

UC Davis

Dermatology Online Journal

Title

Efficacy of gabapentinoids for acute herpes zoster in preventing postherpetic neuralgia: a systematic review of randomized controlled trials

Permalink

<https://escholarship.org/uc/item/6cs8c3m6>

Journal

Dermatology Online Journal, 28(5)

Authors

Menaldi, Sri Linuwih
Halim, Paulus Anthony
Kurniawan, Kristian

Publication Date

2022

DOI

10.5070/D328559238

Copyright Information

Copyright 2022 by the author(s). This work is made available under the terms of a Creative Commons Attribution-NonCommercial-NoDerivatives License, available at <https://creativecommons.org/licenses/by-nc-nd/4.0/>

Peer reviewed

Efficacy of gabapentinoids for acute herpes zoster in preventing postherpetic neuralgia: a systematic review of randomized controlled trials

Sri Linuwih Menaldi¹ MD PhD, Paulus Anthony Halim¹ MD, Kristian Kurniawan² MD

Affiliations: ¹Department of Dermatology and Venereology, Faculty of Medicine Universitas Indonesia, Dr Cipto Mangunkusumo Hospital, Jakarta, Indonesia, ²Faculty of Medicine Universitas Indonesia, Dr Cipto Mangunkusumo Hospital, Jakarta, Indonesia

Corresponding Author: Sri Linuwih Menaldi, Faculty of Medicine Universitas Indonesia, Jalan Salemba Raya No. 4, Kenari, Senen, Central Jakarta, Indonesia 10430, Tel: 62-816997680, Email: susetyo_mr@yahoo.com

Abstract

Gabapentinoids (e.g., gabapentin and pregabalin) have been established as a treatment for postherpetic neuralgia (PHN), but their effects on the prevention of PHN are unclear. This systematic review aimed to evaluate the efficacy of gabapentinoids for acute herpes zoster (HZ) in preventing PHN. PubMed, EMBASE, CENTRAL, and Web of Science were queried December 2020 to collect data on relevant randomized controlled trials (RCTs). A total of four RCTs (including 265 subjects) were retrieved. Overall, the incidence of PHN was lower, but not statistically significant in the gabapentinoid-treated group compared to the control group. Subjects treated with gabapentinoids were more likely to experience adverse events such as dizziness, somnolence, and gastrointestinal symptoms. This systematic review of RCTs showed that the addition of gabapentinoids during acute HZ are not significantly effective in preventing PHN. Nevertheless, the evidence on this subject remains limited. Physicians should carefully weigh the risks and benefits of prescribing gabapentinoids during the acute phase of HZ owing to its side effects.

Keywords: gabapentin, herpes zoster, postherpetic neuralgia, pregabalin

Introduction

Herpes zoster (HZ), also known as shingles, is a reactivation of latent varicella zoster virus leading to

a distinctive clinical manifestation. Postherpetic neuralgia (PHN) is a common sequela of HZ infection adversely affecting the quality of life [1]. Postherpetic neuralgia is a neuropathic syndrome characterized by persistent pain lasting months to years after the alleviation of the HZ rash. Although there is no established definition of PHN, most studies and the consensus define it as pain persisting for more than three months after rash healing [2-4].

Various methods have been proposed to prevent PHN, including vaccination, pharmacological therapies (antivirals, gabapentinoids, and amitriptyline), interventional procedures (nerve blocks), and alternative therapies (lidocaine patches, electrical nerve stimulation, and acupuncture) [5-8]. A Cochrane systematic review showed that administration of antivirals (acyclovir and famciclovir) during acute HZ was no better than a placebo in preventing PHN [9]. Corticosteroids are also ineffective in preventing PHN [10-13]. Vaccination is the only modality that has been demonstrated to reduce the risk of PHN, especially in older adults [14,15].

Despite their efficacy, zoster vaccines are relatively expensive and vaccination rates remain very low, especially in emerging countries. Currently, physicians have limited options for PHN prevention in patients with acute HZ, as vaccines are only effective if given before the onset of infection. Thus, agents that are efficacious in preventing PHN and can be administered during acute HZ are required to reduce patient morbidity associated with PHN.

