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SYSTEMATIC REVIEW

An Investigation of Factors Contributing to Higher Levels of Placebo Response in Clinical Trials in Neuropathic Pain: A Systematic Review and Meta-Analysis

Akio Arakawa · Masayuki Kaneko · Mamoru Narukawa

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Abstract

Background In new drug development in neuropathic pain (NeP), randomized, double-blind, placebo-controlled trials (PCTs) with long treatment durations in a parallel-group design are recommended for confirmatory trials.

Objective This study was conducted to identify potential factors contributing to elevated placebo response in parallel-group PCTs for oral drugs with at least a 4-week treatment duration.

Methods A literature search was conducted through MEDLINE and EMBASE, and was supplemented with data from ClinicalTrials.gov and US/Japanese regulatory approval review information. Using the 30 or 50 % responder rate (RR), logistic regression analyses were performed to investigate the relationship between the degree of placebo response and several potential influencing factors.

Results The search identified 71 trials ($n = 6{,}126$). The estimated 50 % RRs (95 % confidence intervals) in the placebo group were as follows: peripheral neuropathic pain (P-NeP) 23 % (21, 26 %); central neuropathic pain (C-NeP) 14 % (10, 19 %); postherpetic neuralgia (PHN) 19 % (15, 24 %); painful diabetic peripheral neuropathy (pDPN) 26 % (23, 29 %); posttraumatic peripheral neuropathic pain (PT) 15 % (10, 20 %). From the logistic regression analyses, it was found that there was a significant association between placebo response (50 % RR and 30 % RR) and NeP classification ($P < 0.05$). Associations between placebo response and several factors were seen in univariate logistic regression analyses of 50 % RR. Multivariate analyses showed that age and baseline pain intensity in PHN, and treatment duration, trial design (fixed-dose/flexible-dose) and baseline pain intensity in pDPN, were associated with placebo response, suggesting that a reduced placebo response correlated with increasing age and baseline pain intensity, and a higher placebo response correlated with a longer treatment period and flexible dosing regimen. A similar pattern observed in the analysis of 50 % RR was suggested in the analysis of 30 % RR, with the exception of treatment duration. In addition, investigations of trials with at least a 12-week treatment duration in pDPN found associations with the number of patients per site, patient enrolment rate, proportion of male patients and baseline pain intensity, suggesting that a higher placebo response correlated with an increasing number of patients per site, and a reduced placebo response correlated with increasing patient enrolment rate and proportion of male patients and baseline pain intensity.

Conclusion The results of this study suggest that NeP condition, trial design, and demographic and baseline characteristics may contribute to elevated placebo response in clinical trials in patients with NeP. In addition, the magnitude of placebo response and the effect of treatment duration are greater in pDPN than in PHN. These facts should be considered when planning and conducting confirmatory trials in NeP.

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A. Arakawa (✉) · M. Kaneko · M. Narukawa
Department of Clinical Medicine (Pharmaceutical Medicine), Graduate School of Pharmaceutical Sciences, Kitasato University, 5-9-1 Shirokane, Minato-ku Tokyo 108-8641, Japan
e-mail: akio.arakawa@pfizer.com

Key Points

Higher levels of placebo response (50 % responder rate and 30 % responder rate) were suggested in peripheral neuropathic pain than in central neuropathic pain, and in the peripheral neuropathic pain condition of painful diabetic peripheral neuropathy compared with postherpetic neuralgia or posttraumatic peripheral neuropathic pain.

Multivariate logistic regression analyses showed that age and baseline pain intensity in postherpetic neuralgia, and treatment duration, trial design (fixed-dose/flexible-dose) and baseline pain intensity in painful diabetic peripheral neuropathy, were associated with placebo response (50 % responder rate).

These findings should be considered when planning and conducting confirmatory trials in neuropathic pain.

1 Introduction

There has been much clinical research in neuropathic pain (NeP) in recent years, and rapid progress has been made in the development of new drugs in this area. Pain is a subjective phenomenon and often fluctuates over time. Randomized, double-blind, placebo-controlled trials (PCTs) are required for clinical evaluation in a new drug development process. A guidance document on the clinical development of new medicinal products for NeP was published in 2004 and updated in 2007 in the European Union (EU) [1]. In the USA, a draft guidance was published in February 2014 [2]. These guidance documents recommend parallel-group PCTs of long treatment duration (at least 12 weeks) for confirmatory trials in NeP because of its largely chronic nature. The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) recommends the same trial design [3]. Because of the placebo response seen in clinical trials in NeP, superiority (versus placebo) of drugs that have already been shown to be effective in PCTs cannot always be demonstrated in subsequently conducted PCTs [4].

The effect of placebo response in chronic pain has been widely recognized in clinical research, and its contributing factors have been studied [3]. Previous research in NeP has suggested several mechanisms, such as placebo response differing depending on the NeP condition (e.g. placebo response was greater in human immunodeficiency virus [HIV]-associated pain and painful diabetic peripheral neuropathy [pDPN] than in postherpetic neuralgia [PHN] and central neuropathic pain [C-NeP]) [5]; placebo response increasing with duration of treatment [6]; a higher baseline pain score having an effect on placebo response (controversially, some findings have suggested a higher baseline score associated with higher placebo response, but the meta-analysis did not identify the baseline score as a factor associated with placebo response [7–9]); a faster patient recruitment rate related to higher placebo response [7]; a parallel-group design producing a larger placebo response than a cross-over design [10]; and placebo response increasing with year of trial initiation [6, 9].

Systematic reviews of the placebo response to date have included cross-over design trials and trials of short treatment duration. The objective of this study is to identify potential factors contributing to elevated placebo response on the basis of the results of parallel-group PCTs of oral drugs with at least a 4-week treatment duration. In addition to the 50 % responder rate (RR) used as an efficacy measure, 30 % RR data and trials of ≥12 weeks' treatment duration were also investigated where possible.

2 Methods

2.1 Trial Selection and Database Construction

We conducted a literature search of MEDLINE and EMBASE (1995 to January 2014) on January 12, 2014. The following terms identifying conditions classified as NeP were used to search for NeP conditions [11]: 'postherpetic neuralgia', 'diabetic neuropathy', 'polyneuropathy', 'complex regional pain syndrome', 'carpal tunnel syndrome', 'neuropathy', 'HIV sensory neuropathy', 'phantom limb pain', 'postradiation plexopathy', 'radiculopathy', 'trigeminal neuralgia', 'brachial plexus avulsion', 'posttraumatic neuralgia', 'postamputation', 'poststroke pain', 'spinal cord injury', 'multiple sclerosis', 'Parkinson disease', 'myelopathy', 'syringomyelia', 'neuropathic pain' and 'central pain'. The terms 'randomized', 'double-blind' and 'placebo-controlled' were used to search for trial design. Trial results published on ClinicalTrials.gov and disclosed regulatory review information on drugs approved for NeP or conditions classified as NeP in the USA and Japan (Japanese common technical documents [CTDs] and US review reports) were also included.

