR	Venlafaxine 75 mg vs Venlafaxine 150-225 mg vs Placebo Total: 12 (14.81%) vs 18 (21.95%) vs 12 (14.81%) AE: 6 (7.41%) vs 8 (9.76%) vs 3 (3.7%)	Venlafaxine 75 mg vs Venlafaxine 150-225 mg vs Placebo Anorexia: 8.6% (7/81) vs 6.1% (5/82) vs 3.7% (3/81) Dyspepsia: 11.1% (9/81) vs 12.2% (10/82) vs 1.2% (1/81) Flatulence: 1.2% (1/81) vs 7.3% (6/82) vs 3.7% (3/81) Impotence (men only): 10.9% (6/55) vs 11.9% (5/42) vs 0.0% (0/48) Insomnia: 6.2% (5/81) vs 12.2% (10/82) vs 4.9% (4/81) Myalgia: 6.2% (5/81) vs 7.3% (6/82) vs 0.0% (0/81) Nausea: 27.2% (22/81) vs 12.2% (10/82) vs 6.2% (5/81) Sinusitis: 3.7% (3/81) vs 8.5% (7/82) vs 3.7% (3/81) Somnolence: 17.3% (14/81) vs 18.3% (15/82) vs 1.2% (1/81) Sweating increased: 6.2% (5/81) vs 12.2% (10/82) vs 4.9% (4/81) Vomiting: 7.4% (6/81) vs 6.1% (5/82) vs 0.0% (0/81)

Evidence Table 7. Original report: Data abstraction of pregabalin, gabapentin, serotonin-norepinephrine reuptake inhibitors, and topical lidocaine (patch or gel)

Study	Design	Type of pain/ Sample size and characteristics	Intervention	Eligibility	Exclusion
Rowbotham (C) 1998 US Efficacy quality: Fair	RCT Parallel Multicenter	Post-herpetic neuralgia N=225 Mean Age (SD): 74; Range: 39-90 Male: 52.44% Female: 47.56% White: 91% Other: 9%	Gabapentin 3600 mg N=113 Placebo N=116	At least 18 years of age, pain present for more than 3 months after healing of a herpes zoster skin rash; a pain intensity score of at least 40 mm on the 100-mm VAS on the Short-Form McGill Pain Questionnaire at screening and randomization; average daily diary pain score of at least 4 (on a scale of 0-10) during the baseline week, and discontinuance of muscle relaxants, anticonvulsants, mexiletine, topical analgesics, and antiviral agents beginning at least 2 weeks prior to screening	Prior treatment with gabapentin or demonstrated hypersensitivity to the drug or its ingredients, neurolytic or neurosurgical therapy for postherpetic neuralgia, immunocompromised state, significant hepatic or renal insufficiency, significant hematological disease, severe pain other than that caused by postherpetic neuralgia, 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, and any serious or unstable medical or psychological condition.
Sabatowski 2004 Multiple European and Australia Efficacy quality: Fair	RCT Parallel Multicenter	Post-herpetic neuralgia N=238 Mean Age (SD): 72.1; Range: 32-96 Male: 44.96% Female: 55.04% White: 99.2% Black: 0.8%	Pregabalin 150 mg N=81 Pregabalin 300 mg N=76 Placebo N=81	Age 18 years or older, pain present for more than 6 months after healing of herpes zoster rash. Female patients required to be non-pregnant, non-lactating and either postmenopausal, surgically sterilized, or using an appropriate method of contraception. Needed to have completed at least 4 daily pain diaries during the 7 day baseline phase, with an average daily pain score ≥4. Score ≥40 mm on the 100 mm VAS of the Short-Form McGill Pain Questionnaire at baseline and randomization visits.	Active malignancy or any clinically significant respiratory, hematologic, hepatic, or cardiovascular disease. Failure to respond to previous treatment for postherpetic neuralgia with gabapentin at doses ≥1200 mg/day or if they had undergone neurolytic or neurosurgical therapy for postherpetic neuralgia. Skin condition or severe non-postherpetic neuralgia pain that might compromise evaluation of pain caused by postherpetic neuralgia. Creatinine clearance ≤30 ml.min.

Evidence Table 7. Original report: Data abstraction of pregabalin, gabapentin, serotonin-norepinephrine reuptake inhibitors, and topical lidocaine (patch or gel)

Study	Patient-reported pain	Observer-reported pain	Functional capacity
Rowbotham (C) 1998 US Efficacy quality: Fair	Gabapentin vs Placebo Average daily pain, Likert scale (0-10) Mean score: 4.2 (95% CI: 3.78, 4.62) vs 6.0 (95% CI: 5.56, 6.44) at 8 weeks (p<0.001) Global Impression of Change, Moderately or much improved % of patients: 43.2% vs 12.1% at 8 weeks (p=NR) Pain, SF McGill Pain Questionnaire Total Mean score: 11.4 (95% CI: 9.69, 13.11) vs 16.8 (95% CI: 14.83, 18.77) at 8 weeks (p<0.001)	Gabapentin vs Placebo Global impression of improvement, Moderately or much improved % of patients: 39.5% vs 12.9% at 8 weeks	Gabapentin vs Placebo QOL, SF-36 Bodily pain, Mean score: 57.4 (p<0.001; 95% CI: 53.77, 61.03) vs 47.3 (95% CI: 43.61, 50.99) at 8 weeks QOL, SF-36 General health, Mean score: 63.1 (p=0.65; 95% CI: 59.04, 67.16) vs 64.3 (95% CI: 60.15, 68.45) at 8 weeks QOL, SF-36 Mental health, Mean score: 74.6 (p<0.001; 95% CI: 71.54, 77.66) vs 69.9 (95% CI: 66.15, 73.65) at 8 weeks QOL, SF-36 Physical functioning, Mean score: 66.2 (p=0.01; 95% CI: 61.70, 70.70) vs 57.5 (95% CI: 52.04, 62.96) at 8 weeks QOL, SF-36 Vitality, Mean score: 55.1 (p<0.001; 95% CI: 51.36, 58.84) vs 43.7 (95% CI: 39.73, 47.67) at 8 weeks
Sabatowski 2004 Multiple European and Australia Efficacy quality: Fair	Pregabalin 150 mg vs Pregabalin 300 mg vs Placebo Average pain, 11-point numeric scale (0-10) LS mean: 5.14 (p=0.0002; 95% CI: 4.71, 5.57) vs 4.76 (p=0.0001; 95% CI: 4.31, 5.21) vs 6.33 (95% CI: 5.90, 6.76) at 8 weeks Average pain, SF-MPQ VAS (100 mm) LS mean: 52.03 (p=0.0060; 95% CI: 47.01, 57.05) vs 48.41 (p=0.0003; 95% CI: 43.26, 53.56) vs 62.05 (95% CI: 57.03, 67.07) at 8 weeks Global Impression of Change, "much improved" or "very much improved" % of patients: 31% (p=0.064) vs 40% (p=0.002) vs 14% at 8 weeks Response, ≥50% reduction in pain % of patients: 26% (p=0.006) vs 28% (p=0.003) vs 10% at 8 weeks	NR	Pregabalin 150 mg vs Pregabalin 300 mg vs Placebo QOL, SF-36 Bodily Pain LS mean difference from placebo: NR vs 9.58 (p=0.005) vs NA at 8 weeks QOL, SF-36 Mental Health LS mean difference from placebo: 5.72 (p=0.043) vs 6.05 (p=0.043) vs NA at 8 weeks QOL, SF-36 Physical Functioning LS mean difference from placebo: NR at 8 weeks QOL, SF-36 Vitality LS mean difference from placebo: NR vs 7.11 (p=0.044) vs NA at 8 weeks

Evidence Table 7. Original report: Data abstraction of pregabalin, gabapentin, serotonin-norepinephrine reuptake inhibitors, and topical lidocaine (patch or gel)

Study	Other outcomes	Withdrawals/ Withdrawals due to AEs	Specific adverse events
Rowbotham (C) 1998 US Efficacy quality: Fair	Gabapentin vs Placebo Average daily sleep rating score, Likert scale (0-10) Mean score: 2.4 (p<0.001; 95% CI: 1.94, 2.86) vs 3.6 (95% CI: 3.05, 4.15) at 8 weeks	Gabapentin vs Placebo Total: 24 (21.24%) vs 21 (18.1%) AE: 21 (18.58%) vs 14 (12.07%)	Gabapentin vs Placebo Any adverse event: 54.9% (62/113) vs 27.6% (32/116) Ataxia: 7.1% (8/113) vs 0.0% (0/116) Dizziness: 23.9% (27/113) vs 5.2% (6/116) Edema, peripheral: 9.7% (11/113) vs 3.4% (4/116) Infection: 8.0% (9/113) vs 2.6% (3/116) Somnolence: 27.4% (31/113) vs 5.2% (6/116)
Sabatowski 2004 Multiple European and Australia Efficacy quality: Fair	Pregabalin 150 mg vs Pregabalin 300 mg vs Placebo Depression, Zung Self-Rating Depression Scale LS mean: 47.66 (p=0.0560(adjusted); 95% CI: 45.50, 49.82) vs 46.62 (p0.024(adjusted); 95% CI: 44.41, 48.83) vs 50.64 (95% CI: 48.48, 52.80) at 8 weeks Interference with sleep, Sleep interference score LS mean: 3.13 (p=0.0003; 95% CI: 2.72, 3.54) vs 2.81 (p=0.0001; 95% CI: 2.38, 3.24) vs 4.24 (95% CI: 3.83, 4.65) at 8 weeks	Pregabalin 150 mg vs Pregabalin 300 mg vs Placebo Total: 10 (12.35%) vs 16 (21.05%) vs 20 (24.69%) AE: 9 (11.11%) vs 12 (15.79%) vs 8 (9.88%)	Pregabalin 150 mg vs Pregabalin 300 mg vs Placebo Asthenia: 6.2% (5/81) vs 2.6% (2/76) vs 4.9% (4/81) Diarrhea: 4.9% (4/81) vs 5.3% (4/76) vs 4.9% (4/81) Dizziness: 12.3% (10/81) vs 27.6% (21/76) vs 14.8% (12/81) Dry mouth: 11.1% (9/81) vs 6.6% (5/76) vs 3.7% (3/81) Edema, peripheral: 2.5% (2/81) vs 13.2% (10/76) vs 0.0% (0/81) Headache: 11.1% (9/81) vs 10.5% (8/76) vs 3.7% (3/81) Infection: 2.5% (2/81) vs 6.6% (5/76) vs 0.0% (0/81) Somnolence: 14.8% (12/81) vs 23.7% (18/76) vs 7.4% (6/81)

Evidence Table 7. Original report: Data abstraction of pregabalin, gabapentin, serotonin-norepinephrine reuptake inhibitors, and topical lidocaine (patch or gel)

Study	Design	Type of pain/ Sample size and characteristics	Intervention	Eligibility	Exclusion
Serpell 2002 UK and Republic of Ireland Efficacy quality: Fair	RCT Parallel Multicenter	Mixed N=305 Mean Age (SD): 57; Range: 20.3-88.4 Male: 46.23% Female: 53.77%	Gabapentin N=153 Placebo N=152	Male or female, aged at least 18 years, of any race. Required to have a definite diagnosis of neuropathic pain, made and confirmed by an experienced, practicing chronic pain specialist and based on clinical ground of history, examination, and appropriate investigation of symptoms and signs expressed by the patient. Investigators used definitions of diagnostic criteria in the International Association for the Study of Pain Classification of Chronic Pain to support their clinical judgment. Subjects also required to have at least 2 of the following non-specific symptoms: allodynia, burning pain, shooting pain, or hyperalgesia. Symptoms could be associated with any neuropathic pain syndrome. Patients had to complete at least 4 daily pain diaries during the 7 days prior to randomization, yielding an average score of ≥4 out of 11 over this period. Women required to be non-pregnant (using barrier or hormonal contraception where appropriate), non-lactating, postmenopausal, or surgically sterilized.	Failure to respond to previous treatment with gabapentin at ≥900 mg/day or failure to respond to gabapentin at any dose level due to side effects; known creatinine clearance ≤60 ml/min or known renal impairment; clinically significant hepatic, respiratory, hematological illnesses or unstable cardiovascular disease; significant neurological or psychiatric disorders unrelated to causes of neuropathic pain, which in the opinion of the investigator, might impair the assessment of pain; other severe pain that might impair the assessment of pain; any other serious or unstable conditions that might compromise participation in the study; illicit drug or alcohol abuse within the past year.
Siddall 2006 Australia Efficacy quality: Fair	RCT Parallel Multicenter	Spinal cord injury N=137 Mean Age: 50; Range: 21-80 Male: 83% Female: 17% 97.1% white	Pregabalin 150-600 mg (flexible dose) mean dose 460 mg Placebo	Men or women at least 18 years of age with a spinal cord injury (paraplegia or tetraplegia) that had been incurred at least 1 year previously, in whom it had been nonprogressive for at least 6 months. Central neuropathic pain as defined by the IASP classification. Pain must have been chronic, having persisted continuously for at least 3 months or with relapses and remission for at least 6 months, and started after sustaining the spinal cord injury. Score of at least 40 mm on the 100 mm VAS of the SF-McGill Pain Questionnaire at both screening and randomization. Inpatients and outpatients eligible.	Severe pain of another origin that could confound the assessment of central neuropathic pain related to spinal cord injury excluded if they were unable to distinguish between neuropathic pain and other pain such as musculoskeletal pain. Creatine clearance <60 mL/minute, breastfeeding or pregnant women.
Simpson (A) Part 1 2001 US Efficacy quality: Fair	RCT Parallel Single Center	Painful diabetic neuropathy N=60 Mean Age (SD): 50.0 Male: 60% Female: 40%	Gabapentin 900-2700 mg N=30 Placebo N=30	Part 1: Pain attributed to diabetic neuropathy for 3 months to 1.5 years, a diagnosis of diabetes mellitus from 6 months to 17 years, a pain score of at least 40 mm on the 100-mm VAS of the Short-Form McGill Pain Questionnaire, and an average score of 4 on an 11-point Likert scale in daily pain diaries over the next week. Part 2: patients from the gabapentin-treated group in Part 1 who had minimal improvement/no change or worse as determined by the Patient Global Impression of Change and Clinical Global Impression of Change	Part 1: Severe pain other than that attributed to diabetic neuropathy, amputations other than toes, and renal failure with a creatinine clearance of less than 60 mL/min. The following medications taken within 30 days before screening: tricyclic antidepressants, mexiletine, carbamazepine, phenytoin, valproate, dextromethorphan, opioids, capsaicin, NSAIDs, skeletal muscle relaxants, benzodiazepines, and over the counter centrally acting agents.

Evidence Table 7. Original report: Data abstraction of pregabalin, gabapentin, serotonin-norepinephrine reuptake inhibitors, and topical lidocaine (patch or gel)

Study	Patient-reported pain	Observer-reported pain	Functional capacity
Serpell 2002 UK and Republic of Ireland Efficacy quality: Fair	Gabapentin vs Placebo Average daily pain score, Likert scale (0-10) Mean score: 5.6 vs 6.3 at 8 weeks (p=0.048) Global Impression of Change, Very much or much improved % of patients: 34% vs 16% at 8 weeks (p=0.03) Response, >50% reduction in mean pain score from baseline % of patients: 21% vs 14% at 8 weeks (p=0.16)	Gabapentin vs Placebo Global impression of improvement, Very much or much improved % of patients: 38% (p=0.01) vs 18% at 8 weeks	QOL, SF-36: Reported graphically only
Siddall 2006 Australia Efficacy quality: Fair	NR	NR	NR
Simpson (A) Part 1 2001 US Efficacy quality: Fair	Gabapentin vs Placebo Average pain, 11-point Likert scale (0-10) Mean score: 4.0 vs 6.0 at 8 weeks (p<0.01)	Gabapentin vs Placebo Global impression of Change, Much/moderately improved % of patients: 55.5% (p<0.01) vs 25.9% at 8 weeks	Gabapentin vs Placebo QOL, SF-36 Bodily Pain Mean score: 60 (p<0.01) vs 45 at 8 weeks QOL, SF-36 Mental Health Mean score: 80 (p<0.01) vs 65 at 8 weeks QOL, SF-36 Vitality Mean score: 60 (p<0.01) vs 40 at 8 weeks

Evidence Table 7. Original report: Data abstraction of pregabalin, gabapentin, serotonin-norepinephrine reuptake inhibitors, and topical lidocaine (patch or gel)

Study	Other outcomes	Withdrawals/ Withdrawals due to AEs	Specific adverse events
Serpell 2002 UK and Republic of Ireland Efficacy quality: Fair	NR	Gabapentin vs Placebo Total: 32 (21.05%) vs 41 (26.8%) AE: 24 (15.79%) vs 25 (16.34%)	Gabapentin vs Placebo Any adverse event: 76.5% (117/153) vs 67.8% (103/152) Serious AEs: 2.6% (4/153) vs 2.6% % (4/152) Abdominal pain: 6.5% (10/153) vs 3.9% (6/152) Accidental injury: 5.9% (9/153) vs 5.3% (8/152) Diarrhea: 5.2% (8/153) vs 3.9% (6/152) Dizziness: 24.2% (37/153) vs 7.9% (12/152) Flu syndrome: 7.2% (11/153) vs 4.6% (7/152) Headache: 9.2% (14/153) vs 13.8% (21/152) Infection: 9.2% (14/153) vs 12.5% (19/152) Nausea: 9.2% (14/153) vs 9.2% (14/152) Somnolence: 14.4% (22/153) vs 5.3% (8/152)
Siddall 2006 Australia Efficacy quality: Fair	NR	Pregabalin vs Placebo Total: 21 (30%) vs 30 (44.78%) AE: 15 (21.43%) vs 9 (13.43%)	Pregabalin vs Placebo Serious AEs: 18.6% (13/70) vs 11.9% (8/67) Amblyopia: 8.6% (6/70) vs 3.0% (2/67) Amnesia: 10.0% (7/70) vs 3.0% (2/67) Asthenia: 15.7% (11/70) vs 6.0% (4/67) Constipation: 12.9% (9/70) vs 6.0% (4/67) Dizziness: 24.3% (17/70) vs 9.0% (6/67) Dry mouth: 15.7% (11/70) vs 3.0% (2/67) Edema: 20.0% (14/70) vs 6.0% (4/67) Infection: 8.6% (6/70) vs 6.0% (4/67) Myasthenia: 8.6% (6/70) vs 4.5% (3/67) Paresthesia: 5.7% (4/70) vs 1.5% (1/67) Somnolence: 41.4% (29/70) vs 9.0% (6/67) Thinking abnormal: 8.6% (6/70) vs 1.5% (1/67) Urinary incontinence: 5.7% (4/70) vs 3.0% (2/67)
Simpson (A) Part 1 2001 US Efficacy quality: Fair	NR	Gabapentin vs Placebo Total: 3 (10%) vs 3 (10%) AE: 2 (6.67%) vs 2 (6.67%)	Gabapentin vs Placebo Confusion: 7.4% (2/27) vs 0.0% (0/27) Diarrhea: 11.1% (3/27) vs 3.7% (1/27) Dizziness: 22.2% (6/27) vs 3.7% (1/27) Headache: 11.1% (3/27) vs 3.7% (1/27) Nausea: 7.4% (2/27) vs 3.7% (1/27) Somnolence: 22.2% (6/27) vs 3.7% (1/27)

Evidence Table 7. Original report: Data abstraction of pregabalin, gabapentin, serotonin-norepinephrine reuptake inhibitors, and topical lidocaine (patch or gel)

Study	Design	Type of pain/ Sample size and characteristics	Intervention	Eligibility	Exclusion
Tai 2002 US Efficacy quality: Poor	RCT Crossover Single Center	Spinal cord injury-related pain N=7 Mean Age (SD): 35.9; Range: 27-48 Male: 85.71% Female: 14.29%	Gabapentin up to 1800 mg daily N=7 Placebo N=7	Traumatic spinal cord injury, age 18 to 85 years, neuropathic pain confirmed by a spinal cord injury physician, and traumatic injury for greater than 30 days. Score of >4 on the 11-point Neuropathic Pain Scale.	Severe cognitive impairment, pregnancy, seizure disorder, major depression or a score >16 on the Beck Depression Inventory, known hypersensitivity to gabapentin, and renal insufficiency with a creatinine clearance less than 60 mL/minute. A score of >16 on Beck Depression Inventory.
Tasmuth 2002 Finland Efficacy quality: Fair	RCT Crossover Single Center	Cancer-related neuropathic pain N=13 Mean Age (SD): 55; Range: 37-72 Male: 0% Female: 100%	Venlafaxine 37.5 mg N=13 Venlafaxine 75 mg N=11 Placebo N=13 Placebo N=11	Neuropathic pain after treatment for breast cancer. Pain had to be in the anterior chest wall and/or axilla and/or median upper arm in an area with sensory disturbances. Pain had to be moderate in severity.	Relapses or metastases of the breast cancer, clinically overt cardiac, renal, or hepatic disease, concomitant medication with MAO inhibitors or drugs that are significantly metabolized by the P4502D6 isoenzyme or which inhibit this enzyme.

