Systematic Review

Relative Efficacy and Safety of Pharmacotherapeutic Interventions for Diabetic Peripheral Neuropathy: A Systematic Review and Bayesian Network Meta-Analysis

Mir Mahmood Asrar, MPharm[1], Sunita Kumari, MPharm[1], Boya Chandra Sekhar, MPharm[1], Anil Bhansali, MD[2], and Dipika Bansal, MD[1]

From: [1]National Institute of Pharmaceutical Education and Research, Punjab, India; [2]Post Graduate Institute of Medical Education and Research

Address Correspondence: Dipika Bansal, MD Department of Pharmacy Practice, National Institute of Pharmaceutical Education and Research, S.A.S. Nagar (Mohali)-160062, Punjab, India E-mail: dipikabansal079@gmail.com

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Background: Diabetic peripheral neuropathy (DPN) is a most common devitalizing complication of diabetes mellitus, which is primarily characterized by sensory loss, paresthesia, prickling, pain, or allodynia.

Objectives: To evaluate the relative efficacy and safety of the interventions used in the DPN pain management and rank their order.

Study Design: A systematic review and Bayesian network meta-analysis (NMA).

Methods: Randomized, controlled trials were identified through a comprehensive, systematic literature exploration, primarily utilizing the PubMed, EMBASE, Ovid, and Cochrane Library databases. The efficacy and safety outcomes consist of the proportion of patients reporting either 30% or 50% pain reduction and overall withdrawal or withdrawal due to adverse drug events, respectively. Effect estimates from Bayesian NMA were presented as odds ratio (OR) with 95% credible intervals (CrI). Heterogeneity and convergence were assessed by using I2 and deviation information criteria. The risk of bias was evaluated by using Pedro Scale.

Results: A total of 3,246 potentially relevant trials were identified and screened, finally 43 trials consisting of 7,877 randomized patients met the inclusion criteria. Statistically significant treatment difference for 50% pain reduction was reported for duloxetine vs. placebo (OR: 2.50; CrI: 1.62-3.91), mirogabalin vs. placebo (OR: 3.25; CrI: 1.16-9.35), pregabalin vs. placebo (OR: 2.33; CrI: 1.69-3.27), duloxetine vs. carbamazepine (OR: 3.37; CrI: 1.07-10.90), mirogabalin vs. carbamazepine (OR: 4.39; CrI: 1.01-19.63), mirogabalin vs. lamotrigine (OR: 4.05: CrI: 1.07-15.77), pregabalin vs. lamotrigine (OR: 2.90, CrI: 1.19-7.22) and pregabalin vs. nortriptyline (OR: 4.10, CrI: 1.13-5.28). Nortriptyline reported the highest possibility of achieving 30% and 50% pain reduction. Sodium valproate and benztropine reported the highest probability of total withdrawals and withdrawals due to adverse drug events, respectively.

Limitation: The different follow-up time of the included studies can result in the variation of intended results.

Conclusion: Nortriptyline reported the advantage relative to other drugs in achieving 30% and 50% pain reduction from the baseline. Gabapentin reported a significance of 50% pain reduction relative to placebo.

Key words: Diabetic painful neuropathy, network meta-analysis, evidence based medicine, Bayesian analysis

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Diabetic peripheral neuropathy (DPN), also known as sensorimotor neuropathy or distal symmetrical polyneuropathy, is the most common, debilitating complication of diabetes, of which includes ulcer/amputation, autonomic dysfunction, and erectile dysfunction (1). It is primarily characterized by

sensory loss (numbness), paraesthesia, prickling, pain (burning, lancinating, aching), or allodynia. Generally, these symptoms worsen at night (2-4). The major well-recognized risk factors for DPN are advancing age and poor glycemic control; while cigarette smoking, hypertension, obesity, retinopathy, hyperlipidemia, and microalbuminuria have also been recognized as potential risk factors (5). According to the Centers for Disease Control and Prevention, peripheral neuropathy affects about 40% to 50% of all patients with long-standing diabetes (6, 7).

The DPN is a major healthcare challenge to the medical profession and society due to its expansive cost. In the United States, the total annual cost of DPN and related complications' treatment is estimated as $10.91 billion a year, which is posing an economic burden in DPN management (8-10).

Current treatment standards for DPN management focuses on providing symptomatic relief by using non-pharmacological (e.g., dietary modifications, exercise, etc.) and pharmacological interventions. Pharmacological interventions for DPN includes, but are not limited to, anticonvulsants, serotonin–norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs) or other antidepressants, opioids, and opioid-like drugs. Clinical guidelines recommend pain relief in PDN through the use of antidepressants such as amitriptyline and duloxetine, the γ-aminobutyric acid analogs gabapentin and pregabalin, opioids and topical agents such as capsaicin (11). The DPN control may also be achieved by enhancing glycemic control by treating the exact underlying cause of diabetes (12, 13). To our knowledge, the systematic reviews conducted in the past have not provided sufficient evidence to include entire oral interventions to manage DPN in the quantitative network meta-analysis (NMA), or the studies included were of short-term follow-up (14,15). Thus, it fails to determine the best treatment for DPN with minimal adverse effects. So, this study includes all the oral anticonvulsants/antiepileptics, opioids, TCAs, and SNRIs employed in DPN management. Therefore, the aim of this systematic review and NMA is to evaluate the relative efficacy and safety of the interventions in treating DPN by using a Bayesian network meta-analysis approach.

Methods

This systematic review and NMA was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) NMA extension statement (16).

Literature Search

The following clinical studies databases were searched to identify randomized, controlled trials (RCTs) from their inception until January 1, 2020: PubMed, EMBASE, Ovid, and Cochrane Library. Combinations of keywords and medical subject headings (MeSH) terms like "painful diabetic neuropathy," "diabetic neuropathic pain," "randomized controlled trials," were used to locate the studies and are provided in a supplementary file (Supplemental Table 1). The publication bias arising from unpublished data was addressed by performing the searches for unpublished ongoing trials on platforms, such as Clinicaltrials.gov and the International Clinical Trials Registry. Further, we manually searched the references of the original and review articles to find the possible related studies. The search strategy was developed by MA and SK (Supplemental Table 2). Studies were restricted to the English language only.

Inclusion Criteria

For this systematic review and NMA, we searched RCTs. The included RCTs were to be either open-label or blinded, placebo or active comparator, parallel group or crossover, fixed dose or dose ranging, and single- or multi- arm, and must have met the following criteria:

Population: Studies included patients of either gender, aged > 18 years, who have been diagnosed with painful DPN confirmed by the patient's medical history; a diabetic neuropathy symptom (DNS) score of > 1 point (17); a diabetic neuropathy examination (DNE) score of > 3 points (18); a modified neuropathy symptom score (NSS) (19,20); and increased thresholds on the vibration perception test and monofilament test.

Intervention/comparator: The RCTs that assessed safety and efficacy of the following interventions in DPN patients were included: pregabalin, gabapentin, lacosamide, lamotrigine, carbamazepine, oxcarbazepine, valproate, oxycodone, amitriptyline, desipramine, imipramine, duloxetine, and venlafaxine. In multi-arm studies with different doses of the same drug, the most appropriate effective dose was included in the analysis. The combination therapies were included as additional treatment nodes in NMA. A placebo or an active treatment were used as comparators.

Outcomes: The RCTs must have had reported at least one of the following outcomes:

1. Proportion of patients reporting 50% pain reduction after follow-up.
2. Proportion of patients reporting 30% pain reduction after follow-up.

3. Overall withdrawals and withdrawals due to adverse events.

Study Screening

Initially, the search results from databases in endnote were downloaded and transferred into Microsoft Excel (Microsoft, Redmond, WA), where duplicates were identified and removed. The screening was performed in 2 stages by 2 reviewers (MA and SK) working independently as per the inclusion criteria. In stage 1, titles and abstracts of the articles were reviewed; while in stage 2, full texts were obtained for those articles whose titles or abstracts were deemed potentially relevant during stage 1, or where the title or abstract information was not sufficient to make a decision. At both stages, a cross-check was made to ensure consistent application of eligibility criteria. Discrepancies regarding the inclusion of full-text studies were resolved through discussion with a third reviewer (DB). The complete selection process of selection of studies is displayed in the PRISMA diagram (Fig. 1).

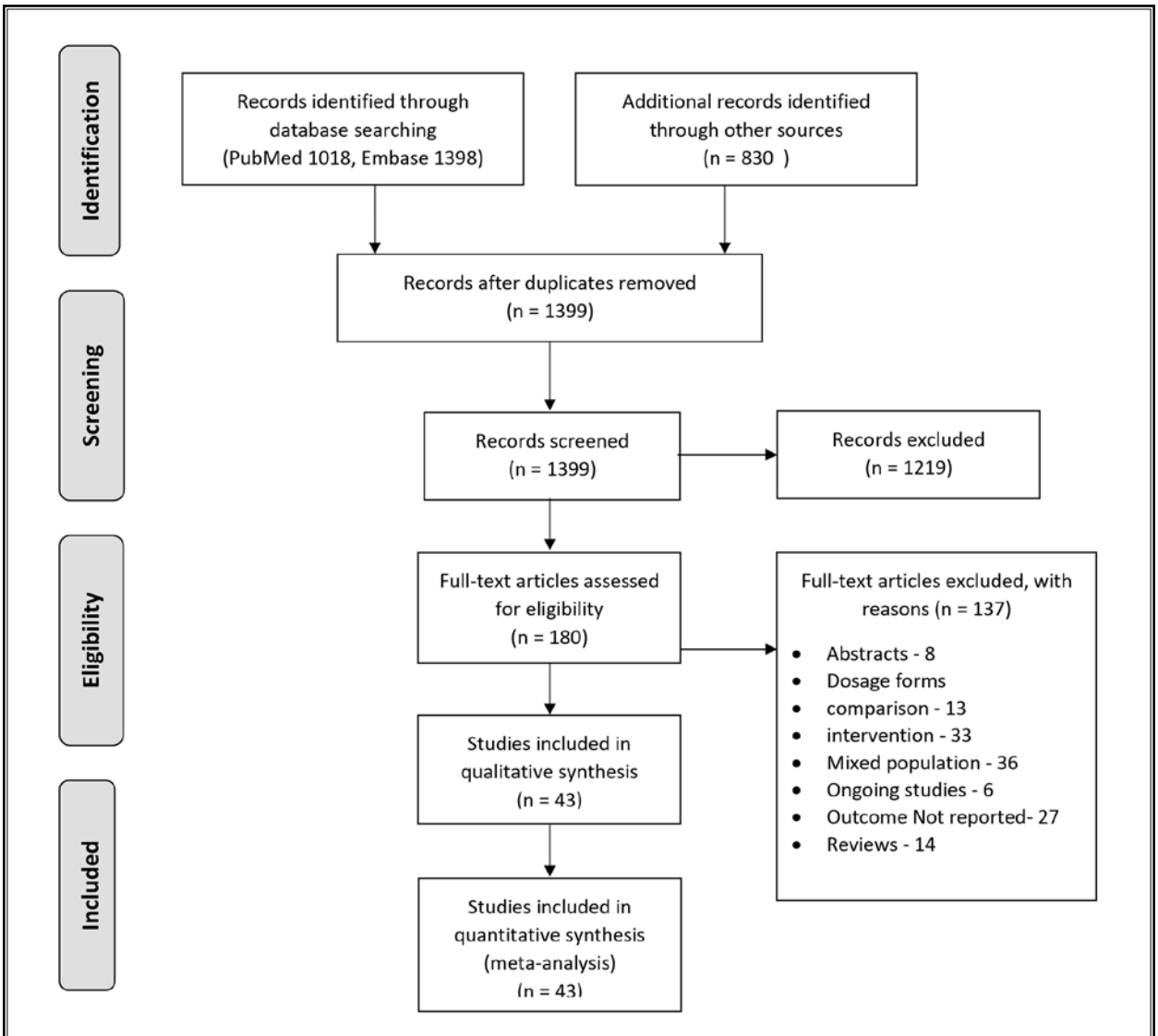

Fig. 1: *PRISMA flow chart*

Exclusion Criteria

Case reports, clinical observations, and studies presenting data published in another study were excluded. Also, studies in which the results of DPN patients could not be segregated from patients with other types of neuropathic pain excluded. Studies having sample size of 10 or less were also excluded.

Data Extraction and Quality Assessment

One reviewer (SK) independently extracted the data of interest from each included study, which was verified by another reviewer (MA). Discrepancies or inconsistencies between the 2 reviewers were resolved by discussion with the third reviewer (DB). A standardized form in Microsoft Excel (Microsoft, Redmond, WA) was used for data extraction and recording of key items.

Handling of Missing Data

Some eligible studies did not address all relevant data, such as standard deviation (SD) or other important variability measures. In such cases, we tried to calculate them through algebraic manipulation of the available information, such as confidence intervals (CIs), *P*- or t-values. If no SDs were reported along with mean scores, then missing data were calculated from the available standard errors (SEs) or CIs (21). In addition, the missing data were also estimated from graphs by using 'WebPlotDigitizer software' (22). Finally, for those RCTs with missing data that could not be estimated, they were excluded and the reasons for exclusion were reported.

