Meta-Analysis

Comparative Efficacy and Safety of Six Antidepressants and Anticonvulsants in Painful Diabetic Neuropathy: A Network Meta-analysis

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Background: Anticonvulsants and antidepressants are mostly used in management of painful diabetic neuropathy (PDN). However there are few direct comparisons between drugs of these classes, making evidence-based decision-making in the treatment of painful diabetic neuropathy difficult.

Objectives: This study aimed to perform a network meta-analysis and benefit-risk analysis to evaluate the comparative efficacy and safety of these drugs in PDN treatment.

Study Design: Comparative effectiveness study.

Setting: Medical Education and Research facility in India.

Methods: A comprehensive data search was done in PubMed, Cochrane, and Embase up to August 2012. We then systematically reviewed the studies which compared any of 6 drugs for the management of PDN: amitriptyline, duloxetine, gabapentin, pregabalin, valproate, and venlafaxine or any of their combinations. We performed a random-effects network meta-analysis to rank treatments in terms of efficacy and safety. We chose the number of patients experiencing ≥ 50% reduction in pain and number of patient withdrawals due to adverse events (AE) as primary outcomes for efficacy and safety, respectively. We also performed benefit-risk analysis, taking efficacy outcome as benefit and safety outcome as risk. Analysis was intention-to-treat.

Results: We included 21 published trials in the analysis. Duloxetine, gabapentin, pregabalin, and venlafaxine were shown to be significantly efficacious compared to placebo with odds ratios (OR) of 2.12, 3.98, 2.78, and 4.43, respectively. Amitriptyline (OR: 7.03, 95% confidence interval [CI]: 1.87, 29.05) and duloxetine (OR: 3.26, 95% CI: 1.04, 9.97) caused more withdrawals than gabapentin. The ranking order of efficacy was gabapentin, venlafaxine, pregabalin, duloxetine/gabapentin, duloxetine, amitriptyline, and placebo and the ranking order of safety was placebo, gabapentin, pregabalin, venlafaxine, duloxetine/gabapentin combination, duloxetine, and amitriptyline. Benefit-risk balance favored the order: gabapentin, venlafaxine, pregabalin, duloxetine/gabapentin combination, duloxetine, placebo, and amitriptyline.

Limitations: We could not include valproate in our analysis owing to the lack of studies reporting the dichotomous efficacy and safety outcomes.

Conclusion: Gabapentin was found to be most efficacious and amitriptyline to be least safe among the treatments included in the study. Gabapentin showed most favorable balance between efficacy and safety.

Key words: Amitriptyline, diabetic neuropathy, duloxetine, gabapentin, network meta-analysis, pain, pregabalin, valproate, valproic acid, venlafaxine

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Painful diabetic neuropathy (PDN), a significant microvascular complication of diabetes, is characterised by the prickling, tingling, burning, electric shock like, freezing pain with allodynia and hyperalgesia in the legs, feet, and hands affecting 21% of diabetic patients (1,2). It is estimated that half of the diabetic patients develop neuropathy and the prevalence of PDN ranges from 10 to 20% in diabetic patients and from 40 to 50% in those with diabetic neuropathy (3). PDN, even though common and often severe, is frequently unreported (12.5%) and more frequently untreated (39.3%) (4). Patients with PDN experience reduced mobility, physical activity, and enjoyment of life; fatigue; limitations in social activity; diabetic foot infections; sleep impairment; anxiety; and depression (5,6). It is reported that increased age, increased duration of diabetes, and poorer glycemic control increases the risk of PDN (7).

The medications commonly used in PDN like antidepressants, anticonvulsants, opioids, and non-steroidal anti-inflammatory drugs (NSAIDs) are moderately effective and poorly tolerated (8). Anticonvulsants and antidepressants have been the mainstay of treatment in patients with PDN (9). Even though placebo controlled clinical trials of these drugs have shown them to be more effective, there exists a paucity of head-to-head comparisons between these drugs and their combinations. Systematic reviews were conducted earlier for the trials comparing the treatments used in PDN, but they have not attempted to rank the efficacy and safety of those treatments.

Network meta-analysis is a meta-analysis in which multiple treatments are compared using direct comparisons of treatments within randomized clinical trials (RCTs) and indirect comparisons across RCTs based on a common comparator (10). We did a network meta-analysis and benefit-risk analysis of RCTs comparing the anticonvulsants and antidepressants recommended by the American Academy of Neurology (11), with placebo or one another in management of PDN, to provide a comparative evaluation and to rank these drugs based on their efficacy and safety.

Methods

Search Strategy

We identified the studies (English) relevant to our network meta-analysis by performing a comprehensive search in databases like PubMed, Cochrane, and EMBASE, published between January 1980 and August 2012. Additional reports were identified from the reference lists of retrieved studies and systematic reviews. Only the published data were sought.

