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

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Abstract

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

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.

The search identified 71 trials (n=6126). The estimated 50%RRs (95% confidence intervals) in the placebo group were as follows: Peripheral NeP; 23% (21–26%), Central NeP; 14% (10–19%), Postherpetic neuralgia (PHN); 19% (15–24%), Painful diabetic peripheral neuropathy (pDPN); 26% (23–29%), Posttraumatic peripheral NeP (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 a reduced placebo response correlated with increasing age and baseline pain intensity, a higher placebo response correlated with longer treatment period and flexible dosing regimen. A similar pattern observed on the analysis of 50% RR was suggested on the analysis of 30% RR, with the exception of treatment duration. In

addition, investigations of trials with at least 12-week treatment duration in pDPN found associations with number of patients per site, patient enrollment rate, proportion of male patients and baseline pain intensity, suggesting a higher placebo response correlated with increasing number of patients per site, a reduced placebo response correlated with increasing patient enrollment rate and proportion of male patients and baseline pain intensity.

The results of the 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 order to minimize the placebo response, the following efforts should be considered in future trials: (1) selecting patients with longer durations of NeP or patients with higher baseline pain intensity in PHN trials, (2) selecting a fixed-dose trial design and trial sites with high performance, and increasing proportion of male patients and patients with higher baseline pain intensity in pDPN trials. In addition, the magnitude of placebo response and the effect of treatment duration are more considerable in pDPN than in PHN. These facts should be considered when planning and conducting confirmatory clinical trials for NeP. PT is considered to be an appropriate NeP clinical situation for evaluating efficacy in the development of new drugs to obtain the approval with a broad NeP indication.

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3. List of Abbreviations

BL	baseline
C-NeP	central neuropathic pain
CI	confidence interval
CRPS	complex regional pain syndrome
CTD	common technical document
EMA	European Medical Agency
FDA	U.S. Food and Drug Administration
HAM-D	Hamilton Rating Scale for Depression
IASP	International Association for the Study of Pain
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IMMPACT	the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials
MADRS	Montgomery-Asberg Depression Scale
MDD	major depressive disorder
MS	multiple sclerosis pain
NA	not available
NeP	neuropathic pain
NNT	number needed to treat
NRS	numerical rating scale
OR	odds ratio
PCT	placebo-controlled trial
pDPN	painful diabetic peripheral neuropathy
PE	patient enrollment
PHN	postherpetic neuralgia
PL	phantom limb pain
P-NeP	peripheral neuropathic pain
PSP	poststroke pain
PT	post-traumatic peripheral neuropathic pain
RR	responder rate
SCI	spinal cord injury pain
VAS	visual analogue scale

4. Introduction

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage [1], and it has a role of warning sign of saving human life. Chronic pain, however, no longer has such a role but reduces patients' quality of life. Pain pathophysiology comprises 2 categories: nociceptive pain and neuropathic pain (NeP). Unlike acute pain (inflammatory pain), NeP is a chronic intractable pain which is difficult to treat, because it does not disappear with the recovery from the causative disease or condition.

NeP is defined as “pain caused by a lesion or disease of the somatosensory system” by the International Association for the Study of Pain (IASP) [2]. Many diseases and conditions are included in NeP, and the pathology is typically classified into peripheral neuropathic pain (P-NeP) and central neuropathic pain (C-NeP), according to the site of lesion (Table 1).

There has been much clinical research in NeP in recent years, and rapid progress has been made in the development of new drugs in this area. In the pharmacological treatment guidelines for NeP, alpha-2-delta ligands (gabapentin and pregabalin), tricyclic antidepressants, and serotonin and noradrenaline reuptake inhibitors are recommended as the first-line therapies [3-6]. But few drugs have been approved for the treatment of NeP and their indication is often limited. In addition, with regard to the efficacy, the number needed to treat (NNT) for 50% pain intensity reduction of the currently available drugs such as pregabalin or gabapentin is approximately 4 to 5 [7]. Under these circumstances, new therapeutic options for the treatment of NeP are needed, which have a broad NeP indication and are easily used in the clinical setting.

Table 1. Common pain disorders/pathologies classified as NeP (classification based on the area of nerve damage) [8]

Neuropathic pain	
Peripheral neuropathic pain	Central neuropathic pain
• Postherpetic neuralgia • Painful diabetic neuropathy • Complex regional pain syndromes • Chemotherapy-induced neuropathy • HIV sensory neuropathy • Neuropathy secondary to tumor infiltration • Phantom limb pain • Postmastectomy pain • Trigeminal neuralgia • Acute/chronic inflammatory demyelinating polyradiculopathy • Alcoholic neuropathy • Entrapment neuropathies (e.g., carpal tunnel syndrome) • Iatrogenic neuropathies (e.g., post-mastectomy pain and post-thoracotomy pain) • Idiopathic sensory neuropathy • Neuropathy due to nerve compression or infiltration by tumor • Nutrition deficiency-related neuropathy • Post-radiation plexopathy • Radiculopathy • Toxic neuropathy • Post-traumatic pain • Brachial plexus avulsion injury* • Glossopharyngeal neuralgia • Autoimmune neuropathy • Chronic cauda equina syndrome*	• Central poststroke pain • Pain after spinal cord injury from trauma • Multiple scleroses pain • Compressive myelopathy due to spinal canal stenosis • Parkinson's disease-related pain • HIV myelopathy • Post-ischemic myelopathy • Post-radiation myelopathy • Syringomyelia / Syringobulbia

* There is a possibility that the pathological condition is applicable to both P-NeP and C-NeP.

Pain is a subjective phenomenon and often fluctuates over time. Randomized, double-blind, placebo-controlled trials (PCTs) are required for the clinical evaluation in a new drug development process.

Types of PCT commonly used in this area include the following designs [9].

(1) Cross-over design (Figure 1A): In this design, each subject is randomized to a sequence of two or more treatments, typically with an interval between each treatment period. This design is attractive primarily because it reduces the number of sample size. In contrast, it has a number of concerns such as carryover effect and complications of analysis and interpretation arising from the loss of subjects [10].

(2) Parallel-group design (Figure 1B): This design is the most common design for confirmatory clinical trials in new drug development. Subjects are randomized to one of the two or more arms, and these treatments will include the investigational product at one or more doses, and one or more control treatments such as placebo and/or an active comparator. The assumptions underlying this design are less complex than for other designs [10].

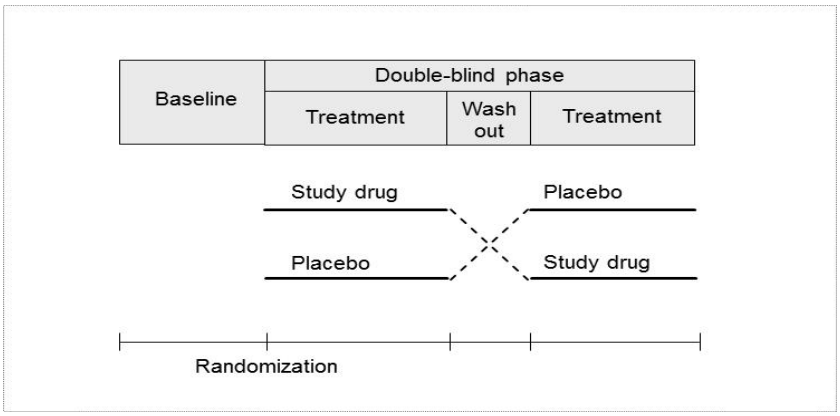
(3) Randomized withdrawal design (Figure 1C): In this design, subjects receiving a test treatment for a specified time at the beginning are randomly assigned to a continued treatment with the test treatment or to a placebo arm. The pre-randomization observation period on treatment can be of any length. This approach can therefore be used to study duration of efficacy when long-term placebo treatment would not be acceptable. It is important to realize that treatment effects observed in this design may be larger than those seen in an unselected population because randomized withdrawal studies are enriched with responders and exclude subjects who cannot tolerate the drug [11, 12].

Clinical trials for NeP conducted by late 1990's typically used a cross-over design, but the

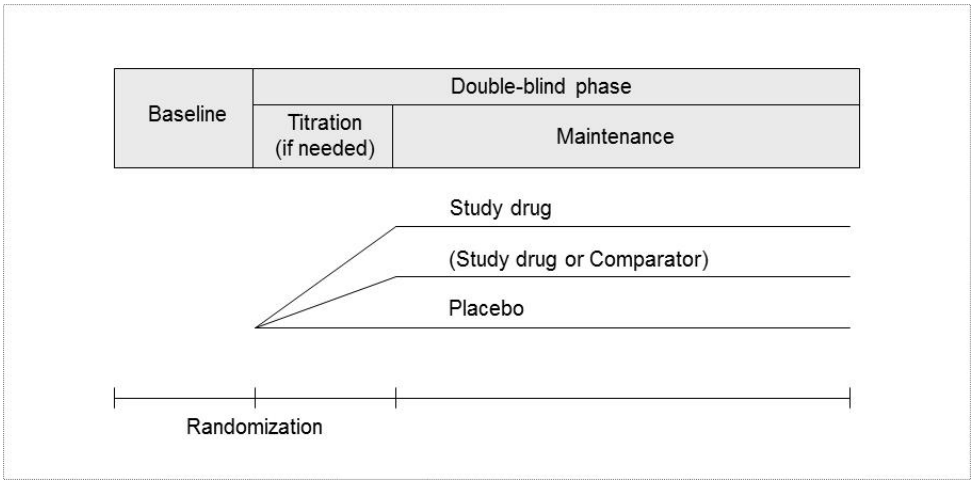
number of PCTs with parallel-group design has been increasing over the last decade [13].

Figure 1. Types of placebo-controlled trial for NeP

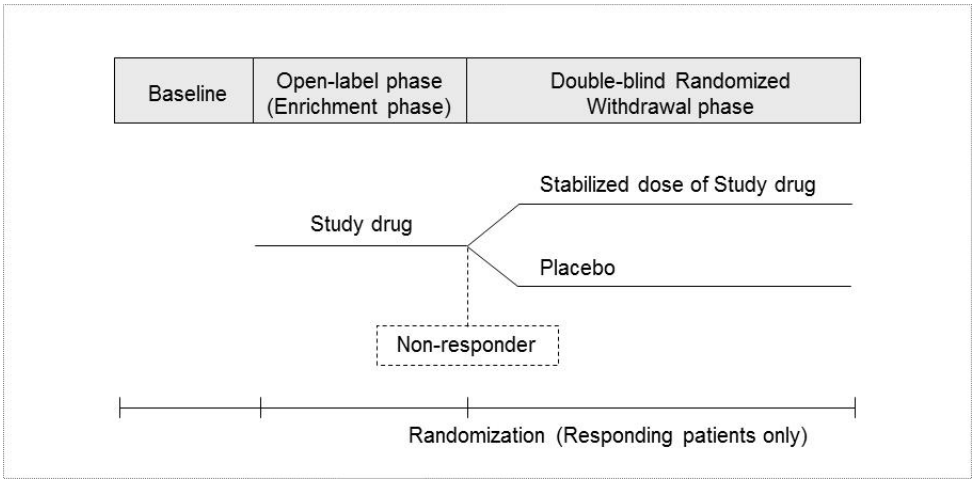
(A) Cross-over design



(B) Parallel-group design



(C) Randomized withdrawal design



A guidance document on the clinical development of new medicinal products in NeP was published in 2004 and updated in 2007 in the EU [14]. In the US, a draft guidance was published in February 2014 [15]. These guidance documents recommend parallel-group, PCTs of long treatment duration (at least 12 weeks) for confirmatory trials in NeP due to its largely chronic nature (Table 2). The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) recommends the same trial design [9].

Table 2. Guidance on the clinical development of new medical products for NeP in the West

	EMA guidance [14]		
Target indication and required clinical trials	Specific condition		Specific pain condition only (e.g. PHN)
	Broad indication	P-NeP	More than one pain condition in P-NeP (FDA draft Guidance: More than two pain conditions in P-NeP [15])
		NeP (both P-NeP and C-NeP)	At least one pain condition in C-NeP, in addition to P-NeP as mentioned above
Confirmatory trial design	Design: Double-blind, Randomized, Placebo-controlled, Parallel-group (Figure 1B) Treatment period: at least 12 weeks Primary endpoint: • 0-10 numerical rating scale (NRS) (Figure 2) • 100 mm visual analogue scale (VAS) (Figure 3)		
Target patients in clinical trials	Pain intensity: Moderate or severe (NRS $\geq$4, VAS $\geq$40) Duration of pain: at least 3 months		

Figure 2. Numerical rating scale (NRS) [16]

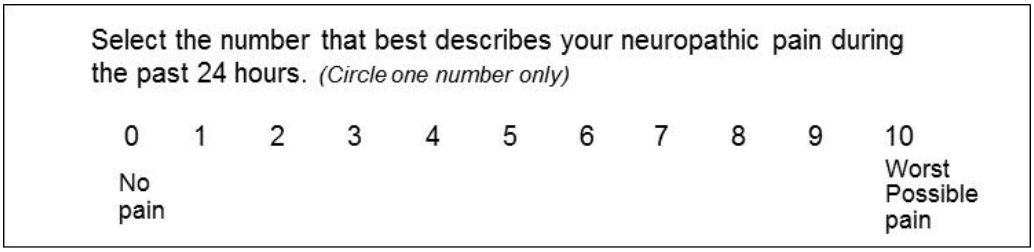
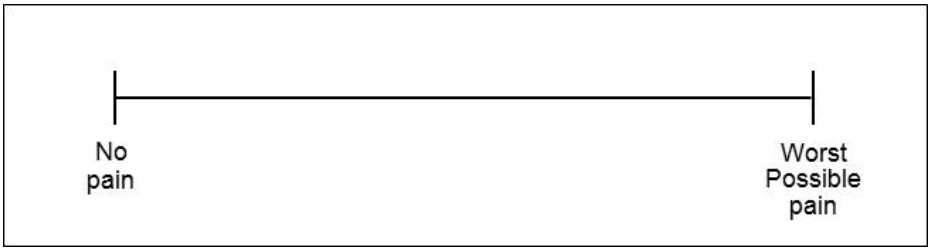


Figure 3. Visual analogue scale (VAS) [17]



The response to placebo in clinical trials for psychiatric diseases such as major depressive disorder (MDD) and schizophrenia is known; it is highly variable and substantial in most cases. Even in the clinical trials of approved drugs, the percentages of negative/failed trials in MDD and schizophrenia were 46% (23/50 trials) and 25% (4/16 trials), respectively [18]. In the 52 PCTs for MDD which are listed in the FDA database, only 21% of antidepressant treatment arms in trials with higher placebo response (≥30% mean change from baseline in the primary efficacy measure) showed statistical significant superiority over placebo compared with 74% in trials with lower placebo response (<30%) [19].