Evidence Table 7. Original report: Data abstraction of pregabalin, gabapentin, serotonin-norepinephrine reuptake inhibitors, and topical lidocaine (patch or gel)

Study	Patient-reported pain	Observer-reported pain	Functional capacity
Tai 2002 US Efficacy quality: Poor	Gabapentin vs Placebo NPS cold pain Average pain intensity (0-10) Mean score: 1.59 vs 1.67 at 4 weeks (p=NS) NPS deep pain Average pain intensity (0-10) Mean score: 4.30 vs 4.50 at 4 weeks (p=NS) NPS dull pain Average pain intensity (0-10) Mean score: 1.67 vs 1.61 at 4 weeks (p=NS) NPS hot pain Average pain intensity (0-10) Mean score: 1.11 vs 4.54 at 4 weeks (p=0.065) NPS itchy pain Average pain intensity (0-10) Mean score: 0.01 vs 0.03 at 4 weeks (p=NS) NPS sensitive pain Average pain intensity (0-10) Mean score: 1.46 vs 1.76 at 4 weeks (p=NS) NPS sharp pain Average pain intensity (0-10) Mean score: 1.37 vs 2.01 at 4 weeks (p=NS) NPS surface pain Average pain intensity (0-10) Mean score: 1.01 vs 2.00 at 4 weeks (p=NS) NPS unpleasant pain Average pain intensity (0-10) Mean score: 3.60 vs 5.33 at 4 weeks (p=0.028) NPS intense pain Average pain intensity (0-10) Mean score: 3.7 vs 5.29 at 4 weeks (p=0.094)	NR	NR
Tasmuth 2002 Finland Efficacy quality: Fair	Venlafaxine 37.5 mg vs Venlafaxine 75 mg vs Placebo vs Placebo Pain intensity, Current VAS (0-100) Median score (range): 13 (0-62) vs 0 (0-35) vs 8 (0-67) vs 0.6 (0-70) at 4 weeks Pain intensity, Current VRS (0-7) Median score (range): 0 (0-4) vs 0 (0-4) vs 1 (0-4) vs 1 (0-2) at 4 weeks Pain relief, Current VAS (0-100) Median score (range): 20 (0-100) vs 42 (0-100) vs 0 (0-69) vs 25 (0-100) at 4 weeks Pain relief, Current VRS (0-5) Median score (range): 1 (0-4) vs 1.5 (0-4) vs 0 (0-3) vs 1 (0-3) at 4 weeks	NR	NR

Evidence Table 7. Original report: Data abstraction of pregabalin, gabapentin, serotonin-norepinephrine reuptake inhibitors, and topical lidocaine (patch or gel)

Study	Other outcomes	Withdrawals/ Withdrawals due to AEs	Specific adverse events
Tai 2002 US Efficacy quality: Poor	NR	NR	NR
Tasmuth 2002 Finland Efficacy quality: Fair	<u>Venlafaxine 37.5 mg vs Venlafaxine 75 mg vs Placebo vs Placebo</u> Depression, Beck Depression Inventory (0-63) Median score (range): 7 vs 7 vs 8 vs 7	NR	<u>Venlafaxine 37.5 mg vs Venlafaxine 75 mg vs Placebo vs Placebo</u> Anorexia: 23.1% (3/13) vs 30.8% (4/13) Constipation: 30.8% (4/13) vs 23.1% (3/13) Difficult to urinate: 15.4% (2/13) vs 15.4% (2/13) Dry mouth: 61.5% (8/13) vs 46.2% (6/13) Fatigue: 69.2% (9/13) vs 76.9% (10/13) Headache: 46.2% (6/13) vs 30.8% (4/13) Nausea: 30.8% (4/13) vs 30.8% (4/13) Nightmares: 15.4% (2/13) vs 30.8% (4/13) Palpitations: 23.1% (3/13) vs 23.1% (3/13) Sweating increased: 61.5% (8/13) vs 53.8% (7/13)

Evidence Table 7. Original report: Data abstraction of pregabalin, gabapentin, serotonin-norepinephrine reuptake inhibitors, and topical lidocaine (patch or gel)

Study	Design	Type of pain/ Sample size and characteristics	Intervention	Eligibility	Exclusion
van Seventer 2006 US and Multiple European Efficacy quality: Fair	RCT Parallel Multicenter	Post-herpetic neuralgia N=368 Mean Age (SD): 70.7 (10.6); Range: 18-92 Male: 45.65% Female: 54.35% White: 98.9% Black: 0.5% Other: 0.5%	Pregabalin 150 mg N=87 Pregabalin 300 mg N=98 Pregabalin 300-600 mg N=90 Placebo N=93	Age ≥18 years, pain for >3 months after healing of herpes zoster lesions, had a VAS pain score ≥40 mm at baseline and at randomization, and had at least 4 daily pain diary entries with a mean daily pain score ≥4 prior to randomization.	Malignancy (with the exception of basal cell carcinoma) within the past 2 years, WBC <2500 mm3, neutrophil count <1500 mm3, or platelet count <100 x 103/mm3; clinically significant or unstable hepatic, respiratory, or hematologic illnesses or psychologic conditions; unstable cardiovascular disease; abnormal 12-lead ECG; history of chronic hepatitis B or C, hepatitis B or C within the past 3 months, or HIV infection; immunocompromise, history of alcohol or illicit drug abuse within the last 2 years; or participation in a clinical trial for an investigational drug or agent within 30 days prior to baseline or participation in a previous trial of pregabalin. Creatinine clearance ≤30 mL/min, previous surgical therapy for postherpetic neuralgia, other severe pain or skin conditions in the affected dermatome that could alter sensation or that might compromise postherpetic neuralgia assessment, or who had used prohibited medications without appropriate washout (at least 7 days prior to baseline phase).

Evidence Table 7. Original report: Data abstraction of pregabalin, gabapentin, serotonin-norepinephrine reuptake inhibitors, and topical lidocaine (patch or gel)

Study	Patient-reported pain	Observer-reported pain	Functional capacity
van Seventer 2006 US and Multiple European Efficacy quality: Fair	Pregabalin 150 mg vs Pregabalin 300 mg vs Pregabalin 300-600mg vs Placebo Average pain, 11-point numerical rating scale (0-10) LS mean: 5.26 (p=0.0077; 95% CI: 4.79, 5.73) vs 5.07 (p=0.0016; 95% CI: 4.62, 5.52) vs 4.35 (p=0.0003; 95% CI: 3.88, 4.82) vs 6.14 (95% CI: 5.69, 6.59) at 13 weeks Global Impression of Change, "much improved" or "very much improved" % of patients: 22.6% vs 27.2% vs 36.5% vs 16.2% at 13 weeks Response, ≥30% reduction in pain % of patients: 39.1% (p≤0.001) vs 40.8% (p≤0.001) vs 52.3% (p≤0.001) vs 17.2% at 13 weeks Response, ≥50% reduction in pain % of patients: 26.4% (p=0.001) vs 26.5% (p=0.001) vs 37.5% (p=0.001) vs 7.5% at 13 weeks	NR	NR

Evidence Table 7. Original report: Data abstraction of pregabalin, gabapentin, serotonin-norepinephrine reuptake inhibitors, and topical lidocaine (patch or gel)

Study	Other outcomes	Withdrawals/ Withdrawals due to AEs	Specific adverse events
van Seventer 2006 US and Multiple European Efficacy quality: Fair	Pregabalin 150 mg vs Pregabalin 300 mg vs Pregabalin 300-600mg vs Placebo Interference with sleep, 11-point numerical rating scale (0-10) Least squares mean: 3.07 (p=0.0007; 95% CI: 2.64, 3.50) vs 2.84 (p=0.0002; 95% CI: 2.43, 3.25) vs 2.17 (p=0.0002; 95% CI: 1.74, 2.60) vs 4.10 (95% CI: 3.69, 4.51) at 13 weeks	Pregabalin 150 mg vs Pregabalin 300 mg vs Pregabalin 300-600mg vs Placebo Total: 26 (29.89%) vs 36 (36.73%) vs 34 (37.78%) vs 34 (36.56%) AE: 7 (8.05%) vs 15 (15.31%) vs 19 (21.11%) vs 5 (5.38%)	Pregabalin 150 mg vs Pregabalin 300 mg vs Pregabalin 300-600mg vs Placebo Amblyopia: 2.3% (2/87) vs 3.1% (3/98) vs 5.6% (5/90) vs 1.1% (1/93) Asthenia: 4.6% (4/87) vs 3.1% (3/98) vs 5.6% (5/90) vs 5.4% (5/93) Ataxia: 3.4% (3/87) vs 6.1% (6/98) vs 12.2% (11/90) vs 0.0% (0/93) Confusion: 3.4% (3/87) vs 3.1% (3/98) vs 3.3% (3/90) vs 1.1% (1/93) Constipation: 1.1% (1/87) vs 8.2% (8/98) vs 8.9% (8/90) vs 2.2% (2/93) Diarrhea: 5.7% (5/87) vs 0.0% (0/98) vs 0.0% (0/90) vs 1.1% (1/93) Diplopia: 0.0% (0/87) vs 0.0% (0/98) vs 3.3% (3/90) vs 0.0% (0/93) Dizziness: 16.1% (14/87) vs 32.7% (32/98) vs 36.7% (33/90) vs 9.7% (9/93) Dry mouth: 5.7% (5/87) vs 4.1% (4/98) vs 12.2% (11/90) vs 0.0% (0/93) Edema, face: 3.4% (3/87) vs 1.0% (1/98) vs 4.4% (4/90) vs 2.2% (2/93) Edema, peripheral: 12.6% (11/87) vs 14.3% (14/98) vs 13.3% (12/90) vs 10.8% (10/93) Edema, peripheral: 3.4% (3/87) vs 3.1% (3/98) vs 5.6% (5/90) vs 3.2% (3/93) Flatulence: 1.1% (1/87) vs 0.0% (0/98) vs 3.3% (3/90) vs 2.2% (2/93) Gait abnormal: 1.1% (1/87) vs 2.0% (2/98) vs 4.4% (4/90) vs 0.0% (0/93) Headache: 4.6% (4/87) vs 1.0% (1/98) vs 4.4% (4/90) vs 3.2% (3/93) Incoordination: 2.3% (2/87) vs 1.0% (1/98) vs 3.3% (3/90) vs 0.0% (0/93) Nausea: 1.1% (1/87) vs 0.0% (0/98) vs 2.2% (2/90) vs 5.4% (5/93) Somnolence: 9.2% (8/87) vs 11.2% (11/98) vs 25.6% (23/90) vs 4.3% (4/93) Sweating increased: 1.1% (1/87) vs 0.0% (0/98) vs 0.0% (0/90) vs 3.2% (3/93) Thinking abnormal: 2.3% (2/87) vs 2.0% (2/98) vs 4.4% (4/90) vs 1.1% (1/93) Vision abnormal: 0.0% (0/87) vs 2.0% (2/98) vs 4.4% (4/90) vs 0.0% (0/93) Weight gain: 3.4% (3/87) vs 8.2% (8/98) vs 8.9% (8/90) vs 0.0% (0/93)

Evidence Table 7. Original report: Data abstraction of pregabalin, gabapentin, serotonin-norepinephrine reuptake inhibitors, and topical lidocaine (patch or gel)

Study	Design	Type of pain/ Sample size and characteristics	Intervention	Eligibility	Exclusion
Wernicke 2006 US	RCT Parallel Multicenter	Painful diabetic neuropathy N=334	Duloxetine 60 mg once daily N=114	Age 18 years or older and presented with diabetic peripheral neuropathic pain caused by type 1 or type 2 diabetes. Pain had to begin in the feet and with relatively symmetric onset. Daily pain must have been present for at least 6 months, and the diagnosis was to be confirmed by a score of at least 3 on the Michigan Neuropathy Screening Instrument. Mean score of 4 or greater (between Visit 2 and visit 3 before randomization), when assessed by 24-hour average pain severity on the 11-point Likert scale from the patient diary, stable glycemic control assessed by a physician investigator, and a HbA1c ≤12%. Only patients who were judged to be reliable and had an educational level and degree of understanding that allowed them to communicate intelligibly were included	Pregnant or breastfeeding, previous renal transplant or current renal dialysis, or serious or unstable cardiovascular, hepatic, renal, respiratory, or hematologic illness, symptomatic peripheral vascular disease, or other medical conditions or psychological conditions that might compromise participation. Current (within 1 year) DSM-IV Axis I diagnosis of major depressive disorder, dysthymia, generalized anxiety disorder, alcohol, or eating disorders, or previous diagnosis or DSM-IV diagnosis of mania, bipolar disorder, or psychosis, historical exposure to drugs known to cause neuropathy, history of substance abuse or dependence within the previous year, positive urine drug screen for any substances of abuse or excluded medication, or a history of a medical condition, including pernicious anemia and hypothyroidism or treatment with a MAO inhibitor or fluoxetine within 30 days of randomization; severe allergic reactions to multiple medications and prior participation in a study of duloxetine.
Efficacy quality: Fair		Age Mean (SD): 60.7 (10.6) Male: 61.08% Female: 38.92% Race/ethnicity White: 78.1% Black: 3.3% Hispanic: 16.2% Other: 2.4%	Duloxetine 60 mg twice daily Total daily dose: 120 mg N=112 Placebo N=108		

Evidence Table 7. Original report: Data abstraction of pregabalin, gabapentin, serotonin-norepinephrine reuptake inhibitors, and topical lidocaine (patch or gel)

Study	Patient-reported pain	Observer-reported pain	Functional capacity
Wernicke 2006 US Efficacy quality: Fair	Duloxetine 60 mg/d vs Duloxetine 120 mg/d vs Placebo 24-hour average pain score, 11-point Likert scale (0=no pain, 10=worst pain) Mean change from baseline: -2.72 (p<0.001; 95% CI: -3.15, -2.29) vs -2.84 (p<0.001; 95% CI: -3.29, -2.39) vs -1.39 (95% CI: -1.84, -0.94) at 12 weeks 24-hour worst pain score, 11-point Likert scale (0=no pain, 10=worst pain) Mean change from baseline: -3.21 (p<0.001; 95% CI: -3.70, -2.72) vs -3.39 (p<0.001; 95% CI: -3.90, -2.88) vs -1.94 (95% CI: -2.43, -1.45) at 12 weeks Average pain severity, BPI Mean change from baseline: -2.66 (p<0.001; 95% CI: -3.11, -2.21) vs -3.05 at 12 weeks (p<0.001; 95% CI: -3.52, -2.58) vs -1.48 (95% CI: -1.93, -1.03) at 12 weeks Improvement, PGI-Improvement Mean change from baseline: 2.61 (p<0.01; 95% CI: -0.21, 5.43) vs 2.40 (p<0.001; 95% CI: -0.13, 4.93) vs 3.17 (95% CI: 0.35, 5.99) at 12 weeks Night pain score, 11-point Likert scale (0=no pain, 10=worst pain) Mean change from baseline: -2.95 (p<0.01; 95% CI: -3.44, -2.46) vs -3.08 (p<0.001; 95% CI: -3.57, -2.59) vs -1.83 (95% CI: -2.30, -1.36) at 12 weeks Worst pain, BPI Mean change from baseline: -3.33 (p<0.001; 95% CI: -3.86, -2.80) vs -3.50 (p<0.001; 95% CI: -4.05, -2.95) vs -1.98 (95% CI: -2.53, -1.43) at 12 weeks	Duloxetine 60 mg/d vs Duloxetine 120 mg/d vs Placebo Severity of pain, CGI-Severity Mean change from baseline: -1.37 (p<0.05; 95% CI: -1.59, -1.15) vs -1.47 (p<0.01; 95% CI: -1.71, -1.23) vs -0.98 (95% CI: -1.22, -0.74) at 12 weeks	Duloxetine 60 mg/d vs Duloxetine 120 mg/d vs Placebo Interference, BPI Interference average of 7 questions Mean change from baseline: -2.36 (p<0.05; 95% CI: -2.73, -1.99) vs -2.79 (p<0.001; 95% CI: -3.16, -2.42) vs -1.72 (95% CI: -2.09, -1.35) at 12 weeks Quality of life, Euro Quality of Life (EQ-5D) Mean change from baseline: 0.15 (p<0.05; 95% CI: 0.11, 0.19) vs 0.15 at 12 weeks (p<0.05; 95% CI: 0.11, 0.19) vs 0.08 (95% CI: 0.04, 0.12) at 12 weeks Quality of life, SF-36 Bodily Pain Mean change from baseline: 15.3 (p<0.05; 95% CI: 11.42, 19.18) vs 20.59 (p<0.01; 95% CI: 16.59, 24.59) vs 12.17 (95% CI: 8.05, 16.29) at 12 weeks Quality of life, SF-36 General Health Mean change from baseline: 5.64 (95% CI: 2.94, 8.34) vs 7.73 (p<0.01; 95% CI: 5.01, 10.45) vs 2.39 (95% CI: -0.39, 5.17) at 12 weeks Quality of life, SF-36 Mental Health Mean change from baseline: 1.63 (95% CI: -1.27, 4.53) vs 3.82 (p<0.05; 95% CI: 0.90, 6.74) vs -0.31 (95% CI: -3.29, 2.67) at 12 weeks Quality of life, SF-36 Physical functioning Mean change from baseline: 11.96 (p<0.01; 95% CI: 8.41, 15.51) vs 11.20 (p<0.01; 95% CI: 7.55, 14.85) vs 3.64 (95% CI: -0.08, 7.36) at 12 weeks Quality of life, SF-36 Vitality Mean change from baseline: 8.47 (95% CI: 5.08, 11.86) vs 6.36 (95% CI: 2.95, 9.77) vs 2.79 (95% CI: -0.70, 6.28) at 12 weeks

Evidence Table 7. Original report: Data abstraction of pregabalin, gabapentin, serotonin-norepinephrine reuptake inhibitors, and topical lidocaine (patch or gel)

Study	Other outcomes	Withdrawals/ Withdrawals due to AEs	Specific adverse events
Wernicke 2006 US Efficacy quality: Fair	Duloxetine 60 mg/d vs Duloxetine 120 mg/d vs Placebo Depression, HAM-D Mean change from baseline: -0.65 (95% CI: -1.16, -0.14) vs 0.19 (p<0.05; 95% CI: -0.32, 0.70) vs -0.64 (95% CI: -1.15, -0.13) at 12 weeks Use of rescue analgesics Median average daily dose, mg: 108.7 vs 3.81 (p<0.001) vs 207.14 at 12 weeks	Duloxetine 60 mg/d vs Duloxetine 120 mg/d vs Placebo Total: 29 (25%) vs 34 (30.36%) vs 23 (21.3%) AE: 17 (14.9%) vs 20 (17.86%) vs 8 (7.41%)	Duloxetine 60 mg/d vs Duloxetine 120 mg/d vs Placebo Constipation: 7.0% (8/114) vs 18.8% (21/112) vs 1.9% (2/108) Diarrhea: 11.4% (13/114) vs 4.5% (5/112) vs 1.9% (2/108) Dizziness: 15.8% (18/114) vs 10.7% (12/112) vs 5.6% (6/108) Fatigue: 12.3% (14/114) vs 12.5% (14/112) vs 2.8% (3/108) Headache: 10.5% (12/114) vs 13.4% (15/112) vs 6.5% (7/108) Insomnia: 5.3% (6/114) vs 9.8% (11/112) vs 1.9% (2/108) Nasopharyngitis: 7.0% (8/114) vs 6.3% (7/112) vs 4.6% (5/108) Nausea: 28.1% (32/114) vs 32.1% (36/112) vs 6.5% (7/108) Somnolence: 7.9% (9/114) vs 15.2% (17/112) vs 0.9% (1/108) Sweating increased: 8.8% (10/114) vs 7.1% (8/112) vs 0.9% (1/108)

