



γ -Aminobutyric Acid and Derivatives Reduce the Incidence of Acute Pain after Herpes Zoster - A Systematic Review and Meta-analysis

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Abstract: Herpes zoster (HZ) causes considerable pain and distress, and γ -Aminobutyric acid (GABA) and its derivatives are assumed to control this, but the available data are inconsistent. This meta-analysis and systematic review aimed to assess the effectiveness of GABA derivatives in the prevention of acute herpetic pain. The meta-analysis was conducted following the PRISMA guidelines using PICO format, registered in PROSPERO number CRD42018095758. PubMed, Web of Science, Ovid, Scopus, and EMBASE databases were searched. Records were included if they were randomized controlled trials of patients undergoing HZ infection, investigating the effect of GABA derivatives *versus* placebo in the treatment of HZ pain. Eligible trials were evaluated for the risk of bias. Then data were extracted and analysed. The number of patients with observed presence of pain after treatment was used to calculate odds ratio in a random effect model with the DerSimonian-Laird estimator. The I^2 statistic was analysed for heterogeneity. The potential risk of bias was measured using Egger's regression test. The meta-analysis included three randomized controlled trials with a total of 297 patients. The incidence of acute HZ pain events for GABA group was significantly lower compared to placebo group, 18/148 vs 44/149, respectively (OR = 0.36; 95% CI = 0.14 to 0.93; Z = 2.11; P = 0.035), Egger's test yielded P = 0.308. In conclusion, the present meta-analysis demonstrates that GABA derivatives reduce the incidence of acute herpetic pain. However, additional, well-designed randomized clinical trials are needed to determine their dose- and time-dependency regarding this symptom.

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1. INTRODUCTION

Reactivated Varicella-Zoster Virus (VZV) in sensory ganglia causes infection of the skin, which is termed as herpes zoster (HZ) [1, 2]. The prevalence of HZ is high. In the USA, around 500000 persons experience reactivation of HZ infection each year and the incidence of HZ in the population having normal immune response is around 1.2 to 3.4 per 1000 patient-year [2]. The clinical manifestation of HZ is defined by a painful, unilateral erythematous maculopapular rash, which normally involves 1-2 dermatomes. The rash evolves into groups of clear vesicles within 48-72 hours, then becomes pustulous, ulcerous and crusty in 7-10 days [1, 3, 4]. The disease causes generalized necrosis of nerves, nerve root and ganglion, lowering the threshold for nociceptive pain and initiating ectopic discharges, accompanied by moderate or severe pain [5, 6]. As a result, excessive peripheral nociception input induces abnormal reorganization of pain transmission system [6, 7]. At the cellular level, the disease upregulates receptors associated with pain, such as transient receptor potential vanilloid 1 (TRPV1), as well as an increasing proportion of voltage-gated sodium channels and potassium voltage-gated channels. There is also evidence of loss of γ -aminobutyric acid (GABA) inhibitory interneuron in the dorsal horn [6].

Most of the patients experience paresthesia, dysesthesia, hyperesthesia and allodynia during the course of this disease. Pain is the most common complaint in HZ infection. It tends to improve spontaneously with time or persist unpredictably [4, 8]. Thus, some patients experience HZ-associated pain after the healing of the skin lesion [8]. HZ-associated pain has been classified into acute zoster pain (acute herpetic neuralgia), subacute zoster pain (subacute herpetic neuralgia) and postherpetic neuralgia (PHN) by time frame [9]. Basically, acute pain can be derived from the initial rash, and it lasts no longer than one month; subacute pain from 1 to 4 months after the onset of the disease; PHN develops four months after the initial lesion [5, 9]. Although most investigators reported persistent pain of PHN for at least three months after the healing of the rash, others described persistent pain as early as 3-4 weeks or until six months after the healing of the rash [1, 5]. All definitions of PHN are arbitrary and range from 1 to 6 months. For clinical trials, neuralgia of 3 or more months has become the most common definition [10-13]. Determination of the point at which acute HZ pain transforms to PHN is controversial [3].

PHN will become more prevalent because of the increasing incidence of HZ and its nature to develop in the elderly, whose number is increasing [7, 14]. However, the prevalence of PHN depends on when it is measured. There is no agreement among scientists on the time point for diagnosis [15]. Pain severity during the acute phase and the extension of the lesion are risk factors of persistent pain development with relative risks 18.0 (Confidence Interval

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(CI) 6.6 - 48.6) and 5.3 (CI 4.2 - 17.2), respectively [16]. Advanced age, the use of immunosuppressives, and cancer were also mentioned as risk factors [1, 2, 5].

An essential treatment objective during acute HZ is to keep the patient comfortable and prevent HZ pain to become chronic [2]. Systemic and local treatments are used for pain relief and patient comfort, apart from antiviral agents. Tricyclic antidepressants, anti-convulsants, opioids, topical lidocaine and topical capsaicin, have been used for analgesic intervention in both acute and chronic forms of zoster pain [1, 2, 5, 13, 17-19]. There are indications for the usefulness of local anaesthesia, neurolytic block of sympathetic nerves, acupuncture, spinal intrathecal injection, intercostal nerve block, spinal cord stimulation, cryotherapy and botulinum toxin injection in order to treat HZ pain [20-22].

Gabapentin is a GABA analogue, binding at the $\alpha 2\text{-}\delta$ sub-unit of voltage-dependent calcium channels. It is assumed to have anti-neuralgic activity and anti-sensitization, modulation of GABAergic, glutaminergic and monoaminergic functions, and disruption of the neuropathic pain development process. It has been shown to inhibit ectopic discharge activities of injured peripheral nerves [1, 19, 23]. Pregabalin is also an analogue of GABA. It has a similar pharmacological profile as gabapentin [12, 24-26]. These agents are well absorbed via oral administration and excreted unchanged in the urine. The drugs do not undergo cytochrome P 450 metabolism [24, 25, 27, 28].