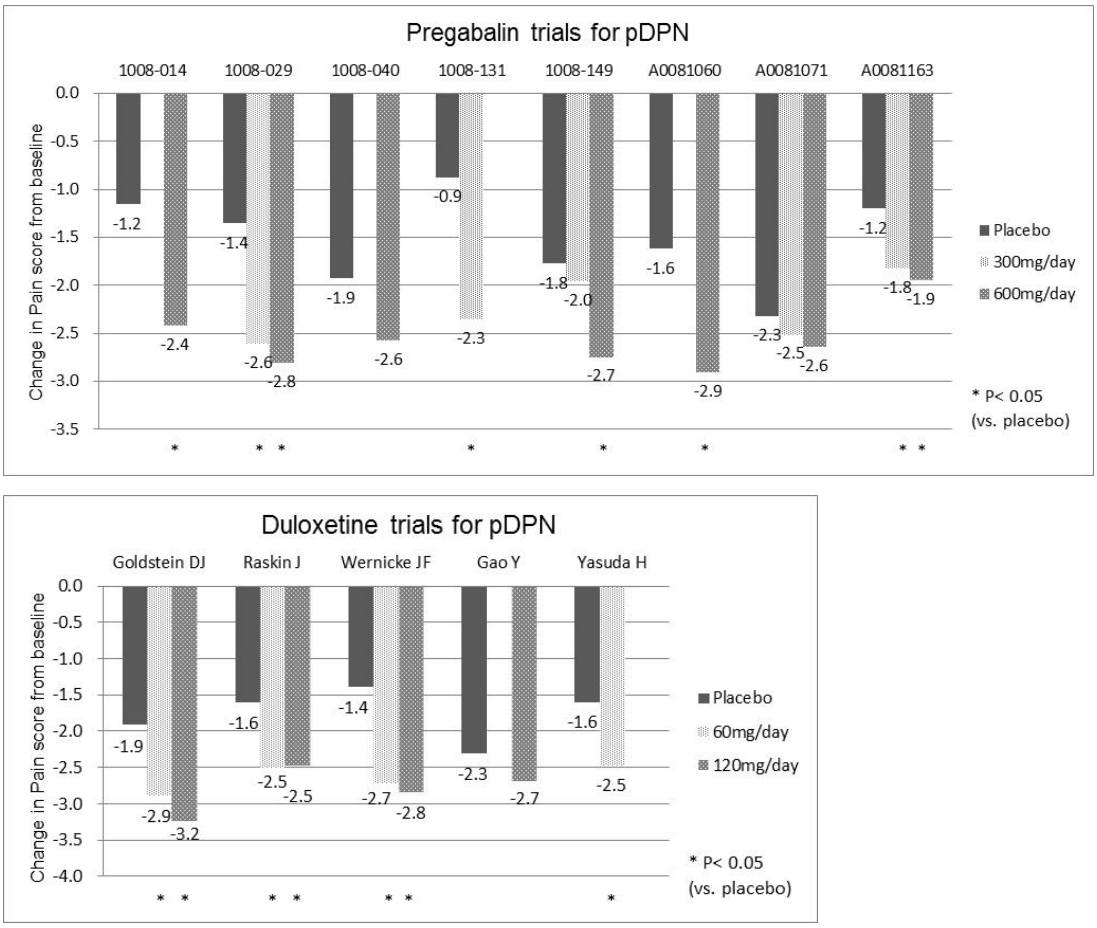
Previous research in psychiatric diseases suggested several potential factors affecting placebo response, such as severity of depression, duration of depressive episode, subtype of depressive disorder, method of patient recruitment, types of patients enrolled in trials, investigator's experience of conducting clinical trials, financial incentive, duration of trial, number of treatment arms, dosing regimen (flexible-dose vs. fixed-dose), reliability/validity/responsiveness of outcome measures, types of assessment method (observer rating or self-report) and publication year in MDD trials [20, 21], and age,

duration of illness, baseline symptom severity, duration of trial and publication year in schizophrenia trials [22-24].

Placebo effect is also an important phenomenon in the clinical setting for the treatment of pain. Due to the placebo response seen in clinical trials in NeP, superiority to placebo of drugs that have already been shown to be effective in PCTs cannot always be demonstrated in subsequently conducted PCTs [25]. For instance, pregabalin and duloxetine, which are recommended for the treatment of neuropathic pain including pDPN in pharmacological treatment guidelines [3-6], could not demonstrate the superiority over placebo in some PCTs (Figure 4) [28-33].

In case that the probability of study success is low, more clinical trials to obtain the minimum number of positive trials will be required for regulatory approval. However, that situation would raise ethical as well as practical issues to proceed with the clinical development of a new drug; we need to enroll and allocate more patients to a placebo group and need more resources and time, which will decrease the chance of delivering the drug to patients who are suffering from NeP. Therefore, more efforts to improve assay sensitivity in the clinical trial and to establish efficient methods for clinical development in this area are needed and I believe that the research to identify factors affecting placebo response in clinical trials for NeP contributes to them.

Figure 4. Clinical trial results for pregabalin and duloxetine in the treatment of pDPN (Placebo-controlled trials)



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 have suggested several mechanisms, such as placebo response differing depending on the NeP condition (e.g., placebo response in HIV-associated pain and pDPN was larger compared to PHN and C-NeP [34]), placebo response increasing with duration of treatment [35], 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 [36-38]), a faster patient recruitment rate related to higher placebo response [36], a parallel-group design producing a larger placebo response than a cross-over design [39], and placebo response increasing with year of trial initiation [35,

38].

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

5. Methods

5.1. Trial Selection and Database Construction

A literature search of MEDLINE and EMBASE (1995 to January 2014) was conducted on January 12, 2014. The following terms identifying conditions classified as NeP were used to search for NeP conditions [40]: 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, neuroapthic 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 of drugs approved for NeP or conditions classified as NeP in the US 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 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 [38]),

(4) Cross-over design or randomized withdrawal design trials.

5.2. Data Extraction

Two types of responder rates, 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 (Table 3) [16, 41].

Table 3. Interpretation of changes in chronic pain clinical trial outcome

Outcome Domain and Measure	Type of Improvement	Change
Pain intensity: 0-10 numerical rating scale	Minimally important	10-20% decrease
	Moderately important	≥ 30% decrease
	Substantial	≥ 50% decrease

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 100 mm VAS were converted to 0-10 scale.

- Study 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 enrollment rate (number of patients/number of sites/month)

- Demographic and baseline characteristics
  - Gender (proportion of male patients)
  - Age
  - Baseline pain intensity
  - Duration of neuropathic pain
- 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)

Other information, such as number of subjects, number of sites, study phase in clinical development, sponsored study or not, publication year, study results (positive or failed), were not included in the analysis because of the following reasons: strongly related to other factors, insufficient data gained, or data not related to study design and baseline characteristics.

5.3. Statistical Analyses

The pooled estimates of 50%RR and 30%RR in the placebo groups were calculated by random effects model. A random effects model was used because of the heterogeneity of placebo response observed in clinical trials for neuropathic pain conditions.

Next, logistic regression analyses were performed in accordance with the following strategy, because, although they were extracted from each of the clinical trial references taking into account their importance for the present research, there were still many potential factors to be considered as explanatory variables.

(1) Univariate logistic regression analysis was performed to identify potential factors affecting the responder rate in the placebo group.

(2) Factors shown to be significant explanatory variables by the univariate logistic regression analysis were further analyzed by multivariate logistic regression analysis using a stepwise approach.

Many diseases and conditions are included in NeP, and the pathology is typically classified into P-NeP and C-NeP, according to the site of lesion [2]. The target patient population of a clinical trial planned for new drug development is usually a specific NeP condition such as PHN or pDPN. Therefore separate analyses were performed by classification or condition if differences in placebo response were observed by NeP classification (P-NeP or C-NeP) or NeP conditions.

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).

6. Results

6.1. Search Results

The literature search and search of disclosed regulatory information identified 89 trials. A total of 71 (n=6126) of these trials yielded data on 50%RR or 30%RR (Figure 5, Table 4) [29-33, 42-113]. The numbers of trials with 50%RR and 30%RR were 63 (n=5540) and 52 (n=4539), respectively. Detailed data of these selected trials are shown in Table 12 (8. Supplementary data).

Most of the trials were investigations in P-NeP. These consisted mainly of 17 trials in postherpetic neuralgia (PHN), 38 trials in painful diabetic peripheral neuropathy (pDPN), and 3 trials in post-traumatic peripheral neuropathic pain (PT). Only a small number of the trials were investigations in C-NeP: 2 trials in spinal cord injury pain and 1 trial each in poststroke pain and multiple sclerosis-associated pain. The treatment duration was at least 12 weeks in 35 of the 71 trials.

Figure 5. Trial selection

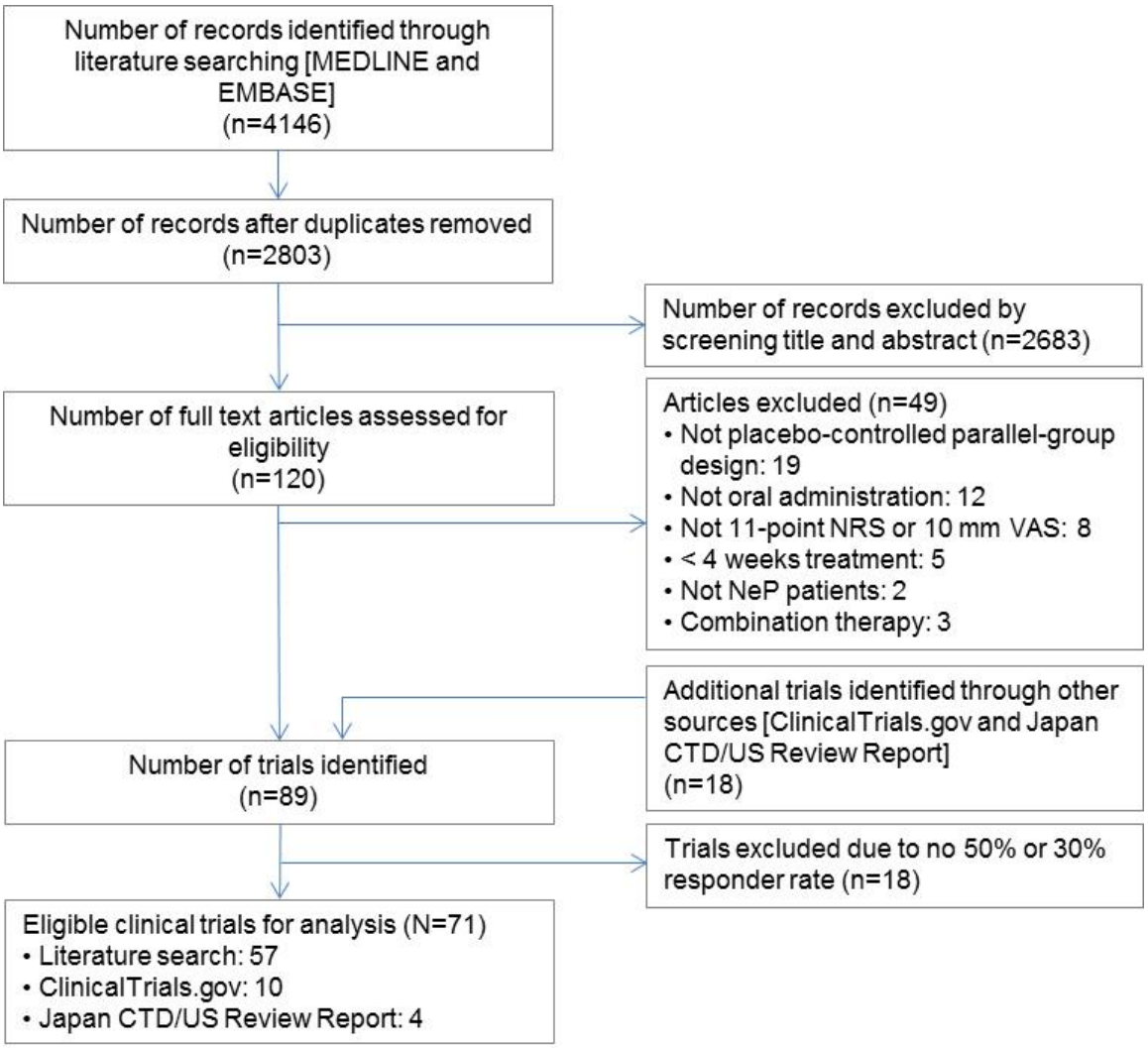


Table 4. Number of selected trials

Pain conditions	Number of trials		
	Total	50%RR	30%RR
Peripheral neuropathic pain (P-NeP)	65 (32)	57 (30)	47 (27)
Postherpetic neuralgia (PHN) [42-62]	17 (5)*	17 (5)*	9 (4)*
Painful diabetic peripheral neuropathy (pDPN) [29-33, 63-96]	38 (23)	32 (22)	29 (19)
Posttraumatic neuropathic pain (PT) [97-99]	3 (0)	3 (0)	3 (0)
HIV sensory neuropathy [100]	1 (1)	1 (1)	1 (1)
Complex regional pain syndrome [101]	1 (1)	0	1 (1)
Phantom limb pain [102]	1 (0)	1 (0)	0
Mixed P-NeP conditions [103-106]	4 (2)	3 (2)	4 (2)
Central neuropathic pain (C-NeP)	5 (3)	5 (3)	5 (3)
Spinal cord injury pian [107-109]	2 (2)	2 (2)	2 (2)
Poststroke pain [110]	1 (1)	1 (1)	1 (1)
Multiple sclerosis pain [111]	1 (0)	1 (0)	1 (0)
Mixed C-NeP conditions [112]	1 (0)	1 (0)	1 (0)
Other (both P-NeP and C-NeP)	1 (0)	1 (0)	0 (0)
Mixed NeP conditions [113]	1 (0)	1 (0)	0 (0)
Total	71 (35)	63 (33)	52 (30)

( ): number of trials with 12 weeks or more treatment duration, *RR* responder rate

*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.

Detailed data of selected trials are shown in Supplementary Table 12.

6.2. Pooled Estimates of Responder Rate in the Placebo Group

6.2.1. 50%RR

In the 63 total trials in NeP, the pooled estimate of 50%RR was 23% (95% CI 20–25%, n=5540). The 50%RR was 23% (95% CI 21–26%, n=4967) in the 57 trials in P-NeP and 14% (95% CI 10–19%, n=421) in the 5 trials in C-NeP. Further analysis of the P-NeP trials revealed that the 50%RR was 19% (95% CI 15–24%, n=1445), 26% (95% CI 23–29%, n=2948), and 15% (95% CI 10–20%, n=239), respectively, in the 17 PHN trials, 32 pDPN trials, and 3 PT trials (Table 5, Figure 6-11A). 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 to PHN or PT.

