Systematic Review and Meta-analysis of the Efficacy of Oral Medications Compared with Placebo Treatment in the Management of Postherpetic Neuralgia

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Aims: To conduct a systematic review to determine the efficacy of oral medications for the management of postherpetic neuralgia (PHN). **Methods:** Three electronic databases were searched: Cochrane Library (up to 7 July 2015), MEDLINE via PubMed (from 1950 to 7 July 2015), and Web of Science (1864 to 7 July 2015). Studies were limited to double-blind, placebo-controlled, randomized controlled trials on oral medications used to treat PHN. Risk of bias was independently assessed in duplicate. **Results:** A total of 256 abstracts were screened by two independent reviewers and 26 full-text articles were assessed for eligibility. A total of 11 relevant articles were selected for inclusion. These 11 articles were included in a qualitative synthesis and 8 were included in a meta-analysis; however, all the included studies had a high or unclear risk of bias and the interventions were heterogenous. In a subgroup analysis of five studies, anticonvulsants (gabapentin, pregabalin, and divalproex sodium) were found to improve short-term pain intensity (standardized mean difference [SMD] = −0.484, 95% confidence interval [CI] = −0.622 to −0.346, $P < .001$). In a second subgroup analysis of five studies, it was found that patients taking anticonvulsants were 2.5 times as likely to have a 50% or more reduction in pain after treatment than patients taking placebo. **Conclusion:** This review has provided favorable but low-quality evidence to support the use of anticonvulsants for PHN. Although statistically significant effects were observed for posttreatment pain and the percent of responders, the number of studies in each subgroup analysis for anticonvulsants was small and the included studies had high or unclear risk of bias. Further high-quality methodologic studies are needed to explore the effects of orally administered anticonvulsants for PHN.
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Keywords: *anticonvulsants, antidepressants, herpes zoster, opioids, postherpetic neuralgia*

Postherpetic neuralgia (PHN) is a chronic, debilitating neuropathic pain disorder characterized by continuous burning pain in the affected dermatome. In the face, the ophthalmic division of the trigeminal nerve is the most commonly affected branch. The etiologic agent for PHN is the herpes zoster virus, which is also known as varicella zoster virus (VZV). VZV causes chicken pox or varicella in children and the virus remains latent in the ganglia until reactivation in late adulthood. Reactivation is characterized by the shingles rash and severe pain. The shingles rash eventually disappears and is followed by PHN. Typical factors related to the reactivation of the zoster virus include old age and a compromised immune system due to infections or malignancies.[1]

PHN by definition is persistent pain in the zoster-affected area for 6 months after resolution of the shingles rash.[2] Clinically, PHN can present as sharp stabbing pain, constant burning pain, or as allodynia. Other features include hypesthesia or anesthesia, hypalgesia, and paresthesia or dysesthesia.[2]

Drug therapies commonly used in PHN patients include anticonvulsants (eg, gabapentin, pregabalin, divalproex sodium, carbamazepine),[3] antidepressants (eg, tricyclic antidepressants [TCAs] such as

amitriptyline, nortriptyline),[4] opioids,[4] and tramadol.[4] These drug therapies might have an effect on the molecular changes that occur in the nerves which lead to a state of chronic pain. Some of these molecular changes happen at the peripheral tissue level while others occur at the level of the central nervous system. Neuronal changes include upregulation of sodium channels, neuronal hyperexcitability, increased glutamate receptors, decrease in GABAergic inhibition, and increased calcium influx. The widespread use of anticonvulsants as therapeutic drugs for neuropathic pain largely relates to their blockade of sodium channels.[3] Opioids provide some pain relief in neuropathic pain states by acting on opioid receptors. TCAs act by blocking norepinephrine and serotonin reuptake, blocking sodium and calcium ion channels, and interacting with adenosine and N-Methyl-D-aspartate (NMDA) receptors.[5] Tramadol has a mechanism similar to both opioids and TCAs; it is a centrally acting μ-opioid receptor agonist and at the peripheral level it inhibits serotonin and norepinephrine reuptake.[5]

Several recent placebo-controlled trials have tested the effect of oral medications commonly used in PHN patients with variable success. The differences between the experimental designs and measures used in these studies and their outcomes prompted this present study, which aimed to conduct a systematic review to determine the efficacy of oral medications for the management of PHN.

Materials and Methods

Inclusion and Exclusion Criteria

Types of Studies. Studies were limited to double-blind, placebo-controlled, randomized controlled trials (RCTs) assessing the effectiveness of oral medications in treating PHN. Studies on neuropathic pain that did not provide data separately for PHN patients were excluded. Articles not available in English and studies conducted in children/adolescents (< 18 years of age) or animals were also excluded.

Types of Participants. Inclusion criteria for patients were adults 18 years or older and with persistent pain in the zoster-affected area after the herpes zoster lesions had resolved with no pathologic, laboratory, or radiographic findings and no other diagnosis associated with the pain. Patients in the study had to have PHN for ≥ 3 months.

Types of Interventions. Interventions were oral medications including anticonvulsants (gabapentin, pregabalin, divalproex sodium), opioids, tramadol, and TCAs.

Primary Outcome. The primary outcome was posttreatment pain intensity (PPI) measured using a visual analog scale (VAS) or a numeric rating scale (NRS). A secondary outcome was the percent of patients with 50% or more reduction in pain.