The key words used in the search were amitriptyline, duloxetine, gabapentin, pregabalin, valproate, valproic acid, venlafaxine, pain, and diabetic neuropathy using the filter of Clinical trials (only in PubMed). We chose only these 6 drugs, 3 each from the class of antidepressants and anticonvulsants since these were recommended as per the guidelines framed by the American Academy of Neurology in the management of PDN in adults. The pharmacokinetic and pharmacodynamic properties of included drugs are depicted in Table 1 (12).

Eligibility Criteria

We have included RCTs evaluating the usefulness of treatments in adults with PDN. Both open labelled and blinded studies were included. The included RCTs were required to report the data of both efficacy and safety, comparing one treatment with another or placebo. The treatments involved the administration of oral anticonvulsants or antidepressants. Both fixed dose and flexible dose regimens were included. The patients in the included studies were both men and women aging 18 years and older with PDN. The quality of the included studies was assessed using the Cochrane risk of bias method. We excluded those studies which were case reports, clinical observations, and long-term safety studies. Studies were excluded that presented data published in another study, and studies in which the results of PDN patients could not be segregated from patients with other types of neuropathic pain. We also excluded the studies having a sample size of less than 10.

Data Extraction

Two reviewers independently assessed studies for eligibility and extracted the data. The disagreements were resolved through discussion with the third author. Information was extracted regarding the characteristics of studies (study design, study duration, number of patients, and treatment arms) and patients (age, duration of diabetes, duration of painful diabetic neuropathy), intervention details (dosing regimen), and outcome measures (efficacy and safety).

We sent 18 letters to authors for additional information on their published studies regarding methods of random sequence generation, allocation concealment, blinding of outcome assessment, and details of the outcome measures. Four of them replied.

Table 1. *Pharmacokinetic and Pharmacodynamic properties of included drugs.*

	Antidepressants			Antiepileptics		
	Duloxetine	**Venlafaxine**	**Amitriptyline**	**Pregabalin**	**Valproate**	**Gabapentin**
Class	SNRI	SNRI	TCA	Calcium channel α2 – δ ligands	Miscellaneous	Calcium channel α2 – δ ligands
Mechanism of action	Inhibits reuptake of norepinephrine and serotonin	Inhibits reuptake of norepinephrine and serotonin	Inhibits reuptake of norepinephrine and serotonin	Binds to an auxiliary subunit (α2 – δ protein) of voltage – gated calcium channels in the central nervous system and reduces the synaptic release of several neurotransmitters	Enhances GABA function by binding to the GABA – A complex or enhancing GABA synthesis or release	Binds to an auxiliary subunit (α2 – δ protein) of voltage – gated calcium channels in the central nervous system and reduces the synaptic release of several neurotransmitters
Dose range (mg per day)	30 – 120	37.5 – 225	10 – 150	150 – 600	500 – 1200*	100 – 3600
Pharmacokinetics						
Bioavailability	32 – 80%	45%	40 – 60%	≥ 90%	90%	Saturable absorption 60% for 900 mg to approximately 27% for 4800 mg
Volume of distribution (L/kg)	10 – 14	7.5	19	0.5	0.2	0.6 – 0.8
Time to reach steady state concentration (days)	3 – 5	≤3	3 – 8	1 – 2	2 – 4	2
Elimination half life (hours)	8 – 17	3 – 7	9 – 27	5 – 6.5	9 – 19	5 – 7
Metabolism	Hepatic, via CYP1A2 and CYP2D6; forms multiple metabolites (inactive)	Hepatic via CYP2D6 to active metabolite, O – desmethyl venlafaxine	Hepatic via CYP1A2, CYP2D6, CYP3A4 and CYP2C	Negligible	Hepatic via glucuronide conjugation (30% to 50% of administered dose) and 40% via mitochondrial beta – oxidation; other oxidative metabolic pathways occur to a lesser extent	Negligible
Route of elimination	Urine (~70%; < 1% of total dose as unchanged drug); faeces (~20%)	Urine (~87%; 5% of total dose as unchanged drug; 29% of total dose as unconjugated form	Urine (18% as unchanged drug); faeces (small amounts)	Urine (90% as unchanged drug; minor metabolites)	Urine (30% to 50% as glucuronide conjugate, < 3% as unchanged drug)	Proportional to renal function; urine (as unchanged drug)

SNRI, Serotonin and norepinephrine reuptake inhibitors; TCA, Tricyclic antidepressants; GABA, Gamma amino butyric acid
* Dose range of valproic acid was taken for the indication of diabetic painful neuropathy from the clinical trials

Outcome Measures

We defined ≥ 50% reduction in pain as the clinically relevant outcome measure for efficacy. We used a hierarchy of outcome measures for efficacy. The number of patients reporting at least 50% reduction in pain on a suitable ordinal scale "Very much improved," "much improved," or "moderately improved" on the Patient Global Impression of Change (PGIC) or Clinical Global Impression of Change (CGIC) scales or at least moderate pain relief on a suitable categorical scale (9,13).

