Meta-Analysis

A Network Meta-Analysis of Randomized Clinical Trials to Assess the Efficacy and Safety of Antiviral Agents for Immunocompetent Patients with Herpes Zoster-Associated Pain

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Background: The most refractory symptom of herpes zoster (HZ) is pain. Approximately 90% of people who have HZ suffer from pain. Early use of antiviral medications has been found to reduce pain across all stages of the disease. Although many antiviral agents via oral or intravenous administration were recommended by clinical practice, the best approach to prevent HZ-associated pain remains uncertain.

Objectives: The purpose of this study was to compare the efficacy and adverse events of various antiviral agents used for the treatment of HZ-associated pain through a network meta-analysis.

Study Design: A systematic review and meta-analysis.

Setting: The Cochrane Register of Controlled Trials, Embase, and PubMed were searched from inception to Feb 2020.

Methods: Randomized clinical trials evaluating antiviral agents currently available for treating HZ-associated pain were included. We extracted data in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and conducted network meta-analyses with random-effects models. The primary outcome was the presence of acute pain at the end of anti-virus treatment, and the secondary outcomes included the presence of pain at 28-30 days after the onset of the acute herpetic rash, the presence of postherpetic neuralgia (PHN), and any other adverse events.

Results: A total of 17 randomized control trials with 5579 participants were included in this study. According to the results of the network meta-analysis, for the treatment of acute pain, there was no significant difference between oral acyclovir and intravenous acyclovir. Furthermore, oral famciclovir was the most effective treatment concerning both the odds ratio (OR) (superior to placebo OR = 0.25; 95% CI: 0.13~0.48) and the surface under the cumulative ranking curve (SUCRA) values of 0.84 for the treatment of acute pain among all the oral antiviral agents. For the presence of pain at 28-30 days, no significant difference was observed in efficacy between all antiviral treatments and placebo concerning the OR; however, oral valaciclovir ranked first (SUCRA values of 0.96). For the presence of NPH, oral famciclovir was determined to be the most effective (SUCRA values of 0.77) treatment with an efficacy of 0.42 (95% CI: 0.18~0.99) versus placebo. For adverse events, there was no significant difference between oral antivirals and placebo; however, intravenous acyclovir ranked last with a score of OR 4.31 (95% CI: 1.26~14.75) versus placebo.

Limitations: The distribution of severity of pain was different in various studies; then, the lack of availability of individual data prevented us from analyzing the effects of the risk factors.

Conclusions: For the treatment of acute pain and PHN, oral famciclovir was the most effective treatment among all the oral antiviral agents. For alleviating pain after 28-30 days, oral valaciclovir appeared to be the most effective among all antiviral agents. Additionally, all oral antiviral agents were well tolerated.

Clinical Trial Registration Information: PROSPERO under the identification CRD42020212834

Key words: Herpes zoster, antiviral agents, acyclovir, famciclovir, valaciclovir, efficacy, pain, network meta-analysis

Given the intrinsic nature of the secondary literature analysis in this study, the Ethics Committee of Chongqing Medical University's Second Hospital waived the ethical approval.

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Herpes zoster (HZ) is caused by the reactivation of varicella-zoster virus (VZV), which, following initial infection, becomes latent and persists in the sensory ganglia of the dorsal root and in cranial nerve ganglia (1). It is estimated to occur at a rate of 3.4 to 4.82/1,000 person-year generally and up to 11/1,000 person-year among patients over 80 years of age (2). The lifetime prevalence of HZ is as high as 25% to 30% and even exceeds 50% for those older than 80 years of age (2).

The most disturbing symptom of HZ in immunocompetent patients is the pain that adversely affects the physical, emotional, and social function of the patient (3,4), along with increased medical costs (5). Pain is experienced by approximately 90% of patients who have HZ (6). Thus, the priority for treatment is to reduce pain and accelerate healing (7). HZ-associated pain can last for variable days from a few days (acute pain) or for months (subacute pain), to many years, even for decades after the rash has healed (chronic pain). Therefore, recent research now supports the validity of defining 3 phases of pain in affected and adjacent dermatomes: (1) acute herpes zoster pain, mostly represents the acute rash convalescence; (2) subacute herpetic neuralgia, mostly persists past the acute phase without becoming chronic pain; (3) postherpetic neuralgia (PHN), is defined as pain lasting 120 days or more after rash onset (8). Pain assessment is a crucial component of clinical research for the treatment of shingles and PHN (9). There may be differences in the pathogenic mechanisms underlying prototypical symptoms and severe pain associated with HZ (10).

The use of antiviral medications could reduce the severity of acute pain, accelerate blister healing, and prevent the occurrence of new lesions in the acute phase (11,12). Therefore, antiviral agents, especially intravenous and oral acyclovir, have been widely used to treat HZ for decades, and many other antiviral medications were recommended to improve the recovery of HZ-associated pain for adults who are immunocompetent within 72 hours (13-15). In recent years, several other antivirus agents have been explored. Valacyclovir was demonstrated to accelerate the resolution of zoster-associated pain compared with oral acyclovir (16). Another antivirus agent, famciclovir, was reported to resolve the zoster-associated pain at a significantly faster rate (17) or as the same effectiveness (41) compared with acyclovir treatment (17). Furthermore, PHN was demonstrated to be reduced most effectively through the use of antiviral medications during the early stages of herpes zoster (18) since severe acute pain in PHN is a risk factor (14). However, since many clinical trials chose acyclovir or placebo as controls, there were few head-to-head comparisons between antiviral agents. Therefore, the best choice of antiviral agents to prevent HZ-associated pain remains uncertain.

All previous systematic reviews and meta-analyses were conducted pairwise. Thus, in this study, we used network meta-analysis (NMA), which has the ability to aggregate and analyze all direct and indirect comparative treatments, in order to compare the effects and safety of antiviral drugs in patients with HZ-associated pain and to provide a complete overview of the effectiveness and adverse effects of current antiviral agents for physician reference.

Methods

This systematic review and meta-analysis were in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) (19).

Data Sources and Searches

Separate literature searches were conducted independently by 2 reviewers (Yidan Liu and Shufang Xiao). Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, and Embase databases were searched from inception through Feb 2020. We also searched ClinicalTrials.gov to get more data. The search strategy is illustrated in detail in Appendix 1. The present study was registered in the International Prospective Register of Systematic Reviews (PROSPERO) with a registration number of CRD42020212834.

Study Selection

Two investigators independently reviewed the eligible reports in detail and abstracted relevant information using a standard extraction sheet. If the disagreement could not be resolved, a third review author was invited to arbitrate. Studies were included if they 1) were randomized controlled trials (RCTs) examining relevant clinical outcomes for immunocompetent participants aged 18 years or older, 2) included current available oral or intravenous antiviral treatments for herpes zoster, 3) included comparisons between different specific monotherapies and/or placebo, 4) included uncomplicated herpes zoster which diagnosed within 96 hours of symptom onset (including ophthalmicus). The exclusion criteria included RCTs featuring patients with immune dysfunction or other serious diseases, using antiviral drugs via different routes of administration (e.g., topical treatment), or diagnosed with complex herpes zoster. We excluded RCTs accessing pain burden via special methods (e.g., the ingenious pain burden scoring system), such as valomaciclovir, FV-100, and amenamevir, that are not inferior to valaciclovir and have high bioavailability and can be taken once daily (20-22). In addition, trials with unreliable data for extraction and overlapping data sets were excluded.

Data Extraction and Study Selection

We extracted information using standard data extraction forms, which included patient baseline characteristics, intervention, the dose of drugs, follow-up duration, and risk of bias. A standard criterion (Cochrane risk of bias tool) was used to assess the inherent risk of bias in trials. Two authors (Yidan Liu and Shufang Xiao) independently evaluated the quality of the studies. In the case of disagreement between the 2 investigators, a third review author was invited to arbitrate. In addition, we use GRADE profiler software to evaluate the quality assessment of articles (Appendix 2).

Outcome Measures

The primary outcome was: the presence of acute pain at the end of anti-virus treatment. The pain was defined as any degree of HZ-associated dermal discomfort. The secondary outcomes were: 1) the presence of subacute pain at 28-30 days after the onset of the acute herpetic rash; 2) the presence of PHN. We defined PHN according to clinical diagnostic criteria as pain persisting or recurring at the site of shingles and lasting at least 120 days after acute herpetic rash onset (8). If the information at 4 months was not available, we used data ranging between 2-6 months (we gave preference to the time point closest to 4 months; if equidistant, we took the longer outcome); 3) the proportion of participants with adverse events (AE) during treatment or within 2 weeks of stopping treatment. Adverse events were categorized as 'serious' or 'not serious.' Serious adverse events were those which led to death, were life-threatening, required inpatient hospitalization, prolonged the existing hospitalization, or resulted in persistent or significant disability. All other adverse events were considered to be nonserious.

Statistical Analyses

We conducted a pairwise meta-analysis and a network meta-analysis simultaneously and calculated the odds ratio (OR) and 95% confidence interval (CI) for each outcome by the random-effects model. A conventional meta-analysis based on Review Manager (RevMan) Version 5.2 (The Cochrane Collaboration, Copenhagen). Heterogeneity was assessed using Chi^2 tests and I^2 statistics, with $P < 0.1$ for the Chi^2 tests or $I^2 > 50\%$ being considered to indicate moderate heterogeneity. This network meta-analysis was performed with STATA version 15.0 (StataCorp., College Station, TX), based on the frequentist models. For each specified outcome, the treatment comparison was presented with a network graph. The treatment efficacy was ranked with the surface under the cumulative ranking curve (SUCRA), which is the cumulative relative probability of a treatment being the best option. A node-splitting approach and the loop-specific method were used to evaluate the potential inconsistency of the model. The publication bias in studies contributing to outcomes was assessed by visual inspection of funnel plots.Network meta-analysis model was shown in Appendix 3.

Results

There were 1037 articles found in our literature search. Two independent reviewers identified 163 articles as potentially suitable after screening the titles and abstracts of these articles and excluded 146. Ultimately, 17 studies with a total of 5579 patients were included in our NMA (Fig. 1 and Appendix 4). The characteristics of the included studies were summarized in Table 1. The network plot for the primary outcome is shown in Fig. 2. Appendix 5 shows the network plot for other outcomes.