Trials meeting any of the following criteria were excluded from the analysis:

1. Primary efficacy endpoint not assessed using an 11-point numerical rating scale (NRS) or 100 mm visual analogue scale (VAS).
2. Efficacy evaluated for less than 4 weeks.
3. Trials using administration methods other than oral formulation, such as intravenous or topical medication (as the types of administration may influence the placebo response [9]).
4. Cross-over design or randomized withdrawal design trials.

2.2 Data Extraction

Two types of RRs, 50 % pain intensity reduction from baseline (50 % RR) and 30 % pain intensity reduction from baseline (30 % RR), commonly used to evaluate efficacy in clinical trials of NeP drugs, were used as measures of placebo response [12, 13].

To identify potential factors contributing to an elevated placebo response, the following data were extracted from the selected clinical trial references. Baseline pain intensity data from a 100 mm VAS were converted to a 0–10 scale.

- *Trial design*: Target pain condition, treatment duration, number of treatment arms, randomization ratio (50 % or less than 50 %), dosing regimen (fixed-dose or flexible-dose).
- *Trial operation or performance*: Number of patients per trial site, patient enrolment rate (number of patients/number of sites/month).
- *Demographic and baseline characteristics*: Gender (proportion of male patients), age, duration of NeP, baseline pain intensity.
- *Other trial conditions*: Rate of dropouts due to any reason, region (West, Asia or both), trial initiation timing (before or after the US regulatory approval of the active ingredient).

2.3 Statistical Analyses

The pooled estimates of 50 % RR and 30 % RR in the placebo groups were calculated by a random-effects model. We used a random-effects model because of the heterogeneity of the placebo response observed in clinical trials in NeP conditions. Univariate logistic regression analysis was performed to identify potential factors affecting the RR in the placebo group. The International Association for the Study of Pain defines NeP as 'pain caused by a lesion or disease of the somatosensory system'. Many diseases and conditions are included in NeP, and the pathology is typically classified into peripheral neuropathic pain (P-NeP) and C-NeP, according to the site of the lesion [14]. Therefore, separate analyses were performed by classification or condition if differences in the placebo response were observed by NeP classification (P-NeP or C-NeP) or NeP conditions. Factors shown to be significant explanatory variables by the univariate logistic regression analysis were further analysed by multivariate logistic regression analysis using a stepwise approach. A statistically significant difference was defined as $P < 0.05$. The analyses were performed using SAS ver. 9.2 (SAS Institute Inc., Cary, NC, USA) and StatsDirect ver. 2.7.9 (StatsDirect Ltd., Altrincham, Cheshire, UK).

3 Results

3.1 Search Results

The literature search and search of disclosed regulatory information identified 89 trials. A total of 71 ($n = 6,126$) of these trials yielded data on 50 % RR or 30 % RR (Fig. 1; Table 1) [15–91]. The numbers of trials with 50 % RR and 30 % RR were 63 ($n = 5,540$) and 52 ($n = 4,539$), respectively. Detailed data of these selected trials are shown in Supplementary Table 1 in the Electronic Supplementary Material. Most of the trials were investigations in P-NeP. These consisted mainly of 17 trials in PHN, 38 trials in pDPN, and three trials in posttraumatic peripheral neuropathic pain (PT). Only a small number of the trials were investigations in C-NeP: two trials in spinal cord injury pain and one trial each in poststroke pain and multiple sclerosis-associated pain. The treatment duration was at least 12 weeks in 35 of the 71 trials.

3.2 Pooled Estimates of Responder Rate in the Placebo Group

3.2.1 50 % Responder Rate

In the 63 total trials in NeP, the pooled estimate of 50 % RR was 23 % (95 % confidence interval [CI] 20, 25 %; $n = 5,540$). In addition, the 50 % RRs were 23 % (95 % CI 21, 26 %; $n = 4,967$) in the 57 trials in P-NeP and 14 % (95 % CI 10, 19 %; $n = 421$) in the five trials in C-NeP. (The pooled estimates of 50 % RR in NeP and P-NeP are shown in Supplementary Figures 1A and 2A, respectively, in the Electronic Supplementary Material.) Further analysis of the P-NeP trials revealed that the 50 % RRs were 19 % (95 % CI 15, 24 %; $n = 1,445$), 26 % (95 % CI 23, 29 %; $n = 2,948$) and 15 % (95 % CI 10, 20 %; $n = 239$) in the 17 PHN trials, 32 pDPN trials

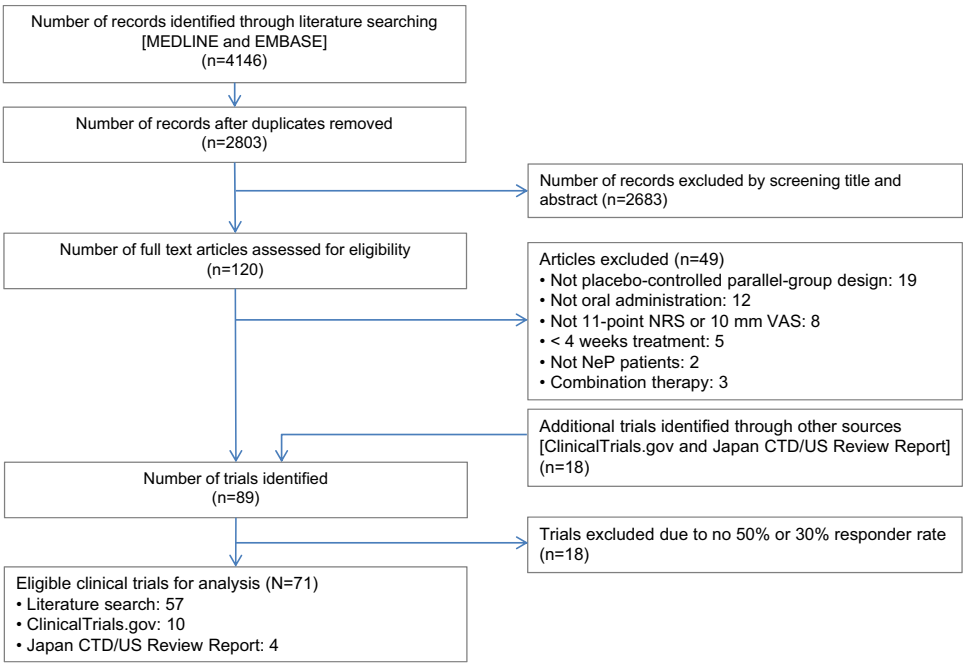


Fig. 1 Trial selection. *NeP* neuropathic pain, *NRS* numerical rating scale, *VAS* visual analogue scale, *CTD* common technical document

