Capsaicin 8% Patch Versus Oral Neuropathic Pain Medications for the Treatment of Painful Diabetic Peripheral Neuropathy: A Systematic Literature Review and Network Meta-analysis

Floortje van Nooten, MSc[1,*]; Maarten Treur, MSc[2]; Krystallia Pantiri, MSc[2]; Malcolm Stoker, PhD[1]; and Mata Charokopou, MSc[2,†]

[1]*Astellas Pharma Europe BV, Medical Affairs, Leiden, The Netherlands; and* [2]*Pharmerit International, Rotterdam, The Netherlands*

ABSTRACT

Purpose: A network meta-analysis (NMA) was performed, aiming to assess the relative efficacy and tolerability of the capsaicin 179-mg (8% weight for weight) cutaneous patch (capsaicin 8% patch) compared with oral, centrally acting agents (ie, pregabalin, gabapentin, duloxetine, amitriptyline) in patients with painful diabetic peripheral neuropathy (PDPN).

Methods: A systematic search of EMBASE/MEDLINE, Cochrane Library, and the National Health Service Centre for Reviews and Dissemination Database of Abstracts of Reviews of Effects was conducted to identify all randomized controlled trials. Data from eligible studies according to predefined inclusion and exclusion criteria were extracted, and analyses were based on aggregate-level data. Efficacy outcomes were the proportions of patients with ≥30% and ≥50% reductions in pain, and tolerability outcomes were somnolence, dizziness, nausea, diarrhea, constipation, headache, fatigue, insomnia, and rate of discontinuation due to adverse events (AEs). Data were analyzed by using a Bayesian NMA. Fixed and random effects models were estimated. Relative treatment effect was presented as odds ratios (ORs) with 95% CIs. Sources of heterogeneity were assessed.

Findings: The NMA included 25 randomized controlled trials. For ≥30% pain reduction, the capsaicin 8% patch was significantly more effective than placebo (OR, 2.28 [95% CI, 1.19–4.03]), exhibited a numerical advantage compared with pregabalin (OR, 1.83 [95% CI, 0.91–3.34]) and gabapentin (OR, 1.66 [95% CI, 0.74–3.23]), and had similar efficacy compared with duloxetine (OR, 0.99 [95% CI, 0.5–1.79]). The evidence available was not sufficient to assess the relative efficacy of amitriptyline. In the NMA for tolerability, the capsaicin 8% patch was only included for headache because the incidence was 0% for the other outcomes. Oral, centrally acting agents had a significantly elevated risk compared with placebo for somnolence (pregabalin, gabapentin, duloxetine, and amitriptyline), dizziness (pregabalin, gabapentin, duloxetine, and amitriptyline), nausea (duloxetine), diarrhea (duloxetine), fatigue (duloxetine), and discontinuation because of AEs (pregabalin, gabapentin, and duloxetine). Compared with pregabalin and gabapentin, duloxetine had a significantly lower risk of dizziness but a significantly higher risk of nausea.

Implications: This NMA suggests that the efficacy observed with the capsaicin 8% patch is similar to that observed with oral agents (ie, pregabalin, duloxetine, gabapentin) in patients with PDPN. The oral agents were associated with a significantly elevated risk of somnolence, dizziness, fatigue, and discontinuation because of AEs compared with placebo. The capsaicin 8% patch was as effective as oral centrally acting agents in these patients with PDPN but

Accepted for publication February 22, 2017.
http://dx.doi.org/10.1016/j.clinthera.2017.02.010
0149-2918/$ - see front matter

*Current affiliation: Dompé Farmaceutici S.p.A., Milan, Italy.
†Current affiliation: UCB Biopharma SPRL, Brüssels, Belgium.

offers systemic tolerability benefits. (*Clin Ther.* 2017;39:787–803) © 2017 The Authors. Published by Elsevier HS Journals, Inc.

Key words: capsaicin patch, duloxetine, gabapentin, network meta-analysis, painful diabetic peripheral neuropathy, pregabalin.

INTRODUCTION

Neuropathies are a common long-term complication of diabetes. They are characterized by the progressive loss of nerve fibers and can affect the somatic peripheral and autonomic nervous systems.[1] Painful diabetic neuropathy occurs in 10% to 20% of patients with diabetes and in 40% to 50% of those with diabetic neuropathies.[2] Symptoms, which include electrical or stabbing sensations, paresthesias, hyperesthesias, burning pain, and deep aching pain,[3] adversely affect health-related quality of life and functioning[4] and can lead to sleep problems, anxiety, and depression.[5]

In the United Kingdom, annual health care costs related to painful diabetic peripheral neuropathy (PDPN) range from an estimated £1612 to £3217 per patient depending on the level of pain severity (2005 costs).[6] In addition, PDPN is associated with productivity losses and disruptions to employment status, driven primarily by impairment while working (presenteeism). In the United Kingdom, the estimated mean annual total cost of lost productivity associated with PDPN is €12,438 per patient (2008 costs).[7]

PDPN is a challenging condition to treat. Evidence-based treatment guidelines principally recommend oral, centrally acting pharmacologic agents (including anticonvulsant drugs, tricyclic antidepressant agents, and serotonin-noradrenaline reuptake inhibitors) for the treatment of neuropathic pain, including PDPN. The specific agents recommended and the strength of the recommendations, however, vary between guidelines.[8–11] Localized and topical treatments are also recognized treatment options, although supporting evidence for their use in patients with PDPN remains limited.[8]

The capsaicin 179 mg (8% weight for weight) cutaneous patch (capsaicin 8% patch)* is a localized treatment that provides effective durable pain relief from a single application in patients with peripheral neuropathic pain.[12–14] In nondiabetic adults, direct comparison has shown the capsaicin 8% patch to be noninferior to pregabalin in the control of neuropathic pain but with a faster onset of analgesia and considerably fewer systemic side effects.[15]

Results from 2 randomized controlled Phase III trials (STEP [A Phase III, Double-Blind, Randomized, Placebo-Controlled, Multicenter Study Evaluating the Efficacy and Safety of QUTENZA™ in Subjects with Painful Diabetic Peripheral Neuropathy][16] and PACE [A Randomized, Controlled, Long-Term Safety Study Evaluating the Effect of Repeated Applications of QUTENZA™ plus Standard of Care Versus Standard of Care Alone in Patients with Painful Diabetic Peripheral Neuropathy][17]) evaluating the capsaicin 8% patch in patients with PDPN have recently been reported. STEP was a 12-week, double-blind, placebo-controlled trial evaluating the efficacy and safety of a single application of the capsaicin 8% patch in 369 patients with PDPN. It found a greater mean reduction in average daily pain score from baseline at weeks 2 to 8 with the capsaicin 8% patch versus placebo (–27.4% vs –20.9%; $P = 0.025$).[16] PACE, a 52-week multicenter randomized study, assessed the longer term safety of repeated applications of the capsaicin 8% patch as add-on therapy to individualized standard of care versus standardof care alone in 468 patients with PDPN. These data formed part of a successful regulatory submission and label variation for the capsaicin 8% patch in Europe to remove the exclusion of patients with diabetes.[18]

Currently, there is no direct clinical evidence comparing the efficacy and tolerability of the capsaicin 8% patch with other pharmacologic agents in patients with PDPN, and it is impractical to conduct randomized active-controlled comparisons for all of the available treatment options. In the absence of direct comparative data, network meta-analyses (NMA) provide a method of estimating differences between competing interventions by integrating data from available trials.[19] NMA combine effect sizes from all possible pairwise comparisons (direct and indirect) to provide an estimate of relative effectiveness. To better understand the efficacy and tolerability of the capsaicin 8% patch compared with oral agents in patients with PDPN, a systematic literature review and NMA were performed.

*Trademark: QUTENZA™ (Astellas Pharma Europe BV, Leiden, The Netherlands).

MATERIALS AND METHODS

Systematic Literature Review

A systematic literature review was performed to identify all published randomized controlled trials of pharmacologic treatments for patients with PDPN. The systematic literature review was conducted in accordance with the guidelines from the Centre for Reviews and Dissemination (CRD).[20]

Search Strategy

EMBASE/MEDLINE, Cochrane Library, and the National Health Service CRD Database of Abstracts of Reviews of Effects were searched on February 18, 2014, for relevant publications. Searches were limited to studies published in English after 1950. The search terms used for each database are presented in the **Appendix** of the **Supplemental Material** in the online version at http://dx.doi.org/10.1016/j.clinthera.2017.02.010. ClinicalTrials.gov was searched to ensure that no studies had been missed and as an additional source of results data.

Study Selection

Studies selected for inclusion were randomized controlled trials (≥4 weeks in duration) of pregabalin, gabapentin, duloxetine, and amitriptyline (ie, oral agents recommended by the National Institute for Health and Care Excellence [NICE] for patients with neuropathic pain[9]) in adult patients with PDPN. The full inclusion and exclusion criteria are presented in **Supplemental Table I** in the online version at http://dx.doi.org/10.1016/j.clinthera.2017.02.010; NICE and Cochrane reviews on the effectiveness and safety of medications for treating PDPN were used as guidance for the inclusion/exclusion criteria.[21–26] Relevant publications were initially identified by reviewing the titles and/or abstracts. Final inclusion of studies was based on a review of the full article or report. Reasons for excluding articles were recorded, and a Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram was created to summarize the study selection process.

Data Extraction

The data extraction was performed by 1 reviewer, and data were entered into a Microsoft Excel template (Microsoft Corporation, Redmond, Washington). Quality control of all extracted data was conducted by a second reviewer. Extracted data included details of publication, study design, treatment, patient baseline characteristics, patient disposition, and efficacy and tolerability outcomes. Data from NICE reviews, Cochrane reviews, or ClinicalTrials.gov were used if the required data were not reported in the original publications. Authors were not contacted for missing data. Dedicated software (xyExtract Graph Digitizer, version 5.1, Wilton P. Silva, Universidade Federal de Campina Grande, Brazil) was used to extract data from graphs when data were only presented in this way. In crossover studies, only first-period results were extracted to exclude any carryover effect, an approach that has been adopted in other reviews.[22]

Quality Assessment

A quality assessment of included studies according to NICE guidelines[27] was performed by 1 reviewer to assess methodologic quality and the risk of bias. Each question was given a grade for each study (yes/no/not clear/not reported/not applicable).

Network Meta-analysis

Study Selection

Studies meeting the inclusion criteria for the systematic literature review were included in the NMA. In addition, relevant studies of the capsaicin 8% patch (STEP[16] and PACE[17]), which were completed but not published at the time the NMA was performed, were also considered for inclusion. In the STEP trial, patients with PDPN were allowed to receive up to 2 other concomitant therapies for the management of pain as long as they had received stable doses for >4 weeks before screening. To account for this potential confounding factor, the STEP trial data included in the NMA were limited to the subpopulation of patients who received no relevant oral concomitant medications (pregabalin, gabapentin, duloxetine or amitriptyline) at baseline (n = 195).[28] The PACE trial was not included in the base case analysis because the capsaicin 8% patch was given as add-on therapy, and the primary study end point was related to safety.

Outcome Measures

Efficacy outcomes included in the present analysis were the proportion of patients with ≥30% pain reduction and the proportion of patients with ≥50% pain reduction relative to baseline; both of these factors are recognized by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials[29]

and the Special Interest Group on Neuropathic Pain of the International Association for the Study of Pain.[30] The tolerability outcomes were adverse events most commonly reported in association with the oral agents (ie, somnolence, dizziness, nausea, diarrhea, headache, constipation, insomnia, fatigue) and the rate of discontinuation due to adverse events.

Heterogeneity Assessment

Potential effect modifiers identified from other meta-analyses, including complete enriched enrollment (ie, enrollment of participants known to respond to a therapy and exclusion of those known not to respond or those at risk of unacceptable adverse effects),[21,23] duloxetine dosing schemes ($\leq$20 vs $\geq$40 mg/d),[25,31] pregabalin dosing schemes ($\leq$150 vs $\geq$300 mg/d),[24] trial duration,[22,23,25] and the trial's sample size, were assessed for heterogeneity for each outcome. Other factors identified during the assessment of the studies (eg, definitions of outcomes, patient baseline characteristics) were also evaluated as effect modifiers. Where heterogeneity was identified and the effect modifier was known from previous studies, relevant trials were excluded from the base case NMA. Where heterogeneity was suspected, scenario analyses were performed to investigate the impact of potential effect modifiers on outcomes.

Statistical Methods

A Bayesian analytical approach was applied to the NMA, which followed NICE[27] and International Society for Pharmacoeconomics and Outcomes Research[32] guidelines. Both fixed effects and random effects models were fitted to the data and considered on the basis of model fit, which was assessed by using the deviance information criterion. Trials with outcomes of 0% in all study arms were considered not to contribute evidence to the treatment effect and were excluded from the analysis.[33] Cochran's Q test and I^2 statistic were used to test for and quantify between-study heterogeneity. Posterior densities for all unknown model parameters in the NMA were estimated by using Markov chain Monte Carlo simulation using WinBUGS codes for NMA models published by NICE.[33]

For each outcome, relative treatment effects are presented as odds ratios (ORs) with 95% CIs. Forest plots of summary statistics were developed for each outcome. A difference in OR was considered statistically significant when the associated 95% CI did not include 1.0. The probability of ranking the best and worst treatment was estimated for each outcome, and the overall cumulative ranking of each treatment was also estimated by using surface under the cumulative ranking (SUCRA) curves. Scenario analyses considering different doses (pregabalin and duloxetine) and various definitions of outcomes were also performed. A planned evaluation for publication bias by using funnel plots was not possible because too few studies ($n < 10$) were available for each pairwise comparison.[34]

RESULTS

Systematic Literature Review

The systematic literature search yielded 500 articles after the removal of duplicates. Of these, 51 full-text publications were reviewed for eligibility; the reasons for exclusion are shown in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart presented in Figure 1. After review of the full-text articles, a total of 24 publications met the inclusion criteria and were fully extracted.

Network Meta-analyses

Network of Evidence

A total of 25 trials were included in the NMA; these comprised 24 studies identified from the literature search plus the STEP[16] trial of the capsaicin 8% patch, which, at the time of the literature search, had not been published. The total network of evidence is shown in Figure 2.