Risk of Bias

Two authors (SK and MA) independently performed the rating of the risk of bias of included RCTs using 11-item PEDro scale (23). The risk of bias was assessed using each item (excluding the item for external validity) and was scored as either present (1) or absent (0) to give a total score out of 10. Trials with score < 7 were to be considered at high risk of bias; those scoring ≥ 7 were to be considered at low risk of bias.

Statistical Analysis

For binary outcome variables, the outcome measure calculated was the odds ratio (OR) along with the 95% CI. Pairwise meta-analysis (PMA) was performed between 2 similar interventions, which have more than 2 trials by using a random effects model. For indirect comparisons, NMA for all treatments to the given outcome was performed within a Bayesian framework using the Winbugs (24). A random effects model was used to perform NMA of different interventions as significant heterogeneity was expected.

A total of 100,000 simulations for each initial value were generated and the first 50,000 simulations were discarded to avoid potential impact on the arbitrary value. The inference of final summary statistics are based on the simulation of an additional 100,000 iterations. Three different initial values used for 3 markov chains. Noninformative priors with vague normal (mean 0, variance 0.0001) and uniform (0-2) prior distributions for efficacy and safety outcomes were used. The goodness of fit is compared with the posterior mean of the total residual deviance and the deviance information criterion (DIC). Convergence was assessed by inspection of trace plots, MC error of monitored nodes.

A network graph was created to show relationships among different interventions compared for a specific outcome by using netmeta package of R programming language (25). The ranking of interventions for the efficacy and safety outcomes were also evaluated by using posterior estimates. An intervention with a larger *P*-value was considered more effective. Therefore, *P*-values were used to evaluate the ranking probabilities for each treatment for a specific outcome. To test the heterogeneity of each PMA, trial variation (σ) and tau statistic were used. The effective number of parameters (pD) were also used to assess the heterogeneity. Inconsistency was evaluated only when a loop exists in the evidence network.

Results

Study Selection

A total of 3,246 potentially relevant trials were identified for screening after a literature searching within several databases. After removal of duplicates, a total of 1,399 unique trials were retained, of which 1,219 trials were excluded following the stage 1 (title/abstract) screening. After stage 2 (full text) screening of the remained 137 trials, finally 43 trials met the full inclusion criteria (Fig. 1). Amongst these 43 trials, 18, 29, 34, and 39 trials assessed 30% pain reduction, 50% pain reduction, total withdrawals from the study, and withdrawal due to ADR, respectively. All the studies were published until April 2019.

Study Characteristics

Amongst the included 43 RCTs, 38 (88%) trials followed parallel assignment, while 5 (12%) trials followed crossover assignment. Forty-one trials were double

blinded (95%), while 2 (5%) trials were open label. Thirty-four studies were multi-centric, while 9 (21%) trials were single-centric. Thirty-six trials were placebo controlled, 6 trials were active-controlled, and 1 trial included both (i.e., placebo and active controlled trial). Twenty-four studies were conducted in North America, 12 in Asia, 3 in North America/Europe, and 1 each in Europe/Africa/Australia, North America/Africa, and North America/Europe/Africa (Table 1).

The included 43 trials were comprising of 7,877 randomized patients and the majority of patients were men (56%). The mean age of the patients was 59 years (range: 53-66 years). The mean duration of diabetes and diabetic neuropathic pain was 11.17 years (range: 4.87-16.70 years) and 3.8 years (range: 1.08-7.10 years), respectively. The baseline mean pain score on NRS-11 was 6.46 (range: 4.95-8.20) (Supplemental Table 3). NRS-11, VAS, and both NRS-11/VAS was employed in 26 (60.5%), 11 (25.6), and 6 (14%) studies, respectively. The intervention duration

Table 1. *Showing the study characteristics of the randomized clinical trials.*

Author	Year	Country	Allocation	Intervention Model	Masking	Location	Comparator	No. of Arms	Diabetes Type	PMS	DB Phase (Weeks)
Arezzo 2008 (39)	2008	USA	R	PA	DB	MC	P	2	B	NRS-11,VAS	12
Backonja 1998 (40)	1998	USA	R	PA	DB	MC	P	2	B	NRS-11,VAS	8
Bansal 2009 (41)	2009	India	R	CO	DB	SC	A	2	T2	NRS-11,VAS	8
Beydoun 2006 (42)	2006	USA	R	PA	DB	MC	P	4	T2	VAS	12
Boyle 2012(43)	2012	UK	R	PA	DB	MC	P	3	B	NRS-11	4
Dogra 2005 (44)	2005	USA, Canada	R	PA	DB	MC	P	2	B	NRS-11,VAS	12
Eisenberg 2001 (45)	2001	Israel	R	PA	DB	SC	P	2	B	NRS-11	8
Gao 2015 (46)	2015	China	R	PA	DB	MC	P	2	B	NRS-11	8
Goldstein 2005 (47)	2005	USA	R	PA	DB	MC	P	4	B	NRS-11	12
Grosskopf 2006 (48)	2006	USA, Germany, UK	R	PA	DB	MC	P	2	B	VAS	16
Jose 2007 (49)	2007	India	R	CO	DB	SC	A	2	T2	NRS-11,VAS	NR
Kaur 2011 (50)	2011	India	R	CO	DB	SC	A	2	T2	VAS	NR
Kochar 2002 (51)	2002	India	R	PA	DB	SC	P	2	T2		NR
Kochar 2004 (52)	2004	India	R	PA	DB	SC	P	2	T2	VAS	NR
Lesser 2004 (53)	2004	USA	R	PA	DB	MC	P	4	B	VAS	5
Nazanin Razazian 2014 (37)	2014	Iran	R	PA	DB	SC	P	3	B	VAS	4
Raskin 2005 (54)	2005	Canada	R	PA	DB	MC	P	3	B	NRS-11	12
Raskin 2014 (55)	2013	USA, SA, Canada	R	PA	DB	MC	P	2	B	NRS-11	13
Rauck 2007 (56)	2007	USA	R	PA	DB	MC	P	2	B	NRS-11	12
Rauck 2013 (57)	2013	USA	R	PA	DB	MC	P	5	B	NRS-11	12
Richter 2005 (58)	2005	USA, Canada	R	PA	DB	MC	P	3	B	VAS	6

Table 1. *Showing the study characteristics of the randomized clinical trials. (continued)*

Author	Year	Country	Allocation	Intervention Model	Masking	Location	Comparator	No. of Arms	Diabetes Type	PMS	DB Phase (Weeks)
Rosenstock 2004 (59)	2004	USA	R	PA	DB	MC	P	2	B	VAS	8
Rowbotham 2004 (38)	2004	USA	R	PA	DB	MC	P	3	B	VAS	6
Sandercock 2012 (60)	2012	USA	R	PA	DB	MC	P	3	B	NRS-11	5
Satoh 2010 (61)	2010	Japan	R	PA	DB	MC	P	3	B	NRS-11	13
Shaibani 2009 (62)	2009	USA	R	PA	DB	MC	P	4	B	NRS-11	16
Tanenberg 2011 (33)	2011	USA, Germany, Canada, Puerto Rico	R	PA	OL	MC	A	3	B	NRS-11	NA
Tolle 2008 (63)	2008	Europe, Australia, South Africa	R	PA	DB	MC	P	4	B		12
Vinik 2007 (Study 1) (64)	2007	USA	R	PA	DB	MC	P	4	B	NRS-11	19
Vinik 2007 (Study 2) (64)	2007	USA	R	PA	DB	MC	P		B	NRS-11	19
Watson 2003 (65)	2003	Canada	R	CO	DB	MC	P	2	B	NRS-11, VAS	8
Wernicke 2006 (66)	2006	USA	R	PA	DB	MC	P	3	B	NRS-11	
Wymer 2009 (67)	2009	USA	R	PA	DB	MC	P	4	B	NRS-11	18
Yasuda 2011 (68)	2011	Japan	R	PA	DB	MC	P	3	B	NRS-11	12
Ziegler 2015 (69)	2015	North America, Europe	R	PA	DB	MC	P,A	3	B	NRS-11	6
Gimbel 2003 (70)	2003	USA	R	PA	DB	MC	P	2	B	NRS-11	6
Vinik 2014 (71)	2014	USA	R	PA	DB	MC	P	2	B	NRS-11	5
Mu 2017 (72)	2017	China	R	PA	DB	MC	P	2	B	VAS	9
Sekar 2017 (73)	2017	India	R	PA	OL	SC	A	2	T2	NRS-11	12
Zakerkish 2017 (74)	2017	Iran	R	PA	DB	SC	A	2	B	VAS	6
Aaron I. Vinik 2014 (71)	2014	USA, Canada	R	PA	DB	MC	P	2	B	NRS-11	12
Allen 2014 (75)	2014	USA, Canada	R	PA	DB	MC	P	2	B	NRS-11	13
Huffiman 2015 (76)	2015	USA, Czech Republic, South Africa, Sweden	R	CO	DB	MC	P	2	B	NRS-11	6

MC: multi-center; DB: double-blind; R: randomized; P: placebo controlled; PA: parallel assignment; A: active control; CO: cross over; OL: open label; T2: type 2 diabetes; B: type 1 & 2 diabetes

Table 2. *League table reporting 50% pain reduction (n = 29).*

	Placebo	Amitriptyline	Carbamazepine	Desvenlafaxine	Duloxetine	Duloxetine_ Gabapentin	Gabapentin	Lacosamide
Placebo								
Amitriptyline	1.6 (0.60-4.25)							
Carbamazepine	0.74 (0.25-2.20)	0.46 (0.11-1.91)						
Desvenlafaxine	1.37 (0.42-4.42)	0.86 (0.19-3.92)	1.85 (0.37-9.10)					
Duloxetine	**2.50 (1.62-3.91)**	1.56 (0.60-4.13)	**3.37 (1.07-10.90)**	1.83 (0.52-6.43)				
Duloxetine_ Gabapentin	2.20 (0.83-5.89)	1.38 (0.37-5.09)	2.97 (0.71-12.46)	1.60 (0.35-7.40)	0.88 (0.34-2.31)			
Gabapentin	3.35 (0.84-14.41)	2.11 (0.38-12.01)	4.54 (0.77-27.97)	2.46 (0.40-15.82)	1.34 (0.31-6.09)	1.52 (0.28-8.82)		
Lacosamide	1.17 (0.38-3.72)	0.74 (0.16-3.32)	1.59 (0.33-7.73)	0.86 (0.17-4.43)	0.47 (0.14-1.61)	0.53 (0.12-2.44)	0.35 (0.06-2.12)	
Lamotrigine	0.80 (0.35-1.86)	0.50 (0.14-1.81)	1.08 (0.27-4.32)	0.59 (0.14-2.47)	0.32 (0.12-0.83)	0.37 (0.10-1.33)	0.24 (0.04-1.22)	0.68 (0.17-2.84)
Mirogabalin	**3.25 (1.16-9.35)**	2.03 (0.50-8.37)	**4.39 (1.01-19.63)**	2.38 (0.51-11.45)	1.3 (0.43-4.02)	1.48 (0.37-6.08)	0.97 (0.16-5.60)	2.76 (0.59-13.20)
Nortriptyline	0.57 (0.16-2.03)	0.36 (0.07-1.64)	0.77 (0.14-4.08)	0.41 (0.07-2.36)	0.23 (0.07-0.75)	0.26 (0.06-1.20)	0.17 (0.02-1.13	0.48 (0.09-2.72)
Oxcarbazepine	2.44 (0.73-8.26)	1.53 (0.32-7.26)	3.29 (0.64-17.00)	1.79 (0.33-9.67)	0.98 (0.27-3.54)	1.11 (0.23-5.25)	0.73 (0.11-4.63)	2.08 (0.39-11.13)
Pregabalin	**2.33 (1.69-3.27)**	1.46 (0.56-3.84)	3.15 (1.09-9.22)	1.70 (0.51-5.79)	0.93 (0.56-1.55)	1.06 (0.40-2.80)	0.70 (0.16-2.93)	1.99 (0.60-6.57)
Tapentadol	1.67 (0.58-4.81)	1.05 (0.25-4.36)	2.25 (0.49-10.27)	1.22 (0.25-5.92)	0.67 (0.21-2.10)	0.76 (0.18-3.21)	0.50 (0.08-2.86)	1.42 (0.30-3.90)
Venlafaxine	1.12 (0.49-2.53)	0.70 (0.20-2.42)	1.51 (0.53-4.36)	0.81 (0.20-3.40)	0.45 (0.18-1.11)	0.51 (0.14-1.77)	0.33 (0.06-1.67)	0.95 (0.23-3.90)

	Lamotrigine	Mirogabalin	Nortriptyline	Oxcarbazepine	Pregabalin	Tapentadol	Venlafaxine
Placebo							
Amitriptyline							
Carbamazepine							
Desvenlafaxine							
Duloxetine							
Duloxetine_ Gabapentin							
Gabapentin							
Lacosamide							
Lamotrigine							
Mirogabalin	**4.05 (1.07-15.77)**						
Nortriptyline	0.71 (0.15-3.26)	**0.17 (0.03-0.90)**					
Oxcarbazepine	3.04 (0.69-13.48)	0.75 (0.15-3.67)	4.31 (0.74-24.92)				
Pregabalin	**2.90 (1.19-7.22)**	0.72 (0.25-2.03)	**4.10 (1.13-5.28)**	0.95 (0.27-3.39)			
Tapentadol	2.07 (0.54-8.00)	0.51 (0.12-2.24)	2.94 (0.56-15.48)	0.68 (0.13-3.39)	0.72 (0.23-2.15)		
Venlafaxine	1.39 (0.43-4.51)	0.34 (0.09-1.26)	1.97 (0.44-8.93)	0.46 (0.11-1.98)	0.48 (0.21-1.08)	0.67 (0.18-2.53)	

Data presented as odds ratio and 95% credible interval

was ranged from 4 to 23 weeks, and the sample size in the intervention group was extended from 18 to 314 patients. Most of the trials enrolled both type 1 and type 2 diabetic patients (n = 36, 84%), while 7 (16%) enrolled only type 2 patients (Table 1).