Table 1 Number of selected trials

Pain conditions	Number of trials		
	Total	50 % RR	30 % RR
P-NeP	65 (32)	57 (30)	47 (27)
PHN [15–35]	17 (5)[a]	17 (5)[a]	9 (4)[a]
pDPN [36–74]	38 (23)	32 (22)	29 (19)
PT [75–77]	3 (0)	3 (0)	3 (0)
HIV sensory neuropathy [78]	1 (1)	1 (1)	1 (1)
Complex regional pain syndrome [79]	1 (1)	0	1 (1)
Phantom limb pain [80]	1 (0)	1 (0)	0
Mixed P-NeP conditions [81–84]	4 (2)	3 (2)	4 (2)
C-NeP	5 (3)	5 (3)	5 (3)
Spinal cord injury pain [85–87]	2 (2)	2 (2)	2 (2)
Poststroke pain [88]	1 (1)	1 (1)	1 (1)
Multiple sclerosis pain [89]	1 (0)	1 (0)	1 (0)
Mixed C-NeP conditions [90]	1 (0)	1 (0)	1 (0)
Other (both P-NeP and C-NeP)	1 (0)	1 (0)	0 (0)
Mixed NeP conditions [91]	1 (0)	1 (0)	0 (0)
Total	71 (35)	63 (33)	52 (30)

Detailed data of selected trials are shown in Supplementary Table 1 in the Electronic Supplementary Material

The numbers in parentheses represent the number of trials with 12 weeks or more treatment duration

C-NeP central neuropathic pain, *HIV* human immunodeficiency virus, *pDPN* painful diabetic peripheral neuropathy, *PHN* postherpetic neuralgia, *P-NeP* peripheral neuropathic pain, *PT* posttraumatic peripheral neuropathic pain, *RR* responder rate

[a] One trial, NCT00592774, was counted as two trials because the trial consisted of two cohorts with different doses and yielded data on responder rates for individual cohort

and three PT trials, respectively (Figs. 2, 3, 4, 5a). These results show that higher levels of placebo response were observed in P-NeP than in C-NeP, and in the P-NeP condition of pDPN compared with PHN or PT.

3.2.2 30 % Responder Rate

In the 52 total trials in NeP, the pooled estimate of 30 % RR was 37 % (95 % CI 34, 41 %; $n = 4{,}539$). In addition, the 30 % RRs were 39 % (95 % CI 35, 42 %; $n = 4{,}118$) in the 47 trials in P-NeP and 26 % (95 % CI 19, 33 %; $n = 421$) in the five trials in C-NeP. (The pooled estimates of 30 % RR in NeP and P-NeP are shown in Supplementary Figures 1B and 2B, respectively, in the Electronic Supplementary Material.) Further analysis of the P-NeP trials revealed that the 30 % RRs were 29 % (95 % CI 21, 37 %; $n = 600$), 42 % (95 % CI 39, 46 %; $n = 2{,}767$) and 30 % (95 % CI 23, 37 %; $n = 239$), respectively, in the nine PHN trials, 29 pDPN trials and three PT trials (Figs. 2, 3, 4, 5b). Although these rates are higher than those seen for a 50 % RR, the same trend in rates by NeP condition is apparent.

3.3 Univariate Logistic Regression Analysis

Univariate logistic regression analysis showed a significant association between placebo response (50 % RR and 30 % RR) and NeP classification categorized as P-NeP or C-NeP (Table 2).

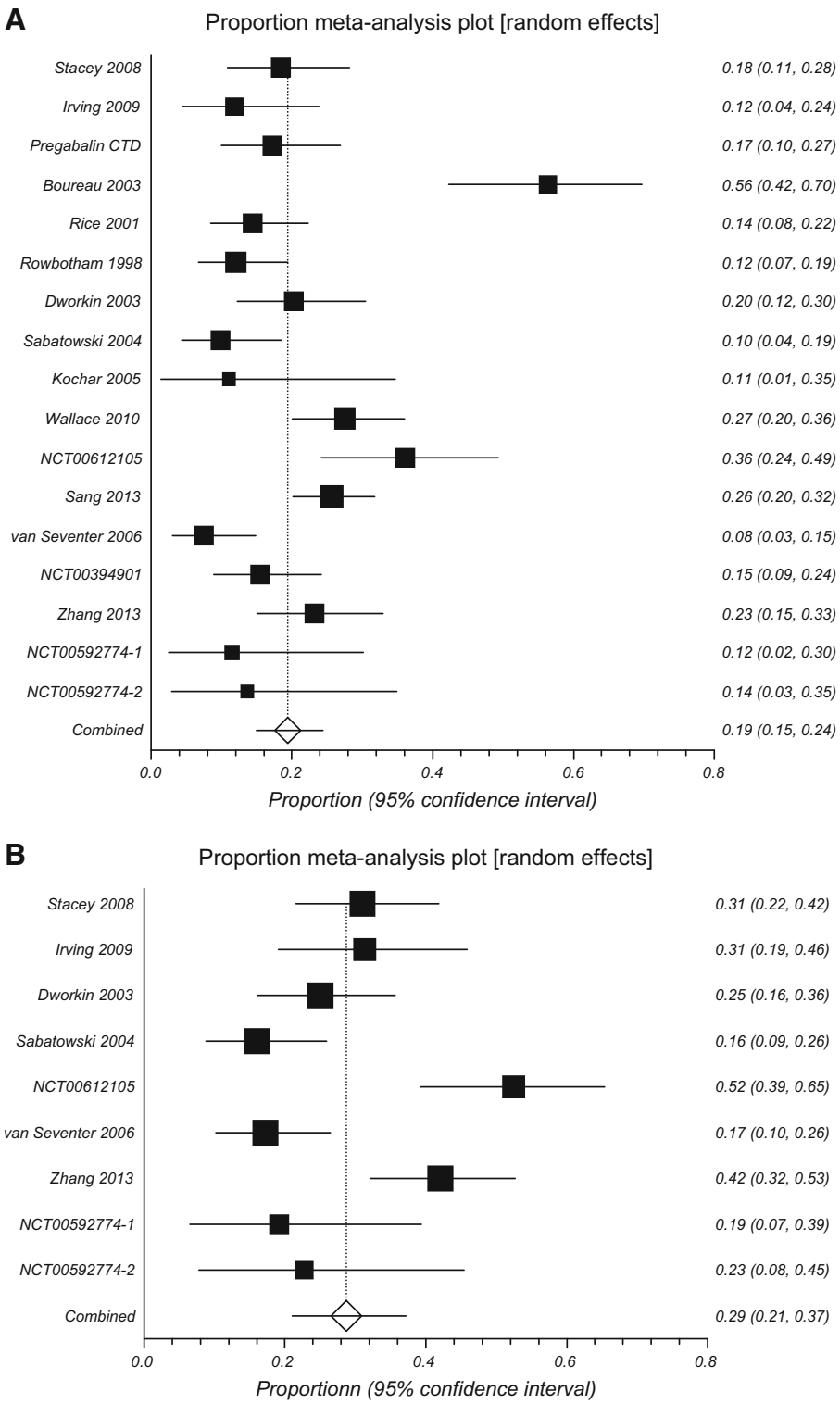


Fig. 2 Forest plot of placebo responder rate in postherpetic neuralgia (**a** 50 % RR, **b** 30 % RR). *RR* responder rate, *CTD* common technical document. NCT00592774 was counted as two trials because the trial consisted of two cohorts with different doses and yielded data on responder rates for individual cohort

Further analysis of P-NeP showed a significant association for the major pain conditions of PHN, pDPN and PT (Table 2).