Previous systematic reviews and meta-analyses demonstrated no effects of steroid agents [29] and antiviral agents [30] in the prevention of PHN. Yet, there is no available clinical guideline or recommendation regarding the optimal dose of GABA derivatives preventing acute zoster pain, and PHN [4]. The results from the few available studies are contradictory. Thus, a complex approach to the effect of GABA derivatives is needed. Therefore, the purpose of this work was to investigate the effectiveness of γ -aminobutyric acid and its derivatives in the reduction of acute herpes zoster pain after herpes zoster, using the powerful tools of meta-analysis.

2. METHODS

This meta-analysis was conducted according to the Preferred Reporting Items for Systematic reviews and Meta-analysis protocol (PRISMA). To investigate the efficacy of GABA and its derivatives to reduce the acute HZ pain occurrence, the following PICO framework was applied. *Population*: herpes zoster; *Intervention*: GABA and its derivatives; *Comparison*: placebo treatment and *Outcome*: the presence of acute HZ pain. The protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) on May 31, 2018 (registration number: CRD42018095758).

2.1. Eligibility Criteria

2.1.1. Types of Studies and Interventions

Randomized controlled trials were eligible for our review; participants of all ages with diagnosed HZ were considered. All degrees of pain severity and all areas of distribution of the disease were acceptable. We considered GABA and its derivatives such as orally administered gabapentin versus placebo treatments after HZ. Other routes of administration were excluded from this review.

2.1.2. Type of Outcome Measurement

Primary outcomes. The primary outcome was the presence of HZ-associated pain after treatments. We divided HZ-associated pain into subgroups depending on their duration from the onset of the initial rashes. We considered the pain acute if it started within a month after the onset of the initial rash, subacute pain between 1 month and four months after the initial rash, and PHN that started four months after the initial lesion [9]. The severity of pain was

measured with reliable methods such as visual analogue scale and numerical rating scale.

Secondary outcomes. Adverse events were considered as secondary outcomes. We defined these phenomena as unfavourable events, either caused by the treatment or by the disease being treated and resulted from causes that appear irrelevant to the treatment or the disease [31].

2.2. Search Methods for Identification of Studies

We performed a search for all randomized controlled trials from five different databases. The language of the literature search was restricted to English.

2.2.1. Electronic Search

The search was performed on August 8, 2018. PubMed, Web of Science, Ovid, Scopus, and EMBASE were searched for relevant studies. The following search terms were applied: herpes zoster, gamma-aminobutyric acid, Gaba, gabapentin, neurontin, and gabapentin were adapted and used in different database platforms. The searching queries are shown in Appendix A. All search results were imported and pooled in EndNote[®] X7 (Thomson Reuter, PA, USA).

2.3. Data Collection and Analysis

2.3.1. Selection of Studies

After removing duplicated records, two review authors (W.S. and T.S.) individually screened the titles and abstracts of imported articles in EndNote for relevant studies. Each author decided which trials were eligible for inclusion criteria and discussed to resolve disagreements about inclusion criteria. Disagreements between reviewers were resolved by discussion or, if necessary, by consulting a third reviewer (G.G).

2.3.2. Data Extraction and Management

Data collection was executed following the PRISMA guidelines. Study characteristics and results were extracted by two reviewers (W.S. and T.S.) independently. Discrepancies in the extracted data were resolved by discussion. The following items were extracted from the included papers: first author, year of publication, country, number of study centres, design of study, size of population, intervention and duration of intervention, demographic data, distribution and severity of lesion, number of dropout participants, reasons for dropouts, primary and secondary outcomes, other relevant information that is not specified in the study protocol.

2.3.3. Assessment of Risk of Bias in the Included Studies

Two authors (W.S. and T.S.) independently assessed the risk of bias of the included trials using the Cochrane Risk of Bias Tool [32]. All key domains, except the other biases domain, were considered to the assessment. The authors independently categorized each study into a low risk of bias if all key domains were low risk; an unclear risk of bias when there were one or more unclear risks of bias in the key domains; and a high risk of bias when there were one or more high risks of bias in the key domains [32]. The risk of bias summary table and figure were generated by the REVMan5 software.

2.3.4. Assessment of Quality of Evidence

The quality of scientific evidence was rated by the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach using GRADEPro[®] (McMaster University, Hamilton, Canada). The quality of evidence is based on the risk of bias, inconsistency in results, indirectness of evidence, imprecision of results, and other considerations such as publication bias, large effect, plausible confounding and dose-response gradient, as described in the handbook for grading the quality of evidence and the

strength of recommendations using the GRADE approach [33]. The quality was judged as high, moderate, low and very low.

2.3.5. Measures of Treatment Effect

The statistical analysis was conducted using Stata 11 SE (Stata Corp LLC, College Station, TX, USA). The number of patients with observed presence of pain in the test groups and control groups was used to calculate the odds ratio (OR). The $OR > 1$ indicates an elevated risk of acute zoster pain in the treatment group compared to the control group, while $OR < 1$ indicates a lower risk in the treatment group. ORs were pooled using the random-effects model with the DerSimonian-Laird estimator and displayed on forest plots as described previously [34, 35]. Summary OR estimation, and 95% confidence interval (CI) were calculated. $P < 0.05$ was considered as a significant difference from summary $OR=1$. Statistical heterogeneity was analyzed using the I^2 statistic to gain probability values; $p < 0.05$ was defined, indicating significant heterogeneity. We investigated the possible signs of a small study effect displaying the studies on a funnel plot and formally conducting the Egger's regression test, where $p < 0.05$ indicates potential risks of bias.

3. RESULTS

3.1. Description of Studies

The characteristics of the included studies are listed in Table 1 and Appendix B.

3.1.1. Results of Search

The literature search yielded a total of 3130 potentially relevant reports. After screening titles and abstracts, six records were relevant to our meta-analysis (Fig. 1). Out of these, three records were excluded because one was an uncontrolled trial; another one was a retrospective study [36, 37], while the third one was an ongoing trial [38]. We extracted the data from the remaining three suitable

records [39-41]. The characteristics of these included studies are described in Table 1, and the outcomes in Table 2.