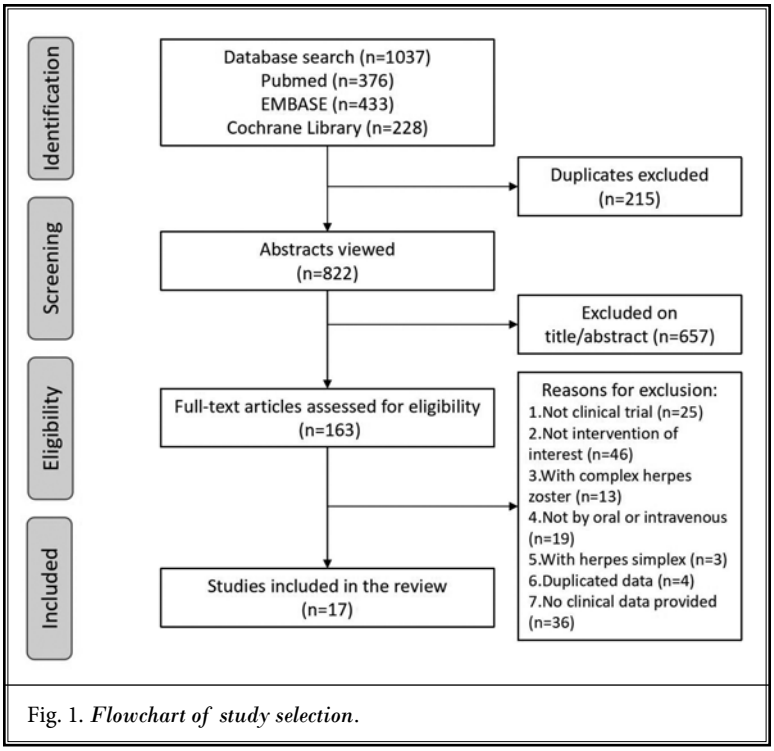

Fig. 1. *Flowchart of study selection.*

Risk of Bias

Regarding the risk of bias (Appendix 6), there was no "high" risk of bias in any study but one. This study was designated as having a "high" risk of bias, because the proportion of prodromal pain was not balanced in groups. The results were summarized in Fig. 3. The graph showed an overview of the authors' judgment about each risk of bias item and was presented as percentages across all included studies (Fig. 4), presenting the risk of bias summary of the 17 RCTs included in our network meta-analysis.

Primary Outcome

Results from pairwise meta-analysis for each outcome is detailed in Appendix 7. There were 14 studies with 5102 patients evaluating the efficacy of antiviral agents for acute pain at the end of antivirus treatment. No significant difference

Table 1. *Characteristics of studies included in the meta-analysis.*

Reference	Methods	Total patients (M/F)	Population	Intervention	Control	Treatment Period	Risk of Bias
B. Bean 1982 (29)	RCT, double-blind	29 (13/16)	patients > 18 years presenting HZ within 72 h	acyclovir (iv) 500 mg/m^2 q8h	5% dextrose	5 days	4
V. Esmann 1982 (30)	RCT, double-blind	56 (20/36)	patients > 18 years presenting HZ within 72 h	acyclovir(iv) 5 mg/kg q8h	mannitol	5 days	6
B. Bean 1983 (31)	RCT, double-blind	40 (18/22)	patients presenting HZ (uncomplicated segmental zoster) within 72h	acyclovir (iv) 10 mg/kg q8h	dextrose	5 days	5
J. McGill 1983 (32)	RCT, double-blind	37 (10/27)	patients >18 years presenting HZ within 96 h	acyclovir (iv) 5 mg/kg q8h	mannitol	5 days	5
M.W. McKendrick 1986 (33)	RCT, double-blind	205 (87/118)	patients > 60 years presenting HZ within 72 h	acyclovir (po) 800 mg quing id	placebo	7 days	5
S.P. Harding 1991 (34)	RCT, double-masked	42 (15/27)	patients presenting HZ (ophthalmicus) within 72 h	acyclovir (po) 800 mg quing id	active drug without acyclovir	10 days	3
N.A. Peterslund 1984 (35)	RCT, double-blind	40 (13/27)	patients > 60 years presenting HZ within 96 h	acyclovir (iv) 5mg/kg q8h	acyclovir (po) 400 mg 5 times/ day	5 days	5
H. Degreef 1994 (17)	RCT, double-blind	545 (238/307)	patients presenting HZ (uncomplicated zoster) within 72 h	famciclovir (po) 250 mg/500 mg/750 mg tid	acyclovir (po) 800 mg 5 times/ day	7 days	6

Table 1 cont. *Characteristics of studies included in the meta-analysis.*

Reference	Methods	Total patients (M/F)	Population	Intervention	Control	Treatment Period	Risk of Bias
M.C. Shen 2004 (36)	RCT, double-blind	55 (36/19)	patients > 18 years presenting HZ (uncomplicated zoster) within 72 h	famciclovir (po) 250 mg tid+placebo	acyclovir (po) 800 mg 5 times/ day +placebo	7 days	5
K.R. Beutner 1995 (26)	RCT, double-blind	1,141 (493/648)	patients > 50 years presenting HZ within 72 h	valaciclovir (po) 1,000 mg tid	acyclovir (po) 800 mg 5 times/ day +placebo	14 days	6
J. Colin 2000 (37)	RCT, double-blind	110 (53/57)	patients > 18 years presenting HZ (herpes zoster ophthalmicus) within 72 h	valaciclovir (po) 1,000 mg tid+placebo bid	acyclovir (po) 800 mg 5 times/ day +placebo tid	7 days	3
W.R. Lin 2001 (38)	RCT, not state the blinding	57 (37/20)	patients > 18 years presenting HZ (localized zoster) within 72 h	valaciclovir (po) 1,000 mg tid	acyclovir (po) 800 mg 5 times/ day	7 days	3
S. Tyring 1995 (39)	RCT, double-blind	419 (221/198)	patients > 18 years presenting HZ (uncomplicated zoster) within 72 h	famciclovir (po) 500 mg/750 mg tid	placebo	7 days	6
J. Söltz-Szöts 1998 (40)	RCT, double-blind	511 (219/292)	patients > 50 years presenting HZ within 72 h	netivudine (po) 20 mg/50 mg/100 mg /200 mg qd	acyclovir (po) 800 mg 5 times/ day	14 days	4
S.K. Tyring 2000 (41)	RCT, double-blind	597 (218/379)	patients > 50 years presenting HZ within 72 h	valaciclovir (po) 1,000 mg tid	famciclovir (po) 500 mg tid	7 days	5
F. Ono 2012 (23)	RCT, not state the blinding	86 (24/62)	patients > 20 years presenting HZ within 72 h or 72h-12 0h	valaciclovir (po)	famciclovir (po) 500 mg tid	7 days	4
S. Wassilew 2005 (42)	RCT, double-blind	2027 (812/1215)	patients > 50 years presenting HZ within 72 h	brivudin (po) 125 mg qd	famciclovir (po) 250 mg tid	7 days	7

was found between oral agents compared with intravenous acyclovir. All specific oral anti-virus agents were associated with a higher OR for acute pain compared with placebo, except oral netivudine, which was not demonstrated to be efficacious compared with placebo (Fig. 5). Oral famciclovir was hierarchically the best and the ORs were, with statistical significance, 0.25 (95% CI: 0.13~0.48) versus placebo, 0.28 (95% CI: 0.15~0.52) versus oral netivudine, and 0.51 (95% CI: 0.33~0.78) versus oral acyclovir, respectively. After famciclovir, oral valaciclovir was ranked second with OR as 0.27 (95% CI: 0.14~0.51) versus placebo while oral brivudin was ranked third with OR as 0.29 (95% CI: 0.14~0.61) (Appendix 8a).

Secondary Outcomes

The Presence of Subacute Pain at 28-30 Days After the Onset of the Acute Herpetic Rash

Eleven studies involving 5166 patients evaluated subacute pain at 28-30 days. Although no significant difference was revealed when antiviral drugs were compared with placebo, oral valaciclovir seemed like the most effective agent with OR as 0.50 (95% CI: 0.29~0.86) versus oral netivudine. In addition, the comparisons between oral antivirals and intravenous acyclovir were not significant apart from oral netivudine, which ranked last according SUCRA (Appendix 8b and 9.1).

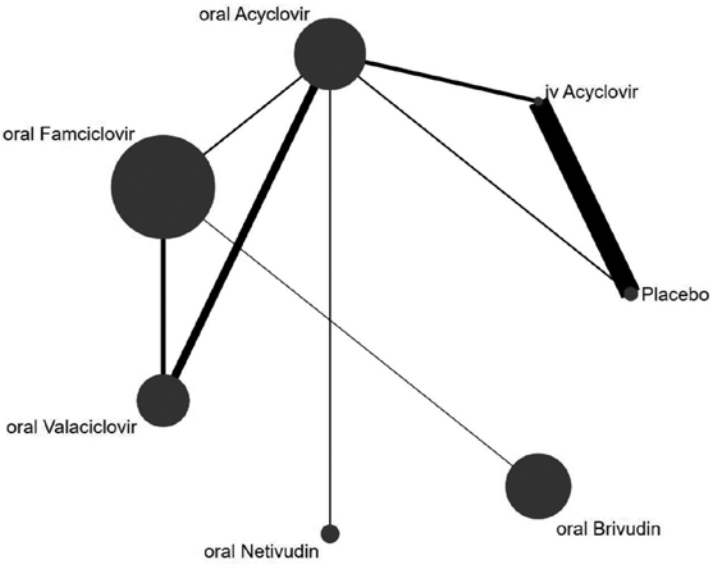

Fig. 2. *Network of the proportion of participants with pain posttreatment.*
Note: The width of the lines is proportional to the number of trials comparing every pair of treatments, and the size of every node is proportional to the number of randomized participants.

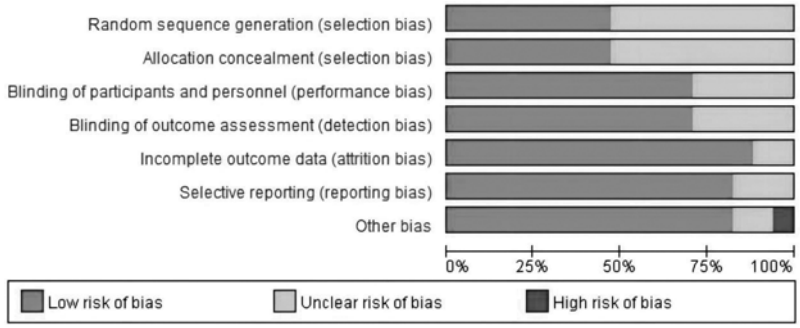

Fig. 3. *Risk of bias graph of included observational studies.*

The Presence of PHN

As for alleviating PHN, oral famciclovir ranked the best effective treatment with OR as 0.42 (95% CI: 0.18~0.99) versus placebo, and oral valaciclovir ranked second with OR as 0.53 (95% CI: 0.18~1.51). The rank of oral bruvidin and intravenous acyclovir were third and fourth, with ORs as 0.56 (95% CI: 0.16~1.97) and 1.05 (95% CI: 0.38~2.96) versus placebo, respectively. Oral netivudine and oral acyclovir ranked the last and second to last, with ORs as 2.38 (95% CI: 0.54~10.49) and 1.13 (95% CI: 0.43~3.00) versus placebo, respectively (Appendix 8c and 9.2).