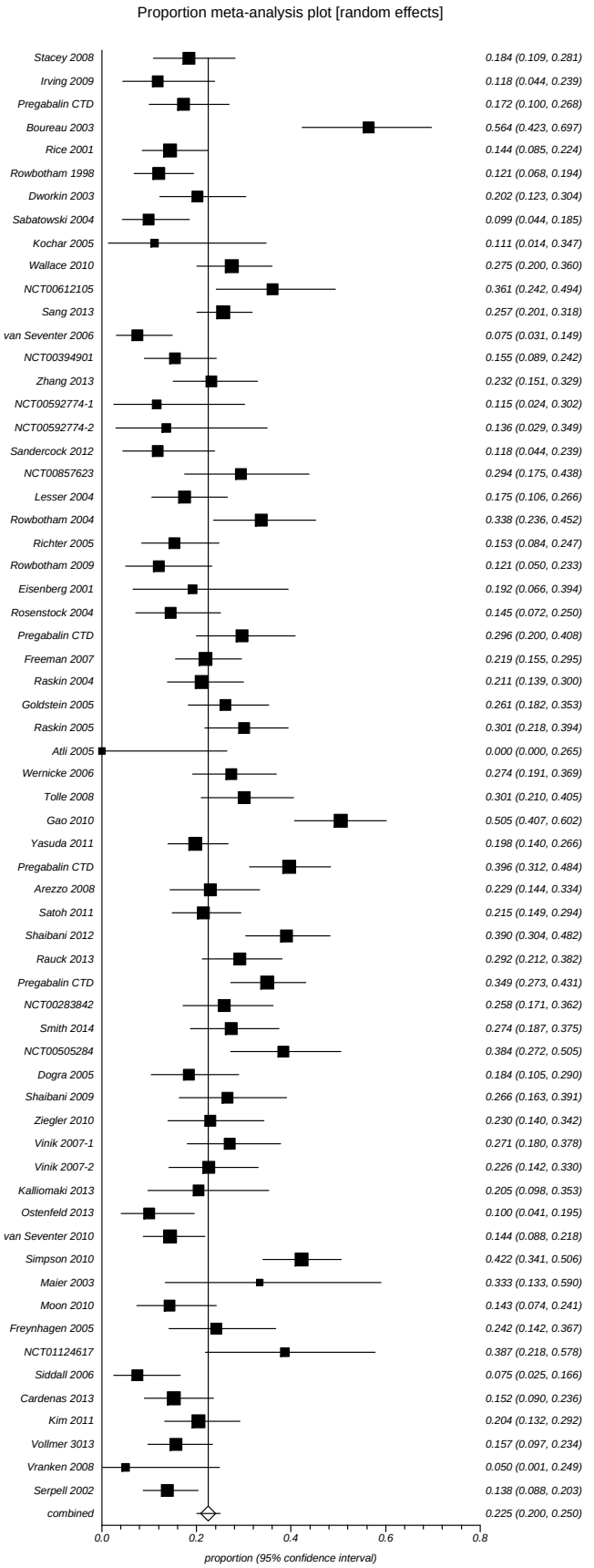
6.2.2. 30%RR

In the 52 total trials in NeP, the pooled estimate of 30%RR was 37% (95% CI 34–41%, n=4539). The 30%RR was 39% (95% CI 35–42%, n=4118) in the 47 trials in P-NeP and 26% (95% CI 19–33%, n=421) in the 5 trials in C-NeP. Further analysis of the P-NeP trials revealed that the 30%RR was 29% (95% CI 21–37%, n=600), 42% (95% CI 39–46%, n=2767), and 30% (95% CI 23–37%, n=239), respectively, in the 9 PHN trials, 29 pDPN trials, and 3 PT trials (Table 5, Figure 6-11B). Although these rates are higher than those seen for 50%RR, the same trend in rates by NeP condition is apparent.

Table 5. Pooled Estimates of Responder Rate in the Placebo Group (50%RR, 30%RR)

Pain conditions	Pooled Estimates of Responder Rate in the Placebo Group (95% CI) [Number of studies]	
	50% RR	30% RR
Neuropathic pain (NeP)	23% (20%, 25%) [63]	37% (34%, 41%) [52]
Peripheral neuropathic pain (P-NeP)	23% (21%, 26%) [57]	39% (35%, 42%) [47]
Postherpetic neuralgia (PHN)	19% (15%, 24%) [17]	29% (21%, 37%) [9]
Painful diabetic peripheral neuropathy (pDPN)	26% (23%, 29%) [32]	42% (39%, 46%) [29]
Posttraumatic neuropathic pain (PT)	15% (10%, 20%) [3]	30% (23%, 37%) [3]
Central neuropathic pain (C-NeP)	14% (10%, 19%) [5]	26% (19%, 33%) [5]

Figure 6. Forest plot of placebo responder rate in NeP (A: 50%RR, B: 30%RR)
(A)



(B)

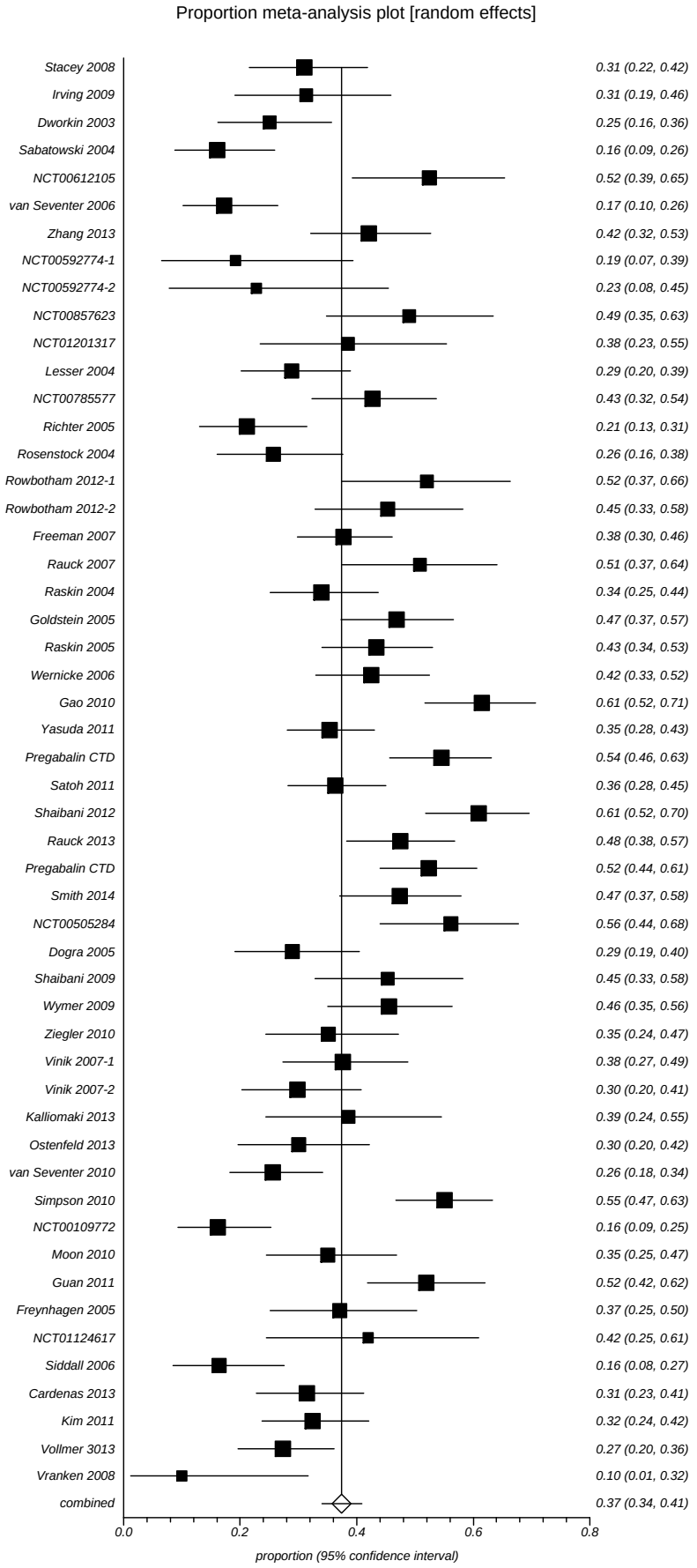
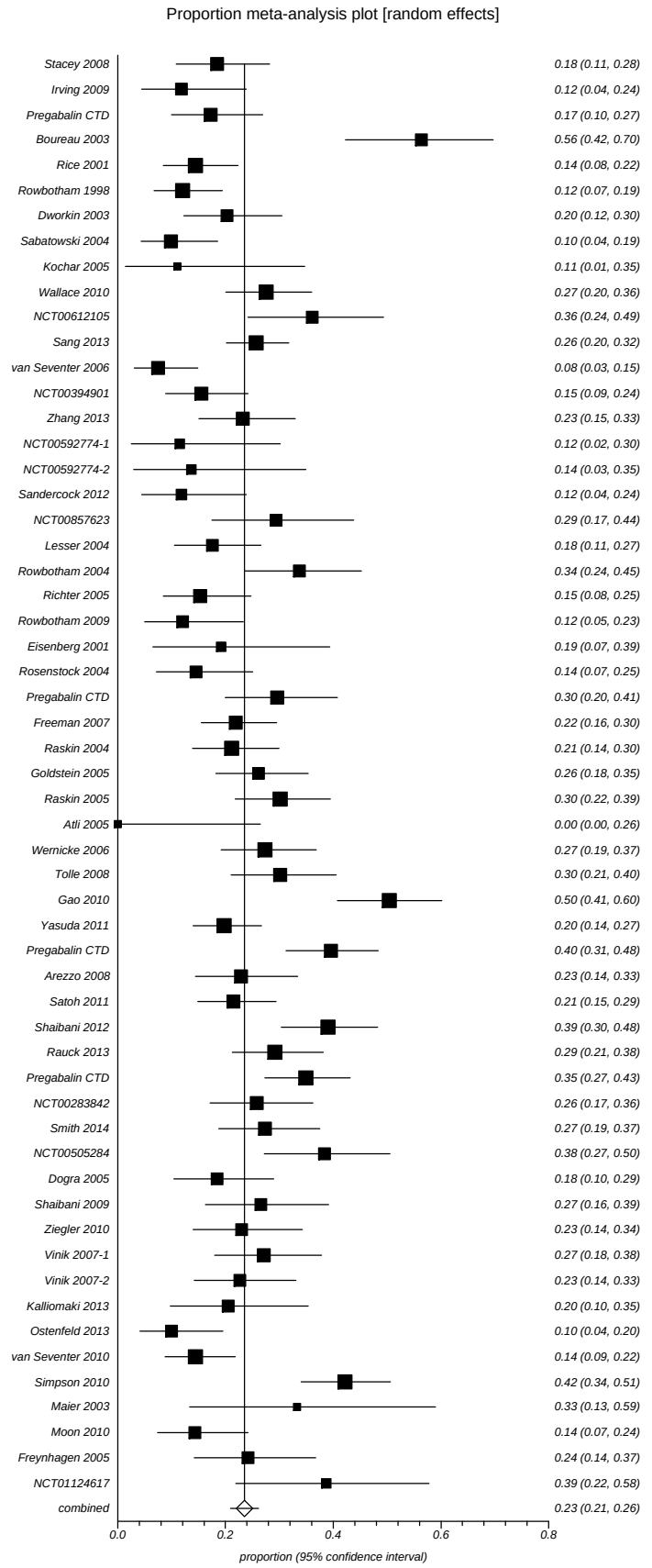

Proportion meta-analysis plot [random effects]
Stacey 2008 0.31 (0.22, 0.42)
Irving 2009 0.31 (0.19, 0.46)
Dworkin 2003 0.25 (0.16, 0.36)
Sabatowski 2004 0.16 (0.09, 0.26)
NCT00612105 0.52 (0.39, 0.65)
van Seventer 2006 0.17 (0.10, 0.26)
Zhang 2013 0.42 (0.32, 0.53)
NCT00592774-1 0.19 (0.07, 0.39)
NCT00592774-2 0.23 (0.08, 0.45)
NCT00857623 0.49 (0.35, 0.63)
NCT01201317 0.38 (0.23, 0.55)
Lesser 2004 0.29 (0.20, 0.39)
NCT00785577 0.43 (0.32, 0.54)
Richter 2005 0.21 (0.13, 0.31)
Rosenstock 2004 0.26 (0.16, 0.38)
Rowbotham 2012-1 0.52 (0.37, 0.66)
Rowbotham 2012-2 0.45 (0.33, 0.58)
Freeman 2007 0.38 (0.30, 0.46)
Rauck 2007 0.51 (0.37, 0.64)
Raskin 2004 0.34 (0.25, 0.44)
Goldstein 2005 0.47 (0.37, 0.57)
Raskin 2005 0.43 (0.34, 0.53)
Wernicke 2006 0.42 (0.33, 0.52)
Gao 2010 0.61 (0.52, 0.71)
Yasuda 2011 0.35 (0.28, 0.43)
Pregabalin CTD 0.54 (0.46, 0.63)
Satoh 2011 0.36 (0.28, 0.45)
Shaibani 2012 0.61 (0.52, 0.70)
Rauck 2013 0.48 (0.38, 0.57)
Pregabalin CTD 0.52 (0.44, 0.61)
Smith 2014 0.47 (0.37, 0.58)
NCT00505284 0.56 (0.44, 0.68)
Dogra 2005 0.29 (0.19, 0.40)
Shaibani 2009 0.45 (0.33, 0.58)
Wymer 2009 0.46 (0.35, 0.56)
Ziegler 2010 0.35 (0.24, 0.47)
Vinik 2007-1 0.38 (0.27, 0.49)
Vinik 2007-2 0.30 (0.20, 0.41)
Kalliomaki 2013 0.39 (0.24, 0.55)
Ostenfeld 2013 0.30 (0.20, 0.42)
van Seventer 2010 0.26 (0.18, 0.34)
Simpson 2010 0.55 (0.47, 0.63)
NCT00109772 0.16 (0.09, 0.25)
Moon 2010 0.35 (0.25, 0.47)
Guan 2011 0.52 (0.42, 0.62)
Freynhagen 2005 0.37 (0.25, 0.50)
NCT01124617 0.42 (0.25, 0.61)
Siddall 2006 0.16 (0.08, 0.27)
Cardenas 2013 0.31 (0.23, 0.41)
Kim 2011 0.32 (0.24, 0.42)
Vollmer 3013 0.27 (0.20, 0.36)
Vranken 2008 0.10 (0.01, 0.32)
combined 0.37 (0.34, 0.41)
0.0
0.2
0.4
0.6
0.8
proportion (95% confidence interval)

Figure 7. Forest plot of placebo responder rate in P-NeP (A: 50%RR, B: 30%RR)
(A)