Because of this observed difference in the placebo response by NeP classification and condition, PHN and pDPN were further analysed separately.

3.3.1 Postherpetic Neuralgia (50 % Responder Rate)

The following factors were significantly associated with placebo response (50 % RR) in relation to PHN: treatment duration (≥12 weeks, <12 weeks), number of treatment arms, randomization ratio, number of patients per site,

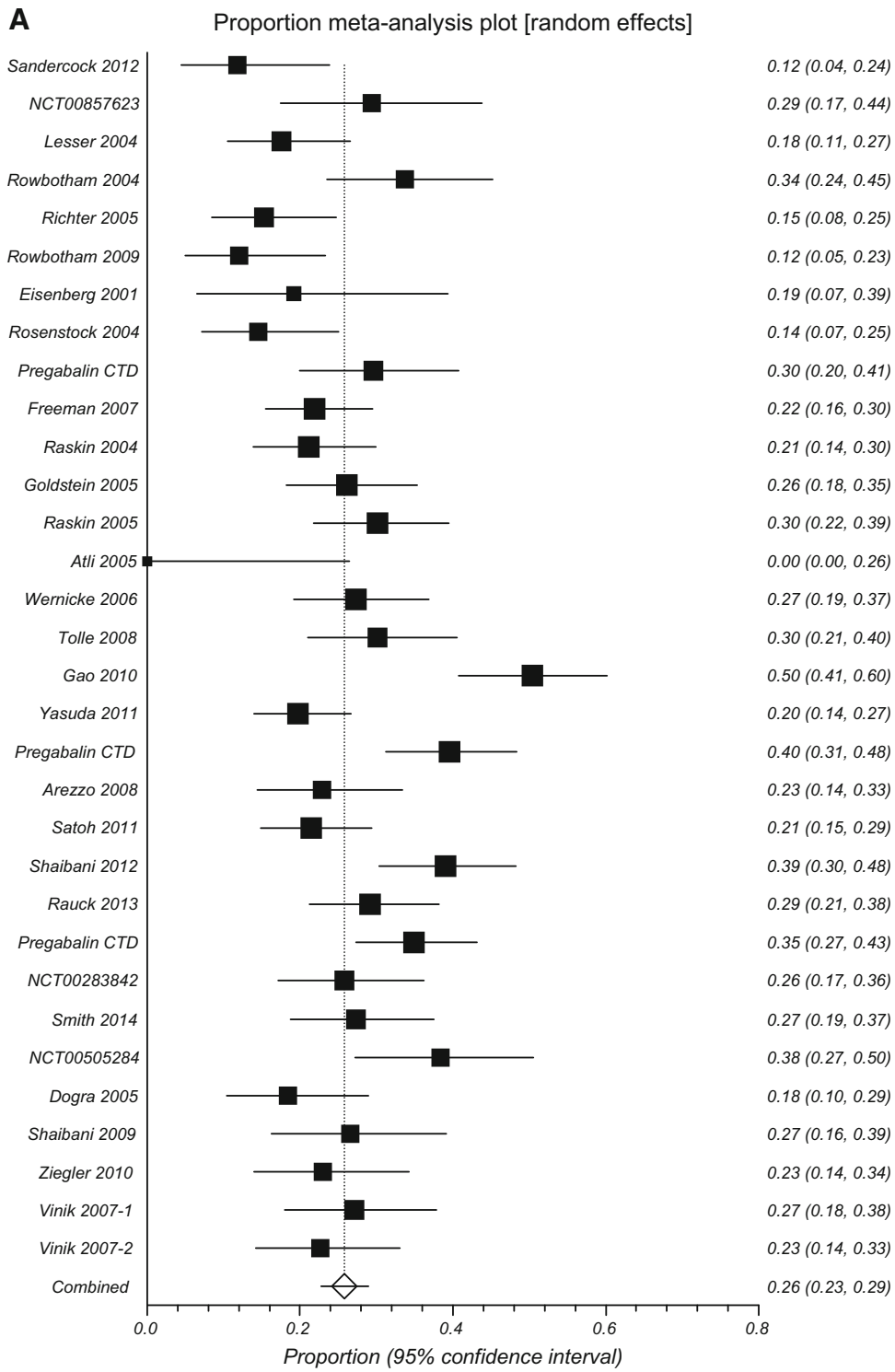
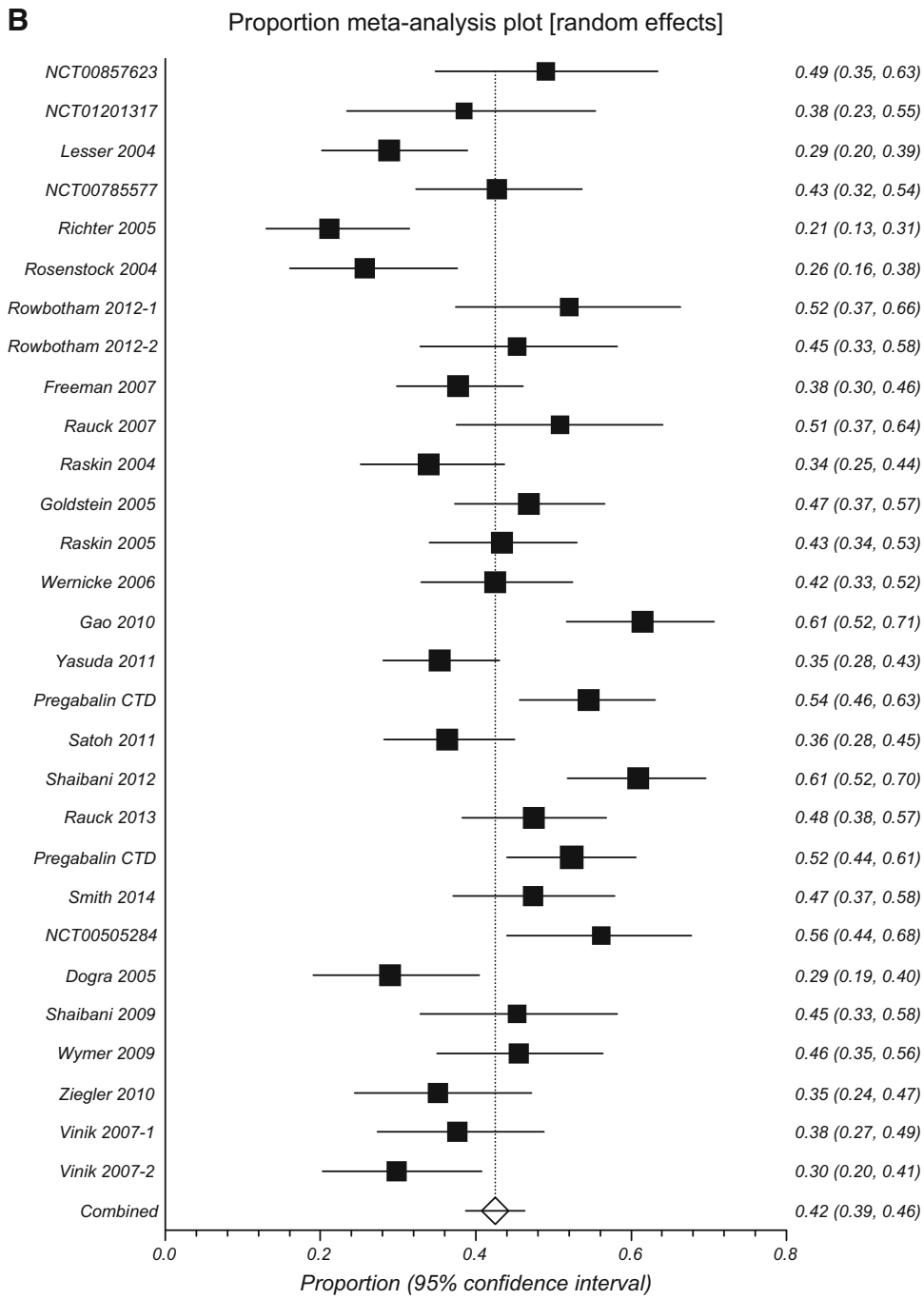