Efficacy Outcomes

50% Pain Reduction

Twenty-nine trials involving 15 interventions reported this outcome (Fig. 2). Statistically significant treatment difference for 50% pain reduction was reported for duloxetine vs. placebo (OR: 2.50; CrI: 1.62-3.91), mirogabalin vs. placebo (OR: 3.25; CrI: 1.16-9.35), pregabalin vs. placebo (OR: 2.33; CrI: 1.69-3.27), duloxetine vs. carbamazepine (OR: 3.37; CrI: 1.07-10.90), mirogabalin vs. carbamazepine (OR: 4.39; CrI: 1.01-19.63), mirogabalin vs. lamotrigine (OR: 4.05: CrI: 1.07-15.77), pregabalin vs. lamotrigine (OR: 2.90, CrI: 1.19-7.22) and pregabalin vs. nortriptyline (OR: 4.10, CrI: 1.13-5.28) (Table 2). Nortriptyline had the greatest possibility of achieving a 50% pain reduction (Table 3).

30% Pain Reduction

Eighteen trials reported this outcome (Supplemental Fig. 1). A statistically significant treatment difference for 30% pain reduction was reported for duloxetine vs. placebo (OR: 1.97; CrI: 1.32-2.87), nortriptyline vs. duloxetine (OR: 0.03; CrI: 0.00-0.22), pregabalin vs. duloxetine (OR: 0.61: CrI: 0.39-0.96), venlafaxine vs. duloxetine (OR: 0.08, CrI: 0.02-0.25), mirogabalin vs. duloxetine_gabapentin (OR: 1.15: CrI: 0.41-3.36), Nortriptyline vs. duloxetine_gabapentin (OR: 0.03; CrI: 0.00-0.27), venlafaxine vs. duloxetine_gabapentin (OR: 0.09; CrI: 0.02-0.31), nortriptyline vs. lacosamide (OR: 0.04, CrI: 0.00-0.29), venlafaxine vs. lacosamide (OR: 0.09; CrI: 0.02-0.33), nortriptyline vs. lamotrigine (OR: 0.07; CrI: 0.00-0.57), venlafaxine vs. lamotrigine (OR: 0.18; CrI: 0.04-0.66), nortriptyline vs. mirogabalin (OR: 0.03, CrI: 0.00-0.25), venlafaxine vs. mirogabalin (OR: 0.08; CrI: 0.02-0.29), venlafaxine vs. oxcarbazepine (OR: 0.08; CrI: 0.02-0.32), venlafaxine vs. pregabalin (OR: 0.13; CrI: 0.04-0.38) and venlafaxine vs. tapentadol (OR: 0.10, CrI: 0.02-0.40) (Supplemental Table 4). Nortriptyline exhibited the highest probability in achieving 30% pain reduction (Supplemental Table 5).

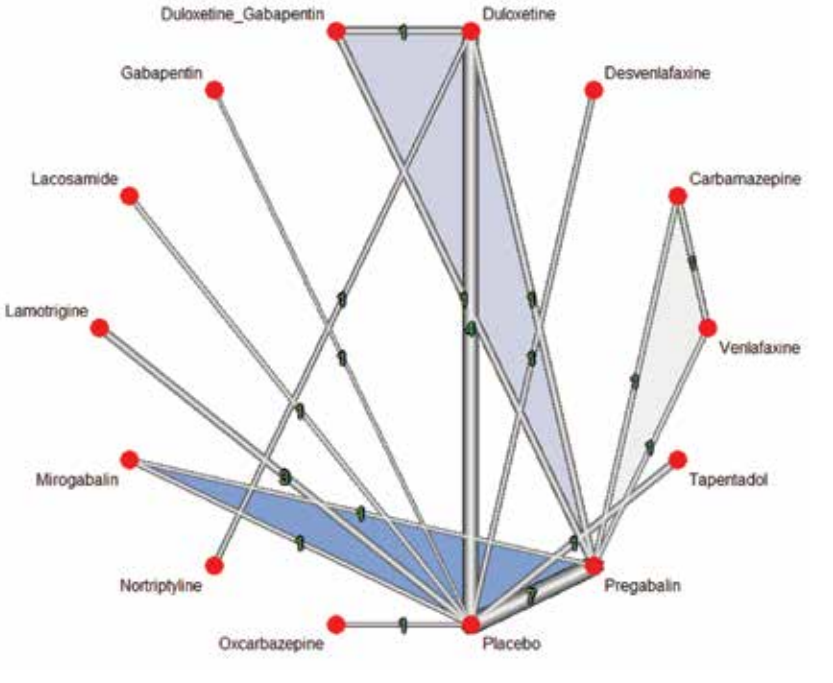

Fig. 2: *Network plot of interventions for reporting fifty percent pain reduction outcome (n = 29)*

Safety Outcomes

Total Withdrawals in Clinical Trials

Thirty-four trials reported total withdrawals (Supplemental Fig. 2). A statistically significant increase in total withdrawals was reported for desvenlafaxine (OR: 3.29; CrI: 1.30-8.60), duloxetine (OR: 1.49; CrI: 1.02-2.18), lacosamide (OR: 2.90; CrI: 1.70-4.85), oxcarbazepine (OR: 3.09; CrI: 1.82-5.22), and pregabalin (OR: 1.07; CrI: 0.78-1.47) compared to the placebo. A statistically significant decrease in total withdrawals was reported for lamotrigine (OR: 0.40; CrI: 0.18-0.84), mirogabalin (OR: 0.25; CrI: 0.07-0.91), oxycodone (OR: 0.22; CrI: 0.07-0.62), pregabalin (OR: 0.37; CrI: 0.20-0.69), sodium valproate (OR: 0.07; CrI: 0.01-0.40), and tapentadol (OR: 0.32; CrI: 0.13-0.81) compared to the lacosamide (Supplemental

Table 6). Sodium valproate (P = 0.672) reported the highest probability of total withdrawals among other interventions (Supplemental Table 7).

Withdrawals Due to Adverse Events

Thirty-nine trials reported withdrawals due to adverse events (AEs) (Supplemental Fig. 3). For the NMA, Supplemental Table 8, presents the league table for withdrawals due to ADR among different treatment groups, 28 comparisons reported the statistically significant difference in withdrawals due to ADR's. A statistically significant increase in withdrawals due to AEs was reported for desvenlafaxine (OR: 7.86; CrI: 2.17-33.30), oxcarbazepine (OR: 6.71; CrI: 3.13-14.69), lacosamide (OR: 4.82; CrI: 2.21-10.13), venlafaxine (OR: 3.92; CrI: 1.41-11.58), amitriptyline (OR: 3.40; CrI: 1.40-7.60), duloxetine (OR: 3.39: CrI: 2.10-5.60), gabapentin encarbil (OR: 3.02; CrI: 1.11-8.65), and pregabalin (OR: 2.03; CrI: 1.39-3.09) compared to the placebo/control. A statistically significant decrease in withdrawals due to AEs was reported for pregabalin (OR: 0.30; CrI: 0.13-0.73) and sodium valproate (OR: 0.09; CrI: 0.01-0.90) compared to the oxcarbazepine (Supplemental Table 8). Benztropine reported the highest probability of withdrawals due to AEs among all the interventions (Supplemental Table 9).

Cluster Analysis

A cluster analysis was performed, where 22 studies comprising 14 interventions were included (Supplemental Figs. 4 and Supplemental Tables 10 and 11). Supplemental Fig. 5 displays the probability of 50% pain reduction and total withdrawal from the trials on X and Y-axis, respectively. A plot presenting carbamazepine [P = 0.371 (50% pain reduction); P = 0.1819 (total withdrawal)], venlafaxine [P = 0.3357 (50% pain reduction); P = 0.0009 (total withdrawal)] and nortriptyline [P = 0.2236 (50% pain reduction); P = 0.0075 (total withdrawal)] on the right, bottom side showing a better efficacy and safety profile, while mirogabalin exhibited a less safety and efficacy profile.

Quality of the Included Studies

A methodological quality assessment was conducted using the PEDro scale. The mean (SD) score was 10.7 (0.7), with the key problem items being blinding, and baseline comparability (Supplemental Table 12).

Pairwise Meta-Analysis

Figure 3 represents the pairwise comparisons in the network. Gabapentin was significantly superior to placebo (OR: 5.6, CrI: 1.6-23.0) in 50% pain reduction compared to desvenlafaxine (OR: 1.4, CrI: 0.48-4.1), lacosamide (OR: 1.2, CrI: 0.42-3.4), lamotrigine (OR: 1.1, CrI: 0.58-2.2), oxcarbazepine (OR: 2.5, CrI: 0.81-7.6) and tapentadaol (OR: 1.7, CrI: 0.64-4.3). carbamazepine (OR: 0.21, CrI: 0.07-0.59), placebo (OR: 0.46, CrI: 0.31-0.64) and venlafaxine (OR: 0.22, CrI: 0.22-0.60) were significantly inferior to pregabalin in terms of 50%

Table 3. *Ranking probability and median ranking of interventions reporting 50% pain reduction (n = 29).*

Intervention	Ranking Probability	Median Rank	95% CrI	
Placebo	0.00359	5	2	7
Amitriptyline	0.01061	8	2	14
Carbamazepine	0.22740	3	1	10
Desvenlafaxine	0.04240	7	1	14
Duloxetine	0.00000	12	8	15
Duloxetine_ Gabapentin	0.00234	11	4	15
Gabapentin	0.00439	14	4	15
Lacosamide	0.06577	6	1	14
Lamotrigine	0.14280	3	1	9
Mirogabalin	0.00061	14	6	15
Nortriptyline	**0.45880**	**2**	**1**	**10**
Oxcarbazepine	0.00648	12	3	15
Pregabalin	0.00000	11	8	14
Tapentadol	0.01435	8	2	15
Venlafaxine	0.02047	6	2	12

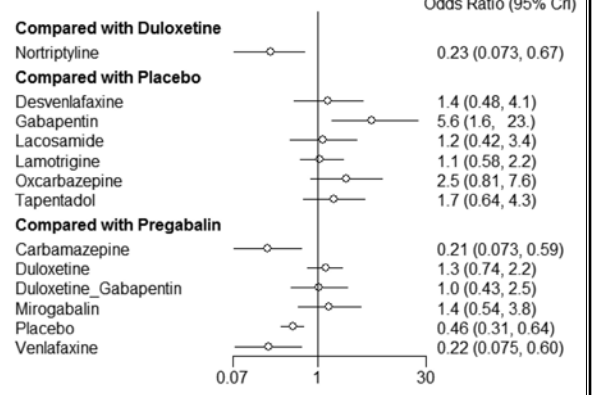

Fig. 3: *Pairwise meta-analysis in NMA for 50% pain reduction.*

pain reduction compared with duloxetine (OR: 1.3, CrI: 0.74-2.2), duloxetine_gabapentin combination (OR: 1.0, CrI: 0.43-2.5 and mirogabalin (OR: 1.4, CrI: 0.54-3.8). Further, desvenlafexine (OR: 7.9, CrI: 2.3-34.0), duloxetine (OR: 3.4, CrI: 2.1-5.6), oxacarbazepine (OR: 6.8, CrI: 3.2-14.0), pregabalin (OR: 2.0, CrI: 1.4-3.0), and venlafaxine (OR: 3.8, CrI: 1.4-11.0) reported significantly higher withdrawals due to AEs compared with placebo (Supplemental Fig. 6).

Heterogeneity and Inconsistency

Moderate heterogeneity was observed for 30% pain reduction (SD: 0.21; 95% CrI; 0.01-0.64), 50% pain reduction (SD: 0.44; 95% CrI; 0.24-0.74), total withdrawal (SD: 0.15; 95% CrI; 0.01-0.58), and withdrawal due to AEs (SD: 0.37; 95% CrI; 0.03-0.78) outcomes between studies regarding treatment effects (Supplemental Table 13). A high degree of convergence was observed in trace plots and history plots. MC error of ORs of interventions compared to each other and placebo were < 5% of the posterior SD, which indicates good convergence.