Efficacy measures after the longest duration of

treatment were used. We selected the number of patient withdrawals due to AE as outcome measures for safety. It was defined as the number of patients with major harms that lead to withdrawal from the study.

Statistical Analysis

We combined the results of all the studies and estimated the relative effects in terms of odds ratio (OR) with 95% confidence intervals (CI). A difference between active treatment and placebo or another active treatment was assumed to be statistically significant when the lower limit of 95% CIs of the OR was > 1. Analysis was performed by the intention-to-treat principle. Multiple-treatment meta-analysis or network meta-analysis are often conducted in a Bayesian framework and estimated using Markov chain Monte Carlo methods, the approach which is recommended by the National Institute for Health and Clinical Excellence (NICE) Decision Support Unit technical support documents on evidence synthesis (14). We performed a random-effects network meta-analysis in ADDIS Version 1.14.1, the software that uses Bayesian Markov chain Monte Carlo methods. Consistency of the RCTs included in the network was checked by applying inconsistency and node-splitting models. The results were considered to show no significant inconsistency when 95% CIs of inconsistency factors included zero. A large P-value (>

0.05) for the comparison between direct and indirect effects in the node splitting analysis also indicates a lack of significant inconsistency. We estimated the ranking probability for each drug, i.e., the most efficacious or the best regimen, the second-best, the third-best, and so on, and presented the results graphically. The overall ranks were interpreted by surface under the cumulative ranking (SUCRA) technique (15). We also conducted a benefit–risk analysis by the Stochastic Multi-criteria Acceptability Analysis (SMAA) model (16) taking number of patients experiencing a 50% reduction in pain as criteria for benefit and number of patient withdrawals as criteria for risk.

Results

We had identified 3,810 titles and abstracts through literature search, excluded 3,773 titles and abstracts after initial screening, and assessed 37 full text articles for eligibility. We had finally included 21 studies published in English which compared 6 active treatments: amitriptyline, duloxetine, duloxetine/gabapentin combination gabapentin, pregabalin, and venlafaxine. Flow chart of selection process is shown in Fig. 1. RCTs evaluating valproate did not meet our eligibility criteria and hence valproate was excluded from our analysis. Seventeen trials were parallel studies and 4 trials were cross-over with wash-out in between treatment periods. Of the

Fig 1. *Flow chart of selection process.*
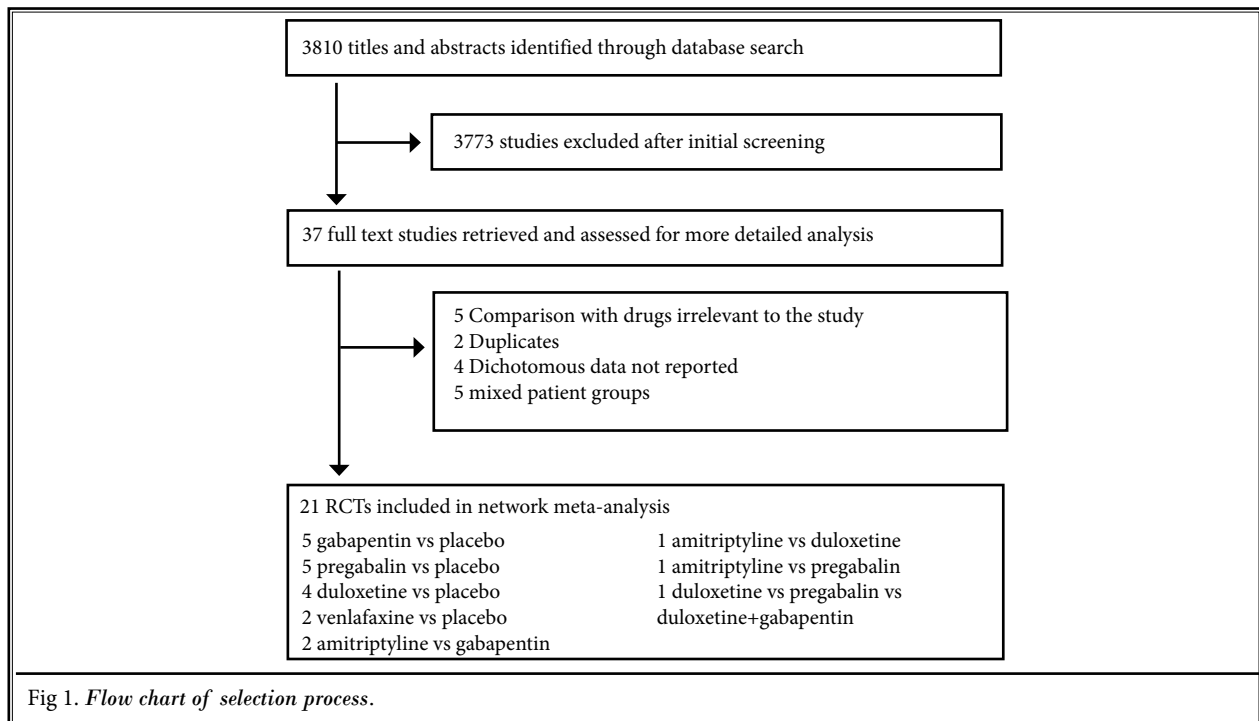
total studies, 16 studies were placebo controlled trials and one study didn't clearly mention randomization. Twenty-one studies (4,219 participants) contributed to the analysis of efficacy outcomes and 17 studies (4,022 participants) contributed to the analysis of safety outcomes. Most trials were 2 grouped studies, 5 trials were 3 grouped, and 2 trials were 4 grouped studies. Overall 4,219 patients were randomly assigned to one of the interventions including the placebo. The mean study duration of all the studies was 10.8 weeks with standard deviation of 3.2 weeks. The mean sample size was 82.7 patients per treatment group. Table 2 shows the characteristics of the included studies (20-40).