Recently, gabapentinoids (gabapentin and pregabalin) have been investigated for the prevention of PHN [16-21]. As an analog of gamma-aminobutyric acid (GABA), they bind to the $\alpha 2-\delta$ site of voltage-dependent calcium channels, resulting in a reduction in neurotransmitter release. Gabapentinoids reduce pain by inhibiting central sensitization of dorsal horn neurons [22,23]. Nonetheless, the use of gabapentinoids during the acute phase of the disease remains controversial [24-26].

Gabapentin has been demonstrated to reduce acute herpetic pain and delay neuropathic pain in mice [19]. Several trials have reported that gabapentin alleviates chronic neuropathic pain. However, its effect on the prevention of PHN is still unclear [27,28]. Gabapentin, added as an analgesic for the treatment of HZ with moderate to severe pain, is recommended by the European consensus-based guidelines for the management of HZ [3]. Therefore, our study aimed to systematically evaluate the effect of gabapentinoids (gabapentin and pregabalin) in the prevention of PHN.

Methods

Systematic review protocol registration

This systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The protocol for this study was registered on the Prospective Register of Systematic Reviews with protocol number CRD42021223402.

Literature search strategy and study selection

Queries of electronic databases (PubMed, EMBASE, CENTRAL, and Web of Science) were performed in December 2020 to identify relevant articles. Text headings and medical subject headings terms used in the searches included: HZ, shingles, PHN, pregabalin, gabapentin, and gabapentinoids. We also searched two clinical trial databases (ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (<https://tapps.who.int/trialsearch/>), together with the reference lists of the included studies and relevant review articles. We contacted

investigators for ongoing trials or if there were any incomplete or missing data.

This review included studies that: 1) investigated the efficacy of gabapentinoids (gabapentin or pregabalin) alone or in combination with antivirals and/or analgesics in patients with HZ on preventing PHN; 2) performed randomization and had a control group randomized controlled trials; 3) were written in English; and 4) were published in a peer-reviewed journal or as a conference paper. On the other hand, excluded studies 1) had only the abstract available; or 2) examined subjects in combination with other treatment modalities other than pharmacologic (invasive treatment, acupuncture, or psychological interventions); or 3) studied PHN in addition to other neuropathic pain syndromes.

Data extraction

One author reviewed all publication titles to eliminate articles not relevant to this review. Two authors reviewed abstracts of the remaining articles to determine inclusion for assessment of the full text. One author extracted data into a standardized data collection form and one senior author verified the accuracy of the extracted data from the source paper. Extracted information included study title and authors, year of publication, study location, sample size, mean age, gender composition of study sample, onset of acute HZ, drug regimen (intervention and control groups), incidence of PHN, and effect estimates.

Risk of bias assessment

We used the Oxford Quality Score as the basis for inclusion, limiting inclusion to studies that were, as a minimum, randomized and double blind [29]. Two authors independently assessed the risk of bias of each study, using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions.

Results

The search strategy for this systematic review is represented using a PRISMA flow diagram (**Figure 1**). The initial search yielded 2,108 records, and ultimately four studies were included for qualitative