Search Strategies

Search strategies based on a combination of controlled vocabulary (MeSH) and free text were developed for MEDLINE and then revised for each database. Language was restricted to English. The references of all eligible trials and reviews were checked for additional studies.

Electronic Searches

The following electronic databases were searched.

- MEDLINE via PubMed was searched (1950 to 8 April 2014). The MEDLINE search strategy was: "postherpetic neuralgia"[All Fields] AND (("therapy"[Subheading] OR "therapy"[All Fields] OR "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields]) OR ("pharmaceutical preparations"[MeSH Terms] OR ("pharmaceutical"[All Fields] AND "preparations"[All Fields]) OR "pharmaceutical preparations"[All Fields] OR "medication"[All Fields]) OR drug[All Fields] OR ("Intervention (Amstelveen)"[Journal] OR "intervention"[All Fields] OR "Interv Sch Clin"[Journal] OR "intervention"[All Fields])) AND (orofacial[All Fields] OR ("face"[MeSH Terms] OR "face"[All Fields] OR "facial"[All Fields]) OR ("mouth"[MeSH Terms] OR "mouth"[All Fields]) OR trigeminal[All Fields]) AND "humans"[MeSH Terms] AND English[lang]).
- The Web of Science was searched (1864 to 8 April 2014) with the following strategy: TOPIC: "postherpetic neuralgia" AND (therapy or medication or drug* or intervention) AND (orofacial OR facial OR mouth OR trigeminal).
- The Cochrane Library was searched (to 8 April 2014) as follows: "postherpetic neuralgia" AND (therapy or medication or drug* or intervention) AND (orofacial OR facial OR mouth OR trigeminal).

Data Collection and Analysis

Selection of Studies. The titles and abstracts of articles resulting from the search strategy were screened independently and in duplicate by two reviewers. If the trial met the inclusion criteria based on the abstract or if a clear decision could not be made, the full articles were then reviewed by both the reviewers (S.S. and L.T.). Disagreements were resolved by a third reviewer (R.E.). Reasons for exclusion were recorded in a table.

Qualitative Synthesis. Data including the characteristics of trial participants, interventions, control groups (if appropriate), and outcomes were

independently extracted by the two reviewers. Characteristics of included studies are presented in Table 1.

Assessment of Risk of Bias. Risk of bias assessment was undertaken as part of the data extraction process by two reviewers following the approach described in the Cochrane Handbook for Systematic Reviews of Interventions.[6] Any disagreements were resolved by the third reviewer. Risk of bias was assessed in six domains: *(1)* random sequence generation (selection bias); *(2)* allocation concealment (selection bias); *(3)* blinding of participants/outcome assessors/data analyst; *(4)* incomplete outcome data (attrition bias); *(5)* selective reporting; and *(6)* other bias (publication bias, funding, unbalance of groups at baseline). A summary of risk of bias assessment for each study is shown in Table 2.

Measures of Treatment Effect. For continuous outcomes of PPI, some authors used a 0–10 VAS while others used a 0–100 VAS or a 0–10 NRS. To measure the treatment effect by using different scales, standardized mean difference (SMD) with 95% confidence intervals (CI) was used. Risk Ratio (RR) with 95% confidence intervals (CI) was calculated to analyze the secondary outcome (the percent of patients with ≥ 50% reduction in pain). All analyses were performed by using Comprehensive Meta-Analysis Software version 2 (Biostat, Englewood).

Heterogeneity of the Outcomes. A few of the outcomes reported in some of the studies could not be included in any meta-analysis due to the heterogeneity of the outcomes. One study reported the percent of patients with ≥ 30% reduction in pain[7] while others reported patients with ≥ 50% reduction in pain.[7,8,15,16,19] Raja et al[9] provided the average percent of pain relief (0 to 100%) instead of the number of patients with a reduction in pain of 50% or more and this outcome could not be included in the meta-analysis. Watson et al[10] used a categorical scale for pain (no pain, mild, moderate, or severe) and another scale for pain relief (excellent, good, poor, no change), while Kishore-Kumar et al[11] used a different categorical scale for pain relief (complete, a lot, slight, none, or pain worsen). Unfortunately, these studies could not be compared with the continuous outcomes most commonly used to report posttreatment pain (VAS or NRS; Table 3) or with the percent of patients with 50% or more reduction in pain.

Statistical Analyses

Only the available data in the published articles were included in this review. Standard errors for the means (SEM) in three studies were converted to standard deviations (SD) using the formula: $SD = SEM \times \sqrt{n}$, with n being the sample size. Studies were included in a meta-analysis only if the RCTs reported similar outcome measures for similar interventions. Cochran's Q test[12] and the I^2 statistic[13] were used to test for statistical heterogeneity. If heterogeneity was found (Q P value < .05) or less than three studies were available for analysis, estimates of effect were combined using a random-effects model; otherwise, the fixed-effects model was applied. Two meta-analyses were conducted, one for each outcome: PPI (measured on a VAS or NRS) and the percent of patients with ≥ 50% reduction in pain. SMD with 95% CI were reported for PPI due to the fact that two types of scales were included (VAS and NRS). RR was reported in order to compare the percent of patients with ≥ 50% decrease in pain between the treatment and the placebo groups.

Subgroup Analysis and Investigation of Heterogeneity

Subgroup analyses for anticonvulsants (n = 5), TCAs (n = 1), opioids (n = 1), and tramadol (n = 1) were calculated and shown for visual purposes despite the small sample size. A sensitivity analysis with only studies that had a low risk of bias could not be conducted due to the small sample size (n = 1).