(B)

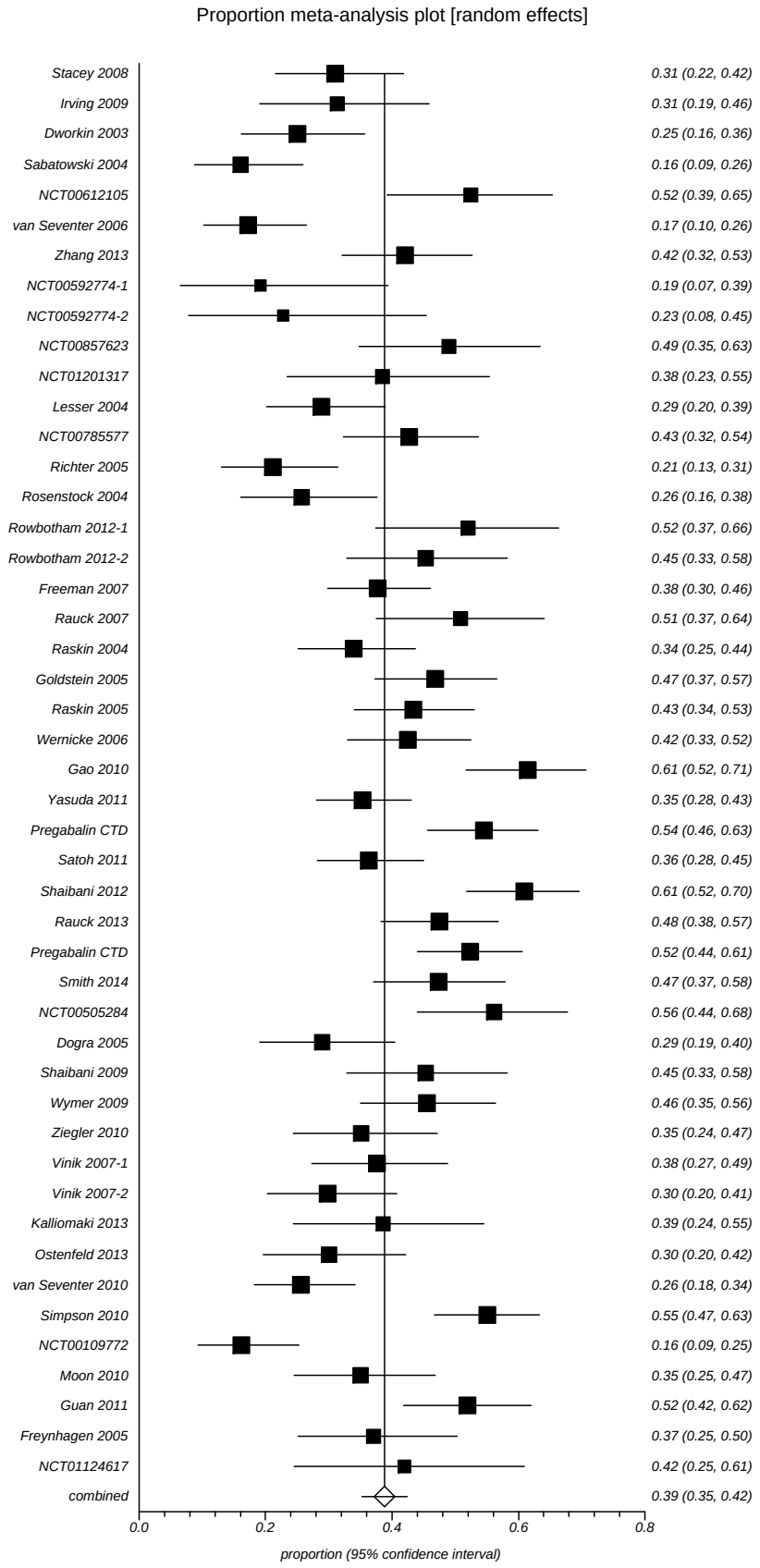
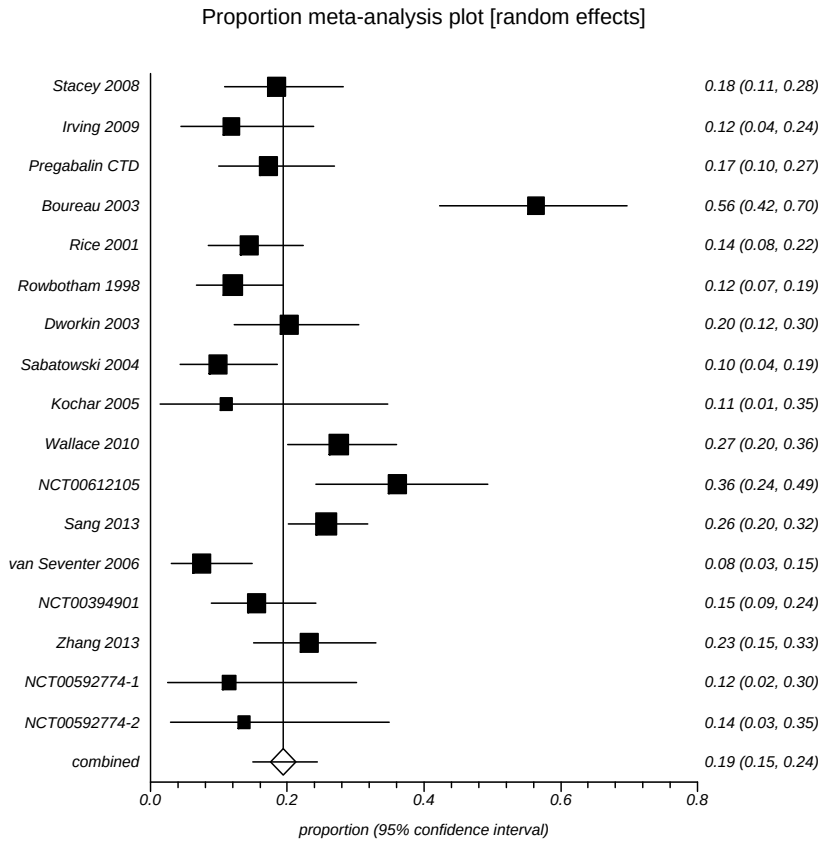

Proportion meta-analysis plot [random effects]
Stacey 2008 0.31 (0.22, 0.42)
Irving 2009 0.31 (0.19, 0.46)
Dworkin 2003 0.25 (0.16, 0.36)
Sabatowski 2004 0.16 (0.09, 0.26)
NCT00612105 0.52 (0.39, 0.65)
van Seventer 2006 0.17 (0.10, 0.26)
Zhang 2013 0.42 (0.32, 0.53)
NCT00592774-1 0.19 (0.07, 0.39)
NCT00592774-2 0.23 (0.08, 0.45)
NCT00857623 0.49 (0.35, 0.63)
NCT01201317 0.38 (0.23, 0.55)
Lesser 2004 0.29 (0.20, 0.39)
NCT00785577 0.43 (0.32, 0.54)
Richter 2005 0.21 (0.13, 0.31)
Rosenstock 2004 0.26 (0.16, 0.38)
Rowbotham 2012-1 0.52 (0.37, 0.66)
Rowbotham 2012-2 0.45 (0.33, 0.58)
Freeman 2007 0.38 (0.30, 0.46)
Rauck 2007 0.51 (0.37, 0.64)
Raskin 2004 0.34 (0.25, 0.44)
Goldstein 2005 0.47 (0.37, 0.57)
Raskin 2005 0.43 (0.34, 0.53)
Wernicke 2006 0.42 (0.33, 0.52)
Gao 2010 0.61 (0.52, 0.71)
Yasuda 2011 0.35 (0.28, 0.43)
Pregabalin CTD 0.54 (0.46, 0.63)
Satoh 2011 0.36 (0.28, 0.45)
Shaibani 2012 0.61 (0.52, 0.70)
Rauck 2013 0.48 (0.38, 0.57)
Pregabalin CTD 0.52 (0.44, 0.61)
Smith 2014 0.47 (0.37, 0.58)
NCT00505284 0.56 (0.44, 0.68)
Dogra 2005 0.29 (0.19, 0.40)
Shaibani 2009 0.45 (0.33, 0.58)
Wymer 2009 0.46 (0.35, 0.56)
Ziegler 2010 0.35 (0.24, 0.47)
Vinik 2007-1 0.38 (0.27, 0.49)
Vinik 2007-2 0.30 (0.20, 0.41)
Kalliomaki 2013 0.39 (0.24, 0.55)
Ostenfeld 2013 0.30 (0.20, 0.42)
van Seventer 2010 0.26 (0.18, 0.34)
Simpson 2010 0.55 (0.47, 0.63)
NCT00109772 0.16 (0.09, 0.25)
Moon 2010 0.35 (0.25, 0.47)
Guan 2011 0.52 (0.42, 0.62)
Freynhagen 2005 0.37 (0.25, 0.50)
NCT01124617 0.42 (0.25, 0.61)
combined 0.39 (0.35, 0.42)
0.0
0.2
0.4
0.6
0.8
proportion (95% confidence interval)

Figure 8. Forest plot of placebo responder rate in PHN (A: 50%RR, B: 30%RR)
(A)



(B)

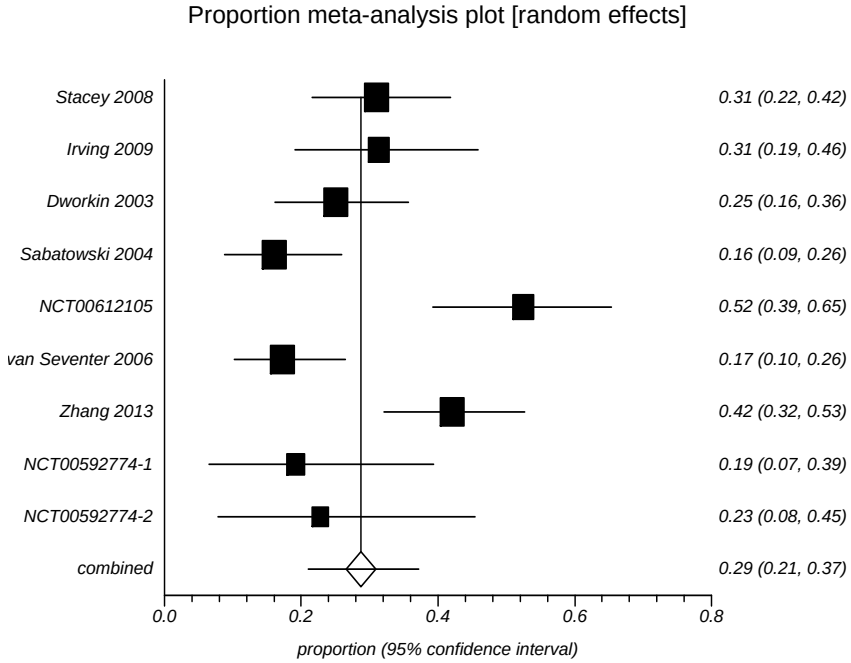
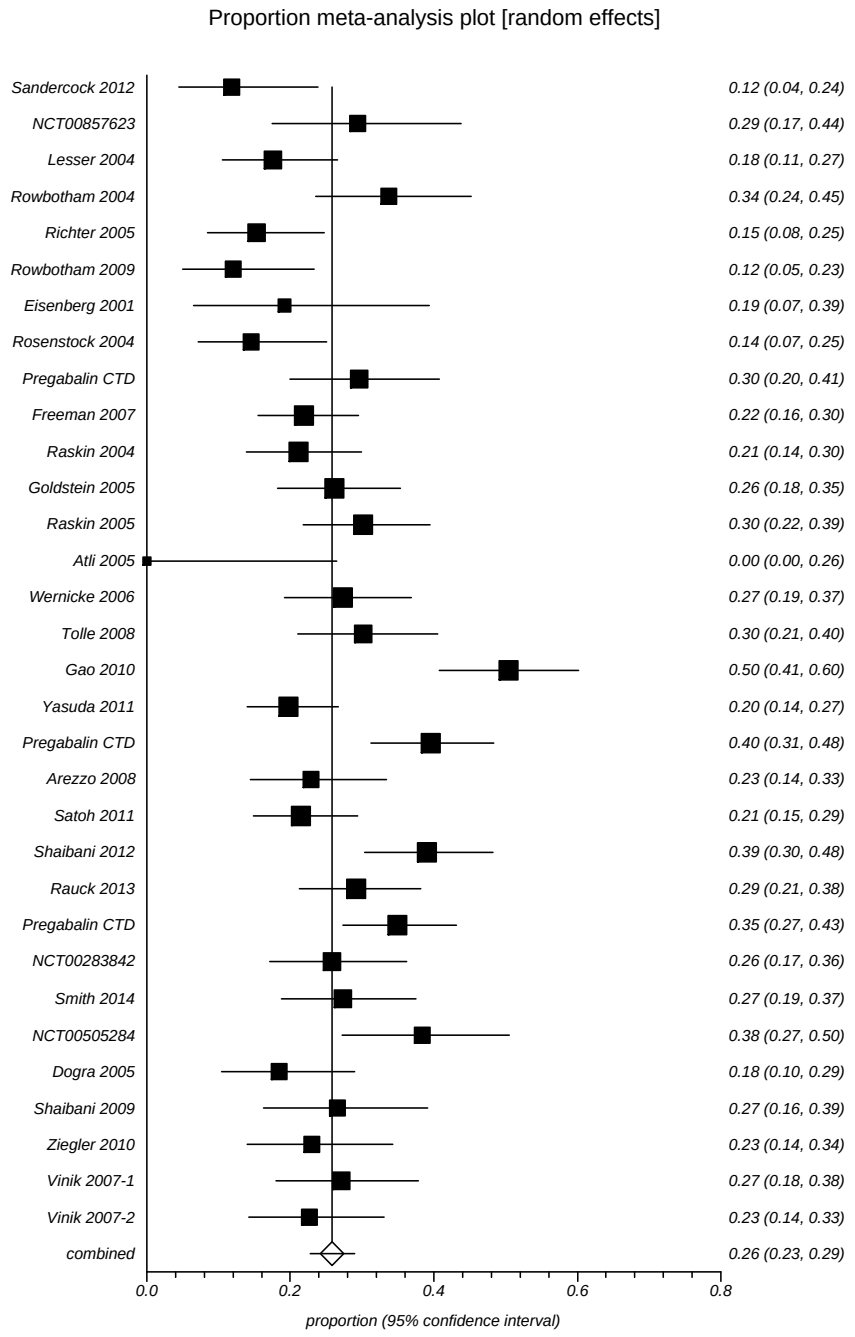


Figure 9. Forest plot of placebo responder rate in pDPN (A: 50%RR, B: 30%RR)
(A)



(B)