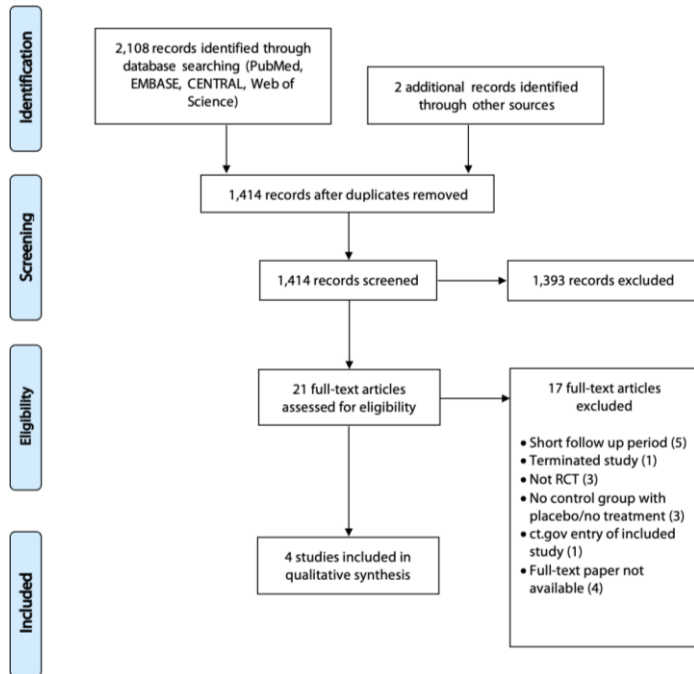


Figure 1. PRISMA 2009 flow diagram.

analysis. Summary of risk of bias assessment for the included studies is presented in Figure 2.

Study characteristics

Table 1 displays the characteristics of the four included studies, with a total of 265 subjects, of which 129 were in the treatment group (85

gabapentin, 44 pregabalin) and 136 were in the placebo group. Two studies compared oral gabapentin versus a control/placebo group and the other two investigated pregabalin. These studies recruited participants during the acute phase of HZ. Selected subjects were adults aged 30–80 years old, with the majority being older than 50 years. Most studies included acute HZ patients presenting with moderate to severe pain. One study excluded patients who received zoster vaccinations, whereas the others did not mention vaccination. Shared exclusion criteria include a history of hypersensitivity to treatment, a psychiatric diagnosis, pregnancy and lactation, severe hepatic or renal dysfunction, and current therapy with anticonvulsants or antidepressants. There were no significant differences in the baseline subject characteristics.

Treatment regimen

All studies administered gabapentin or pregabalin in addition to a standard treatment of antivirals (acyclovir or valacyclovir) and analgesics (Table 2). Only one study did not add antivirals. Two studies administered gabapentinoids for 3-4 weeks, whereas the others administered the drug for up to 12 weeks. Although the placebo/standard treatment was similar, the intervention regimens were different in terms of dose and titration method. Most studies started with minimum dose that was titrated over time with evaluation of its side effects. One study did not titrate or increase the dosing over time.

Incidence of postherpetic neuralgia

The outcome measures for incidence of PHN were reported differently in different studies (Table 1). Two studies defined PHN as the presence of pain at week 12 after acute HZ rash, one study at 90 days, and one at >6 months. Likert and VAS pain scales were used in two studies each. The study by Bulilete et al. reported the proportion of subjects with any (VAS>0) and moderate-severe (VAS>4) pain at week 12. Overall, the incidences of PHN in the treated groups were lower than those in the control groups. However, one study with a low risk of bias reported higher incidence of PHN in subjects receiving gabapentin. Nevertheless, the differences in PHN incidence were not statistically significant in any of the studies.

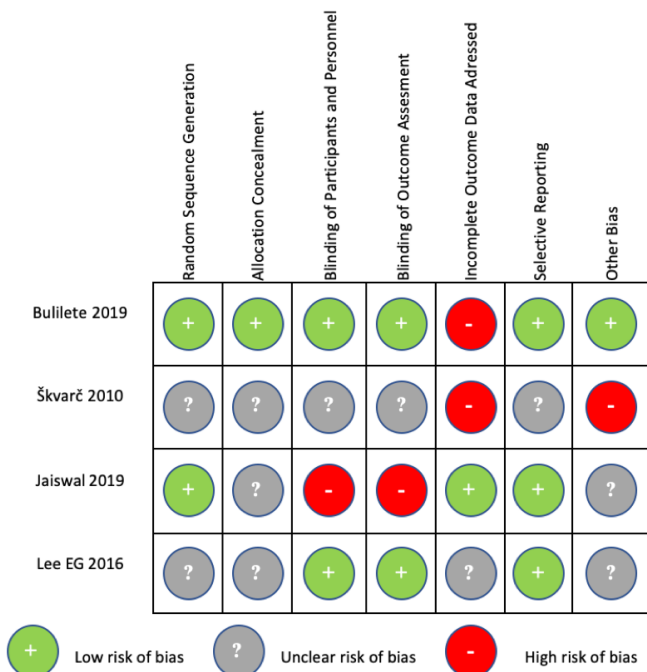


Figure 2. Risk of bias.