Discussion

This study presents a comprehensive systematic review and Bayesian meta-analysis of efficacy and safety of 18 oral pharmacotherapeutic interventions (amitriptyline, benztropine, carbamazepine, desvenlafaxine, duloxetine, duloxetine+gabapentin, gabapentin, gabapentin encarbil, lacosamide, lamotrigine, oxcarbazepine, oxycodone, pregabalin, sodium valproate, tapentadol, mirogabalin, nortriptyline, and venlafaxine) employed in the DPN management. A total of 43 RCTs, comparing these oral interventions with placebo and/or an active drug, were included in this study. These interventions are recommended in different clinical practice guidelines for neuropathic pain and most of these cited in the literature are those of the American Academy of Neurology (AAN), the National Institute for Health and Care Excellence (NICE), the European Federation of Neurological Societies (EFNS), and the Neuropathic Pain Special Interest Group of International Association for the Study of Pain (NEUPSIG) (26, 27,28). To our knowledge, this is the most comprehensive, comparative, and effective analysis conducted to date for this DPN management. This analysis also makes it possible to indirectly compare the active treatments where direct head to head comparisons were not possible.

A total of 7,877 patients were involved in these 43 RCTs. The results of this study confirms the association of DPN with male gender, age, and duration of diabetes. These results are consistent with the previous studies (29-31). Further, our study adds to these previous efforts by providing a more complete understanding of the current body of evidence on comparative effectiveness of analgesic interventions for painful diabetic neuropathy.

Using a Bayesian NMA of 43 RCTs in this study, we found that nortriptyline displayed superiority to other interventions in achieving 50% and 30% pain reduction in the management of DPN. However, by using pairwise meta-analysis, gabapentin was reported significantly superior in achieving 50% pain reduction. While, in 6 weeks, double-blind randomized, controlled trial conducted in patients with diabetic peripheral neuropathic pain demonstrated that duloxetine was more superior than nortriptyline in achieving 50% reduction (32). Furthermore, in a study, duloxetine was reported to be noninferior compared to the pregabalin in relieving pain in patients with DPN. Another study showed that duloxetine, amitriptyline, and pregabalin also reduced pain compared to the placebo, but none of these drugs were superior as supported by no significant difference in clinical efficacy between amitriptyline, duloxetine, and pregabalin (33). In consonance with the systematic review conducted by Collins et al (34), which reported antidepressants and anticonvulsants are effective in pain relief.

In agreement with the NeupSIG 2015, EFNS 2010, CPS 2014, and NICE 2013 guidelines, our study reported nortriptyline (TCAs) very effective in pain reduction relative to others (27,28,35,36). Further, the cluster analysis reported carbamazepine, venlafaxine and nortriptyline with a better efficacy and safety profile. Mirogabalin exhibited a less safety and efficacy profile, which is not recommended by the clinical guidelines as an initial choice in DPN management. Further, gabapentin reported very effective in 50% pain reduction in pairwise meta-analysis compared with placebo. Gabapentin is recommended as a first line choice in neuropathic pain by NICE clinical guidelines (36).

In the present study, venlafaxine was ranked second and carbamazepine third in improving the DPN patients. Though the data regarding the efficacy of venlafaxine in DPN are limited in the current NMA and only 2 authors studied the effectiveness of venlafaxine (37,38). The study conducted by Razazian et al (37) compared the efficacy of venlafaxine, pregabalin, and carbamazepine in DPN patients and results showed that pregabalin was superior in relieving pain compared to carbamazepine, and venlafaxine.

While the study conducted by Hia et al (77) showed that venlafaxine was superior in improving quality of life in DPN patients compared to the carbamazepine in improving quality of life. Rowbotham et al (38) also reported that venlafaxine was effective and safe in relieving pain associated with diabetic neuropathy.

Additionally, benztropine was ranked first and carbamazepine second, and sodium valproate third for withdrawals due to ADRs. In a study, most of the AEs were reported with pregabalin and least ADRs were reported with the carbamazepine (37). While withdrawals due to ADRs were at a maximum with venlafaxine and least were with carbamazepine.

Heterogeneity between trial interventions evaluating mean pain reduction (50% and 30%), total withdrawal, and withdrawal due to AEs was generally low in the present analysis. The major limitation of the study was different follow-up of the included studies. Even though, included studies reported well baseline demographic data, many RCTs did not report some parameters like, duration of DPN, response to previous interventions used for management of DPN, which may affect the treatment outcomes.

Conclusion

In conclusion, nortriptyline reported the advantage relative to other drugs in achieving 30% and 50% pain reduction from the baseline. Desvenlafexine reported the highest total withdrawals and withdrawals due to AEs compared to other drugs.

Supplemental files available at painphysicianjournal.com

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Supplemental Table 1. *Search Strategy in PubMed.*

S.no	Search Strategy	Number of Hits
1	((Polyneuropathy, Diabetic[Title/Abstract]) OR Polyneuropathies, Diabetic[Title/Abstract]) OR Diabetic Polyneuropathies[Title/Abstract]) OR Diabetic Polyneuropathy[Title/Abstract]) OR Diabetic Amyotrophies[Title/Abstract]) OR Amyotrophy, Diabetic[Title/Abstract]) OR Amyotrophies, Diabetic[Title/Abstract]) OR Diabetic Amyotrophy[Title/Abstract]) OR Simplices, Diabetic Mononeuropathy[Title/Abstract]) OR Simplex, Diabetic Mononeuropathy[Title/Abstract]) OR Mononeuropathy Simplices, Diabetic[Title/Abstract]) OR Mononeuropathy Simplex, Diabetic[Title/Abstract]) OR Diabetic Mononeuropathy Simplices[Title/Abstract]) OR Diabetic Mononeuropathy Simplex[Title/Abstract]) OR Mononeuropathy, Diabetic[Title/Abstract]) OR Mononeuropathies, Diabetic[Title/Abstract]) OR Diabetic Mononeuropathies[Title/Abstract]) OR Diabetic Mononeuropathy[Title/Abstract]) OR Polyneuropathy, Diabetic Asymmetric[Title/Abstract]) OR Polyneuropathies, Diabetic Asymmetric[Title/Abstract]) OR Diabetic Asymmetric Polyneuropathies[Title/Abstract]) OR Asymmetric Polyneuropathy, Diabetic[Title/Abstract]) OR Asymmetric Polyneuropathies, Diabetic[Title/Abstract]) OR Diabetic Asymmetric Polyneuropathy[Title/Abstract]) OR Asymmetric Diabetic Proximal Motor Neuropathy[Title/Abstract]) OR Symmetric Diabetic Proximal Motor Neuropathy[Title/Abstract]) OR Neuralgia, Diabetic[Title/Abstract]) OR Painful Diabetic Neuropathy[Title/Abstract]) OR Painful Diabetic Neuropathies[Title/Abstract]) OR Neuropathy, Painful Diabetic[Title/Abstract]) OR Neuropathies, Painful Diabetic[Title/Abstract]) OR Diabetic Neuropathies, Painful[Title/Abstract]) OR Diabetic Neuropathy, Painful[Title/Abstract]) OR Neuralgias, Diabetic[Title/Abstract]) OR Diabetic Neuralgias[Title/Abstract]) OR Diabetic Neuralgia[Title/Abstract]) OR Neuropathy, Diabetic Autonomic[Title/Abstract]) OR Neuropathies, Diabetic Autonomic[Title/Abstract]) OR Diabetic Autonomic Neuropathies[Title/Abstract]) OR Autonomic Neuropathy, Diabetic[Title/Abstract]) OR Autonomic Neuropathies, Diabetic[Title/Abstract]) OR Neuropathy, Diabetic[Title/Abstract]) OR Neuropathies, Diabetic[Title/Abstract]) OR Diabetic Neuropathy[Title/Abstract])) OR "Diabetic Neuropathies"[Mesh]	26490
2	"Randomized Controlled Trials as Topic"[Mesh] OR "Controlled Clinical Trials as Topic"[Mesh] OR "Clinical Trials as Topic"[Mesh] OR "Randomized Controlled Trial"[Publication Type] OR "Controlled Clinical Trial"[Publication Type] OR "Clinical Trial" [Publication Type] OR "Random Allocation"[Mesh] OR "Single-Blind Method"[Mesh] OR "Double-Blind Method"[Mesh] OR "Research Design"[Mesh] OR "Comparative Study" [Publication Type] OR "Evaluation Studies" [Publication Type] OR "Evaluation Studies as Topic"[Mesh] OR "Drug Therapy"[Mesh] OR "drug therapy"[Subheading] OR "Follow-Up Studies"[Mesh] OR "Cross-Over Studies"[Mesh] OR "Prospective Studies"[Mesh] OR "Clinical Study" [Publication Type] OR "Controlled Before-After Studies"[Mesh] OR "Multicenter Studies as Topic"[Mesh] OR "Multicenter Study" [Publication Type] OR "Placebos"[Mesh] OR Random*[tiab] OR "latin square"[tiab] OR pragmatic trial*[tiab] OR clinical article*[tiab] OR placebo*[tiab] OR ((singl*[tiab] OR doubl*[tiab] OR trebl*[tiab] OR tripl*[tiab]) OR (mask*[tiab] OR blind*[tiab] OR dumm*[tiab])) OR RCT*[tiab] OR ((comparative[tiab] OR control*[tiab] OR clinical[tiab] OR prospectiv*[tiab]) OR (study[tiab] OR studies[tiab] OR trial*[tiab])) OR volunteer*[tiab] OR "Cross-Over"[tiab] OR crossover[tiab] OR allocat*[tiab] OR assign*[tiab] OR factorial[tiab]	16364990
3	((((((((((((((((((venlafaxine[Title/Abstract]) OR duloxetine[Title/Abstract]) OR ("Serotonin and Noradrenaline Reuptake Inhibitors"[Mesh])) OR imipramine[Title/Abstract]) OR desipramine[Title/Abstract]) OR amitriptyline[Title/Abstract]) OR "Antidepressive Agents, Tricyclic"[Mesh]) OR oxycodone[Title/Abstract]) OR "Analgesics, Opioid"[Mesh]) OR valproate[Title/Abstract]) OR oxcarbazepine[Title/Abstract]) OR carbamazepine[Title/Abstract]) OR lamotrigine[Title/Abstract]) OR lacosamide[Title/Abstract]) OR gabapentin[Title/Abstract]) OR pregabalin[Title/Abstract]) OR "Antidepressive Agents"[Mesh]) OR antiepileptics[Title/Abstract]) OR "Anticonvulsants"[Mesh]) OR Anticonvulsants[Title/Abstract]	186456
4	#1 AND #2 AND #3	1018

Supplemental Table 2. *Development of search strategy in EMBASE.*

No.	Query	Number of hits
#20	#1 AND #2 AND #19	1398
#19	#3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18	759406
#18	'imipramine'/exp OR 'imipramine'	36344
#17	'desipramine'/exp OR 'desipramine'	22193
#16	'venlafaxine'/exp OR 'venlafaxine'	20244
#15	'valproic acid'/exp OR 'valproic acid'	60386
#14	'pregabalin'/exp OR 'pregabalin'	12546
#13	'oxycodone'/exp OR 'oxycodone'	16846

Supplemental Table 2. *Development of search strategy in EMBASE. (continued)*

No.	Query	Number of hits
#12	'oxcarbazepine'/exp OR 'oxcarbazepine'	10174
#11	'lamotrigine'/exp OR 'lamotrigine'	23542
#10	'lacosamide'/exp OR 'lacosamide'	3135
#9	'gabapentin'/exp OR 'gabapentin'	28356
#8	'carbamazepine'/exp OR 'carbamazepine'	63229
#7	'duloxetine'/exp OR 'duloxetine'	10052
#6	'capsaicin'/exp OR 'capsaicin'	22045
#5	'amitriptyline'/exp OR 'amitriptyline'	38786
#4	'antidepressant agent'/exp OR 'antidepressant agent'	414743
#3	'anticonvulsive agent'/exp OR 'anticonvulsive agent'	389452
#2	'diabetic neuropathy'/exp OR 'diabetic neuropathy'	24883
#1	'clinical trial'/exp OR 'clinical trial'	1651286

Supplemental Table 3. *Showing the baseline clinical parameters of the randomized clinical trials.*