Evidence Table 8. Original report: Data abstraction of other antiepileptics and tricyclic antidepressants

Study	Design	Type of pain Sample size and characteristics	Intervention
Beydoun 2006 US Efficacy quality: Fair	RCT Parallel	Painful diabetic neuropathy N=347 Age Mean (SD): 60.7 Male: 62.8% Female: 37.2%	Oxcarbazepine 600 mg daily N=83 Oxcarbazepine 1200 mg daily N=87 Oxcarbazepine 1800 mg daily N=88 Placebo N=89
Campbell 1966 England Efficacy quality: Poor	RCT Crossover	Trigeminal neuralgia N=70 Age Mean (SD): 59 Range: 20-84 Male: 34% Female: 66%	Carbamazepine N=36 Placebo N=34
Cardenas 2002 US Efficacy quality: Fair	RCT Parallel Multicenter	Spinal cord injury-related pain N=84 Age Mean (SD): 41.4 Range: 21-64 Male: 79.8% Female: 20.2%	Amitriptyline 10-125 mg daily N=44 Benztropine mesylate 0.5 mg daily N=40

Evidence Table 8. Original report: Data abstraction of other antiepileptics and tricyclic antidepressants

Study	Eligibility	Exclusion
Beydoun 2006 US Efficacy quality: Fair	Men and non-pregnant women, 18 years of age or older, with a diagnosis of diabetes mellitus (type 1 or 2), and pain attributed to diabetic neuropathy for 6 months to 5 years. Pain rating score of at least 50 units on a 100-unit VAS at the screening visit, stable glycemic control (as evidenced by a hemoglobin A1c level of <=11% at baseline), and baseline serum sodium levels >=35 mmol/L. VAS must have averaged at least 40 units during the pre-randomization phase, with <25% variability in the last 7 days prior to randomization.	Patients with other types of pain, clinically significant medical or psychiatric illnesses, a prior history of hyponatremia or non-compliance, drug or alcohol abuse in the preceding year, amputations other than the toes, treatment with lithium or MAO inhibitors, previous treatment with oxcarbazepine, or a history of sensitivity to carbamazepine or its metabolites.
Campbell 1966 England Efficacy quality: Poor	Trigeminal neuralgia, in pain at the time of entry.	"A few" patients rejected because of difficulty in attending regularly due to age, infirmity, or geography. Pain symptomatic of disseminated sclerosis.
Cardenas 2002 US Efficacy quality: Fair	Spinal cord injury more than 6 months ago; pain for at least 3 months; and average pain rating in the last month of at least 3 on a scale of 0-10.	Less than age 18 or more than 65 years of age, history of cardiovascular disease, abnormalities in a screening ECG, seizures, hyperthyroidism, or glaucoma; if female, were pregnant or unwilling to use a contraceptive during the study; were on any type of antidepressant medication, were consuming more than two alcoholic drinks per day; or met psychiatric diagnostic criteria for a major depressive episode.

Evidence Table 8. Original report: Data abstraction of other antiepileptics and tricyclic antidepressants

Study	Patient-reported pain	Functional capacity	Withdrawals Withdrawals due to adverse events
Beydoun 2006 US Efficacy quality: Fair	Oxcarbazepine 600 mg vs Oxcarbazepine 1200 mg vs Oxcarbazepine 1800 mg vs Placebo Average daily pain score, VAS (0-100) Mean change from baseline: -25.9 vs -29.0 vs -26.5 vs -19.1 at 16 weeks Global Impression of Change, Much or very much improved % of patients: 36.4% vs 50.0% vs 49.3% vs 37.3% at 16 weeks	Oxcarbazepine 600 mg vs Oxcarbazepine 1200 mg vs Oxcarbazepine 1800 mg vs Placebo Quality of life, SF-36 Data NR, no difference from placebo at 16 weeks (p=NS)	Oxcarbazepine 600 mg vs Oxcarbazepine 1200 mg vs Oxcarbazepine 1800 mg vs Placebo Total: 16 (19.28%) vs 34 (39.08%) vs 48 (54.55%) vs 17 (19.1%) AE: 9 (10.84%) vs 20 (22.99%) vs 36 (40.91%) vs 6 (6.74%)
Campbell 1966 England Efficacy quality: Poor	Carbamazepine vs Placebo Improvement, % change on a numeric scale (0-3) Mean change from baseline: 58% (p<0.01) vs 26% at 2 weeks	NR	NR
Cardenas 2002 US Efficacy quality: Fair	Amitriptyline vs Benztropine mesylate Interference with activities, BPI Mean score: 29.8 (95% CI: 23.18, 36.42) vs 22.2 (95% CI: 19.94, 24.46) at 6 weeks Pain intensity, API (0-10) Mean score: 4.5 (95% CI: 3.94, 5.06) vs 4.0 (95% CI: 3.38, 4.62) at 6 weeks	Amitriptyline vs Benztropine mesylate Disability, CHART Mean score: 384.1 (95% CI: 357.24, 410.96) vs 63.7 (95% CI: 58.03, 69.37) at 6 weeks Disability, FIM Mean score: 66.3 (95% CI: 61.37, 71.23) vs 24.4 (95% CI: 18.08, 30.72) at 6 weeks	NR

Evidence Table 8. Original report: Data abstraction of other antiepileptics and tricyclic antidepressants

Study	Specific adverse events
Beydoun 2006 US Efficacy quality: Fair	Oxcarbazepine 600 mg vs Oxcarbazepine 1200 mg vs Oxcarbazepine 1800 mg vs Placebo Dizziness: 6.0% (5/83) vs 18.8% (16/85) vs 34.5% (30/87) vs 2.2% (2/89) Fatigue: 4.8% (4/83) vs 12.9% (11/85) vs 14.9% (13/87) vs 6.7% (6/89) Headache: 10.8% (9/83) vs 10.6% (9/85) vs 11.5% (10/87) vs 7.9% (7/89) Nausea: 2.4% (2/83) vs 15.3% (13/85) vs 19.5% (17/87) vs 5.6% (5/89) Somnolence: 2.4% (2/83) vs 5.9% (5/85) vs 10.3% (9/87) vs 3.4% (3/89) Tremor: 1.2% (1/83) vs 1.2% (1/85) vs 12.6% (11/87) vs 2.2% (2/89)
Campbell 1966 England Efficacy quality: Poor	NR
Cardenas 2002 US Efficacy quality: Fair	Amitriptyline vs Benztropine mesylate Any adverse event: 97.7% (43/44) vs 90.0% (36/40)

Evidence Table 8. Original report: Data abstraction of other antiepileptics and tricyclic antidepressants

Study	Design	Type of pain Sample size and characteristics	Intervention
Dalessio 1966 US	RCT Crossover Single Center	Trigeminal neuralgia N=10	Carbamazepine 600 mg N=10
Efficacy quality: Poor			Placebo N=10
Dogra 2005 US	RCT Parallel Multicenter	Painful diabetic neuropathy N=146	Oxcarbazepine mean 1445 mg N=69
Efficacy quality: Fair		Age Mean (SD): 60.1 Male: 58.2% Female: 41.8%	Placebo N=77
Eisenberg 2001 Israel	RCT Parallel Single Center	Painful diabetic neuropathy N=53	Lamotrigine 200-400 mg N=27
Efficacy quality: Fair		Age Mean (SD): 55.2 Male: 62.26% Female: 37.74%	Placebo N=26

Evidence Table 8. Original report: Data abstraction of other antiepileptics and tricyclic antidepressants

Study	Eligibility	Exclusion
Dalessio 1966 US Efficacy quality: Poor	NR	NR
Dogra 2005 US Efficacy quality: Fair	Male or female outpatients, age 18 or older, established clinical diagnosis of diabetes mellitus (type 1 or 2); stable diabetic control as evidence by a) hemoglobin A1c level <=11% at baseline; b) average HA1c over the 6 months prior to study entry within 1 unit (%) of baseline; history of neuropathic pain between 6 months and 5 years in duration; pain rating of >=50 units on the VAS at the first screening visit; average pain score of 50 units over 4 of the last 7 days prior to randomization; <=25% variation in the severity of the pain in the 7 days prior to randomization, as assessed from the electronic diary information recorded daily during the screening phase.	Presence of other pain that could confound assessment of neuropathic pain of diabetic origin; currently or had previously taken oxcarbazepine; presence of skin lesions that could affect the ability to assess neuropathic pain or if they had undergone amputations (other than toes); history of renal insufficiency; hyponatremia; chronic infectious disease; known hypersensitivity to oxcarbazepine or carbamazepine.
Eisenberg 2001 Israel Efficacy quality: Fair	1) Established diagnosis of diabetes mellitus (type 1 or 2); 2) no change had been made in their antihyperglycemic medications within 3 weeks before screening; 3) evidence of peripheral neuropathy was indicated by at least tow of the three following measures: a) medical history, b) neurologic examination, or c) abnormal nerve conduction test results; 4) pain attributed to diabetic neuropathy had been present for at least 6 months; and 5) a mean pain intensity of at least 4 on an 11-point numerical pain scale during the week before randomization.	1) age younger than 18 or older than 75 years; 2) impaired renal or liver function; 3) known epilepsy; 4) presence of other painful conditions; 5) receipt of anticonvulsants, antidepressants, or membrane-stabilizing agent s for reasons other than pain relief, or use of opioids; and 6) participation in any clinical trial within 30 days before screening.

Evidence Table 8. Original report: Data abstraction of other antiepileptics and tricyclic antidepressants

Study	Patient-reported pain	Functional capacity	Withdrawals Withdrawals due to adverse events
Dalessio 1966 US Efficacy quality: Poor	Carbamazepine vs Placebo Pain relief, Significant change in pain: % of patients: 100% vs 0% at 3 days (p<0.002)	NR	NR
Dogra 2005 US Efficacy quality: Fair	Oxcarbazepine vs Placebo Average daily pain score, VAS (0-100) Mean change from baseline: -24.3 (p=0.0108; 95% CI: -30.72, -17.88) vs -14.7 (95% CI: -20.60, -8.80) at 16 weeks Response, 30% or greater decrease in VAS % of patients: 45.6% (p=0.0288) vs 28.9% at 16 weeks Response, 50% or greater decrease in VAS % of patients: 35.2% (p=0.0156) vs 18.4% at 16 weeks	Oxcarbazepine vs Placebo Quality of life, SF-36 Mental Health Mean score: 47.2 vs 50.2 at 16 weeks (p=0.03) Quality of life, SF-36 other subscales Mean score: data not reported, no difference from placebo at 16 weeks	Oxcarbazepine vs Placebo Total: 25 (36.23%) vs 15 (19.48%) AE: 19 (27.54%) vs 6 (7.79%)
Eisenberg 2001 Israel Efficacy quality: Fair	Lamotrigine vs Placebo Average pain intensity, numerical scale (0-10) Mean score: 4.2 (95% CI: 4.16, 4.24) vs 5.3 (95% CI: 5.26, 5.34) at 6 weeks Average pain, McGill Pain Questionnaire, words Mean score: 12.5 (95% CI: 12.16, 12.84) vs 10.7 at 6 weeks Response, 50% or greater reduction in pain % of patients: 44.4% vs 19.2% at 6 weeks (p=0.05)	Lamotrigine vs Placebo Disability, Pain Disability Index Mean score: 3.8 (95% CI: 3.54, 4.06) vs 4.3 at 6 weeks	NR

Evidence Table 8. Original report: Data abstraction of other antiepileptics and tricyclic antidepressants

Study	Specific adverse events
Dalessio 1966 US Efficacy quality: Poor	NR
Dogra 2005 US Efficacy quality: Fair	<u>Oxcarbazepine vs Placebo</u> Back pain: 9.1% (5/55) vs 2.9% (2/70) Blurred vision: 1.8% (1/55) vs 1.4% (1/70) Diarrhea: 1.8% (1/55) vs 5.7% (4/70) Dizziness: 12.7% (7/55) vs 1.4% (1/70) Fatigue: 5.5% (3/55) vs 1.4% (1/70) Headache: 9.1% (5/55) vs 1.4% (1/70) Nausea: 3.6% (2/55) vs 1.4% (1/70) Somnolence: 9.1% (5/55) vs 0.0% (0/70) Tremor: 3.6% (2/55) vs 1.4% (1/70) Vomiting: 3.6% (2/55) vs 1.4% (1/70)
Eisenberg 2001 Israel Efficacy quality: Fair	<u>Lamotrigine vs Placebo</u> Dizziness: 12.5% (3/24) vs 18.2% (4/22) Headache: 8.3% (2/24) vs 9.1% (2/22) Nausea: 16.7% (4/24) vs 18.2% (4/22) Rash: 8.3% (2/24) vs 0.0% (0/22) Somnolence: 4.2% (1/24) vs 18.2% (4/22) Stomach problems: 12.5% (3/24) vs 4.5% (1/22)

Evidence Table 8. Original report: Data abstraction of other antiepileptics and tricyclic antidepressants

Study	Design	Type of pain Sample size and characteristics	Intervention
Finnerup 2002 Denmark Efficacy quality: Fair	RCT Crossover Single Center	Spinal cord injury-related pain N=22 Age Mean (SD): 49 Range: 27-63 Male: 81.82% Female: 18.18%	Lamotrigine 200-400 mg N=30 Placebo N=30
Gilron (B) 2001 US Efficacy quality: Poor	RCT Crossover	Trigeminal neuralgia N=3 Age Mean (SD): 53 Range: 40-66 Male: 33.33% Female: 66.67%	Topiramate mean 308 mg (range 75-600 mg) N=3 Placebo N=3

Evidence Table 8. Original report: Data abstraction of other antiepileptics and tricyclic antidepressants

Study	Eligibility	Exclusion
Finnerup 2002 Denmark Efficacy quality: Fair	Outpatients of a rehabilitation center for spinal cord injury, with neuropathic pain after traumatic spinal cord injury at or below level of spinal lesion. Other reasons for pain were either excluded or considered highly unlikely. Age 18-70 and pain intensity >=3 on a 0-10 point numeric rating scale.	Known concomitant cerebral damage or dementia (total score on the MMSE below 26), pregnant or lactating women and fertile women with inappropriate contraception (a negative pregnancy test was required), previous serious allergic reaction or hypersensitivity to lamotrigine, serious hepatic or renal disease or other significant illness.
Gilron (B) 2001 US Efficacy quality: Poor	Idiopathic trigeminal neuralgia (which may include recurrent trigeminal neuralgia following invasive peripheral nerve or intracranial procedures).	Multiple sclerosis or continuous pain and dense sensory loss related to an invasive procedure (i.e., anesthesia dolorosa.

Evidence Table 8. Original report: Data abstraction of other antiepileptics and tricyclic antidepressants

Study	Patient-reported pain	Functional capacity	Withdrawals Withdrawals due to adverse events
Finnerup 2002 Denmark Efficacy quality: Fair	<u>Lamotrigine vs Placebo</u> Average daily pain score, Numeric rating scale (0-10) Median change from baseline: 1 vs 0 at 9 weeks (p=0.11) Pain, McGill Pain Questionnaire Median score: 19 vs 18.5 at 9 weeks (p=0.76) Pain, McGill Pain Questionnaire, words chosen Median score: 11 vs 9 at 9 weeks (p=0.81) Response, Moderate or greater pain relief % of patients: 31.8% vs 13.6% at 9 weeks (p=0.06)	<u>Lamotrigine vs Placebo</u> Quality of life, SF-36 Mental Component summary Median score: 60.7 vs 61.9 at 9 weeks (p=0.80) Quality of life, SF-36 Physical component summary Median score: 32.6 vs 33.9 at 9 weeks (p=1.00)	<u>Lamotrigine vs Placebo</u> Total: 3 (10%) vs 5 (16.67%) AE: 1 (3.33%) vs 2 (6.67%)
Gilron (B) 2001 US Efficacy quality: Poor	<u>Topiramate vs Placebo</u> Average daily pain score, 0-10 Mean score: 2.4 (p=0.04) vs 4.1 at 12 weeks	NR	NR

Evidence Table 8. Original report: Data abstraction of other antiepileptics and tricyclic antidepressants

Study	Specific adverse events
Finnerup	Lamotrigine vs Placebo
2002	Any adverse event: 48.1% (13/27) vs 50.0% (14/28)
Denmark	CNS AEs: 44.4% (12/27) vs 32.1% (9/28)
	Gastrointestinal AEs: 14.8% (4/27) vs 10.7% (3/28)
Efficacy quality: Fair	Skin AEs: 14.8% (4/27) vs 14.3% (4/28)
Gilron (B)	NR
2001	
US	
Efficacy quality: Poor	

Evidence Table 8. Original report: Data abstraction of other antiepileptics and tricyclic antidepressants

Study	Design	Type of pain Sample size and characteristics	Intervention
Hammack	RCT	Cisplatinum-induced neuropathic pain	Nortriptyline
2002	Crossover		N=26
US	Multicenter	N=51	
			Placebo
Efficacy quality: Fair		Age	N=25
		Mean (SD): 59.5	
		Male: NR%	
		Female: NR%	

Evidence Table 8. Original report: Data abstraction of other antiepileptics and tricyclic antidepressants

Study	Eligibility	Exclusion
Hammack 2002 US Efficacy quality: Fair	Age 18 or older, have received cisplatin chemotherapy, and have had painful paresthesia for at least 1 months attributed to cisplatin neuropathy. Required to have evidence on examination of a sensory peripheral neuropathy in which alternate causes were reasonably excluded (i.e., diabetes, thyroid dysfunction, monoclonal gammopathy, HIV neuropathy, heritable neuropathy, paraneoplastic neuropathy, and B12 deficiency.	History of diabetes, glaucoma, prostatism, dementia, HIV infection, major psychiatric disease, significant cardiac disease, or postural hypotension; other identified causes of sensory neuropathy and paresthesia; pregnant or lactating women; patients who had used another antidepressant, opioid analgesics, or other adjuvant analgesic (i.e. anticonvulsants, clonazepam, or mexiletine) in the week prior to commencing the study; having used another investigational agent for pain control during the study or within the preceding 30 days.

Evidence Table 8. Original report: Data abstraction of other antiepileptics and tricyclic antidepressants

Study	Patient-reported pain	Functional capacity	Withdrawals Withdrawals due to adverse events
Hammack 2002 US Efficacy quality: Fair	Nortriptyline vs Placebo Improvement, 13-item descriptor scale Mean difference from placebo (%): 24% (p=0.014; 95% CI: 6%-42%) at 6 weeks Severity of pain, Verbal descriptor scale (5 points) Mean change from baseline: -0.5 vs -0.4 at 4 weeks (p=0.99) Severity of pain, Visual analogue scale (0-100) Mean change from baseline: -7.7 vs -2.7 at 4 weeks (p=0.78)	Nortriptyline vs Placebo Interference, Verbal descriptor scale (5 points) Mean change from baseline: -0.3 vs 0.2 at 4 weeks (p=0.04) Quality of life, Visual analogue scale (0-100) Mean change from baseline: -4.6 vs -7.7 at 4 weeks (p=0.74)	Nortriptyline vs Placebo Total: 2 (7.69%) vs 4 (16%) AE: 2 (7.69%) vs 4 (16%)

Evidence Table 8. Original report: Data abstraction of other antiepileptics and tricyclic antidepressants

Study	Specific adverse events
Hammack	Nortriptyline vs Placebo
2002	Constipation: 41.3% (19/46) vs 22.2% (10/45)
US	Difficult to urinate: 4.3% (2/46) vs 6.7% (3/45)
	Dry mouth: 63.0% (29/46) vs 31.1% (14/45)
Efficacy quality: Fair	Nausea: 8.7% (4/46) vs 6.7% (3/45)
	Sedation: 30.4% (14/46) vs 26.7% (12/45)

Evidence Table 8. Original report: Data abstraction of other antiepileptics and tricyclic antidepressants

Study	Design	Type of pain Sample size and characteristics	Intervention
Kalso	RCT	Cancer-related neuropathic pain	Amitriptyline
1995	Crossover		50 mg
Finland	Single Center	N=15	N=15
Efficacy quality: Fair		Age	Amitriptyline
		Mean (SD): 56.0	100 mg
		Range: 39-72	N=15
		Male: 0%	Placebo
		Female: 100%	N=15

Evidence Table 8. Original report: Data abstraction of other antiepileptics and tricyclic antidepressants

Study	Eligibility	Exclusion
Kalso 1995 Finland	Neuropathic pain following treatment for breast cancer. Pain had to be either in the anterior chest wall, and/or axilla and/or medial upper arm in an area with sensory disturbances.	Relapses or metastases of the breast cancer and clinically overt cardiac, renal, or hepatic disease.