The study design details and key characteristics of enrolled patients for all 25 studies are presented in Table I. The oral agents evaluated in the trials were as follows: pregabalin (13 trials), duloxetine (8 trials), gabapentin (7 trials), and amitriptyline (4 trials). Most trials included placebo as a comparator (22 trials). Most studies had a parallel design (only 2 were crossover studies); the majority were conducted in North America (62%), with the remainder conducted in Asia (19%) and Europe (12%). Trial duration ranged from 4 to 15 weeks, and the number of study participants ranged from 25 to 804. Variation in baseline characteristics was observed; mean age ranged from 48 to 76 years, and mean baseline pain score (11-point numeric rating scale) ranged from 5.5 to 7.3. Most studies required a minimum pain

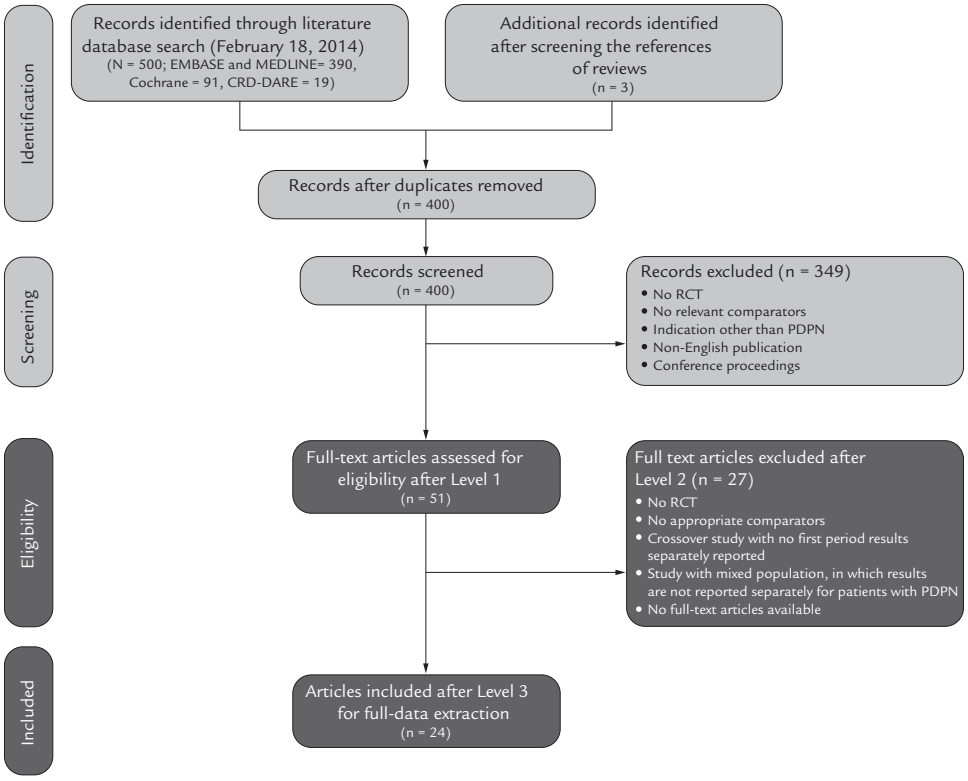


Figure 1. Systematic literature review: flowchart of study selection. CRD-DARE = Centre for Reviews and Dissemination Database of Abstracts of Reviews of Effects; PDPN = painful diabetic peripheral neuropathy; RCT = randomized controlled trial.

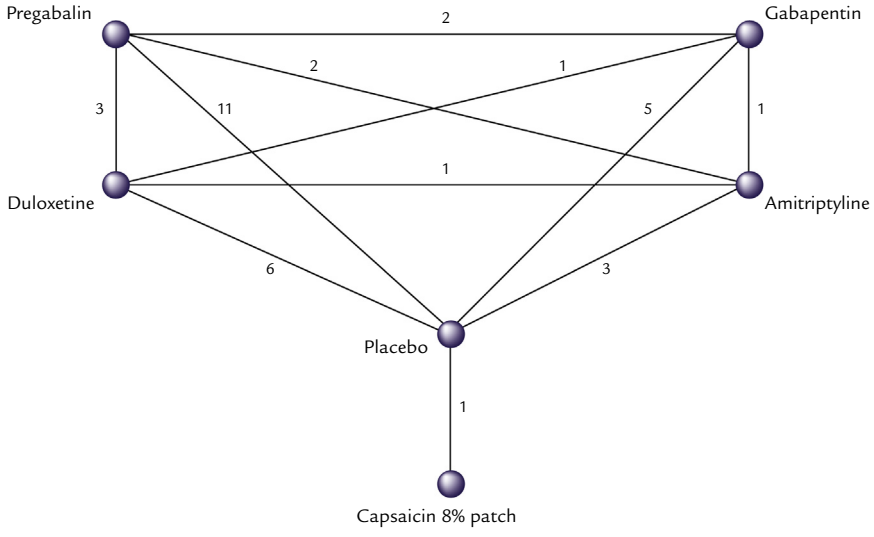


Figure 2. Network meta-analysis: network of evidence. Connecting lines indicate the existing direct pairwise comparisons between 2 treatments. Each number represents the number of studies providing evidence for each comparison. The number of comparisons is greater than the number of trials because some trials have >2 treatment arms.

Table I. Study design details and patient baseline characteristics (25 studies).

Reference	Treatment		No. of Patients		Patient Characteristics at Baseline					
							Baseline Pain Score*		Diabetes, %	
	Drug (dose)	Duration, wk	Per Study	Per Treatment Arm	Mean Age, y	Mean Duration of PDPN, y	Mean	SD	Type 1	Type 2
Arezzo et al, 2008[48]	Pregabalin (600 mg/d)	13	167	82	58.2	4.9	6.3	1.5	4.9	95.1
	Placebo			85	58.3	4.4	6.6	1.6	10.6	89.4
Backonja et al, 1998[54]	Gabapentin (3600 mg/d)	8	165	84	53	–	6.4†	–	25	75
	Placebo			81	53	–	6.5‡	–	25	75
Boyle et al, 2012[35]	Pregabalin (300–600 mg/d)	4	83	27	66.3	–	3.1	–	18.5	81.5
	Duloxetine (60–120 mg/d)			28	65	–	3.4	–	14.3	85.7
	Amitriptyline (50–75 mg/d)			28	64.2	–	3.5	–	7.1	92.9
Dallocchio et al, 2000[38]	Gabapentin (2400 mg/d)	12	25	13	71	2.8	2.9	0.8	0	100
	Amitriptyline (90 mg/d)			12	71	1.8	2.8	0.8	0	100
Devi et al, 2012[57]	Gabapentin (300–1800 mg/d)	12	152	50	57.2	0.8	60.1	17.6	–	
	Duloxetine (20–120 mg/d)			50	58.5	1.2	57.1	16.1	–	
	Pregabalin (75–300 mg/d)			52	55.4	1.2	64.9	18.9	–	
Gao et al, 2010[45]	Duloxetine (flexible dose 60–120 mg)	12	215	106	58.6	3.1	5.5§	1.3	–	
	Placebo			109	59.9	3.3	5.5	1.4	–	
Goldstein et al, 2005[50]	Duloxetine (20 mg/d)	12	457	115	60.3	3.7	5.9	1.6	14.8	85.2
	Duloxetine (60 mg/d)			114	59.2	3.8	6	1.7	12.3	87.7
	Duloxetine (120 mg/d)			113	60.5	3.5	5.9	1.4	9.7	90.3
	Placebo			115	60.4	4	5.8	1.5	9.6	90.4
Gorson et al, 1999[56]	Gabapentin (900 mg/d)	6	40	19	62‖	4‖	–	–	–	
	Placebo			21			–	–	–	
Jiang et al, 2011[58]	Pregabalin (600 mg/d)	4	40	20	55.1	–	70.8	18.8	–	
	Placebo			20	59.7	–	75.4	12.9	–	
Lesser et al, 2004[47]	Pregabalin (75 mg/d)	5	337	77	61.3	–	6.7	1.3	7.8	92.2
	Pregabalin (300 mg/d)			81	59	–	6.2	1.4	6.2	93.8
	Pregabalin (600 mg/d)			82	62	–	6.2	1.5	7.3	92.7
	Placebo			97	57.8	–	6.6	1.5	14.4	85.6
Max et al, 1987[37]	Amitriptyline (150 mg/d)	6	37	37¶	52	2‖ (median)	0.91	–	–	
	Placebo (benztropine)				61		1.2	–	–	
Raskin et al, 2005[44]	Duloxetine (60 mg/d)	12	348	116	58.3	4.5	5.5	1.1	19.8	80.2
	Duloxetine (120 mg/d)			116	59	4.5	5.7	1.3	14.7	85.3
	Placebo			116	59.2	4	5.5	1.3	12.1	87.9
Rauck et al, 2013[46]	Gabapentin enacarbil (1200 mg/d)	13	420	62	57.5	–	6.6	1.5	–	
	Gabapentin enacarbil (2400 mg/d)			56	60.8	–	6.3	1.2	–	
	Gabapentin enacarbil (3600 mg/d)			117#	57.5	–	6.5	1.4	–	
	Pregabalin (300 mg/d)			66	57.7	–	6.5	1.3	–	
	Placebo			120	60.1	–	6.5	1.3	–	

(continued)

Table I. (continued).

Reference	Treatment		No. of Patients		Patient Characteristics at Baseline					
	Drug (dose)	Duration, wk	Per Study	Per Treatment Arm	Mean Age, y	Mean Duration of PDPN, y	Baseline Pain Score* Mean	Baseline Pain Score* SD	Diabetes, % Type 1	Diabetes, % Type 2
Richter et al, 2005[52]	Pregabalin (150 mg/d)	6	246	79	56.3	–	6.5	1.3	8.9	91.1
	Pregabalin (600 mg/d)			82	57.8	–	6.7	1.7	2.4	97.6
	Placebo			85	57.1	–	6.9	1.6	16.5	83.5
Rosenstock et al, 2004[53]	Pregabalin (300 mg/d)	8	146	76	59.2	–	6.5	–	–	
	Placebo			70	60.3	–	6.1	–	–	
Sandercock et al, 2012[51]	Gabapentin ER, 3000 mg/d (single dose)	4	147	46	58	–	6.7	1.3	2.2	97.8
	Gabapentin ER, 3000 mg/d (1200 mg morning, 1800 mg)			50	60	–	6.4	1.5	4.0	96.0
	Placebo			51	58	–	6.7	1.4	7.8	92.2
Satoh et al, 2011[43]	Pregabalin (300 mg/d)	14	314	136**	61.3	4.3	6	1.4	4.5	95.5
	Pregabalin (600 mg/d)			45**	62.2	4.5	6.1	1.3	2.2	97.8
	Placebo			136**	61.3	4.2	6.1	1.4	3.7	96.3
Shabbir et al, 2011[36]	Amitriptyline (10–75 mg/d)	6	210	70	22–76‖	0.5‖		–		
	Pregabalin (75–300 mg/d)			70						
	Placebo			70						
Simpson, 2001 (part I)[55]										
	Gabapentin (3600 mg/d)	8	60	30	48	–	6.4	–	20.0	80.0
	Placebo			30	52	–	6.5	–	16.7	83.3
Simpson et al, 2017[16]	Capsaicin 8% patch	12	195‡‡	105	64.1	5.4	6.7	1.4	–	
	Placebo			90	62.3	5.7	6.2	1.5	–	
Smith et al, 2014[42]	Pregabalin (300 mg/d)	15	194	99	57	–	6.6	1.7	–	
	Placebo			95	58	–	6.5	1.3	–	
Tesfaye et al, 2013[41]	Duloxetine (60 mg/d)	8	804	401	61.5	–	6	1.6	–	
	Pregabalin (300 mg/d)			403	61.9	–	6	1.6	–	
Tölle et al, 2008[49]	Pregabalin (150 mg/d)	12	395	99	58.5	3.7– 4.4‖	6.2	–	15.0	85.0
	Pregabalin (300 mg/d)			99	57.3		6.4	–	15.0	85.0
	Pregabalin (600 mg/d)			101	59.7		6.6	–	15.0	85.0
	Placebo			96	58.9		6.4	–	15.0	85.0
Wernicke et al, 2006[39]	Duloxetine (60 mg/d)	12	334	114	59.7	3.6	6.1	1.6	8.8	91.3
	Duloxetine (120 mg/d)			112	61.5	4.4	6.2	1.5	8.0	92.0
	Placebo			108	60.8	3.5	5.9	1.4	10.2	89.8
Yasuda et al, 2011[40]	Duloxetine (40 mg/d)	12	339	86‡‡	62.1	4.6	5.8	1.2	5.8	93.0
	Duloxetine (60 mg/d)			86	59.7	4.2	5.8	1.2	4.7	95.4
	Placebo			167	60.8	4.2	5.8	1.2	4.8	95.2

(continued)

Table 1. (continued).

ER = extended release; PDPN = painful diabetic peripheral neuropathy.
††Relates to the subgroup of patients who did not receive any concomitant oral medications.
*Assessed on an 11-point numerical rating scale, except for the following studies, which used other measures: 5-point (0–4) categorical scale (0, no pain; 1, mild pain; 2, moderate pain; 3, severe pain; 4, excruciating pain)[38]; visual analog scale (0–100)[57,58]; and verbal rating scale (13-item word list).[37]
†The pain score is reported for 82 patients (efficacy population).
‡The pain score is reported for 80 patients (efficacy population).
§Assessed on the Brief Pain Inventory 11-point numerical rating scale.
||Data reported are for the whole study population.
¶A total of 37 patients assigned to receive both treatments. Data on patient characteristics at baseline relate to the 29 patients who completed the study.
#The baseline characteristics relate to 116 patients in this group.
**In total, 317 patients were randomized to receive pregabalin 300 mg/d (n = 136), 600 mg/d (n = 45), and placebo (n = 136). However, the patient characteristics at baseline, and the analyses for efficacy and safety, included 314 patients (ie, pregabalin 300 mg/d [n = 134], 600 mg/d [n = 45], and placebo [n = 135]) because 3 patients randomized to treatment were excluded because of protocol violations.
‡‡The efficacy analysis was conducted by using data on all randomized patients with at least 1 postbaseline assessment. One patient in the duloxetine 40 mg/d group did not receive the study drug and was not included in the assessment.

duration of 3 to 6 months, stable glycemic control, and a minimum baseline numeric rating scale pain score of 4. The quality assessment suggested that studies were generally of good quality, although the reporting was often not clear (Table II).

Heterogeneity Assessment

The magnitude of treatment effect decreased in trials of longer duration (12–15 weeks) compared with those of shorter duration (4–8 weeks) for both efficacy outcomes (see Supplemental Figure 1 in the online version at http://dx.doi.org/10.1016/j.clinthera.2017.02.010). Tolerability outcomes were not affected by trial duration (data not shown). Therefore, trials with a duration $\leq$8 weeks were excluded from the NMA of efficacy outcomes to create a homogeneous evidence network of trials that were comparable to the capsaicin 8% patch STEP trial (duration of 12 weeks). This approach is consistent with other Cochrane and NICE reviews.[21–23,25] In addition, only trials that used an 11-point pain rating scale were included in the NMA. As a result, all 4 trials of amitriptyline were excluded from the assessment of efficacy outcomes due to short treatment duration (ie, 4 weeks[35] and 6 weeks[36]) or the use of different pain instruments (ie, a 13-item verbal rating scale[37] or a 5-item categorical scale[38]) for which there is no supporting literature to convert the scales to an 11-point scale (Table I). No adjustment was made for trials of different sizes because no differences in treatment effect were evident when the number of participants was considered (data not shown). None of the studies reported complete enriched enrollment; hence, no study was excluded from the base case analysis on the basis of this criterion.

Efficacy Outcomes

For both efficacy outcomes, goodness-of-fit was similar for both fixed effects and random effects models (see Supplemental Table II in the online version at http://dx.doi.org/10.1016/j.clinthera.2017.02.010); data for the fixed effects models only are presented. Forest plots of the pairwise comparisons are presented in Figure 3, and the cumulative ranking (SUCRA) for each treatment is presented in Table III. For both efficacy outcomes, the data extracted from each trial are presented in Supplemental Table III in the online version at http://dx.doi.org/10.1016/j.clinthera.2017.02.010, and rankings

Table II. Quality assessment of studies.