Author	Intervention	Duration of DPN (Years) Mean(SD)	Duration of Diabetes (years) Mean(SD)	Male n (%)	Age (Years) Mean(SD)	HBA1c (%)	Baseline Pain Score	Total Randomized
Arezzo 2008	Pregabalin	4.9(3.4)	10.3(8.2)	58(70.7)	58.2 (9.6)		6.28 (1.47)	82
Arezzo 2008	Placebo	4.4 (3.7)	10.3 (8.6)	45 (52.9)	58.3 (10.9)		6.58 (1.58)	85
Backonja 1998	Gabapentin		12.0 (9.6)	49 (58.3)	53.0 (10.5)		6.4	84
Backonja 1998	Placebo		11.2 (8.7)	50 (61.7)	53.0 (10.2)		6.5	81
Bansal 2009								51
Beydoun 2006	Oxcarbazepine	2.4 (1.4)	10.3 (9.2)	47 (53)	59.3 (9.3)	7.6 (1.3)	71.3 (15.6)	88
Beydoun 2006	Placebo	2.9 (2.0)	9.7 (8.1)	50 (56)	62.1 (10.3)	7.2 (1.2)	70.8 (13.2)	89
Boyle 2012	Pregabalin		15.2 (16.6)	19 (70.4)	66.3 (7.5)	7.7 (1.6)		27
Boyle 2012	Duloxetine		13.8 (8.7)	19 (67.9)	65.0 (9.6)	7.9 (1.5)		28
Boyle 2012	Amitriptyline		13.8 (8.7)	19 (67.9)	64.2 (9.6)	8.2 (1.4)		28
Dogra 2005	Oxcarbazepine	2.6 (1.8)	9.4 (8.5)	37 (54)	59.7 (10.4)	7.7 (1.2)	71.5 (15.8)	69
Dogra 2005	Placebo	2.7 (1.7)	10.4 (8.3)	48 (62)	60.5 (8.1)	7.4 (1.3)	74.3 (13.7)	77
Eisenberg 2001	Lamotrigine	3.6 (0.7)	13.9 (1.7)	17 (63)	52.7 (2.1)	8.2 (0.3)	6.4 (0.1)	27
Eisenberg 2001	Placebo	3.8 (0.6)	9.6 (1.1)	16 (61.5)	57.8 (1.7)	8.4 (0.4)	6.6 (0.1)	26
Gao 2015	Duloxetine	3.5 (3.9)	11.5 (6.8)	91 (44.8)	61.6 (9.7)		5.7 (1.7)	203
Gao 2015	Placebo	3.1 (3.1)	11.4 (7.5)	91 (45.0)	61.2 (9.4)		5.6 (1.7)	202
Goldstein 2005	Duloxetine	3.5 (2.8)	10.1 (9.0)	68 (60.2)	60.5 (10.8)		5.9 (1.4)	113
Goldstein 2005	Placebo	4.0 (4.1)	11.4 (11.3)	59 (51.3)	60.4 (10.5)		5.8 (1.5)	115
Grosskopf 2006	Oxcarbazepine	2.9 (2.0)	9.8 (8.5)	40 (56)	60.8 (10.6)		72.0 (14.2)	71
Grosskopf 2006	Placebo	2.9 (1.8)	11.9 (9.4)	38 (54)	61.4 (10.6)		70.7 (13.6)	70
Jose 2007	Amitriptyline	1.08 (0.48)	4.87 (2.45)		4.6 (0.35)	8.94 (2.14)	70 (5.7)	23
Jose 2007	Lamotrigine	1.08 (0.48)	4.87 (2.45)		56 (50-62)	8.94 (2.14)	74 (3)	23
Kaur 2011	Amitriptyline, Duloxetine							58

Supplemental Table 3. *Showing the baseline clinical parameters of the randomized clinical trials. (continued)*

Author	Intervention	Duration of DPN (Years) Mean(SD)	Duration of Diabetes (years) Mean(SD)	Male n (%)	Age (Years) Mean(SD)	HBA1c (%)	Baseline Pain Score	Total Randomized
Kochar 2002	Sodium valproate		9.2 (6.17)	16 (57.14)	58.46 (7.61)		5 (1.95)	29
Kochar 2002	Placebo		8.1 (6.16)	13 (54.17)	53.88 (8.34)		4.95 (1.85)	28
Kochar 2004	Sodium valproate		8.85 (4.18)	12 (57.2)	54.38 (8.77)	8.78 (1.26)	6 (1.95)	21
Kochar 2004	Placebo		8.80 (3.84)	9 (50)	56.24 (8.75)	8.58 (1.10)	5.71 (1.70)	18
Lesser 2004	Pregabalin			52 (63.4)	62.0 (9.7)		6.2 (1.5)	82
Lesser 2004	Placebo			59 (60.8)	57.8 (11.6)		6.6 (1.5)	97
Nazanin Razazian 2014	Carbamazepine	1.9 (0.2)	13.7 (5.6)	41 (48.2)	58.3 (10.4)	8.8 (2.1)	74.5 (12.9)	85
Nazanin Razazian 2014	Venlafaxine	1.9 (0.3)	14.2 (6.1)	29 (33.7)	55.4 (11.1)	9.1 (2.3)	74.5 (12.9)	86
Nazanin Razazian 2014	Pregabalin	1.9 (0.3)	12.7 (6.0)	31 (36)	55.1 (9.6)	8.3 (1.8)	82.3 (13.4)	86
Raskin 2005	Duloxetine	4.5 (4.6)	13.9 (9.7)	45 (52.6)	59.0 (9.6)		5.7 (1.3)	116
Raskin 2005	Placebo	4.0 (3.5)	12.8 (8.6)	53 (45.7)	59.2 (9.8)		5.5 (1.3)	116
Raskin 2013	Pregabalin	5	12.2	75 (51.0)	58.8 (9.2)		6.8 (1.2)	147
Raskin 2013	Placebo	5.2	12.7	80 (54.4)	58.3 (10.5)		6.7 (1.3)	147
Rauck 2007	Lacosamide	3.5 (1.4)	11.1 (8.5)	29 (48.3)	54.8 (9.43)		6.6 (1.6)	60
Rauck 2007	Placebo	3.2 (2.4)	9.7 (7.2)	27 (45.8)	55.3 (10.59)		6.5 (1.7)	59
Rauck 2013	Gabapentin enacarbil			71 (61)	57.5 (9.87)		6.48 (1.43)	117
Rauck 2013	Pregabalin			34 (52)	57.7(10.59)		6.51 (1.27)	66
Rauck 2013	Placebo			73 (61)	60.1(10.63)		6.49 (1.26)	120
Richter 2005	Pregabalin		9.3 (8.8)	46 (56)	57.8 (9.5)	8.2 (1.4)		82
Richter 2005	Placebo		10.6 (8.3)	46 (54)	57.1 (10.3)	8.1 (1.4)		85
Rosenstock 2004	Pregabalin		9.3 (10.5)	42 (55.3)	59.2 (12.3)		6.5	76
Rosenstock 2004	Placebo		9.4 (10.3)	40 (57.1)	60.3 (10.3)		6.1	70
Rowbotham 2004	Venlafaxine	5.3 (3.96)		42 (51)	58.0 (11.5)		67.3	82
Rowbotham 2004	Placebo	5.3 (5.4)		48 (59)	60.0 (9.5)		68.8	81
Sandercock 2012	G-GR-QD 3000 mg PM (gabapentin)		11.0 (11.7)	17 (37.0)	58 (8.0)	7.58 (1.4)	6.71 (1.34)	46
Sandercock 2012	Placebo		10.3 (7.4)	32 (62.7)	58 (9.1)	7.11 (1.4)	6.74 (1.37)	51
Satoh 2010	Pregabalin	4.5 (3.9)	14.5 (9.6)	32 (71.1)	62.2 (10.3)	7.6 (1.1)	6.1 (1.3)	45
Satoh 2010	Placebo	4.2 (3.1)	14 (9.1)	103 (76.3)	61.3 (9.6)	7.6 (1.1)	6.1 (1.4)	135
Shaibani 2009	Lacosamide	3.0 (1.5)		70 (51.1)	59.1 (9.8)	6.9 (1.3)	6.3 (1.4)	137
Shaibani 2009	Placebo	3.1 (1.6)		39 (59.1)	59.5 (8.3)	7.0 (1.3)	6.2 (1.6)	66
Tanenberg 2011	Pregabalin	4.3 (3.4)	12.5 (11.0)	76 (56.7)	61.9 (10.7)	7.5 (1.6)	5.6 (1.9)	134
Tanenberg 2011	Duloxetine_ Gabapentin	4.2 (3.5)	10.0 (7.8)	83 (61.5)	61.9 (10.8)	7.2 (1.5)	5.7 (1.8)	135

Supplemental Table 3. *Showing the baseline clinical parameters of the randomized clinical trials. (continued)*

Author	Intervention	Duration of DPN (Years) Mean(SD)	Duration of Diabetes (years) Mean(SD)	Male n (%)	Age (Years) Mean(SD)	HBA1c (%)	Baseline Pain Score	Total Randomized
Tanenberg 2011	Duloxetine	4.8 (4.8)	12.3 (9.7)	83 (60.1)	60.9 (10.2)	7.6 (1.5)	5.7 (1.7)	138
Tolle 2008	Pregabalin			61 (60.4)	59.70 (11.3)			101
Tolle 2008	Placebo			51 (53.1)	58.93 (11.7)			96
Vinik 2007 (Study 1)	Lamotrigine	2.69 (1.38)	10.97 (10.4)	46 (51)	59.6 (10.4)		6.2 (1.4)	90
Vinik 2007 (Study 1)	Placebo	2.55 (1.4)	8.52 (7.35)	59 (66)	59.8 (10.3)		6.3 (1.5)	90
Vinik 2007 (Study 2)	Lamotrigine	2.7 (1.25)	9.0 (7.1)	49 (54)	59.0 (12.6)		6.5 (1.5)	90
Vinik 2007 (Study 2)	Placebo	3.05 (1.4)	10.2 (9.2)	50 (56)	61.6 (11.3)		6.1 (1.7)	90
Watson 2003	Oxycodone			19			67.0 (14.9)	22
Watson 2003	Placebo			19			67.0 (14.9)	23
Wernicke 2006	Duloxetine	4.4 (5.9)	9.9 (10.0)	61 (54.5)	61.5 (9.9)		6.2 (1.5)	112
Wernicke 2006	Placebo	3.5 (3.2)	11.1 (9.1)	69 (63.9)	60.8 (10.6)		5.9 (1.4)	108
Wymer 2009	Lacosamide	3.2 (1.7)		54 (58)	57.1 (8.4)			93
Wymer 2009	Placebo	3.3 (1.5)		43 (46)	58.3 (9.8)			93
Yasuda 2011	Duloxetine	4.2 (3.7)		62 (72.1)	59.7 (12.1)	7.11 (0.90)	5.76 (1.17)	86
Yasuda 2011	Placebo	4.2 (4.4)		129 (77.2)	60.8 (9.2)	7.04 (0.90)	5.78 (1.17)	167
Ziegler 2015	Pregabalin	5.3 (4.38)	13.2 (10.23)	36 (51)	59.6 (8.75)	7.2 (1.11)	6.6 (1.26)	70
Ziegler 2015	Placebo	6.1 (5.02)	15.0 (12.58)	36 (58)	58.9 (8.60)	7.4 (1.25)	6.6 (1.27)	62
Gimbel 2003	Oxycodone			45 (54.9)	59.0 (10.2)	7.6 (1.4)	6.9 (1.4)	82
Gimbel 2003	Placebo			38 (49.4)	58.8 (12.4)	7.9 (1.5)	6.8 (1.3)	77
Vinik 2014	Mirogabalin	6.1 (5.26)		32 (56.1)	59.3 (8.54)	7.6 (1.21)		57
Vinik 2014	Pregabalin	5.7 (5.00)		32 (57.1)	59.5 (9.40)	7.5 (1.46)		56
Vinik 2014	Placebo	5.9 (4.61)		56 (50.0)	60.2 (9.57)	7.3 (1.25)		112
Yiming 2017	Pregabalin	2.2	10.1	154 (49.2)	60.2 (10.3)		6.65 (1.12)	314
Yiming 2017	Placebo	2.4	11	139 (45.3)	60.9 (9.5)		6.67 (1.15)	309
Sekar 2017	Gabapentin						67.72 (16.93)	50
Sekar 2017	Amitriptyline						65.92 (12.89)	50
Zakerkish 2017	Nortriptyline			31 (46.27)			71.8(16.5)	67
Zakerkish 2017	Duloxetine			25 (37.3)			74.7 (19.2)	67
Aaron I. Vinik 2014	Tapentadol				58.5 (10.63)		7.3 (1.30)	166

Supplemental Table 3. *Showing the baseline clinical parameters of the randomized clinical trials. (continued)*

Author	Intervention	Duration of DPN (Years) Mean(SD)	Duration of Diabetes (years) Mean(SD)	Male n (%)	Age (Years) Mean(SD)	HBA1c (%)	Baseline Pain Score	Total Randomized
Aaron I. Vinik 2014	Placebo				59 (9)		7.3 (1.30)	152
Allen 2014	Desvenlafaxine	5.93 (4.7)	14.3 (12.4)	52 (75)	61.1 (10.0)		6.48 (1.42)	69
Allen 2014	Placebo	7.1 (5.9)	16.7 (14.0)	65 (72)	59.0 (8.5)		6.61 (1.60)	90
Huffiman 2015	Pregabalin	4.7 (4.3)	12.3 (8.2)	61 (60.4)	59.1 (8.5)			101
Huffiman 2015	Placebo	4.8 (4.6)	10.3 (8.0)	71 (69.6)	58.4 (9.3)			102