Table 1. Characteristics of the included studies.

Study	Study design	Postherpetic neuralgia definition	Population
Bulilete [16] (Spain, 2019)	Randomized, double blind, placebo-controlled study	Pain (VAS ≥ 0) at week 12 after HZ rash	>50 y.o.; within 72 h of rash onset; moderate-severe pain (VAS: 4–10).
Škvarč [17] (Slovenia, 2010)	Randomized, double-blind placebo-controlled study	Pain > 6 months after resolution of HZ rash	30–80 y.o.; within 7–14 days of HZ; pain ≥ 4 (on a 10-point Likert scale)
Jaiswal [18] (India, 2019)	Prospective, randomized controlled study	Pain ≥ 90 days after the onset of HZ rash	>40 y.o. subject with acute HZ presenting with rash
Lee [21] (South Korea, 2016)	Prospective randomized controlled study	Pain (≥ 4 on 10-point Likert scale) after 12 weeks from initial treatment	>50 y.o.; within 4 days of rash; moderate to severe pain (≥ 4 on 10-point Likert scale)

HZ, herpes zoster; VAS, visual analog scale; y.o., years old.

Adverse events

Reported adverse effects among the included studies were dizziness, somnolence, vertigo, dry mouth, and abdominal pain. No serious side effects were reported. One study reported that dizziness and somnolence were significantly higher in patients receiving pregabalin [17, 16]. Overall, the incidence of side effects was higher in the intervention group.

Additional outcome measures

The study by Bulilete et al. concluded that patients in the gabapentin group had more sleep problems (measured by the Medical Outcomes Study Sleep Scale) and a lower quality of life (measured by Short-Form 12) [16]. Lee et al. measured quality of life using the Dermatology Life Quality Index and found that the mean difference was not significant [21]. Jaiswal et al. reported better patient satisfaction with pain control in the pregabalin group (96.7%) compared to that of the control group (76.9%), ($P < 0.05$), [18].

Discussion

Gabapentinoids have been prescribed by physicians to reduce acute HZ pain and prevent PHN. Few consensus-based guidelines recommend gabapentinoids in addition to standard analgesics, particularly in patients with moderate to severe zoster pain [3,4]. Recent trials and reviews of the efficacy of gabapentinoids in acute HZ for preventing PHN have shown differing results, which prompted the present systematic review of RCTs.

The duration of treatment differed among all studies. However, all studies started from a low to medium dose of gabapentin (up to 1800mg/day) or pregabalin (up to 300mg/day). Previous studies have estimated that pregabalin has a similar efficacy compared to gabapentin at one-sixth the dose of the latter; thus, the doses of gabapentin and pregabalin used in the included studies are comparable [30]. A higher dose of gabapentinoids did not correlate with a lower incidence of PHN. An open label study administered up to 3600mg/day of gabapentin during acute HZ in 133 subjects and reported a lower incidence of PHN relative to previously published data of patients not receiving gabapentin [20]. However, the study lacked a control group, so the quality of evidence is low.

Neither short (3–4 weeks) nor extended (12 weeks) courses of gabapentinoids were significantly effective in preventing PHN. The duration of treatment was shorter than the period of observation except in the study by Lee et al, in which the intervention group received gabapentin until PHN evaluation. The analgesic property of gabapentin could mask the pain experienced by subjects and bias the result in favor of the intervention group.

A previous review concluded that GABA and its derivate could reduce the incidence of HZ-associated pain in the first month after the onset of rash. However, the review did not address the incidence of pain 12 weeks after rash onset [31].

There have been no reports of serious side effects of gabapentinoid treatment. Both gabapentin and pregabalin cause similar side effects. Dizziness, somnolence, and gastrointestinal symptoms were the predominant side effects reported, similar to other trials of gabapentin and pregabalin [22,28]. These side effects might lead to patient drop-out from trials, as reported by Bulilete et al. [16]. The study by Lee et al. reported a higher rate of drop-out in the gabapentin group, but the reason for drop-out was not stated in the study [21]. In contrast, two studies included reported that the pregabalin group had a drop-out rate of zero [17,18]. This suggests that pregabalin may be better tolerated than gabapentin, although pregabalin and gabapentin had similar adverse event profiles [32,33].