Adverse Events

Based on our NMA, intravenous acyclovir was associated with the highest OR for any adverse events (AEs) 4.31 (95% CI: 1.26~14.75) compared with placebo, which could cause transient renal impairment or thrombophlebitis while most oral agents only cause nausea, vomiting, headaches, dizziness, diarrhea, or constipation (Appendix 10). It is thought that oral famciclovir is most tolerable for the least number of patients experiencing adverse effects, with no significant difference compared to placebo. Moreover, with regard to the number of patients reporting no-serious AEs, the ORs of oral valaciclovir, oral brivudin, and oral acyclovir were 0.72 (95% CI: 0.17~2.99), 0.75 (95% CI: 0.14~4.15), 0.98 (95% CI: 0.36~2.69), compared to placebo, respectively. Additionally, some serious AEs happened in treatment, but none of them were thought to relate to the antiviral drugs (Appendix 8d and 9.3).

Consistency Analysis

The network side split was used to conduct consistency analyses. The *P*-values for direct comparison and indirect comparison in all network meta-analyses were larger than 0.1, indicating that their results were highly consistent and reliable.

The results of direct and indirect estimates by the loop-specific method were presented in the appendix. There were no significant inconsistent loops except for the circle of oral famciclovir - oral acyclovir - oral valaciclovir for pain at 3-6 months, which might be the result of the variable following time (Appendix 11).

Risks of Publication Bias

The results of publication bias in studies contributing to primary outcome and AEs were displayed in the appendix, and the risks of publication bias were generally low (Appendix 12).

Sensitivity Analyses and Quality Assessment

The results of the sensitivity analysis for the omission of the last efficacy drug (oral netivudine) are presented in Appendix 13. A comparison of all antiviral drugs with placebo showed significant differences in preventing acute pain; oral famciclovir and valaciclovir ranked first and second, respectively, followed by oral brivudin and intravenous acyclovir. Antiviral drugs did not significantly reduce the number of people who experienced subacute pain at 28-30 days. Compared to placebo, only oral famciclovir significantly decreased the presence of PHN (OR 0.42, 95% CI: 0.18~-0.99). With intravenous acyclovir, the OR of experiencing an adverse event was 4.31 (95% CI: 1.26~14.75) times higher than with placebo. Overall, the results of sensitivity analyses agree with the results of all studies included in this meta-analysis.

In sensitivity analyses that included only trials with pain after 4 months, we discovered that oral famciclovir was superior to brivudin as it significantly differed from placebo, and oral netivudine was the least effective.

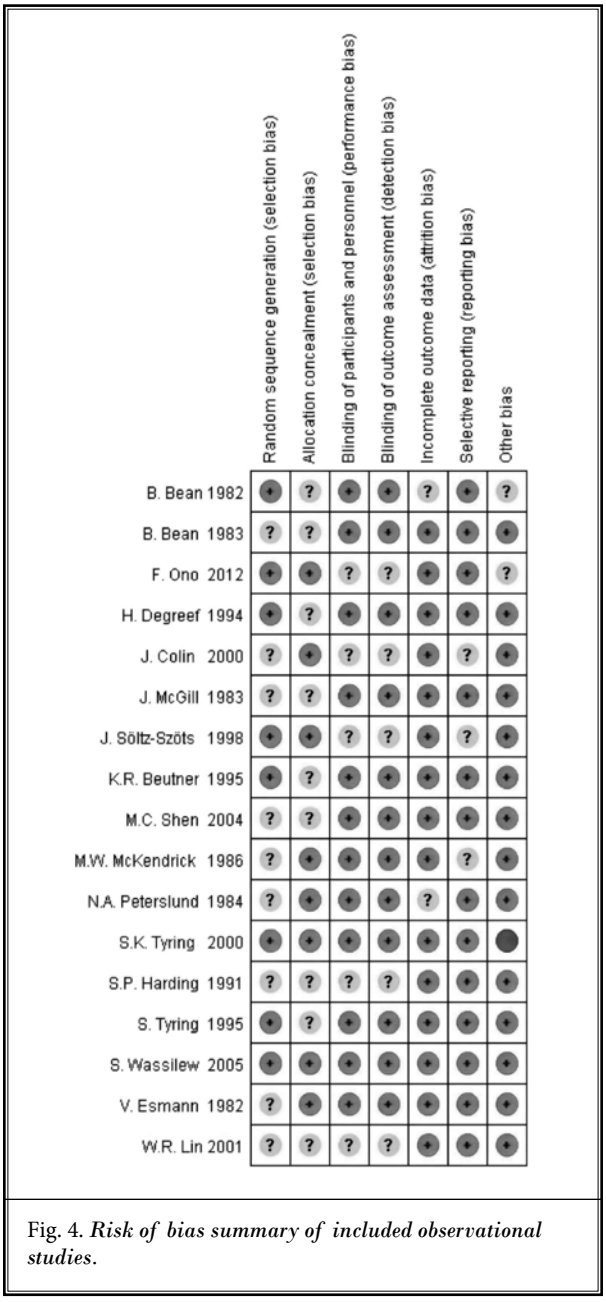

Fig. 4. *Risk of bias summary of included observational studies.*

Discussion

Zoster-associated pain at the acute phase and PHN are extremely disturbing symptoms, though HZ is a self-limitation disease in most immunocompetent patients. Since a number of oral antiviral agents have been developed following the discovery of intravenous acyclovir, many anti-virus agents were only compared with placebo or oral acyclovir. Which is the best choice for the treatment of HZ? This is an essential and important issue in clinical practice. However, there was no conclusive evidence as to the superiority of antiviral agents before. NMA is unique for estimating multiple direct and indirect comparisons. Our study is the first NMA to evaluate and quantify the relative effectiveness of various antivirals for the prevention of herpes zoster-related pain in immunocompetent patients. Our findings provide some reference for clinical applications.

Firstly, for acute pain relief, we found that oral famciclovir, followed by oral valacyclovir were associated with higher ORs compared with oral acyclovir, whereas there was no significant difference between oral antiviral agents and intravenous acyclovir. The findings of our study were consistent with that of

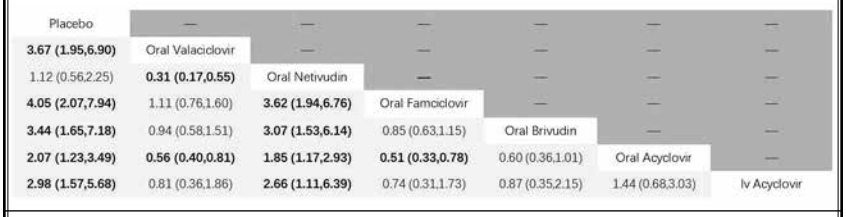

Fig. 5. *Network meta-analysis of the presence of acute pain at the end of treatment.* Note: Comparisons between treatments should be read from left to right, and the estimate is in the cell in common between the column-defining treatment and the row-defining treatment. Efficacy posttreatment values are given as all-cause discontinuation (odds ratios [ORs]); an OR of less than 1.00 favors the column-defining treatment. Data in parentheses represent 95% credible intervals. Significant results are set in boldface.

the included clinical study in that treatment with famciclovir within 48 hours of the onset of the rash alleviated herpes zoster-related pain more quickly than treatment with acyclovir (17,23). Not surprisingly, the effectiveness of all active interventions included in the study, except netivudine, was significantly superior to placebo. Netivudine is a novel antiviral compound with greater in vitro activity against the varicella-zoster virus; however, this new agent has not shown high efficacy in this network meta-analysis.

Secondly, as for the subacute herpetic neuralgia, our study included more direct and indirect evidence showing that none of the included antiviral treatments had better effect on pain than placebos at 28-30 days after the onset of HZ. Although valaciclovir was ranked first in efficacy in SUCRA and McDonald et al (24) found famiclovir ranked first for that valaciclovir produced a 36% reduction in pain at 21-30 days (RR 0.64, 95% CI: 0.59~0.70), and famiclovir was superior to acyclovir with a 46% reduction in pain at 28-30 days (RR 0.54, 95% CI, 0.48~0.68), compared with oral acyclovir. In addition, a previous meta-analysis found that oral acyclovir reduced the incidence of pain at one month (RR 0.83, 95% CI: 0.71~0.96) (25). Our meta-analysis also indicated a tendency towards reducing the incidence of pain with oral acyclovir compared with placebo; however, there was no significant difference. Nevertheless, our results may be subject to some publication bias and need to be interpreted with caution.

Thirdly, for PHN, based on our network meta-analysis results, oral famciclovir was the only drug that showed significant efficacy when compared to placebo for PHN and ranked first in efficacy in SUCRA. Oral valaciclovir and brivudin ranked second and third, respectively, with superiority over oral acyclovir. It is in accordance with a previous meta-analysis by McDonald et al (24) that valaciclovir significantly reduced the incidence of HZ-associated pain for periods of up to 112 days. Additionally, our assessment was supported by a controlled trial in which the use of valaciclovir decreased the duration of PHN compared with acyclovir and reduced the proportion of patients whose pain lasted 6 months (19.3% vs 25.7%) (26). A Cochrane review published in 2009 analyzing RCTs demonstrated that oral acyclovir did not significantly reduce the incidence of NPH at 6 months and 4 months (25), which is in line with our findings.

There may be different pathogenic mechanisms underlying prototypical symptoms and severe pain associated with HZ in each stage (10). In acute HZ, the varicella-zoster virus replicates in the ganglion and adjacent cells, leading to inflammation and acute pain. In addition, neuroplasticity has been recognized as a cause of peripheral and central sensitization in PHN, though the mechanisms are not fully understood. Besides, the pain associated with subacute herpetic neuralgia can be injurious or neuropathic (9). Although, researchers have speculated that PHN may be prevented by reducing nerve damage and inflammation caused by viral replication and then attenuating central sensitization by inhibiting the transmission of nociceptive afferent signals (27). Finally, antiviral drugs, while effective in reducing acute pain, do not have the advantages of reducing subacute pain and PHN in our study. Hence, we could speculate that the antiviral agents, which seemed to be more effective in alleviating inflammation and injuries related pain than in neuropathic adverse reactions, were not necessarily more effective in PHN, although there was a tendency as a matter of fact.