Fig. 3 Forest plot of placebo responder rate in painful diabetic peripheral neuropathy (**a** 50 % RR, **b** 30 % RR). *RR* responder rate, *CTD* common technical document

patient enrolment rate, age, baseline pain intensity, duration of NeP and trial initiation timing (Table 3).

The results suggest that a higher placebo response correlated with trial initiation timing, and a reduced placebo response correlated with the following factors: increasing number of treatment arms, randomization ratio, number of patients per site, patient enrolment rate, age, baseline pain intensity, longer treatment period and longer duration of NeP. A significant association was not observed for dosing regimen (fixed-dose, flexible-dose), gender, dropout rate or region.

Fig. 3 continued



3.3.2 *Painful Diabetic Peripheral Neuropathy (50 % Responder Rate)*

The following factors were significantly associated with placebo response (50 % RR) in pDPN: treatment duration, dosing regimen, number of patients per site, gender and baseline pain intensity (Table 3). A significant association was not observed for number of treatment arms, randomization ratio, patient enrolment rate, age, duration of NeP, dropout rate, region or trial initiation timing. The results suggest that a higher placebo response correlated with longer treatment period, flexible dosing regimen and increasing number of patients per site, and a reduced placebo response correlated with increasing proportion of male patients and baseline pain intensity.

3.3.3 *Painful Diabetic Peripheral Neuropathy (30 % Responder Rate)*

A similar pattern to that observed in the analysis of 50 % RR was observed in the analysis of 30 % RR, with the exception that a significant association with trial initiation timing was found for 30 % RR (Table 3).

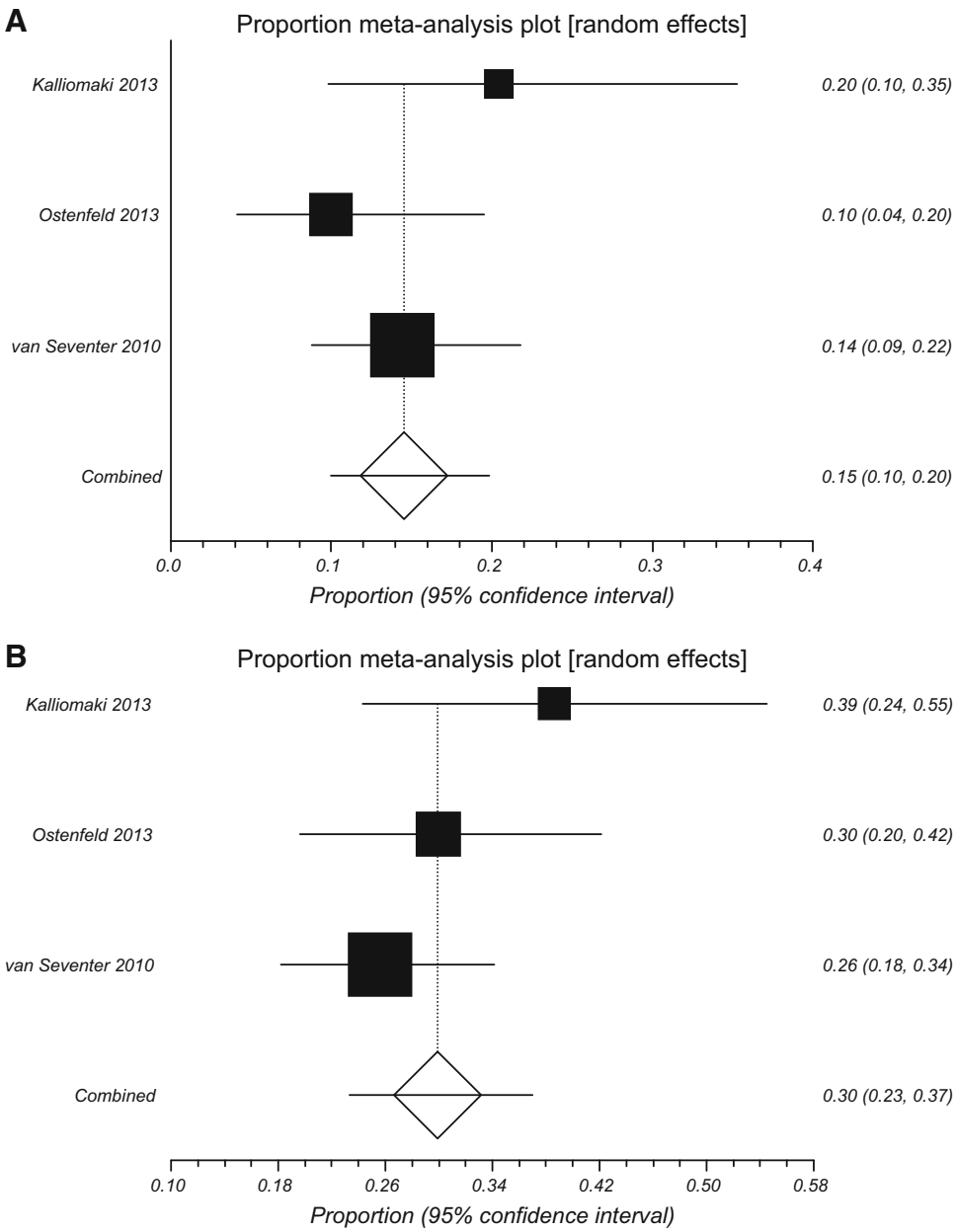


Fig. 4 Forest plot of placebo responder rate in posttraumatic peripheral neuropathic pain (**a** 50 % RR, **b** 30 % RR). *RR* responder rate

3.3.4 Painful Diabetic Peripheral Neuropathy (50 % Responder Rate, Trials with ≥12 Weeks Treatment Duration)

The following factors were significantly associated with placebo response (50 % RR) in trials with a treatment duration of ≥12 weeks: dosing regimen, number of patients per site, patient enrolment rate, gender and baseline pain intensity (Table 3). The results suggest that a higher placebo response correlated with flexible dosing regimen, increasing number of patients per site and patient enrolment rate, and a reduced placebo response correlated with increasing proportion of male patients and baseline pain intensity.