Levels of Evidence and Summary of the Review Findings

Quality of evidence assessment and summary of the findings were conducted with the software GRADEprofiler (GRADEpro), following the Cochrane Collaboration and GRADE Working Group recommendations.

Results

The initial search strategy yielded 273 studies plus 15 additional records identified through a hand search of reviews and included studies. After duplicates were removed, the remaining 257 abstracts were assessed by two reviewers for inclusion. Based on the abstracts and titles, 26 relevant manuscripts were selected for full review. Of these 26 manuscripts, a total of 11 were considered relevant for inclusion. A PRISMA flowchart shows a summary of the results (Fig 1). The primary reasons for exclusion of the 231 studies based on the abstracts were: it was based on an animal study (n = 5); review/systematic review/protocol for review (n = 108); guidelines or recommendations (n = 13); case reports or case series (n = 13); different outcome (n = 17); a conference abstract that was not available (n = 1); did not report on oral medications (n = 19); the participants were not PHN patients or data were not provided for PHN patients (n = 42); or was not a randomized placebo-controlled trial (n = 13).

Table 1 Characteristics of Included Studies

Study	Year Country Sample size[a] Gender (%)	Age of the patients (y)	Treatment group, dose (n = number of patients in that group)
Boureau et al[18]	2003 France n = 127 M (27.6) F (72.4)	35–85 Mean age treated: 65.7 Mean age placebo: 67.9	Tramadol, 100 mg/day to 400 mg/day (n = 64, randomized) Placebo (n = 63, randomized)
Kishore-Kumar et al[11]	1990 USA n = 26 M (65.4) F (34.6)	38–79 Median = 62	Desipramine, average dose 167 mg/day (n = 26) Benztropine, "active placebo" (n = 26)
Kochar et al[19]	2005 India n = 40 M (55.0) F (45.0)	Mean age treated: 56.4 Mean age placebo: 58.0	Divalproex sodium, 1,000 mg/day × 8 wk (n = 22) Placebo (n = 18)
Max et al[17]	1988 USA n = 62 M (53.4) F (46.6)	25–86 Mean = 72	Placebo + amitriptyline, 12.5–150 mg/d (n = 10) Placebo + lorazepam, 12.5 to 150 mg/d (n = 11) Amitriptyline (12.5 to 150 mg/d) + lorazepam (0.5 to 6 mg/d) (n = 10) Lorazepam (0.5 to 6 mg/d) + amitriptyline (12.5 to 150 mg/d) (n = 10)
Raja et al[9]	2002 USA n = 76 M (44.7) F (55.3)	32–90 Mean = 71	Completed all 3 treatments (n = 44) Opioid, max dose MS Contin 240 mg TCA, max dose nortriptyline 160 mg Placebo
Rice and Maton[8]	2001 UK, Republic of Ireland n = 334 M (41.3) F (58.7)	22–95 Mean = 75	Gabapentin, 1,800 mg (n = 93) Gabapentin, 2,400 mg (n = 85) Placebo (n = 94)
Rowbotham et al[14]	1998 USA n = 229 M (52.4) F (47.6)	39–90 Mean = 73.5	Gabapentin, flexible dose, maximum dose 3,600 mg/d (n = 89) Placebo (n = 95)
Sabatowski et al[15]	2004 Europe, Australia n = 238 M (45.0) F (55.0)	32–96 Mean = 71.2	Pregabalin, 150 mg/d (n = 81) Pregabalin, 300 mg/d (n = 76) Placebo (n = 81)
Stacey et al[7]	2008 USA n = 269 M (55.8) F (44.2)	40–93 Mean = 67.3	Pregabalin, flexible dose, average dose 396 g/d (n = 91) Pregabalin, flexible dose, 295 g/day (n = 88) Placebo (n = 90)
Van Seventer et al[16]	2006 Netherlands n = 368 M (45.7) F (54.3)	18–92 Mean = 70.7	Pregabalin, 300/600 mg/d (n = 90), 300 mg/d (n = 98), 150 mg/d (n = 87) Placebo (n = 93)
Watson et al[10]	1982 Canada n = 24 M (66.7) F (33.3)	49–81 Mean = 66	Amitriptyline, flexible dose, 25–138 mg/d (n = 24) Placebo (n = 24)

[a]Number of patients was randomized. PHN = postherpetic neuralgia; VAS = visual analog scale; NRS = numeric rating scale; RCT = randomized controlled trial; TCA = tricyclic antidepressants.