3.1.2. Included Studies

Three trials with a total of 297 participants were included. Inclusion and exclusion criteria were clearly stated in two reports [39, 40]. However, an additional work, an abstract, did not state any detailed information regarding the primary outcome [41]. Thus, we could extract data only from two studies [39, 40]. These studies recruited participants at different time points of the infection. The study conducted by Lee *et al.*, [39] involved participants of 50 years of age or more, while the other study [40] included patients aged 30-80 years. There were no significant differences in the demographic data (*e.g.*, gender, age) of the treatment and the placebo group. The distribution of herpes rash was reported in both studies [39, 40]. Shared exclusion criteria in both trials consisted of allergy to treatment, psychiatric diagnosis, pregnancy and lactation, anti-convulsant therapies, antidepressant therapies, the use of clonidine or ketamine or local anaesthesia. None of the trials mentioned HZ vaccination of the participants, and there were no notes on special populations, such as immunocompromised patients involved in these studies.

Apart from the standard treatments of HZ, some treatment modalities were introduced as additional treatments to reduce herpetic pain and prevent PHN development. One trial [40] applied antiviral agents and 75 mg of pregabalin twice a day. In the other trial [39], participants received 300 mg of gabapentin three times per day combined with 1000 mg of Valacyclovir and 650 mg of acetaminophen three times daily. Lee *et al.*, used stepwise doses of gabapentin every day, up to 900 mg three times a day [39]. Participants in the trial of Wang *et al.*, [41] received standard treatments, either gabapentin or placebo. The authors did not state more details about the treatments. None of the included trials reported their methods of randomization. Follow-up was performed by phone calls [40] and

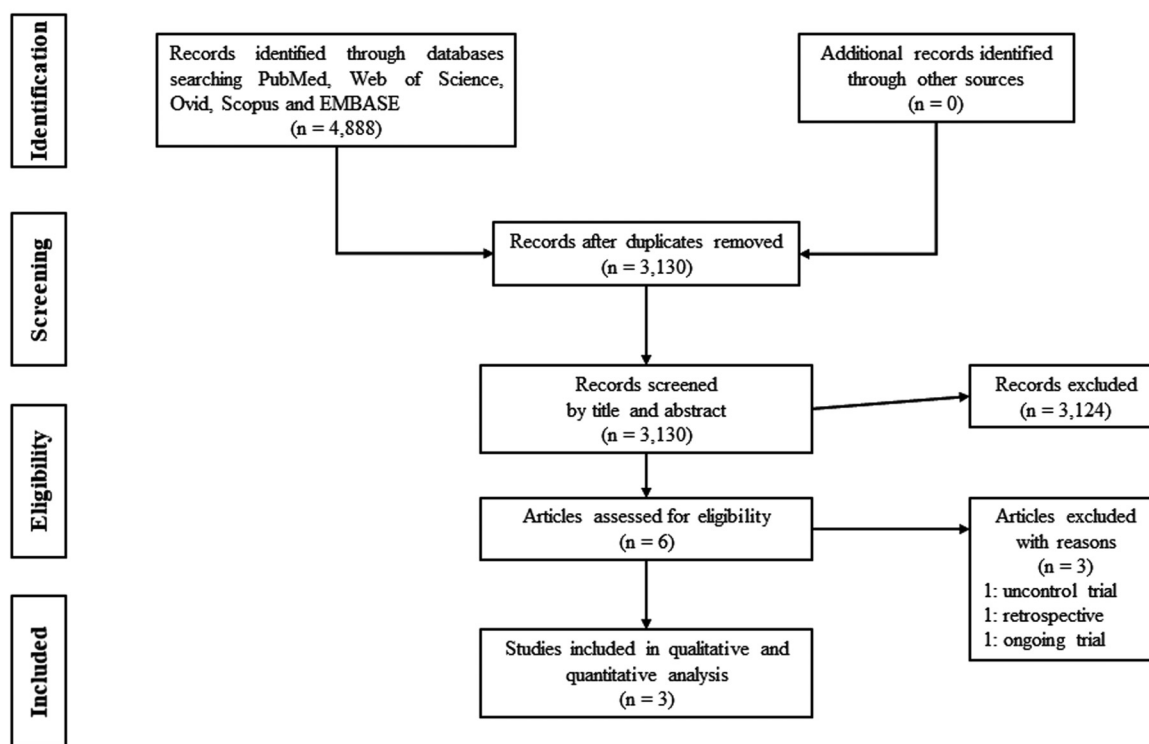


Fig. (1). PRISMA 2009 flow diagram for identification of relevant studies.

Table 1. Summary of study characteristics.

First Author	Country	Intervention	Duration of Treatment	Study Size (Test/Placebo)	Mean Age	Sex (M/F)	Time Receiving Treatment	Antiviral Treatment
Skvarc N. <i>et al.</i> 2010	Slovenia	<ul style="list-style-type: none"> 75 mg pregabalin <i>po bid</i> (150 mg/day) placebo <i>po bid</i> [can rise to 150 mg <i>po bid</i> (300 mg/day)] 	3 weeks treatment period	29 (14/15)	Test: 67±13 Placebo: 63±13	10/19	Test:12±2 (days) Placebo: 11±2 (days)	Test: 80% Placebo: 100%
Wang Q. <i>et al.</i> 2013	Korea	<ul style="list-style-type: none"> Standard treatment Standard treatment with gabapentin 	Not reported	120 (60/60)	Not reported	Not reported	Not reported	Yes
Lee E.G. <i>et al.</i> 2016	China	<ul style="list-style-type: none"> 1000 mg valacyclovir <i>tid</i> for 7 days + 650mg acetamenophen <i>tid</i> + Gabapentin 300 mg <i>tid</i> [stepwise in 3 days (900mg/day)] Placebo (1000 mg valacyclovir <i>tid</i> for 7 days + 650 mg acetamenophen <i>tid</i>) 	12 weeks in some cases it was extend to 24 weeks	148 (74/74)	treatment/control (age range): 24/25(50-59), 23/24(60-69), 13/11(≥70)	43/77	within 96 hrs after onset of rash	Yes

Abbreviations: RCT, randomized clinical trial.