Efficacy quality: Fair

Evidence Table 8. Original report: Data abstraction of other antiepileptics and tricyclic antidepressants

Study	Patient-reported pain	Functional capacity	Withdrawals Withdrawals due to adverse events
Kalso 1995 Finland Efficacy quality: Fair	Amitriptyline 50 mg vs Amitriptyline 100 mg vs Placebo Pain intensity, VAS (10 cm) Median score (breast scar area): 1.8 vs 0.2 vs 2.6 at 1 week Pain intensity, VAS (10 cm) Median score (ipsilateral arm): 1.9 vs 0.5 (p<0.05) vs 2.5 at 1 week Pain intensity, VRS (8-point) Median score (breast scar area): 2.2 vs 1.9 (p<0.05) vs 2.3 at 1 week Pain intensity, VRS (8-point) Median score (ipsilateral arm): 2.6 vs 1.8 (p<0.05) vs 3.1 at 1 week Pain relief, VRS (5-point) Median score (breast scar area): 3.0 vs 3.0 (p<0.05) vs 1.0 at 1 week Pain relief, VRS (5-point) Median score (ipsilateral arm): 3.0 vs 3.0 (p<0.05) vs 1 at 1 week Pain, MPQ Total score Median score (breast scar region): NR vs 1151 (p<0.05) vs 3221 at 1 week Pain, MPQ Total score Median score (ipsilateral arm): NR vs 1757 (p<0.01) vs 2766 at 1 week	NR	NR

Evidence Table 8. Original report: Data abstraction of other antiepileptics and tricyclic antidepressants

Study	Specific adverse events
Kalso	Amitriptyline 50 mg vs Amitriptyline 100 mg vs Placebo
1995	Anorexia: 20.0% (3/15) vs 20.0% (3/15) vs 21.4% (6/28)
Finland	Constipation: 40.0% (6/15) vs 13.3% (2/15) vs 10.7% (3/28)
	Difficult to urinate: 20.0% (3/15) vs 0.0% (0/15) vs 3.6% (1/28)
Efficacy quality: Fair	Dizziness: 6.7% (1/15) vs 0.0% (0/15) vs 0.0% (0/28)
	Dry mouth: 86.7% (13/15) vs 26.7% (4/15) vs 32.1% (9/28)
	Fatigue: 80.0% (12/15) vs 40.0% (6/15) vs 50.0% (14/28)
	Headache: 33.3% (5/15) vs 20.0% (3/15) vs 28.6% (8/28)
	Nausea: 20.0% (3/15) vs 20.0% (3/15) vs 17.9% (5/28)
	Nightmares: 40.0% (6/15) vs 26.7% (4/15) vs 32.1% (9/28)
	Palpitations: 46.7% (7/15) vs 33.3% (5/15) vs 32.1% (9/28)
	Paresthesia: 0.0% (0/15) vs 0.0% (0/15) vs 3.6% (1/28)
	Sweating increased: 80.0% (12/15) vs 40.0% (6/15) vs 50.0% (14/28)

Evidence Table 8. Original report: Data abstraction of other antiepileptics and tricyclic antidepressants

Study	Design	Type of pain Sample size and characteristics	Intervention
Kieburtz 1998 US Efficacy quality: Fair	RCT Parallel Multicenter	HIV-related neuropathic pain N=145 Age Mean (SD): 40 Male: 95.9% Female: 4.1% Race/ethnicity White: 70% Black: 21.4% Hispanic: 8.3% Other: 1.4%	Amitriptyline 25-100 mg N=47 Mexiletine 150 mg N=48 Benztropine mesylate 0.125 mg N=50
Kishore-Kumar 1990 US Efficacy quality: Poor	RCT Crossover Single Center	Post-herpetic neuralgia N=26 Age Mean (SD): 62 Range: 38-79 Male: 65.38% Female: 34.62%	Desipramine mean 167 mg N=26 Benztropine mesylate 0.5-1 mg N=26
Kochar (A) 2002 India Efficacy quality: Fair	RCT Parallel Single Center	Painful diabetic neuropathy N=52 Age Mean (SD): 56.3 Male: 55.77% Female: 44.23%	Valproic acid/divalproex/sodium valproate 600 mg N=29 Placebo N=28

Evidence Table 8. Original report: Data abstraction of other antiepileptics and tricyclic antidepressants

Study	Eligibility	Exclusion
Kieburtz 1998 US Efficacy quality: Fair	HIV infection and clinical symptoms and signs sufficient for a diagnosis of painful neuropathy defined as 1) primary symptoms of symmetrical pain, burning or tingling discomfort in the feet for a least 2 weeks, and rated on the pain intensity scale as at least mild all the time or moderate for a total of at least 2 hours per day; and additionally, either 2) diminished or absent ankle reflexes or 3) distal diminution of vibratory sense or diminished pain and temperature sensation in the legs as assessed by study clinicians, many not being neurologists. Additional criteria being on a stable dosage (if taken by the subject) of dideoxynucleoside analogs for at least 8 weeks before randomization and of cimetidine for at least 2 weeks before randomization and having serum liver function enzyme levels less than five times the upper limit of normal.	If painful neuropathy was clearly attributable to another neuropathic drug (e.g., cisplatin, nitrofurantoin), if they were taking cardiac antiarrhythmic agents or tricyclic or tetracyclic antidepressants, or if they had a greater than 50% change in the dosage per week of medications for pain control in the week before entry. Diabetes mellitus, documented history of cardiac disease, or EKG demonstrating a malignant arrhythmia and those with a history of seizure disorder.
Kishore-Kumar 1990 US Efficacy quality: Poor	Postherpetic neuralgia and 1) daily pain, persisting at least 3 months after a segmental herpes zoster eruption and 2) normal cognitive and communicative ability, as judged by performance in completing a pain diary, paper-and-pencil psychologic tests, and telephone conversations.	1) presence of another type of pain as severe as the postherpetic neuralgia, 2) depression severe enough (e.g., suicidal ideation) to mandate immediate treatment with tricyclic medications, and 3) medical contraindications to the use of desipramine.
Kochar (A) 2002 India Efficacy quality: Fair	Patients with type 2 diabetes with painful neuropathy attending the diabetes clinic at one hospital.	Liver disease, pulmonary tuberculosis, thyroid disorders, uremia, vitamin deficiency, hereditary and paraneoplastic neuropathy, alcoholism, and patients on steroid therapy.

Evidence Table 8. Original report: Data abstraction of other antiepileptics and tricyclic antidepressants

Study	Patient-reported pain	Functional capacity	Withdrawals Withdrawals due to adverse events
Kieburtz 1998 US Efficacy quality: Fair	Amitriptyline vs Mexiletine vs Benztropine mesylate Global Impression of Change, Moderate, a lot, or complete relief % of patients: 50% (p=0.164) vs 45.8% vs 48% at Week 8 Pain intensity, Gracely Pain Scale Mean change from baseline: 0.31 (p=0.38; 95% CI: 0.21, 0.41) vs 0.23 vs 0.20 at Week 8	NR	Amitriptyline vs Mexiletine vs Benztropine mesylate Total: 13 (27.66%) vs 14 (29.17%) vs 12 (24%) AE: 3 (6.38%) vs 4 (8.33%) vs 4 (8%)
Kishore-Kumar 1990 US Efficacy quality: Poor	Desipramine vs Benztropine mesylate Average pain intensity, Verbal descriptor scale (Gracely pain scale) Mean score: data NR, desipramine superior to placebo at 6 weeks (p<0.001) Pain relief, Moderate or better relief % of patients: 63% vs 11% at 6 weeks	NR	Desipramine vs Benztropine mesylate Total: 5 (19.23%) vs 3 (11.54%) AE: 5 (19.23%) vs 3 (11.54%)
Kochar (A) 2002 India Efficacy quality: Fair	Valproic acid vs Placebo Pain, McGill Pain Score Mean score: 3.41 (p=0.028; 95% CI: 2.73, 4.09) vs 4.6 (95% CI: 3.81, 5.39) at 4 weeks	NR	NR

Evidence Table 8. Original report: Data abstraction of other antiepileptics and tricyclic antidepressants

Study	Specific adverse events
Kieburtz	Amitriptyline vs Mexiletine vs Benztropine mesylate
1998	Confusion: 2.1% (1/47) vs 0.0% (0/48) vs 4.0% (2/50)
US	Difficult to urinate: 0.0% (0/47) vs 6.3% (3/48) vs 2.0% (1/50)
	Dizziness: 0.0% (0/47) vs 2.1% (1/48) vs 0.0% (0/50)
Efficacy quality: Fair	Nausea: 0.0% (0/47) vs 20.8% (10/48) vs 20.0% (10/50)
	Sedation: 21.3% (10/47) vs 0.0% (0/48) vs 0.0% (0/50)
Kishore-Kumar	Desipramine vs Benztropine mesylate
1990	Bad taste: 10.5% (2/19) vs 10.5% (2/19)
US	Constipation: 73.7% (14/19) vs 15.8% (3/19)
	Difficult to urinate: 26.3% (5/19) vs 5.3% (1/19)
Efficacy quality: Poor	Dizziness: 36.8% (7/19) vs 26.3% (5/19)
	Dry mouth: 73.7% (14/19) vs 47.4% (9/19)
	Insomnia: 21.1% (4/19) vs 0.0% (0/19)
	Itching: 0.0% (0/19) vs 10.5% (2/19)
	Palpitations: 10.5% (2/19) vs 0.0% (0/19)
	Sedation: 31.6% (6/19) vs 0.0% (0/19)
	Shakiness: 10.5% (2/19) vs 5.3% (1/19)
	Sweating increased: 21.1% (4/19) vs 0.0% (0/19)
Kochar (A)	NR
2002	
India	
Efficacy quality: Fair	

Evidence Table 8. Original report: Data abstraction of other antiepileptics and tricyclic antidepressants

Study	Design	Type of pain Sample size and characteristics	Intervention
Kochar (B) 2004 India Efficacy quality: Fair	RCT Parallel	Painful diabetic neuropathy N=39 Age Mean (SD): 55.2 Male: 53.85% Female: 46.15%	Valproic acid/divalproex/sodium valproate 500 mg N=22 Placebo N=21

Evidence Table 8. Original report: Data abstraction of other antiepileptics and tricyclic antidepressants

Study	Eligibility	Exclusion
Kochar (B) 2004 India Efficacy quality: Fair	1) Diabetes for at least 6 months on stable dosage of insulin or oral hypoglycemic agent and having reasonable diabetic control (HvA1c <11%), 2) daily neuropathic pain of at least moderate severity for >3 months, which interfered with daily activity or sleep, 3) pain intensity of >4 on a visual analogue pain scale, and 4) written consent to participate in the study.	Liver disease, pulmonary tuberculosis, thyroid disorders, uremia, vitamin deficiency, hereditary and paraneoplastic neuropathy, alcoholism, or on steroid therapy.

Evidence Table 8. Original report: Data abstraction of other antiepileptics and tricyclic antidepressants

Study	Patient-reported pain	Functional capacity	Withdrawals Withdrawals due to adverse events
Kochar (B) 2004 India Efficacy quality: Fair	Valproic acid vs Placebo Pain intensity, Present Pain Intensity Mean score: 1.33 (p<0.001; 95% CI: 0.04, 2.62) vs 2.61 (95% CI: 0.81, 4.41) at 3 months Pain, SF-McGill Pain Questionnaire Mean score: 9.66 (p<0.001; 95% CI: -2.02, 21.34) vs 17.88 (95% CI: 7.26, 28.50) at 3 months Pain, VAS (0-10) Mean score: 3.0 (p<0.001; 95% CI: -1.16, 7.16) vs 6.0 (95% CI: 2.39, 9.61) at 3 months	NR	NR

Evidence Table 8. Original report: Data abstraction of other antiepileptics and tricyclic antidepressants

Study	Specific adverse events
Kochar (B) 2004 India Efficacy quality: Fair	NR

Evidence Table 8. Original report: Data abstraction of other antiepileptics and tricyclic antidepressants

Study	Design	Type of pain Sample size and characteristics	Intervention
Kochar (C) 2005 India Efficacy quality: Fair	CT Parallel Single Center	Painful diabetic neuropathy N=40 Age Mean (SD): 57.24 Male: 55% Female: 45%	Valproic acid/divalproex/sodium valproate 1000 mg daily N=23 Placebo N=22
Leijon 1989 Sweden Efficacy quality: Fair	CT Crossover Single Center	Central/post-stroke neuropathic pain N=15 Age Mean (SD): 66 Range: 53-74 Male: 80% Female: 20%	Amitriptyline 25 + 50 mg BID Total daily dose: 75 mg N=15 Carbamazepine 400 mg BID Total daily dose: 800 mg N=14 Placebo N=15

Evidence Table 8. Original report: Data abstraction of other antiepileptics and tricyclic antidepressants

Study	Eligibility	Exclusion
Kochar (C) 2005 India Efficacy quality: Fair	Post-herpetic neuralgia patients in a hospital-based outpatient department; first 48 consecutive attenders who gave consent; adult patients having persistent pain for >6 months after onset of herpes zoster rash and at least 40/100mm point on visual analog scale and 4/11 point on Likert scale	Insufficient pain score on subsequent examination (visual analog scale <40) or withdrawn consent; no topical or other oral drugs during study
Leijon 1989 Sweden Efficacy quality: Fair	Unequivocal stroke episode; should seek remedy for constant or intermittent pain after stroke; pain was not nociceptive, peripheral neuropathic or psychogenic in origin	Known contraindication to both amitriptyline and carbamazepine; could not be evaluated in a satisfactory way

Evidence Table 8. Original report: Data abstraction of other antiepileptics and tricyclic antidepressants

Study	Patient-reported pain	Functional capacity	Withdrawals Withdrawals due to adverse events
Kochar (C) 2005 India Efficacy quality: Fair	Valproic acid vs Placebo Pain intensity, Present Pain Intensity Mean score: 1.95 (p<0.0001; 95% CI: -0.58, 4.48) vs 3.22 (95% CI: 1.26, 5.18) at 8 weeks Pain, 11-point Likert scale (0-10) Mean score: 3.63 (p<0.0001; 95% CI: -0.96, 8.22) vs 5.33 (95% CI: 2.04, 8.62) at 8 weeks Pain, SF-McGill Pain Questionnaire Mean score: 11.9 (p<0.0001; 95% CI: -0.88, 24.68) vs 16.11 (95% CI: 9.45, 22.77) at 8 weeks Pain, VAS (0-100) Mean score: 31.27 (p<0.0001; 95% CI: -27.12, 89.66) vs 54.94 (95% CI: 20.58, 89.30) at 8 weeks Response, At least 50% pain relief % of patients: 59.1% vs 11.1% at 8 weeks	NR	NR
Leijon 1989 Sweden Efficacy quality: Fair	Amitriptyline vs Carbamazepine vs Placebo Global Impression of Change, Improved % of patients: 66.7% (p<0.05) vs 35.7% vs 6.7% at 4 weeks Pain intensity, 10-step verbal rating scale Mean score: 4.2 (p<0.05; 95% CI: 3.39, 5.01) vs 4.2 (95% CI: 3.31, 5.09) vs 5.3 (95% CI: 4.29, 6.31) at 4 weeks	NR	Amitriptyline vs Carbamazepine vs Placebo Total: 0 (0%) vs 0 (0%) vs 0 (0%) AE: 0 (0%) vs 0 (0%) vs 0 (0%)

Evidence Table 8. Original report: Data abstraction of other antiepileptics and tricyclic antidepressants

Study	Specific adverse events
Kochar (C) 2005 India Efficacy quality: Fair	NR
Leijon 1989 Sweden Efficacy quality: Fair	Amitriptyline vs Carbamazepine vs Placebo Any adverse event: 93.3% (14/15) vs 92.9% (13/14) vs 46.7% (7/15)

Evidence Table 8. Original report: Data abstraction of other antiepileptics and tricyclic antidepressants

Study	Design	Type of pain Sample size and characteristics	Intervention
Max (A) 1987 US	RCT Crossover Single Center	Painful diabetic neuropathy N=37	Amitriptyline mean 90 mg N=37
Efficacy quality: Fair		Age Mean (SD): 57 Male: 58.62% Female: 41.38%	Benztropine mesylate 1 mg N=37
Max (B) 1991 US	RCT Crossover	Painful diabetic neuropathy N=24	Desipramine N=24 Benztropine mesylate
Efficacy quality: Fair		Age Mean (SD): 62 Range: 21-71 Gender Male: 62.5% Female: 37.5%	N=24
Max (C) 1988 US	RCT Crossover Single Center	Post-herpetic neuralgia N=58	Amitriptyline 12.5-150 mg (mean 65 mg) N=58
Efficacy quality: Fair		Age Mean (SD): 72 Range: 25-86 Male: 53.45% Female: 46.55%	Lorazepam 0.5-6 mg (mean 2.4 mg) N=58 Placebo N=58

Evidence Table 8. Original report: Data abstraction of other antiepileptics and tricyclic antidepressants

Study	Eligibility	Exclusion
Max (A) 1987 US Efficacy quality: Fair	1) symptoms and signs of diffuse, predominantly sensory neuropathy or single or multiple mononeuropathy; 2) pain during some part of every day; and 3) active diabetes or a history of diabetes, with a fasting glucose over 180 mg/dl on at least one occasion.	1) evidence of another etiology for neuropathy; 2) another painful condition at least as severe as the neuropathic pain; 3) cognitive or language impairment revealed by difficulty in completing the pain diary, paper-and-pencil psychological tests, and telephone conversations; 4) contraindications to amitriptyline therapy, including heart block, unstable cardiovascular disease, or gait impairment; and 5) severe depression with suicide risk.
Max (B) 1991 US Efficacy quality: Fair	1) Symptoms and signs of diffuse, predominantly sensory neuropathy or single or multiple mononeuropathy; 2) daily pain, persisting at least 3 months; 3) active diabetes or a history of diabetes; and 4) normal cognitive and communicative ability, as judged by performance in completing a pain diary, paper-and-pencil psychological tests, and telephone conversations.	1) evidence of another etiology for neuropathy; 2) presence of another type of pain as severe as the neuropathic pain; 3) depression severe enough (e.g., suicidal ideation) to mandate immediate treatment with tricyclic medication; and 4) medical contraindications to the use of desipramine.
Max (C) 1988 US Efficacy quality: Fair	1) daily pain, persisting at least 3 months after a segmental herpes zoster eruption, and 2) normal cognitive and communicative ability, as judged by performance in completing a pain diary, paper-and-pencil psychological tests, and telephone conversations.	1) presence of another type of pain as severe as the postherpetic neuralgia, 2) depression severe enough (e.g., suicidal ideation) to mandate immediate treatment with tricyclic medication, and 3) medical contraindications to the use of amitriptyline or lorazepam.