Finally, no serious adverse events have been reported among the anti-viral agents, and they are all well tolerated. However, some of the obvious side effects of intravenous acyclovir (including transient kidney injury and thrombophlebitis) have been noted, which can be avoided with caution.

Limitations

This study has some limitations. Firstly, there were differences within the study design, so that the distribution of severity of pain was different in various studies, which we attempted to harmonize to make

comparisons between antivirals. Secondly, we obtained some of the data from survival curves of pictures, but we deemed it acceptable with the low heterogeneity and natural incidence of pain. Thirdly, our study was limited by the lack of availability of individual data, such as age, gender, presence of prodromal symptoms, and the severity of the rash and pain, which were thought to be independent predictors of PHN (28). This prevented us from analyzing the effects of the risk factors. There was, however, no significant inconsistency between the included studies, and the distribution of pain was similar in both.

Conclusion

For the treatment of PHN at the acute phase, oral famciclovir was the most effective treatment among all the oral antiviral agents. For alleviating pain after 28-30 days, oral valaciclovir appeared to be the most effective among all antiviral agents. Additionally, all oral antiviral agents were well tolerated.

Supplemental material available at www.painphysicianjournal.com

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Appendix 1. *Full search strategy for each database*

1.2.1 PubMed

#1 Search (((Herpes Zoster) OR (Zona)) OR (Zoster)) OR (Shingles)

#2 Search ((((((((((Antiviral Agents) OR (Agents, Antiviral)) OR (Antivirals)) OR (Antiviral Drugs)) OR (Drugs, Antiviral)) OR (amenamevir)) OR (Valacyclovir)) OR (Famciclovir)) OR (Penciclovir) OR (Brivudin)) OR (Aciclovir)

#3 Search (((((((randomized[Publication Type]) OR (controlled clinical trial[Publication Type])) OR (randomized[Title/Abstract])) OR (placebo[Title/Abstract])) OR (drug therapy[MeSH Subheading])) OR (randomly[Title/Abstract])) OR (trial[Title/Abstract])) OR (groups[Title/Abstract])

#4 #1 and #2 and #3

1.2.2 Cochrane

#1 "Herpes zonster" or "shingles" or "zona" or "zoster"

#2 MeSH descriptor: [Herpes Zoster] explode all trees

#3 #1 or #2

#4 MeSH descriptor: [antiviral agents] explode all trees

#5 "antiviral agents" or "antivirals" or "agents" or "antiviral" or "antiviral drugs"or"drugs" or "amenamevir or "Valacyclovir" or "Famciclovir" or "Penciclovir" or "Brivudin" or "Aciclovir"

#6 #4 or #5

#7 #3 and #6

1.2.3 Embase

#1 'disseminated herpes zoster'/exp OR 'disseminated herpes zoster' OR (disseminated AND ('herpes'/exp OR herpes) AND ('zoster'/exp OR zoster) OR 'herpes zoster infection'/exp OR 'herpes zoster infection' OR ('herpes/exp OR herpes) AND ('zoster'/exp OR zoster) AND ('infection'/exp OR infection)) OR "herpes zoster neuralgia'/exp OR "herpes zoster neuralgia' OR ('herpes'/exp OR herpes) AND ("zoster'/exp OR zoster) AND ("neuralgia'/exp OR neuralgia)) OR "herpes zoster paralysis'/exp OR 'herpes zoster paralysis' OR ('herpes'exp OR herpes) AND ('zoster'/exp OR zoster AND ('paralysis'/exp OF paralysis)) OR 'shingles'/exp OR shingies OR 'varicella zoster infection'/exp OR 'varicella zoster infection' OR (varicella/exp OR varicella) AND ('zoster'/exp OR zoster) AND ('infection'/exp OR infection)) OR 'varella'/lexp OR varicella OR 'zoster virus infection' OR ('zoster'/exp OR zoster) AND ("virus'/exp OR virus) AND ('infection'/exp OR infection)) OR 'aricellovius infection'/exp OR 'aricellovirus infection" OR (varicellovirus'/exp OR varicellovirus) AND ('infection'exp OR infection)) OR 'zoster'exp OR zoster OR 'zoster, herpes'/exp OR 'zoster, herpes' OR (zoster, AND ('herpes'lexp OR herpes)) "herpes zoster'/exp

#2 'herpes zoster'/exp

#3 'antivirus agent'/exp

#4 'agent, virucidal'/exp OR 'agent, virucidal' OR 'anti viral agent'lexp OR 'anti viral agent" OR 'antiviral agent/exp 'OR 'antiviral agent" OR 'antiviral agents'/exp OR "antviral agents' "OR "antiviral drug'/expOR 'antiviral drug' OR 'antiviral substance'/exp OR 'antiviral substance' OR 'viral inhibitor'/exp OR 'viral inhibitor' OR 'virostatic agent'/exp OR 'virostatic agent' OR 'virucidal agent'/exp OR 'virucidal agent' OR 'virucide agent'/exp OR "virucide agent' OR 'viru pressor'/exp OR 'virus repressor' OR 'antiviral'/exp OR antiviral OR 'antivirals'/exp OR antivirals OR 'virucide'/exp OR virucide OR 'virustatic'/exp OR virustatic R 'virustatic agent'/exp OR 'virustatic agent'

#5 'amenamevir'/exp

#6 'valaciclovir'/exp

#7 'famciclavir'/exp

#8 'penciclov'/exp

#9 '5 (2 bromovinyl) 2' deoxyuridine'/exp

#10 'acicovir'/exp

#11 #1 OR #2

#12 #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10

#13 #11 AND #12

Databases and Trial registers	Citations
Databases:	
Pubmed	376
Cochrane	228
Embase	433
Total (databases)	1037
Trial registers:	
USA (ClinicalTrials.gov)	34
Total (trial registers)	34

Appendix 2. *The summary of findings table in GRADE (Grading of Recommendations Asseesment Development, and Evaluation.*

Interventions for [Condition] in [Population]							
Outcomes	**Intervention and Comparison intervention**	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
		Assumed risk	**Corresponding risk**				
		With comparator	**With intervention**				
the presence of acute pain at the end of anti-virus treatment							
	placebo/iv acyclovir	Study population		OR 2.93 (1.42 to 6.07)	162 (4 studies)	⊕⊕⊖⊖ low	
		229 per 1000	465 per 1000 (297 to 643)				
		Moderate					
		134 per 1000	312 per 1000 (180 to 484)				
	placebo/oral acyclovir	Study population		OR 2.09 (1.2 to 3.66)	205 (1 study)	⊕⊕⊖⊖ low	
		380 per 1000	562 per 1000 (424 to 692)				
		Moderate					
		380 per 1000	562 per 1000 (424 to 692)				
	iv acyclovir/ oral acyclovir	Study population		OR 0.66 (0.18 to 2.35)	40 (1 study)	⊕⊕⊖⊖ low	
		450 per 1000	351 per 1000 (128 to 658)				
		Moderate					
		450 per 1000	351 per 1000 (128 to 658)				
	oral acyclovir/ oral famciclovir	Study population		OR 1.96 (1.07 to 3.59)	545 (1 study)	⊕⊕⊕⊖ moderate	
		820 per 1000	899 per 1000 (830 to 942)				
		Moderate					
		820 per 1000	899 per 1000 (830 to 942)				
	oral acyclovir/ oral valaciclovir	Study population		OR 1.67 (0.98 to 2.85)	927 (3 studies)	⊕⊕⊕⊖ moderate	
		833 per 1000	893 per 1000 (830 to 934)				
		Moderate					
		719 per 1000	810 per 1000 (715 to 879)				
	oral acyclovir/ oral netivudin	Study population		OR 0.54 (0.34 to 0.86)	511 (1 study)	⊕⊕⊕⊖ moderate	
		760 per 1000	631 per 1000 (518 to 731)				
		Moderate					
		760 per 1000	631 per 1000 (518 to 731)				
	oral famciclovir/ oral valaciclovir	Study population		OR 0.9 (0.59 to 1.39)	683 (2 studies)	⊕⊕⊖⊖ low	
		859 per 1000	846 per 1000 (783 to 895)				
		Moderate					
		791 per 1000	773 per 1000 (691 to 840)				
	oral famciclovir/ oral brivudin	Study population		OR 0.85 (0.63 to 1.15)	2027 (1 study)	⊕⊕⊕⊕ high	
		915 per 1000	901 per 1000 (871 to 925)				
		Moderate					
		915 per 1000	901 per 1000 (871 to 925)				

Appendix 2 cont.

Interventions for [Condition] in [Population]							
Outcomes	**Intervention and Comparison intervention**	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
		Assumed risk	**Corresponding risk**				
		With comparator	**With intervention**				
the presence of subacute pain at 28-30 days after the onset of the acute herpetic rash							
	placebo/iv acyclovir	Study population		OR 1.27 (0.46 to 3.5)	85 (2 studies)	⊕⊕⊖⊖ low	
		457 per 1000	516 per 1000 (279 to 746)				
		Moderate					
		444 per 1000	504 per 1000 (269 to 736)				
	placebo/oral famciclovir	Study population		OR 1.44 (0.93 to 2.23)	419 (1 study)	⊕⊕⊖⊖ low	
		648 per 1000	726 per 1000 (632 to 804)				
		Moderate					
		648 per 1000	726 per 1000 (631 to 804)				
	oral acyclovir/ oral famciclovir	Study population		OR 0.87 (0.48 to 1.6)	600 (2 studies)	⊕⊕⊕⊖ moderate	
		769 per 1000	743 per 1000 (615 to 842)				
		Moderate					
		669 per 1000	637 per 1000 (492 to 764)				
	oral acyclovir/ oral valaciclovir	Study population		OR 1.42 (1.08 to 1.85)	927 (3 studies)	⊕⊕⊕⊖ moderate	
		528 per 1000	613 per 1000 (547 to 674)				
		Moderate					
		281 per 1000	357 per 1000 (297 to 420)				
	oral acyclovir/ oral netivudin	Study population		OR 0.64 (0.41 to 0.98)	511 (1 study)	⊕⊕⊖⊖ low	
		569 per 1000	458 per 1000 (351 to 564)				
		Moderate					
		569 per 1000	458 per 1000 (351 to 564)				
	oral famciclovir/ oral valaciclovir	Study population		OR 0.85 (0.6 to 1.21)	683 (2 studies)	⊕⊕⊖⊖ low	
		642 per 1000	603 per 1000 (518 to 684)				
		Moderate					
		646 per 1000	608 per 1000 (523 to 688)				
	oral famciclovir/ oral brivudin	Study population		OR 0.85 (0.72 to 1.02)	2027 (1 study)	⊕⊕⊕⊕ high	
		569 per 1000	529 per 1000 (488 to 574)				
		Moderate					
		569 per 1000	529 per 1000 (487 to 574)				

Appendix 2 cont.