Most trials were rated to be of good methodological quality, despite most of the trials not mentioning the procedures for allocation concealment and blinding of outcome assessment.

Efficacy

Twenty-one RCTs compared 3 antidepressants, 2 anticonvulsants, and one combination. Eight trials studied gabapentin, 7 pregabalin, 6 duloxetine, 4 amitriptyline, 2 venlafaxine, and one trial studied duloxetine/gabapentin combination. Duloxetine, gabapentin, pregabalin, and venlafaxine have significantly superior relative effect compared to placebo with OR and 95% CIs of

Table 2. *Characteristics of included studies.*

Study	Investigational drugs	Daily dose (mg)	Group allocation	Blinding	Study size	Design	Study duration
Arezzo et al, 2008 (20)	**Pregabalin	600	R	DB	167	Parallel	13 weeks
Backonja et al, 1998 (21)	*Gabapentin	900 – 3600	R	DB	165	Parallel	8 weeks
Bansal et al, 2009 (22)	Amitriptyline Pregabalin	10 – 50 150 – 600	R	DB	102	Cross over, 2 week wash out	14 weeks
Dallocchio et al, 2000 (23)	Gabapentin Amitriptyline	1200 – 2400 30 – 90	R	OL	25	Parallel	12 weeks
Goldstein et al, 2005 (24)	*Duloxetine	20, 60, 120	R	DB	457	Parallel	12 weeks
Gorson et al, 1999 (25)	*Gabapentin	300 – 900	R	DB	80	Cross over, 3 week wash out	15 weeks
Kadiroglu et al, 2008 (26)	*Venlafaxine	75	R	U	60	Parallel	8 weeks
Kaur et al, 2011 (27)	Amitriptyline Duloxetine	20 – 60 10 – 50	R	DB	130	Cross over, 2 week wash out	14 weeks
Lesser et al, 2004 (28)	*Pregabalin	300, 600	R	DB	337	Parallel	5 weeks
Morella et al, 1999 (29)	Gabapentin Amitriptyline	900 – 1800 25 – 75	R	DB	50	Cross over, one week wash out	13 weeks
Raskin et al, 2005 (30)	*Duloxetine	60, 120	R	DB	348	Parallel	12 weeks
Rosenstock et al, 2004 (31)	*Pregabalin	300	R	DB	146	Parallel	8 weeks
Rowbotham et al, 2004 (32)	*Venlafaxine	150 – 225	R	DB	245	Parallel	6 weeks
Sandercock, 2012 (33)	*Gabapentin	3000, 1200 & 1800 (div)	R	DB	147	Parallel	4 weeks
Satoh et al, 2011 (34)	*Pregabalin	300, 600	R	DB	317	Parallel	14 weeks
Simpson, 2001 (35)	*Gabapentin	300 – 3600	R	DB	60	Parallel	8weeks
Perez and Sanchez, 2000 (36)	*Gabapentin	600 – 1200	U	DB	32	Parallel	3 months
Tanenberg et al, 2011 (37)	Dul/Gbp Pregabalin Duloxetine	60/900 – 3600 300 60	R	OL	407	Parallel	12 weeks
Tolle et al, 2008 (38)	*Pregabalin	150, 300, 600	R	DB	395	Parallel	12 weeks
Wernicke et al, 2006 (39)	*Duloxetine	-60, 120	R	DB	334	Parallel	12 weeks
Gao et al, 2010 (40)	*Duloxetine	60 – 120	R	DB	215	Parallel	12 weeks

* - indicates Placebo also used as investigational drug with daily does not indicated. R = Randomized, U = Unknown, DB = Double-blind, OL = Open label, Dul/Gbp = Duloxetine/Gabapentin combination

Table 3. Relative effects of efficacy (number of patients experiencing least 50% reduction in pain) and safety (number of patient withdrawals due to adverse events) of drugs.