3.4 Multivariate Logistic Regression Analysis

3.4.1 Postherpetic Neuralgia (50 % Responder Rate)

The factors significantly associated with placebo response on univariate logistic regression analysis (treatment duration, number of treatment arms, number of patients per site, patient enrolment rate, age, baseline pain intensity and trial initiation timing) were further analysed by multivariate logistic regression analysis. The factor of duration of NeP was excluded from the analysis because of the limited number of trials. The results obtained from 13 trials showed a significant association for the two factors of age and baseline pain intensity, suggesting a reduced placebo response with

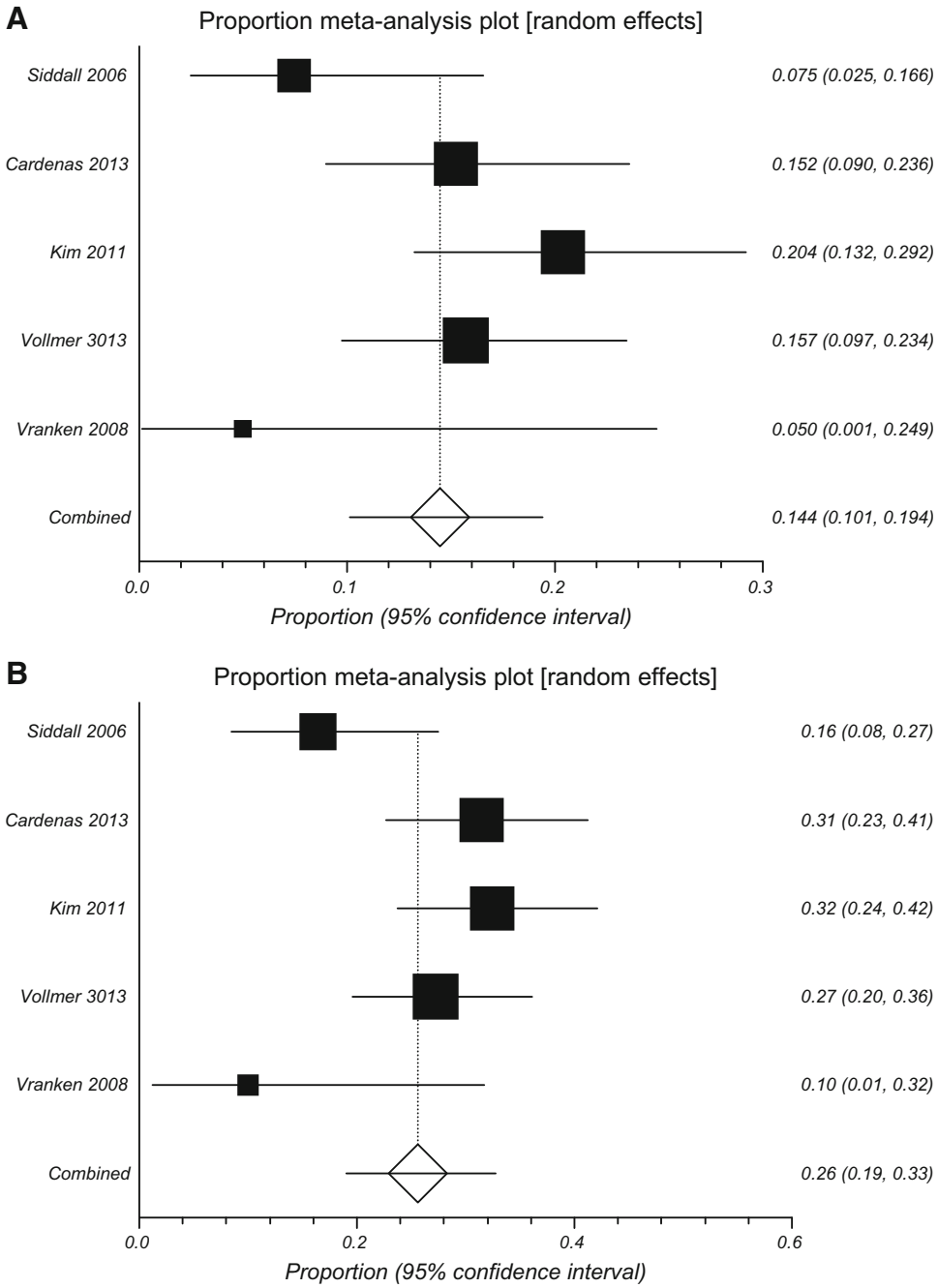


Fig. 5 Forest plot of placebo responder rate in central neuropathic pain (**a** 50 % RR, **b** 30 % RR). *RR* responder rate

increasing age (OR 0.433; 95 % CI 0.321, 0.583; $P < 0.0001$) and increasing baseline pain intensity (OR 0.212; 95 % CI 0.102, 0.444; $P < 0.0001$).

3.4.2 Painful Diabetic Peripheral Neuropathy (50 % Responder Rate)

The factors significantly associated with placebo response on univariate logistic regression analysis (treatment duration, dosing regimen, number of patients per site, gender and baseline pain intensity) were further analysed by multivariate logistic regression analysis. The results obtained from 26 trials showed a significant association for the three factors of treatment duration, dosing regimen (fixed-dose/flexible-dose) and baseline pain intensity, suggesting that a higher placebo response correlated with longer treatment period (OR 1.266; 95 % CI 1.003, 1.599; $P = 0.0469$) and flexible dosing regimen (OR 1.811; 95 % CI 1.446, 2.269; $P < 0.0001$), and a reduced placebo response correlated with increasing baseline pain intensity (OR 0.729; 95 % CI 0.627, 0.847; $P < 0.0001$).