Included Studies

The 11 articles fitting the inclusion criteria were RCTs with oral medications for patients with PHN. The included studies contained trials with groups receiving gabapentin,[8,14] pregabalin,[7,15,16] TCAs,[9,10,11,17] tramadol,[18] divalproex sodium,[19] and opioids[9] compared with groups receiving placebo. The mean age of the patients in the included studies varied from 56 to

Inclusion criteria	Study design	Risk of bias
(1) PHN for at least 3 mo and maximum of 1 y; *(2)* 18–85 y of age; *(3)* At least 40 mm on a standard 100-mm VAS.	RCT	Low
(1) Daily pain persisting at least 3 mo after a segmental herpes zoster eruption; and *(2)* normal cognitive and communicative ability, as judged by performance in completing a pain diary, paper-and-pencil psychologic tests, and telephone conversations.	Crossover	Unclear
Adult patients having persistent pain for 46 mo after the onset of herpes zoster rash with at least 40 mm on a 100-mm VAS and at least 4 on an 11-point Likert scale.	RCT	Unclear
(1) Daily pain persisting at least 3 mo after a segmental herpes zoster eruption; and *(2)* normal cognitive and communicative ability, as judged by performance in completing a pain diary, paper-and-pencil psychological tests, and telephone conversations.	Crossover	Unclear
(1) Patients with PHN; *(2)* age > 18 y; *(3)* pain persisting for ≥ 3 mo after the resolution of the cutaneous lesions; and *(4)* typical pain intensity of ≥ 4 (0 to 10 NRS) during the previous wk.	Crossover	Unclear
(1) Men and women with PHN aged at least 18 y, of any race; *(2)* Women were required to be nonpregnant, nonlactating, postmenopausal, or surgically sterilized; *(3)* Pain had to have been present for more than 3 mo after the healing of the acute herpes zoster skin rash with an average pain score of ≥ 4 on an 11-point Likert scale.	RCT	Unclear
(1) ≥ 18 y; *(2)* pain present for more than 3 mo after healing of herpes zoster skin rash; *(3)* a pain intensity score of at least 40 mm on the 100-mm VAS at screening and at randomization; *(4)* average daily diary pain score of at least 4 (on a scale of 0–10 NRS) during the baseline wk; and *(5)* discontinuance of other drugs beginning at least 2 wk prior to screening.	RCT	Unclear
(1) Pain present for more than 6 mo after healing of the herpes zoster rash; *(2)* Men or women ≥ 18 y; *(3)* Female patients were required to be nonpregnant, nonlactating, and either postmenopausal, surgically sterilized, or using an appropriate method of contraception; *(4)* At least four daily pain diaries during the 7-d baseline phase with an average daily pain score of ≥ 4; *(5)* Score ≥ 40 mm on the 100-mm VAS at the baseline and randomization visits.	RCT	High
(1) Pain persisting at least 3 mo after the healing of herpes zoster skin rash; *(2)* Pain score of ≥ 40 mm on a 100-mm VAS; *(3)* Creatinine clearance of at least 60 ml/min.	RCT	High
(1) ≥ 18 y; *(2)* Had pain more than 3 mo after healing of herpes zoster lesions; *(3)* A pain of ≥ 40 mm on a 100-mm VAS; *(4)* Had at least four daily pain diary entries of score 4 or greater.	RCT	High
(1) Had typical severe PHN for at least 3 mo.	Crossover	High

75 years old. When documented, the majority of the patients in the studies were Caucasian. Six studies excluded patients with any serious or unstable condition. Four studies excluded pregnant or breastfeeding women. Studies ranged from 4 to 13 weeks in duration (Table 1).

Table 2 Summary of Risk of Bias for Eligible Studies Based on Risk of Bias Tool[6]

Study	Random sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Selective reporting	Other potential bias	Overall bias
Boureau et al[18]	–	–	–	–	–	–	–
Kochar et al[19]	?	–	–	–	–	–	?
Kishore-Kumar et al[11]	?	?	?	–	–	–	?
Max et al[17]	?	?	?	–	–	–	?
Raja et al[9]	–	–	?	–	–	–	?
Rice and Maton[8]	–	–	?	–	–	–	?
Rowbotham et al[14]	–	–	?	–	–	–	?
Sabatowski et al[15]	–	–	–	–	–	+	+
Stacey et al[7]	?	?	+	–	–	+	+
Van Seventer et al[16]	?	?	?	–	+	+	+
Watson et al[10]	?	?	?	+	+	-	+

+ = high risk of bias; – = low risk of bias; ? = unclear risk of bias.

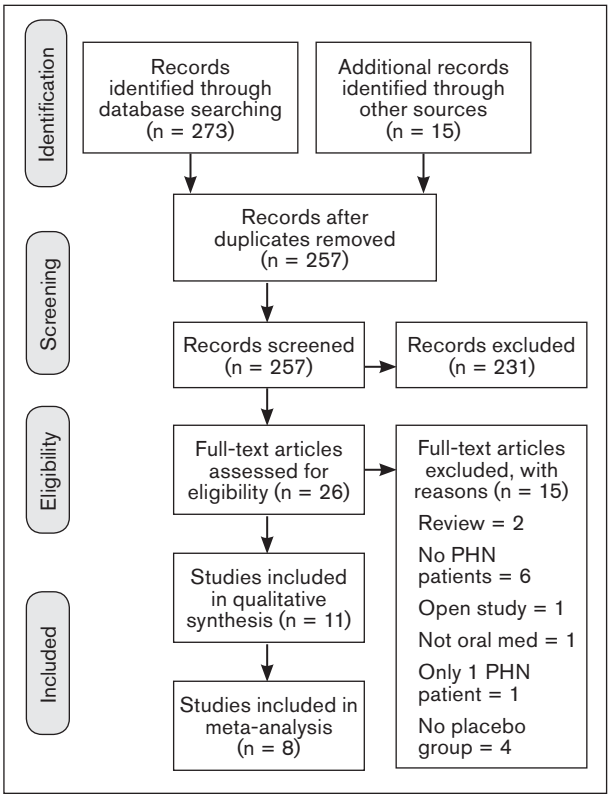


Fig 1 PRISMA flow diagram describing the number of studies identified, screened, and included in this systematic review.