Interventions for [Condition] in [Population]							
Outcomes	**Intervention and Comparison intervention**	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
		Assumed risk	**Corresponding risk**				
		With comparator	**With intervention**				
the presence of PHN							
	placebo/iv acyclovir	Study population		OR 1.05 (0.23 to 4.7)	122 (3 studies)	⊕⊖⊖⊖ very low	
		286 per 1000	296 per 1000 (84 to 653)				
		Moderate					
		316 per 1000	327 per 1000 (96 to 685)				
	placebo/oral acyclovir	Study population		OR 0.92 (0.28 to 3.03)	60 (1 study)	⊕⊕⊖⊖ low	
		241 per 1000	226 per 1000 (82 to 491)				
		Moderate					
		241 per 1000	226 per 1000 (82 to 490)				
	placebo/oral famciclovir	Study population		OR 2.33 (1.54 to 3.53)	419 (1 study)	⊕⊕⊖⊖ low	
		300 per 1000	500 per 1000 (398 to 602)				
		Moderate					
		300 per 1000	500 per 1000 (398 to 602)				
	oral acyclovir/ oral famciclovir	Study population		OR 4.02 (2.24 to 7.21)	545 (1 study)	⊕⊕⊖⊖ low	
		59 per 1000	202 per 1000 (123 to 312)				
		Moderate					
		59 per 1000	201 per 1000 (123 to 311)				
	oral acyclovir/ oral valaciclovir	Study population		OR 1.6 (1.17 to 2.19)	870 (2 studies)	⊕⊕⊖⊖ low	
		207 per 1000	294 per 1000 (234 to 363)				
		Moderate					
		141 per 1000	208 per 1000 (161 to 264)				
	oral acyclovir/ oral netivudin	Study population		OR 0.48 (0.24 to 0.93)	511 (1 study)	⊕⊕⊖⊖ low	
		201 per 1000	108 per 1000 (57 to 190)				
		Moderate					
		201 per 1000	108 per 1000 (57 to 190)				
	oral famciclovir/ oral valaciclovir	Study population		OR 1.1 (0.78 to 1.54)	597 (1 study)	⊕⊖⊖⊖ very low	
		320 per 1000	341 per 1000 (268 to 420)				
		Moderate					
		320 per 1000	341 per 1000 (269 to 420)				

Appendix 2 cont.

Interventions for [Condition] in [Population]							
Outcomes	**Intervention and Comparison intervention**	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
		Assumed risk	**Corresponding risk**				
		With comparator	**With intervention**				
	oral famciclovir/ oral brivudin	Study population		OR 0.76 (0.58 to 0.99)	2027 (1 study)	⊕⊕⊕⊖ moderate	
		140 per 1000	110 per 1000 (86 to 139)				
		Moderate					
		140 per 1000	110 per 1000 (86 to 139)				
the proportion of participants with adverse events							
	placebo/iv acyclovir	Study population		OR 0.24 (0.08 to 0.69)	106 (3 studies)	⊕⊕⊖⊖ low	
		429 per 1000	153 per 1000 (57 to 341)				
		Moderate					
		300 per 1000	93 per 1000 (33 to 228)				
	placebo/oral acyclovir	Study population		OR 1.02 (0.52 to 2.02)	251 (2 studies)	⊕⊕⊖⊖ low	
		194 per 1000	197 per 1000 (111 to 327)				
		Moderate					
		310 per 1000	314 per 1000 (189 to 476)				
	placebo/oral famciclovir	Study population		OR 1.29 (0.72 to 2.31)	419 (1 study)	⊕⊕⊖⊖ low	
		121 per 1000	151 per 1000 (90 to 241)				
		Moderate					
		121 per 1000	151 per 1000 (90 to 241)				
	oral acyclovir/ oral famciclovir	Study population		OR 2.34 (0.34 to 15.95)	600 (2 studies)	⊕⊖⊖⊖ very low	
		215 per 1000	390 per 1000 (85 to 814)				
		Moderate					
		201 per 1000	371 per 1000 (79 to 800)				
	oral acyclovir/ oral valaciclovir	Study population		OR 1.23 (0.89 to 1.7)	927 (3 studies)	⊕⊕⊕⊖ moderate	
		623 per 1000	670 per 1000 (595 to 737)				
		Moderate					
		94 per 1000	113 per 1000 (85 to 150)				
	oral acyclovir/ oral netivudin	Study population		OR 1.45 (0.94 to 2.24)	511 (1 study)	⊕⊕⊖⊖ low	
		441 per 1000	534 per 1000 (426 to 639)				
		Moderate					
		441 per 1000	534 per 1000 (426 to 639)				

Appendix 2 cont.

Interventions for [Condition] in [Population]							
Outcomes	**Intervention and Comparison intervention**	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
		Assumed risk	**Corresponding risk**				
		With comparator	**With intervention**				
	oral famciclovir/ oral valaciclovir	Study population		OR 1.18 (0.84 to 1.64)	683 (2 studies)	⊕⊕⊖⊖ low	
		295 per 1000	330 per 1000 (260 to 407)				
		Moderate					
		180 per 1000	206 per 1000 (156 to 265)				
	oral famciclovir/ oral brivudin	Study population		OR 0.84 (0.64 to 1.12)	2027 (1 study)	⊕⊕⊕⊖ moderate	
		118 per 1000	101 per 1000 (79 to 130)				
		Moderate					
		118 per 1000	101 per 1000 (79 to 130)				

Appendix 3. *Network meta-analysis model*

NMA model description—Random Effects Model for Dichotomous Data in State

network setup r n, studyvar(study) trtvar(treat)
network meta consistency
network meta inconsistency

network rank min
sucra prob*, rankogr lab("Placebo" "Iv Acyclovir" "Oral Acyclovir" "Oral Famciclovir" "Oral Valaciclovir" "Oral Netivudin" "Oral Brivudin")

network sidesplit all

network setup r n, studyvar(study) trtvar(treat)
network meta inconsistency
network meta consistency
network forest, xtitle(Log odds ratio and 95% CI)
intervalplot, eform lab("Placebo" "Iv Acyclovir" "Oral Acyclovir" "Oral Famciclovir" "Oral Valaciclovir" "Oral Netivudin" "Oral Brivudin") null(1) textsize(2)

netleague, eform lab("Placebo" "Iv Acyclovir" "Oral Acyclovir" "Oral Famciclovir" "Oral Valaciclovir" "Oral Netivudin" "Oral Brivudin") sort("Iv Acyclovir" "Oral Acyclovir" "Oral Famciclovir" "Oral Valaciclovir" "Oral Netivudin" "Oral Brivudin" "Placebo")

network convert pairs
netfunnel _y _stderr _t1 _t2 , bycomparison ytitle(Standard error of logor)

ifplot _y _stderr _t1 _t2 study, tau2(loop)

netweight _y _stderr _t1 _t2, color(navy) symbol(circle)

Appendix 4. *References for included trials*

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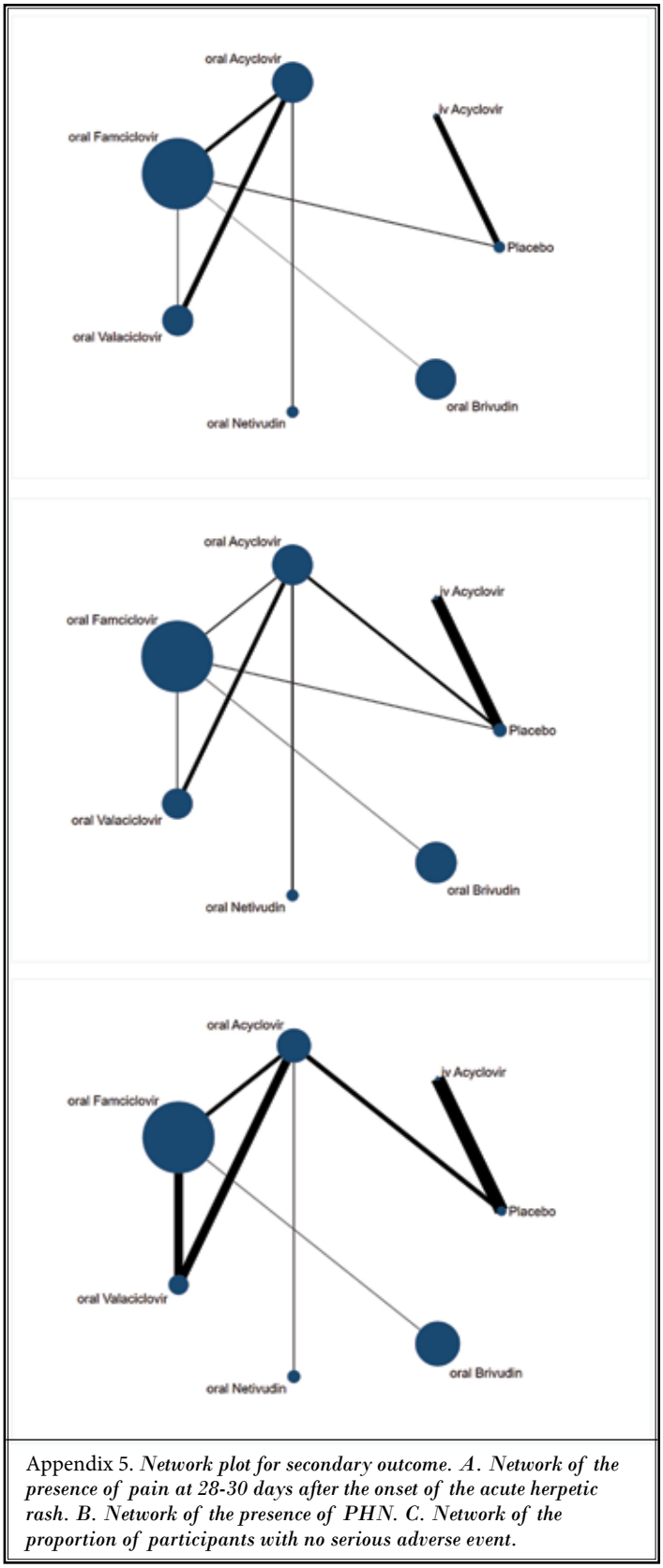


Appendix 5. *Network plot for secondary outcome. A. Network of the presence of pain at 28-30 days after the onset of the acute herpetic rash. B. Network of the presence of PHN. C. Network of the proportion of participants with no serious adverse event.*

Appendix 6 *Risk of bias assessment*

Risk of bias graph:
it is a chart of the comprehensive assessment of each bias risk item
Each item in the tool includes one or more specific entries in a 'Risk of bias'. Within each item, we record what was reported to have happened in the study to support a subsequent judgement. Acording to the details of each risk of every study, a judgement of 'Low risk' of bias, 'High risk' of bias, or 'Unclear risk' of bias are given out.