Table 2 Relationships between placebo responder rates and neuropathic pain (NeP) conditions: univariate logistic regression analyses

Variable	50 % RR				30 % RR			
	n	*P* value	OR	95 % CI	*n*	*P* value	OR	95 % CI
NeP classification: P-NeP vs. C-NeP	62	<0.0001	0.539	0.409, 0.710	52	<0.0001	0.561	0.448, 0.701
Pain condition (1): PHN vs. pDPN	49	<0.0001	1.446	1.242, 1.683	38	<0.0001	1.816	1.500, 2.200
Pain condition (2): PT vs. pDPN	35	<0.0001	1.486	1.234, 1.789	32	<0.0001	1.344	1.163, 1.552

NeP classification coded as 0 = P-NeP, 1 = C-NeP; pain condition (1) coded as 0 = PHN, 1 = pDPN; pain condition (2) coded as 0 = PT, 1 = pDPN [0: reference category]

CI confidence interval, *C-NeP* central neuropathic pain, *OR* odds ratio, *pDPN* painful diabetic peripheral neuropathy, *PHN* postherpetic neuralgia, *P-NeP* peripheral neuropathic pain, *PT* posttraumatic peripheral neuropathic pain, *RR* responder rate

3.4.3 Painful Diabetic Peripheral Neuropathy (30 % Responder Rate)

The factors significantly associated with placebo response on univariate logistic regression analysis (treatment duration, dosing regimen, number of patients per site, gender, baseline pain intensity and trial initiation timing) were further analysed by multivariate logistic regression analysis. The results obtained from 22 trials showed a significant association for two factors of dosing regimen and baseline pain intensity, suggesting that a higher placebo response correlated with a flexible dosing regimen (OR 1.480; 95 % CI 1.193, 1.837; $P = 0.0004$), and a reduced placebo response correlated with increasing baseline pain intensity (OR 0.707; 95 % CI 0.621, 0.803; $P < 0.0001$).

3.4.4 Painful Diabetic Peripheral Neuropathy (50 % Responder Rate, Trials With ≥12 Weeks Treatment Duration)

The factors significantly associated with placebo response on univariate logistic regression analysis (dosing regimen, number of patients per site, patient enrolment rate, gender and baseline pain intensity) were further analysed by multivariate logistic regression analysis. The results obtained from 16 trials showed a significant association for the four factors of number of patients per site, patient enrolment rate, proportion of male patients and baseline pain intensity, suggesting that a higher placebo response correlated with increasing number of patient per site (OR 1.081; 95 % CI 1.039, 1.125; $P = 0.0001$), and a reduced placebo response correlated with increasing patient enrolment rate (OR 0.729; 95 % CI 0.590, 0.901; $P = 0.0034$), proportion of male patients (OR 0.704; 95 % CI 0.509, 0.973; $P = 0.0337$) and baseline pain intensity (OR 0.804; 95 % CI 0.680, 0.950; $P = 0.0104$).

4 Discussion

In our study, we estimated the magnitude of the placebo response as measured by 50 and 30 % RRs, and performed a logistic regression analysis to identify factors influencing the placebo response in parallel-group PCTs of oral NeP drugs of relatively long treatment duration commonly used for confirmatory clinical trials. The results showed differences in placebo response by NeP classification and condition, which suggested that higher levels of placebo response were observed in P-NeP than in C-NeP, and in the P-NeP condition of pDPN compared with PHN and PT. The estimated 50 % RRs in the placebo group were 19 % (95 % CI 15, 24 %) in PHN, 26 % (95 % CI 23, 29 %) in pDPN and 14 % (95 % CI 10, 19 %) in C-NeP. These findings demonstrated higher placebo response than in the previous research including trials with cross-over design and short duration of treatment, i.e. 11.5 % (95 % CI 8.4, 14.5 %) in PHN, 20.2 % (95 % CI 14.6, 25.8 %) in pDPN and 7.2 % (95 % CI 2.1, 12.3 %) in C-NeP [5]. These results indicate that the higher placebo response may be influenced by trial design and longer treatment duration. A 30 % RR is also considered as a clinically meaningful improvement. We found the same trend in rates by NeP condition, though higher placebo response rates were observed in 30 % RR (29 % in PHN, 42 % in pDPN and 26 % in C-NeP) compared with 50 % RR.

On univariate logistic regression analysis, associations with placebo response (50 % RR) were observed for the following factors in PHN or pDPN: treatment duration, dosing regimen categorized as fixed-dose or flexible-dose, number of treatment arms, randomization ratio, number of patients per site, patient enrolment rate, age, gender (proportion of male patients), baseline pain intensity, duration of NeP and trial timing. The 30 % RR could not be analysed for PHN because of the limited number of trials, but 30 % RR as well as 50 % RR in trials with ≥12 week treatment duration were analysed in

Table 3 Relationships between placebo responder rates and potential factors: univariate logistic regression analyses

Variable	PHN (50 % RR)				pDPN (50 % RR)				pDPN (30 % RR)				pDPN (50 % RR; 12 weeks)			
	n	*P* value	OR	95 % CI	*n*	*P* value	OR	95 % CI	*n*	*P* value	OR	95 % CI	*n*	*P* value	OR	95 % CI
Trial design																
Treatment duration	17	0.0075	0.635	0.455, 0.886	32	<0.0001	1.522	1.247, 1.858	29	0.0008	1.343	1.131, 1.594	–	–	–	–
Number of arms	17	<0.0001	0.714	0.606, 0.841	32	0.8292	0.990	0.907, 1.081	29	0.4824	1.028	0.952, 1.109	22	0.4677	0.965	0.876, 1.062
Randomization ratio	17	0.0034	0.675	0.519, 0.878	32	0.1493	1.151	0.951, 1.394	29	0.2783	1.099	0.927, 1.303	22	0.375	1.111	0.880, 1.402
Dosing regimen	17	0.8192	0.962	0.688, 1.344	32	<0.0001	1.719	1.386, 2.132	29	0.0008	1.432	1.161, 1.767	22	0.0001	1.590	1.252, 2.019
Trial operation																
Number of patients per site	17	0.0021	0.932	0.891, 0.975	28	0.0083	1.018	1.005, 1.032	25	0.0024	1.030	1.011, 1.050	18	<0.0001	1.056	1.031, 1.083
Patient enrolment rate	15	0.0001	0.551	0.408, 0.746	25	0.0942	1.116	0.981, 1.269	25	0.7045	1.023	0.909, 1.153	17	0.0182	1.171	1.027, 1.336
Baseline characteristics																
Gender, male rate	17	0.8184	0.970	0.749, 1.256	32	<0.0001	0.578	0.472, 0.707	29	<0.0001	0.677	0.568, 0.808	22	<0.0001	0.631	0.512, 0.778
Age, median	15	<0.0001	0.439	0.333, 0.578	31	0.1009	1.151	0.973, 1.362	28	0.1329	1.125	0.965, 1.311	21	0.8693	1.017	0.836, 1.235
Baseline pain intensity	14	<0.0001	0.241	0.119, 0.487	29	<0.0001	0.713	0.623, 0.816	25	<0.0001	0.715	0.630, 0.811	20	0.0002	0.745	0.640, 0.868
Duration of NeP	10	<0.0001	0.498	0.404, 0.613	18	0.366	0.930	0.795, 1.088	19	0.6205	1.038	0.894, 1.206	15	0.0736	0.840	0.694, 1.017
Other trial conditions																
Dropout rate	16	0.1012	0.784	0.586, 1.049	32	0.9173	1.009	0.857, 1.187	27	0.1172	1.131	0.970, 1.319	22	0.3922	0.922	0.767, 1.110
Region	17	0.1334	0.665	0.391, 1.133	31	0.3717	1.110	0.883, 1.394	28	0.8638	1.019	0.823, 1.261	21	0.8404	1.025	0.807, 1.302
Trial initiation timing	17	<0.0001	1.825	1.400, 2.378	32	0.0731	1.165	0.986, 1.378	29	0.0281	1.193	1.019, 1.397	22	0.0853	1.178	0.977, 1.420