Excluded Studies

After the full-text review, 15 articles were excluded: 2 were reviews, 6 did not provide data for PHN patients, 1 was an open study, 1 did not use an oral medication, 1 had only one patient, and 4 included no placebo group.

Risk of Bias in Included Studies

Risk of bias results for individual studies are shown in Fig 2 and Table 2.

Random Sequence Generation. The sequence generation method was described well in five studies[8,9,14,15,18] at low risk and unclear in the remaining six articles.[7,10,11,16,17,19]

Allocation Concealment. The allocation concealment strategy was reported in six studies at low risk[8,9,14,15,18,19] and was not reported in the other five articles, which were deemed at unclear risk.[7,10,11,16,17]

Blinding. Since the blinding strategy was not explained in 7 of the 11 studies, an unclear risk was assigned.[8–11,14,16,17] In one study,[7] the investigators clearly knew the group allocation for each patient, resulting in high risk of bias. Blinding strategies of three studies were described well and were considered at low risk for this domain.[15,18,19]

Incomplete Outcome Data. Watson et al[10] was the only article with incomplete outcome data, resulting in high risk. There were 24 participants in the study; however, at follow-up, the article only discussed 22 patients. The two dropout patients were not discussed.

Selective Reporting. Two articles had selective reporting and were at high risk of bias.[10,16]

Other Potential Sources of Bias. Three articles had high risk of potential sources of bias.[7,15,16] The sponsoring pharmaceutical company of the study by Sabatowski et al[15] managed the study, performed the biostatistical analysis, and provided editorial assistance for the preparation of the paper. The studies by Stacey et al[7] and Van Seventer et al[16] were also funded by this sponsor.

Overall Assessment of Risk of Bias

Of the 11 RCTs included in this systematic review, the overall assessment of risk of bias showed 1 study at low risk,[18] 4 at high risk,[7,10,15,16] and 6 studies at unclear overall risk.[8,9,11,14,17,19]

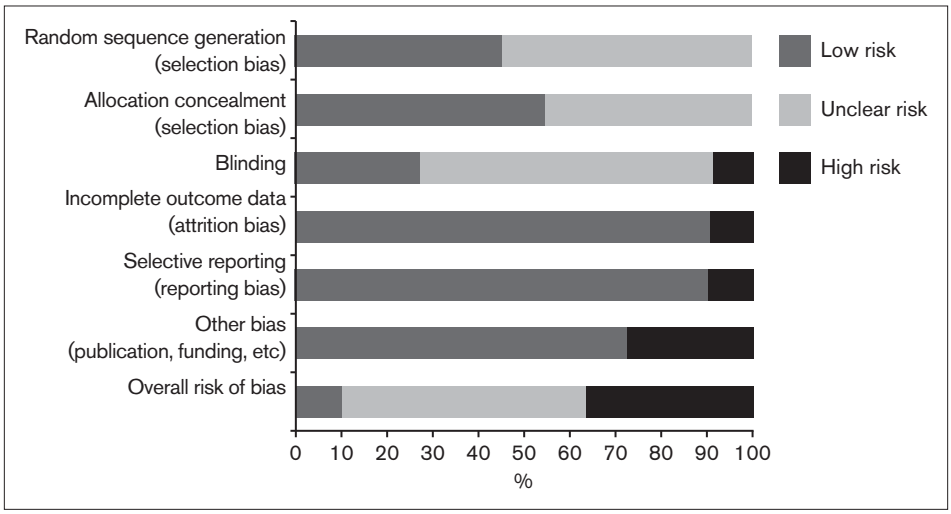


Fig 2 Graph of risk of bias for eligible studies based on Risk of Bias tool.[6]

Table 3 Posttreatment Pain Intensity in Treatment and Placebo Groups

Study	Drug (daily dose)	Pain scale; treatment duration	Treatment group (Mean ± SD)	Sample size in treated group	Placebo group (Mean ± SD)	Sample size in placebo group	*P* value
Boureau et al[18]	Tramadol	0–100 VAS; 43 d	24.6 ± 22.4	53	31.8 ± 25.3	55	–
Kochar et al[19]	Divalproex sodium (1,000 mg)	0–100 VAS; 8 wk	31.27 ± 139.73	22	54.94 ± 74.37	18	–
Raja et al[9]	TCAs	0–10 VAS; 8 wk	5.1 ± 2.3	44	6.0 ± 2.0	44	< .001
Raja et al[9]	Opioids	0–10 VAS; 8 wk	4.4 ± 2.4	44	6.0 ± 2.0	44	< .001
Rice and Maton[8]	Gabapentin (1,800 mg)[a]	0–10 VAS; 7 wk	4.3	115	5.3	111	.01
Rowbotham et al[14]	Gabapentin (flexible dose)	0–10 VAS; 8 wk	4.2 ± 2.3	113	6.0 ± 2.4	116	< .001
Sabatowski et al[15]	Pregabalin (150 mg)[b]	0–100 VAS; 8 wk	52.03 ± 22.9	80	62.05 ± 22.9	80	.006
Van Seventer et al[16]	Pregabalin (150 mg)[b]	0–10 NRS;13 wk	5.26 ± 2.24	87	6.14 ± 2.22	93	.0077

[a]Only data of the lowest dose of 1,800 mg of gabapentin were included in this meta-analysis, not the 2,400-mg data.
[b]Only data of the lowest dose of 150 mg of pregabalin were included in this meta-analysis, not the 300-mg or 600-mg data.
VAS = visual analog scale; NRS = numeric rating scale.