Table 2. Summary of study outcomes.

First Author	Primary Outcome (Test/Placebo)	Secondary Outcome (Test/Placebo)	Statistical Methods	Note
Skvarc N. <i>et al.</i> 2010	1-3 months (42.86%/46.67%) 6 months (14.29%/20%)	Vertigo (50%/33.33%) Dizziness (64.29%/26.67%) Somnolence (64.29%/26.67%) Fatigue (57.14%/53.33%) Diplopia (14.29%/20%) Constipation (28.57%/13.33%) Flatulence (14.29%/13.33%)	According to the authors data were analysed using appropriate statistical tests without further specification. $P < 0.05$	PHN - after 6 months
Wang Q. <i>et al.</i> 2013	1 month (13%/45%)	Not reported	Statistical test were performed based on the intent-to-treat population	PHN - after 1 month
Lee E.G. <i>et al.</i> 2016	¼ month (57.5%/40.8%) ¾ month (28.8%/16.3%) 1 ¼ month (19.2%/6.1%) 2 months (9.6%/6.1%) 3 months (3.8%/6.1%)	Dizziness (13.33%/5%) Fatigue (6.67%/5%) Constipation (8.33%/6.67%) Appetite change (5%/5%) Dyspepsia (11.67%/10%) Edema (5%/1.67%) Headache (1.67%/1.67%) Nausea (11.67%/8.33%) Sedation (1.67%/0%)	Independent t-test, χ^2 , Fisher's exact, Binary logistic regression, $P < 0.05$	PHN - persisting pain more than 3 months

physicians' inspection [39], while Wang *et al.* [41] did not describe the method of follow-up. Loss of participants during the follow-ups was reported in the works of Lee *et al.*, [39] and Skvarc *et al.*, [40],

but the former one did not give any details on the reasons for drop-outs.

The outcome measurements were reported in different ways, including the presence of zoster pain after treatment. Every trial reported different cut-off times. Skvarc *et al.*, reported the incidence of subacute herpetic neuralgia (1-3 months) and PHN (6 months) [40], while Lee *et al.*, reported the presence of pain at weeks 1, 3, 5 and 8 and PHN incidence (3 months) [39]. Wang *et al.*, reported the presence of zoster pain at months 1, 3, 6 and 12 [41]. The Likert's pain scale was used in two trials [39, 40], while the third trial [41] did not explain the tools of pain measurement. Dermatology life quality index was used by Lee *et al.*, whereas sleep disturbance was measured by Skvarc *et al.* [39, 40]. Two included trials [39, 40] reported adverse events during the treatment period. The most frequently reported adverse events in both studies were dizziness, somnolence, fatigue and constipation.

3.1.3. Excluded Studies

Out of the six studies remaining after screening by title and abstract, one report was excluded because it was an uncontrolled, non-randomized study [36]. Another study was also excluded because it was retrospective [37]. Our search yielded one ongoing study, in which the investigators declared a progression of 70%, but the results of this study have not been published. Therefore, we could not include this trial in our meta-analysis [38].

3.1.4. Risk of Bias in the Included Studies

All of the included trials were rated as poor quality because there were high risks of bias and unclear risks of bias in many key domains. The risk of bias assessment graph and the summary show the judgement of the reviewers (Fig. 2 and Fig. S1).

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Lee E.G. et al. 2016	?	?	?	+	-	+	+
Skvarc N. & Kamenik M. 2010	?	?	?	?	-	+	+
Wang Q 2013	?	?	?	?	?	-	?

Fig. (2). Risk of Bias Assessment summary: review authors' judgements about each methodological quality item presented in different aspect from each included study.

All included trials were single-center randomized studies, but only the trial of Skvarc and coworkers was a randomized, double-

blinded, placebo-controlled study [40]. The work of Lee and coinvestigators was a phased, randomized, controlled study [39]. Nevertheless, none of the studies described the method of randomization. In two studies, there was no information about hiding allocation [39, 40]. The study conducted by Wang *et al.*, was a randomized trial, but the method used for randomization was not described [41].

3.1.5. Blinding

Blinding of participants and personnel was unclear in all studies, because of the insufficient information provided. Only one study described the method used for blinding of outcome assessment [39]. Skvarc *et al.*, did not clearly mention how the outcome assessment was blinded [40].

3.1.6. Incomplete Outcome Data

The included studies reported different time frames and duration of follow-ups. Lee *et al.*, followed up the patients for three months [39], Skvarc *et al.*, for six months [40] and Wang *et al.*, for 12 months [41]. The number of participants who completed the follow-ups and those having dropped out prior to the completion of the study was described in each of the three studies. It was the study of Skvarc *et al.*, alone that described the reasons for dropouts [40]. The reasons for dropouts were not described in the trials conducted by Wang *et al.*, and Lee *et al.*, however, they had considerably lower dropouts than the study of Skvarc *et al.* [39, 41].

3.1.7. Selective Reporting

Two studies reported all pre-specified and expected outcomes of interest as planned protocol [39, 40]. One trial reported an incomplete outcome [41].

3.1.8. Other Potential Sources of Bias

The publication bias was assessed by visual evaluation using a funnel plot. However, the limited number of studies did not allow realistic evaluation (Fig. S2), as described in section 10.4.3.1 of the Cochrane Handbook [32].

3.1.9. Quality of Evidence

The result of the GRADE assessment is shown in Table 3. In the beginning, all RCTs were considered as high-quality evidence; however, we had to downgrade them because of the very high risk of bias, including publication bias. Therefore, the overall quality of evidence is very low.