Among the studies, the definition for PHN varied by the severity of pain (any pain or moderate to severe only) and time (three or four months after onset or until the resolution of the rash). Furthermore, previous literature and consensus have varying definitions of PHN. The European S2K guideline defines PHN as a chronic pain disorder after resolution of acute HZ infection that persists ≥ 3 months [3]. The Indonesian Herpes Study Group 2014 Guideline defines PHN as persistent pain in the affected dermatome three months after the resolution of the HZ rash [4]. The study by Lee et al. defined PHN only if subjects had moderate-severe pain, in contrast to the other studies and the consensus [21].

The European consensus-based guidelines for the management of HZ recommend that gabapentin or pregabalin may be added to analgesics for the treatment of HZ infection if moderate or severe pain is present [3]. Previous studies reported no

significant difference in pain relief in acute HZ patients treated with gabapentin in combination compared to standard analgesics alone [16,34]. However, other studies have shown a beneficial effect of gabapentinoids in reducing acute herpetic pain [31,35,36].

This study is the first, to the best of our knowledge, to systematically review the current available data on the use of gabapentinoids for acute HZ in preventing PHN. The results of this systematic review reveal that gabapentinoids have limited effects on preventing PHN if given during acute HZ. As the benefits of gabapentinoids for acute pain in HZ are minimal, physicians are not recommended to routinely prescribe gabapentin or pregabalin for patients with acute HZ owing to their side effects.

Studies regarding the use of gabapentinoids during the acute phase of HZ remain limited and most studies do not describe their methods adequately. The lack of common treatment regimens and outcome measures has impeded a formal meta-analysis of these works.

Conclusion

This systematic review of RCTs showed that the addition of gabapentinoids during acute HZ are not significantly effective in preventing PHN. Nevertheless, the evidence on this subject remains limited. Physicians should carefully weigh the risks and benefits of prescribing gabapentinoids during the acute phase of HZ owing to its side effects.

Potential conflicts of interest

The authors declare no conflicts of interest.

References

1. Johnson RW, Bouhassira D, Kassianos G, et al. The impact of herpes zoster and post-herpetic neuralgia on quality-of-life. *BMC Med.* 2010;8:37. [PMID: 20565946].
2. Dworkin RH, Portenoy RK. Pain and its persistence in herpes zoster. *Pain.* 1996;67:241-51. [PMID: 8951917].
3. Gross GE, Eisert L, Doerr HW, et al. S2k guidelines for the diagnosis and treatment of herpes zoster and postherpetic neuralgia. *J Dtsch Dermatol Ges.* 2020;18:55-78. [PMID: 31951098].
4. Pusponegoro E, Nilasari H, Lumintan H, et al. Indonesian 2014 guide book on herpes zoster. Faculty of Medicine Universitas Indonesia, Jakarta; 2014.
5. Ankit S, Zeng T, Chen Y, et al. The current treatment and prevention of post herpetic neuralgia. *Yangtze Med.* 2018;02:28-38. [DOI: 10.4236/ym.2018.21003].
6. Saguil A, Kane S, Mercado M, Lauters R. Herpes zoster and postherpetic neuralgia: prevention and management. *Am Fam Physician.* 2017;96:656-63. [PMID: 29431387].
7. Makharita MY. Prevention of post-herpetic neuralgia from dream