Evidence Table 8. Original report: Data abstraction of other antiepileptics and tricyclic antidepressants

Study	Patient-reported pain	Functional capacity	Withdrawals Withdrawals due to adverse events
Max (A) 1987 US Efficacy quality: Fair	<u>Amitriptyline vs Benztropine mesylate</u> Pain relief, Reporting greater pain relief with amitriptyline % of patients: 79.3% (p<0.0001) vs 3.4% at 12 weeks	NR	NR
Max (B) 1991 US Efficacy quality: Fair	<u>Desipramine vs Benztropine mesylate</u> Pain intensity, Verbal descriptor scale (Gracely) Mean score: data reported graphically, desipramine superior to placebo at 6 weeks (p<0.01) Pain relief, Moderate or better relief % of patients: 55% vs 11% at 6 weeks	NR	<u>Desipramine vs Benztropine mesylate</u> Total: 2 (8.33%) vs 2 (8.33%) AE: 2 (8.33%) vs 1 (4.17%)
Max (C) 1988 US Efficacy quality: Fair	<u>Amitriptyline vs Lorazepam vs Placebo</u> Average pain intensity Mean score: reported graphically only at 6 weeks Pain relief, Moderate or greater relief % of patients: reported graphically only at 6 weeks	NR	NR

Evidence Table 8. Original report: Data abstraction of other antiepileptics and tricyclic antidepressants

Study	Specific adverse events
Max (A)	Amitriptyline vs Benztropine mesylate
1987	Any adverse event: 96.6% (28/29) vs 86.2% (25/29)
US	Constipation: 13.8% (4/29) vs 0.0% (0/29)
	Difficult to urinate: 3.4% (1/29) vs 3.4% (1/29)
Efficacy quality: Fair	Dizziness: 27.6% (8/29) vs 10.3% (3/29)
	Dry mouth: 89.7% (26/29) vs 69.0% (20/29)
	Mood change: 6.9% (2/29) vs 0.0% (0/29)
	Sedation: 65.5% (19/29) vs 41.4% (12/29)
	Tinnitus: 3.4% (1/29) vs 0.0% (0/29)
Max (B)	Desipramine vs Benztropine mesylate
1991	Constipation: 30.0% (6/20) vs 20.0% (4/20)
US	Dry mouth: 40.0% (8/20) vs 45.0% (9/20)
	Insomnia: 35.0% (7/20) vs 15.0% (3/20)
Efficacy quality: Fair	Orthostatic symptoms: 30.0% (6/20) vs 5.0% (1/20)
	Palpitations: 15.0% (3/20) vs 5.0% (1/20)
	Sedation: 40.0% (8/20) vs 40.0% (8/20)
	Sweating increased: 15.0% (3/20) vs 5.0% (1/20)
Max (C)	Amitriptyline vs Lorazepam vs Placebo
1988	Concentration poor: 5.2% (3/58) vs 0.0% (0/58) vs 0.0% (0/58)
US	Difficult to urinate: 12.1% (7/58) vs 0.0% (0/58) vs 0.0% (0/58)
	Dizziness: 19.0% (11/58) vs 32.8% (19/58) vs 24.1% (14/58)
Efficacy quality: Fair	Dry mouth: 62.1% (36/58) vs 29.3% (17/58) vs 39.7% (23/58)
	Mood change: 5.2% (3/58) vs 17.2% (10/58) vs 0.0% (0/58)
	Sedation: 62.1% (36/58) vs 65.5% (38/58) vs 39.7% (23/58)
	Tinnitus: 5.2% (3/58) vs 0.0% (0/58) vs 3.4% (2/58)

Evidence Table 8. Original report: Data abstraction of other antiepileptics and tricyclic antidepressants

Study	Design	Type of pain Sample size and characteristics	Intervention
McCleane 1999 UK Efficacy quality: Poor	RCT Parallel Single Center	Mixed N=74 Age Mean (SD): 45.9 Male: 47.3% Female: 52.7%	Lamotrigine 200 mg N=36 Placebo N=38
Otto 2004 Denmark Efficacy quality: Fair	RCT Crossover	Polyneuropathy N=31 Age Mean (SD): 60 Range: 34-81 Male: 61.29% Female: 38.71%	Valproic acid/divalproex/sodium valproate 1500 mg N=37 Placebo N=37
Panerai 1990 Italy Efficacy quality: Poor	RCT Crossover	Mixed N=39 Age Mean (SD): 49.0 Male: 56.41% Female: 43.59%	Nortriptyline N=39 Chlorimipramine N=39 Placebo N=39
Raja 2002 US Efficacy quality: Fair	RCT Crossover	Post-herpetic neuralgia N=76 Age Mean 71 (range 32-90) 45% male, 55% female 88% white, 11% black, 1% other	Nortriptyline mean 89 mg; switched to desipramine if not tolerated Placebo

Evidence Table 8. Original report: Data abstraction of other antiepileptics and tricyclic antidepressants

Study	Eligibility	Exclusion
McCleane 1999 UK Efficacy quality: Poor	Adult patients presenting to a Pain Clinic with intractable neuropathic pain (diagnosed on the presence of at least 3 of the cardinal symptoms of neuropathic pain-shooting/lancinating, burning, numbness, allodynia, paresthesia,/dysesthesia). All patients had failed to respond to a previous trial of codeine based analgesics or non-steroidal antiinflammatory drugs.	Known sensitivity to lamotrigine or already taking an anticonvulsant.
Otto 2004 Denmark Efficacy quality: Fair	Polyneuropathy >=6 months confirmed by electrophysiologic tests, and age >20 years. At study entry during 1-week off medication patients had a median pain rating of at least 4 on a 0 to 10 point numeric scale for total pain	Causes of pain other than polyneuropathy, previous allergic reactions to valproic acid, pregnancy and lactating, liver disease, thrombocytopenia, and severe terminal illness.
Panerai 1990 Italy Efficacy quality: Poor	Men and women, in- or outpatients, aged 18-80 years, affected by central pain lasting at least 6 months following limb amputation, phantom or stump pain, postherpetic neuropathy or post-traumatic nerve lesions.	Clinically evident heart or renal failure, severe liver disease, A-V conduction disturbances or class III or IV left ventricular arrhythmias, epilepsy, glaucoma, prostatic hypertrophy, pregnancy or nursing, and known hypersensitivity to tricyclic antidepressants.
Raja 2002 US Efficacy quality: Fair	Age >18 years, pain persisting for >=3 months after the resolution of the cutaneous lesions, and typical pin intensity of >=4 (0 to 10 numerical rating scale) during the previous week.	History of substance abuse or an allergic reaction to an opioid or a tricyclic antidepressant, a myocardial infarction in the previous 3 months, cardia conduction defects, severe pulmonary disease, or encephalopathy, HIV positive, life expectancy <6 months; patients on MAO inhibitors or with severe depression precluding withdrawal from antidepressants.

Evidence Table 8. Original report: Data abstraction of other antiepileptics and tricyclic antidepressants

Study	Patient-reported pain	Functional capacity	Withdrawals Withdrawals due to adverse events
McCleane 1999 UK Efficacy quality: Poor	Lamotrigine vs Placebo Pain, VAS (0-10) Mean change from baseline: -0.01 vs 0.03 at 8 weeks	Lamotrigine vs Placebo Mobility, VAS (0-10) Mean change from baseline: -0.36 vs -0.17 at 8 weeks Quality of life, VAS (0-10) Mean change from baseline: -0.38 vs -0.15 at 8 weeks	NR
Otto 2004 Denmark Efficacy quality: Fair	Valproic acid vs Placebo Pain relief, Complete, good, or moderate relief % of patients: 9.7% (p=0.13) vs 25.8% at 4 weeks Pain, Numeric scale (0-10) Median score: 5 (p=0.24) vs 6 at 4 weeks	NR	NR
Panerai 1990 Italy Efficacy quality: Poor	Nortriptyline vs Chlorimipramine vs Placebo Pain intensity, VAS (0-100 mm) Mean score: reported graphically only, nortriptyline and chlorimipramine both superior to placebo at 3 weeks (p<0.0001)	NR	Nortriptyline vs Chlorimipramine vs Placebo Total: 7 (17.95%) vs 1 (2.56%) vs 7 (17.95%) AE: 2 (5.13%) vs 0 (0%) vs 1 (2.56%)
Raja 2002 US Efficacy quality: Fair	NR	NR	NR

Evidence Table 8. Original report: Data abstraction of other antiepileptics and tricyclic antidepressants

Study	Specific adverse events
McCleane 1999 UK Efficacy quality: Poor	NR
Otto 2004 Denmark Efficacy quality: Fair	NR
Panerai 1990 Italy Efficacy quality: Poor	Nortriptyline vs Chlorimipramine vs Placebo Any adverse event: 56.4% (22/39) vs 59.0% (23/39) vs 25.6% (10/39)
Raja 2002 US Efficacy quality: Fair	NR

Evidence Table 8. Original report: Data abstraction of other antiepileptics and tricyclic antidepressants

Study	Design	Type of pain Sample size and characteristics	Intervention
Raskin (A)	RCT	Painful diabetic neuropathy	Topiramate
2004	Parallel		mean 320 mg
US	Multicenter	N=317	N=208
Efficacy quality: Fair		Age	Placebo
		Mean (SD): 59.2 (9.8)	N=109
		Male: 49.53%	
		Female: 50.47%	
		White: 87.4%	
		Black: 11.4%	
		Other: 1.3%	

Evidence Table 8. Original report: Data abstraction of other antiepileptics and tricyclic antidepressants

Study	Eligibility	Exclusion
Raskin (A) 2004 US Efficacy quality: Fair	Men and women aged 18 to 75 years with a history of symmetric painful diabetic neuropathy in the lower extremities for at least 3 months but <=10 years. Diabetic neuropathy was confirmed by clinical, electrophysiologic, or quantitative sensory testing, and subjects were required to have maintained stable glycemic control (HbA1c <=11%) with oral hypoglycemics, insulin, or diet for at least 3 months before randomization. Women were required to practice adequate contraception during the study or be incapable of becoming pregnant	Other potential causes of peripheral neuropathy (including drug-induced neuropathy), another painful condition that was more severe than the diabetic neuropathy, a degenerative neurologic disorder, open ulcer, amputation, active infection, or Charcot joint, a history of nephrolithiasis, attempted suicide, suicidal tendencies, or substance abuse, or a clinically significant medical condition, including abnormal renal or hepatic function, symptomatic coronary artery or peripheral vascular disease, malignancy within the past 5 years, or major psychiatric disorder. Subjects also excluded if they required continued treatment with anticonvulsant or antipsychotic therapy, if they used acetazolamide, triamterene, zonisamide, or an investigational drug or device within 30 days before enrollment, if they took multiple daily doses of any narcotic analgesic on a regular basis, or if they had a history of topiramate hypersensitivity, topiramate treatment failure for a painful condition, or any topiramate treatment within 30 days before enrollment.

Evidence Table 8. Original report: Data abstraction of other antiepileptics and tricyclic antidepressants

Study	Patient-reported pain	Functional capacity	Withdrawals Withdrawals due to adverse events
Raskin (A) 2004 US Efficacy quality: Fair	Topiramate vs Placebo Global Impression of Efficacy, Good, very good, or excellent efficacy % of patients: 53.8% vs 33.9% at 12 weeks Pain intensity (current pain), 5-point numeric scale (1-5) Mean score: data reported graphically only (p=0.093) Pain intensity (worst pain), 5-point numeric scale (1-5) Mean score: data reported graphically only (p=0.003) Pain intensity, VAS (0-100) Mean score: 46.2 (p=0.038) vs 54.0 at 12 weeks Response, >30% decrease in VAS % of patients: 49.5% (p=0.004) vs 33.9% at 12 weeks Response, >50% decrease in VAS % of patients: 35.6% (p=0.005) vs 21.1% at 12 weeks	Topiramate vs Placebo Quality of life, SF-36 Mental Component Summary Mean score: 46.9 (p=0.023; 95% CI: 45.28, 48.52) vs 49.9 (95% CI: 48.00, 51.80) at 12 weeks Quality of life, SF-36 Physical Component Summary Mean score: 37.2 (p=0.066; 95% CI: 35.76, 38.64) vs 34.9 (95% CI: 33.14, 36.66) at 12 weeks	Topiramate vs Placebo Total: 102 (49.04%) vs 29 (26.61%) AE: 52 (25%) vs 9 (8.26%)

Evidence Table 8. Original report: Data abstraction of other antiepileptics and tricyclic antidepressants

Study	Specific adverse events
Raskin (A)	Topiramate vs Placebo
2004	Accidental injury: 3.8% (8/211) vs 7.3% (8/109)
US	Anorexia: 10.9% (23/211) vs 0.9% (1/109)
	Bad taste: 6.6% (14/211) vs 0.0% (0/109)
Efficacy quality: Fair	Concentration poor: 5.2% (11/211) vs 0.9% (1/109)
	Diarrhea: 11.4% (24/211) vs 3.7% (4/109)
	Dizziness: 7.1% (15/211) vs 5.5% (6/109)
	Fatigue: 7.1% (15/211) vs 1.8% (2/109)
	Headache: 5.7% (12/211) vs 9.2% (10/109)
	Joint pain: 3.8% (8/211) vs 5.5% (6/109)
	Nausea: 9.5% (20/211) vs 5.5% (6/109)
	Paresthesia: 8.5% (18/211) vs 1.8% (2/109)
	Sinusitis: 6.2% (13/211) vs 5.5% (6/109)
	Somnolence: 10.0% (21/211) vs 3.7% (4/109)
	Upper respiratory tract infection: 9.0% (19/211) vs 5.5% (6/109)

Evidence Table 8. Original report: Data abstraction of other antiepileptics and tricyclic antidepressants

Study	Design	Type of pain Sample size and characteristics	Intervention
Robinson 2004 US Efficacy quality: Fair	RCT Parallel Single Center	Phantom limb pain N=39 Age Mean (SD): 44.8 Male: 87.2% Female: 12.8%	Amitriptyline N=20 Benztropine mesylate N=19
Rockliff 1966 US Efficacy quality: Poor	RCT Crossover Single Center	Trigeminal neuralgia N=9 Age Mean (SD): 64.8 Range: 37-81 Male: 11.11% Female: 88.89%	Carbamazepine 600 mg N=9 Placebo N=9
Rull 1969 Mexico Efficacy quality: Fair	RCT Crossover	Painful diabetic neuropathy N=30 Age Mean 54.2 (range 21-81) 30% male, 70% female	Carbamazepine 600 mg Placebo

Evidence Table 8. Original report: Data abstraction of other antiepileptics and tricyclic antidepressants

Study	Eligibility	Exclusion
Robinson 2004 US Efficacy quality: Fair	Amputation more than 6 months before enrollment, pain for at least 3 months, and average pain rating in the last month of at least 2 on a scale of 0 to 10.	Less than 18 years or more than 65 years of age, history of cardiovascular disease or seizures, were pregnant, on any type of antidepressant medication, or reported consuming more than 2 alcoholic drinks per day. Those 50 years or older had a screening ECG and were excluded if they had conducting abnormalities.
Rockliff 1966 US Efficacy quality: Poor	Active, typical trigeminal neuralgia.	Atypical facial pain or postherpetic neuralgia.
Rull 1969 Mexico Efficacy quality: Fair	Diabetic patients with well established subjective sensory manifestations of somatic neuropathy.	NR

Evidence Table 8. Original report: Data abstraction of other antiepileptics and tricyclic antidepressants

Study	Patient-reported pain	Functional capacity	Withdrawals Withdrawals due to adverse events
Robinson 2004 US Efficacy quality: Fair	<u>Amitriptyline vs Benztropine mesylate</u> Average pain intensity (Phantom Limb Pain), Numeric rating scale (0-10) Mean score: 3.1 (95% CI: 1.92, 4.28) vs 3.1 (95% CI: 1.80, 4.40) at 6 weeks Average pain intensity (Residual Limb Pain), Numeric rating scale (0-10) Mean score: 3.1 (95% CI: 2.14, 4.06) vs 2.3 (95% CI: 1.40, 3.20) at 6 weeks Average pain, SF McGill Pain Questionnaire Mean score: 11.6 (95% CI: 7.22, 15.98) vs 12.5 (95% CI: 8.63, 16.37) at 6 weeks Interference with activities, BPI Mean score: 30.3 (95% CI: 16.89, 43.71) vs 24.2 (95% CI: 14.58, 33.82) at 6 weeks	<u>Amitriptyline vs Benztropine mesylate</u> Activities of Daily Living, FIM Instrument Mean score: 74.5 (95% CI: 66.26, 82.74) vs 79.1 (95% CI: 77.62, 80.58) at 6 weeks Disability, CHART Mean score: 360 (95% CI: 297.77, 422.23) vs 417 (95% CI: 383.28, 450.72) at 6 weeks Quality of life, Satisfaction with Life Scale Mean score: 21.2 (95% CI: 18.40, 24.00) vs 21.8 (95% CI: 17.89, 25.71) at 6 weeks (p0.004, worse than placebo)	<u>Amitriptyline vs Benztropine mesylate</u> Total: 2 (10%) vs 0 (0%) AE: 2 (10%) vs 0 (0%)
Rockliff 1966 US Efficacy quality: Poor	<u>Carbamazepine vs Placebo</u> Response, Patients preferring carbamazepine: % of patients: 88.9% vs 0% at 24 hours (p=NR)	NR	NR
Rull 1969 Mexico Efficacy quality: Fair	NR	NR	NR

Evidence Table 8. Original report: Data abstraction of other antiepileptics and tricyclic antidepressants

Study	Specific adverse events
Robinson 2004 US Efficacy quality: Fair	Amitriptyline vs Benztropine mesylate Blurred vision: 5.6% (1/18) vs 26.3% (5/19) Constipation: 22.2% (4/18) vs 15.8% (3/19) Diarrhea: 5.6% (1/18) vs 5.3% (1/19) Difficult to urinate: 5.6% (1/18) vs 5.3% (1/19) Dizziness: 11.1% (2/18) vs 15.8% (3/19) Dry mouth: 72.2% (13/18) vs 68.4% (13/19) Gastrointestinal AEs: 0.0% (0/18) vs 15.8% (3/19) Headache: 0.0% (0/18) vs 5.3% (1/19) Insomnia: 11.1% (2/18) vs 10.5% (2/19) Nausea: 11.1% (2/18) vs 0.0% (0/19) Palpitations: 0.0% (0/18) vs 10.5% (2/19) Somnolence: 50.0% (9/18) vs 47.4% (9/19) Sweating increased: 0.0% (0/18) vs 5.3% (1/19) Tinnitus: 5.6% (1/18) vs 5.3% (1/19) Tremor: 0.0% (0/18) vs 5.3% (1/19)
Rockliff 1966 US Efficacy quality: Poor	NR
Rull 1969 Mexico Efficacy quality: Fair	NR

Evidence Table 8. Original report: Data abstraction of other antiepileptics and tricyclic antidepressants

Study	Design	Type of pain Sample size and characteristics	Intervention
Shlay	RCT	HIV-related neuropathic pain	Amitriptyline
1998	Parallel		75 mg
US	Multicenter	N=136	N=71
Efficacy quality: Fair		Age	Placebo
		Mean (SD): 40.0	N=65
		Male: 91.2%	
		Female: 8.8%	
		Race/ethnicity	
		White: 60.3%	
		Black: 25%	
		Hispanic: 11.8%	
		Other: 3%	

Evidence Table 8. Original report: Data abstraction of other antiepileptics and tricyclic antidepressants

Study	Eligibility	Exclusion
Shlay 1998 US Efficacy quality: Fair	Aged 13 or older, documented HIV infection, symptoms of HIV-related lower extremity peripheral neuropathy, diagnosed by a physician based on history and clinical exam, and have completed a baseline pain diary prior to randomization.	Being treated for an acute opportunistic infection or malignancy except nonsystemic Kaposi sarcoma, pregnant, or had taken a tricyclic antidepressant or MAO inhibitor 2 weeks before randomization.