Selection bias:
1. Random sequence generation.
   - 1.1 Support for judgement: Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.
   - 1.2 Review authors' judgement: Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence.
2. Allocation concealment.
   - 2.1 Support for judgement: Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment.
   - 2.2 Review authors' judgement: Selection bias (biased allocation to interventions) due to inadequate. Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment.

Performance bias:
1. Blinding of participants and personnel
   - 1.1 Support for judgement: Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.
   - 1.2 Review authors' judgement: Selection bias (biased allocation to interventions) due to inadequate. Performance bias due to knowledge of the allocated interventions by participants and personnel during the study.

Detection bias:
1. Blinding of outcome assessment
   - 1.1 Support for judgement: Describe all measures used, if any, to blind outcome assessors from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.
   - 1.2 Review authors' judgement: Detection bias due to knowledge of the allocated interventions by outcome assessors.

Attrition bias:
1. Incomplete outcome data
   - 1.1 Support for judgement: Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported, and any re-inclusions in analyses performed by the review authors.
   - 1.2 Review authors' judgement: Attrition bias due to amount, nature or handling of incomplete outcome data.

Reporting bias:
1. Selective reporting.
   - 1.1 Support for judgement: State how the possibility of selective outcome reporting was examined by the review authors, and what was found.
   - 1.2 Review authors' judgement: Reporting bias due to selective outcome reporting.

Other bias:
1. Other sources of bias.
   - 1.1 Support for judgement: State any important concerns about bias not addressed in the other domains in the tool. If particular questions/entries were prespecified in the review's protocol, responses should be provided for each question/entry.
   - 1.2 Review authors' judgement: Bias due to problems not covered elsewhere in the appendix.

Appendix 7. *Results from pairwise meta-analysis for each outcome: numbers, estimates and heterogeneity*
a. Summary numbers of studies and patients from pair-wise meta-analysis of direct comparisons.

	Presence of acute pain (N / n)*	**Presence of pain at 28-30 days (N / n)**	**Presence of PHN (N / n)**	**Participant with no serious adverse event (N / n)**
Placebo vs.				
Iv Acyclovir	4/162	2/85	3/122	3/106
Oral Acyclovir	1/205	NA	1/60	2/251
Oral Famciclvr	NA	1/419	1/419	
Iv Acyclovir vs.				
Oral Acyclovir	1/40	NA	NA	NA
Oral Acyclovir vs.				
Oral Famciclovir	1/545	2/600	1/545	2/600
Oral Valaciclovir	3/927	3/927	2/870	2/167
Oral Netivudin	1/511	1/511	1/511	1/511
Oral Famciclovir vs.				
Oral Valaciclovir	2/683	1/597	1/597	2/683
Oral Brivudin	1/2027	1/2027	1/2027	1/2027

*N = number of studies; n = number of patients.

*b. Summary estimates from pair-wise meta-analysis of direct comparisons**

	Presence of acute pain OR (95% CI)	**Presence of pain at 28-30 days OR (95% CI)**	**Presence of PHN OR (95% CI)**	**Participant with no serious adverse event OR (95% CI)**
Placebo vs.				
Iv Acyclovir	**2.93 [1.42, 6.07]**	1.27 [0.46, 3.50]	1.05 [0.23, 4.70]	0.24 [0.08, 0.69]
Oral Acyclovir	**2.09 [1.20, 3.66]**	NA	0.92 [0.28, 3.03]	1.02 [0.52, 2.02]
OralFamciclvr	NA	1.44 [0.93, 2.23]	**2.33 [1.54, 3.53]**	1.29 [0.72, 2.31]
Iv Acyclovir vs.				
Oral Acyclovir	0.66 [0.18, 2.35]	NA	NA	NA
Oral Acyclovir vs.				
Oral Famciclovir	**1.96 [1.07, 3.59]**	0.87 [0.48, 1.60]	**4.02 [2.24, 7.21]**	2.34 [0.34, 15.95]
Oral Valaciclovir	1.67 [0.98, 2.85]	**1.42 [1.08, 1.85]**	**1.60 [1.17, 2.19]**	1.23 [0.89, 1.70]
Oral Netivudin	**0.54 [0.34, 0.86]**	**0.64 [0.41, 0.98]**	**0.48 [0.24, 0.93]**	1.45 [0.94, 2.24]
Oral Famciclovir vs.				
Oral Valaciclovir	0.90 [0.59, 1.39]	0.85 [0.60, 1.21]	1.10 [0.78, 1.54]	1.18 [0.84, 1.64]
Oral Brivudin	0.85 [0.63, 1.15]	0.85 [0.72, 1.02]	0.76 [0.58, 0.99]	0.84 [0.64, 1.12]

* N= number of studies; n= number of patients.
Significant results are bolded and undersored.

Appendix 7 cont. *c. Heterogeneity test result, I^2 and heterogeneity estimate*

Presence of acute pain				
	No. of studies	***P* value**	**I^2**	**τ^2**
Placebo vs iv acyclovir	4	0.61	0.0%	0.0000
Oral acyclovir as oral valaciclovir	3	0.23	31.0%	0.07
Oral famciclovir as oral valaciclovir	2	0.55	0.0%	0.0000

Presence of pain at 28-30 days				
	No. of studies	***P* value**	**I^2**	**τ^2**
Placebo vs iv acyclovir	2	0.26	21.0%	0.13
Oral acyclovir as oral famciclovir	2	0.24	28.0%	0.07
Oral acyclovir as oral valaciclovir	3	0.47	0.0%	0.0000
oral famciclovir as oral valaciclovir	2	0.30	7.0%	0.01

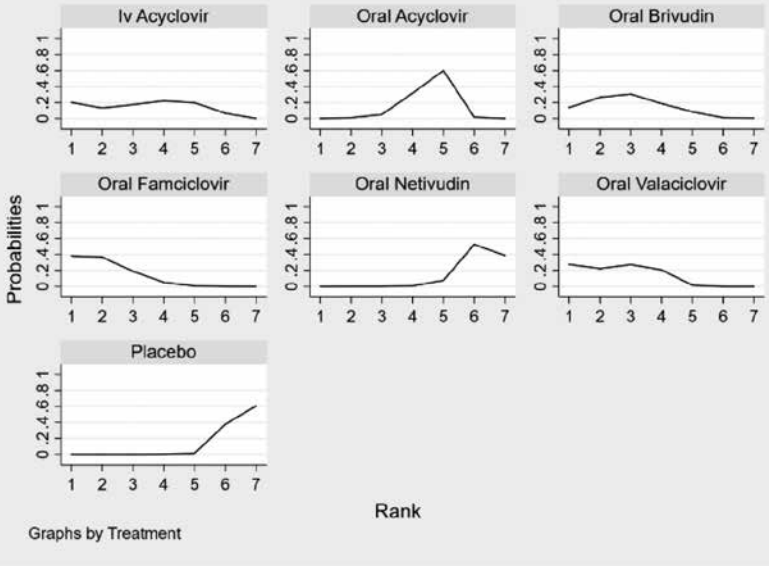
Presence of PHN				
	No. of studies	***P* value**	**I^2**	**τ^2**
Placebo vs iv acyclovir	4	0.06	65.0%	1.13
Oral acyclovir as oral valaciclovir	2	0.65	0.0%	0.0000

Participant with no serious adverse event				
	No. of studies	***P* value**	**I^2**	**τ^2**
Placebo vs iv acyclovir	3	0.76	0.0%	0.0000
Placebo vs oral acyclovir	2	0.96	0.0%	0.0000
Oral acyclovir as oral famciclovir	2	0.003	88.0%	1.71
Oral acyclovir as oral valaciclovir	3	0.64	0.0%	0.0000
oral famciclovir as oral valaciclovir	2	0.54	0.0%	0.0000

Appendix 8. *Treatment ranking and SUCRA plot for each outcome*
a. Treatment ranking and SUCRA plot for mean overall change in the presence of acute pain

Treatment ranking		
Rank	**Treatments**	**SUCRA (%)**
1	Oral famciclovir	84.3
2	Oral valaciclovir	75.6
3	Oral brivudine	68.9
4	Iv acyclovir	61.9
5	Oral acyclovir	40.6
6	Oral Netivudin	11.9
7	Placebo	6.8

* Larger SUCRAs denote more effective interventions.

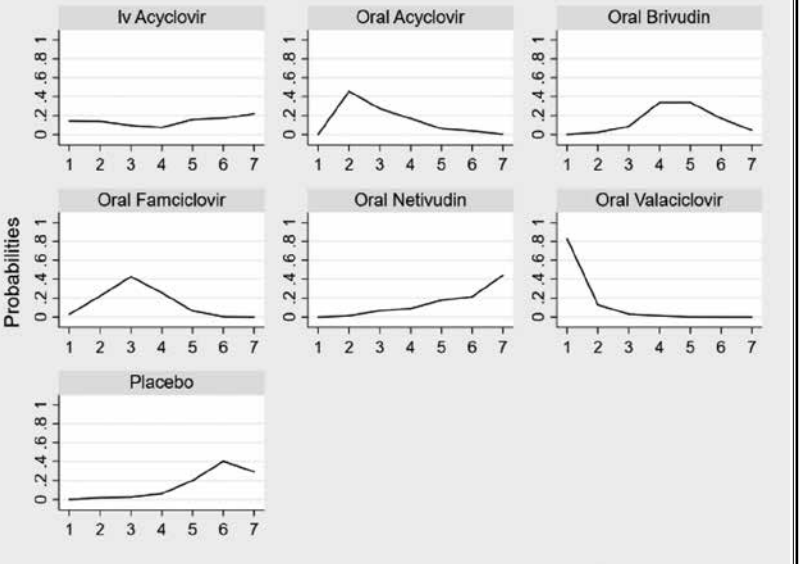


Supplemental Fig. 13a. *Cumulative probability plots (Random Effects model)*

Appendix 8 cont. *b. Treatment ranking and SUCRA plot for the presence of pain at 28-30 days*

Treatment ranking		
Rank	**Treatments**	**SUCRA (%)**
1	Oral valaciclovir	96.0
2	Oral acyclovir	67.4
3	Oral famciclovir	64.7
4	Iv acyclovir	44.0
5	Oral brivudin	38.7
6	Placebo	19.7
7	Oral Netivudin	19.4

* Larger SUCRAs denote more effective interventions.