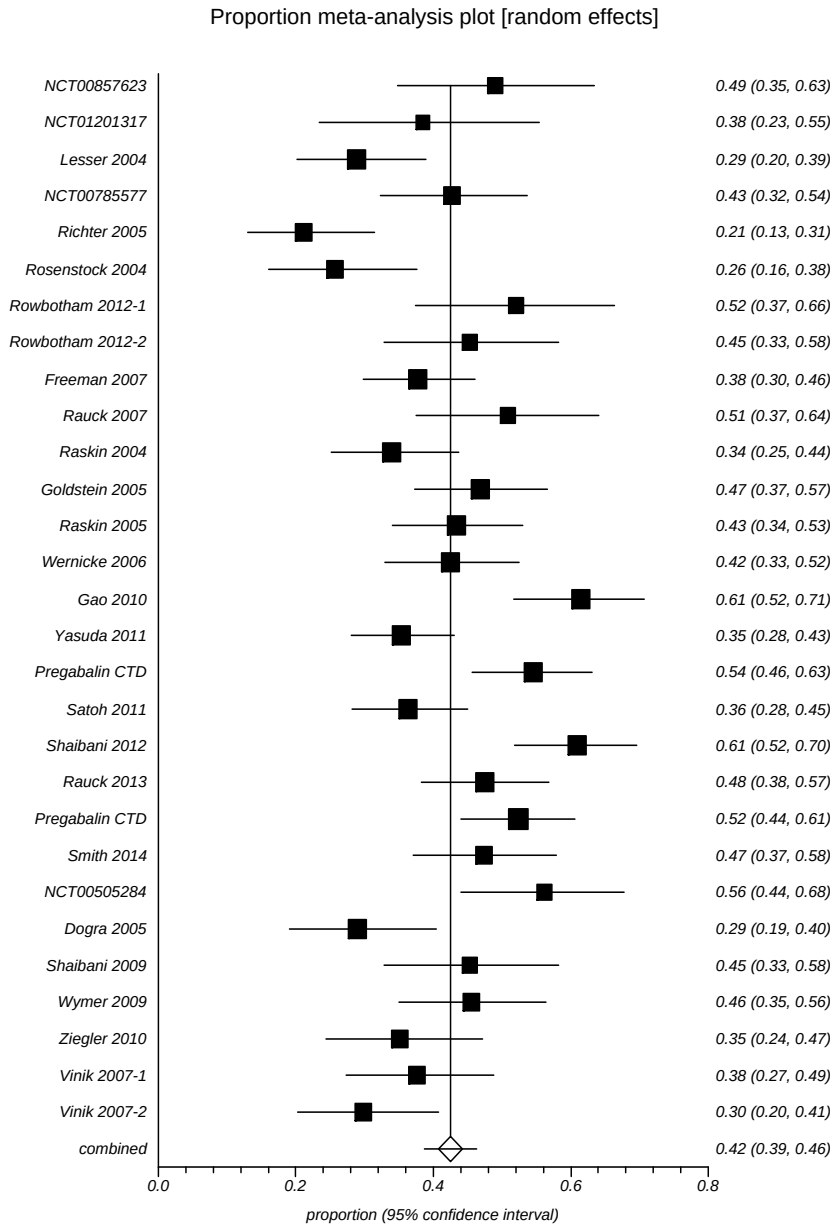
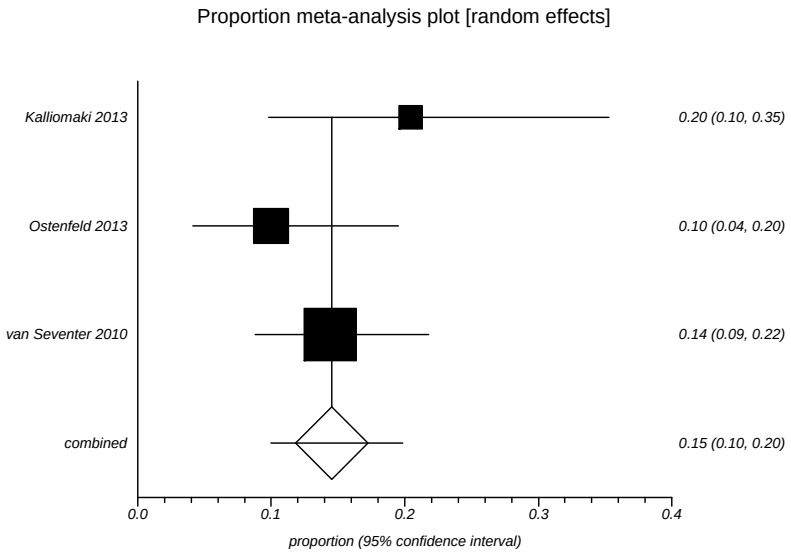

Proportion meta-analysis plot [random effects]
NCT00857623
NCT01201317
Lesser 2004
NCT00785577
Richter 2005
Rosenstock 2004
Rowbotham 2012-1
Rowbotham 2012-2
Freeman 2007
Rauck 2007
Raskin 2004
Goldstein 2005
Raskin 2005
Wernicke 2006
Gao 2010
Yasuda 2011
Pregabalin CTD
Satoh 2011
Shaibani 2012
Rauck 2013
Pregabalin CTD
Smith 2014
NCT00505284
Dogra 2005
Shaibani 2009
Wymer 2009
Ziegler 2010
Vinik 2007-1
Vinik 2007-2
combined
0.49 (0.35, 0.63)
0.38 (0.23, 0.55)
0.29 (0.20, 0.39)
0.43 (0.32, 0.54)
0.21 (0.13, 0.31)
0.26 (0.16, 0.38)
0.52 (0.37, 0.66)
0.45 (0.33, 0.58)
0.38 (0.30, 0.46)
0.51 (0.37, 0.64)
0.34 (0.25, 0.44)
0.47 (0.37, 0.57)
0.43 (0.34, 0.53)
0.42 (0.33, 0.52)
0.61 (0.52, 0.71)
0.35 (0.28, 0.43)
0.54 (0.46, 0.63)
0.36 (0.28, 0.45)
0.61 (0.52, 0.70)
0.48 (0.38, 0.57)
0.52 (0.44, 0.61)
0.47 (0.37, 0.58)
0.56 (0.44, 0.68)
0.29 (0.19, 0.40)
0.45 (0.33, 0.58)
0.46 (0.35, 0.56)
0.35 (0.24, 0.47)
0.38 (0.27, 0.49)
0.30 (0.20, 0.41)
0.42 (0.39, 0.46)
0.0
0.2
0.4
0.6
0.8
proportion (95% confidence interval)

Figure 10. Forest plot of placebo responder rate in PT (A: 50%RR, B: 30%RR)
(A)



(B)

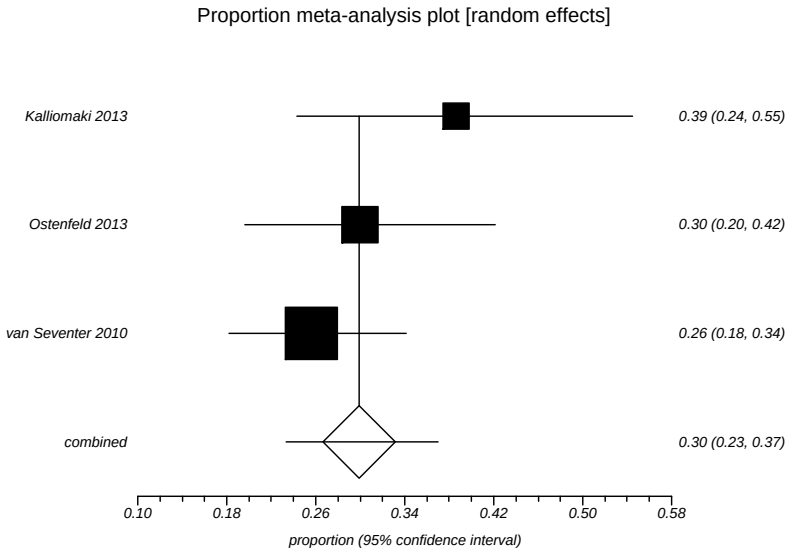
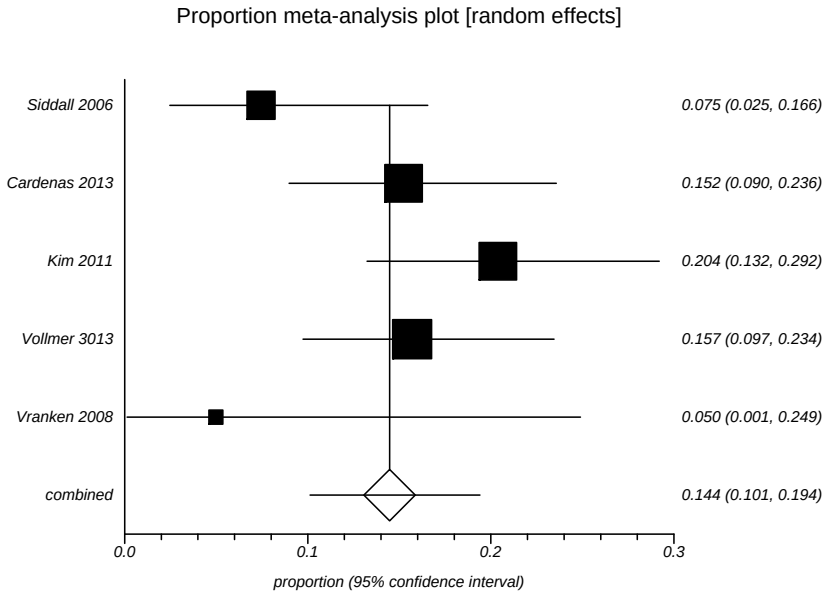
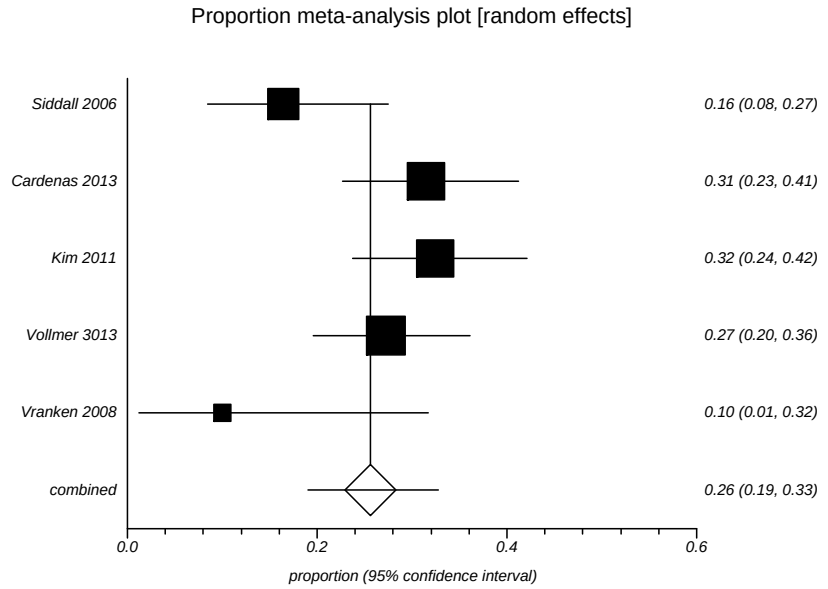


Figure 11. Forest plot of placebo responder rate in C-NeP (A: 50%RR, B: 30%RR)
(A)



(B)



6.3. 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 6). Further analysis of P-NeP showed a significant association for the major pain conditions of PHN, pDPN and PT (Table 6).

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

Table 6. Relationships between placebo responder rates and neuropathic pain 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

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

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]

6.3.1. PHN (50%RR)

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, patient enrollment rate, age, baseline pain intensity, duration of neuropathic pain, and trial initiation timing (Table 7).

The results suggest 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 enrollment rate, age and baseline pain intensity, longer treatment period and longer duration of neuropathic pain. A significant association was not observed for dosing regimen (fixed-dose, flexible-dose), gender, dropout rate, or region.

6.3.2. pDPN (50%RR)

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 7). A significant association was not observed for number of treatment arms, randomization ratio, patient enrollment rate, age, duration of neuropathic pain, dropout rate, region, or trial initiation timing. The results suggest 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.

6.3.3. pDPN (30%RR)

A similar pattern to that observed on the analysis of 50% RR was observed on the analysis of 30% RR, with the exception that a significant association with trial initiation timing was found for the 30%RR (Table 7).

6.3.4. pDPN (50%RR, 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 enrollment rate, gender, and baseline pain intensity (Table 7). The results suggest a higher placebo response correlated with flexible dosing regimen, increasing number of

patients per site and patient enrollment rate, and a reduced placebo response correlated with increasing proportion of male patients and baseline pain intensity.

Table 7. 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 enrollment 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 neuropathic pain	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

RR: responder rate, OR: odds ratio, CI: confidence interval, PHN: postherpetic neuralgia, pDPN: painful diabetic peripheral neuropathy

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 enrollment 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 US, 1 = trial started after approval [0 : reference category]

6.4. Multivariate Logistic Regression Analysis

6.4.1. PHN (50%RR)

The factors significantly associated with placebo response on univariate logistic regression analysis (treatment duration, number of treatment arms, number of patients per site, patient enrollment rate, age, baseline pain intensity, and trial initiation timing) were further analyzed by multivariate logistic regression analysis. The factor of duration of neuropathic pain was excluded from the analysis due to 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 increasing age and increasing baseline pain intensity (Table 8).

Table 8. Relationships between placebo responder rates and potential factors in PHN: Multivariate logistic regression analyses

Variable	Univariate Logistic Regression Analysis			Multivariate Logistic Regression Analysis		
	P value	OR	95% CI	*P* value	OR	95% CI
Treatment duration	0.0075	0.635	0.455, 0.886	Excluded		
Number of arms	<0.0001	0.714	0.606, 0.841	Excluded		
Number of patient per site	0.0021	0.932	0.891, 0.975	Excluded		
PE rate	0.0001	0.551	0.408, 0.746	Excluded		
Age	<0.0001	0.439	0.333, 0.578	<0.0001	0.433	0.321, 0.583
Baseline pain intensity	<0.0001	0.241	0.119, 0.487	<0.0001	0.212	0.102, 0.444
Trial initiation timing	< 0.0001	1.825	1.400, 2.378	Excluded		
Randomization ratio	0.0034	0.675	0.519, 0.878	-*		
Duration of NeP	<0.0001	0.498	0.404, 0.613	-*		

* Randomized ratio and duration of NeP were excluded from analysis

6.4.2. pDPN (50%RR)

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 analyzed by multivariate logistic regression analysis. The results obtained from 26 trials showed a significant association for the three factors of treatment period, dosing regimen (fixed-dose/flexible-dose) and baseline pain intensity, suggesting a higher placebo response correlated with longer treatment duration, flexible dosing regimen and a reduced placebo response with increasing baseline pain intensity (Table 9).