Evidence Table 8. Original report: Data abstraction of other antiepileptics and tricyclic antidepressants

Study	Patient-reported pain	Functional capacity	Withdrawals Withdrawals due to adverse events
Shlay 1998 US Efficacy quality: Fair	Amitriptyline vs Placebo Average pain intensity, Gracely Scale (0.0 to 7.75) Mean change from baseline: -0.23 (p=0.38; 95% CI: -0.22 to 0.08) vs -0.18 at 6 weeks Average pain intensity, Gracely Scale (0.0 to 7.75) Mean change from baseline: -0.26 (p=0.99; 95% CI: -0.18 to 0.19) vs -0.30 at 14 weeks Pain relief, Moderate or more pain relief % of patients: 46.4% (p=0.81) vs 46.7% at 6 weeks Pain relief, Moderate or more pain relief % of patients: 50.8% (p=0.68) vs 50.9% at 14 weeks	Amitriptyline vs Placebo Quality of life, Medical Outcome Study, Physical functioning Mean change from baseline: 5.9 (p=0.94; 95% CI: -8.3 to 8.9) vs 0.6 at 14 weeks Quality of life, Medical Outcome Study, Physical functioning Mean change from baseline: 7.1 (p=0.17; 95% CI: -2.7 to 15.5) vs 5.1 at 6 weeks	NR

Evidence Table 8. Original report: Data abstraction of other antiepileptics and tricyclic antidepressants

Study	Specific adverse events
Shlay 1998 US Efficacy quality: Fair	NR

Evidence Table 8. Original report: Data abstraction of other antiepileptics and tricyclic antidepressants

Study	Design	Type of pain Sample size and characteristics	Intervention
Simpson (B) 2003 US Efficacy quality: Fair	RCT Parallel Multicenter	HIV-related neuropathic pain N=227 Age Mean (SD): 44.5 Range: 26-67 Male: 89.43% Female: 10.57% White: 59.9% Black: 33.5% Other: 6.6%	Lamotrigine 400 mg N=62 Lamotrigine 600 mg N=88 Placebo N=30 Placebo N=47
Simpson (C) 2000 US Efficacy quality: Fair	RCT Parallel Multicenter	HIV-related neuropathic pain N=29	Lamotrigine 300 mg N=20 Placebo N=22

Evidence Table 8. Original report: Data abstraction of other antiepileptics and tricyclic antidepressants

Study	Eligibility	Exclusion
Simpson (B) 2003 US Efficacy quality: Fair	Aged 18 to 65 years, weighed at least 40 kg, had HIV-associated sensory neuropathy (either distal sensory polyneuropathy or antiretroviral toxic neuropathy), and scored at least 60 on the Karnofsky Performance Scale. To be characterized as having HIV-associated sensory neuropathy, patients had to have experienced symptoms of neuropathic pain in both distal lower extremities for at least 6 weeks and exhibited either diminished reflexes at the ankles compared with the knees or distal diminution of sensations of vibration, pain, or temperature in the legs, as established by a neurologist. Must have been experiencing pain in spite of previous symptomatic treatment for neuropathy	Other neurologic disorders that could confound the diagnosis of peripheral neuropathy, such as myelopathy. Any use of valproate within 4 weeks before randomization and any previous or current use of lamotrigine.
Simpson (C) 2000 US Efficacy quality: Fair	HIV-infected subjects with distal sensory polyneuropathy established by a study neurologist, based on the following criteria: primary symptoms of burning or dysesthetic pain in both feet for at least 2 weeks, rated on the Gracely Pain scale as at least "mild" all of the time or "moderate" for a total of at least 2 hours a day, and either absent or diminished ankle reflexes (as compared to the knees) or distal diminution of either vibration sensation or pain and temperature sensation. Also, either no neurotoxic antiretroviral therapy (stavudine, didanosine, zalcitabine) for at least 8 weeks before randomization into the trial or a history of a stable dose of those agents for at least 8 weeks before randomization.	Alternative causes for neuropathy (e.g., diabetes mellitus, hereditary neuropathy, or vitamin B12 deficiency) or current treatment with drugs that could be considered as contributing to the subject's neuropathy (other than antiretroviral medications). Patients receiving valproic acid, acute active opportunistic infections (excluding oral thrush, orogenital or rectal herpes, and mycobacterium avium-intracellular bacteriemia) within 2 weeks before randomization or major, active psychiatric disorders. Women who were pregnant, breast feeding, or planning a pregnancy.

Evidence Table 8. Original report: Data abstraction of other antiepileptics and tricyclic antidepressants

Study	Patient-reported pain	Functional capacity	Withdrawals Withdrawals due to adverse events
Simpson (B) 2003 US Efficacy quality: Fair	Lamotrigine 400 mg vs Lamotrigine 600 mg vs Placebo vs Placebo Average daily pain score, Gracely pain score Mean change from baseline: -0.27 vs -0.30 vs -0.10 vs -0.27 at 11 weeks Average pain, McGill Pain Assessment Mean change from baseline: -6.9 (p<0.05) vs -6.8 vs -1.6 vs -8.7 at 11 weeks Global Impression of Change, Marked or moderate improvement % of patients: 53% (p<0.05 for marked) vs 60% vs 30% vs 45% at 11 weeks Pain intensity, VAS (0-100) Mean change from baseline: -27.1 (p<0.05) vs -23.3 vs -9.0 vs -21.3 at 11 weeks Response, at least 30% reduction in VAS % of patients: 57% (p<0.05) vs 52% vs 23% vs 45% at 11 weeks	NR	Lamotrigine 400 mg vs Lamotrigine 600 mg vs Placebo vs Placebo Total: 17 (27.42%) vs 17 (19.32%) vs 7 (23.33%) vs 14 (29.79%) AE: 5 (8.06%) vs 5 (5.68%) vs 2 (6.67%) vs 5 (10.64%)
Simpson (C) 2000 US Efficacy quality: Fair	Lamotrigine vs Placebo Average pain, Gracely pain score (log 10) Mean score: 0.52 (p=0.05; 95% CI: 0.36, 0.68) vs 0.88 (95% CI: 0.69, 1.07) at 14 weeks Severity of pain, Worst pain (Gracely pain score, log 10) Mean change from baseline: -0.63 (p=0.17; 95% CI: -0.70, -0.56) vs -0.35 (95% CI: -0.40, -0.30) at 14 weeks	NR	NR

Evidence Table 8. Original report: Data abstraction of other antiepileptics and tricyclic antidepressants

Study	Specific adverse events
Simpson (B)	Lamotrigine 400 mg vs Placebo
2003	Diarrhea: 10.7% (16/150) vs 9.1% (7/77)
US	Headache: 10.7% (16/150) vs 10.4% (8/77)
	Infection: 11.3% (17/150) vs 9.1% (7/77)
Efficacy quality: Fair	Nausea: 11.3% (17/150) vs 10.4% (8/77)
	Rash: 14.0% (21/150) vs 11.7% (9/77)
Simpson (C)	NR
2000	
US	
Efficacy quality: Fair	

Evidence Table 8. Original report: Data abstraction of other antiepileptics and tricyclic antidepressants

Study	Design	Type of pain Sample size and characteristics	Intervention
Sindrup (A) 1989 Denmark Efficacy quality: Poor	RCT Crossover	Painful diabetic neuropathy N=13 Age Mean (SD): 49.2 Male: 44.44% Female: 55.56%	Imipramine 50 or 75 mg N=13 Placebo N=13
Thienel 2004 Multiple Efficacy quality: Fair	RCT Parallel Multicenter	Painful diabetic neuropathy N=1269 Age Mean (SD): 58.3 Range: 21-81 Male: 57.8% Female: 42.2%	Topiramate 100 mg N=253 Topiramate 200 mg N=372 Topiramate 400 mg N=260 Placebo N=384
Vestergaard 2001 Denmark Efficacy quality: Fair	RCT Crossover Multicenter	Central/post-stroke neuropathic pain N=30 Age Mean (SD): 59 Range: 37-77 Male: 60% Female: 40%	Lamotrigine 200 mg N=30 Placebo N=30

Evidence Table 8. Original report: Data abstraction of other antiepileptics and tricyclic antidepressants

Study	Eligibility	Exclusion
Sindrup (A) 1989 Denmark Efficacy quality: Poor	Diabetics with one or more symptoms and signs of peripheral neuropathy.	Ankle/arm systolic blood pressure index below 0.8, or serum creatinine >130 mcM, suspicion of alcohol abuse or current depression.
Thienel 2004 Multiple Efficacy quality: Fair	Adults ages 18-75 years with type 1 or type 2 diabetes controlled by oral hypoglycemics and/or insulin or by diet alone, with bilateral and simultaneous symptoms of painful peripheral polyneuropathy for at least 6 months. Antidiabetic regimens had to be stable for at least 3 months before study entry; baseline dosages were to be maintained throughout the study. HbA1c levels less than 11% and creatinine clearance of at least 60 ml/min. Females had to be postmenopausal, surgically incapable of bearing children, or practicing an acceptable method of birth control and have a negative pregnancy test within 14 days of study entry.	Polyneuropathy due to causes other than diabetes, diabetic ulceration of extremities, non-traumatic amputation, hospitalization within past 3 months for hyper-/hypoglycemia while adherent to appropriate diabetic therapy, significant history (within previous 2 years) of unstable medical disease, progressive or degenerative neurologic disorders, history of hepatitis or HIV, any mental impairment that would confound participation, history of alcohol or drug abuse within previous year or suicide attempt, malignancy within previous 5 years, history of nephrolithiasis, experimental drug or device use within previous 30 days, previous participation in a topiramate trial or treatment with topiramate. Recent history (6 months) of significant psychiatric or mood disorder or requiring electroconvulsive or medical therapy (neuroleptics, tricyclic antidepressants, MAO inhibitors, centrally acting sympathomimetics); patients requiring chronic use of simple analgesics, e.g., acetaminophen, or opioids to control pain; patients who failed 3 or more previous pain control regimens other than simple analgesics or opioids.
Vestergaard 2001 Denmark Efficacy quality: Fair	Patients with a previous stroke episode and who had pain for more than 3 months; older than age 18 and had had pain following as stroke for which nociceptive, peripheral neuropathic, and a psychogenic origin was considered highly unlikely. Baseline median pain intensity on a scale 0 to 10 (0= no pain, 10= unbearable pain) was required to be >=4.	Dementia or any other severe cognitive impairment, diabetic neuropathy, malignant disease, recent MI, severe heart insufficiency, liver/renal failure, or a known allergy to lamotrigine; positive history for alcohol or drug abuse, or females who were pregnant or lactating.

Evidence Table 8. Original report: Data abstraction of other antiepileptics and tricyclic antidepressants

Study	Patient-reported pain	Functional capacity	Withdrawals Withdrawals due to adverse events
Sindrup (A) 1989 Denmark Efficacy quality: Poor	Imipramine vs Placebo Pain relief, Most relieved of symptoms % of patients: 88.9% vs 11% at 3 weeks (p<0.01) Pain, Lower score on a 6-item scale (0-2) % of patients: 88.9% vs 11% at 3 weeks (p=0.01)	NR	Imipramine vs Placebo Total: 1 (7.69%) vs 2 (15.38%) AE: 1 (7.69%) vs 2 (15.38%)
Thienel 2004 Multiple Efficacy quality: Fair	Topiramate 100 mg vs Topiramate 200 mg vs Topiramate 400 mg vs Placebo Average pain, VAS (0-100) Mean score (study 001): 36.1 (p=0.043; 95% CI: 32.63, 39.57) vs 38.3 (p=0.138; 95% CI: 35.41, 41.19) vs 39.7 (p=0.612; 95% CI: 36.43, 42.97) vs 43.1 (95% CI: 40.35, 45.85) at 18 weeks Mean score (Study 002): NR vs 37.8 (p=0.247; 95% CI: 34.91, 40.69) vs 39.3 (p=0.482; 95% CI: 36.10, 42.50) vs 41.6 (95% CI: 38.74, 44.46) at 22 weeks Mean score (Study 003): 44.7 (p=0.156; 95% CI: 41.06, 48.34) vs 44.7 (p=0.096; 95% CI: 41.78, 47.62) vs NR vs 55.3 (95% CI: 53.19, 57.41) at 22 weeks	NR	Topiramate 100 mg vs Topiramate 200 mg vs Topiramate 400 mg vs Placebo Total: 116 (45.85%) vs 197 (52.96%) vs 151 (58.08%) vs 156 (40.62%) AE: 41 (16.21%) vs 93 (25%) vs 79 (30.38%) vs 32 (8.33%)
Vestergaard 2001 Denmark Efficacy quality: Fair	Lamotrigine vs Placebo Average pain, Likert scale (0-10) Median score: 5 (p=0.01) vs 7 at 8 weeks Global Pain Rating, 0-5 Median score: 3 (p=0.02) vs 4 at 8 weeks	Lamotrigine vs Placebo Interference, 1-5 Median score: 3 vs 4 at 8 weeks (p=0.11)	Lamotrigine vs Placebo Total: 4 (13.33%) vs 6 (20%) AE: 0 (0%) vs 0 (0%)

Evidence Table 8. Original report: Data abstraction of other antiepileptics and tricyclic antidepressants

Study	Specific adverse events
Sindrup (A) 1989 Denmark Efficacy quality: Poor	Imipramine vs Placebo Dry mouth: 61.5% (8/13) vs 30.8% (4/13)
Thienel 2004 Multiple Efficacy quality: Fair	Topiramate 100 mg vs Topiramate 200 mg vs Topiramate 400 mg vs Placebo Anorexia: 5.1% (13/253) vs 12.1% (45/372) vs 11.9% (31/260) vs 3.1% (12/384) Bad taste: 4.0% (10/253) vs 8.1% (30/372) vs 8.1% (21/260) vs 1.0% (4/384) Confusion: 3.2% (8/253) vs 3.0% (11/372) vs 6.9% (18/260) vs 1.0% (4/384) Fatigue: 11.1% (28/253) vs 16.9% (63/372) vs 20.0% (52/260) vs 10.9% (42/384) Memory difficulty: 3.2% (8/253) vs 5.1% (19/372) vs 6.9% (18/260) vs 2.1% (8/384) Nausea: 9.9% (25/253) vs 12.9% (48/372) vs 13.1% (34/260) vs 7.0% (27/384) Paresthesia: 9.1% (23/253) vs 14.0% (52/372) vs 11.9% (31/260) vs 4.9% (19/384) Somnolence: 7.9% (20/253) vs 12.1% (45/372) vs 8.8% (23/260) vs 3.9% (15/384) Weight loss: 4.0% (10/253) vs 8.9% (33/372) vs 6.9% (18/260) vs 1.0% (4/384)
Vestergaard 2001 Denmark Efficacy quality: Fair	Lamotrigine vs Placebo CNS AEs: 26.7% (8/30) vs 43.3% (13/30) Gastrointestinal AEs: 23.3% (7/30) vs 6.7% (2/30) Respiratory AEs: 13.3% (4/30) vs 16.7% (5/30) Skin AEs: 16.7% (5/30) vs 10.0% (3/30)

Evidence Table 8. Original report: Data abstraction of other antiepileptics and tricyclic antidepressants

Study	Design	Type of pain Sample size and characteristics	Intervention
Vrethem 1997 Sweden Efficacy quality: Fair	RCT Crossover	Polyneuropathy N=37 Age Mean (SD): 61.1 Range: 35-83 Male: 47.22% Female: 52.78%	Amitriptyline 75 mg N=37 Maprotiline 75 mg N=37 Placebo N=37
Watson 1982 Canada Efficacy quality: Fair	RCT Crossover	Post-herpetic neuralgia N=24 Age Mean (SD): 66 Range: 49-81 Male: 33.33% Female: 66.67%	Amitriptyline 75 mg (median) N=24 Placebo N=24
Zakrzewska 1997 UK Efficacy quality: Fair	RCT Crossover	Trigeminal neuralgia N=14 Age Mean (SD): 60 Range: 44-75 Male: 57.14% Female: 42.86%	Lamotrigine 400 mg N=14 Placebo N=14

Evidence Table 8. Original report: Data abstraction of other antiepileptics and tricyclic antidepressants

Study	Eligibility	Exclusion
Vrethem 1997 Sweden Efficacy quality: Fair	Daily moderate or severe polyneuropathic pain for at least 6 months. No indication of central, nociceptive, or psychogenic pain. At least 2 of the following symptoms and signs were required for the diagnosis of polyneuropathy: distal sensory impairment (touch, vibration, proprioception, pain), distal bilateral muscle weakness or atrophy, bilateral decrease, or loss or tendon reflexes.	Other neurologic diseases.
Watson 1982 Canada Efficacy quality: Fair	NR	NR
Zakrzewska 1997 UK Efficacy quality: Fair	Refractory trigemina neuralgia; diagnosis made according to the following criteria: suffering from paroxysmal pain, pain was in the distribution of the trigeminal nerve, pain was shooting, stabbing or electric shock-like in character, and the pain cold potentially be provoked by innocuous stimuli. Pain in the distribution of the trigeminal nerve for at least 3 consecutive days immediately prior to entering the study. McGill Pain Questionnaire was used to support the diagnosis and measure the pain levels at screen.	Surgery for trigeminal neuralgia (including nerve injections but excluding local anesthetic injections) within the last year. Patients with facial pain other than idiopathic trigeminal neuralgia were only entered if it was diagnosed and the patients was able to differentiate it from trigeminal neuralgia.

Evidence Table 8. Original report: Data abstraction of other antiepileptics and tricyclic antidepressants

Study	Patient-reported pain	Functional capacity	Withdrawals Withdrawals due to adverse events
Vrethem 1997 Sweden Efficacy quality: Fair	<u>Amitriptyline vs Maprotiline vs Placebo</u> Response, 20% reduction in verbal scale (0-10) % of patients: 63% vs 50% vs 22% at 4 weeks Response, Improved, much improved, or pain free % of patients: 67% (p<0.001) vs 42% (p<0.05) vs NR at 4 weeks	NR	<u>Amitriptyline vs Maprotiline vs Placebo</u> AE: 3 (8.11%) vs 2 (5.41%) vs 0 (0%)
Watson 1982 Canada Efficacy quality: Fair	<u>Amitriptyline vs Placebo</u> Response, Good or excellent response % of patients: 66.7% (p<0.001) vs 4.2% at 3 weeks	NR	NR
Zakrzewska 1997 UK Efficacy quality: Fair	<u>Lamotrigine vs Placebo</u> Average daily pain score: Reported graphically only Global Impression of Improvement, Composite efficacy index % of patients preferring lamotrigine: 85% (95% CI: 61%-97%) at 2 weeks Improvement, Pain better or much better % of patients: 76.9% vs 57.1% at 2 weeks	NR	<u>Lamotrigine vs Placebo</u> Total: 0 (0%) vs1 (7.14%) AE: 0 (0%) vs 0 (0%)

Evidence Table 8. Original report: Data abstraction of other antiepileptics and tricyclic antidepressants

Study	Specific adverse events
Vrethem 1997 Sweden Efficacy quality: Fair	Amitriptyline vs Maprotiline vs Placebo Cold feet: 0.0% (0/35) vs 2.9% (1/34) vs 0.0% (0/33) Difficult to urinate: 2.9% (1/35) vs 0.0% (0/34) vs 0.0% (0/33) Dry mouth: 34.3% (12/35) vs 41.2% (14/34) vs 6.1% (2/33) Hyperglycemia: 2.9% (1/35) vs 0.0% (0/34) vs 0.0% (0/33) Nausea: 2.9% (1/35) vs 2.9% (1/34) vs 0.0% (0/33) Nose stuffy: 2.9% (1/35) vs 0.0% (0/34) vs 0.0% (0/33) Sedation: 34.3% (12/35) vs 8.8% (3/34) vs 9.1% (3/33) Tachycardia: 0.0% (0/35) vs 2.9% (1/34) vs 0.0% (0/33) Thirst (severe): 2.9% (1/35) vs 2.9% (1/34) vs 0.0% (0/33) Urticaria: 0.0% (0/35) vs 2.9% (1/34) vs 0.0% (0/33) Vertigo: 20.0% (7/35) vs 29.4% (10/34) vs 3.0% (1/33)
Watson 1982 Canada Efficacy quality: Fair	NR
Zakrzewska 1997 UK Efficacy quality: Fair	Lamotrigine vs Placebo Amblyopia: 7.7% (1/13) vs 0.0% (0/14) Any adverse event: 53.8% (7/13) vs 50.0% (7/14) Asthenia: 7.7% (1/13) vs 7.1% (1/14) Ataxia: 7.7% (1/13) vs 0.0% (0/14) Constipation: 23.1% (3/13) vs 14.3% (2/14) Difficult to urinate: 7.7% (1/13) vs 7.1% (1/14) Diplopia: 15.4% (2/13) vs 0.0% (0/14) Dizziness: 38.5% (5/13) vs 7.1% (1/14) Nausea: 23.1% (3/13) vs 7.1% (1/14) Somnolence: 23.1% (3/13) vs 7.1% (1/14) Sweating increased: 7.7% (1/13) vs 7.1% (1/14) Tremor: 7.7% (1/13) vs 7.1% (1/14) Vomiting: 15.4% (2/13) vs 0.0% (0/14)