Question	Answer, %				
	Yes	No	Not Clear	Not Reported	Not Applicable
Was randomization conducted appropriately?	68	0	28	4	0
Was the concealment of treatment allocation adequate?	44	0	44	8	4
Were the groups similar at the outset of the study in terms of prognostic factors?	96	0	0	4	0
Were the care providers, participants, and outcome assessors blind to treatment allocation?	84	4	0	8	4
Were there any unexpected imbalances in dropouts between groups?	0	96	0	4	0
Is there any evidence to suggest that the authors measured more outcomes than they reported?	8	92	0	0	0
Did the analysis include an intention-to-treat analysis?	72	12	8	8	0
If so, was this appropriate?	32	8	48	8	4
Were appropriate the methods used to account for missing data?	28	20	8	44	0

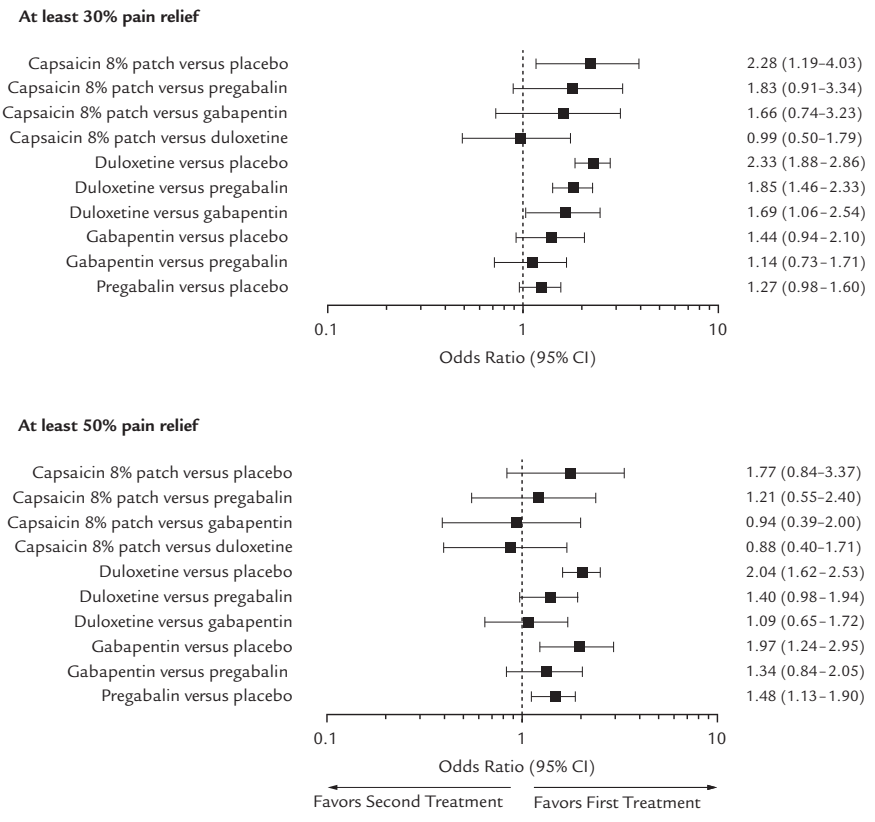


Figure 3. Network meta-analysis (direct and indirect comparisons combined): efficacy outcomes (fixed effects model).

Table III. Network meta-analysis: Cumulative ranking for efficacy and tolerability outcomes.

Outcome	Mean Surface Under the Cumulative Curve, %*				
	Capsaicin 8% Patch	Pregabalin	Gabapentin	Duloxetine	Amitriptyline
Efficacy outcomes					
≥30% pain reduction	81.2	33.0	44.6	89.2	–
≥50% pain reduction	54.9	38.2	73.5	81.5	–
Tolerability outcomes					
Somnolence	–	40.2	48.1	6.1	0.6
Dizziness	–	35.0	36.3	74.7	4.0
Nausea	–	65.5	42.1	0.4	–
Headache	10.6	83.3	60.4	28.8	–
Fatigue	–	61.4	22.3	29.1	–
Constipation	–	41.1	49.9	86.9	1.0
Diarrhea	–	67.9	60.1	2.8	–
Discontinuation due to adverse events	–	46.2	34.3	19.5	–

*A larger surface under the cumulative ranking curve indicates a greater probability that the drug will be ranked as the best treatment.

and cumulative rankograms for both outcomes are presented in Supplemental Table IV and Supplemental Figure 2 in the online version at http://dx.doi.org/10.1016/j.clinthera.2017.02.010, respectively. Statistical testing for heterogeneity is presented in Supplemental Table V in the online version at http://dx.doi.org/10.1016/j.clinthera.2017.02.010.

At Least 30% Pain Reduction

Ten studies reported the number of patients with a ≥30% reduction in pain. Nine studies were included in the base case analysis[16,39–46]; 1 trial was excluded due to shorter treatment duration (≤8 weeks).[47] The capsaicin 8% patch was significantly more likely to achieve ≥30% pain reduction than placebo (OR, 2.28 [95% CI, 1.19–4.03]) (Figure 3). Pairwise comparisons indicated numerical advantages for the capsaicin 8% patch compared with pregabalin (OR, 1.83 [95% CI, 0.91–3.34]) and gabapentin (OR, 1.66 [95% CI, 0.74–3.23]) and similar efficacy for the capsaicin 8% patch compared with duloxetine (OR, 0.99 [95% CI, 0.5–1.79]); none of the differences was statistically significant. The cumulative probability (ie, SUCRA) of being the best treatment for this outcome was 81.2% for the capsaicin 8% patch and 89.2% for duloxetine (Table III). The I^2 statistic, where applicable, indicated low heterogeneity (see Supplemental Table V in the online version at http://dx.doi.org/10.1016/j.clinthera.2017.02.010). Scenario analyses that excluded 3 studies with different end point definitions[39–41] showed no major differences compared with the base case analysis (data not shown).

At Least 50% Pain Reduction

Eighteen trials reported the number of patients with ≥50% pain reduction. Eleven trials were included in the base case analysis[16,39,40,42–46,48–50]; the remainder were excluded because of shorter treatment duration (≤8 weeks).[36,41,47,51–54] The capsaicin 8% patch had a numerical advantage compared with placebo for achieving ≥50% pain reduction (OR, 1.77 [95% CI, 0.84–3.37]) but similar efficacy compared with pregabalin (OR, 1.21 [95% CI, 0.55–2.4]), gabapentin (OR, 0.94 [95% CI, 0.39–2.0]), and duloxetine (OR, 0.88 [95% CI, 0.4–1.71]); none of the differences were statistically significant (Figure 3). The cumulative probability that the capsaicin 8% patch was the most effective treatment for this outcome was 54.9% (Table III). The I^2 statistic, where applicable, indicated low heterogeneity (see Supplemental Table V in the online version at http://dx.doi.org/10.1016/j.clinthera.2017.02.010). Scenario analyses, which considered different doses of pregabalin (≤150 and

≥300 mg/d) and duloxetine (≤20 and ≥40 mg/d), as well as exclusion of studies with different end point definitions,[39,40] showed no major differences compared with the base case analysis (data not shown).

Tolerability Outcomes

For all tolerability outcomes, data for fixed effects models are presented as goodness-of-fit was slightly better for the fixed effects models compared with the random effects models (see **Supplemental Table II** in the online version at http://dx.doi.org/10.1016/j.clinthera.2017.02.010). The capsaicin 8% patch was only included in the NMA for headache because the incidence of the adverse events for the other tolerability outcomes of interest in the STEP[16] trial was 0% in both study arms (see Statistical Methods). The data for insomnia were not analyzed because they were only reported by 1 study (see **Supplemental Table VI** in the online version at http://dx.doi.org/10.1016/j.clinthera.2017.02.010). The results of the pairwise comparisons are presented in **Figure 4**, and the cumulative ranking (SUCRA) for each treatment is

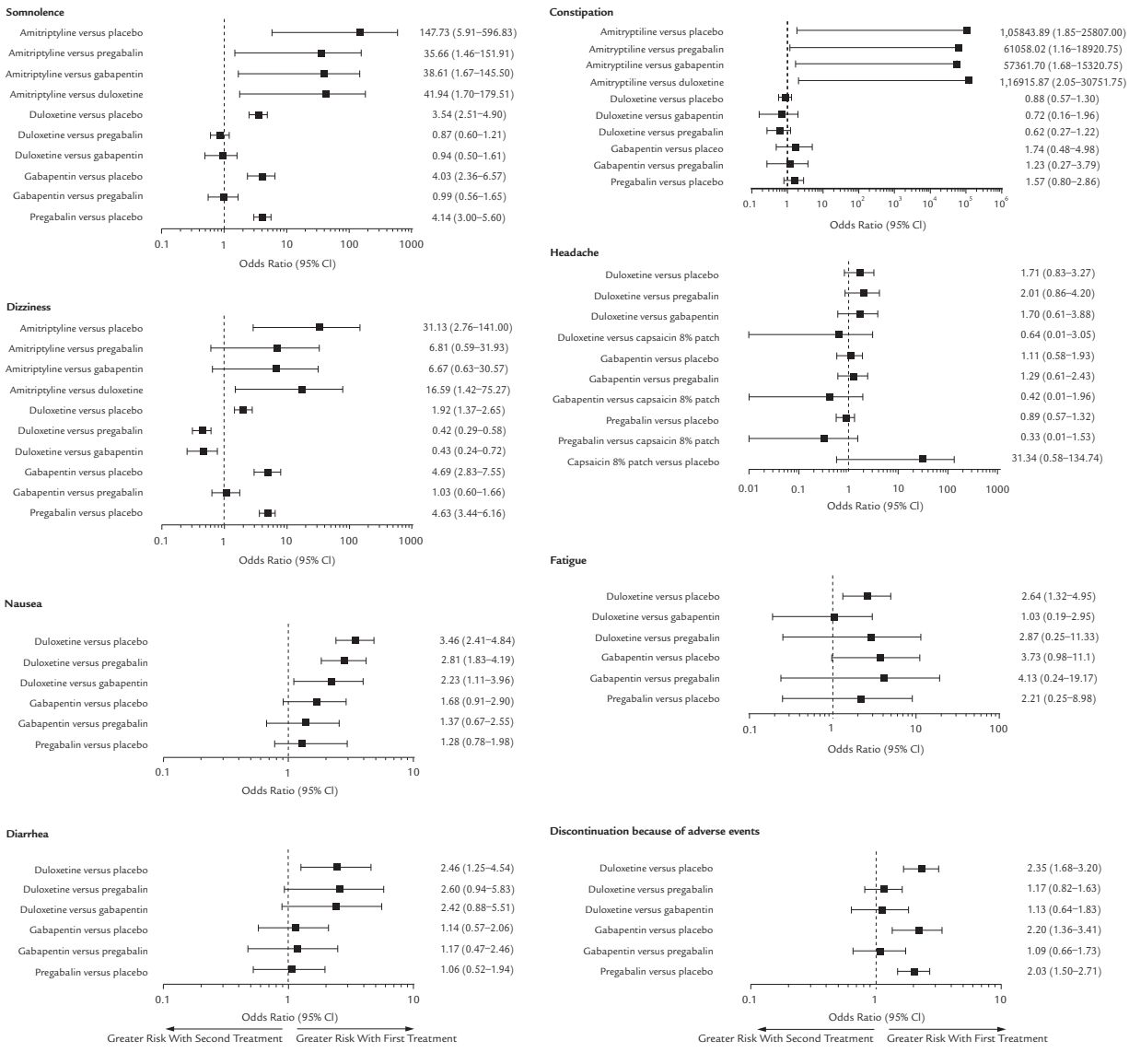


Figure 4. Network meta-analysis (direct and indirect comparisons combined): tolerability outcomes (fixed-effects model).

presented in Table III. The data extracted from each trial are presented in Supplemental Table VI in the online version at http://dx.doi.org/10.1016/j.clinthera.2017.02.010, and rankings and cumulative rankograms are presented in Supplemental Table VII and Supplemental Figure 3 in the online version at http://dx.doi.org/10.1016/j.clinthera.2017.02.010, respectively. Statistical testing for heterogeneity is presented in Supplemental Table VIII in the online version at http://dx.doi.org/10.1016/j.clinthera.2017.02.010.

Somnolence

Twenty studies reported the incidence of somnolence, and 19 of them were included in the base case analysis.[38–43,45–57] One trial was excluded because it used a crossover design, and tolerability data were not reported from the first phase of treatment.[37] Pregabalin (OR, 4.14 [95% CI, 3.00–5.60]), gabapentin (OR, 4.03 [95% CI, 2.36–6.57]), duloxetine (OR, 3.54 [95% CI, 2.51–4.90]), and amitriptyline (OR, 147.73 [95% CI, 5.91–596.83]) were associated with a significantly increased risk of somnolence compared with placebo; there were no significant differences between treatments (Figure 4). I^2 statistics indicated low heterogeneity for all comparisons, except for the pregabalin versus placebo comparison, for which significant heterogeneity was shown ($P = 0.016$) (see Supplemental Table VIII in the online version at http://dx.doi.org/10.1016/j.clinthera.2017.02.010). This finding was evaluated in a scenario analysis in which 1 study was excluded from the analysis.[46] The results indicated that the risk of somnolence (vs placebo) was considerably higher with gabapentin (OR, 6.53 [95% CI, 2.91–13.4]) than with pregabalin (OR, 4.01 [95% CI, 2.84–5.57]) or duloxetine (OR, 3.51 [95% CI, 2.46–4.87]).

Dizziness

Twenty studies reported the incidence of dizziness, and 19 of them were included in the base case analysis[38–43,45–55,57,58]; 1 trial was excluded because it had a crossover design.[37] All agents were associated with a significantly elevated risk of dizziness compared with placebo (pregabalin OR, 4.63 [95% CI, 3.44–6.16]; gabapentin OR, 4.69 [95% CI, 2.83–7.55]; duloxetine OR, 1.92 [95% CI, 1.37–2.65]; amitriptyline OR, 31.13 [95% CI, 2.76–141.00]) (Figure 4). Pairwise comparisons found that duloxetine had a significantly lower risk of dizziness compared with pregabalin (OR, 0.42 [95% CI, 0.29–0.58]) and gabapentin (OR, 0.43 [95% CI, 0.24–0.72]). I^2 statistics indicated low heterogeneity for all comparisons except for pregabalin versus placebo for which significant heterogeneity was shown ($P = 0.029$) (see Supplemental Table VIII in the online version at http://dx.doi.org/110.1016/j.clinthera.2017.02.010). This outcome was addressed in a scenario analysis in which 1 study[46] was excluded; no significant differences were observed compared with the base case analysis (data not shown).

Nausea

Twelve studies reported the incidence of nausea, and all were included in the base case analysis.[†] Duloxetine had a significantly higher risk of nausea than placebo (OR, 3.46 [95% CI, 2.41–4.84]), pregabalin (OR, 2.81 [95% CI, 1.83–4.19]), and gabapentin (OR, 2.23 [95% CI, 1.11–3.96]) (Figure 4). Pregabalin and gabapentin were also associated with numerically increased risks of nausea versus placebo, although the differences were not statistically significant. I^2 statistics indicated low heterogeneity (see Supplemental Table VIII in the online version at http://dx.doi.org/10.1016/j.clinthera.2017.02.010).

Diarrhea

Ten studies reported the incidence of diarrhea, and all were included in the base case analysis.[39,40,42,45–47,52–54,55] Duloxetine had a significantly higher risk of diarrhea compared with placebo (OR, 2.46 [95% CI, 1.25–4.54]) (Figure 4). Pregabalin and gabapentin were also associated with an increased risk of diarrhea versus placebo, although the differences were not statistically significant. Pairwise comparisons indicated that pregabalin had the lowest risk of diarrhea compared with the other treatments, but there were no significant differences between treatments. I^2 statistics indicated low heterogeneity (see Supplemental Table VIII in the online version at http://dx.doi.org/10.1016/j.clinthera.2017.02.010).

Constipation

Eleven studies reported the incidence of constipation, and all were included in the base case analysis.[‡] Amitriptyline, pregabalin, and gabapentin had an

[†]References 39–42,45,46,50,51,53–55,57.

[‡]References 38–40,42,43,45–47,50,52,53.

increased risk of constipation compared with placebo, but the difference was only statistically significant with amitriptyline (Figure 4). Pairwise comparisons indicated that duloxetine had the lowest risk of constipation compared with the other treatments.