3.2. Effects of Interventions

3.2.1. Primary Outcome: The Presence of Acute Zoster Pain After Treatment

The three included trials compared the effects of GABA and its derivatives with placebo treatment involving 297 participants. Our meta-analysis showed that the incidence of acute zoster pain in the GABA and derivatives group was significantly lower compared to the placebo group, 18/148 vs 44/149, respectively (OR = 0.36; 95% CI = 0.14 to 0.93; Z = 2.11; P = 0.035; Fig. 3). Our analysis indicated that GABA and its derivatives could prevent acute zoster pain in a considerable number of patients after HZ infection. The Egger's test suggested no sign of statistical bias (P = 0.308).

3.2.2. Secondary Outcome: The Presence of Adverse Events During Treatment

The adverse events were evaluated in many aspects such as somnolence, fatigue, diplopia, constipation, flatulence, change in appetite, dyspepsia, oedema, headache, nausea, sedation, and dry mouth. The data showed no serious side effects (Fig. 4). However, some fatigue, constipation and dizziness have been reported in the studies of Skvarc *et al.*, and Lee *et al.*, [39, 40].

Table 3. Rating the quality of evidence using GRADE approach.

Certainty Assessment							No. of Patients		Effect		Certainty
No. of studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	GABA	Placebo/no Treatment	Relative (95% CI)	Absolute (95% CI)	
Prevalence of Acute Herpes Zoster Pain After GABA and Derivatives Use											
3	randomised trials	very serious ^a	not serious	not serious	not serious	publication bias strongly suspected ^b	18/148 (12.2%)	44/149 (29.5%)	OR 0.36 (0.14 to 0.93)	164 fewer per 1.000 (from 15 fewer to 240 fewer)	⊕○○○ VERY LOW

Notes: ^a Each RCT has a high risk of bias in major domains and some unclear risk of biases.

^b We can access only to abstract information.

Abbreviations: CI, Confidence interval; OR, Odds ratio.

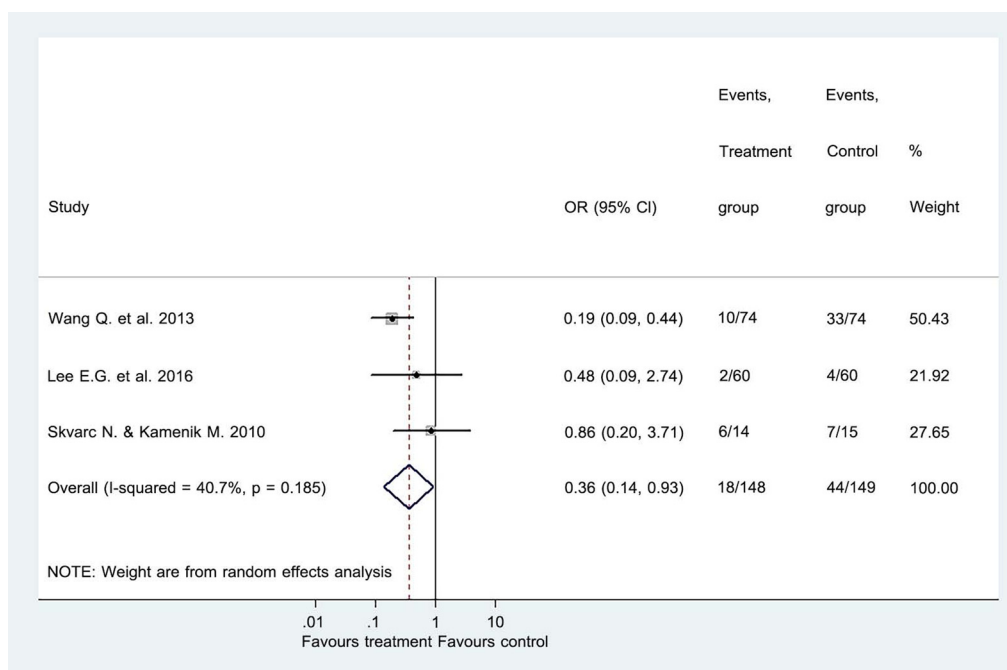


Fig. (3). Forest plot of comparison I: GABA or its derivatives vs placebo, primary outcome measurement. The presence of PHN after treatment. . Note: Odd ratio (OR), Confident Interval (CI).

3.2.3. Additional Outcome Measure not Specified in the Protocol: Quality of Life

Only one trial reported results concerning the quality of life, using the Dermatology Life Quality Index (DLQI) between tested and controlled groups during the follow-up. The mean difference DLQI between the gabapentin-treated group and the placebo group was not significant [39].

4. DISCUSSION

The aim of the present study was to investigate the effectiveness of GABA and its derivatives in reducing acute pain incidence in patients having HZ. We could only include three randomized trials involving 297 participants from Slovenia, Korea and China,

yielding an inhomogeneous patient population. The results showed that the treatment with GABA and its derivatives significantly reduced the number of patients with acute zoster pain. However, the absence of acute herpetic pain in one of the trials may be due to a slightly different experimental design [39], because they continued administering gabapentin beyond one month and gabapentin might mask the presence of pain.