Evidence Table 9. Original report: Quality assessment of included trials

Author Year Country	Quality rating	Randomization adequate	Allocation concealment adequate	Groups similar at baseline	Eligibility criteria specified	Outcome assessors masked	Care provider masked
Backonja 1998 US	Fair	Yes	Method not described	Yes	Yes	Unclear, reported as double blind	Unclear, reported as double blind
Beydoun 2006 US	Fair	Yes	Yes	Yes	Yes	Unclear, reported as double blind	Unclear, reported as double blind
Bone 2002 UK and Ireland	Fair	Yes	Yes	NR Only baseline pain levels reported as NSD between groups	Yes	Unclear, reported as double blind	Unclear, reported as double blind
Campbell 1966 England	Poor	Yes	Method not described	No 6% of carbamazepine first group vs 29% of placebo first group had been injected for pain; otherwise similar	No	NR	NR
Cardenas 2002 US	Fair	Method not described	Yes	Yes	Yes	Yes	Yes
Chandra 2006 India	Fair	Yes	Yes	Yes	Yes	Yes	Yes
Dalessio 1966 US	Poor	Method not described	Method not described	NR	No	Unclear, reported as double blind	Unclear, reported as double blind

Evidence Table 9. Original report: Quality assessment of included trials

Author Year Country	Patients masked	Reporting of attrition crossover adherence and contamination	Carryover effects handling (if crossover design)	Withdrawal rate high (>85%)	Loss to follow-up Differential or high	Intent-to-treat analysis (at least 95% analyzed)
Backonja 1998 US	Yes	Attrition: Yes Crossover: No Adherence: Yes Contamination: No	NA	Yes 16.7% gabapentin, 19.8% placebo	No	Yes <5% not analyzed
Beydoun 2006 US	Yes	Attrition: Yes Crossover: No Adherence: Yes Contamination: No	NA	Yes	No	Yes Used LOCF, but number analyzed not clear
Bone 2002 UK and Ireland	Yes	Attrition: Yes Crossover: No Adherence: Yes Contamination: No	Washout	Yes 5/19 (26.3%) withdrew	No	Yes
Campbell 1966 England	Yes	Attrition: Yes Crossover: Yes Adherence: No Contamination: No		No	No	No 70/76 analyzed
Cardenas 2002 US	Yes	Attrition: Yes Crossover: No Adherence: Yes Contamination: No	NA	No 11/84 (13.1%)	No	Yes
Chandra 2006 India	Yes	Attrition: Yes Crossover: No Adherence: Yes Contamination: No	NA	No 7.9% overall (2/38 nortriptyline, 4/38 gabapentin)	No	No 70/76 analyzed (92.1%)
Dalessio 1966 US	Unclear, reported as double blind	Attrition: Yes Crossover: No Adherence: No Contamination: No	None	Yes 20%	No	Yes

Evidence Table 9. Original report: Quality assessment of included trials

Author Year Country	Post randomization or post enrollment exclusions	Number Screened Eligible Enrolled	Exclusion criteria specified	Funding
Backonja 1998 US	Yes lack of compliance (n=6 total)	Screened: 232 Eligible: 221 Enrolled: 165	Yes	Parke-Davis
Beydoun 2006 US	No	Screened: NR Eligible: NR Enrolled: 347	Yes	Novartis
Bone 2002 UK and Ireland	No	Screened: 33 Eligible: 27 Enrolled: 19	Yes	Pfizer provided study medication
Campbell 1966 England	Yes 7/77 post-randomization exclusions	Screened: NR Eligible: NR Enrolled: 77	No	Not reported (Geigy Pharmaceuticals supplied carbamazepine)
Cardenas 2002 US	No	Screened: 282 Eligible: 157 Enrolled: 84	Yes	Government funded (NIH and Dept of Education)
Chandra 2006 India	No	Screened: 110 Eligible: 79 Enrolled: 76	Yes	Pfizer (partly)
Dalessio 1966 US	No	Screened: NR Eligible: NR Enrolled: 10	No	Geigy provided study drug, otherwise NR

Evidence Table 9. Original report: Quality assessment of included trials

Author Year Country	Quality rating	Randomization adequate	Allocation concealment adequate	Groups similar at baseline	Eligibility criteria specified	Outcome assessors masked	Care provider masked
Dallocchio 2000 Italy	Fair	Method not described	Method not described	Yes	Yes	No	No
Dogra 2005 US	Fair	Yes	Method not described	Yes	Yes	Unclear, reported as double blind	Unclear, reported as double blind
Drewes 1994 Denmark	Fair	Method not described	Method not described	NR Crossover	Yes	Yes	Unclear, reported as double blind
Dworkin 2003 US	Fair	Yes	Yes	Yes	Yes	Yes	Yes
Eisenberg 2001 Israel	Fair	Yes	Method not described	No duration of sx's longer in lamotrigine arm	Yes	Unclear, reported as double blind	Unclear, reported as double blind
Finnerup 2002 Denmark	Fair	Yes	Yes	NR	Yes	Unclear, reported as double blind	Unclear, reported as double blind
Freynhagen 2005 Multiple European	Fair	Method not described	Method not described	Yes	Yes	Unclear, reported as double blind	Unclear, reported as double blind
Galer (A) 2002 US	Poor	Method not described	Method not described	Yes	Yes	Unclear, reported as double blind	Unclear, reported as double blind

Evidence Table 9. Original report: Quality assessment of included trials

Author Year Country	Patients masked	Reporting of attrition crossover adherence and contamination	Carryover effects handling (if crossover design)	Withdrawal rate high (>85%)	Loss to follow-up Differential or high	Intent-to-treat analysis (at least 95% analyzed)
Dallocchio 2000 Italy	No	Attrition: Yes Crossover: No Adherence: No Contamination: No	NA	No	No	Yes
Dogra 2005 US	Unclear, reported as double blind	Attrition: Yes Crossover: No Adherence: Yes Contamination: No	NA	Yes 40/146	No	Yes
Drewes 1994 Denmark	Yes	Attrition: Yes Crossover: No Adherence: No Contamination: No	Washout	No	No	Yes
Dworkin 2003 US	Yes	Attrition: Yes Crossover: No Adherence: Yes Contamination: No	NA	Yes 34.8% pregabalin, 11.9% placebo	No	Yes LOCF
Eisenberg 2001 Israel	Yes	Attrition: Yes Crossover: No Adherence: Yes Contamination: No	NA	Yes 13/59 (22%)	No	No
Finnerup 2002 Denmark	Yes	Attrition: Yes Crossover: No Adherence: Yes Contamination: No	Washout	Yes	No	No 22/30 analyzed
Freynhagen 2005 Multiple European	Yes	Attrition: Yes Crossover: No Adherence: Yes Contamination: No	NA	Yes 129/338 (38.2%)	No	Yes 2/338 not analyzed (<1%)
Galer (A) 2002 US	Unclear, reported as double blind	Attrition: No Crossover: No Adherence: No Contamination: No	NA	Unable to determine	Unable to determine	No Only analyzed those with final data; Number randomized NR (only number analyzed)

Evidence Table 9. Original report: Quality assessment of included trials

Author Year Country	Post randomization or post enrollment exclusions	Number Screened Eligible Enrolled	Exclusion criteria specified	Funding
Dallocchio 2000 Italy	No	Screened: NR Eligible: NR Enrolled: 25	Yes	Not reported
Dogra 2005 US	No	Screened: 289 Eligible: 156 Enrolled: 146	Yes	Novartis
Drewes 1994 Denmark	Yes 1/20	Screened: NR Eligible: NR Enrolled: 20	Yes	Rhone-Poulenc Rorer A/S
Dworkin 2003 US	excluded for lack of efficacy (n=6)	Screened: 245 Eligible: 188 Enrolled: 173	Yes	Pfizer
Eisenberg 2001 Israel	No	Screened: 160 Eligible: NR Enrolled: 59	Yes	Glaxo-Wellcome
Finnerup 2002 Denmark	No	Screened: 436 Eligible: 100 Enrolled: 30	Yes	Foundation and government; Glaxo provided medication
Freynhagen 2005 Multiple European	Yes 7.3% for lack of compliance of other reason	Screened: 503 Eligible: NR Enrolled: 338	Yes	Pfizer
Galer (A) 2002 US	Unable to determine	Screened: 150 Eligible: NR Enrolled: NR	No	Endo Pharmaceuticals

Evidence Table 9. Original report: Quality assessment of included trials

Author Year Country	Quality rating	Randomization adequate	Allocation concealment adequate	Groups similar at baseline	Eligibility criteria specified	Outcome assessors masked	Care provider masked
Galer (B) 1999 US	Fair	Method not described	Method not described	NR	Yes	Unclear, reported as double blind	Unclear, reported as double blind
Gilron (A) 2005 Canada	Fair	Method not described	Yes	Yes	Yes	Unclear, reported as double blind	Yes
Gilron (B) 2001 US	Poor	Method not described	Method not described		Yes	Unclear, reported as double blind	Yes
Goldstein 2005 US	Fair	Yes	Yes	Yes More women in placebo group (48.7% vs 35%, p=0.033); otherwise similar	Yes	Unclear, reported as double blind	Unclear, reported as double blind
Gorson 1999	Fair	Method not described	Method not described	NR	Yes	Unclear, reported as double blind	Unclear, reported as double blind
Hahn 2004 Germany	Fair	Method not described	Yes	Yes	Yes	Unclear, reported as double blind	Unclear, reported as double blind
Hammack 2002 US	Fair	Balanced allocation	Not applicable	Yes	Yes	Unclear, reported as double blind	Yes

Evidence Table 9. Original report: Quality assessment of included trials

Author Year Country	Patients masked	Reporting of attrition crossover adherence and contamination	Carryover effects handling (if crossover design)	Withdrawal rate high (>85%)	Loss to follow-up Differential or high	Intent-to-treat analysis (at least 95% analyzed)
Galer (B) 1999 US	Yes	Attrition: Yes Crossover: No Adherence: No Contamination: No	NR	No	No	Yes
Gilron (A) 2005 Canada	Yes	Attrition: Yes Crossover: No Adherence: No Contamination: No	Analysis	Yes Attrition 16/57	Unable to determine	Unable to determine Not clear- states no patients excluded for missing data, but number analyzed not explicit, and 16 withdrawals
Gilron (B) 2001 US	Yes	Attrition: Yes Crossover: No Adherence: No Contamination: No	Washout	No	No	Yes
Goldstein 2005 US	Yes	Attrition: Yes Crossover: No Adherence: No Contamination: No	NA	Yes	No	No 347/457 analyzed for primary outcome
Gorson 1999	Unclear, reported as double blind	Attrition: No Crossover: No Adherence: No Contamination: No	Washout	No	No	Yes
Hahn 2004 Germany	Yes	Attrition: Yes Crossover: No Adherence: Yes Contamination: No	NA	Yes 19%	No	No 24/26 analyzed (92.3%)
Hammack 2002 US	Yes	Attrition: Yes Crossover: No Adherence: Yes Contamination: No	Washout	No	No	Yes Imputation for missing data

Evidence Table 9. Original report: Quality assessment of included trials

Author Year Country	Post randomization or post enrollment exclusions	Number Screened Eligible Enrolled	Exclusion criteria specified	Funding
Galer (B) 1999 US	No <5% (1 patient who had a stroke)	Screened: NR Eligible: NR Enrolled: 33	Yes	Hind Health Care, Inc.
Gilron (A) 2005 Canada	Unable to determine Reasons for withdrawal NR (13/57)	Screened: 86 Eligible: 70 Enrolled: 57	Yes	Government (Canadian Institutes of Health Research). Study medication provided by Pfizer and Aventis-Pharma
Gilron (B) 2001 US	No	Screened: NR Eligible: NR Enrolled: 3	Yes	Government (NIH) and Ortho-McNeil
Goldstein 2005 US	Yes 17 subjects in total due to sponsor decision or protocol violation	Screened: 763 Eligible: 457 Enrolled: 457	Yes	Eli Lilly and PRN Consulting
Gorson 1999	No	Screened: NR Eligible: NR Enrolled: 40	Yes	Warner-Lambert (Parke-Davis Pharmaceuticals)
Hahn 2004 Germany	No	Screened: NR Eligible: NR Enrolled: 26	Yes	Pfizer
Hammack 2002 US	Yes 6/57	Screened: NR Eligible: NR Enrolled: 57	Yes	

Evidence Table 9. Original report: Quality assessment of included trials

Author Year Country	Quality rating	Randomization adequate	Allocation concealment adequate	Groups similar at baseline	Eligibility criteria specified	Outcome assessors masked	Care provider masked
Kalso 1996 Finland	Fair	Method not described	Yes	NR	Yes	Unclear, reported as double blind	Yes
Kieburtz 1998 US	Fair	Yes		Yes	Yes	Yes	Yes
Killian 1968 US	Poor	Method not described	Method not described	NR	Yes	Unclear, reported as double blind	Yes
Kishore-Kumar 1990 US	Poor	Method not described	Method not described	NR	Yes	Unclear, reported as double blind	Unclear, reported as double blind
Kochar (A) 2002 India	Fair	Method not described	Method not described	Yes	Yes	Unclear, reported as double blind	Unclear, reported as double blind
Kochar (B) 2004 India	Fair	Method not described	Method not described	NR Baseline characteristics reported on 39/43 analyzed	Yes	Yes	Unclear, reported as double blind
Kochar (C) 2005 India	Fair	Method not described	Method not described	Yes Baseline data reported for 40/45 completers only	Yes	Unclear, reported as double blind	Unclear, reported as double blind
Kvinesdal 1984 Denmark	Fair	Method not described	Method not described	NR Crossover	Yes	Unclear, reported as double blind	Unclear, reported as double blind

Evidence Table 9. Original report: Quality assessment of included trials

Author Year Country	Patients masked	Reporting of attrition crossover adherence and contamination	Carryover effects handling (if crossover design)	Withdrawal rate high (>85%)	Loss to follow-up Differential or high	Intent-to-treat analysis (at least 95% analyzed)
Kalso 1996 Finland	Yes	Attrition: Yes Crossover: No Adherence: Yes Contamination: No		Yes 5/20 (25%)	No	No
Kieburtz 1998 US	Yes	Attrition: Yes Crossover: No Adherence: Yes Contamination: No	NA	Yes 35/145 (24%)	No	No
Killian 1968 US	Yes	Attrition: No Crossover: No Adherence: No Contamination: No	NA	Unable to determine	Unable to determine	No 36/42 analyzed
Kishore-Kumar 1990 US	Yes	Attrition: Yes Crossover: No Adherence: No Contamination: No	None	Yes 7/26	No	No 19/26 (73%)
Kochar (A) 2002 India	Unclear, reported as double blind	Attrition: Yes Crossover: No Adherence: Yes Contamination: No	NA	No	No	No
Kochar (B) 2004 India	Unclear, reported as double blind	Attrition: Yes Crossover: No Adherence: Yes Contamination: No	NA	No	No	No
Kochar (C) 2005 India	Unclear, reported as double blind	Attrition: Yes Crossover: No Adherence: Yes Contamination: No	NA	No	No	No
Kvinesdal 1984 Denmark	Yes	Attrition: Yes Crossover: No Adherence: Yes Contamination: No	None	Yes	No	No

Evidence Table 9. Original report: Quality assessment of included trials

Author Year Country	Post randomization or post enrollment exclusions	Number Screened Eligible Enrolled	Exclusion criteria specified	Funding
Kalso 1996 Finland	Yes 1/20 excluded due to noncompliance	Screened: NR Eligible: NR Enrolled: 20	Yes	Academy of Finland, Paulo Foundation, Centre for International Mobility
Kieburtz 1998 US	No	Screened: NR Eligible: NR Enrolled: 145	Yes	Government (NIH); medication provided by Boehringer-Ingelheim.
Killian 1968 US	Unable to determine	Screened: NR Eligible: NR Enrolled: 42		
Kishore-Kumar 1990 US	No	Screened: NR Eligible: NR Enrolled: 26	Yes	Not reported
Kochar (A) 2002 India	Yes	Screened: 60 Eligible: NR Enrolled: 57	Yes	Not reported
Kochar (B) 2004 India	No	Screened: 48 Eligible: 44 Enrolled: 43	Yes	Not reported
Kochar (C) 2005 India	No	Screened: 48 Eligible: 45 Enrolled: 45	Yes	Not reported
Kvinesdal 1984 Denmark	No	Screened: NR Eligible: NR Enrolled: 15	Yes	Not reported (tablets provided by Dumex Ltd)

Evidence Table 9. Original report: Quality assessment of included trials

Author Year Country	Quality rating	Randomization adequate	Allocation concealment adequate	Groups similar at baseline	Eligibility criteria specified	Outcome assessors masked	Care provider masked
Leijon 1989 Sweden	Fair	Method not described	Method not described	NR	Yes	Yes	Yes
Lesser 2004 US	Fair	Method not described	Yes	Yes	Yes	Unclear, reported as double blind	Unclear, reported as double blind
Levendoglu 2004 Turkey	Fair	Method not described	Method not described	NR	Yes	Unclear, reported as double blind	Unclear, reported as double blind
Max (A) 1987 US	Fair	Method not described	Method not described	NR	Yes	Yes	Yes
Max (B) 1991 US	Fair	Method not described	Method not described	NR	Yes	Unclear, reported as double blind	Yes
Max (C) 1988 US	Fair	Method not described	Method not described	NR	Yes	Unclear, reported as double blind	Unclear, reported as double blind
McCleane 1999 UK	Poor	Yes	Method not described	NR Data only reported for 74/100 patients completing trial	Yes	Unclear, reported as double blind	Unclear, reported as double blind

Evidence Table 9. Original report: Quality assessment of included trials

Author Year Country	Patients masked	Reporting of attrition crossover adherence and contamination	Carryover effects handling (if crossover design)	Withdrawal rate high (>85%)	Loss to follow-up Differential or high	Intent-to-treat analysis (at least 95% analyzed)
Leijon 1989 Sweden	Yes	Attrition: Yes Crossover: No Adherence: No Contamination: No	Washout	No	No	No
Lesser 2004 US	Yes	Attrition: Yes Crossover: No Adherence: No Contamination: No	NA	No	No	Yes
Levendoglu 2004 Turkey	Yes	Attrition: Yes Crossover: No Adherence: No Contamination: No	Washout	No	No	Yes
Max (A) 1987 US	Yes	Attrition: Yes Crossover: No Adherence: Yes Contamination: No	None	Yes	No	No
Max (B) 1991 US	Yes	Attrition: Yes Crossover: No Adherence: No Contamination: No	None	Yes 16.7% withdrew	No	No 20/24 analyzed (83.3%)
Max (C) 1988 US	Yes	Attrition: Yes Crossover: No Adherence: No Contamination: No	Washout	Yes 21/62 (34%)	No	No 41/62 who completed both arms (partial sensitivity analysis on 11/21)
McCleane 1999 UK	Yes	Attrition: Yes Crossover: No Adherence: No Contamination: No	NA	Yes	No	No 74/100 analyzed

Evidence Table 9. Original report: Quality assessment of included trials

Author Year Country	Post randomization or post enrollment exclusions	Number Screened Eligible Enrolled	Exclusion criteria specified	Funding
Leijon 1989 Sweden	No	Screened: 27 Eligible: 15 Enrolled: 15	Yes	Government and foundation (County Council of Ostergotland and Swedish Association of the Neurologically Disabled)
Lesser 2004 US	No	Screened: 578 Eligible: NR Enrolled: 338	Yes	Pfizer
Levendoglu 2004 Turkey	No	Screened: NR Eligible: NR Enrolled: 20	Yes	No funds received
Max (A) 1987 US	Unable to determine	Screened: NR Eligible: NR Enrolled: 37	Yes	Not reported
Max (B) 1991 US	No	Screened: NR Eligible: NR Enrolled: 24	Yes	Not reported
Max (C) 1988 US	Unable to determine	Screened: NR Eligible: NR Enrolled: NR	Yes	
McCleane 1999 UK	Unable to determine	Screened: NR Eligible: NR Enrolled: 100	Yes	Not reported

Evidence Table 9. Original report: Quality assessment of included trials

Author Year Country	Quality rating	Randomization adequate	Allocation concealment adequate	Groups similar at baseline	Eligibility criteria specified	Outcome assessors masked	Care provider masked
Meier 2003 Germany and Switzerland	Poor	Yes	Method not described	NR	Yes	Yes	Yes
Morello 1999 US	Fair	Method not described		NR	Yes	No	Yes
Otto 2004 Denmark	Fair	Yes	Yes	NR	Yes	Unclear, reported as double blind	Unclear, reported as double blind
Panerai 1990 Italy	Poor	Method not described	Method not described	NR No baseline data on drop-outs	Yes	Unclear, reported as double blind	Unclear, reported as double blind
Raja 2002 US	Fair	Yes	Yes	NR Crossover	Yes	Unclear, reported as double blind	Yes
Raskin (A) 2004 US	Fair	Yes	Method not described	No weight higher in topiramate group (101.4 vs 95.7 kg, p=0.028	Yes	Unclear, reported as double blind	Unclear, reported as double blind
Raskin (B) 2005 and 2006 US	Fair	Yes	Yes	Yes	Yes	Unclear, reported as double blind	Unclear, reported as double blind
Rice 2001 UK	Fair	Yes	Yes	Yes	Yes	Unclear, reported as double blind	Unclear, reported as double blind