Headache

Twelve studies reported the incidence of headache, and all were included in the base case analysis.[28,39,42,45–47,49,51–55] No significant differences in the risk of headache were observed with any active treatment compared with placebo. Pairwise comparisons indicated that pregabalin and the capsaicin 8% patch had the lowest and highest risk of headache, respectively. I^2 statistics indicated low heterogeneity for all comparisons (see Supplemental Table VIII in the online version at http://dx.doi.org/10.1016/j.clinthera.2017.02.010).

Fatigue

Six studies reported the incidence of fatigue, and all were included in the base case analysis.[39,42,45,46,50,56] A significantly increased risk of fatigue was observed for duloxetine compared with placebo (OR, 2.64 [95% CI, 1.32–4.95]), whereas the risk was numerically greater for gabapentin (OR, 3.73 [95% CI, 0.98–11.10]) and pregabalin (OR, 2.21 [95% CI, 0.25–8.98]) compared with placebo. Pairwise comparisons indicated that gabapentin and duloxetine had the highest risk of fatigue.

Discontinuation Due to Adverse Events

Twenty-one studies reported data for discontinuation because of adverse events, and 19 of them were included in the base case analysis.[9–55,57,58] Two trials were excluded, 1 due to crossover design[37] and the other because it had a short treatment period of 28 days, which limits the ability to measure this end point.[35] Pregabalin (OR, 2.03 [95% CI, 1.5–2.71]), gabapentin (OR, 2.2 [95% CI, 1.36–3.41]), and duloxetine (OR, 2.35 [95% CI, 1.68–3.2]) significantly increased the risk of discontinuation because of adverse events compared with placebo (Figure 4). Pairwise comparisons indicated no statistically significant differences between treatments. I^2 statistics indicated low heterogeneity (see Supplemental Table VIII in the online version at http://dx.doi.org/10.1016/j.clinthera.2017.02.010).

DISCUSSION

The present study provides insight into the relative efficacy of the capsaicin 8% patch compared with oral, centrally acting agents recommended by NICE (ie, pregabalin, duloxetine, gabapentin) in the treatment of patients with PDPN. In the absence of direct comparisons between the capsaicin 8% patch and the oral agents, the present NMA considered data from 25 randomized controlled trials, including the placebo-controlled STEP trial.[16] The results suggest that the capsaicin 8% patch provides efficacy similar to duloxetine in terms of delivering pain relief, with duloxetine recommended as a treatment of choice for PDPN in most clinical guidelines.[8,9,11] The capsaicin 8% patch also exhibited numerical advantages compared with pregabalin or gabapentin for providing meaningful pain relief (ie, $\geq$30% pain reduction), as well as similar efficacy for the more stringent outcome of $\geq$50% pain relief. The findings were unaffected in scenario analyses that considered different doses for pregabalin and duloxetine, and different definitions of outcomes. Cumulative rankings showed that the capsaicin 8% patch ranked second or third for efficacy outcomes. To our knowledge, this study is the first to provide an assessment of the relative efficacy of the capsaicin 8% patch compared with oral pharmacologic agents in patients with PDPN. The findings from this NMA were recognized by the European Medicines Agency in their assessment report for the label extension for the capsaicin 8% patch.[59]

For the assessment of tolerability, we evaluated adverse events commonly reported in association with centrally acting agents. The capsaicin 8% patch has a tolerability profile that is characterized by self-limited local adverse events and a very low risk of systemic events, making it difficult to identify adverse events in common with oral agents. For example, in the STEP trial, application-site reactions were reported in 34% of patients treated with the capsaicin 8% patch, but no systemic adverse events of interest were observed.[16] Because the capsaicin 8% patch is applied for 30 to 60 minutes only, discontinuation (by patch removal) because of adverse events is also unlikely. This scenario is supported by the STEP trial, which reported no treatment-related discontinuations after a single application of the capsaicin 8% patch. Because trials with 0% outcomes in both study arms do not contribute to the evidence of treatment effect in NMA,[33] the STEP trial data could only be included for headache as part of the tolerability analyses. This analysis indicated an increased risk of headache relative to all comparators, including placebo.

However, it was based on a very low number of events (n = 4 for capsaicin 8% patch) and a low-level heterogeneity across all comparisons. Headache may be unexpected based on the mechanism of action, but it is an uncommon AE observed in 1% to 4% of patients in clinical studies of capsaicin 8% patch.[12–15] The NMA for the other tolerability outcomes showed that pregabalin, duloxetine, gabapentin, and amitriptyline had a significantly elevated risk of somnolence and dizziness compared with placebo. Furthermore, pregabalin, duloxetine, and gabapentin significantly increased the risk of discontinuation because of adverse events, and they were also associated with an elevated risk of nausea and diarrhea compared with placebo, although the difference was only statistically significant for duloxetine. Overall, the capsaicin 8% patch may have a tolerability advantage compared with the oral agents with respect to systemic adverse events.

Many systematic reviews with meta-analyses of pharmacologic treatments for patients with neuropathic pain have been reported in the literature or performed to support treatment guidelines,[9–11] although fewer of them relate specifically to patients with PDPN.[60–65] None of the PDPN-specific meta-analyses have included the capsaicin 8% patch. However, the findings of these meta-analyses for the oral agents are consistent with our own, despite using slightly different search strategies and analytical techniques. Using ≥50% pain relief as an efficacy outcome, they reported significant differences in favor of duloxetine,[60,61] pregabalin,[60,61,63,64] and gabapentin[60] compared with placebo, and similar efficacy between active agents.[60,61] As in our own analysis, these other analyses of pregabalin,[61,63,64] gabapentin,[61] and duloxetine were also associated with significantly increased risks of somnolence and dizziness compared with placebo, as well as a significantly increased risk of discontinuation because of adverse events.[60]

The current analysis has several strengths and limitations, which should be considered when interpreting the findings. The systematic literature search was performed with prospectively defined eligibility criteria to identify all relevant published studies and to minimize any selection bias. Consistent with the critical outcomes used to generate the NICE guidelines,[9,21] only data for ≥30% and ≥50% pain reduction was used as evidence for efficacy, and the mean change in pain score from baseline was not considered. The impact of effect modifiers was assessed both qualitatively and quantitatively to select sufficiently homogeneous data sets for each of the outcomes. Where heterogeneity was identified (eg, drug dosages, end point definitions, trial duration), relevant trials were either excluded from the base case analysis or relevant scenario analyses were performed, although it was not possible to control for all variables (eg, differences in patient inclusion criteria, use of concomitant medications, imputation methods). Another NICE-recommended agent, amitriptyline, was included in our NMA, but the trial data were restricted such that it was not possible to obtain any relative estimates of efficacy. There were limited tolerability data for amitriptyline and the capsaicin 8% patch; consequently, the uncertainty surrounding the OR estimates for these treatments were considerable due to small sample sizes. The data from the STEP trial used in the NMA were from a subgroup of patients (ie, those who did not receive any relevant concomitant medication), rather than the total study sample.[16] Because the studies included in the NMA were ≤15 weeks in duration, it was impossible to estimate the long-term relative effects of these agents.

CONCLUSIONS

This NMA suggests that pain relief with the capsaicin 8% patch is similar to that observed with pregabalin, duloxetine, and gabapentin in patients with PDPN. These oral agents were associated with a significantly elevated risk of somnolence, dizziness, and discontinuation because of adverse events compared with placebo; none of these events was reported in association with the capsaicin 8% patch. Localized treatment with the capsaicin 8% patch had similar efficacy but offered tolerability benefits in terms of systemic adverse events compared with NICE-recommended oral agents in patients with PDPN.

ACKNOWLEDGMENTS

This study was sponsored by Astellas Pharma Europe BV. Editorial support was provided by Harriet Lamb and Tyrone Daniel of Bioscript Medical and funded by Astellas Pharma Inc.

Ms. Charokopou, Mr. Treur, and Ms. Pantiri performed the analyses. Ms. van Nooten and Dr. Stoker participated in the study research. Employees of Astellas participated in the study design, analysis, decision to publish, and preparation of the

manuscript. All authors provided critical revisions of the publication for intellectual content and approved the final version for submission.

CONFLICTS OF INTEREST

Astellas funded the analyses performed by Pharmerit and the medical writing assistance performed by Bioscript Medical. Astellas provided support in the form of salaries for Ms. van Nooten and Dr. Stoker.

Ms. Charokopou was employed by Pharmerit at the time of analysis and is now employed by UCB Biopharma SPRL. Mr. Treur and Ms. Pantiri are employed by Pharmerit. Ms. van Nooten and Dr. Stoker were employed by Astellas at the time of analysis. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

SUPPLEMENTARY MATERIAL

Supplemental materials accompanying this article can be found in the online version at http://dx.doi.org/10.1016/j.clinthera.2017.02.010.

REFERENCES

1. Boulton AJ, Malik RA, Arezzo JC, Sosenko JM. Diabetic somatic neuropathies. *Diabetes Care*. 2004;27:1458–1486.
2. Veves A, Backonja M, Malik RA. Painful diabetic neuropathy: Epidemiology, natural history, early diagnosis, and treatment options. *Pain Med*. 2008;9:660–674.
3. Boulton AJ, Vinik AI, Arezzo JC, et al. American Diabetes Association. Diabetic neuropathies: a statement by the American Diabetes Association. *Diabetes Care*. 2005;28:956–962.
4. Davies M, Brophy S, Williams R, Taylor A. The prevalence, severity, and impact of painful diabetic peripheral neuropathy in type 2 diabetes. *Diabetes Care*. 2006;29:1518–1522.
5. Alleman CJ, Westerhout KY, Hensen M, et al. Humanistic and economic burden of painful diabetic peripheral neuropathy in Europe: a review of the literature. *Diabetes Res Clin Pract*. 2015;109:215–225.
6. Currie CJ, Poole CD, Woehl A, et al. The financial costs of healthcare treatment for people with type 1 or type 2 diabetes in the UK with particular reference to differing severity of peripheral neuropathy. *Diabet Med*. 2007;24:187–194.
7. Taylor-Stokes G, Pike J, Sadosky A, et al. Association of patient-rated severity with other outcomes in patients with painful diabetic peripheral neuropathy. *Diabetes Metab Syndr Obes*. 2011;4:401–408.
8. Bril V, England J, Franklin GM, et al. American Academy of Neurology; American Association of Neuromuscular and Electrodiagnostic Medicine; American Academy of Physical Medicine and Rehabilitation. Evidence-based guideline: treatment of painful diabetic neuropathy: Report of the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. *Neurology*. 2011;76:1758–1765.
9. National Institute for Health and Care Excellence (NICE). Neuropathic pain—pharmacological management. NICE clinical guideline CG173, Full guideline, November 2013. http://www.nice.org.uk/guidance/cg173/evidence.
10. Finnerup NB, Attal N, Haroutounian S, et al. Pharmacotherapy for neuropathic pain in adults: A systematic review and meta-analysis. *Lancet Neurol*. 2015 162–173.
11. Attal N, Cruccu G, Baron R, et al. European Federation of Neurological Societies. EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. *Eur J Neurol*. 2010;17. 1113–e88.
12. Backonja M, Wallace MS, Blonsky ER, et al. NGX-4010 C116 Study Group. NGX-4010, a high-concentration capsaicin patch, for the treatment of postherpetic neuralgia: a randomised, double-blind study. *Lancet Neurol*. 2008;7:1106–1112.
13. Irving GA, Backonja MM, Dunteman E, et al. NGX-4010 C117 Study Group. A multicenter, randomized, double-blind, controlled study of NGX-4010, a high-concentration capsaicin patch, for the treatment of postherpetic neuralgia. *Pain Med*. 2011;12:99–109.
14. Simpson DM, Brown S, Tobias J, NGX-4010 C107 Study Group. Controlled trial of high-concentration capsaicin patch for treatment of painful HIV neuropathy. *Neurology*. 2008;70:2305–2313.
15. Haanpää M, Cruccu G, Nurmikko TJ, et al. Capsaicin 8% patch versus oral pregabalin in patients with peripheral neuropathic pain. *Eur J Pain*. 2016;20:316–328.
16. Simpson DM, Robinson-Papp J, Van J, et al. Capsaicin 8% patch in painful diabetic peripheral neuropathy: a randomised, double-blind, placebo-controlled study. *J Pain*. 2017;18:42–53.
17. Vinik AI, Perrot S, Vinik EJ, et al. Capsaicin 8% patch repeat treatment versus standard of care in painful diabetic peripheral neuropathy: a randomised, open-label, 52-week study. 51st EASD Annual Meeting, Stockholm, Sweden, 14–18 September 2015 (abstract 1068). http://www.easdvirtualmeeting.org.
18. European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP). CHMP post-authorisation summary of positive opinion for Qutenza, July 2015. http://www.ema.europa.eu/docs/en_GB/docu

ment_library/Summary_of_opinion/human/000909/WC500190411.pdf.
19. Jansen JP, Fleurence R, Devine B, et al. Interpreting indirect treatment comparisons and network meta-analysis for health-care decision making: report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: part 1. *Value Health*. 2011;14:417–428.
20. Centres for Review and Dissemination. Systematic reviews: CRD's guidance for undertaking reviews in health care. CRD, University of York; 2009. https://www.york.ac.uk/crd/guidance/.
21. National Institute for Health and Care Excellence (NICE). Neuropathic pain—pharmacological management. NICE clinical guideline CG173 Appendix D, 2013. http://www.nice.org.uk/guidance/cg173/evidence.
22. Moore R, Derry S, Aldington D, et al. Amitriptyline for neuropathic pain and fibromyalgia in adults. *Cochrane Database Syst Rev*. 2012;12. CD008242.
23. Moore R, Wiffen P, Derry S, McQuay H. Gabapentin for chronic neuropathic pain and fibromyalgia in adults. *Cochrane Database Syst Rev*. 2011;3. CD007938.
24. Moore RA, Straube S, Wiffen PJ, et al. Pregabalin for acute and chronic pain in adults. *Cochrane Database Syst Rev*. 2009;3. CD007076.
25. Lunn MP, Hughes RA, Wiffen PJ. Duloxetine for treating painful neuropathy or chronic pain. *Cochrane Database Syst Rev*. 2009;4. CD007115.
26. Saarto T, Wiffen PJ. Antidepressants for neuropathic pain. *Cochrane Database Syst Rev*. 2007;4. CD005454.
27. National Institute for Health and Care Excellence. PMG9. Guide to the methods of technology appraisal 2013: NICE article, April 2013. http://www.nice.org.uk/article/pmg9/chapter/foreword.
28. Astellas Pharma Europe BV, Qutenza. Number responders and incidence of headache in the STEP study, split by study medication, for patients without concomitant pain medication. Data on file. PAIN/17/0001/APEL.
29. Dworkin RH, Turk DC, Wyrwich KW, et al. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. *J Pain*. 2008;9:105–121.
30. Haanpää M, Attal N, Backonja M, et al. NeuPSIG guidelines on neuropathic pain assessment. *Pain*. 2011;152:14–27.
31. Snedecor SJ, Sudharshan L, Cappelleri JC, et al. Systematic review and meta-analysis of pharmacological therapies for painful diabetic peripheral neuropathy. *Pain Pract*. 2014;14:167–184.
32. Hoaglin DC, Hawkins N, Jansen JP, et al. Conducting indirect-treatment-comparison and network-meta-analysis studies: report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: part 2. *Value Health*. 2011;14:429–437.
33. Dias S, Sutton AJ, Ades AE, Welton NJ. NICE DSU Technical Support Document 2: a generalized linear modeling framework for pairwise and network meta-analysis of randomised controlled trials. 2011 (April 2014 update). 1–98. http://www.nicedsu.org.uk.
34. Higgins JPT, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration; 2011. www.cochrane-handbook.org.
35. Boyle J, Eriksson ME, Gribble L, et al. Randomized, placebo-controlled comparison of amitriptyline, duloxetine, and pregabalin in patients with chronic diabetic peripheral neuropathic pain: Impact on pain, polysomnographic sleep, daytime functioning, and quality of life. *Diabetes Care*. 2012;35:2451–2458.
36. Shabbir B, Shafi F, Mahboob F. Amitriptyline vs pregabalin in painful diabetic neuropathy: a randomised placebo-based study. *Pakistan J Med Heal Sci*. 2011;5:745–747.
37. Max MB, Culnane M, Schafer SC, et al. Amitriptyline relieves diabetic neuropathy pain in patients with normal or depressed mood. *Neurology*. 1987;37:589–596.
38. Dallocchio C, Buffa C, Mazzarello P, Chiroli S. Gabapentin vs. amitriptyline in painful diabetic neuropathy: an open-label pilot study. *J Pain Symptom Manage*. 2000;20:280–285.
39. Wernicke JF, Pritchett YL, D'Souza DN, et al. A randomized controlled trial of duloxetine in diabetic peripheral neuropathic pain. *Neurology*. 2006;67:1411–1420.
40. Yasuda H, Hotta N, Nakao K, et al. Superiority of duloxetine to placebo in improving diabetic neuropathic pain: results of a randomized controlled trial in Japan. *J Diabetes Investig*. 2011;2:132–139.
41. Tesfaye S, Wilhelm S, Lledo A, et al. Duloxetine and pregabalin: high-dose monotherapy or their combination? The "COMBO-DN study"—a multinational, randomized, double-blind, parallel-group study in patients with diabetic peripheral neuropathic pain. *Pain*. 2013;154:2616–2625.
42. Smith T, DiBernardo A, Shi Y, et al. Efficacy and safety of carisbamate in patients with diabetic neuropathy or postherpetic neuralgia: Results from 3 randomized, double-blind placebo-controlled trials. *Pain Pract*. 2014;14:332–342.
43. Satoh J, Yagihashi S, Baba M, et al. Efficacy and safety of pregabalin for treating neuropathic pain associated with diabetic peripheral neuropathy: a 14 week, randomized, double-blind, placebo-controlled trial. *Diabet Med*. 2011;28:109–116.
44. Raskin J, Pritchett YL, Wang F, et al. A double-blind, randomized multicenter trial comparing duloxetine with placebo in the management of diabetic peripheral neuropathic pain. *Pain Med*. 2005;6:346–356.
45. Gao Y, Ning G, Jia WP, et al. Duloxetine versus placebo in the treatment of patients with diabetic neuropathic