Supplemental Table 4. *League table reporting 30% pain reduction.*

	Placebo	Amitriptyline	Carbamazepine	Duloxetine	Duloxetine_ Gabapentin	Lacosamide	Lamotrigine
Placebo							
Amitriptyline	0.99 (0.43-2.24)						
Carbamazepine	0.58 (0.15-2.03)	0.59 (0.13-2.52)					
Duloxetine	1.97 (1.32-2.87)	2.00 (0.88-4.54)	3.37 (0.94-13.27)				
Duloxetine_ Gabapentin	1.78 (0.85-3.66)	1.81 (0.64-4.96)	3.03 (0.76-13.17)	0.90 (0.45-1.82)			
Lacosamide	1.68 (0.94-3.02)	1.70 (0.62-4.74)	2.88 (0.74-12.31)	0.85 (0.43-1.74)	0.95 (0.37-2.41)		
Lamotrigine	0.86 (0.47-1.58)	0.87 (0.31-2.42)	1.48 (0.37-6.34)	0.44 (0.21-0.91)	0.48 (0.19-1.25)	0.51 (0.22-1.19)	
Mirogabalin	2.05 (0.93-4.63)	2.08 (0.68-6.55)	3.53 (0.83-16.57)	1.04 (0.44-2.54)	1.15 (0.41-3.36)	1.22 (0.46-3.31)	2.39 (0.89-6.59)
Nortriptyline	0.06 (0.00-0.45)	0.06 (0.00-0.52)	0.10 (0.00-1.17)	0.03 (0.00-0.22)	0.03 (0.00-0.27)	0.04 (0.00-0.29)	0.07 (0.00-0.57)
Oxcarbazepine	2.10 (0.86-5.07)	2.11 (0.63-7.18)	3.57 (0.77-17.95)	1.07 (0.40-2.81)	1.18 (0.38-3.71)	1.25 (0.42-3.58)	0.82 (2.43-7.11)
Pregabalin	1.21 (0.83-1.71)	1.22 (0.55-2.74)	2.07 (0.62-7.57)	0.61 (0.39-0.96)	0.68 (0.34-1.36)	0.72 (0.36-1.41)	1.40 (0.68-2.80)
Tapentadol	1.51 (0.72-3.12)	1.52 (0.51-4.55)	2.58 (0.60-11.57)	0.76 (0.34-1.77)	0.84 (0.30-2.38)	0.90 (0.35-2.29)	1.75 (0.67-4.52)
Venlafaxine	0.16 (0.04-0.48)	0.16 (0.04-0.60)	0.27 (0.0-0.70)	0.08 (0.02-0.25)	0.09 (0.02-0.31)	0.09 (0.02-0.33)	0.18 (0.04-0.66)

	Mirogabalin	Nortriptyline	Oxcarbazepine	Pregabalin	Tapentadol	Venlafaxine
Placebo						
Amitriptyline						
Carbamazepine						
Duloxetine						
Duloxetine_ Gabapentin						
Lacosamide						
Lamotrigine						
Mirogabalin						
Nortriptyline	0.03 (0.00-0.25)					
Oxcarbazepine	1.03 (0.30-3.32)	35.20 (3.90-1061.0)				
Pregabalin	0.59 (0.25-1.30)	19.73 (2.67-556.7)	0.57 (0.22-1.48)			
Tapentadol	0.74 (0.24-2.14)	25.17 (2.95-762.0)	0.72 (0.23-2.28)	1.25 (0.56-2.84)		
Venlafaxine	0.08 (0.02-0.29)	2.67 (0.24-88.61)	0.08 (0.02-0.32)	0.13 (0.04-0.38)	0.10 (0.02-0.40)	

Supplemental Table 5. *Ranking probability and median ranking of interventions reporting 30% pain reduction.*

Intervention	Ranking Probability	Median Rank	95% CrI	
Placebo	0	5	4	8
Amitriptyline	0.00015	5	3	11
Carbamazepine	0.00101	3	2	11
Duloxetine	0	11	8	13
Duloxetine_ Gabapentin	0.00002	10	5	13
Lacosamide	0.00002	10	5	13
Lamotrigine	0.00023	4	3	9
Mirogabalin	0.00001	11	5	13
Nortriptyline	**0.77760**	**1**	**1**	**3**
Oxcarbazepine	0.00004	12	5	13
Pregabalin	0	7	4	10
Tapentadol	0.00015	9	4	13
Venlafaxine	0.22080	2	1	2

{AU: What is the significance of the bold information?}

Supplemental Table 6. *League table reporting total withdrawal (n = 34).*

	Placebo	Amitriptyline	Benztropine	Carbamazepine	Desvenlafaxine	Duloxetine	Duloxetine_ Gabapentin	Gabapentin	Gabapentin Encarbil
Placebo									
Amitriptyline	1.10 (0.09-15.17)								
Benztropine	0.69 (0.14-3.46)	0.61 (0.03-11.58)							
Carbamazepine	0.81 (0.22-2.73)	0.72 (0.04-11.32)	1.18 (0.15-8.55)						
Desvenlafaxine	**3.29 (1.30-8.60)**	2.98 (0.19-42.16)	4.81 (0.75-30.06)	4.07 (0.88-20.09)					
Duloxetine	**1.49 (1.02-2.18)**	1.35 (0.10-16.06)	2.15 (0.41-10.97)	1.83 (0.52-6.92)	0.45 (0.16-1.23)				
Duloxetine_ Gabapentin	0.95 (0.46-1.97)	0.87 (0.06-11.25)	1.37 (0.23-7.88)	1.18 (0.30-4.82)	0.29 (0.09-0.94)	0.64 (0.31-1.29)			
Gabapentin	1.04 (0.45-2.48)	0.95 (0.08-10.17)	1.52 (0.25-9.12)	1.29 (0.29-6.13)	0.31 (0.09-0.94)	0.70 (0.28-1.82)	1.09 (0.37-3.46)		
Gabapentin Encarbil	1.38 (0.66-2.82)	1.25 (0.08-16.44)	2.00 (0.33-11.38)	1.70 (0.43-7.12)	0.42 (0.12-1.36)	0.93 (0.41-2.06)	1.44 (0.53-3.94)	1.33 (0.42-3.96)	
Lacosamide	**2.90 (1.70-4.85)**	2.65 (0.18-32.37)	4.17 (0.77-22.29)	3.57 (0.95-14.12	0.88 (0.29-2.54)	1.95 (1.01-3.71)	**3.06 (1.23-7.41)**	2.80 (0.98-7.49)	2.11 (0.86-5.16)
Lamotrigine	1.15 (0.64-1.98)	1.04 (0.07-12.82)	1.65 (0.29-8.74)	1.41 (0.37-5.56)	0.35 (0.11-1.01)	0.77 (0.38-1.50)	1.21 (0.47-2.97)	1.11 (0.38-2.95)	0.83 (0.33-2.08)
Mirogabalin	0.73 (0.21-2.33)	0.66 (0.04-9.93)	1.05 (0.14-7.51)	0.89 (0.16-5.06)	0.22 (0.05-0.98)	0.49 (0.14-1.66)	0.77 (0.19-3.03)	0.70 (0.16-2.93)	0.53 (0.13-2.10)
Nortriptyline	2.73 (0.77-10.52)	2.52 (0.13-40.89)	3.96 (0.51-31.31)	3.38 (0.59-21.33)	0.82 (0.17-4.38)	1.84 (0.54-6.73)	2.86 (0.70-12.68)	2.63 (0.56-13.02)	1.98 (0.47-9.16)
Oxcarbazepine	**3.09 (1.82-5.22)**	2.78 (0.20-34.98)	4.45 (0.80-23.94)	**3.81 (1.00-15.30)**	0.94 (0.31-2.72)	**2.08 (1.08-3.96)**	3.25 (1.31-8.0)	**3.0 (1.06-7.88)**	2.25 (0.92-5.51)
Oxycodone	0.63 (0.25-1.54)	0.56 (0.04-7.77)	0.90 (0.24-3.37)	0.78 (0.17-3.67)	0.19 (0.05-0.70)	0.42 (0.16-1.12)	0.66 (0.20-2.09)	0.60 (0.17-2.03)	0.45 (0.14-1.45)
Pregabalin	**1.07 (0.78-1.47)**	0.97 (0.07-11.53)	1.55 (0.30-7.78)	1.32 (0.41-4.57)	0.33 (0.12-0.86)	0.72 (0.46-1.12)	1.13 (0.55-2.31)	1.03 (0.41-2.49)	0.78 (0.38-1.64)
Sodium valproate	0.21 (0.02-1.06)	0.18 (0.01-3.67)	0.29 (0.02-2.85)	0.25 (0.02-2.14)	0.06 (0.01-0.40)	0.14 (0.02-0.75)	0.22 (0.02-1.32)	0.20 (0.02-1.24)	**0.15 (0.02-0.90)**
Tapentadol	0.92 (0.43-1.95)	0.83 (0.06-10.83)	1.33 (0.22-7.67)	1.13 (0.27-5.06)	0.28 (0.08-0.92)	0.62 (0.26-1.43)	0.97 (0.34-2.76)	0.89 (0.28-2.69)	0.67 (0.23-1.92)
Venlafaxine	2.30 (0.78-6.94)	2.06 (0.13-30.69)	3.34 (0.48-22.48)	2.81 (0.97-9.16)	0.70 (0.16-2.95)	1.54 (0.49-4.89)	2.42 (0.69-8.67)	2.21 (0.54-8.80)	1.67 (0.46-6.03)

Supplemental Table 6. *League table reporting total withdrawal (n = 34). (continued)*

Lacosamide	Lamotrigine	Mirogabalin	Nortriptyline	Oxcarbazepine	Oxycodone	Pregabalin	Sodium valproate	Tapentadol	Venlafaxine
0.40 (0.18-0.84)									
0.25 (0.07-0.91)	0.64 (0.17-2.34)								
0.94 (0.24-4.04)	2.39 (0.61-10.44)	3.77 (0.68-22.54)							
1.07 (0.51-2.26)	**2.70 (1.27-5.89)**	**4.22 (1.18-16.12)**	1.13 (0.26-4.50)						
0.22 (0.07-0.62)	0.55 (0.19-1.61)	0.86 (0.20-3.98)	0.23 (0.04-1.10)	**0.20 (0.07-0.58)**					
0.37 (0.20-0.69)	0.94 (0.50-1.80)	1.47 (0.44-5.17)	0.39 (0.10-1.43)	**0.35 (0.19-0.64)**	1.71 (0.66-4.51)				
0.07 (0.01-0.40)	0.18 (0.02-1.04)	0.28 (0.02-2.19)	**0.08 (0.01-0.61)**	**0.07 (0.01-0.37)**	0.32 (0.03-2.16)	0.19 (0.02-1.02)			
0.32 (0.13-0.81)	0.80 (0.32-2.10)	1.26 (0.31-5.32)	0.34 (0.07-1.47)	**0.30 (0.12-0.75)**	1.47 (0.45-4.77)	0.86 (0.38-1.96)	4.44 (0.74-43.05)		
0.80 (0.24-2.69)	2.01 (0.60-6.99)	3.19 (0.93-16.47)	0.85 (0.15-4.41)	0.75 (0.22-2.54)	3.67 (0.90-15.04)	2.15 (0.77-6.23)	11.33 (1.52-122.1)	2.49 (0.67-9.54)	

Supplemental Table 7. *Ranking probability and median ranking of interventions reporting total withdrawal from clinical trial (n = 34).*

Intervention	Ranking Probability	Median Rank	95% CrI	
Placebo	0.00000	8	5	11
Amitriptyline	0.09616	9	1	19
Benztropine	0.08576	4	1	17
Carbamazepine	0.04465	6	1	16
Desvenlafaxine	0.00005	17	11	19
Duloxetine	0.00000	13	8	15
Duloxetine_Gabapentin	0.00466	7	2	14
Gabapentin	0.00375	8	2	16
Gabapentin Encarbil	0.00059	12	4	17
Lacosamide	0.00000	17	13	19
Lamotrigine	0.00063	10	4	15
Mirogabalin	0.05321	5	1	15
Nortriptyline	0.00051	16	5	19
Oxcarbazepine	0.00000	17	14	19
Oxycodone	0.03173	4	1	13
Pregabalin	0.00001	9	5	13
Sodium valproate	0.67180	1	1	9
Tapentadol	0.00638	7	2	15
Venlafaxine	0.00017	15	6	19