- to reality: A ten-step model. *Pain Physician*. 2017;20:e209-20. [PMID: 28158158].
8. Bianchi L, Piergiorgio C, Marietti R, et al. Effectiveness and safety of lidocaine patch 5% to treat herpes zoster acute neuralgia and to prevent postherpetic neuralgia. *Dermatol Ther*. 2021;34:e14590. [PMID: 33244838].
 9. Chen N, Li Q, Yang J, et al. Antiviral treatment for preventing postherpetic neuralgia. *Cochrane Database Syst Rev*. 2014;CD006866. [PMID: 24500927].
 10. Srebrnik A, Brandsen R, Brenner S. Corticosteroid treatment in the prevention of postherpetic neuralgia. *J Dermatol Treat*. 1991;2:11-3. [DOI: 10.3109/09546639109089046]
 11. Han Y, Zhang J, Chen N, et al. Corticosteroids for preventing postherpetic neuralgia. *Cochrane Database Syst Rev*. 2013;CD005582. [PMID: 23543541].
 12. Kowalsky DS, Wolfson AB. Corticosteroids for preventing postherpetic neuralgia after herpes zoster infection. *Acad Emerg Med*. 2019;26:686-7. [PMID: 30421477]
 13. Voros J, Koyfman A, Foran M. Do corticosteroids prevent postherpetic neuralgia? *Ann of Emerg Med*. 2014;63:351-2. [PMID: 24041781]
 14. Gagliardi AM, Andriolo BN, Torloni MR, et al. Vaccines for preventing herpes zoster in older adults. *Cochrane Database Syst Rev*. 2019;CD008858. [PMID: 31696946].
 15. Chen N, Li Q, Zhang Y, et al. Vaccination for preventing postherpetic neuralgia. *Cochrane Database Syst Rev*. 2011;CD007795. [PMID: 21412911].
 16. Bulilete O, Leiva A, Rullán M, et al. Efficacy of gabapentin for the prevention of postherpetic neuralgia in patients with acute herpes zoster: A double blind, randomized controlled trial. *PLoS ONE*. 2019;14:e0217335. [PMID: 31166976].
 17. Skvarc NK, Kamenik M. Effects of pregabalin on acute herpetic pain and postherpetic neuralgia incidence. *Wien Klin Wochenschr*. 2010;122:49-53. [PMID: 20517672].
 18. Jaiswal R, Saini M, Dayal S, et al. A comparative study to evaluate the analgesic effect of amitriptyline and pregabalin in acute phase of herpes zoster. *Int J Sci Res*. 2019;8:81-2. [DOI: 10.36106/ijstr].
 19. Kuraishi Y, Takasaki I, Nojima H, et al. Effects of the suppression of acute herpetic pain by gabapentin and amitriptyline on the incidence of delayed postherpetic pain in mice. *Life Sci*. 2004;74:2619-26. [PMID: 15041444].
 20. Lapolla W, Digiorio C, Haitz K et al. Incidence of postherpetic neuralgia after combination treatment with gabapentin and valacyclovir in patients with acute herpes zoster: open-label study. *Arch Dermatol*. 2011;147:901-7. [PMID: 21482862].
 21. Lee EG, Lee HJ, Hyun DJ, et al. Efficacy of low dose gabapentin in acute herpes zoster for preventing postherpetic neuralgia: a prospective controlled study. *Dermatol Ther*. 2016;29:184-90. [PMID: 26799145].
 22. Bockbrader HN, Burger P, Knapp L, Corrigan BW. Population pharmacokinetics of pregabalin in healthy subjects and patients with chronic pain or partial seizures. *Epilepsia*. 2011;52:248-57. [PMID: 21269291].
 23. Chang CY, Challa CK, Shah J, Eloy JD. Gabapentin in acute postoperative pain management. *BioMed Res Int*. 2014;2014:631756. [PMID: 24829909].
 24. Rowbotham M, Harden N, Stacey B, et al. Gabapentin for the treatment of postherpetic neuralgia: a randomized controlled trial. *JAMA*. 1998;280:1837-42. [PMID: 9846778].
 25. Stacey BR, Barrett JA, Whalen E, et al. Pregabalin for postherpetic neuralgia: placebo-controlled trial of fixed and flexible dosing regimens on allodynia and time to onset of pain relief. *J Pain*. 2008;9:1006-17. [PMID: 18640074].
 26. Green CB, Stratman EJ. Prevent rather than treat postherpetic neuralgia by prescribing gabapentin earlier in patients with herpes zoster: comment on "incidence of postherpetic neuralgia after combination treatment with gabapentin and valacyclovir in patients with acute herpes zoster". *Arch Dermatol*. 2011;147:908. [PMID: 21844449].
 27. Chincholkar M. Gabapentinoids: pharmacokinetics, pharmacodynamics and considerations for clinical practice. *Br J Pain*. 2020;14:104-14. [PMID: 32537149].
 28. Goodman CW, Brett AS. Gabapentinoids for pain: potential unintended consequences. *Am Fam Physician*. 2019;100:672-5. [PMID: 31790179].
 29. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials*. 1996;17:1-12. [PMID: 8721797].
 30. Bockbrader HN, Budhwani MN, Wesche DL. Gabapentin to pregabalin therapy transition: a pharmacokinetic simulation. *Am J Ther*. 2013;20:32-6. [PMID: 23018586].
 31. Sadaeng W, Márta K, Mátrai P, et al. γ -aminobutyric acid and derivatives reduce the incidence of acute pain after herpes zoster - a systematic review and meta-analysis. *Curr Pharm Des*. 2020;26:3026-38. [PMID: 32503401].
 32. Gilron I, Flatters SJL. Gabapentin and pregabalin for the treatment of neuropathic pain: a review of laboratory and clinical evidence. *Pain Res and Manag*. 2006;11:16A-29A. [PMID: 651712].
 33. Davari M, Amani B, Amani B, et al. Pregabalin and gabapentin in neuropathic pain management after spinal cord injury: a systematic review and meta-analysis. *Korean J Pain*. 2020;33:3-12. [PMID: 31888312].
 34. Dworkin RH, Barbano RL, Tyring SK, et al. A randomized, placebo-controlled trial of oxycodone and of gabapentin for acute pain in herpes zoster. *Pain*. 2009;142:209-17. [PMID: 19195785].
 35. Berry JD, Petersen KL. A single dose of gabapentin reduces acute pain and allodynia in patients with herpes zoster. *Neurology*. 2005;65:444-7. [PMID: 16087911].
 36. Kanodia SK, Seth AK, Dixit AM. Dose related efficacy of gabapentin in acute herpetic neuralgia among geriatric patients. *Indian J Dermatol*. 2012;57:362-5. [PMID: 23112355].