The mechanism of action of GABA to prevent or decrease HZ-associated pain is not fully understood. Nevertheless, it is clear that the pathophysiology of the development and progress of PHN includes both central and peripheral disorders of the nervous system. Neuronal transmission is achieved by a wide range of neurotransmitters and regulatory peptides such as acetylcholine [42], noradrenaline [43], ATP [44], nitric oxide [45], GABA [46], chole-

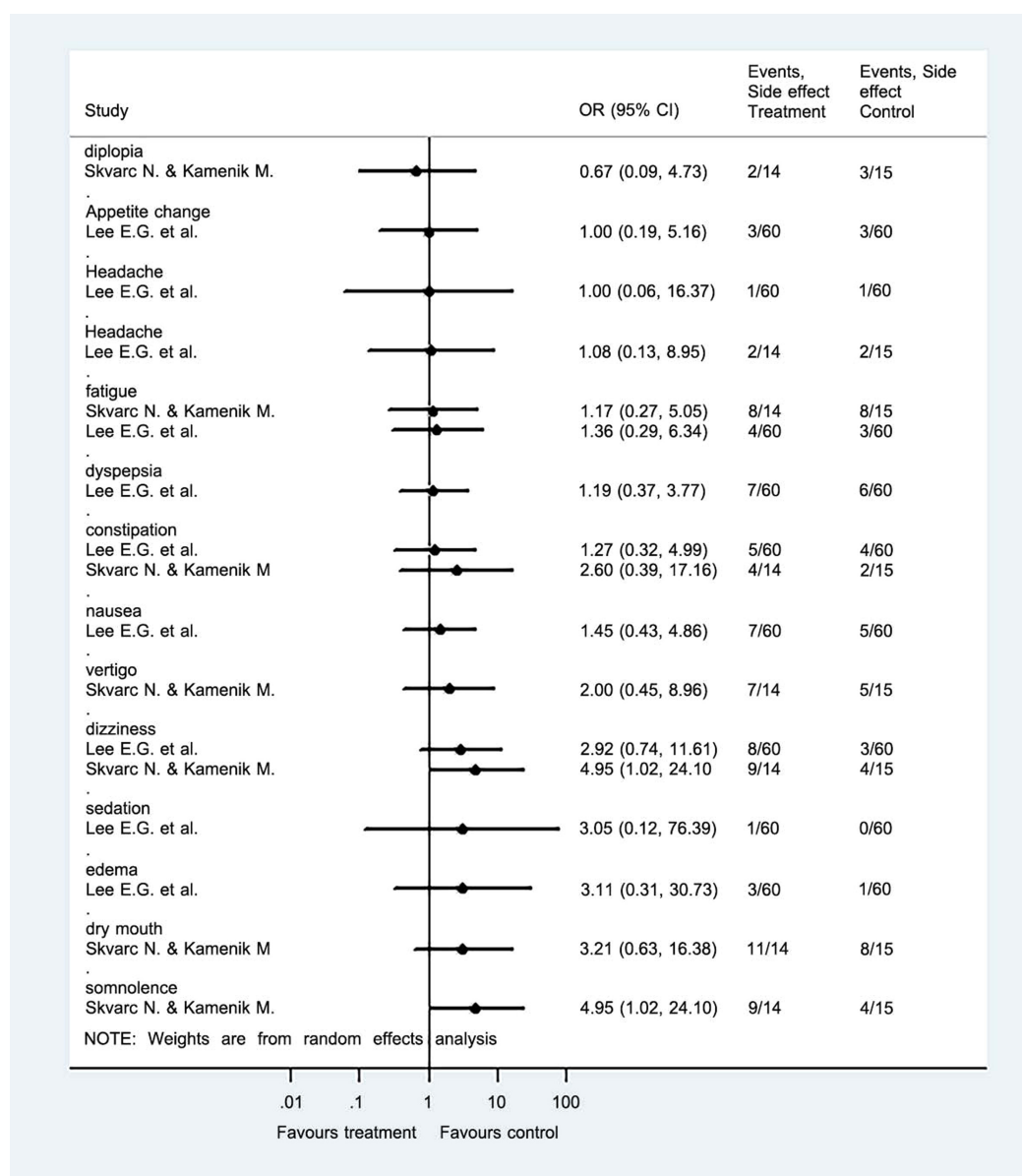


Fig. (4). Forest plot of comparison II: GABA or its derivatives vs placebo, secondary outcome measurement. The presence of adverse events during treatment. Note: Odd ratio (OR), Confident Interval (CI).

cystokinin [47], gastrin [48], GRP [49], VIP [50], galanin [51], bombesin [52] and BPC 157 [53]. Among these, GABA seems to be very important in pain control, because of the descending GABA-ergic neuronal nerve fibres inhibiting peripheral nociceptive signals [46]. Acute HZ-induced pain is one of the processes which could be controlled by GABA receptor activation. During the acute HZ, the virus becomes activated and propagates via axonal transport along the affected nerves, leading to an inflammatory immune response, which then causes the damage of peripheral and central neurons [54, 55]. Thus, peripheral nerves lose their ability to suppress nociceptive pain signals, thereby decreasing the threshold of nociceptive sensory activation and producing spontaneous ectopic discharges. The consequence is peripheral sensitization, that is, the appearance of disproportionate pain in response to normally non-painful stimuli [56]. At the cellular level, PHN upregulates transient receptor potential vanilloid 1, which is typically associated with pain [57], and increases the expression of voltage-gated sodium channels and potassium voltage-gated channels [58]. Experimental data suggest that these changes can be blocked by the GABA-like

compounds and also by sodium channel blockers [58]. Furthermore, it has been shown that the loss of GABA-ergic inhibitory interneurons at the dorsal horn leads to the loss of descending inhibition [57]. Therefore, the loss of GABA-ergic neurotransmission seems to play an important role in the development of acute HZ-associated pain [6, 57, 58].

The optimal dosage of GABA-like compounds is still to be determined. Case reports and clinical trials suggest the use of gabapentin from 900 to 3600 mg/day to treat PHN and other neuropathic pains [1, 2, 5, 59-64]. In response to such treatments, patients had decreased daily pain scores, improved mood and sleep quality and improved quality of life. Dizziness, somnolence, dry mouth and oedema were the most reported adverse events [1, 5, 59, 60, 62-64]. Other recorded adverse events were ataxia and weight gain [61]. These adverse events usually occurred at the beginning of the treatment and at higher dosages. Therefore, slow dose titration was suggested to reduce their occurrence [1, 2, 5, 59-64]. Alternatively, pregabalin was also applied in clinical trials in PHN patients with a dosage of 150 - 600 mg/day for 8 - 13 weeks, resulting in reduced

mean pain scores and the same adverse events as in the case of gabapentin [12, 65-68]. Gabapentin and pregabalin had been shown to have higher analgesic efficacy than oxycodone and amitriptyline in comparative studies [69, 70]. The recommended dose of gabapentin for zoster pain is 1800-3600 mg/day, administered in stepwise increase, starting with 300 mg/day. Pregabalin is reported to have fewer side effects than gabapentin [25]. Its suggested initial dose is 150 mg/day, which can be increased up to 300 mg/day within a week and then increased again to 600 mg/day after 2-4 weeks. Its maximal recommended daily dose is 600 mg [3, 28, 68].