Table 9. Relationships between placebo responder rates and potential factors in pDPN: Multivariate logistic regression analyses

Variable	Univariate Logistic Regression Analysis			Multivariate Logistic Regression Analysis		
	P value	OR	95% CI	*P* value	OR	95% CI
Treatment duration	<0.0001	1.522	1.247, 1.858	0.0469	1.266	1.003, 1.599
Dosing regimen (Fixed/Flex)	<0.0001	1.719	1.386, 2.132	<0.0001	1.811	1.446, 2.269
Number of patients per site	0.0083	1.018	1.005, 1.032	Excluded		
Gender	<0.0001	0.578	0.472, 0.707	Excluded		
Baseline pain intensity	<0.0001	0.713	0.623, 0.816	<0.0001	0.729	0.627, 0.847

6.4.3. pDPN (30%RR)

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 analyzed by multivariate logistic regression analysis. The results obtained from 22 trials showed a significant association for two factors of dosing regimen and the baseline pain intensity, suggesting a higher placebo response correlated with flexible dosing regimen and a reduced placebo response correlated with increasing baseline pain intensity (Table 10).

Table 10. Relationships between placebo responder rates and potential factors in pDPN: Multivariate logistic regression analyses

Variable	Univariate Logistic Regression Analysis			Multivariate Logistic Regression Analysis		
	P value	OR	95% CI	*P* value	OR	95% CI
Treatment duration	0.0008	1.343	1.131, 1.594	Excluded		
Dosing regimen	0.0008	1.432	1.161, 1.767	0.0004	1.480	1.193, 1.837
Number of patients per site	0.0024	1.030	1.011, 1.050	Excluded		
Gender	<0.0001	0.677	0.568, 0.808	Excluded		
Baseline pain intensity	<0.0001	0.715	0.630, 0.811	<0.0001	0.707	0.621, 0.803
Trial initiation timing	0.0281	1.193	1.019, 1.397	Excluded		

6.4.4. pDPN (50%RR, 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 enrollment rate, gender, and baseline pain intensity) were further analyzed 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 enrollment rate, proportion of male patients and baseline pain intensity, suggesting a higher placebo response correlated with increasing number of patient per site, a reduced placebo response correlated with increasing patient enrollment rate, proportion of male patients and baseline pain intensity (Table 11).

Table 11. Relationships between placebo responder rates and potential factors in pDPN: Multivariate logistic regression analyses

Variable	Univariate Logistic Regression Analysis			Multivariate Logistic Regression Analysis		
	P value	OR	95% CI	*P* value	OR	95% CI
Dosing regimen	0.0001	1.590	1.252, 2.019	Excluded		
Number of patients per site	<0.0001	1.056	1.031, 1.083	0.0001	1.081	1.039, 1.125
Patient enrollment rate	0.0182	1.171	1.027, 1.336	0.0034	0.729	0.590, 0.901
Gender, Male rate	<0.0001	0.631	0.512, 0.778	0.0337	0.704	0.509, 0.973
Baseline pain intensity	<0.0001	0.713	0.623, 0.816	0.0104	0.804	0.680, 0.950

7. Discussion

7.1. Pooled Estimates of Responder Rate

In this study, the magnitude of placebo response as measured by 50% and 30% responder rate was estimated, and a logistic regression analysis was performed 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 to PHN and PT. The estimated 50%RRs in the placebo group were 19% (95% CI 15–24%) in PHN, 26% (23–29%) in pDPN and 14% (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% (8.4–14.5%) in PHN, 20.2% (14.6–25.8%) in pDPN and 7.2% (2.1–12.3%) in C-NeP [34]. These results indicate that the higher placebo response may be influenced by trial design and treatment duration. 30%RR is also considered as a clinically meaningful improvement. The same trend in rates by NeP condition was found though higher placebo response was observed in 30%RR (29% in PHN, 42% in pDPN and 26% in C-NeP) compared with 50%RR.

According to the EU guidance for the 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 at least one C-NeP model for the claim of a broad NeP indication [14]. According to the US draft guidance, at least three separate P-NeP clinical situations should be studied [15]. 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 neuropathic pain clinical situations. Although only a limited number of trials were

performed in PT, a similar placebo response 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.

7.2. Logistic Regression Analysis

7.2.1. PHN

On univariate logistic regression analysis, associations with placebo response (50%RR) were observed for the following factors in PHN: treatment duration, number of treatment arms, number of patients per site, patient enrollment rate, age, baseline pain intensity, and trial initiation timing. 30%RR could not be analyzed for PHN due to the limited number of trials. Multivariate logistic regression analysis showed a stronger association with placebo response (50%RR) for age and baseline pain intensity in PHN. The results suggested 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 lamotorigine and duloxetine clinical trials [36,37], the meta-analysis of neuropathic pain clinical trials including cross-over design trials did not identify this factor [39]. The results also suggested 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 one year in patients with PHN increases with age [114]. The intractability of pain may also increase with age. These results indicate that the placebo response may have been lower in PHN patient population with a longer duration of illness and more severe pain symptoms. Spearman's rank correlation coefficient (0.624)

showed a relatively strong relationship between mean age and mean duration of NeP (8. Supplementary data: Figure 12).

These findings indicate that placebo response may potentially be limited by selecting patients with longer durations of NeP or patients with higher baseline pain intensity in PHN trials.

7.2.2. pDPN

On univariate logistic regression analysis, associations with placebo response (50%RR) were observed for the following factors in pDPN: treatment duration, dosing regimen, number of patients per site, gender, and baseline pain intensity. The 30%RR results showed a similar pattern to that observed for 50%RR. Multivariate logistic regression analysis showed a stronger association with placebo response (50%RR) for treatment duration, dosing regimen and baseline pain intensity in pDPN. The results suggested a reduced placebo response correlated with increasing baseline pain intensity.

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 ≥12 weeks in pDPN, but not in PHN. In the trials with ≥12 week treatment duration, the higher pooled estimates were observed in pDPN as compared with PHN (50%RR: 15% in PHN and 28% in pDPN, 30%RR: 26% in PHN and 44% in pDPN) (8. Supplementary data: Figure 13, Figure 14). The observation suggests that more attention should be paid to placebo response in clinical trials in pDPN with longer treatment durations and it highlights the importance of selecting NeP clinical situations for clinical trials in the new drug development process. The results for pDPN also suggested that flexible-dose designs yield higher levels of placebo response than

fixed-dose design. The patient's expectation of pain treatment benefit is a known factor for placebo response [115,116]. Study design may influence placebo response because of patient's expectation. According to previous research of clinical trials for opioid analgesics, flexible-dose design trials were more likely to be positive [117], and the same finding was reported in the evaluation of antidepressant clinical trials [20].

The 50%RR in trials with ≥12 week treatment duration were analyzed in pDPN. Among the trial operation-related factors, number of patients per site and patient enrollment rate were associated with placebo response in pDPN trials with ≥12 week treatment duration. Higher placebo response was reported in patients enrolled in sites with faster recruitment rate in lamotorigine clinical trials [36]. In contrast, this finding suggests a higher placebo response correlated with the increasing number of patients per site and a reduced placebo response correlated with the increasing patient enrollment rate in the trial-level data. The results also suggested that the proportion of male patients was associated with placebo response. Although the meta-analysis of neuropathic pain clinical trials did not identify this factor, higher placebo response in female patients was observed in the research using patient data on lamotorigine clinical trials for pDPN [36]. In the clinical trials for pregabalin, the differences in mean change pain score from baseline between active treatment and placebo in female patients were smaller than those in male patients in both PHN and pDPN trials conducted in Japan, but the trend was not observed in trials conducted in the West. In addition, there was no differences in mean change pain score from baseline between female and male patients in SCI trials for pregabalin and in pDPN trials for duloxetine [118-120]. More accumulation of evidence regarding clinical trial with ≥12 week treatment duration is needed for further understanding.

These findings indicate that placebo response may potentially be limited by selecting a fixed-dose trial design, male patients, trial sites with high performance, or patients with

higher baseline pain intensity in pDPN trials.

7.2.3. Other consideration

In general, the difference in trial design could result in difference in the dropout rate after treatment initiation. However, univariate logistic regression analysis for both PHN and pDPN did not show an association between placebo response and dropout rate.

A higher placebo response in clinical trials for migraine conducted in Asian countries compared with Western countries has been reported and the reason for the higher placebo response is unclear [121,122]. Although the trials analyzed did not include many trials conducted in the Asian region, a significant association was not observed between placebo response and trial location. There was only one clinical trial conducted in both Western and Asian countries identified in the present research [109], but the number of multinational clinical trials is expected to increase.

Although the placebo effect is considered to be related to many types of mechanisms including patients' expectations, the improvement of pain intensity in patients treated with placebo in clinical trials was the focus in the present research. It was confirmed that, in the clinical trials for approved drugs, there was an increasing possibility of study failure in association with higher placebo response. The thresholds of placebo response for failed study seemed to be approximately 30% in 50%RR and 45% in 30%RR, respectively (8. Supplementary data: Figure 15).

The present research showed similar findings to the previous research in MDD in some aspects, e.g. severity of illness, duration of episode, duration of trial. On the other hand, a different pattern was observed for NeP and MDD in relation to study design, e.g. number of treatment arms and flexible-dose vs. fixed-dose designs. In MDD, trials with a greater number of active treatment arms can be expected to increase placebo response because the

patients know that the percentage of patients receiving placebo is low. The result of a meta-analysis of 51 antidepressant clinical trials showed that 60% of the active treatment arms in flexible-dose design showed statistically significant efficacy compared to placebo, whereas only 31% in fixed-dose design [123]. The reason for the differences between NeP and MDD is unclear, but it may be related to the assessment method in addition to the patients' expectation. While patient self-reported measure such as NRS or VAS are used in NeP trials, observer rating scales such as HAM-D or MADRS are widely used in MDD trials [19]; substantially larger placebo response in observer ratings compared with self-report was reported [21].

7.2.4. Limitation

Publication bias may be present in this study and impose some limitations as only a limited number of trials were available in NeP conditions other than PHN and pDPN. Overall, this research included fewer trials in C-NeP than P-NeP, precluding a separate analysis of specific NeP conditions. Although double-blind, placebo-controlled trials were analyzed, there may be some variation in the results because this research looked only at the placebo group and the difference in efficacy compared with the active treatment group was not taken into account. Other potential factors such as types of mechanism of action, percentage of patients with evoked pain (hyperalgesia or allodynia), and hemoglobin A1c in pDPN were not studied due to limited number of trials with such information. More research and accumulation of evidence are needed for further understanding and will expand the knowledge of the placebo effect.

8. Conclusions

The results of the 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 order to minimize the placebo response, the following efforts should be considered in future trials: (1) selecting patients with longer durations of NeP or patients with higher baseline pain intensity in PHN trials, (2) selecting a fixed-dose trial design and trial sites with high performance, and increasing proportion of male patients and patients with higher baseline pain intensity in pDPN trials. In addition, the magnitude of placebo response and the effect of treatment duration are more considerable in pDPN than in PHN. These facts should be considered when planning and conducting confirmatory clinical trials for NeP. PT is considered to be an appropriate NeP clinical situation for evaluating efficacy in the development of new drugs to obtain the approval with a broad NeP indication.

9. Acknowledgements

I would like to express my sincere gratitude to Prof. Masahiro Takeuchi for providing me this precious opportunity to conduct my research at Kitasato University.

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10. Supplementary data

Table 12. Detailed data of selected trials

	Trial	Reference	Pain condition	Active treatment	Treatment period (weeks)	Region	Number of sites	Patient Enrollment Rate	Number of patients per site	Number of arms	Randomization ratio	Dosing regimen	Drop out Rate	Age	Proportion of male patients	Duration of NeP	BL Pain Intensity	30% RR (n/N)	50% RR (n/N)
1	Stacey 2008	[42]	PHN	Pregabalin	4	West	42	0.33	6.4	3	33%	Flexible	17%	65.6	0.57	2.1	6.5	27/87	16/87
2	Irving 2009	[43]	PHN	Gabapentin	4	West	33	0.77	4.8	3	33%	Fixed	NA	69	0.49	NA	6.59	16/51	6/51
3	Pregabalin CTD: Study 1008-030	[44,45]	PHN	Pregabalin	5	West	29	NA	8.8	3	33%	Fixed	10%	71.3	0.52	NA	6.6	NA	15/87
4	Boureau 2003	[46]	PHN	Tramadol	6	West	77	0.10	1.6	2	50%	Fixed	9%	67.9	0.20	0.6	6	NA	31/55
5	Rice 2001	[47]	PHN	Gabapentin	7	West	48	1.07	7.0	3	33%	Fixed	15%	74.9	0.41	2.2	6.4	NA	16/111
6	Rowbotham 1998: Study 945-211	[48,49]	PHN	Gabapentin	8	West	16	1.54	14.3	2	50%	Flexible	18%	72.6	0.48	2.5	6.5	NA	14/116
7	Dworkin 2003: Study 1008-127	[50,51]	PHN	Pregabalin	8	West	29	1.99	6.0	2	50%	Fixed	12%	70.5	0.52	2.9	6.4	21/84	17/84
8	Sabatowski 2004: Study 1008-045	[52,53]	PHN	Pregabalin	8	West	53	0.31	4.5	3	33%	Fixed	25%	73.2	0.46	3.7	6.6	13/81	8/81
9	Kochar 2005	[54]	PHN	Valproate	8	Asia	1	NA	48.0	2	50%	Fixed	18%	56.4	0.56	0.7	6.1	NA	2/18
10	Wallace 2010	[55]	PHN	Gabapentin	10	West	95	0.36	4.3	3	33%	Fixed	22%	66	0.59	NA	6.78	NA	36/131
11	NCT00612105	[56]	PHN	Retigabine	10	West	45	0.17	4.2	2	33%	Flexible	11%	61.2	0.42	NA	NA	32/61	22/61