pain in China. *Chin Med J (Engl)*. 2010;123:3184–3192.
46. Rauck R, Makumi CW, Schwartz S, et al. A randomized, controlled trial of gabapentin enacarbil in subjects with neuropathic pain associated with diabetic peripheral neuropathy. *Pain Pract*. 2013;13:485–496.
47. Lesser H, Sharma U, LaMoreaux L, Poole RM. Pregabalin relieves symptoms of painful diabetic neuropathy: a randomized controlled trial. *Neurology*. 2004;63:2104–2110.
48. Arezzo JC, Rosenstock J, Lamoreaux L, Pauer L. Efficacy and safety of pregabalin 600 mg/d for treating painful diabetic peripheral neuropathy: A double-blind placebo-controlled trial. *BMC Neurol*. 2008;8:33.
49. Tölle T, Freynhagen R, Versavel M, et al. Pregabalin for relief of neuropathic pain associated with diabetic neuropathy: A randomized, double-blind study. *Eur J Pain*. 2008;12:203–213.
50. Goldstein DJ, Lu Y, Detke MJ, et al. Duloxetine vs. placebo in patients with painful diabetic neuropathy. *Pain*. 2005;116:109–118.
51. Sandercock D, Cramer M, Biton V, Cowles VE. A gastroretentive gabapentin formulation for the treatment of painful diabetic peripheral neuropathy: efficacy and tolerability in a double-blind, randomized, controlled clinical trial. *Diabetes Res Clin Pract*. 2012;97:438–445.
52. Richter RW, Portenoy R, Sharma U, et al. Relief of painful diabetic peripheral neuropathy with pregabalin: a randomized, placebo-controlled trial. *J Pain*. 2005;6:253–260.
53. Rosenstock J, Tuchman M, LaMoreaux L, Sharma U. Pregabalin for the treatment of painful diabetic peripheral neuropathy: a double-blind, placebo-controlled trial. *Pain*. 2004;110:628–638.
54. Backonja M, Beydoun A, Edwards KR, et al. Gabapentin for the symptomatic treatment of painful neuropathy in patients with diabetes mellitus: a randomized controlled trial. *JAMA*. 1998;280:1831–1836.
55. Simpson DA. Gabapentin and venlafaxine for the treatment of painful diabetic neuropathy. *J Clin Neuromuscul Dis*. 2001;3:53–62.
56. Gorson KC, Schott C, Herman R, et al. Gabapentin in the treatment of painful diabetic neuropathy: a placebo controlled, double blind, crossover trial. *J Neurol Neurosurg Psychiatry*. 1999;66:251–252.
57. Devi P, Madhu K, Ganapathy B, et al. Evaluation of efficacy and safety of gabapentin, duloxetine, and pregabalin in patients with painful diabetic peripheral neuropathy. *Indian J Pharmacol*. 2012;44:51–56.
58. Jiang W, Ladd S, Martsberger C, et al. Effects of pregabalin on heart rate variability in patients with painful diabetic neuropathy. *J Clin Psychopharmacol*. 2011;31:207–213.
59. European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP). Assessment report. Qutenza, international nonproprietary name: capsaicin. Procedure No. EMEA/H/C/000909/II/0039. EMA/545605/2015, 2015. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000909/WC500195227.pdf.
60. Rudroju N, Bansal D, Talakokkula ST, et al. Comparative efficacy and safety of six antidepressants and anticonvulsants in painful diabetic neuropathy: A network meta-analysis. *Pain Physician*. 2013;16:E705–E714.
61. Quilici S, Chancellor J, Löthgren M, et al. Meta-analysis of duloxetine vs. pregabalin and gabapentin in the treatment of diabetic peripheral neuropathic pain. *BMC Neurol*. 2009;9:6.
62. Griebeler ML, Morey-Vargas OL, Brito JP, et al. Pharmacologic interventions for painful diabetic neuropathy: An umbrella systematic review and comparative effectiveness network meta-analysis. *Ann Intern Med*. 2014;161:639–649.
63. Hurley RW, Lesley MR, Adams MC, et al. Pregabalin as a treatment for painful diabetic peripheral neuropathy: A meta-analysis. *Reg Anesth Pain Med*. 2008;33:389–394.
64. Zhang SS, Wu Z, Zhang LC, et al. Efficacy and safety of pregabalin for treating painful diabetic peripheral neuropathy: A meta-analysis. *Acta Anaesthesiol Scand*. 2015;59:147–159.
65. Wolff RF, Bala MM, Westwood M, et al. 5% Lidocaine medicated qplaster in painful diabetic peripheral neuropathy (DPN): A systematic review. *Swiss Med Wkly*. 2010;140:297–306.

Address correspondence to: Floortje van Nooten, MSc, Dompé Farmaceutici S.p.A., Milan, Italy. E-mail: floortjevannooten@hotmail.com

SUPPLEMENTARY MATERIAL

Appendix A. Systematic literature review: search terms for databases

The tables below present an overview of the search terms (including syntax, quotation marks and Boolean operators) per topic that were entered in the different databases.

Search Terms: Embase and Medline

Topic	Search #	Search terms	Number of hits (February 18, 2014)
Limits	1	[humans]/lim AND [english]/lim	11,285,047
Disease	2	(('pain'/exp OR 'pain' OR painful) AND (diabet* OR 'diabetic'/exp OR 'diabetic' OR 'diabetes'/exp OR 'diabetes') AND (neuropath* OR neuropathic OR 'neuropathy'/exp OR 'neuropathy' OR neuropathies) OR (diabet* AND neuropath*)) OR pdpn OR pdn OR 'dpn'/exp OR 'dpn' OR neuropath* NEAR/10 diabet*	62,796
RCT	3	rct OR 'randomized controlled trial'/exp OR 'randomized controlled trial' OR (random* AND (control* OR clinical*) AND (trial* OR stud*))	834,060
Pregabalin	4	'pregabalin'/exp OR pregabalin OR 'lyrica'/exp OR lyrica	7065
Gabapentin	5	'gabapentin'/exp OR gabapentin OR 'neurontin'/exp OR neurontin OR 'neurotonin'/exp OR neurotonin	20,240
Duloxetine	6	duloxetin* OR 'cymbalta'/exp OR cymbalta OR 'ariclaim'/exp OR ariclaim OR 'xeristar'/exp OR xeristar OR 'yentreve'/exp OR yentreve	6362
TCA – amitriptyline	7	'amitriptyline'/exp OR amitriptyline OR 'sarotex'/exp OR sarotex OR 'tryptizol'/exp OR tryptizol OR tryptomer OR 'elavil'/exp OR elavil	33,597
Combined	8	#1 AND #2 AND #3 AND (#4 OR #5 OR #6 OR #7)	390

dpn = diabetic painful neuropathy; lim = limits; pdpn = painful diabetic peripheral neuropathy; pdn = painful diabetic neuropathy; RCT = randomized controlled trial; TCA = tricyclic antidepressant.
/exp = Inclusion of sub-terms/derivatives (explosion search). If a term has any more specific, or narrower, index terms within the Emtree thesaurus, they are also automatically retrieved as part of the search. Also 'search as free text' has been selected, for all terms entered in the search box. They are all searched together with the Boolean AND and OR operators
*= Indicates a variable truncation.

Search Terms: Cochrane Library

Topic	Search #	Search terms	Number of hits (February 18 2014)
Disease	1	((“diabetic” or “diabetes”) and (“neuropathy” or “neuropathic”) and (pain or “painful”)) or “PDPN” or PDN or “DPN”	828
RCT	2	(“randomized controlled trial”) or (“randomize” and (“controlled” or clinical) and (“trial” or “study”))	354,170
Pregabalin	3	“pregabalin” or “Lyrica”	455
Gabapentin	4	“gabapentin” or neurotonin or “Neurontin”	870
Duloxetine	5	“duloxetine” or duloxetin or “Cymbalta” or ariclaim or xeristar	514
TCA - amitriptyline	6	“amitriptyline” or Sarotex or “Tryptizol” or Tryptomer or “Elavil"	2288
Combined	7	#1 and #2 and (#3 or #4 or #5 or #6)	180*

DPN = diabetic painful neuropathy; PDPN = painful diabetic peripheral neuropathy; PDN = painful diabetic neuropathy; RCT = randomized controlled trial; TCA = tricyclic antidepressant.
All terms have been searched in all text (e.g., ‘Search All Text’). Also, word variations have been searched, for all terms entered in the search box. They are all searched together with the Boolean AND and OR operators.
*All results (169): Cochrane reviews (67), other reviews (13), trials (91), methods studies (2), economic evaluations (6), Cochrane groups (1). The 91 hits for trials were screened for inclusion/exclusion.

Search Terms: National Health Service Centre for Review and Dissemination

Topic	Search #	Search terms	Number of hits (February 18 2014)
			DARE
Disease	1	((diabetic OR diabetes) AND (neuropathy OR neuropathic OR neuropathies) AND (pain OR painful)) OR PDN OR DPN OR PDNP	56
RCT	2	(randomized controlled trial) OR (randomize AND (controlled OR clinical) AND (trial OR study))	117
Combined	3	#1 AND #2	19

DARE = Database of Abstracts of Reviews of Effects, focused primarily on systematic review.
DPN = diabetic painful neuropathy; PDPN = painful diabetic peripheral neuropathy; PDN = painful diabetic neuropathy; RCT = randomized controlled trial.

Supplementary Table I–VIII.

Supplementary Table I. Systematic literature review: inclusion and exclusion criteria.

Variable	Inclusion criteria	Exclusion criteria
Population	PDPN	Neuropathic pain other than PDPN
	PDPN mixed population trials eligible if trial results were reported separately for PDPN patients	Animal studies/experiments
	Humans and adults	
Study design	RCT investigating safety and efficacy	Non-RCT
	Enriched enrollment randomized withdrawal trials	
Language	English	Not English
Treatments	Pregabalin	Treatment which is not pregabalin, gabapentin, duloxetine, or TCA other than amitriptyline.
	Gabapentin	
	Duloxetine	
	Amitriptyline	
Publication date	Published after 1950	Published before 1950
Publication type	Full texts	Reviews (with the exception reported in the ''inclusion criteria'')
	Data from reviews were extracted only if original publications do not provide the required data	Editorials
		Errata
		Letters (to editor)
		Notes
Treatment duration	$\geq$ 4 weeks	$<$ 4 weeks
PDPN study sample	$\geq$ 10	$<$ 10
Crossover studies	Only if first period results available	First period results not available

PDPN = painful diabetic peripheral neuropathy; RCT = randomized controlled trial; TCA = tricyclic antidepressant.

Supplementary Table II. Network meta-analysis: model fit and selection statistics by outcome for fixed-effect and random-effects models.

Outcome	Deviance information criterion	
	Fixed-effect model	Random-effects model
Efficacy outcomes		
≥ 30% pain reduction	136.83	136.34
≥ 50% pain reduction	163.07	166.34
Tolerability outcomes		
Somnolence	181.39	181.39
Dizziness	190.35	189.97
Nausea	138.41	137.69
Diarrhea	104.51	103.12
Constipation	124.13	99.24
Fatigue	55.85	52.04
Headache	115.77	114.47
Discontinuation due to adverse events	215.15	214.29

Supplementary Table III. Network meta-analysis: source data for efficacy outcomes.

Study	Treatment	Endpoint definition	N_{event}	N_{total}
≥ 30% pain reduction				
Astellas Pharma Europe B.V.[1]	Capsaicin 8% patch	Defined as ≥ 30% pain reduction, respectively, from baseline to endpoint (Week 12)	49	105
	Placebo		29	90
Gao 2010[2]	Duloxetine (flexible dose 60–120 mg)	Defined as ≥ 30% pain reduction, respectively, from baseline to endpoint	74	106
	Placebo		67	109
Raskin 2005[3]	Duloxetine (60 mg/d)	Defined as a 30% reduction from baseline to endpoint in the 24-hour average pain score	77	113
	Duloxetine (120 mg/d)		73	114
	Duloxetine pooled		150	227
	Placebo		49	113
Rauck 2013[4]	Pregabalin (300 mg/d)	Defined as a 30% reduction in the mean 24-hour average pain intensity score from baseline to the end of maintenance treatment	28	66
	Gabapentin enacarbil (1200 mg/d)		31	62
	Gabapentin enacarbil (2400 mg/d)		25	56
	Gabapentin enacarbil (3600 mg/d)		66	116
	Gabapentin pooled		122	234
	Placebo		57	120
Satoh 2011[5]	Pregabalin (300 mg/d)	Defined as ≥ 30% reduction in mean pain score from baseline to end-point	66	134
	Pregabalin (600 mg/d)		25	45
	Pregabalin pooled		91	179
	Placebo		49	135
Smith 2014[6]	Pregabalin (300 mg/d)	Defined as 30% reduction from baseline in the mean of the last 7 daily average pain scores of the treatment period	49	99
	Placebo		45	95
Tesfaye 2013[7]	Pregabalin (300 mg/d)	Defined as a 30% reduction in BPI-MSF 24-hour average pain	138	374
	Duloxetine (60 mg/d)		195	375
Wernicke 2006[8]	Duloxetine (60 mg/d)	Defined as a 30% reduction from baseline to endpoint in the 24-hour average pain severity with a	69	110
	Duloxetine (120 mg/d)		77	111
	Duloxetine pooled		146	221

(continued)

Supplementary Table III. (continued).