Supplemental Table 8. *League table reporting withdrawal due to adverse events.*

	Placebo	**Amitriptyline**	**Benztropine**	**Carbamazepine**	**Desvenlafaxine**	**Duloxetine**	**Duloxetine_ Gabapentin**	**Gabapentin**
Placebo								
Amitriptyline	**3.40 (1.40-7.60)**							
Benztropine	0.12 (0.00-1.98)	**0.04 (0.00-0.70)**						
Carbamazepine	0.43 (0.05-2.34)	**0.13 (0.01-0.85)**	3.49 (0.10-193.60)					
Desvenlafaxine	**7.86 (2.17-33.30)**	2.34 (0.52-12.88)	**69.04 (3.12-3168)**	**18.92 (2.16-244.3)**				
Duloxetine	**3.39 (2.10-5.60)**	1.0 (0.44-2.55)	**28.81 (1.63-1099)**	**7.93 (1.39-72.54)**	0.43 (0.10-1.73)			
Duloxetine_ Gabapentin	2.35 (0.85-6.64)	0.69 (0.21-2.61)	20.19 (0.96-842)	5.56 (0.79-58.14)	0.30 (0.05-1.58)	0.69 (0.26-1.89)		
Gabapentin	1.30 (0.38-4.71)	0.38 (0.09-1.84)	11.16 (0.52-487)	3.11 (0.37-37.27)	0.16 (0.03-1.03)	0.38 (0.10-1.50)	0.56 (0.11-2.79)	
Gabapentin Encarbil	**3.02 (1.11-8.65)**	0.89 (0.26-3.49)	**25.67 (1.28-1092)**	**7.12 (1.0-76.81)**	0.38 (0.07-2.03)	0.89 (0.29-2.78)	1.28 (0.31-5.34)	2.33 (0.46-11.60)
Lacosamide	**4.82 (2.21-10.13)**	1.43 (0.47-4.51)	**40.63 (2.13-1589)**	**11.21 (1.70-114.2)**	0.61 (0.12-2.66)	1.42 (0.56-3.41)	2.06 (0.55-6.99)	3.71 (0.83-14.99)
Lamotrigine	1.35 (0.62-2.87)	0.40 (0.16-1.06)	11.41 (0.62-451)	3.14 (0.49-30.59)	0.17 (0.03-1.77)	0.40 (0.16-0.94)	0.58 (0.16-1.96)	1.03 (0.23-4.30)
Oxcarbazepine	**6.71 (3.13-14.69)**	1.98 (0.66-6.55)	**57.55 (2.98-2263)**	**15.70 (2.44-159.30)**	0.85 (0.17-3.82)	1.98 (0.79-4.96)	2.87 (0.78-10.11)	**5.17 (1.16-21.72)**
Oxycodone	1.77 (0.39-9.17)	0.52 (0.09-3.42)	**14.62 (1.53-422)**	4.30 (0.40-59.79)	0.22 (0.03-1.77)	0.52(0.10-2.88)	0.75 (0.12-5.12)	1.36 (0.19-10.38)
Pregabalin	**2.03 (1.39-3.09)**	0.60 (0.27-1.47)	17.13 (0.99-657)	4.71 (0.90-43.45)	0.22 (0.03-1.77)	0.60 (0.35-1.05)	0.86 (0.32-2.41)	1.56 (0.41-5.74)
Sodium valproate	0.62 (0.06-5.29)	0.18 (0.02-1.88)	5.26 (0.14-331)	1.47 (0.08-29.53)	0.08 (0.01-0.98)	1.08 (0.02-1.64)	0.26 (0.02-2.84)	0.47 (0.03-5.78)
Tapentadol	1.75 (0.57-5.39)	0.51 (0.13-2.22)	14.86 (0.72-647)	4.15 (0.53-46.45)	0.22 (0.04-1.23)	0.52 (0.15-1.75)	0.75 (0.16-3.34)	1.35 (0.24-7.09
Venlafaxine	**3.92 (1.41-11.58)**	1.15 (0.34-4.58)	**33.24 (1.67-1451)**	**9.20 (1.81-77.27)**	0.50 (0.09-2.66)	1.15 (0.38-3.73)	1.66 (0.40-7.00)	**3.01 (1.59-15.16)**

Supplemental Table 8. *League table reporting withdrawal due to adverse events. (continued)*

Gabapentin Encarbil	Lacosamide	Lamotrigine	Oxcarbazepine	Oxycodone	Pregabalin	Sodium valproate	Tapentadol	Venlafaxine
1.61 (0.42-5.53)								
0.45 (0.12-1.55)	0.28 (0.10-0.83)							
2.22 (0.61-7.92)	1.39 (0.49-4.19)	**4.96 (1.71-15.07)**						
0.59 (0.09-3.95)	0.37 (0.07-2.31)	1.30 (0.25-8.05)	0.26 (0.05-1.60)					
0.67 (0.24-1.89)	0.42 (0.18-1.04)	1.51 (0.67-3.61)	**0.30 (0.13-0.73)**	1.15 (0.21-5.67)				
0.20 (0.02-2.18)	0.13 (0.01-1.26)	0.45 (0.04-4.57)	**0.09 (0.01-0.90)**	0.34 (0.02-5.0)	0.30 (0.03-2.66)			
0.58 (0.12-2.60)	0.36 (0.10-1.46)	**1.29 (1.34-5.15)**	0.26 (0.07-1.03)	0.99 (0.14-6.55)	0.86 (0.25-2.80)	2.85 (0.24-37.94)		
1.30 (0.31-5.44)	0.81 (0.23-3.12)	2.88 (0.84-10.94)	0.58 (0.16-2.19)	2.23 (0.32-14.56)	1.93 (0.69-5.47)	6.38 (0.63-82.64)	2.24 (0.49-10.71)	

Supplemental Table 9. *Ranking probability and median ranking of interventions reporting total withdrawal due to ADR from clinical trial (n = 34).*

Intervention	Ranking Probability	Median Rank	95% CrI	
Placebo	0.00149	4	2	7
Amitriptyline	0.00004	12	6	16
Benztropine	0.67900	1	1	8
Carbamazepine	0.18100	2	1	9
Desvenlafaxine	0.00001	16	9	17
Duloxetine	0.00000	12	9	15
Duloxetine_Gabapentin	0.00054	10	4	16
Gabapentin	0.00877	6	2	14
Gabapentin Encarbil	0.00011	11	5	16
Lacosamide	0.00001	14	9	17
Lamotrigine	0.00210	6	3	11
Oxcarbazepine	0.00000	16	11	17
Oxycodone	0.00035	8	2	16
Pregabalin	0.00000	8	6	11
Sodium valproate	0.12390	3	1	15
Tapentadol	0.00269	7	3	15
Venlafaxine	0.00000	13	6	17

Supplemental Table 10. *League table reporting total withdrawals (n = 22).*

	Placebo	Carbamazepine	Desvenlafaxine	Duloxetine	Duloxetine_ Gabapentin	Gabapentin
Placebo						
Carbamazepine	0.93 (0.27-3.20)					
Desvenlafaxine	**3.28 (1.33-8.36)**	3.52 (0.75-16.43)				
Duloxetine	**1.54 (1.06-2.25)**	1.65 (0.46-5.86)	0.47 (0.17-1.25)			
Duloxetine_Gabapentin	1.04 (0.51-2.15)	1.12 (0.28-4.40)	0.32 (0.10-1.02)	0.68 (0.34-1.36)		
Gabapentin	2.60 (0.40-27.00)	2.73 (0.30-41.63)	0.79 (0.10-9.80)	1.69 (0.25-18.24)	2.48 (0.33-30.07)	
Lacosamide	**4.22 (1.85-9.77)**	**4.54 (1.03-20.59)**	1.29 (0.37-4.55)	**2.76 (1.10-6.86)**	**4.07 (1.33-12.01)**	1.62 (0.14-12.78)
Lamotrigine	1.14 (0.64-1.97)	1.23 (0.31-4.64)	0.35 (0.12-1.00)	0.75 (0.37-1.42)	1.11 (0.43-2.64)	0.44 (0.04-3.18)
Mirogabalin	0.55 (0.18-1.56)	0.59 (0.11-2.78)	**0.16 (0.04-0.67)**	0.36 (0.11-1.05)	0.53 (0.14-1.83)	0.21 (0.02-1.79)
Nortriptyline	2.78 (0.77-10.59)	3.03 (0.49-18.63)	0.86 (0.17-4.25)	1.82 (0.54-6.51)	2.69 (0.67-11.41)	1.08 (0.07-10.59)
Oxcarbazepine	2.37 (0.94-6.00)	2.56 (0.54-11.85)	0.73 (0.19-2.63)	1.55 (0.57-4.14)	2.29 (0.70-7.28)	0.91 (0.08-7.31)
Pregabalin	1.24 (0.92-1.76)	1.34 (0.41-4.36)	0.38 (0.14-1.01)	0.81 (0.53-1.28)	1.20 (0.60-2.45)	0.48 (0.04-3.27)
Tapentadol	0.91 (0.44-1.89)	0.98 (0.23-4.13)	**0.28 (0.08-0.88)**	0.59 (0.26-1.33)	0.88 (0.31-2.38)	0.35 (0.03-2.58)
Venlafaxine	2.66 (0.93-8.12)	2.82 (0.98-8.73)	0.81 90.20-3.44)	1.73 (0.57-5.51)	2.55 (0.74-9.23)	1.04 (0.08-9.20)

Supplemental Table 10. *League table reporting total withdrawals (n = 22). (continued)*

Lacosamide	Lamotrigine	Mirogabalin	Nortriptyline	Oxcarbazepine	Pregabalin	Tapentadol	Venlafaxine
0.27 (0.10-0.72)							
0.13 (0.03-0.49)	0.48 (0.14-1.58)						
0.66 (0.14-3.18)	2.44 (0.62-10.63)	5.14 (0.98-29.95)					
0.56 (0.16-1.95)	2.08 (0.71-6.28)	**4.36 (1.08-18.73)**	0.85 (0.17-4.06)				
0.29 (0.12-0.73)	1.08 (0.59-2.17)	2.27 (0.80-7.29)	0.45 (0.12-1.63)	0.52 (0.20-1.42)			
0.22 (0.07-0.65)	0.79 (0.71-8.30)	1.66 (0.46-6.44)	0.32 (0.07-1.39)	0.38 (0.12-1.25)	0.73 (0.32-1.58)		
0.63 (0.17-2.53)	2.23 (0.71-8.30)	**4.83 (1.11-23.17)**	0.94 (0.19-5.07)	1.12 (0.27-4.80)	2.13 (0.77-6.17)	2.93 (0.82-11.15)	

Supplemental Table 11. *Ranking probability and median ranking of interventions reporting total withdrawal from clinical trial (n = 22).*

Intervention	Ranking Probability	Median Rank	95% CrI	
Placebo	0.00745	4	2	7
Carbamazepine	0.18190	3	1	11
Desvenlafaxine	0.00045	12	7	14
Duloxetine	0.00013	8	5	11
Duloxetine_Gabapentin	0.05020	5	1	10
Gabapentin	0.04692	11	1	14
Lacosamide	0.00010	13	9	14
Lamotrigine	0.02257	6	2	10
Mirogabalin	0.57590	1	1	8
Nortriptyline	0.00755	11	3	14
Oxcarbazepine	0.00246	10	4	14
Pregabalin	0.00023	6	3	9
Tapentadol	0.10320	3	1	10
Venlafaxine	0.00093	11	4	14

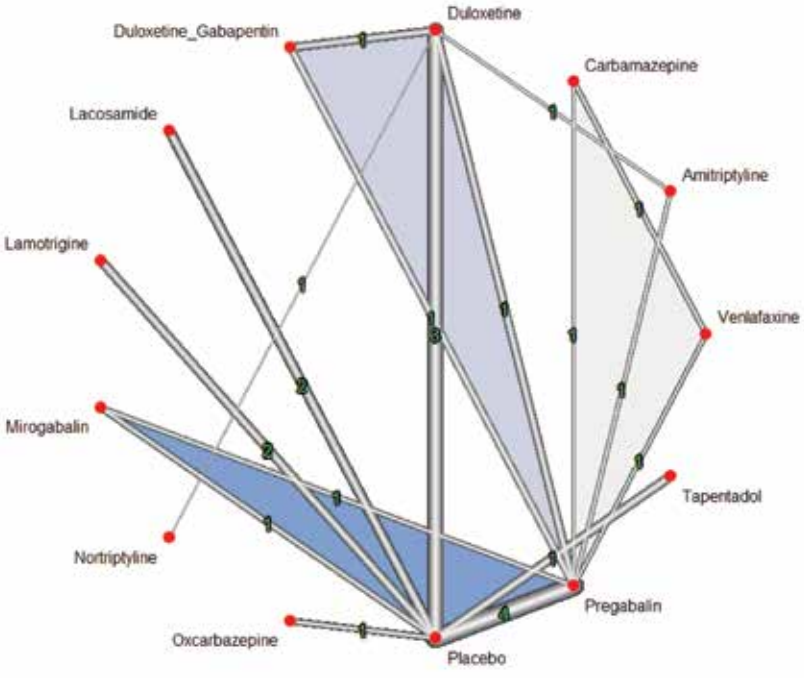
Supplemental Table 12. *Reporting the quality of the studies employing the PEDro checklist.*