	Trial	Reference	Pain condition	Active treatment	Treatment period (weeks)	Region	Number of sites	Patient Enrollment Rate	Number of patients per site	Number of arms	Randomization ratio	Dosing regimen	Drop out Rate	Age	Proportion of male patients	Duration of NeP	BL Pain Intensity	30% RR (n/N)	50% RR (n/N)
12	Sang 2013	[57]	PHN	Gabapentin	10	West	89	0.34	5.1	2	50%	Fixed	16%	65.9	0.36	1.8	6.5	NA	59/230
13	van Seventer 2006	[58]	PHN	Pregabalin	13	West	76	0.60	4.9	4	25%	Fixed	37%	70.9	0.43	3.6	6.85	16/93	7/93
14	NCT00394901, Ogawa 2010	[59,60]	PHN	Pregabalin	13	Asia	50	0.67	7.4	4	25%	Fixed	16%	71.1	0.57	2.8	6.3	NA	15/97
15	Zhang 2013	[61]	PHN	Gabapentin	13	West	72	0.37	5.2	4	25%	Fixed	32%	61.7	0.53	NA	6.33	40/95	22/95
16	NCT00592774	[62]	PHN	Perampanel	15	West	47	0.41	3.1	5	40%	Fixed	42%	NA	0.58	NA	NA	5/26	3/26
17	NCT00592774	[62]	PHN	Perampanel	15	West	47	0.41	3.1	5	40%	Fixed	18%	NA	0.64	NA	NA	5/22	3/22
18	Sandercock 2012	[63]	pDPN	Gabapentin	4	West	24	0.85	6.1	3	33%	Fixed	4%	58	0.63	NA	6.74	NA	6/51
19	NCT00857623	[64]	pDPN	AZD2066	4	West	19	1.31	6.7	2	50%	Fixed	15%	57	0.52	NA	NA	25/51	15/51
20	NCT01201317	[65]	pDPN	AZD2423	4	West	20	0.82	6.7	3	33%	Fixed	20%	56.4	0.51	NA	NA	15/39	NA
21	Lesser 2004: Study 1008-029	[66,67]	pDPN	Pregabalin	5	West	44	0.84	7.5	4	25%	Fixed	8%	57.8	0.61	NA	6.6	28/97	17/97
22	NCT00785577	[68]	pDPN	LY545694	5	West	13	1.23	21.0	5	33%	Fixed	12%	55.3	0.58	NA	NA	38/89	NA
23	Rowbotham 2004	[69]	pDPN	Venlafaxine	6	West	12	NA	20.4	3	33%	Flexible	14%	60	0.59	5.4	6.88	NA	27/80
24	Richter 2005	[70]	pDPN	Pregabalin	6	West	29	0.70	8.5	3	33%	Fixed	15%	57.1	0.54	NA	6.9	18/85	13/85
25	Rowbotham 2009	[71]	pDPN	ABT-594	7	West	29	1.10	9.2	4	25%	Fixed	22%	60.2	0.58	NA	6.5	NA	7/58

	Trial	Reference	Pain condition	Active treatment	Treatment period (weeks)	Region	Number of sites	Patient Enrollment Rate	Number of patients per site	Number of arms	Randomization ratio	Dosing regimen	Drop out Rate	Age	Proportion of male patients	Duration of NeP	BL Pain Intensity	30% RR (n/N)	50% RR (n/N)
26	Eisenberg 2001	[72]	pDPN	Lamotrigine	8	Asia	1	NA	53.0	2	50%	Fixed	15%	57.8	0.62	3.8	6.6	NA	5/26
27	Rosenstock 2004: Study 1008-131	[73,74]	pDPN	Pregabalin	8	West	25	1.83	5.8	2	50%	Fixed	11%	60.3	0.57	NA	6.1	18/70	10/69
28	Rowbotham 2012	[75]	pDPN	ABT-894	8	West	47	0.48	6.0	5	20%	Fixed	NA	59.6	0.55	4.4	6.62	26/50	NA
29	Rowbotham 2012	[75]	pDPN	ABT-894	8	West	26	0.42	4.8	2	50%	Fixed	NA	56.5	0.62	5.3	6.79	29/64	NA
30	Pregabalin CTD: Study 1008-040	[76]	pDPN	Pregabalin	8	West	49	0.39	5.2	3	33%	Fixed	24%	60.6	0.57	NA	6.3	NA	24/81
31	Freeman 2007	[77]	pDPN	Tramadol/acetaminophen	9	West	46	0.48	6.8	2	50%	Fixed	29%	55.1	0.58	3.7	7.12	55/146	32/146
32	Rauck 2007	[78]	pDPN	Lacosamide	10	West	38	0.19	3.1	2	50%	Flexible	19%	55.3	0.46	3.7	6.5	30/59	NA
33	Raskin 2004	[79]	pDPN	Topiramate	12	West	39	0.62	8.3	2	33%	Flexible	27%	58.9	0.53	3.2	6.91	37/109	23/109
34	Goldstein 2005	[29,80]	pDPN	Duloxetine	12	West	NA	NA	NA	4	25%	Fixed	24%	60.4	0.51	4.0	5.8	52/111	29/111
35	Raskin 2005	[30,80]	pDPN	Duloxetine	12	West	26	3.32	13.4	3	33%	Fixed	14%	59.2	0.46	4.0	5.5	49/113	34/113
36	Atli 2005	[81]	pDPN	Zonisamide	12	West	1	NA	25.0	2	50%	Fixed	8%	61.5	0.42	NA	6.63	NA	0/12
37	Wernicke 2006	[31,80]	pDPN	Duloxetine	12	West	28	1.18	11.9	3	33%	Fixed	21%	60.8	0.64	3.5	5.9	45/106	29/106
38	Tolle 2008	[82]	pDPN	Pregabalin	12	West	58	0.44	6.8	4	25%	Fixed	18%	58.9	0.53	NA	6.4	NA	28/93

	Trial	Reference	Pain condition	Active treatment	Treatment period (weeks)	Region	Number of sites	Patient Enrollment Rate	Number of patients per site	Number of arms	Randomization ratio	Dosing regimen	Drop out Rate	Age	Proportion of male patients	Duration of NeP	BL Pain Intensity	30% RR (n/N)	50% RR (n/N)
39	Gao 2010	[32]	pDPN	Duloxetine	12	Asia	11	1.71	19.5	2	50%	Flexible	16%	59.9	0.46	3.3	5.5	67/109	55/109
40	Yasuda 2011	[33,80]	pDPN	Duloxetine	12	Asia	73	0.31	4.6	3	50%	Fixed	10%	60.8	0.77	4.2	5.78	59/167	33/167
41	Pregabalin CTD: Study A0081030	[83]	pDPN	Pregabalin	12	Both	47	0.71	8.8	2	33%	Flexible	18%	57.3	0.39	2.8	6.36	73/134	53/134
42	Arezzo 2008	[84]	pDPN	Pregabalin	13	West	23	0.72	7.3	2	50%	Fixed	28%	58.3	0.53	4.4	6.58	NA	19/83
43	Satoh 2011	[85]	pDPN	Pregabalin	13	Asia	62	0.36	5.1	3	40%	Fixed	12%	61.3	0.76	4.2	6.1	49/135	29/135
44	Shaibani 2012	[86]	pDPN	Dextromethorphan/Quinidine	13	West	47	0.57	8.1	3	33%	Fixed	28%	62	0.55	3.8	4.4	75/123	48/123
45	Rauck 2013	[87]	pDPN	Gabapentin	13	West	85	0.60	4.9	5	29%	Fixed	25%	60.1	0.61	NA	6.49	57/120	35/120
46	Pregabalin CTD: Study A0081071	[88]	pDPN	Pregabalin	13	West	50	0.43	9.2	3	33%	Fixed	23%	59.9	0.57	NA	6.4	78/149	52/149
47	NCT00283842	[89]	pDPN	Desvenlafaxine	13	West	51	0.34	8.0	5	20%	Fixed	17%	59	0.72	NA	NA	NA	23/89
48	Smith 2014	[90]	pDPN	Carisbamate	15	West	67	0.36	5.8	4	25%	Fixed	22%	58	0.60	NA	6.45	45/95	26/95
49	NCT00505284	[91]	pDPN	Perampanel	15	West	NA	NA	NA	5	20%	Fixed	14%		0.48	NA	NA	41/73	28/73
50	Dogra 2005	[92]	pDPN	Oxcarbazepine	16	West	22	0.63	6.6	2	50%	Fixed	20%	60.5	0.62	2.7	7.43	22/76	14/76
51	Shaibani 2009	[93]	pDPN	Lacosamide	18	West	84	0.62	5.6	4	14%	Fixed	32%	59.5	0.59	3.1	6.2	29/64	17/64

	Trial	Reference	Pain condition	Active treatment	Treatment period (weeks)	Region	Number of sites	Patient Enrollment Rate	Number of patients per site	Number of arms	Randomization ratio	Dosing regimen	Drop out Rate	Age	Proportion of male patients	Duration of NeP	BL Pain Intensity	30% RR (n/N)	50% RR (n/N)
52	Wymer 2009	[94]	pDPN	Lacosamide	18	West	53	0.70	7.0	4	25%	Fixed	28%	58.3	0.46	3.3	6.6	41/90	NA
53	Ziegler 2010	[95]	pDPN	Lacosamide	18	West	52	0.76	6.9	3	20%	Fixed	20%	58.3	0.45	3.0	6.6	26/74	17/74
54	Vinik 2007-1	[96]	pDPN	Lamotrigine	19	West	NA	NA	NA	4	25%	Fixed	31%	59.8	0.66	2.6	6.3	32/85	23/85
55	Vinik 2007-2	[96]	pDPN	Lamotrigine	19	West	NA	NA	NA	4	25%	Fixed	36%	61.6	0.56	3.1	6.1	25/84	19/84
56	Kalliomaki 2013	[97]	PT	AZD2423	4	West	36	0.21	3.7	3	33%	Fixed	9%	55.1	0.57	NA	5.98	17/44	9/44
57	Ostenfeld 2013	[98]	PT	Losmapimod	4	West	20	0.92	8.4	2	50%	Fixed	10%	52	0.40	NA	6.5	21/70	7/70
58	van Seventer 2010	[99]	PT	Pregabalin	8	West	44	0.22	5.8	2	50%	Flexible	23%	51	0.59	4.4	6.3	32/125	18/125
59	Simpson 2010	[100]	HIV	Pregabalin	14	West	40	0.34	7.6	2	50%	Flexible	19%	46.8	0.79	6	6.7	81/147	62/147
60	NCT00109772	[101]	CRPS	Lenalidomide	12	West	27	0.19	6.8	2	50%	Fixed	16%	45.1	0.15	NA	NA	15/93	NA
61	Maier 2003	[102]	PL	Memantine	4	West	1	NA	36.0	2	50%	Fixed	17%	61	0.17	NA	5.2	NA	6/18
62	Moon 2010	[103]	mixed P-NeP	Pregabalin	8	Asia	10	1.07	24.1	2	33%	Flexible	21%	61.3	0.41	2.6	6.31	27/77	11/77
63	Guan 2011	[104]	mixed P-NeP	Pregabalin	8	Asia	8	2.22	38.6	2	33%	Flexible	17%	60	0.44	2.5	6.4	53/102	NA
64	Freynhagen 2005	[105]	mixed P-NeP	Pregabalin	12	West	60	0.39	5.6	3	20%	Flexible	46%	61.7	0.57	4.2	6.6	23/62	15/62
65	NCT01124617	[106]	mixed P-NeP	Tapentadol	12	Asia	32	0.39	2.8	2	33%	Flexible	19%	68.6	0.55	NA	6.9	13/31	12/31

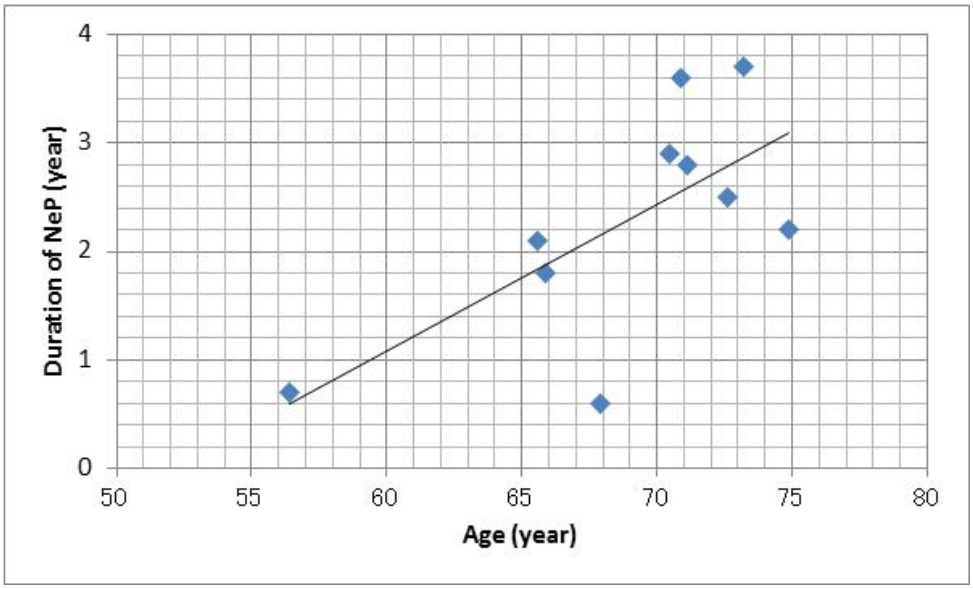
	Trial	Reference	Pain condition	Active treatment	Treatment period (weeks)	Region	Number of sites	Patient Enrollment Rate	Number of patients per site	Number of arms	Randomization ratio	Dosing regimen	Drop out Rate	Age	Proportion of male patients	Duration of NeP	BL Pain Intensity	30% RR (n/N)	50% RR (n/N)
66	Siddall 2006	[107, 108]	SCI	Pregabalin	12	West	8	0.78	17.1	2	50%	Flexible	45%	49.8	0.81	10.4	6.73	11/67	5/67
67	Cardenas 2013	[109]	SCI	Pregabalin	16	Both	60	0.08	3.7	2	50%	Flexible	15%	45.6	0.85	8.1	6.5	33/105	16/105
68	Kim 2011	[110]	PSP	Pregabalin	12	Asia	32	0.30	6.9	2	50%	Flexible	17%	57.1	0.64	2.5	6.3	35/108	22/108
69	Vollmer 3013	[111]	MS	Duloxetine	6	West	22	0.52	10.9	2	50%	Fixed	10%	52.7	0.23	7.6	5.3	33/121	19/121
70	Vranken 2008	[112]	mixed C-NeP	Pregabalin	4	West	1	13.33	40.0	2	50%	Flexible	20%	54.7	0.50	NA	7.4	2/20	1/20
71	Serpell 2002	[113]	mixed NeP	Gabapentin	8	West	35	1.39	8.8	2	50%	Flexible	27%	56.1	0.51	4.4	7.3	NA	21/152

RR: responder rate, CTD: common technical document, NA: not available, Fixed: fixed-dose design, Flexible: flexible-dose design, BL: baseline, NeP: neuropathic pain, PHN: postherpetic neuralgia, pDPN: painful diabetic peripheral neuropathy, PT: posttraumatic peripheral neuropathic pain, HIV: HIV sensory neuropathy, CRPS: complex regional pain syndrome, PL: phantom limb pain, P-NeP: peripheral neuropathic pain, SCI: spinal cord injury pain, PSP: poststroke pain, MS: multiple sclerosis pain, C-NeP: central neuropathic pain

Patient Enrollment Rate: total number of patients/total number of sites/month, Number of patients per site: total number of patients/total number of sites

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.