Evidence Table 9. Original report: Quality assessment of included trials

Author Year Country	Patients masked	Reporting of attrition crossover adherence and contamination	Carryover effects handling (if crossover design)	Withdrawal rate high (>85%)	Loss to follow-up Differential or high	Intent-to-treat analysis (at least 95% analyzed)
Meier 2003 Germany and Switzerland	Yes	Attrition: Yes Crossover: No Adherence: No Contamination: Yes	Washout	Yes 18/58 (31%)	No	No 40/58 analyzed (69%)
Morello 1999 US	Yes	Attrition: Yes Crossover: Yes Adherence: Yes Contamination: No	Washout	Yes	No	No
Otto 2004 Denmark	Yes	Attrition: Yes Crossover: No Adherence: Yes Contamination: No	NR	No	No	No
Panerai 1990 Italy	Unclear, reported as double blind	Attrition: Yes Crossover: No Adherence: No Contamination: No	Washout	Yes	No	No 24/39 (62%) analyzed
Raja 2002 US	Yes	Attrition: Yes Crossover: No Adherence: No Contamination: No	Washout	Yes	Unable to determine	Unable to determine
Raskin (A) 2004 US	Yes	Attrition: Yes Crossover: No Adherence: Yes Contamination: No	NA	Yes	No	Yes
Raskin (B) 2005 and 2006 US	Yes	Attrition: Yes Crossover: No Adherence: No Contamination: No	NA	No	No	Yes 340/348 randomized analyzed for primary endpoint
Rice 2001 UK	Yes	Attrition: Yes Crossover: No Adherence: Yes Contamination: No	NA	Yes 18.6%	No	No 306/334 were analyzed=91.6%

Evidence Table 9. Original report: Quality assessment of included trials

Author Year Country	Post randomization or post enrollment exclusions	Number Screened Eligible Enrolled	Exclusion criteria specified	Funding
Meier 2003 Germany and Switzerland	Yes 3/58 excluded for non-permitted medications	Screened: 67 Eligible: 61 Enrolled: 58	Yes	IBSA (Pambio-Noranco, Switzerland)
Morello 1999 US	No 3/28 pre-randomization exclusions	Screened: NR Eligible: 28 Enrolled: 25	Yes	Not reported
Otto 2004 Denmark	Yes	Screened: 95 Eligible: 63 Enrolled: 37	Yes	Not reported
Panerai 1990 Italy	No	Screened: NR Eligible: NR Enrolled: 39	Yes	Not reported
Raja 2002 US	Yes	Screened: 103 Eligible: 85 Enrolled: 76	Yes	NIH
Raskin (A) 2004 US	No	Screened: 553 Eligible: NR Enrolled: 323	Yes	Ortho-McNeil
Raskin (B) 2005 and 2006 US	Yes 1.8 and 2.6% due to physician decision or protocol violation	Screened: 475 Eligible: NR Enrolled: 348	Yes	Eli Lilly
Rice 2001 UK	Yes 2.4% withdrew because of "other" reason, not specified	Screened: 411 Eligible: 359 Enrolled: 334	Yes	Pfizer

Evidence Table 9. Original report: Quality assessment of included trials

Author Year Country	Quality rating	Randomization adequate	Allocation concealment adequate	Groups similar at baseline	Eligibility criteria specified	Outcome assessors masked	Care provider masked
Richter 2005 US	Fair	Yes	Method not described	Yes	Yes	Unclear, reported as double blind	Unclear, reported as double blind
Robinson 2004 US	Fair	Method not described	Yes	Yes	Yes	Yes	Yes
Rockliff 1966 US	Poor	Method not described		NR	Yes	Unclear, reported as double blind	Unclear, reported as double blind
Rosenstock 2004 US	Fair	Method not described	Method not described	Yes	Yes	Unclear, reported as double blind	Unclear, reported as double blind
Rowbotham (A) 1996 US	Fair	Method not described	Method not described	NR	Yes	Unclear, reported as double blind	Unclear, reported as double blind
Rowbotham (B) 2004 US	Fair	Method not described	Method not described	Yes	Yes	Unclear, reported as double blind	Unclear, reported as double blind
Rowbotham (C) 1998 US	Fair	Yes	Method not described	Yes	Yes	Unclear, reported as double blind	Unclear, reported as double blind
Rull 1969 Mexico	Fair	Method not described	Method not described	NR	Yes	Yes	Yes

Evidence Table 9. Original report: Quality assessment of included trials

Author Year Country	Patients masked	Reporting of attrition crossover adherence and contamination	Carryover effects handling (if crossover design)	Withdrawal rate high (>85%)	Loss to follow-up Differential or high	Intent-to-treat analysis (at least 95% analyzed)
Richter 2005 US	Yes	Attrition: Yes Crossover: No Adherence: No Contamination: No	NA	No Attrition P: 15%, I1: 5%, I2: 12%	No	Yes 3 patients in placebo group not analyzed (<5%)
Robinson 2004 US	Yes	Attrition: Yes Crossover: No Adherence: Yes Contamination: No	NA	No	No	No
Rockliff 1966 US	Yes	Attrition: No Crossover: No Adherence: No Contamination: No	None	Unable to determine	Unable to determine	Unable to determine
Rosenstock 2004 US	Yes	Attrition: Yes Crossover: No Adherence: Yes Contamination: No	NA	No	No	Yes
Rowbotham (A) 1996 US	Yes	Attrition: Yes Crossover: No Adherence: Yes Contamination: No	Washout	No 35/40 completed	No	No 35/40 (87.5%) analyzed
Rowbotham (B) 2004 US	Yes	Attrition: Yes Crossover: No Adherence: No Contamination: No	NA	Yes 42/245 withdrew (17.1%)	No	Yes Analyzed has >=1 dose, 3 FU measures, and used LOCF
Rowbotham (C) 1998 US	Yes	Attrition: Yes Crossover: No Adherence: Yes Contamination: No	NA	Yes 19.7%	No	Yes
Rull 1969 Mexico	Yes	Crossover: No Adherence: No Contamination: No	NR	No	Unable to determine	Unable to determine

Evidence Table 9. Original report: Quality assessment of included trials

Author Year Country	Post randomization or post enrollment exclusions	Number Screened Eligible Enrolled	Exclusion criteria specified	Funding
Richter 2005 US	No	Screened: 396 Eligible: 261 Enrolled: 246	Yes	Pfizer
Robinson 2004 US	No	Screened: 457 Eligible: 218 Enrolled: 39	Yes	Government (NIH)
Rockliff 1966 US	Unable to determine	Screened: NR Eligible: NR Enrolled: NR	Yes	Geigy Pharmaceuticals
Rosenstock 2004 US	Yes lack of compliance (n=5)	Screened: 225 Eligible: 165 Enrolled: 146	Yes	Pfizer
Rowbotham (A) 1996 US	Yes 2/40 (5%)	Screened: NR Eligible: NR Enrolled: 40	Yes	Harry Hind and NIH
Rowbotham (B) 2004 US	Yes 3/245 for protocol violation	Screened: NR Eligible: NR Enrolled: 245	Yes	Wyeth
Rowbotham (C) 1998 US	Yes excluded for lack of compliance (n=3 overall)	Screened: 292 Eligible: NR Enrolled: 229	Yes	Parke-Davis
Rull 1969 Mexico	Unable to determine		No	Not reported

Evidence Table 9. Original report: Quality assessment of included trials

Author Year Country	Quality rating	Randomization adequate	Allocation concealment adequate	Groups similar at baseline	Eligibility criteria specified	Outcome assessors masked	Care provider masked
Sabatowski 2004 Multiple European and Australia	Fair	Yes	Method not described	Yes	Yes	Unclear, reported as double blind	Unclear, reported as double blind
Serpell 2002 UK and Republic of Ireland	Fair	Yes	Yes	Yes	Yes	Unclear, reported as double blind	Unclear, reported as double blind
Shlay 1998 US	Fair	Method not described	Yes	Yes	Yes	Yes	Unclear, reported as double blind
Siddall 2006 Australia	Fair	Yes	Method not described	Yes	Yes	Unclear, reported as double blind	Yes
Simpson (A) Part 1 2001 US	Fair	Method not described	Method not described	Yes	Yes	Unclear, reported as double blind	Unclear, reported as double blind
Simpson (A) Part 2 2001 US	Fair	Method not described	Method not described	NR Yes for pain score, other characteristics NR	Yes	Unclear, reported as double blind	Unclear, reported as double blind
Simpson (B) 2003 US	Fair	Method not described	Method not described	Yes	Yes	Unclear, reported as double blind	Unclear, reported as double blind

Evidence Table 9. Original report: Quality assessment of included trials

Author Year Country	Patients masked	Reporting of attrition crossover adherence and contamination	Carryover effects handling (if crossover design)	Withdrawal rate high (>85%)	Loss to follow-up Differential or high	Intent-to-treat analysis (at least 95% analyzed)
Sabatowski 2004 Multiple European and Australia	Yes	Attrition: Yes Crossover: No Adherence: Yes Contamination: No	NA	Yes	No	Yes TT population was 238/253 (94.1%) randomized and received one dose of study medication
Serpell 2002 UK and Republic of Ireland	Yes	Attrition: Yes Crossover: No Adherence: No Contamination: No	NA	Yes 23.8%	No I 5%, P 6%	Unable to determine Number analyzed for efficacy not reported
Shlay 1998 US	Yes	Attrition: Yes Crossover: No Adherence: No Contamination: No	NA	Yes 48/136 (35%)	No	Yes
Siddall 2006 Australia	Yes	Attrition: Yes Crossover: No Adherence: No Contamination: No	NA	Yes 51/137 (37.2%)	No	Yes 136/137 analyzed (99.3%)
Simpson (A) Part 1 2001 US	Yes	Attrition: Yes Crossover: No Adherence: No Contamination: No	NA	No	No	No 54/60 analyzed
Simpson (A) Part 2 2001 US	Yes	Attrition: Yes Crossover: No Adherence: No Contamination: No	NA	No	No	Yes
Simpson (B) 2003 US	Unclear, reported as double blind	Attrition: Yes Crossover: No Adherence: Yes Contamination: No	NA	Yes	No	Yes

Evidence Table 9. Original report: Quality assessment of included trials

Author Year Country	Post randomization or post enrollment exclusions	Number Screened Eligible Enrolled	Exclusion criteria specified	Funding
Sabatowski 2004 Multiple European and Australia	Yes 3.8%	Screened: 307 Eligible: 253 Enrolled: 238	Yes	Parke-Davis/Pfizer
Serpell 2002 UK and Republic of Ireland	No	Screened: 351 Eligible: 327 Enrolled: 307	Yes	Parke-Davis
Shlay 1998 US	No	Screened: NR Eligible: NR Enrolled: 136	Yes	National Institute of Allergy and Infectious Disease
Siddall 2006 Australia	No	Screened: 165 Eligible: 143 Enrolled: 137	Yes	Pfizer
Simpson (A) Part 1 2001 US	Unable to determine	Screened: NR Eligible: NR Enrolled: 60	Yes	Not reported
Simpson (A) Part 2 2001 US	No	Eligible: 12 Enrolled: 11	Yes	Not reported
Simpson (B) 2003 US	No	Screened: NR Eligible: NR Enrolled: 227	Yes	GlaxoSmithKline

Evidence Table 9. Original report: Quality assessment of included trials

Author Year Country	Quality rating	Randomization adequate	Allocation concealment adequate	Groups similar at baseline	Eligibility criteria specified	Outcome assessors masked	Care provider masked
Simpson (C) 2000 US	Fair	Yes	Yes	No CD4 count higher in lamotrigine group (p=0.01); baseline characteristics reported for	Yes	Unclear, reported as double blind	Unclear, reported as double blind
Sindrup (A) 1989 Denmark	Poor	Method not described	Method not described	NR	Yes	Unclear, reported as double blind	Unclear, reported as double blind
Sindrup (B) 1990 Denmark	Poor	Method not described	Method not described	NR	Yes	Unclear, reported as double blind	Yes
Sindrup (C) 2003 Denmark	Fair	Yes	Yes	NR	Yes	Unclear, reported as double blind	Yes
Tai 2002 US	Poor	Yes	Method not described	NR	Yes	Unclear, reported as double blind	Unclear, reported as double blind

Evidence Table 9. Original report: Quality assessment of included trials

Author Year Country	Patients masked	Reporting of attrition crossover adherence and contamination	Carryover effects handling (if crossover design)	Withdrawal rate high (>85%)	Loss to follow-up Differential or high	Intent-to-treat analysis (at least 95% analyzed)
Simpson (C) 2000 US	Yes	Attrition: Yes Crossover: No Adherence: No Contamination: No	NA	Yes	No	Yes
Sindrup (A) 1989 Denmark	Yes	Attrition: Yes Crossover: No Adherence: No Contamination: No	NR	Yes	No	No 9/13 analyzed (69.2%)
Sindrup (B) 1990 Denmark	Yes	Attrition: Yes Crossover: No Adherence: No Contamination: No	Washout	Yes 7/26 (26.9%) withdrew	No	No 19/26 (73.1%) analyzed
Sindrup (C) 2003 Denmark	Yes	Attrition: Yes Crossover: No Adherence: Yes Contamination: Yes	Washout	Yes	No	Yes
Tai 2002 US	Yes	Attrition: Yes Crossover: No Adherence: Yes Contamination: No	Washout	Yes 50%	No 2/14 (14.2%)	No 7/14 (50%) not analyzed

Evidence Table 9. Original report: Quality assessment of included trials

Author Year Country	Post randomization or post enrollment exclusions	Number Screened Eligible Enrolled	Exclusion criteria specified	Funding
Simpson (C) 2000 US	No	Screened: NR Eligible: NR Enrolled: 42	Yes	Glaxo Wellcome
Sindrup (A) 1989 Denmark	Yes 1/13 (MI)	Screened: NR Eligible: NR Enrolled: 13	Yes	Research Foundation of Vejle County, Denmark. Medication and placebo provided by Ciba-Geigy.
Sindrup (B) 1990 Denmark	Unable to determine	Screened: NR Eligible: NR Enrolled: 26		Danish Diabetes Association; Ciba-Geigy provided medications and placebo tablets.
Sindrup (C) 2003 Denmark	Yes 1/40 excluded due to high concentration of tramadol	Screened: 70 Eligible: 20 Enrolled: 40	Yes	Government and hospital research foundation, medication provided by Wyeth and Nycomed.
Tai 2002 US	Yes 1/14 excluded for lack of compliance	Screened: NR Eligible: NR Enrolled: 14	Yes	American Academy of Physical Medicine and Rehabilitation and Eastern Paralyzed Veterans Association

Evidence Table 9. Original report: Quality assessment of included trials

Author Year Country	Quality rating	Randomization adequate	Allocation concealment adequate	Groups similar at baseline	Eligibility criteria specified	Outcome assessors masked	Care provider masked
Tasmuth 2002 Finland	Fair	Yes	Method not described	NR Baseline characteristics not reported by order of randomization	Yes	Unclear, reported as double blind	Unclear, reported as double blind
Thienel 2004 Multiple	Fair	Yes	Yes	Yes	Yes	Unclear, reported as double blind	Unclear, reported as double blind
van Seventer 2006 US and Multiple European	Fair	Method not described	Method not described	Yes	Yes	Unclear, reported as double blind	Unclear, reported as double blind
Vestergaard 2001 Denmark	Fair	Yes	Yes	NR	Yes	Unclear, reported as double blind	Unclear, reported as double blind
Vrethem 1997 Sweden	Fair	Method not described	Method not described	NR	Yes	Yes	Yes
Watson 1982 Canada	Fair	Method not described	Method not described	NR	No	Unclear, reported as double blind	Yes

Evidence Table 9. Original report: Quality assessment of included trials

Author Year Country	Patients masked	Reporting of attrition crossover adherence and contamination	Carryover effects handling (if crossover design)	Withdrawal rate high (>85%)	Loss to follow-up Differential or high	Intent-to-treat analysis (at least 95% analyzed)
Tasmuth 2002 Finland	Unclear, reported as double blind	Attrition: Yes Crossover: No Adherence: Yes Contamination: No	Washout	No 2/15 (13.3%) withdrew	No	No 13/15 patients enrolled analyzed (86.7%)
Thienel 2004 Multiple	Yes	Attrition: Yes Crossover: No Adherence: Yes Contamination: No	NA	Yes 41-58%	No	Unable to determine 1259/1269 in safety population analyzed; # randomized unclear
van Seventer 2006 US and Multiple European	Unclear, reported as double blind	Attrition: Yes Crossover: No Adherence: Yes Contamination: No	NA	Yes 35.1%	No	Yes 368/370 (99.5%) analyzed
Vestergaard 2001 Denmark	Yes	Attrition: Yes Crossover: Yes Adherence: No Contamination: Yes	Washout	Yes	No	No 27/30 (85%)
Vrethem 1997 Sweden	Yes	Attrition: No Crossover: No Adherence: No Contamination: No	Washout	Yes 7/37 (19%)	Unable to determine	No
Watson 1982 Canada	Yes	Attrition: No Crossover: No Adherence: No Contamination: No	Washout	No	No	Unable to determine

Evidence Table 9. Original report: Quality assessment of included trials

Author Year Country	Post randomization or post enrollment exclusions	Number Screened Eligible Enrolled	Exclusion criteria specified	Funding
Tasmuth 2002 Finland	Yes 1 patient excluded for non-compliance	Screened: 45 Eligible: NR Enrolled: 15	Yes	Helsinki University Central Hospital Research Funds;
Thienel 2004 Multiple	Unable to determine See above	Screened: NR Eligible: NR Enrolled: 1269	Yes	Johnson & Johnson
van Seventer 2006 US and Multiple European	No	Screened: 435 Eligible: 387 Enrolled: 370	Yes	Pfizer
Vestergaard 2001 Denmark	No	Screened: NR Eligible: NR Enrolled: 30	Yes	Danish Medical Research Council and Danish Pain Research Center. Glaxo Wellcome provided medication and technical support and patient transport costs.
Vrethem 1997 Sweden	Unable to determine	Screened: NR Eligible: NR Enrolled: 37	Yes	
Watson 1982 Canada	Unable to determine	Screened: NR Eligible: NR Enrolled: 24	No	Not reported

Evidence Table 9. Original report: Quality assessment of included trials

Author Year Country	Quality rating	Randomization adequate	Allocation concealment adequate	Groups similar at baseline	Eligibility criteria specified	Outcome assessors masked	Care provider masked
Wernicke 2006 US	Fair	Yes	Yes	No Higher BPI average interference score in duloxetine 120 mg group; otherwise similar	Yes	Yes	Yes
Zakrzewska 1997 UK	Fair	Method not described	Method not described	Yes	Yes	Unclear, reported as double blind	Yes

Evidence Table 9. Original report: Quality assessment of included trials

Author Year Country	Patients masked	Reporting of attrition crossover adherence and contamination	Carryover effects handling (if crossover design)	Withdrawal rate high (>85%)	Loss to follow-up Differential or high	Intent-to-treat analysis (at least 95% analyzed)
Wernicke 2006 US	Yes	Attrition: Yes Crossover: No Adherence: No Contamination: No	NA	Yes	No	Yes 327/334 randomized analyzed
Zakrzewska 1997 UK	Yes	Attrition: Yes Crossover: No Adherence: No Contamination: No	Washout	No	No	Yes

Evidence Table 9. Original report: Quality assessment of included trials

Author Year Country	Post randomization or post enrollment exclusions	Number Screened Eligible Enrolled	Exclusion criteria specified	Funding
Wernicke 2006 US	Yes 12/334 excluded	Screened: 561 Eligible: NR Enrolled: 334	Yes	Eli Lilly
Zakrzewska 1997 UK	No	Screened: NR Eligible: NR Enrolled: 14	Yes	Glaxo Wellcome