Effects of Interventions (Quantitative Analyses)

Primary Outcome

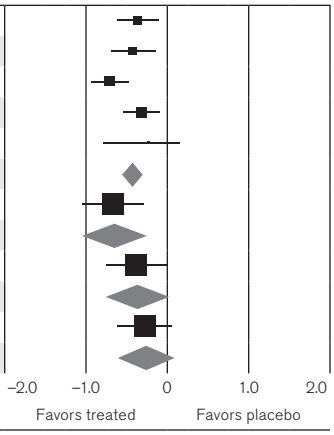
Seven studies reporting means and SD (or standard errors [SE], which were converted to SD) of posttreatment pain by using a VAS or NRS, as well as sample size for each group,[8,9,14–16,18,19] were included in a meta-analysis. The lowest available dosage reported by the authors was used when more than one dosage was reported; this corresponded to 150 mg of pregabalin for Van Seventer et al[16] and Sabatowski et al,[15] and 1,800 mg of gabapentin for Rice and Maton[8] (Table 3).

Due to the heterogeneity of the interventions, pooled results including all oral medications were not shown, but subgroup analysis for anticonvulsants (n = 5), opioids (n = 1), TCA (n = 1), and tramadol (n = 1) were conducted (Table 4).

Subgroup Analysis: Anticonvulsants. Five studies compared anticonvulsants (gabapentin, pregabalin, or divalproex sodium) with placebo.[8,14–16,19] No statistically significant heterogeneity was found among these five studies (Cochran's Q *P* value = .184; I^2 = 36%). Pooled results were very similar when the random-effects model or the fixed-effects model was used. Anticonvulsants using the smallest dose reported significantly improved pain compared with

Table 4 Statistical Analyses of Oral Medication vs Placebo in Reducing Posttreatment Pain Intensity with Subgroup Analyses for Anticonvulsants

		Statistics for each study				
Study name	Medication	SMD	Lower limit of 95% CI	Upper limit of 95% CI	*P* value	SMD and 95% CI
Van Seventer et al[16]	Anticonvulsants	−0.395	−0.690	−0.100	.009	
Sabatowski et al[15]	Anticonvulsants	−0.457	−0.771	−0.143	.004	
Rowbotham et al[14]	Anticonvulsants	−0.766	−1.034	−0.497	.000	
Rice and Maton[8]	Anticonvulsants	−0.346	−0.608	−0.083	.010	
Kochar et al[9]	Anticonvulsants	−0.249	−0.874	0.376	.435	
	Anticonvulsants (total)	**−0.484**	**−0.622**	**−0.346**	**.000**	
Raja et al[9]	Opioids	−0.724	−1.156	−0.293	.001	
	Opioids (total)	**−0.724**	**−1.156**	**−0.293**	**.001**	
Raja et al[9]	TCA	−0.418	−0.840	0.005	.053	
	TCA (total)	**−0.418**	**−0.840**	**0.005**	**.053**	
Boureau et al[18]	Tramadol	−0.301	−0.680	0.078	.120	
	Tramadol (total)	**−0.301**	**−0.680**	**0.078**	**.120**	



SMD = standardized mean difference; CI = confidence interval.

Table 5 Number and Percent of Patients Responding with ≥ 50% Reduction in Pain in Anticonvulsants and Placebo Groups

Study	Drug (daily dose)	Pain scale; treatment duration	Responders in treated group (n/total [%])	Responders in control group (n/total [%])	*P* value
Kochar et al[19]	Divalproex sodium 1,000 mg/day vs placebo	VAS 0–100; 8 wk	13/22 (59.1)	2/18 (11.1)	–
Rice and Maton[8]	Gabapentin 1,800 mg vs placebo[a]	VAS 0–10; 7 wk	37/115 (32.2)	16/111 (14.4)	.001
Sabatowski et al[15]	Pregabalin 150 mg vs placebo[b]	VAS 0–100; 8 wk	21/81 (25.9)	8/81 (9.9)	.006
Stacey et al[7]	Pregabalin 300 mg vs placebo[c]	VAS 0–10; 4 wk	35/88 (39.7)	17/90 (18.9)	.0001
Van Seventer et al[16]	Pregabalin 150 mg vs placebo[b]	NRS 0–10; 13 wk	23/87 (26.4)	7/93 (7.5)	.001

[a]Only data of the lowest dose of 1,800 mg of gabapentin were included in this meta-analysis, not the 2,400-mg data.
[b]Only data of the lowest dose of 150 mg of pregabalin were included in this meta-analysis, not the 300-mg or 600-mg data.
[c]Only data of the fixed dose of 300 mg of pregabalin were included in this meta-analysis, not the pregabalin flexible-dose data.
VAS = visual analog scale; NRS = numeric rating scale.

placebo (SMD = −0.484; 95% CI = −0.622 to −0.346; $P < .001$) (Table 4). Of these five studies, two articles had high risk of bias[15,16] and three had unclear risk.[8,14,19]

Slightly improved results were found when the highest dose was used for each study; this corresponded to 600 mg of pregabalin for Van Seventer et al,[16] 300 mg of pregabalin for Sabatowski et al,[15] and 2,400 mg of gabapentin for Rice and Maton.[8] Anticonvulsants significantly improved pain compared with placebo when the highest dose reported by the authors was used in the models (SMD = −0.601; 95% CI = −0.740 to −0.461; $P < .001$).