Amitriptyline	0.46 (0.15, 1.34)	0.33 (0.08, 1.30)	0.14 (0.03, 0.53)	0.10 (0.03, 0.29)	0.31 (0.11, 0.87)	0.31 (0.04, 2.30)
0.92 (0.42, 2.00)	**Duloxetine**	0.72 (0.29, 1.90)	0.31 (0.10, 0.96)	0.21 (0.12, 0.36)	0.66 (0.36, 1.30)	0.67 (0.12, 4.37)
0.85 (0.24, 2.94)	0.93 (0.33, 2.67)	**Duloxetine + Gabapentin**	0.42 (0.10, 1.65)	0.30 (0.11, 0.79)	0.93 (0.36, 2.36)	0.92 (0.15, 7.02)
0.49 (0.21, 1.09)	0.53 (0.24, 1.07)	0.58 (0.16, 1.83)	**Gabapentin**	0.70 (0.25, 1.85)	2.18 (0.73, 6.68)	2.18 (0.34, 15.22)
1.95 (0.90, 4.26)	2.12 (1.29, 3.50)	2.27 (0.79, 6.60)	3.98 (2.29, 7.68)	**Placebo**	3.14 (1.87, 5.46)	3.12 (0.67, 18.57)
0.71 (0.30, 1.54)	0.76 (0.41, 1.40)	0.82 (0.28, 2.28)	1.44 (0.71, 3.06)	0.36 (0.22, 0.58)	**Pregabalin**	0.99 (0.19, 6.36)
0.44 (0.11, 1.45)	0.48 (0.15, 1.32)	0.51 (0.11, 1.96)	0.90 (0.28, 2.72)	0.23 (0.08, 0.55)	0.63 (0.19, 1.74)	**Venlafaxine**

Note: The numbers in the cell represent the odds ratio (95% credibility interval) of the column defining treatment relative to the row defining treatment
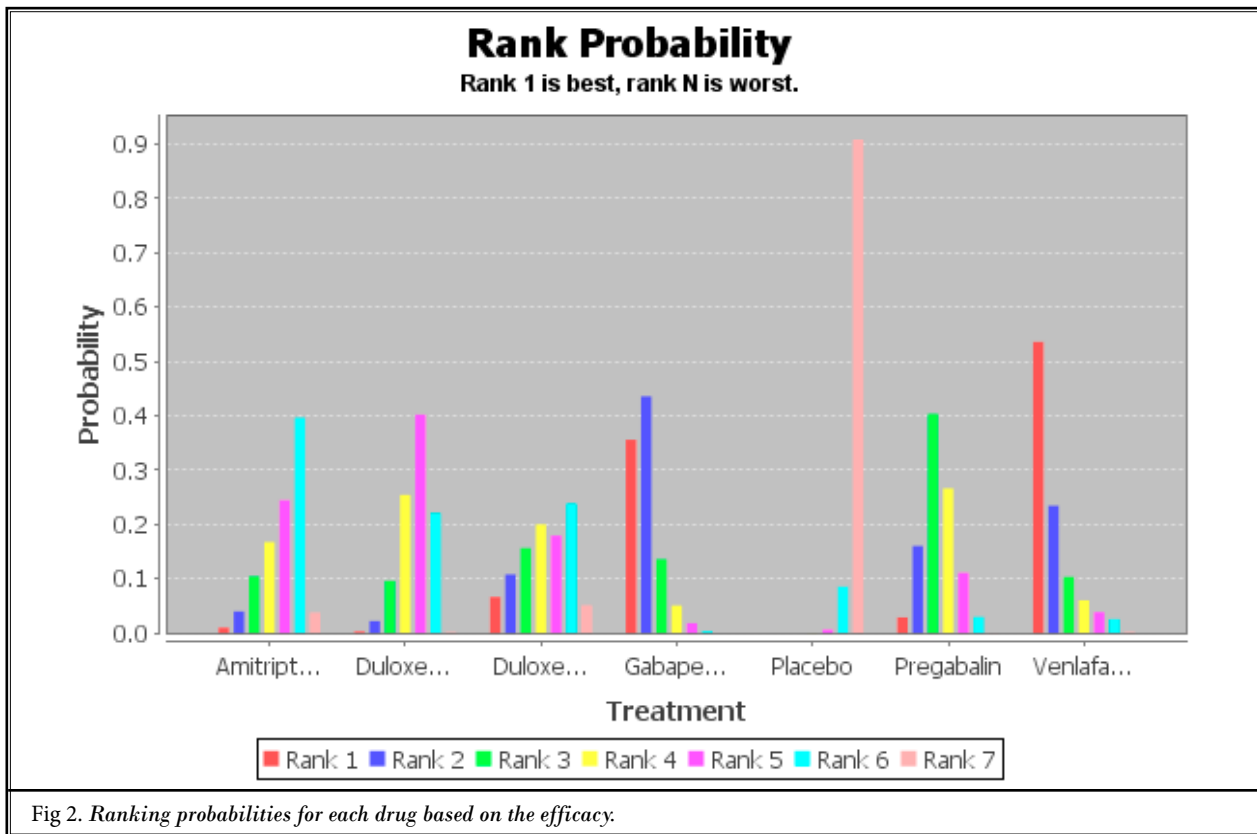☐ Efficacy (OR with 95% CrI)   ☐ Safety (OR with 95% CrI)