There is no guideline for using and dosing GABA and its derivatives to prevent acute HZ pain. One randomized controlled trial suggested the application of gabapentin from 300 mg/day initially and then an increased dose of 1,800 mg/day [38] while Lee and his colleagues used 900mg/day of gabapentin [39] but Skvarc *et al.*, used 150-300 mg/day of pregabalin [40]. There was no dose given in the report of Wang *et al.* [41]. Our pilot literature search indicated that there were very few well-designed studies to investigate GABA derivatives. Therefore, we decided to design our PICO to pool different types of GABA derivatives and compare them to the placebo. Thus, we ignored the difference between GABA compounds which certainly have differences in potency, adverse reactions, pharmacokinetics and pharmacodynamics characteristics. Also, further studies are needed to determine whether the applied doses were lower than the optimal to prevent acute HZ pain. Nevertheless, the presently available data indicate that the application of GABA-like compounds in this respect is very promising.

Our present meta-analysis indicated no serious side effects of GABA-like compounds. The most commonly reported adverse reactions of GABA compounds are somnolence, dizziness, ataxia, fatigue and peripheral oedema, which may incidentally be the cause of patient withdrawal from the treatment [71, 72]. Only the study of Skvarc *et al.*, showed a significant difference in dizziness and somnolence between the pregabalin treated group and the placebo group [40]. Other events were not significantly different between the treatment and placebo groups. A previous analysis of adverse events from gabapentin in patients treated with PHN reported an increasing chance of peripheral oedema after a higher than 1,800 mg/day of gabapentin dose [71]. The meta-analysis on the safety of gabapentin showed that gabapentin increased the risk of adverse events significantly and nine out of eleven studies in which the applied dose was higher than 1800 mg/day [73]. Another meta-analysis on the adverse event profile of pregabalin also showed an increasing risk of adverse events in a dose-dependent manner [74]. All clinical trials included in our analysis used lower doses of gabapentin and pregabalin than the dose reported to cause adverse events.

The treatments for pain control during HZ may reduce the magnitude of the initiation phase of nociceptor-evoked central sensitivity. The application of antiviral agents limits the destruction of primary afferent nociceptor caused by the virus during acute infection and decreases pain perception as well. These procedures can reduce central sensitization [7]. There are convincing reasons for combining antiviral therapy with the effective relief of acute HZ pain as soon as possible, continuing it until the infection has completely been resolved [7]. It will decrease the risk of persistent pain below the level achieved by antiviral drugs used alone [5]. The antiviral agent should be administered within 72 hours of rash onset in order to decrease the severity of viral load [2, 3]. A currently published protocol suggests starting the administration of gabapentin at the same time as starting antiviral therapy [38]. In the included trials, the administration of gabapentin or pregabalin was not started at the same time after the onset of the disease. We have to note that the initiation time of treatment might affect the results of individual studies and the following meta-analyses.

4.1. Strengths and Limitations

The results of the present meta-analysis revealed that the administration of GABA and its derivatives is effective in preventing acute HZ pain in HZ patients. Moreover, this study is the first meta-analysis on the effect of GABA and its derivatives to reduce the incidence of acute HZ pain. It may pave the way for the prevention of long-lasting complications of HZ infection like PHN. However, there are significant limitations to our work, such as lacking high-quality evidence, low number of studies, high risk of bias, different definitions of the outcome, follow-up duration, and testing with different agents. Accordingly, the results should be interpreted considering such limitations.

4.2. Implications for Research and Clinical Practice

Our results suggest that GABA and its derivatives decrease the incidence of acute HZ pain. However, the heterogeneity of studies is high, and the quality of evidence is very low. Additionally, there is a need for evidence to verify that GABA compounds can prevent HZ-associated pain in more-extended follow-up periods. Further well-standardized, randomized clinical trials with a large number of participants are needed to clarify the beneficial effect of GABA and its derivatives on HZ-associated pain. The dosage, duration of treatment and follow-up time should be considered in these research protocols. The studies should put more emphasis on the characteristics of pain, distribution and severity of herpetic lesions, and the changes in the quality of life. Additionally, the bias of reports should be decreased to obtain more reliable data.

CONCLUSION

Our meta-analysis revealed that the administration of GABA and its derivatives reduce the incidence of HZ-associated pain in the first month after the onset of rash. However, because of the low number and moderate power of RCTs, which could be included, the presently available evidence is weak. Therefore, additional, well-designed randomized clinical trials are needed on the matter.

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

SUPPLEMENTARY MATERIAL

Supplementary material is available on the publisher's website along with the published article.