Treatment duration coded as 0 = less than 12 weeks, 1 = 12 weeks or more; randomization ratio coded as 0 = 50 %, 1 = less than 50 %; dosing regimen coded as 0 = fixed-dose design, 1 = flexible-dose design; patient enrolment rate: number of randomized patients/site/month; male rate coded as 0 = less than 50 %, 1 = 50 % or more; age coded as 0 = median or less, more than median (median: PHN 69.0, DPN 59.2); dropout rate coded as 0 = less than 20 %, 1 = 20 % or more; region coded as 0 = West, 1 = Asia; trial initiation timing coded as 0 = trial started before approval in the USA, 1 = trial started after approval [0: reference category]

CI confidence interval, NeP neuropathic pain, *OR* odds ratio, *pDPN* painful diabetic peripheral neuropathy, *PHN* postherpetic neuralgia, *RR* responder rate

pDPN. The 30 % RR results showed a pattern similar to that observed for 50 % RR. Multivariate logistic regression analysis showed a stronger association with placebo response (50 % RR) for age and baseline pain intensity in PHN and for treatment duration, dosing regimen and baseline pain intensity in pDPN. The results for both PHN and pDPN suggested that a reduced placebo response correlated with increasing baseline pain intensity. Although higher baseline score was associated with higher placebo response measured by change from baseline in NRS in previous research using patient data on lamotrigine and duloxetine clinical trials [7, 8], the meta-analysis of NeP clinical trials including cross-over design trials did not identify this factor [10].

In both PHN and pDPN, baseline pain intensity was consistently identified as a predictor of placebo response. In contrast, a different pattern was observed for PHN and pDPN in relation to age, treatment regimen and treatment duration. An increase in placebo response was observed for treatment durations $\geq$12 weeks in pDPN, but not in PHN. The observation suggests that more attention should be paid to placebo response in clinical trials in pDPN with longer treatment durations.

The results for PHN suggested that a reduced placebo response correlated with increasing age. Although the limited number of trials investigating duration of NeP precludes rigorous analysis, univariate logistic regression also showed an association between placebo response and duration of NeP. A connection between age and duration of NeP is assumed by the fact that the percentage of pain lasting more than 1 year in patients with PHN increases with age [92]. The intractability of pain may also increase with age. These results indicate that the placebo response may have been lower in the PHN patient population with a longer duration of illness and more severe pain symptoms.

The results for pDPN suggested that flexible-dose designs yield higher levels of placebo response than fixed-dose designs. The patient's expectation of pain treatment benefit is a known factor for placebo response [93, 94]. Study design may influence placebo response because of the patient's expectation. According to previous research in clinical trials of opioid analgesics, flexible-dose design trials were more likely to be positive [95], and the same finding was reported in an evaluation of antidepressant clinical trials [96]. In general, the difference in trial design could result in a difference in the dropout rate after treatment initiation. However, univariate logistic regression analysis did not show an association between placebo response and dropout rate.

Among the trial operation-related factors, the number of patients per site and patient enrolment rate were associated with placebo response in pDPN trials with $\geq$12 week treatment duration. Higher placebo response was reported in patients enrolled in sites with a faster recruitment rate in lamotrigine clinical trials [7]. On the other hand, our finding suggests that a higher placebo response correlated with an increasing number of patients per site and a reduced placebo response correlated with an increasing patient enrolment rate in the trial-level data. The results also suggested that the proportion of male patients was associated with placebo response. Higher placebo response in female patients was observed in the research using patient data from lamotrigine clinical trials in pDPN [7].

A higher placebo response has been reported in clinical trials in migraine conducted in Asian countries, compared with Western countries, and the reason for the higher placebo response is unclear [97, 98]. Although the trials that were analysed did not include many trials conducted in the Asian region, a significant association was not observed between placebo response and trial location.

According to the EU guidance for new drug clinical development, efficacy should be demonstrated in more than one well-established clinical situation of P-NeP, e.g. PHN and pDPN, and in at least one C-NeP model for the claim of a broad NeP indication [1]. According to the US draft guidance, at least three separate P-NeP clinical situations should be studied [2]. Of the NeP conditions covered in the present study, PHN and pDPN accounted for the most trials in P-NeP, and these are considered well-established NeP clinical situations. Although only a limited number of trials were performed in PT, a placebo response similar to that observed with PHN was shown, suggesting that PT is an appropriate NeP clinical situation for evaluating efficacy in the development of new drugs.

Publication bias may have been present in this study and may have imposed some limitations, as only a limited number of trials in NeP conditions other than PHN and pDPN were available. Overall, our research included fewer trials in C-NeP than in P-NeP, precluding a separate analysis of specific NeP conditions. Although we analysed double-blind PCTs, there may have been some variation in the results because our research looked only at the placebo group, and the difference in efficacy compared with the active treatment group was not taken into account.

The results of our research suggest that trial design and demographic and baseline characteristics may contribute to elevated placebo response in clinical trials in NeP. These findings indicate that placebo response may potentially be limited by selecting a fixed-dose trial design, male patients and trial sites with high performance in pDPN trials, patients with longer durations of NeP in PHN trials, or patients with higher baseline pain intensity in PHN and pDPN trials. Further, the increase in the placebo response with increased treatment duration, which was observed in

pDPN but not in PHN, indicates that more attention should be paid to treatment duration in the planning and conduct of clinical trials in pDPN, and it highlights the importance of the selection of NeP clinical situations for clinical trials in the new drug development process. Although the placebo effect is considered to be related to many types of mechanisms, including patients' expectations, we have focused on the improvement of pain intensity in patients treated with placebo in clinical trials in the present research. More research and accumulation of evidence are needed for further understanding and will expand the knowledge of the placebo effect.

5 Conclusion

The results of this study suggest that the NeP condition, trial design, demographic characteristics and baseline characteristics may contribute to elevated placebo response in clinical trials in patients with NeP. In addition, the magnitude of the placebo response and the effect of treatment duration are more considerable in DPN than in PHN. These facts should be considered when planning and conducting confirmatory clinical trials in NeP.

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