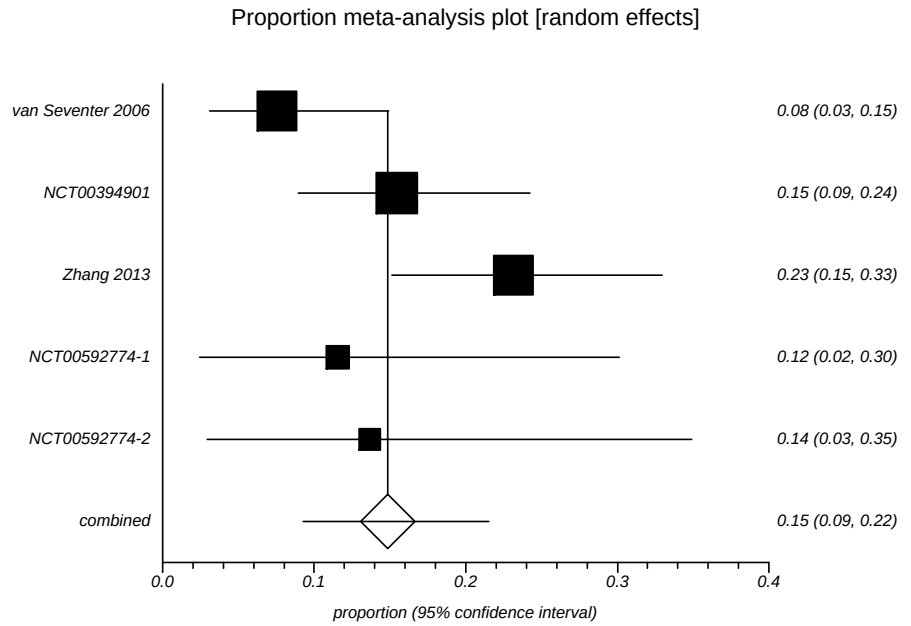
Figure 12. Relationship between duration of NeP and mean age in PHN trials



Spearman's rank correlation coefficient (95% CI) = 0.624 (-0.009, 0.900)

Figure 13. Forest plot of placebo responder rate in PHN trials with ≥12 week treatment duration (A: 50%RR, B: 30%RR)

(A)



(B)

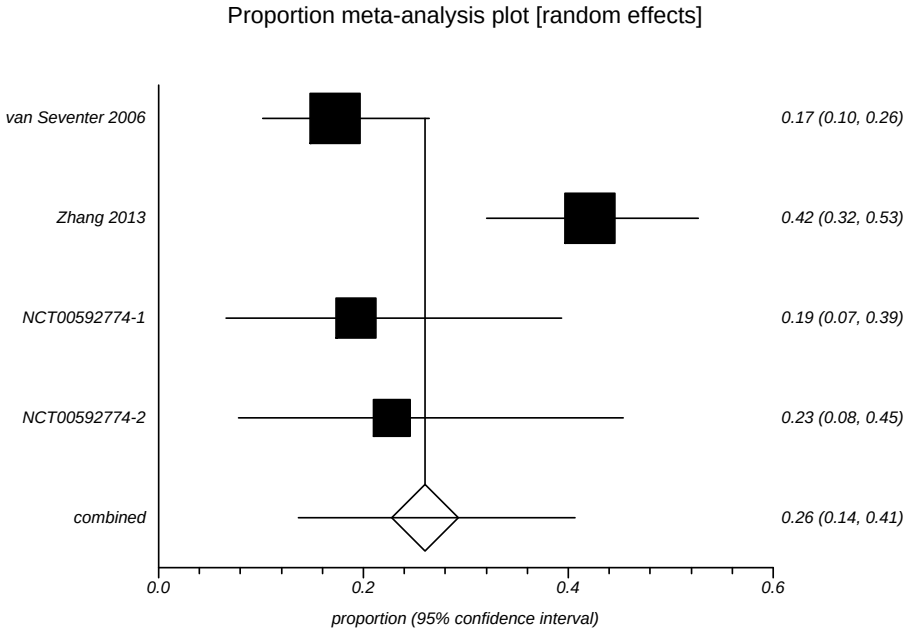
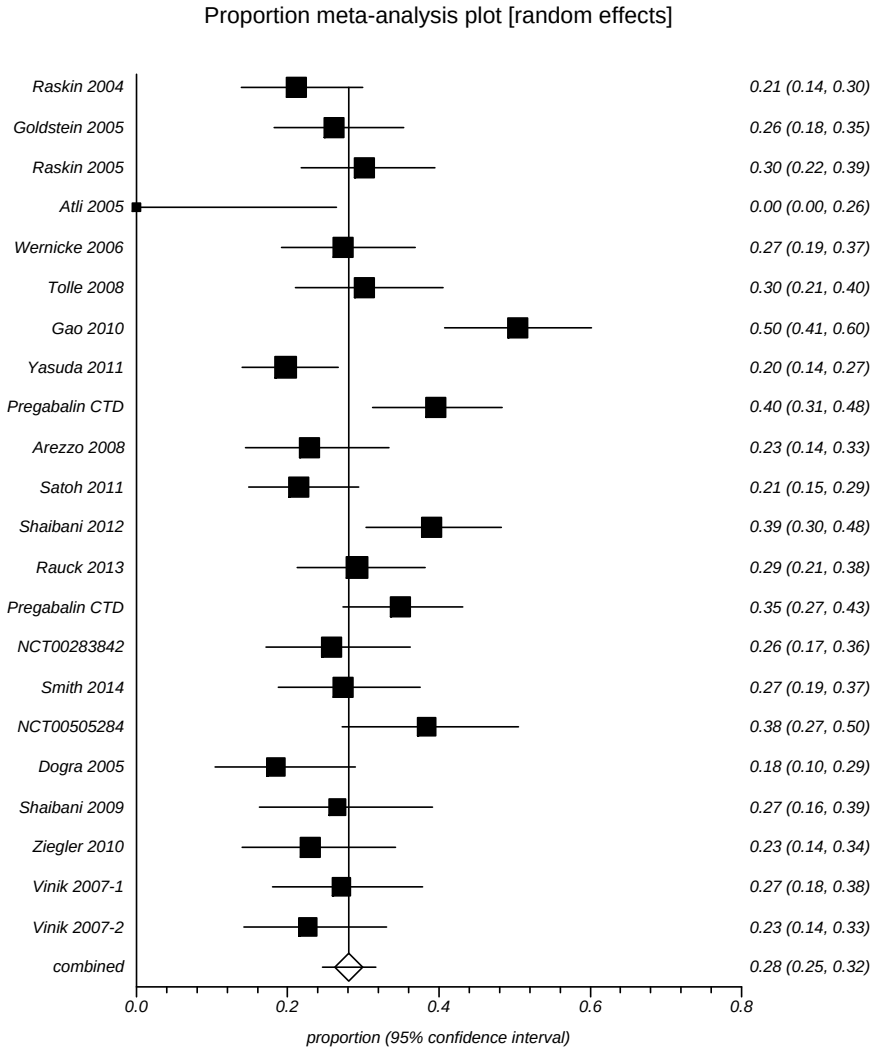


Figure 14. Forest plot of placebo responder rate in pDPN trials with ≥12 week treatment duration (A: 50%RR, B: 30%RR)
(A)



(B)

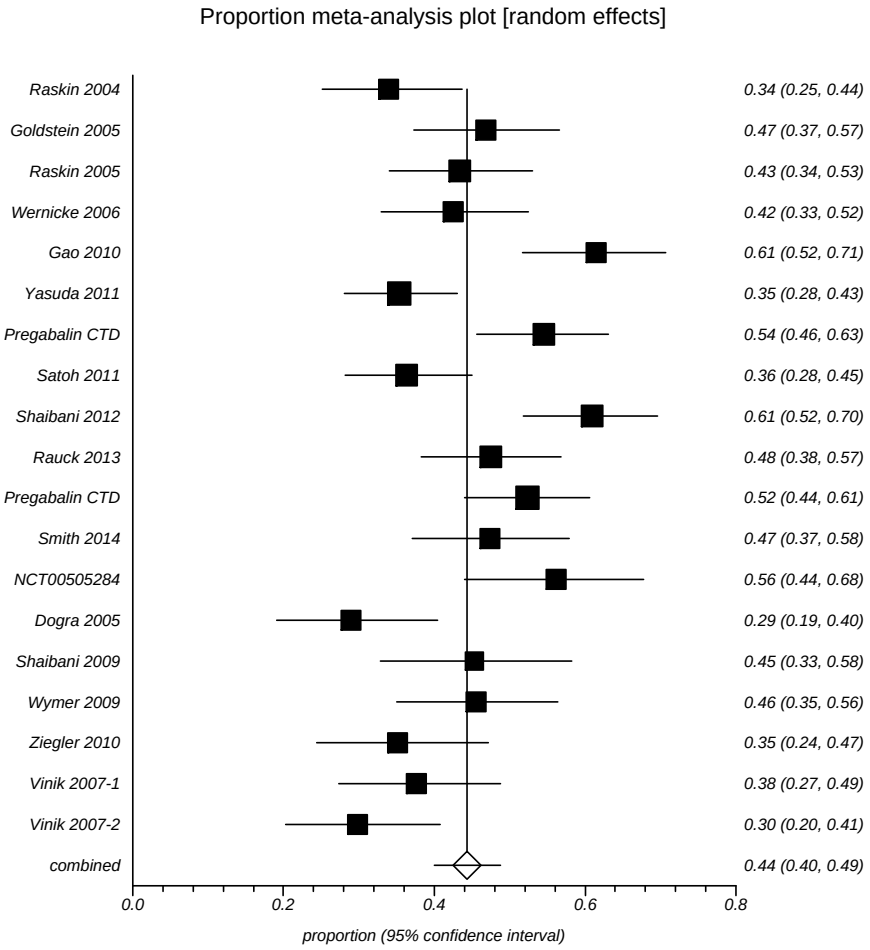
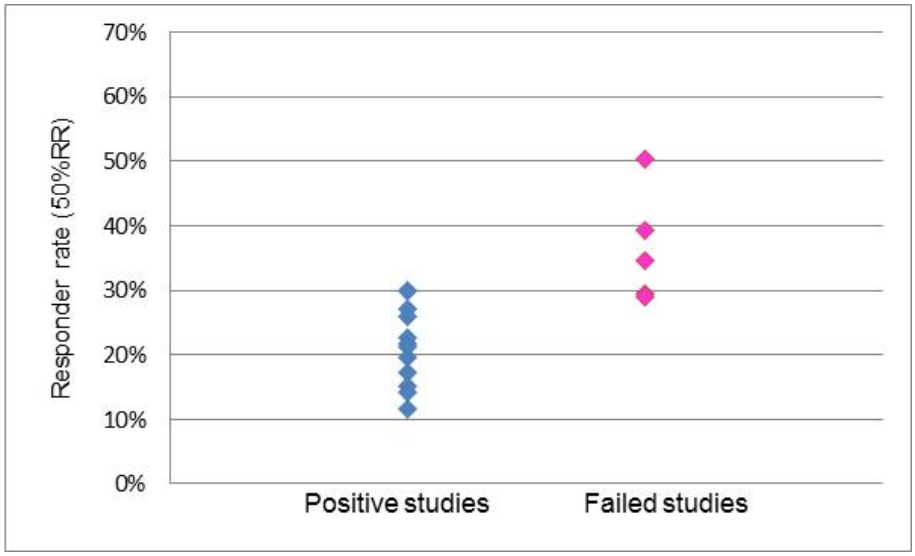
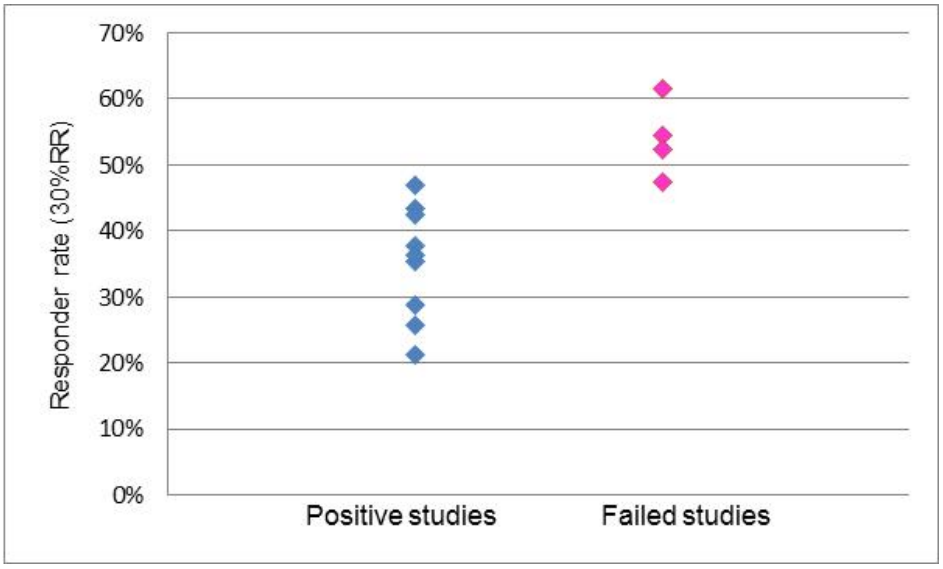

Proportion meta-analysis plot [random effects]
Raskin 2004
Goldstein 2005
Raskin 2005
Wernicke 2006
Gao 2010
Yasuda 2011
Pregabalin CTD
Satoh 2011
Shaibani 2012
Rauck 2013
Pregabalin CTD
Smith 2014
NCT00505284
Dogra 2005
Shaibani 2009
Wymer 2009
Ziegler 2010
Vinik 2007-1
Vinik 2007-2
combined
0.34 (0.25, 0.44)
0.47 (0.37, 0.57)
0.43 (0.34, 0.53)
0.42 (0.33, 0.52)
0.61 (0.52, 0.71)
0.35 (0.28, 0.43)
0.54 (0.46, 0.63)
0.36 (0.28, 0.45)
0.61 (0.52, 0.70)
0.48 (0.38, 0.57)
0.52 (0.44, 0.61)
0.47 (0.37, 0.58)
0.56 (0.44, 0.68)
0.29 (0.19, 0.40)
0.45 (0.33, 0.58)
0.46 (0.35, 0.56)
0.35 (0.24, 0.47)
0.38 (0.27, 0.49)
0.30 (0.20, 0.41)
0.44 (0.40, 0.49)
0.0
0.2
0.4
0.6
0.8
proportion (95% confidence interval)

Figure 15. Placebo responder rate in pDPN for approved drugs (A: 50%RR, B: 30%RR)

(A)



(B)



Positive studies: Statistical significant superiority was observed in the primary endpoint.
Failed studies: Statistical significant superiority was not observed in the primary endpoint.

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