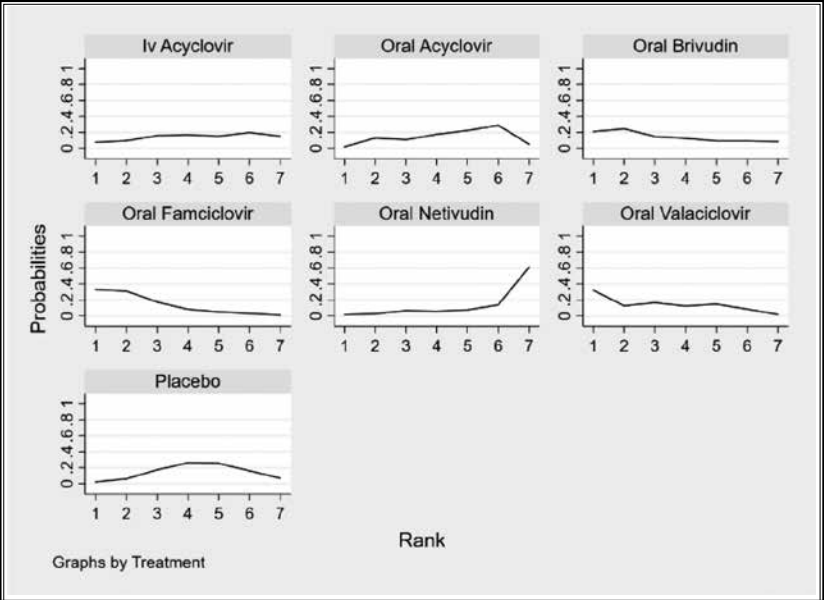


Supplemental Fig. 13b. *Cumulative probability plots (Random Effects model)*

Appendix 8 cont. *c. Treatment ranking and SUCRA plot for the presence of PHN*

Treatment ranking		
Rank	**Treatments**	**SUCRA (%)**
1	Oral famciclovir	77.3
2	Oral valaciclovir	66.9
3	Oral brivudine	62.1
4	Iv acyclovir	43.0
5	Placebo	43.0
6	Oral acyclovir	41.2
7	Oral Netivudin	16.4

* Larger SUCRAs denote more effective interventions.

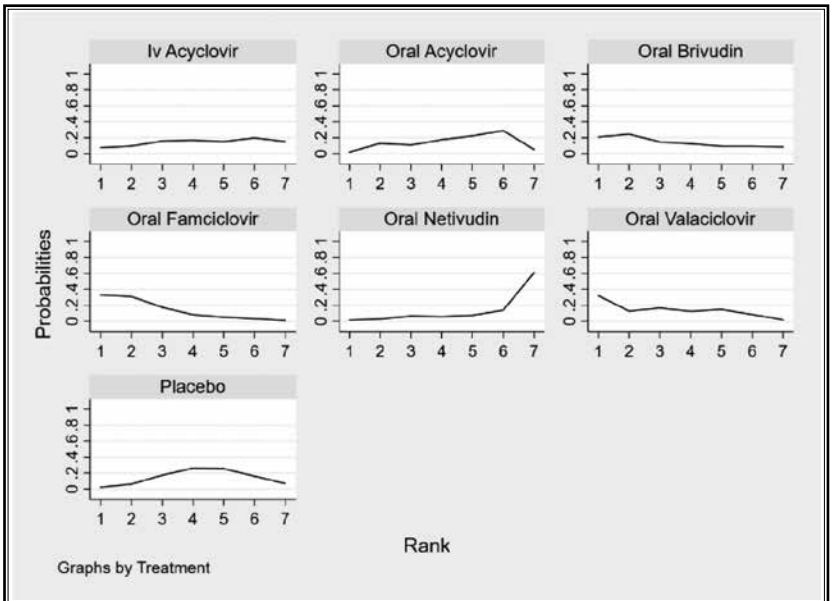


Supplemental Fig. 13c. *Cumulative probability plots (Random Effects model)*

d. Treatment ranking and SUCRA plot for the participant with no-serious adverse events

Treatment ranking		
Rank	**Treatments**	**SUCRA (%)**
1	Oral famciclovir	79.1
2	Oral brivudin	67.2
3	Oral Netivudin	63.9
4	Placebo	48.0
5	Oral acyclovir	45.1
6	Oral valaciclovir	42.2
7	Iv acyclovir	4.6

* Larger SUCRAs denote more effective interventions.



Supplemental Fig. 13d. *Cumulative probability plots (Random Effects model)*

Appendix 9. *Network meta-analysis of second outcomes*

Appendix 8.1. *Presence of pain at 28-30 days (OR[95% Crl])*

Interventions are reported in alphabetical order. Comparisons between treatments should be read from left to right, and the estimate is in the cell in common between the column-defining treatment and the row-defining treatment. For Participant with pain at 28-30 days, an odds ration (OR) below 1 favors the column-defining treatment.

Placebo						
1.56 (0.84,2.89)	**Oral Valaciclovir**					
0.77 (0.35,1.69)	0.50 (0.29,0.86)	**Oral Netivudin**				
1.44 (0.89,2.31)	0.92 (0.62,1.36)	1.86 (1.00,3.45)	**Oral Famciclovir**			
1.23 (0.71,2.10)	0.79 (0.49,1.25)	1.58 (0.81,3.09)	0.85 (0.66,1.10)	**Oral Brivudin**		
1.22 (0.65,2.27)	0.78 (0.59,1.02)	1.57 (0.98,2.52)	0.85 (0.57,1.26)	0.99 (0.62,1.59)	**Oral Acyclovir**	
1.22 (0.50,2.95)	0.78 (0.27,2.27)	1.57 (0.49,5.07)	0.85 (0.31,2.31)	0.99 (0.35,2.80)	1.00 (0.34,2.92)	**Iv Acyclovir**

Bold: Treatment

Appendix 9.2. *Presence of PHN (OR [95% Crl])*

Interventions are reported in alphabetical order. Comparisons between treatments should be read from left to right, and the estimate is in the cell in common between the column-defining treatment and the row-defining treatment. For Participant with pain at 2-6 months, an odds ratio (OR) below 1 favors the column -defining treatment.

Placebo						
1.90 (0.66,5.46)	**Oral Valaciclovir**					
0.42 (0.10,1.85)	0.22 (0.06,0.83)	**Oral Netivudin**				
2.37 (1.01,5.56)	1.24 (0.58,2.65)	5.64 (1.47,21.64)	**Oral Famciclovir**			
1.79 (0.51,6.36)	0.94 (0.28,3.14)	4.27 (0.83,21.97)	0.76 (0.30,1.93)	**Oral Brivudin**		
0.88 (0.33,2.34)	0.46 (0.23,0.94)	2.10 (0.69,6.43)	0.37 (0.18,0.79)	0.49 (0.15,1.63)	**Oral Acyclovir**	
0.95 (0.34,2.66)	0.50 (0.11,2.18)	2.26 (0.37,13.80)	0.40 (0.11,1.52)	0.53 (0.10,2.70)	1.07 (0.26,4.45)	**Iv Acyclovir**

Bold: Treatment

Appendix 9.3. *Participant with no serious adverse event (OR [95% Crl])*

Interventions are reported in alphabetical order. Comparisons between treatments should be read from left to right, and the estimate is in the cell in common between the column-defining treatment and the row-defining treatment. For Participant with no serious adverse event, an odds ratio (OR) below 1 favors the column -defining treatment.

Placebo						
1.39 (0.33,5.76)	**Oral Valaciclovir**					
1.48 (0.33,6.69)	1.07 (0.24,4.81)	**Oral Netivudin**				
1.58 (0.42,6.00)	1.14 (0.42,3.06)	1.07 (0.26,4.41)	**Oral Famciclovir**			
1.33 (0.24,7.36)	0.96 (0.22,4.12)	0.90 (0.15,5.32)	0.84 (0.29,2.46)	**Oral Brivudin**		
1.02 (0.37,2.80)	0.74 (0.27,2.01)	0.69 (0.22,2.11)	0.65 (0.27,1.55)	0.77 (0.19,3.05)	**Oral Acyclovir**	
0.23 (0.07,0.80)	0.17 (0.03,1.10)	0.16 (0.02,1.10)	0.15 (0.02,0.91)	0.17 (0.02,1.44)	0.23 (0.05,1.12)	**Iv Acyclovir**

Bold: Treatment

Appendix 10. *Number of patients with serious adverse event*

Comparisons	**Number of trials**	**Events/total (%)**	
		Group 1	**Group 2**
Valaciclovir VS acyclovir	2	2/88 (2.2%)	1/79(1.2%)
Netivudine VS Acyclovir	1	2/408 (0.4%)	0/103(0%)
Valaciclovir VS famciclovir	2	5/346 (1.4%)	4/337 (1.1%)
brivudin vs famciclovir	1	22/1019 (2.2%)	17/1008(1.7%)

Appendix 11. *Assessment of incoherence for each outcome*

a. Evaluation of the incoherence

Tests of local incoherence revealed that the percentages for inconsistent loops were to be expected according to empirical data with the methods of Veroniki et al (Int J Epidemiol 2013; 42:332-45).

Presence of acute pain					
Loop	**IF**	**z-value**	***P* value**	**95%CI**	τ^2
Placebo-iv acyclovir-oral acyclovir	0.081	0.101	0.920	(0.00,1.65)	0.000
Oral acyclovir-oral famciclovir-oral valaciclovir	0.025	0.054	0.957	(0.00-0.94)	0.014

*These loops are formed only by multi-arm trials.

Presence of pain at 28-30 days					
Loop	**IF**	**z-value**	***P* value**	**95%CI**	τ^2
Oral acyclovir-oral famciclovir-oral valaciclovir	0.499	1.608	0.108	(0.00-1.11)	0.000

Presence of PHN					
Loop	**IF**	**z-value**	***P* value**	**95%CI**	τ^2
Oral acyclovir-oral famciclovir-oral valaciclovir	1.010	2.651	0.008	(0.26-1.76)	0.000
Placebo-Oral acyclovir-oral famciclovir	0.457	0.643	0.520	(0.00-1.85)	0.000

*These loops are formed only by multi-arm trials.