Appendix A

Searching Queries

1. The search string used in the PubMed database was (“herpes zoster”[MeSH Terms] OR “shingles”[All Fields]) AND (“gamma-aminobutyric acid”[MeSH Terms] OR “gaba”[All Fields] OR “gabapentin”[All Fields] OR neurontin[All Fields] OR “pregabalin”[All Fields]).
2. The search string used in the Web of Science database was ((gaba) OR (gamma-aminobutyric acid) OR (gabapentin) OR (neurontin) OR (pregabalin)) AND (herpes zoster).
3. The search string used in the EMBASE database was ["herpes zoster"] AND [("gamma-aminobutyric acid" OR "gaba" OR "gabapentin" OR neurontin OR "pregabalin")].
4. The search string used in the Scopus database was [(ALL (gamma AND aminobutyric AND acid) OR ALL (gaba) OR ALL (gabapentin) OR ALL (neurontin) OR ALL (pregabalin))] AND [ALL (herpes AND zoster)].
5. The search string used in the Ovid database was [herpes zoster.mp. [mp=ab, bc, bo, bt, cb, cc, ds, ge, gn, mc, mi, mq, or, ps, sq, st, ti, tm, tn, tx, rn, ct, sh, ot, nm, hw, kf, px, rx, an, ui, on, sy]] AND [(gamma-aminobutyric acid or gamma aminobutyric acid or gaba or gabapentin or neurontin or pregabalin).mp. [mp=ab, bc, bo, bt, cb, cc, ds, ge, gn, mc, mi, mq, or, ps, sq, st, ti, tm, tn, tx, rn, ct, sh, ot, nm, hw, kf, px, rx, an, ui, on, sy]].

Appendix B

Characteristics of included studies

Lee *et al.*, 2016

Methods	Prospective Randomized Controlled Study
Participants	120 participants (60 intervention, 60 control) who were diagnosed with acute herpes zoster, aged 50 and over and complaining about moderate to severe pain
Interventions	Intervention: 1000 mg valacyclovir HCL <i>tid</i> for 7 days + 650 mg acetaminophen <i>tid</i> + Gabapentin 300mg <i>tid</i> [stepwise in 3 days (900 mg/day)] Placebo: (1000 mg valacyclovir HCL <i>tid</i> for 7 days + 650mg acetaminophen <i>tid</i>)
Outcomes	PHN incidence Adverse events
Notes	No conflict of interest

Risk of Bias Table

Bias	Authors' Judgement	Support for Judgement
Random sequence generation (selection bias)	Unclear risk	Comment: There is no information about randomization.
Allocation concealment (selection bias)	Unclear risk	Comment: There is no information about concealment.
Blinding of participants and personnel (performance bias)	Unclear risk	Comment: There is no information about blinding.
Blinding of outcome assessment (detection bias)	Low risk	Quote: "The evaluators were different from the physician who prescribed, and they had no information to which group the patient was assigned"
Incomplete outcome data (attrition bias)	High risk	Quote: "Among them, 52 and 49 patients had completed follow-up period, respectively" Note: The authors did not mention any dropout reasons.
Selective reporting (reporting bias)	Low risk	Quote: "The incidences of PHN in the gabapentin group was 3.8% (2/52) which was lower than that in the control group [6.1%, (3/49)]. But the difference did not reach statistical significance (p50<0.672)." Note: The trial has a protocol summary and explain statistical analysis method. The outcome was reported as a plan and it had detail in statistics.
Other bias	Low risk	Note: Study appears to be free of other sources of risk

Skvarc *et al.*, 2010

Methods	Prospective Randomized Double-blind Placebo-controlled Study
Participants	29 participants (14 intervention, 15 control), out patients aged 30 - 80 years who had herpes zoster pain, and assessed equal or more than 4 on a 0 - 10 point Likert scale during the period between day 7 and day 14 of acute disease
Interventions	Intervention: 75 mg pregabalin po <i>bid</i> (150mg/day) Placebo: placebo drug po <i>bid</i> Can rise to 150 mg po <i>bid</i> (300 mg/day)
Outcomes	PHN incidence Adverse events
Notes	-

Risk of Bias Table

Bias	Authors' Judgement	Support for Judgement
Random sequence generation (selection bias)	Unclear risk	Comment: There is no information about randomization
Allocation concealment (selection bias)	Unclear risk	Comment: There is no information about concealment.
Blinding of participants and personnel (performance bias)	Unclear risk	Comment: There is no information about blinding.
Blinding of outcome assessment (detection bias)	Unclear risk	Quote: "patients assessed their intensity of pain, allodynia, hyperalgesia, and burning, prickling, tingling and electric shock-like sensations"
Incomplete outcome data (attrition bias)	High risk	Quote: "In the pregabalin group, nine patients withdrew from the study prematurely: five because of adverse effects and four because of disappearance of pain; in the placebo group, six patients withdrew prematurely: three because of adverse effects and three because of disappearance of pain" Note: high proportion of withdrawal from study
Selective reporting (reporting bias)	Low risk	Quote: "All pre-specified and expected outcomes of interest are reported"
Other bias	Low risk	Note: Study appears to be free of other sources of risk

Wang *et al.*, 2013

Methods	Randomized Controlled Study
Participants	148 participants
Interventions	Intervention: standard therapy with gabapentin Placebo: standard therapy
Outcomes	Incidence of PHN
Notes	Only abstract access

Risk of Bias Table

Bias	Authors' Judgement	Support for Judgement
Random sequence generation (selection bias)	Unclear risk	Note: The author mentioned that participants were randomly assigned to receive treatment, but we do not know how it was done, because we had access only the abstract.
Allocation concealment (selection bias)	Unclear risk	Note: The authors indicated only that participants were randomly assigned to receive treatment, but we do not know how it was done, because we had access only the abstract. It was not described in the abstract.
Blinding of participants and personnel (performance bias)	Unclear risk	Note: The authors did not mention any details about the blinding of participants and personnel in the abstract.
Blinding of outcome assessment (detection bias)	Unclear risk	Note: The authors did not mention any details about the blinding of outcome assessment in the abstract.
Incomplete outcome data (attrition bias)	Unclear risk	Quote: "123 patients completed 1-year follow up." Note: 16.89% did not completed 1-year follow up. However, the proportion of dropout is low, the authors did not state any dropout reason.
Selective reporting (reporting bias)	High risk	Quote: "At 3, 6, 12 months post - therapy, the incidence of PHN was still significantly lower in the gabapentin group than in the standard group" Note: The authors reported incomplete outcome results.
Other bias	Unclear risk	Note: We cannot assess other bias because we did not have enough data from the abstract.

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