Study	Treatment	Endpoint definition	N_{event}	N_{total}
	Placebo	30% reduction from baseline at a week ≥ 2 weeks before the last, and with ≥ 20% reduction from baseline at every week in between	45	106
Yasuda 2011[9]	Duloxetine (40 mg/d)	Defined as the percentage of	47	85
	Duloxetine (60 mg/d)	patients who achieved a 30%	51	86
	Duloxetine pooled	reduction of 24-hour average	98	171
	Placebo	pain score from baseline to each point of measurement over 12 weeks	59	167
≥ 50% pain reduction				
Arezzo 2008[10]	Pregabalin (600 mg/d)	Defined as ≥ 50% reduction in	40	82
	Placebo	mean pain score from baseline to endpoint	20	85
Astellas Pharma Europe B.V.[1]	Capsaicin 8% patch	Defined as ≥ 50% pain reduction,	29	105
	Placebo	respectively, from baseline to endpoint (Week 12)	17	90
Gao 2010[2]	Duloxetine (flexible dose 60–120 mg)	Defined as ≥ 50% pain reduction,	57	106
	Placebo	respectively, from baseline to endpoint	55	109
Goldstein 2005[11]	Duloxetine (20 mg/d)	Defined as ≥ 50% reduction in	46	112
	Duloxetine (60 mg/d)	mean pain score from baseline	55	112
	Duloxetine (120 mg/d)	to endpoint	57	110
	Duloxetine pooled		158	334
	Placebo		29	101
Raskin 2005[3]	Duloxetine (60 mg/d)	Defined as ≥ 50% reduction in	57	113
	Duloxetine (120 mg/d)	mean pain score from baseline	44	114
	Duloxetine pooled	to endpoint	101	227
	Placebo		34	113
Rauck 2013[4]	Pregabalin (300 mg/d)	Defined as a 50% reduction in the	14	66
	Gabapentin enacarbil (1200 mg/d)	mean 24-hour average pain	26	62
	Gabapentin enacarbil (2400 mg/d)	intensity score from baseline to	15	56
	Gabapentin enacarbil (3600 mg/d)	the end of maintenance	46	116
	Gabapentin pooled	treatment	87	234
	Placebo		35	120
Smith 2014[6]	Pregabalin (300 mg/d)	Defined as ≥ 50% reduction from	32	99
	Placebo	baseline in the mean of the last 7 daily average pain scores of the treatment period	26	95
Satoh 2011[5]	Pregabalin (300 mg/d)	Defined as ≥ 50% reduction in	39	134
	Pregabalin (600 mg/d)	mean pain score from baseline	16	45
	Pregabalin pooled	to endpoint	55	179
	Placebo		29	135
Tölle 2008[12]	Pregabalin (150 mg/d)	Defined as ≥ 50% reduction in	34	99
	Pregabalin (300 mg/d)	mean pain score from baseline	33	99
	Pregabalin (600 mg/d)	to endpoint	46	101
	Pregabalin pooled		113	299
	Placebo		29	96
Wernicke 2006[8]	Duloxetine (60 mg/d)	Defined as a 50% reduction in BPI-MSF 24-hour average pain	47	110
	Duloxetine (120 mg/d)		59	111
	Duloxetine pooled		106	221
	Placebo		29	106
Yasuda 2011[9]	Duloxetine (40 mg/d)	Defined as the percentage of	32	85
	Duloxetine (60 mg/d)	patients who achieved a 50%	35	86
	Duloxetine pooled	reduction of 24-hour average	67	171
	Placebo	pain score from baseline to each point of measurement over 12 weeks	33	167

BPI-MSF = Brief Pain Inventory Modified Short Form; N_{event} = number of patients with event; N_{total} = total number of patients.

Supplementary Table IV. Network meta-analysis: probability and ranking results for efficacy outcomes (fixed-effects model).

Drug	Probability (95% credibility intervals), %*	Probability best, %	Probability worst, %	Rank†
≥ 30% pain reduction				
Placebo	42.6 (39.3–45.8)	0	92.2	5
Capsaicin 8% patch	61.4 (47.3–74.6)	41.9	0.5	2
Pregabalin	48.3 (43.3–53.3)	0	2.9	4
Gabapentin	51.1 (41.7–60.4)	0.7	4.4	3
Duloxetine	63.2 (59.3–67.0)	57.5	0	1
≥ 50% pain reduction				
Placebo	27.8 (25.3–30.4)	0	92.3	5
Capsaicin 8% patch	39.3 (24.8–56.0)	22.9	7.5	3
Pregabalin	36.2 (31.1–41.4)	0.5	0.1	4
Gabapentin	42.6 (32.9–52.7)	33.7	0.1	2
Duloxetine	43.8 (39.4–48.3)	42.8	0	1

*Estimated by applying odds ratio against placebo to the weighted average placebo probability in the network.
†Ranks are based on the probability of being the best, i.e., demonstrating higher proportion of patients reporting the outcome of interest.

Supplementary Table V. Network meta-analysis: heterogeneity of input data for efficacy outcomes.

Treatment comparison	Studies, n	Q-statistic (*P*-value)*	I-square, %
≥ 30% pain reduction			
Pregabalin, placebo	3	1.9 (0.39)	0
Duloxetine, placebo	4	3.1 (0.37)	4.6
Duloxetine, pregabalin	1	–	–
Gabapentin, placebo	1	–	–
Gabapentin, pregabalin	1	–	–
Capsaicin 8% patch, placebo	1	–	–
≥ 50% pain reduction			
Pregabalin, placebo	5	5.6 (0.23)	28.4
Duloxetine, placebo	5	6.3 (0.18)	36.1
Gabapentin, placebo	1	–	–
Gabapentin, pregabalin	1	–	–
Capsaicin 8% patch, placebo	1	–	–

Heterogeneity can only be assessed if > 1 study provides data on a treatment comparison.
*A *P*-value ≤ 0.1 indicates statistical significance.

Supplementary Table VI. Network meta-analysis: source data for tolerability outcomes.

Study	Treatment	Somnolence		Dizziness		Nausea		Diarrhea		Constipation		Fatigue		Insomnia		Headache		Discontinuation due to adverse events	
		N_{event}	N_{total}	N_{event}	N_{total}	N_{event}	N_{total}	N_{event}	N_{total}	N_{event}	N_{total}	N_{event}	N_{total}	N_{event}	N_{total}	N_{event}	N_{total}	N_{event}	N_{total}
Arezzo 2008	Pregabalin (600 mg/d)	11	82	27	82	–	–	–	–	–	–	–	–	–	–	–	–	14	82
	Placebo	5	85	5	85	–	–	–	–	–	–	–	–	–	–	–	–	10	85
Backonja 1998	Gabapentin (3600 mg/d)	19	84	20	84	7	84	9	84	–	–	–	–	–	–	9	84	7	84
	Placebo	5	81	4	81	4	81	7	81	–	–	–	–	–	–	3	81	5	81
Dallocchio 2000	Amitriptyline (30–90 mg/d)	6	12	3	12	–	–	–	–	4	12	–	–	–	–	–	–	–	–
	Gabapentin (1200–2400 mg/d)	1	13	2	13	–	–	–	–	0	13	–	–	–	–	–	–	–	–
Devi 2012	Gabapentin (300–1800 mg/d)	1	50	2	50	1	50	–	–	–	–	–	–	–	–	–	–	6	50
	Duloxetine (20–120 mg/d)	1	50	2	50	1	50	–	–	–	–	–	–	–	–	–	–	6	50
	Pregabalin (75–300 mg/d)	0	52	1	52	1	52	–	–	–	–	–	–	–	–	–	–	2	52
Gao 2010	Duloxetine (flexible dose 60–120 mg)	17	106	16	106	32	106	10	106	11	106	8	106	–	–	6	106	15	106
	Placebo	6	109	12	109	13	109	6	109	9	109	8	109	–	–	6	109	4	109
Goldstein 2005	Duloxetine (20 mg/d)	9	115	7	115	16	115	–	–	6	115	1	115	–	–	–	–	5	115
	Duloxetine (60 mg/d)	23	114	11	114	19	114	–	–	17	114	3	114	–	–	–	–	15	114
	Duloxetine (120 mg/d)	32	113	26	113	31	113	–	–	12	113	8	113	–	–	–	–	22	113
	Duloxetine pooled	64	342	44	342	66	342	–	–	35	342	12	342	–	–	–	–	42	342
	Placebo	9	115	8	115	11	115	–	–	4	115	0	115	–	–	–	–	6	115
Gorson 1999	Gabapentin (900 mg/d)	6	19	–	–	–	–	–	–	–	–	4	19	–	–	–	–	–	–
	Placebo	0	21	–	–	–	–	–	–	–	–	0	21	–	–	–	–	–	–
Jiang 2011	Pregabalin (600 mg/d)	–	–	2	15	–	–	–	–	–	–	–	–	–	–	–	–	3	20
	Placebo	–	–	0	14	–	–	–	–	–	–	–	–	–	–	–	–	0	20
Lesser 2004	Pregabalin (75 mg/d)	3	77	6	77	–	–	4	77	0	77	–	–	–	–	5	77	2	77
	Pregabalin (300 mg/d)	19	81	22	81	–	–	1	81	3	81	–	–	–	–	7	81	3	81
	Pregabalin (600 mg/d)	22	82	32	82	–	–	3	82	7	82	–	–	–	–	8	82	10	82
	Pooled	44	240	60	240	–	–	8	240	10	240	–	–	–	–	20	240	15	240
	Placebo	4	97	5	97	–	–	7	97	1	97	–	–	–	–	10	97	3	97
Raskin 2005	Duloxetine (60 mg/d)	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	5	116
	Duloxetine (120 mg/d)	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	14	116
	Duloxetine pooled	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	19	232
	Placebo	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	3	116
Rauck 2013	Pregabalin (300 mg/d)	69	966	9	66	3	66	5	66	6	66	4	66	–	–	6	66	6	66
	Gabapentin enacarbil (1200 mg/d)	2	62	9	62	7	62	3	62	3	62	3	62	–	–	3	62	5	62
	Gabapentin enacarbil (2400 mg/d)	7	56	8	56	4	56	2	56	4	56	3	56	–	–	4	56	12	56
	Gabapentin enacarbil (3600 mg/d)	14	116	16	116	7	116	6	116	4	116	5	116	–	–	4	116	21	117
	Gabapentin pooled	23	234	33	234	18	234	11	234	11	234	11	234	–	–	11	234	38	235
	Placebo	5	120	7	120	9	120	6	120	4	120	3	120	–	–	9	120	11	120
Richter 2005	Pregabalin (150 mg/d)	4	79	8	79	–	–	4	79	3	79	–	–	–	–	6	79	2	79
	Pregabalin (600 mg/d)	18	82	31	82	–	–	2	82	5	82	–	–	–	–	13	82	7	82

(continued)

Supplementary Table VI. (continued).

Study	Treatment	Somnolence		Dizziness		Nausea		Diarrhea		Constipation		Fatigue		Insomnia		Headache		Discontinuation due to adverse events	
		N_{event}	N_{total}	N_{event}	N_{total}	N_{event}	N_{total}	N_{event}	N_{total}	N_{event}	N_{total}	N_{event}	N_{total}	N_{event}	N_{total}	N_{event}	N_{total}	N_{event}	N_{total}
	Pooled	22	161	39	161	–	–	6	161	8	161	–	–	–	–	19	161	9	161
	Placebo	3	85	2	85	–	–	3	85	4	85	–	–	–	–	9	85	4	85
Rosenstock 2004	Pregabalin (300 mg/d)	15	76	27	76	6	76	3	76	4	76	–	–	–	–	5	76	8	76
	Placebo	2	70	8	70	6	70	2	70	0	70	–	–	–	–	7	70	2	70
Sandercock 2009	Gabapentin ER (3000 mg/d single dose)	6	47	8	47	2	47	–	–	–	–	–	–	–	–	2	47	2	46
	Gabapentin ER (3000 mg/d; 1,200 mg morning; 1,800 mg evening)	2	49	6	49	3	49	–	–	–	–	–	–	–	–	3	49	2	50
	Pooled	8	96	14	96	5	96	–	–	–	–	–	–	–	–	5	96	4	96
	Placebo	0	51	0	51	0	51	–	–	–	–	–	–	–	–	2	51	2	51
Satoh 2011	Pregabalin (300 mg/d)	28	134	26	134	–	–	–	–	4	134	–	–	–	–	–	–	17	136
	Pregabalin (600 mg/d)	18	45	17	45	–	–	–	–	2	45	–	–	–	–	–	–	13	45
	Pooled	46	179	43	179	–	–	–	–	6	179	–	–	–	–	–	–	30	181
	Placebo	11	135	9	135	–	–	–	–	1	135	–	–	–	–	–	–	7	136
Simpson (part I) 2001	Gabapentin (3600 mg/d)	6	30	6	30	2	30	3	30	–	–	–	–	–	–	3	30	2	30
	Placebo	1	30	1	30	1	30	1	30	–	–	–	–	–	–	1	30	2	30
Smith 2014	Pregabalin (300 mg/d)	10	98	9	98	2	98	2	98	2	98	3	98	–	–	4	98	10	29
	Placebo	1	93	4	93	3	93	1	93	6	93	2	93	–	–	7	93	28	21
Tesfaye 2013	Duloxetine (60 mg/d)	40	401	29	401	57	401	–	–	–	–	–	–	–	–	–	–	35	401
	Pregabalin (300 mg/d)	44	403	61	403	26	403	–	–	–	–	–	–	–	–	–	–	39	403
Tölle 2008	Pregabalin (300 mg/d)	4	99	9	99	–	–	–	–	–	–	–	–	–	–	3	99	11	99
	Pregabalin (600 mg/d)	8	101	14	101	–	–	–	–	–	–	–		–	–	1	101	13	101
	Pregabalin pooled	17	299	26	299	–	–	–	–	–	–	–	–	–	–	9	299	29	299
	Placebo	1	96	2	96	–	–	–	–	–	–	–	–	–	–	5	96	3	96
Wernicke 2006	Duloxetine (60 mg/d)	9	114	18	114	32	114	13	114	8	114	14	114	6	114	12	114	17	114
	Duloxetine (120 mg/d)	17	112	12	112	36	112	5	112	2	112	14	112	11	112	15	112	20	112
	Duloxetine pooled	26	226	30	226	68	226	18	226	10	226	28	226	17	226	27	226	37	226
	Placebo	1	108	6	108	7	108	2	108	21	108	3	108	2	108	7	108	8	108
Yasuda 2011	Duloxetine (60 mg/d)	16	85	6	85	10	85	4	85	6	85	–	–	–	–	–	–	9	86
	Duloxetine (120 mg/d)	21	86	5	86	14	86	7	86	5	86	–	–	–	–	–	–	12	86
	Duloxetine pooled	37	171	11	171	24	171	11	171	11	171	–	–	–	–	–	–	21	172
	Placebo	14	167	9	167	3	167	6	167	9	167	–	–	–	–	–	–	9	167
Astellas Pharma Europe B.V.	Capsaicin 8% patch	–	–	–	–	–	–	–	–	–	–	–	–	–	–	4	105	–	–
	Placebo	–	–	–	–	–	–	–	–	–	–	–	–	–	–	1	90	–	–

ER = extended release; N_{event} = number of patients with event; N_{total} = total number of patients.

Supplementary Table VII. Network meta-analysis: probability and ranking results for tolerability outcomes (fixed-effects model).