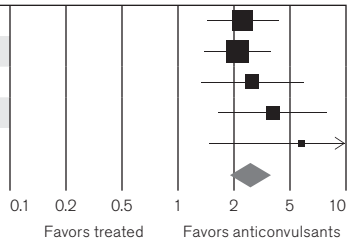
Secondary Outcome

In the meta-analysis of five studies that reported the percent of patients with a 50% or more reduction in posttreatment pain (Table 5), no significant heterogeneity was found (Cochran's Q P value = .647; I^2 = 0%). According to the fixed-effects model, anticonvulsants (gabapentin 1,800 mg[8]; pregabalin at 150 mg[15,16] or 300 mg[7]; divalproex sodium 1,000 mg[19]) significantly reduced pain by 50% or more compared with placebo when the smallest dose of the drug reported by the authors (RR = 2.506; 95% CI = 1.865 to 3.369; $P < .001$) was used. Patients in the treated group were 2.5 times as likely to have a 50% or more reduction in pain after treatment compared with the placebo group (Table 6). Of the five studies included in this subgroup analysis, three were at high risk[7,15,16] and two at unclear risk of bias.[8,19]

Improved results (RR = 2.901; 95% CI = 2.169 to 3.880; $P < .001$) were obtained by using the largest dose reported by the authors (2,400 mg of gabapentin,[8] and 600 mg of pregabalin[16]).

Table 6 Statistical Analyses of Anticonvulsants vs Placebo in Percent of Responders Reporting ≥ 50% Reduction in Pain

		Statistics for each study				
Study name	Medication	RR	Lower limit of 95% CI	Upper limit of 95% CI	*P* value	RR and 95% CI
Rice and Maton[8]	Gabapentin (1,800 mg)	2.286	1.342	3.893	.002	
Stacey et al[7]	Pregabalin (300 mg)	2.106	1.278	3.469	.003	
Sabatowski et al[15]	Pregabalin (150 mg)	2.616	1.232	5.556	.012	
Van Seventer et al[16]	Pregabalin (150 mg)	3.520	1.589	7.797	.002	
Kochar et al[19]	Divalproex sodium (1,000 mg)	5.324	1.376	20.596	.015	
		2.506	1.865	3.369	.000	



RR = risk ratio; CI = confidence interval.

Grades of Evidence

Quality of assessment, including grades of evidence, and a summary of findings are presented in Table 7 for five trials on the effects of anticonvulsants in treating PHN.

Discussion

This systematic review has shown that there is favorable but low-quality evidence to support the use of anticonvulsants for decreasing the intensity of pain associated with PHN. The systematic review showed five studies on anticonvulsants and one study on opioids in which the drug treatment was significantly more effective than placebo. Subgroup analysis showed anticonvulsants significantly improved pain compared with placebo. In a meta-analysis with five studies reporting on reduction of pain by 50% or more, pooled results showed patients taking anticonvulsants were 2.5 times more likely to have a reduction in pain by 50% or more compared with placebo.

Although the study on opioids[9] showed a significant effect, one crossover study is not sufficient to recommend or discredit the use of opioids for PHN. Similarly, the individual studies reporting on TCAs[9] and tramadol[18] did not show significance in the meta-analysis and the small sample sizes do not allow for support or discredit of the use of these medications in PHN patients. Further research is necessary.

Overall Completeness and Applicability of Evidence

The systematic review was conducted mainly by two individual reviewers. The abstracts, and if deemed necessary the full article, were reviewed for inclusion/exclusion criteria and risk of bias. A third reviewer intervened in case of lack of consensus. A limitation of this review was the lack of access to EMBASE, an international biomedical database for biomedical researchers, due to the lack of funds. Some studies could have been missed due to this fact.

Overall, the results of the systematic review were applicable to both males and females as both genders were present in each of the reviewed studies. All of the studies except one[19] had a mean or median age of over 60 years (Table 1). When documented, most of the patients were Caucasian. Pregnant women, breastfeeding mothers, and medically compromised patients were often excluded from the studies. Since the included studies ranged from 4 to 13 weeks in duration, this review cannot comment on the long-term efficacy or side effects of these medications.

Quality of the Evidence

Only double-blinded, randomized, placebo-controlled trials were included in this systematic review by choice of the authors, as high-quality RCTs with a placebo group provide the best evidence. However, of the 11 RCTs included in the qualitative analysis, 6 of the studies were at overall unclear risk of bias,[8,9,11,14,17,19] 4 were at high risk,[7,10,15,16] and only 1 was at low risk of bias.[18]

Only studies reporting similar outcomes for similar interventions were pooled together. A subgroup analysis including only five studies of anticonvulsants[8,14–16,19] showed a significant reduction in pain in the treated group compared with the placebo group; however, two of these articles had high risk of bias[15,16] and three had unclear risk.[8,14,19] Although a second subgroup analysis showed patients taking anticonvulsants were 2.5 times as likely to have a 50% or more reduction in pain compared with placebo, the studies had high risk[7,15,16] or unclear risk of bias[8,19] and there were only five studies in this subgroup analysis as well.