Table 2. Outcomes of the included studies.

Study	Sample Size	Standard Treatment	Control	Intervention (Duration)	Gabapentinoids Dose	PHN Incidence n/N (%)
Bulilete [16] 2019	Control: 42 Intervention: 33 Total: 75	Valacyclovir hydrochloride (1000mg TID) for 7 days and analgesics	Placebo + standard treatment	Gabapentin (5 weeks) + standard treatment	Initial: 300mg QD Maximum: 600mg TID Titration: Dose increases each day, maximum dose in 7 days	Control: 4/42 (9.5) Intervention: 6/33 (18.2) P=0.144
Škvarč [17] 2010	Control: 15 Intervention: 14 Total: 29	Analgesics (naproxen, tramadol, or both)	Placebo + standard treatment	Pregabalin (3 weeks) + standard treatment	Initial: 75mg BID Maximum: 150mg BID Titration: Dose increased to maximum if tolerated.	Control: 3/15 (20) Intervention: 2/14 (14) P=1
Jaiswal [18] 2019	Control: 30 Intervention: 30 Total: 60	Acyclovir 800mg five times a day for 7–10 days; analgesics (paracetamol, tramadol, or diclofenac)	Standard treatment	Pregabalin (12 weeks) + standard treatment	Initial: 75mg BID Titration: None.	Control: 8/30 (26.7) Intervention: 5/30 (16.7) P=0.5321
Lee [21] 2016	Control: 49 Intervention: 52 Total: 101	Valacyclovir 1000mg TID for 7 days; paracetamol 650mg TID	Standard treatment	Gabapentin (12 weeks) + standard treatment	Initial: 300mg QD Maximum: 300mg TID Titration: Dose increase every day over 3 days (300, 600, and 900 mg/day).	Control: 3/49 (6.1) Intervention: 2/52 (3.8) P=0.67

BID, twice a day; QD, once a day; TID, three times a day.