Drug	Probability (95% credibility intervals), %*	Probability best, %	Probability worst, %	Rank†
Somnolence				
Placebo	5.6 (4.4–6.9)	0	100	5
Pregabalin	19.5 (16.2–23.1)	0.8	0	2
Gabapentin	19.0 (12.7–26.8)	0.2	0	3
Duloxetine	17.2 (13.9–20.8)	0.2	0	4
Amitriptyline	69.0 (26.4–97.2)	98.9	0	1
Dizziness				
Placebo	6.3 (5.1–7.6)	0	99.9	4.5
Pregabalin	23.4 (19.9–27.2)	5.8	0	2
Gabapentin	23.5 (16.3–32.3)	3.4	0	3
Duloxetine	11.2 (8.9–13.9)	0	0	4.5
Amitriptyline	53.4 (15.5–90.2)	90.8	0.1	1
Nausea				
Placebo	7.0 (5.4–8.9)	0	77.5	4
Pregabalin	8.6 (5.9–12)	0	18.2	3
Gabapentin	11.0 (6.8–16.6)	1.1	4.3	2
Duloxetine	20.4 (16.7–24.5)	98.9	0	1
Diarrhea				
Placebo	4.4 (3.2–5.9)	0.1	31.8	4
Pregabalin	4.5 (2.5–7.4)	2.8	39.4	3
Gabapentin	4.9 (2.7–8)	4.1	28.6	2
Duloxetine	10.0 (5.8–15.9)	93.0	0.2	1
Constipation				
Placebo	6.7 (5.1–8.5)	0	14.7	5
Pregabalin	9.9 (5.6–16.2)	1.8	4.2	2
Gabapentin	10.5 (3.4–25.2)	0.3	18.4	3
Duloxetine	5.8 (4.2–7.9)	0.1	62.4	4
Amitriptyline	69.1 (11.9–100)	97.8	0.3	1
Headache				
Placebo	6.7 (5.2–8.4)	0.2	14.5	4
Pregabalin	5.9 (4.2–7.9)	0.1	54.6	5
Gabapentin	7.3 (4.1–11.6)	2.8	22.3	3
Duloxetine	10.7 (5.8–18.1)	16.0	3.1	2
Capsaicin 8% patch	32.2 (4.0–90.1)	80.9	5.5	1
Fatigue				
Placebo	3.5 (2.1–5.4)	0	62.9	4
Pregabalin	6.5 (0.9–22.2)	17.0	35.0	3
Gabapentin	10.9 (3.7–25.3)	51.7	2.0	1

(continued)

Supplementary Table VII. (continued).

Drug	Probability (95% credibility intervals), %*	Probability best, %	Probability worst, %	Rank†
Duloxetine	8.3 (5.0–12.7)	31.3	0.2	2
Discontinuation due to adverse events				
Placebo	6.1 (5.0–7.4)	0	99.9	4
Pregabalin	11.6 (9.5–14.0)	11.3	0	3
Gabapentin	12.4 (8.5–17.1)	34.5	0.1	2
Duloxetine	13.2 (10.5–16.3)	54.1	0	1

*Estimated by applying odds ratio against placebo to the weighted average placebo probability in the network.
†Ranks are based on the probability of being the worst, i.e., demonstrating higher proportion of patients reporting the adverse event.

Supplementary Table VIII. Network meta-analysis: heterogeneity of the input data for tolerability outcomes.

Treatment comparison	Studies, n	Q-statistic (p-value)*	I-square, %
Somnolence			
Pregabalin, placebo	8	17.2 (0.016)	59.2
Duloxetine, placebo	4	2.0 (0.574)	0
Gabapentin, placebo	4	1.2 (0.7431)	0
Duloxetine, pregabalin	1	–	–
Gabapentin, pregabalin	1	–	–
Amitriptyline, gabapentin	1	–	–
Dizziness			
Pregabalin, placebo	9	17.2 (0.029)	53.4
Duloxetine, placebo	4	1.5 (0.6794)	0
Gabapentin, placebo	3	0.6 (0.7321)	0
Duloxetine, pregabalin	1	–	–
Gabapentin, pregabalin	1	–	–
Amitriptyline, gabapentin	1	–	–
Nausea			
Pregabalin, placebo	3	0.8 (0.687)	0
Duloxetine, placebo	4	5.5 (0.138)	45.8
Gabapentin, placebo	3	0.7 (0.713)	0
Duloxetine, pregabalin	1	–	–
Gabapentin, pregabalin	1	–	–
Diarrhea			
Pregabalin, placebo	5	2.4 (0.670)	0
Duloxetine, placebo	3	1.2 (0.546)	0
Gabapentin, placebo	2	0.5 (0.473)	0
Constipation			
Pregabalin, placebo	5	6.7 (0.150)	40.7
Duloxetine, placebo	4	20.4 (<0.001)	85.3
Gabapentin, placebo	1	–	–
Amitriptyline, gabapentin	1	–	–
Fatigue			
Pregabalin, placebo	1	–	–
Duloxetine, placebo	3	4.5 (0.105)	55.6
Gabapentin, placebo	2	1.45 (0.228)	31.2
Headache			
Pregabalin, placebo	6	2.4 (0.787)	0
Duloxetine, placebo	2	0.8 (0.386)	0
Gabapentin, placebo	3	0.8 (0.658)	0
Capsaicin 8% patch, placebo	1	–	–
Discontinuation due to adverse events			
Pregabalin, placebo	9	6.0 (0.653)	0
Duloxetine, placebo	5	0.8 (0.937)	0
Gabapentin, placebo	3	0.1 (0.929)	–

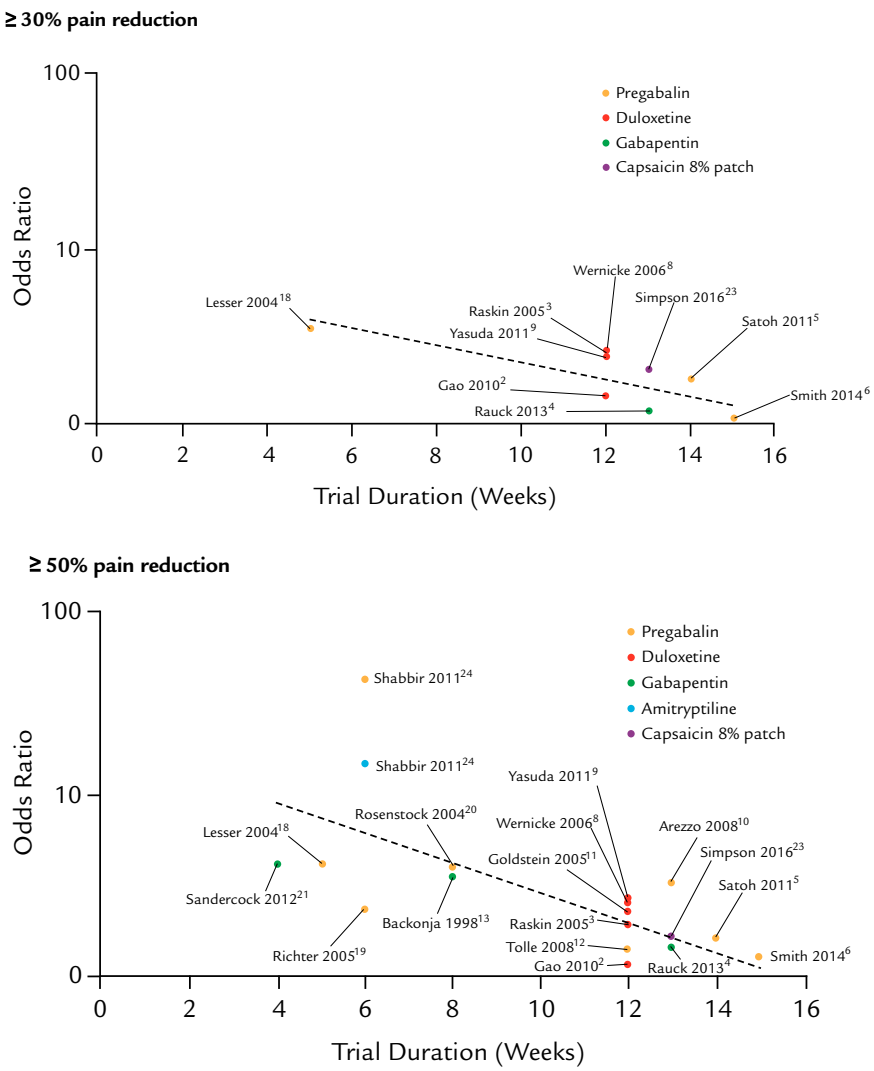
(continued)

Supplementary Table VIII. (continued).

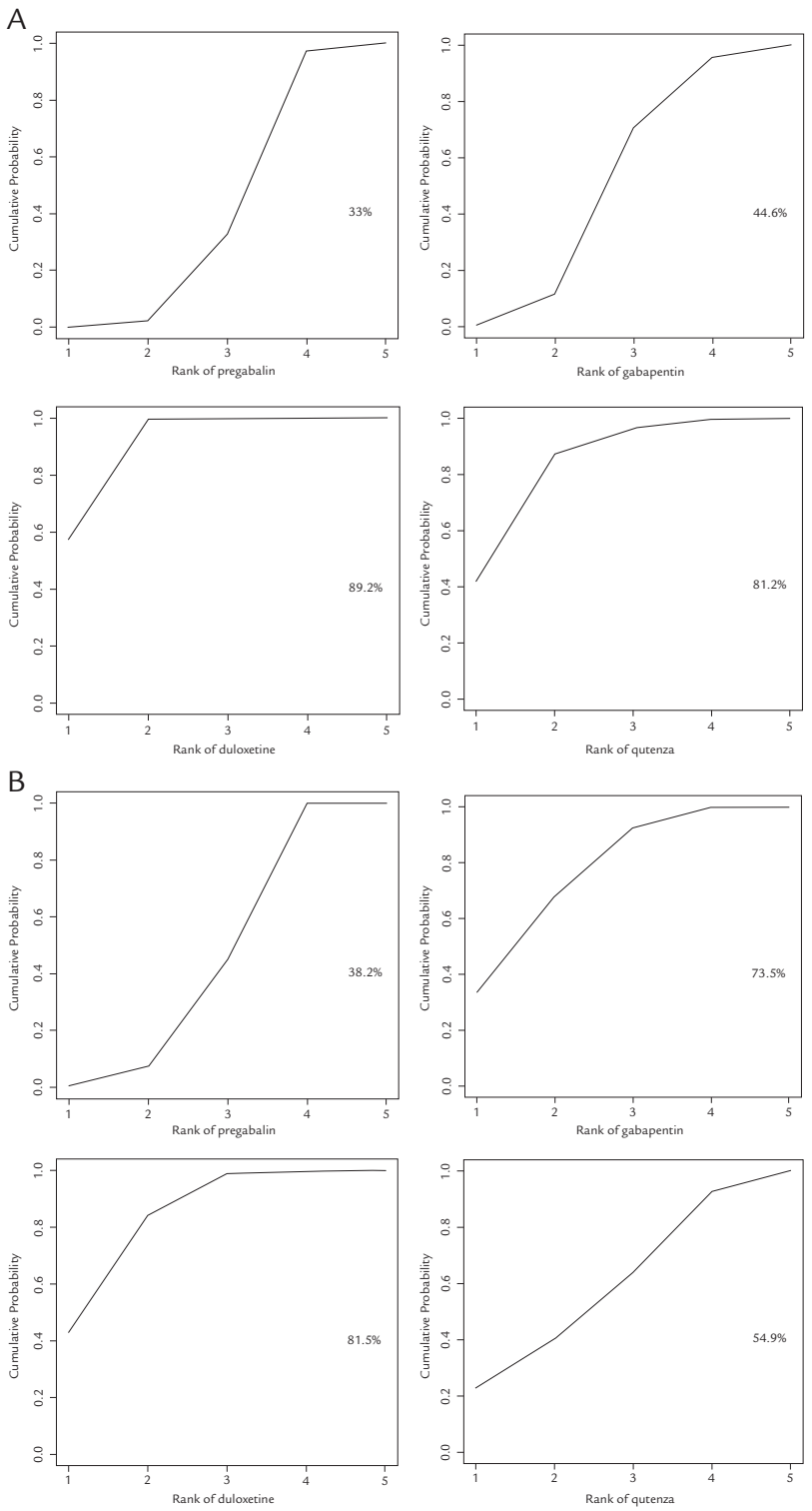
Treatment comparison	Studies, n	Q-statistic (p-value)*	I-square, %
Duloxetine, pregabalin	1	–	–
Gabapentin, pregabalin	1	–	–

Heterogeneity can only be assessed if > 1 studies provide data on a treatment comparison.
*A *P*-value ≤ 0.1 indicates statistical significance.

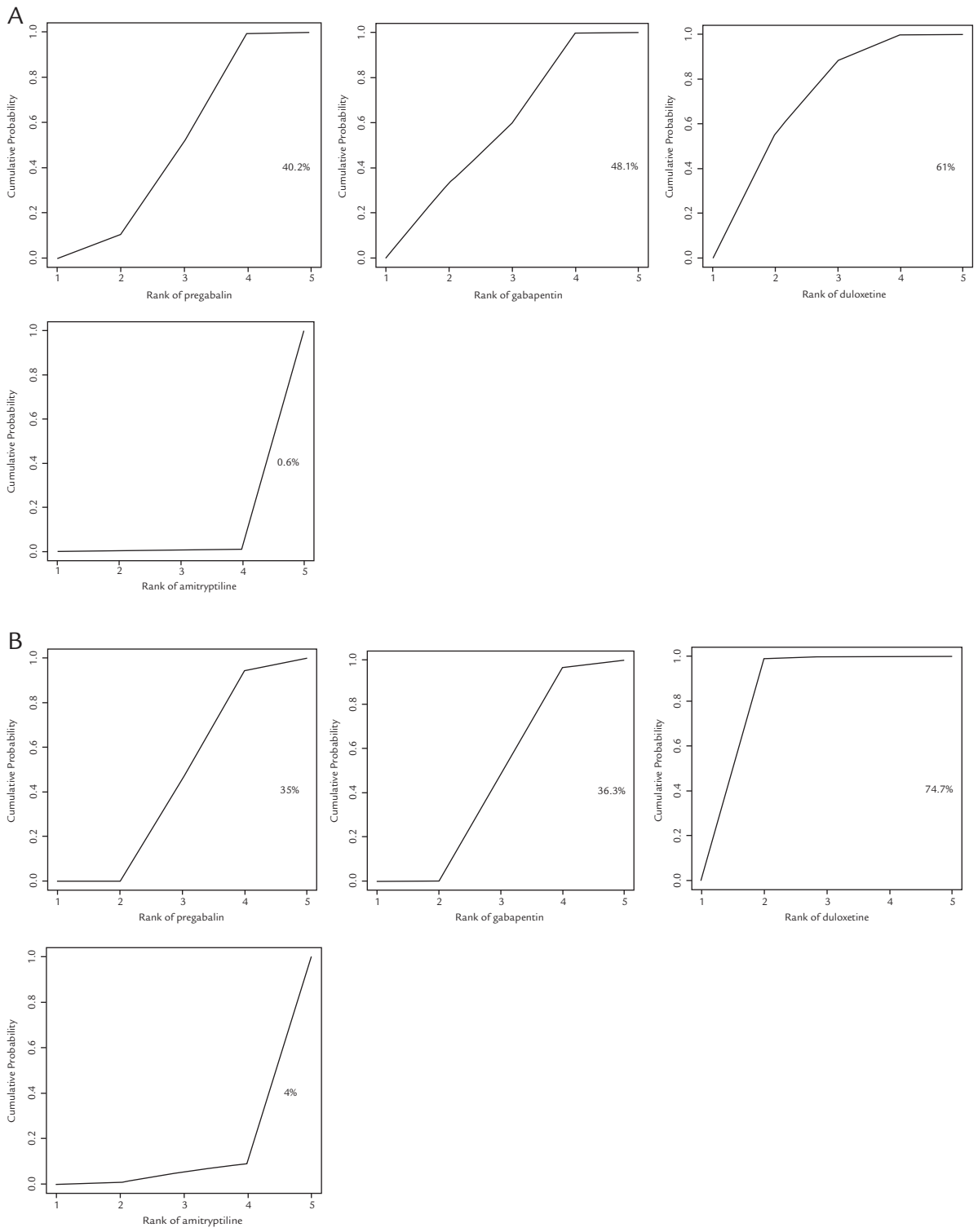
Supplementary Figure 1–3.