Fig 2. *Ranking probabilities for each drug based on the efficacy.*

2.12 (1.29, 3.5), 3.98 (2.29, 7.68), 2.78 (1.72, 4.62), and 4.43 (1.81, 12.93), respectively, as shown in Table 3. No significant difference in the relative effect was found between the active comparators. Venlafaxine (OR: 1.59, 95% CI: 0.57, 5.2) and gabapentin (OR: 1.44, 95% CI: 0.71, 3.06) were shown to be more efficacious than pregabalin, though it was not statistically significant. Gabapentin was shown to be the most efficacious treatment followed by venlafaxine, pregabalin, duloxetine/gabapentin, duloxetine, amitriptyline, and placebo. The ranking was given according to the ranking probabilities shown in the Fig. 2.

The results were shown to be consistent from the inconsistency model analysis and node-splitting analysis. Inconsistency factors measured as median (95% CI) for the loops amitriptyline, duloxetine, pregabalin was -0.03 (-1.33, 0.91), amitriptyline, duloxetine, gabapentin, placebo, pregabalin was 0.01 (-1.09, 1.18), and duloxetine, placebo, pregabalin was 0.07 (-0.63, 1.1).

Safety

We considered the number of patient withdrawals due to AE as outcome for safety. Seventeen RCTs compared 3 antidepressants, 2 anticonvulsants, and one combination. Seven trials studied pregabalin, 6 duloxetine, 4 gabapentin, 3 amitriptyline, one venlafaxine, and one trial studied duloxetine/gabapentin combination. The number of patient withdrawals due to AE was significantly higher for amitriptyline, duloxetine, duloxetine/gabapentin, and pregabalin compared to placebo with OR (CI) of 10.24 (3.49, 31.19), 4.69 (2.74, 8.17), 3.38 (1.27, 9.39), and 3.14 (1.87, 5.46), respectively, as shown in Table 3. In the active treatment comparisons, amitriptyline (OR: 7.03, 95% CI: 1.87, 29.05) and duloxetine (OR: 3.26, 95% CI: 1.04, 9.97) caused significantly more withdrawals due to AE than gabapentin. Amitriptyline caused most patient withdrawals due to AE followed by duloxetine, duloxetine/gabapentin combination, ven-

lafaxine, pregabalin, gabapentin, and placebo based on ranking probabilities shown in Fig. 3. The results were consistent with inconsistency factors for loops amitriptyline, duloxetine, pregabalin; and amitriptyline, duloxetine, gabapentin, placebo, pregabalin; and duloxetine, placebo, pregabalin being 0.03 (-1.2, 1.42), -0.1 (-2.15, 1.17), and 0.21 (-0.52, 1.46), respectively.