Table 7 Quality of Assessment and Summary of Findings (GRADE)

Question: Should Anticonvulsants Be Used for PHN?

Participants (studies) Follow-up	Quality assessment: Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence[c]
Posttreatment pain intensity (Primary outcome; measured with VAS; better indicated by lower values)						
786 (5 studies) 8 wk	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	Reporting bias strongly suspected[b]	⊕⊕⊖⊖ LOW[a,b] due to risk of bias, publication bias
Percent of responders reporting ≥ 50% decrease in pain (Secondary outcome; assessed with VAS)						
786 (5 studies) 8 wk	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	Reporting bias strongly suspected[b]	⊕⊕⊖⊖ LOW[a,b] due to risk of bias, publication bias

[a]All five studies had unclear or high risk of bias. [b]Only five studies included in this analysis, small sample size.
[c]GRADE Working Group grades of evidence: High quality (⊕⊕⊕⊕) = further research is very unlikely to change the confidence in the estimate of effect; Moderate quality (⊕⊕⊕⊖) = further research is likely to have an important impact on the confidence in the estimate of effect and may change the estimate; Low quality (⊕⊕⊖⊖) = further research is very likely to have an important impact on the confidence in the estimate of effect and is likely to change the estimate; Very low quality (⊕⊖⊖⊖) = the authors are very uncertain about the estimate.
RR = risk ratio; CI = confidence interval; SD = standard deviation.

Heterogeneity

Only papers reporting on similar outcomes were pooled together in a meta-analysis. Two main outcomes were analyzed separately in this systematic review: PPI and the percent of patients with 50% or more reduction in pain. Many different drugs were analyzed and subgroup analyses, grouped by class of oral medication, were undertaken for anticonvulsants (n = 5 studies), opioids (n = 1), TCAs (n = 1), and tramadol (n = 1). The secondary outcome, percent of patients with 50% or more reduction in pain, was reported in five studies. The heterogeneity of interventions and outcomes made it difficult to compare a larger number of studies in a meta-analysis and therefore decreased the strength of the evidence. A few studies that used different doses of medications were included in this systematic review, and so results were pooled by using the lowest dose, and additional models were run using the highest dose.

Comparison with Other Studies or Reviews

The results of several other studies and reviews agree with the results of this systematic review. A systematic review with meta-analysis by Meng et al[20] showed that gabapentin is an effective and well-tolerated treatment for patients with PHN, which agrees with the present results. In a systematic review by Snedecor et al[21] of PHN and other types of neuropathic pain, it was shown that in studies with 50 or more patients, opioids produced the greatest mean pain reduction. In the present systematic review, the study by Raja et al[9] showed a significant effect on pain by opioids; however, the evidence was weak as it was provided by only one crossover study. Snedecor et al[21] also showed that pregabalin ≥ 300 mg/day was the most effective intervention for ≥ 30% and ≥ 50% pain reduction. The present review agrees with Meng et al[20] and Snedecor et al[21] that anticonvulsants can be an effective method for decreasing pain in PHN patients.

A Cochrane review[22] on antidepressants for neuropathic pain concluded that antidepressants were effective for a variety of neuropathic pains and that both TCAs and venlafaxine had a number needed to treat (NNT) of approximately 3. However, that review[22] included different types of neuropathic pain and was not specific to PHN. In the present systematic review, individual studies on gabapentin,[8,14] pregabalin,[15,16] divalproex sodium,[19] and opioids,[9] but not TCAs[9] or tramadol,[18] showed a significant effect. Due to the small number of studies (n = 1) reporting on TCAs, tramadol, and opioids, this systematic review was inconclusive about the effects of these treatments.

Clinical Implications

Since gabapentin, pregabalin, and divalproex sodium were all effective in reducing pain in PHN patients, the next question is which medication is appropriate for a particular patient. The small sample sizes in the subgroup analyses do not allow for a conclusion either way for opioids, TCAs, or tramadol. Since gabapentin and pregabalin tend to have fewer interactions with other medications, they may be a first choice when de-

Summary of findings				
Study event rates (n/total [%])			Anticipated absolute effects (time frame is short term)	
With control	With anticonvulsants	RR (95% CI)	Risk with control	Risk difference with anticonvulsants (95% CI)
–	–	–	–	The mean posttreatment pain intensity in the intervention groups was 0.484 SD lower (0.622 to 0.346 lower)
50/393 (12.7)	129/393 (32.8)	RR 2.506 (1.865 to 3.369)	127 responders per 1,000	192 more responders per 1,000 (from 110 more to 301 more)

ciding which medication is appropriate for the patient. Divalproex sodium may be used as a second-choice drug, but has more side effects than gabapentin or pregabalin.[23] Although TCAs and tramadol were not significant in reducing pain in this meta-analysis, these medications are used to treat neuropathic pain. It is important to consider the patient's medical history when choosing a medication. In a study by Gilron et al,[24] it was shown that a combination of low doses of gabapentin and nortriptyline was actually more efficacious in treating neuropathic pain than either medication alone. Additionally, with lower doses there is a lower chance of side effects. Lastly, because of the potential abuse of opioids, these medications should be used as a last resort or for breakthrough pain.

Conclusions

Future studies conducted to confirm the lowest dose for a significant reduction in pain for gabapentin and pregabalin would be useful. It would also be beneficial to have long-term studies to evaluate long-term outcomes and potential side effects. Further research on opioids is necessary to provide guidelines for practitioners.

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