Participant with no serious adverse					
Loop	**IF**	**z-value**	***P* value**	**95%CI**	τ^2
Oral acyclovir-oral famciclovir-oral valaciclovir	0.929	1.566	0.553	(0.00,4.00)	1.073

*These loops are formed only by multi-arm trials.

b. Evaluation of the incoherence by node-splitting model

Tests of incoherence by node-splitting method fitted the node-splitting model of Dias et al (Stat Med 2010; 29:932-44). The results reported the estimated direct and indirect treatment effects and their difference; the P-value for the difference is the test of incoherence.

Presence of acute pain							
Comparisons	**Direct**		**Indirect**		**Difference**		
	Coef	**SE**	**Coef**	**SE**	**Coef**	**SE**	***P* value**
Placebo-Iv acyclovir	-1.076205	.3707715	-1.156811	.7091779	.0806062	.8002529	0.920
Placebo-oral acyclovir	-.7384443	.2848387	-.6578292	.7478418	-.0806151	.8002502	0.920
Ivl acyclovir- oral acyclovir	.4183685	.6494616	.3377618	.4675516	.0806067	.800253	0.920
oral acyclovir- oral famciclovir	-.6715733	.3314097	-.6469359	.358225	-.0246374	.4880041	0.960
oral acyclovir- oral valacyclovir	-.5549759	.2434562	-.5796101	.4108503	.0246342	.4880041	0.960
oral acyclovir- oral netivudin *	.6148037	.2347984	1.099315	1252.724	-.484511	1252.724	1.000
oral famciclovir- oral valacyclovir	.0919627	.2428253	.1165959	.4112142	-.0246332	.4879915	0.960
famciclovir - oral brivudin *	.1653505	.1538458	2.336735	1394.81	-2.171384	1394.81	0.999

*All the evidence about these contrasts comes from the trials which directly compare them.

Appendix 11. *Assessment of incoherence for each outcome*
b. (continued) Evaluation of the incoherence by node-splitting model

Presence of pain at 28-30 days							
Comparisons	**Direct**		**Indirect**		**Difference**		
	Coef	**SE**	**Coef**	**SE**	**Coef**	**SE**	***P* value**
Placebo-Iv acyclovir	.	.	.	.	.	.	.
Placebo-oral famciclovir *	-.3627575	.2431192	-.095548	233.1555	-.2672095	233.155	0.999
oral acyclovir- oral famciclovir	.0662819	.2205762	-.432806	.2182737	.4990879	.310318	0.108
oral acyclovir- oral valacyclovir	-.3481592	.137427	.1509291	.2782284	-.4990883	.310318	0.108
oral acyclovir- oral netivudin *	.4514575	.2402735	.1206717	1359.632	.3307857	1359.623	1.000
oral famciclovir- oral valacyclovir	.084647	.1695796	-.4144411	.2598846	.4990881	.3103179	0.108
famciclovir - oral brivudin *	.1593402	.128806	1.166863	2548.591	-1.007523	2548.591	1.000

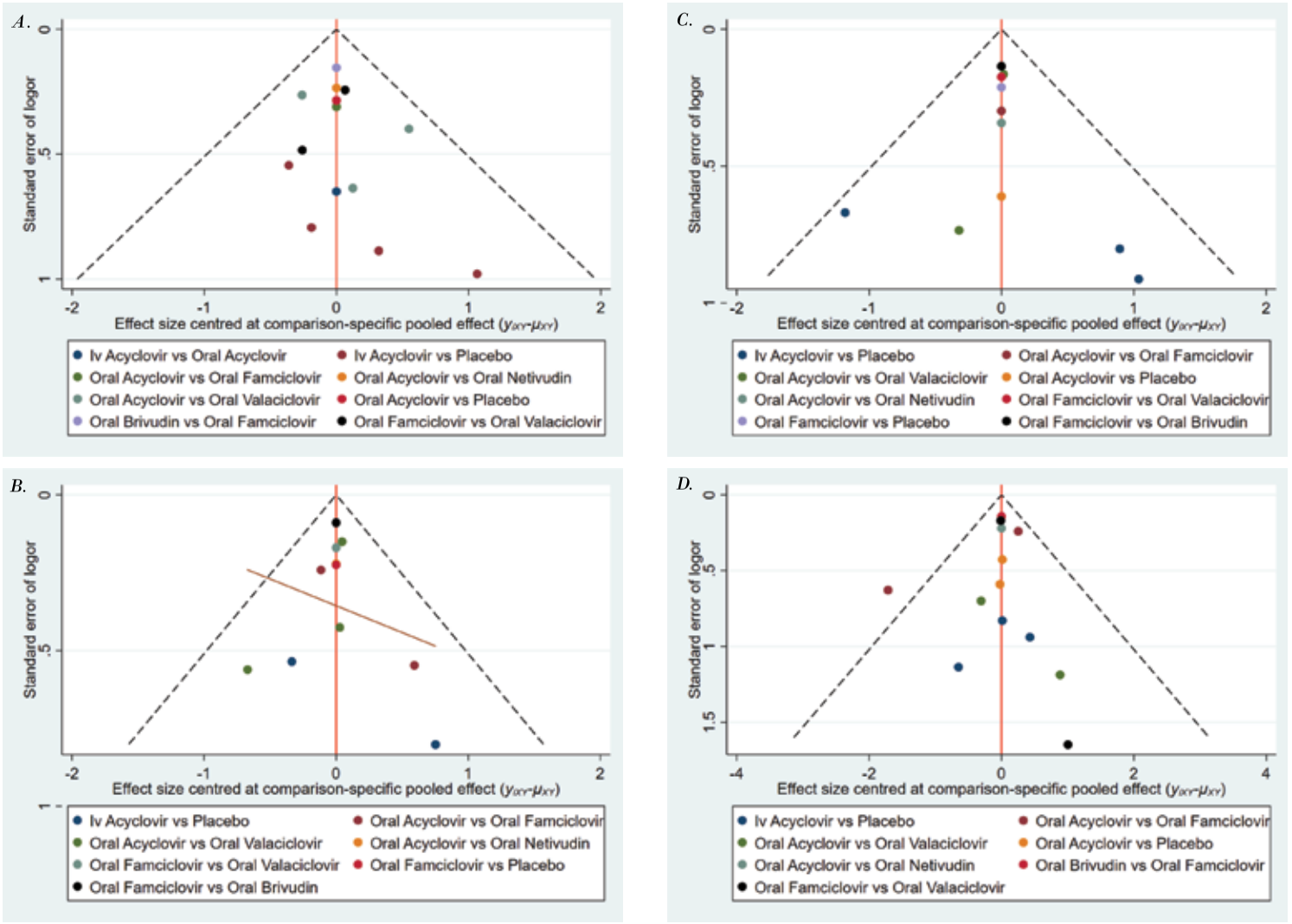
*All the evidence about these contrasts comes from the trials which directly compare them.

Presence of PHN							
Comparisons	**Direct**		**Indirect**		**Difference**		
	Coef	**SE**	**Coef**	**SE**	**Coef**	**SE**	***P* value**
Placebo-Iv acyclovir	.	.	.	.	.	.	.
Placebo-oral acyclovir	.0870114	.8526897	.1700465	.8150934	-.08300351	1.1796	0.944
Placebo-oral famciclovir	-.8455542	.6317218	-.9285857	.9961845	.0830315	1.1796	0.944
oral acyclovir- oral famciclovir	-1.390041	.4125397	-.548912	.4785705	-.8411291	.631837	0.180
oral acyclovir- oral valacyclovir	-.4992414	.3219098	-1.381089	.4718878	.8818472	.5981403	0.140
oral acyclovir- oral netivudin *	.7437153	.5704.85	-.7453565	1641.736	1.489072	1648.736	0.999
oral famciclovir- oral valacyclovir	-.0910968	.3061438	.7907485	.5138284	-.8818453	.5981176	0.140
Oral famciclovir - oral brivudin *	.2770042	.4760065	1.705703	1973.857	-1.428699	1973.857	0.999

*All the evidence about these contrasts comes from the trials which directly compare them.

Participant with no-serion adverse event							
Comparisons	**Direct**		**Indirect**		**Difference**		
	Coef	**SE**	**Coef**	**SE**	**Coef**	**SE**	***P* value**
Placebo-Iv acyclovir	.	.	.	.	.	.	.
Placebo-oral acyclovir *	-.0205165	.5148348	.2768651	293.1291	-.2973816	293.1295	0.999
oral acyclovir- oral famciclovir	-.6628281	.5636958	.1619141	.9758952	-.8247422	1.122198	0.462
oral acyclovir- oral valacyclovir	.1078107	.7691519	-.7169296	.8094498	.8247403	1.122189	0.462
oral acyclovir- oral netivudin *	-.372521	.5711945	.2627204	1184.463	-.6352413	1184.463	1.000
oral famciclovir- oral valacyclovir	-.0541029	.6108545	.7706396	.9665564	-.8247425	1.1222	0.462
Oral famciclovir - oral brivudin *	.17027	.5455675	.9944797	2159.045	-.8242098	2159.045	1.000

*All the evidence about these contrasts comes from the trials which directly compare them.



Appendix 12. *Comparison-adjusted funnel plot for each outcome from the network meta-analysis*
The comparison-adjusted funnel plot was conducted to assess small-study effects within network meta-analysis.
a. Comparison-adjusted funnel plot for presence of acute pain. b. Comparison-adjusted funnel plot for presence of pain at 28-30 days. c. Comparison-adjusted funnel plot for presence of PHN. d. Comparison-adjusted funnel plot for participant with pain with no-seriou adverse event

Appendix 13. *Sensitivity analyses for each outcome*
Summary of the network sensitivity analyses

The potential modifiers for sensitivity analyses we choose are listed below:

Sensitivity analyses	**Presence of acute pain**	**Presence of pain at 28-30 days**	**Presence of PHN**	**the participant with no-serious adverse event**
Omitting the drugs with no significant difference with placebo	√	√	√	√
omitting trials with no date for the person with pain at 4 mounths			√	

*We did not perform sensitivity analysis with omitting trials where missing data
*We did not perform subgroup analysis with omitting trials where missing data, such as the different race of participant, the degrade of pain, the usage of painkiller, the sponsor of trail, prodromal pain time or excluding all studies where any item of the Cochrane risk of bias assessments was high or unclear.