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Total Score
Arezzo 2008	1	1	1	1	1	1	1	1	1	1	1	11
Backonja 1998	1	1	1	1	1	1	1	1	1	1	1	11
Bansal 2009	1	1	1	0	1	1	1	1	1	1	1	10
Beydoun 2006	1	1	1	1	1	1	1	1	1	1	1	11
Boyle 2012	1	1	0	1	1	1	1	1	1	1	1	10
Dogra 2005	1	1	1	1	1	1	1	1	1	1	1	11
Eisenberg 2001	1	1	1	1	1	1	1	1	1	1	1	11
Gao 2015	1	1	1	1	1	1	1	1	1	1	1	11
Goldstein 2005	1	1	1	1	1	1	1	1	1	1	1	11
Grosskopf 2006	1	1	1	1	1	1	1	1	1	1	1	11
Jose 2007	1	1	1	0	1	1	1	1	1	1	1	10
Kau r2011	1	1	1	0	1	1	1	1	1	1	1	10
Kochar 2002	1	1	1	1	1	1	1	1	1	1	1	11
Kochar 2004	1	1	1	1	1	1	1	1	1	1	1	11
Lesser 2004	1	1	1	1	1	1	1	1	1	1	1	11
Nazanin Razazian 2014	1	1	1	1	1	1	1	1	1	1	1	11
Raskin 2005	1	1	1	1	1	1	1	1	1	1	1	11
Raskin 2013	1	1	1	1	1	1	1	1	1	1	1	11
Rauck 2007	1	1	1	1	1	1	1	1	1	1	1	11
Rauck 2013	1	1	1	1	1	1	1	1	1	1	1	11
Richter 2005	1	1	1	1	1	1	1	1	1	1	1	11
Rosenstock 2004	1	1	1	1	1	1	1	1	1	1	1	11
Rowbotham 2004	1	1	1	1	1	1	1	1	1	1	1	11
Sandercock 2012	1	1	1	1	1	1	1	1	1	1	1	11
Satoh 2010	1	1	1	1	1	1	1	1	1	1	1	11
Shaibani 2009	1	1	1	1	1	1	1	1	1	1	1	11
Tanenberg 2011	1	1	1	1	0	0	0	1	1	1	1	8
Tolle 2008	1	1	1	1	1	1	1	1	1	1	1	11
Vinik 2007 (Study 1)	1	1	1	1	1	1	1	1	1	1	1	11
Vinik 2007 (Study 2)	1	1	1	1	1	1	1	1	1	1	1	11
Watson 2003	1	1	1	0	1	1	1	1	1	1	1	10
Wernicke 2006	1	1	1	1	1	1	1	1	1	1	1	11
Wymer 2009	1	1	1	1	1	1	1	1	1	1	1	11
Yasuda 2011	1	1	1	1	1	1	1	1	1	1	1	11
Ziegler 2015	1	1	1	1	1	1	1	1	1	1	1	11
Gimbel 2003	1	1	1	1	1	1	1	1	1	1	1	11
Vinik 2014	1	1	1	1	1	1	1	1	1	1	1	11
Yiming 2017	1	1	1	1	1	1	1	1	1	1	1	11
Sekar 2017	1	1	1	1	0	0	0	1	1	1	1	8
Zakerkish 2017	1	1	1	1	1	1	1	1	1	1	1	11
Aaron I. Vinik 2014	1	1	1	1	1	1	1	1	1	1	1	11
Allen 2014	1	1	1	1	1	1	1	1	1	1	1	11
Huffiman 2015	1	1	1	1	1	1	1	1	1	1	1	11

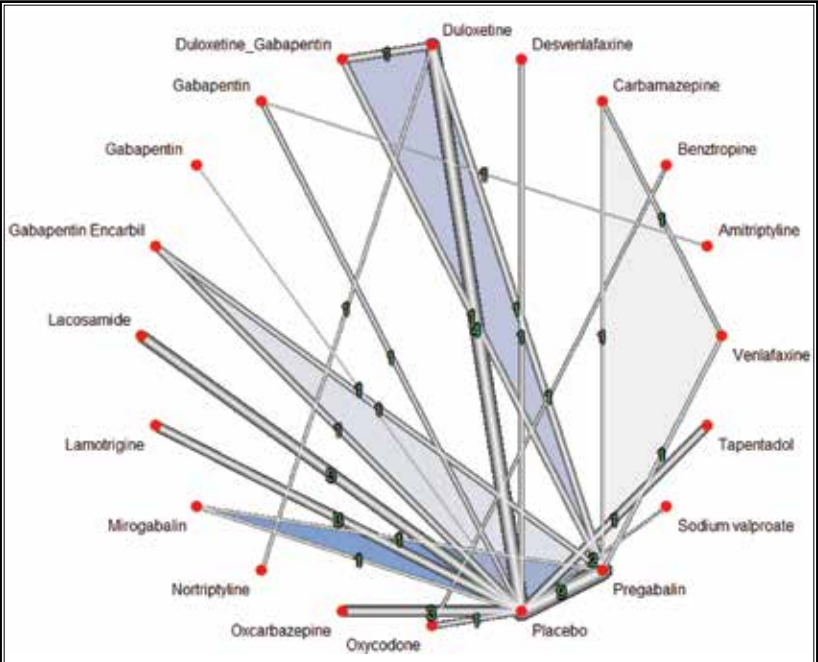
PEDro Items: 1. Eligibility criteria; 2. Randomization; 3. Concealed allocation; 4. Baseline comparability; 5. Patient blinding; 6. Clinician blinding; 7. Assessor blinding; 8. Adequate follow-up > 85%, 9. Intention to treat analysis; 10. Between group statistical comparisons; 11. Point measures and measures of variability

Supplemental Table 13. *Model fit assessment and heterogeneity parameter in network meta-analyses.*

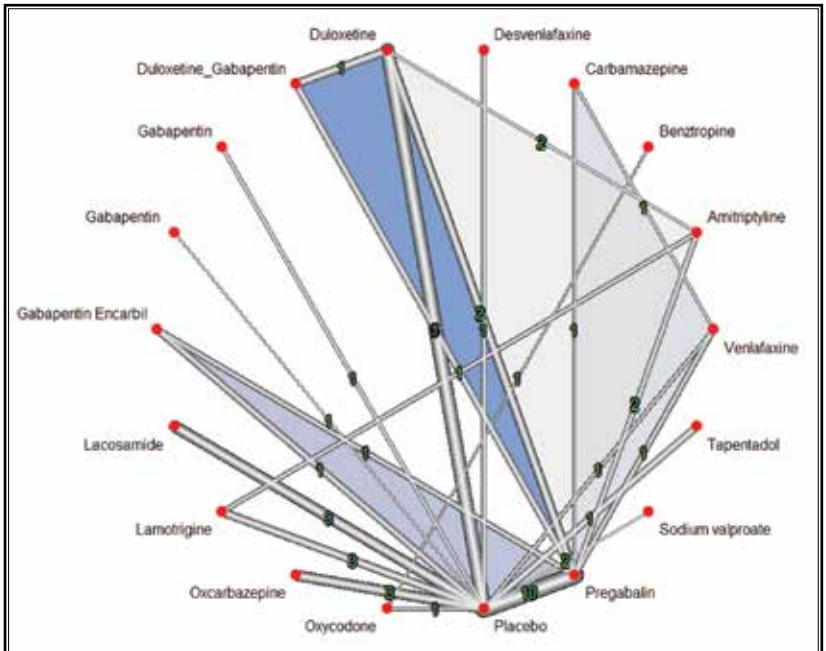
Outcome	SD	Tau	PD	DIC
30% pain reduction	0.21 (0.01-0.64)	23.52 (2.47-7675.0)	33.85	261.49
50% pain reduction (n = 22)	0.35 (0.08-0.75)	8.30 (1.79-149.5)	42.31	313.98
50% pain reduction (n = 29)	0.44 (0.24-0.74)	5.09 (1.81-17.54)	55.13	403.97
Total Withdrawal (n = 22)	0.15 (0.01-0.58)	24.5 (3.01-6998)	39.03	296.68
Total Withdrawal (n = 34)	0.22 (0.02-0.59)	20.63 (2.83-3154)	57.84	440
Withdrawal ADR	0.37 (0.03-0.78)	7.36 (1.67-1113)	63.10	445.82



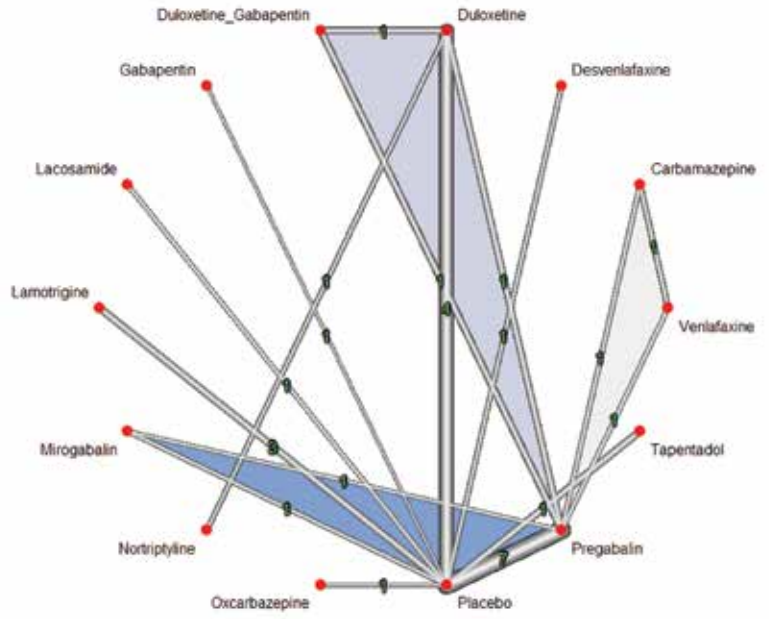
Supplemental Fig 1. *Network plot of interventions for reporting 30% pain reduction outcome.*



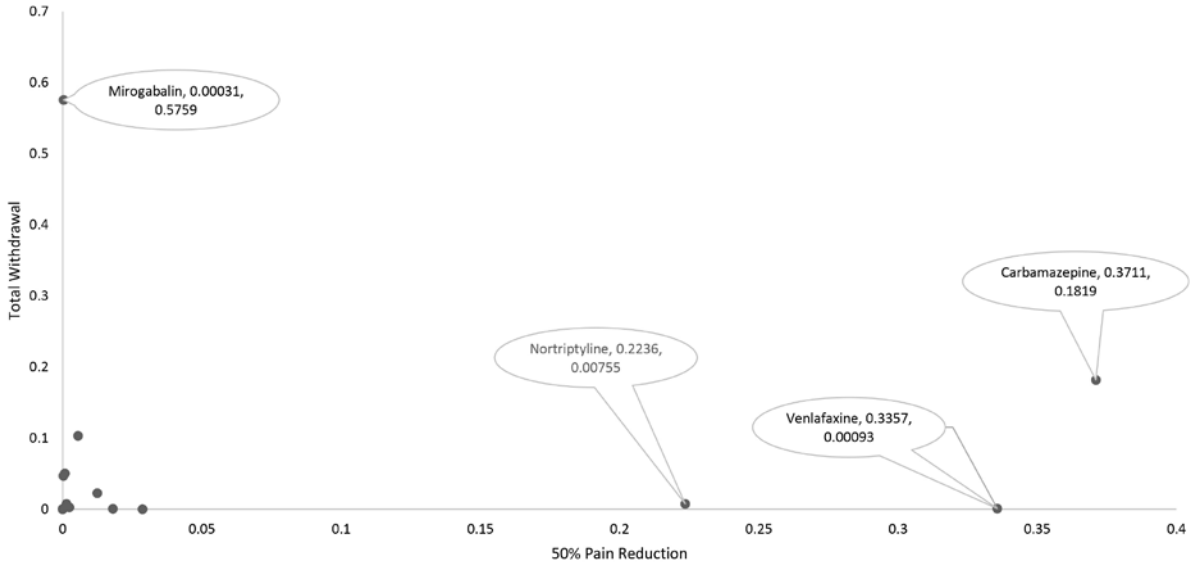
Supplemental Fig 2. *Network plot of interventions for reporting total withdrawal in the clinical trials (n = 34).*



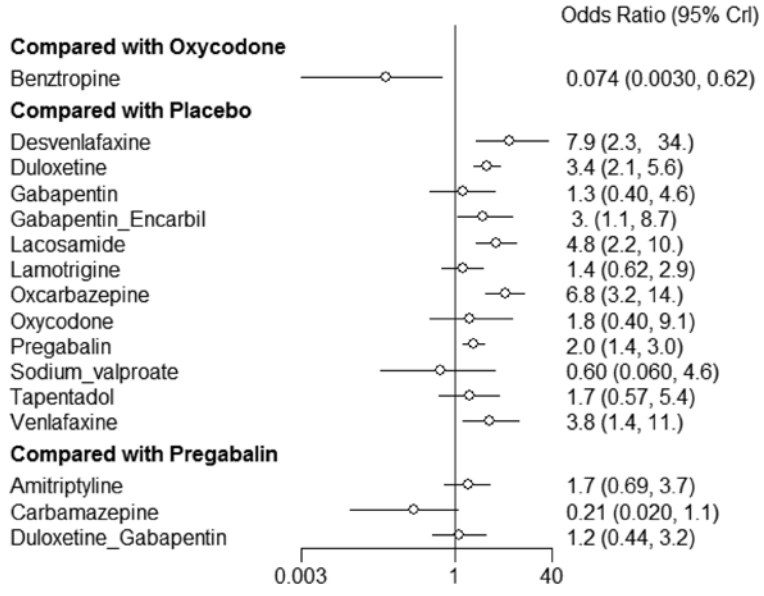
Supplemental Fig 3. *Network plot of interventions reporting total withdrawals due to adverse events in the clinical trials (n = 34).*



Supplemental Fig 4. *Network plot of interventions for reporting 50% pain reduction outcome and total withdrawal from the trials. (n = 22).*



Supplemental Fig 5. *Cluster analysis plot of the efficacy and safety outcomes. The interventions located in the lower right corner were superior to other.*



Supplemental Fig 6. *Pairwise meta-analysis in NMA for withdrawals due to adverse events.*