Benefit-risk Analysis

We conducted a benefit-risk analysis taking the number of patients experiencing a 50% reduction in pain as criteria for benefit and number of patient withdrawals due to AE as criteria for risk. Thus, 21 studies contributed to benefit and 17 studies contributed to risk criteria. The log-odds ratio, or mean difference, with placebo as the common comparator for amitriptyline, duloxetine, duloxetine/gabapentin, gabapentin, pregabalin, and venlafaxine was respectively 0.67 ± 0.39, 0.75 ± 0.25, 0.83 ± 0.53, 1.39 ± 0.30, 1.02 ± 0.25, 1.51 ± 0.50 for benefit and 2.32 ± 0.56, 1.55 ± 0.29, 1.22 ± 0.51, 0.34 ± 0.51, 1.15 ± 0.27, and 1.12 ± 0.83 for risk. The most favorable balance between benefit and risk was shown for gabapentin followed by venlafaxine, pregabalin, duloxetine/gabapentin combination, placebo, duloxetine, and amitriptyline. Ranking probabilities for each drug based on the benefit-risk balance is shown in Fig. 4.
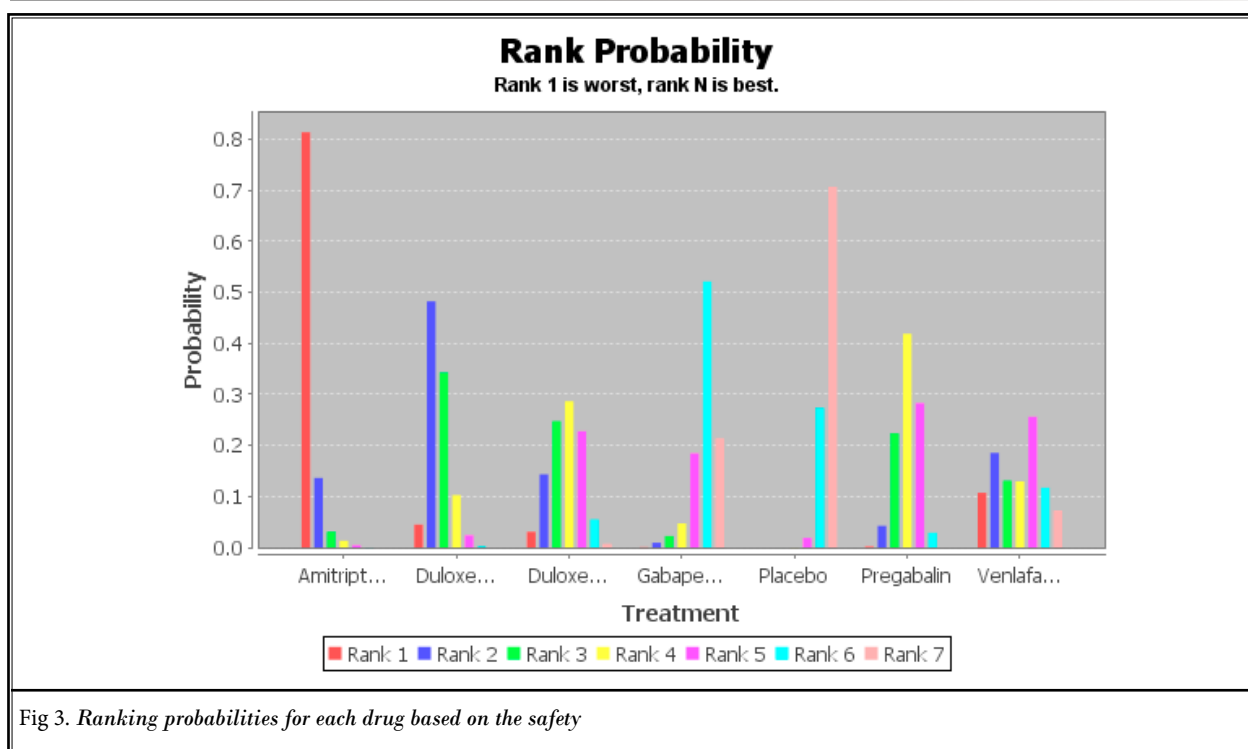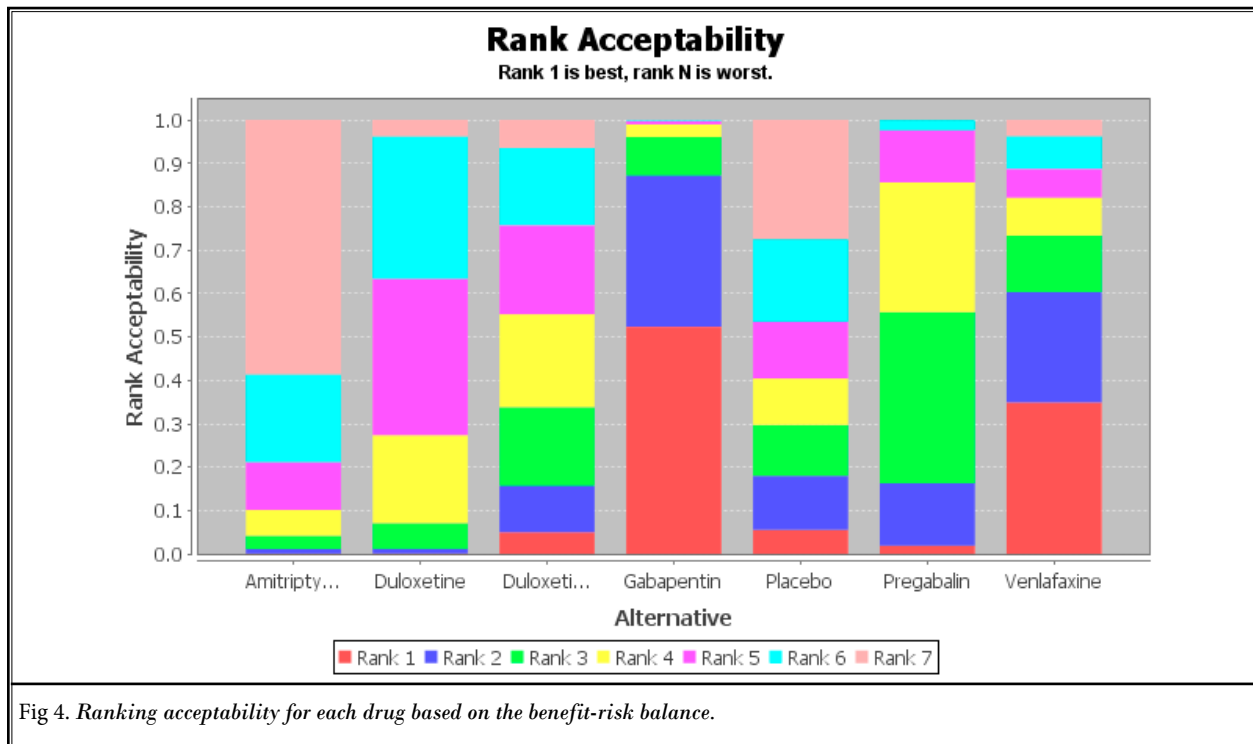