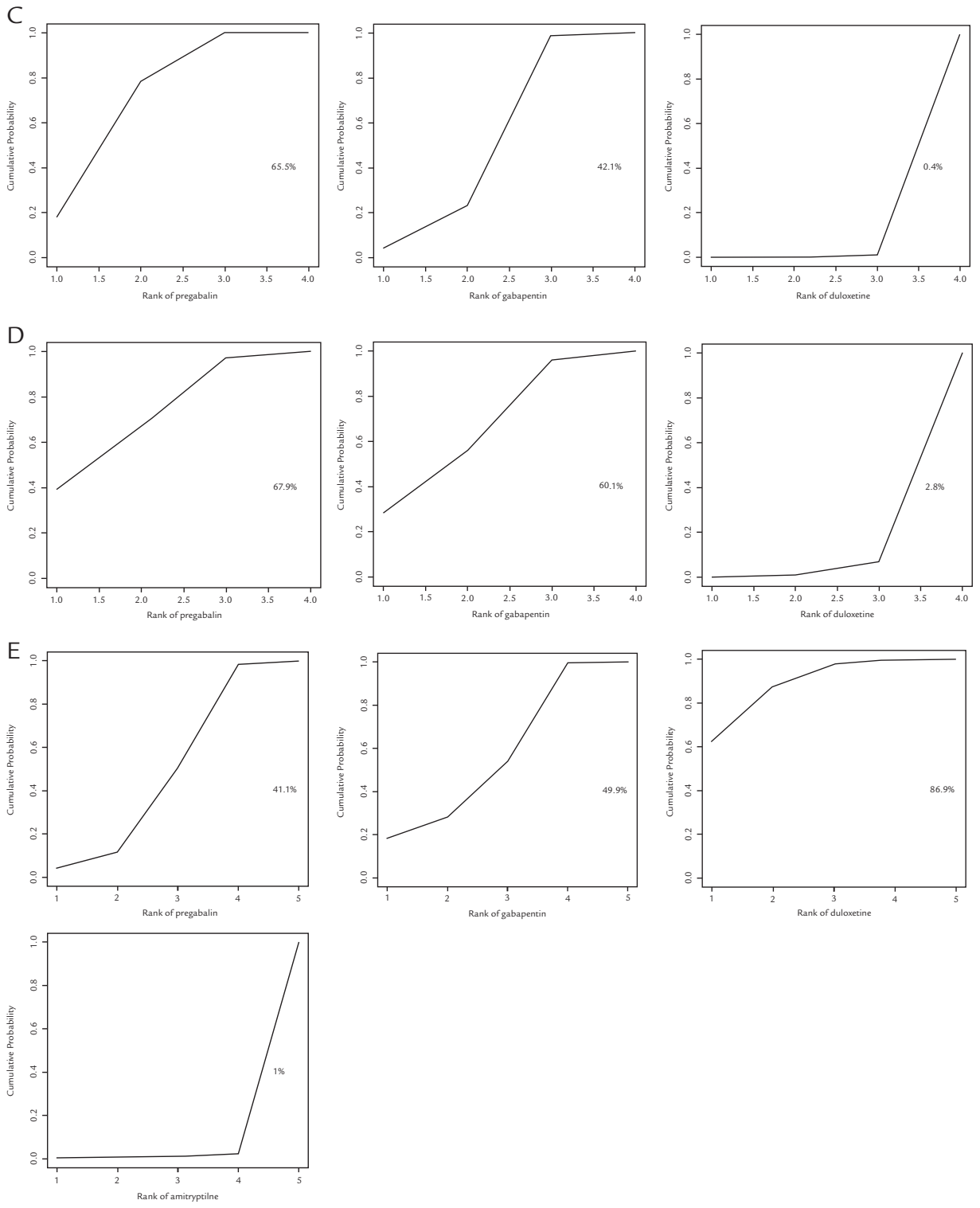
Supplementary Figure 1. Treatment effect (odds ratio) versus trial duration (weeks) for comparisons of placebo on efficacy outcomes. Note that Tesfaye et al. 2013 is not included in either analysis because it did not include a placebo group.



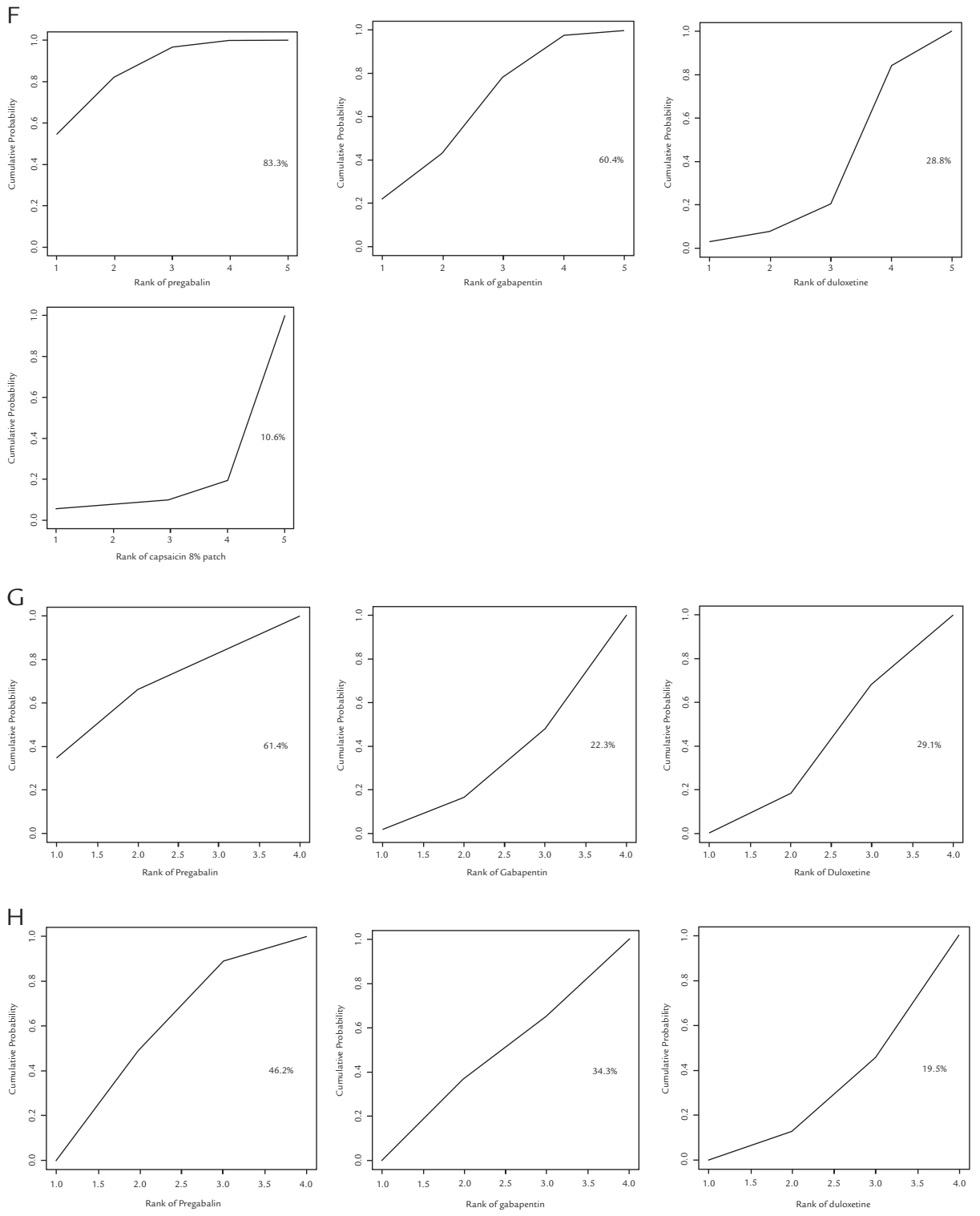
Supplementary Figure 2. Cumulative ranking plots based on being the best treatment for efficacy outcomes: $\geq$ 30% pain reduction (A) and $\geq$ 50% pain reduction (B).



Supplementary Figure 3. Cumulative ranking plots based on being the best treatment for tolerability outcomes: (A) somnolence (B); dizziness; (C) nausea; (D) diarrhea; (E) constipation; (F) headache; (G) fatigue; and (H) discontinuation due to adverse events.



Supplementary Figure 3. Continued.



Supplementary Figure 3. Continued.

REFERENCES

1. Astellas Pharma Europe B.V., Qutenza. Number responders and incidence of headache in the STEP study, split by study medication, for patients without concomitant pain medication. Data on file. PAIN/17/0001/APEL.
2. Gao Y. Ning G, Jia WP, Zhou ZG, Xu ZR, Liu ZM, Liu C, Ma JH, Li Q, Cheng LL, Wen CY, Zhang SY, Zhang Q, Desaiah D, Skljarevski V. Duloxetine versus placebo in the treatment of patients with diabetic neuropathic pain in China. *Chin Med J (Engl)*. 2010;123(22):3184–3192.
3. Raskin J, Pritchett YL, Wang F, D'Souza DN, Waninger AL, Iyengar S, Wernicke JF. A double-blind, randomized multicenter trial comparing duloxetine with placebo in the management of diabetic peripheral neuropathic pain. *Pain Med*. 2005;6(5):346–356.
4. Rauck R, Makumi CW, Schwartz S, Graff O, Meno-Tetang G, Bell CF, Kavanagh ST, McClung CL. A randomized, controlled trial of gabapentin enacarbil in subjects with neuropathic pain associated with diabetic peripheral neuropathy. *Pain Pract*. 2013;13(6):485–496.
5. Satoh J, Yagihashi S, Baba M, Suzuki M, Arakawa A, Yoshiyama T, Shoji S. Efficacy and safety of pregabalin for treating neuropathic pain associated with diabetic peripheral neuropathy: a 14 week, randomized, double-blind, placebo-controlled trial. *Diabet Med*. 2011;28(1):109–116.
6. Smith T, DiBernardo A, Shi Y, Todd MJ, Brashear HR, Ford LM. Efficacy and safety of carisbamate in patients with diabetic neuropathy or postherpetic neuralgia: results from 3 randomized, double-blind placebo-controlled trials. *Pain Pract*. 2014;14(4):332–342.
7. Tesfaye S, Wilhelm S, Lledo A, Schacht A, Tölle T, Bouhassira D, Cruccu G, Skljarevski V, Freynhagen R. Duloxetine and pregabalin: high-dose monotherapy or their combination? The "COMBO-DN study" - a multinational, randomized, double-blind, parallel-group study in patients with diabetic peripheral neuropathic pain. *Pain*. 2013;154(12):2616–2625.
8. Wernicke, JF, Pritchett YL, D'Souza DN, Waninger A, Tran P, Iyengar S, Raskin J. A randomized controlled trial of duloxetine in diabetic peripheral neuropathic pain. *Neurology*. 2006;67(8):1411–1420.
9. Yasuda H, Hotta N, Nakao K, Kasuga M, Kashiwagi A, Kawamori R. Superiority of duloxetine to placebo in improving diabetic neuropathic pain: Results of a randomized controlled trial in Japan. *J Diabetes Investig*. 2011;2:132–139.
10. Arezzo JC, Rosenstock J, Lamoreaux L, Pauer L. Efficacy and safety of pregabalin 600 mg/d for treating painful diabetic peripheral neuropathy: a double-blind placebo-controlled trial. *BMC Neurol*. 2008;8:33.
11. Goldstein DJ, Lu Y, Detke MJ, Lee TC, Iyengar S. Duloxetine vs. placebo in patients with painful diabetic neuropathy. *Pain*. 2005;116(1–2):109–118.
12. Tölle T, Freynhagen R, Versavel M, Trostmann U, Young JP Jr. Pregabalin for relief of neuropathic pain associated with diabetic neuropathy: a randomized, double-blind study. *Eur J Pain*. 2008;12(2):203–213.
13. Backonja M, Beydoun A, Edwards KR, Schwartz SL, Fonseca V, Hes M, LaMoreaux L, Garofalo E. Gabapentin for the symptomatic treatment of painful neuropathy in patients with diabetes mellitus: a randomized controlled trial. *JAMA*. 1998;280(21):1831–1836.
14. Dallocchio C, Buffa C, Mazzarello P, Chiroli S. Gabapentin vs. amitriptyline in painful diabetic neuropathy: an open-label pilot study. *J Pain Symptom Manage*. 2000;20(4);280–285.
15. Devi P, Madhu K, Ganapathy B, Sarma G, John L, Kulkarni C. Evaluation of efficacy and safety of gabapentin, duloxetine, and pregabalin in patients with painful diabetic peripheral neuropathy. *Indian J Pharmacol*. 2012;44(1):51–56.
16. Gorson KC, Schott C, Herman R, Ropper AH, Rand WM. Gabapentin in the treatment of painful diabetic neuropathy: a placebo controlled, double blind, crossover trial. *J Neurol Neurosurg Psychiatry*. 1999;66(2):251–252.
    Jiang W, Ladd S, Martsberger C, Feinglos M, Spratt SE, Kuchibhatla M, Green J, Krishnan R. Effects of pregabalin on heart rate variability in patients with painful diabetic neuropathy. *J Clin Psychopharmacol*. 2011;31(2):207–213.
17. Jiang W, Ladd S, Martsberger C, Feinglos M, Spratt SE, Kuchibhatla M, Green J, Krishnan R. Effects of pregabalin on heart rate variability in patients with painful diabetic neuropathy. *J Clin Psychopharmacol*. 2011;31(2):207–213.
18. Lesser H, Sharma U, LaMoreaux L, Poole RM. Pregabalin relieves symptoms of painful diabetic neuropathy: a randomized controlled trial. *Neurology*. 2004;63(11):2104–2110.
19. Richter RW, Portenoy R, Sharma U, Lamoreaux L, Bockbrader H, Knapp LE. Relief of painful

diabetic peripheral neuropathy with pregabalin: a randomized, placebo-controlled trial. *J Pain*. 2005;6(4):253–260.

20. Rosenstock J, Tuchman M, LaMoreaux L, Sharma, U. Pregabalin for the treatment of painful diabetic peripheral neuropathy: a double-blind, placebo-controlled trial. *Pain*. 2004;110(3):628–638.
21. Sandercock D, Cramer M, Biton V, Cowles VE. A gastroretentive gabapentin formulation for the treatment of painful diabetic peripheral neuropathy: efficacy and tolerability in a double-blind, randomized, controlled clinical trial. *Diabetes Res Clin Pract*. 2012;97(3):438–445.
22. Simpson DA. Gabapentin and venlafaxine for the treatment of painful diabetic neuropathy. *J Clin Neuromuscul Dis*. 2001;3(2):53–62.
23. Simpson DM, Robinson-Papp J, Van J, Stoker M, Jacobs H, Snijder RJ, Schregardus D, Long SK, Lambourg B, Katz N. Capsaicin 8% patch in painful diabetic peripheral neuropathy: a randomised, double-blind, placebo-controlled study. *J Pain*. 2016.
24. Shabbir B, Shafi F, Mahboob F. Amitriptyline vs pregabalin in painful diabetic neuropathy: a randomised placebo-based study. *Pakistan J Med Heal Sci*. 2011;5:745–747.