Fig 3. *Ranking probabilities for each drug based on the safety*

Fig 4. *Ranking acceptability for each drug based on the benefit-risk balance.*

DISCUSSION

We conducted a network meta-analysis for the comparison of efficacy and safety of the first line antidepressants and anticonvulsants used in the treatment of PDN. This analysis makes it possible the indirect comparison of active treatments where direct head to head comparisons were lacking. We aimed to include 6 treatments, 3 each from the class of antidepressants and anticonvulsants: amitriptyline, duloxetine, gabapentin, pregabalin, valproate, and venlafaxine, which are considered to have scientifically sound and clinically relevant evidence as per the guidelines framed by the American Academy of Neurology. But we could not include valproate in our analysis owing to the lack of studies reporting the dichotomous efficacy and safety outcomes. One study reported the dichotomous outcome for efficacy, but only in the valproate arm and not in the placebo arm, leading to exclusion of that study.

It was found that many clinical trials fail to predict outcome because they often include a small sample size. In a study conducted by Moore et al (17), it was shown that only large trials could possibly determine efficacy of a treatment. In such cases it may be imperative to pool up the individual studies and generate the sufficient sample size to determine the usefulness of a

specific drug. Conventional meta-analyses are limited by their ability to access only the evidence from direct comparisons between 2 treatments. Network meta-analysis expands the scope of a conventional pair-wise meta-analysis by simultaneously analyzing both direct and indirect comparisons of multiple interventions.

PDN is a chronic disease and the effects of treatments on the progression of disease need to be considered. The treatment period of the studies included in our analysis was less than 4 months. Thus, the efficacy and the safety of these treatments over a longer period of time could not be evaluated. We have excluded the long-term safety studies of the treatments from our analysis because they report only the safety outcomes and possible inclusion of such studies was thought to induce inconsistency and affect the overall results of the network meta-analysis. In this study, we have included 50% reduction in pain as the primary outcome for efficacy since it is considered to be a gold standard in the evaluation of pain relief. However, in a trial conducted by Kadiroglu et al, the authors have reported 60% reduction in pain, which we considered to be similar to 50% reduction in pain and included in the analysis. AE reported in the studies were diverse because the drugs belong to different classes. We did not investigate the

specific side effects; however, we found the incidence of cardinal AE, namely peripheral edema and euphoria, in patients on pregabalin in ranges of (3.9% to 36.6%) and (3.7% to 6.2%), respectively. While performing the benefit-risk analysis, we could not assign the AE to risk since nausea was the only common AE among all the drugs. Nausea being a common AE for any drug, we could not rely on it as a criteria for risk. Hence, we chose the number of patient withdrawals due to AE as the criteria for risk.

The results of our study was found to be consistent with the study conducted by Boyle et al (18), which showed no significant difference between amitriptyline, duloxetine, and pregabalin. Another trial conducted by Devi et al (19) comparing gabapentin, duloxetine, and pregabalin showed no significant difference between the treatments with pregabalin demonstrating a superior onset of pain reduction. In our analysis, gabapentin was shown to be the most efficacious drug followed by venlafaxine among the treatments analyzed. This might be due to the lack of sufficient number of studies (only 2 studies comparing venlafaxine were included in the analysis) or due to the assumption made by the authors in the study by Kadiroglu et al (26). We could not include any trials comparing amitriptyline with placebo in our study since the 2 trials (18,19) comparing them did not report the dichotomous data in one of the treatment arms. We have also excluded 5 trials comparing pregabalin and placebo since they included mixed patient population, i.e., patients with both PDN and post herpetic neuralgia.

The results from our analysis emphasize the need for conducting longer duration trials and studies comparing the active treatments. It is proposed to use common pain measurement scales for evaluation of pain relief and also to include the dichotomous data in the trials. Even though treatment guidelines for the management of PDN are available, it is suggested that treatment should be given by the physician, taking the patient's response into consideration.

Conclusion

The treatments included in the analysis were shown to be superior to placebo in relieving pain, but no significant superiority was shown among the active treatments. Gabapentin demonstrated the best efficacy and amitriptyline showed the least safety among the treatments included. Gabapentin was found to have the most favorable balance between benefit and risk.

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