Understanding the Placebo Response

In Neuropathic Pain Drug Treatment Trials

by

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CERTIFICATE OF APPROVAL

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ABSTRACT

Background: Early trials of tricyclic antidepressants showed efficacy against neuropathic pain compared with placebo. Later trials of anticonvulsants demonstrated less efficacy than antidepressants, but a greater placebo effect. Head-to-head trials comparing pharmacotherapies for neuropathic pain are limited. Indirect comparisons from placebo-controlled trials could provide information about comparative effectiveness. However, differences in placebo response rates could affect the reliability of indirect comparisons.

Objectives: To improve the interpretation of trial evidence through better understanding of the placebo response in neuropathic pain trials by determining study-specific predictors of the placebo response and study-specific predictors of pain reduction attributable to treatment after controlling for the placebo response.

Methods: Meta-regression techniques were used to identify study-specific predictors of the placebo response as well as predictors of pain relief while controlling for the placebo response in pharmacotherapy trials. Data from an existing systematic review on treatments for neuropathic pain were used to identify qualifying randomized, placebo-controlled trials, with updated searches to identify published and unpublished studies current through March 2014. The primary outcome variable was whether ≥50 percent reduction in pain from baseline to study endpoint had occurred. Predictor variables included study design characteristics (e.g., parallel trial, size of trial, length of trial), drug characteristics (e.g., drug category, flexibility of dosing), population characteristics (e.g., diagnosis, baseline pain level, gender distribution), and other time and space variables (e.g., when the study was published or completed, geographic location of study).

Sensitivity analyses involving only parallel group studies, studies of pregabalin, and studies of only painful diabetic peripheral neuropathy were conducted. In addition, the predictors for proportion of patients with ≥30 percent pain reduction were compared with the predictors for ≥50 percent pain reduction.

Results: Thirty-nine placebo-controlled trials, analyzed as 40 studies, reported the primary outcome (one study randomized patients to two included medications in addition to placebo and was analyzed as two studies). Dosing flexibility, baseline pain levels, gender distribution, and whether or not patients had painful diabetic neuropathy were included in the final model predicting the proportion of patients reporting at least a 50 percent pain reduction in the placebo group. After controlling for the placebo response, length of treatment on the study drug was inversely correlated with treatment effect. In sensitivity analyses, length of treatment accounted for 100 percent of the between-study variance in published and unpublished studies, parallel group trials, studies enrolling only patients with painful diabetic neuropathy, trials of pregabalin, and studies in which the outcome variable was ≥30 percent pain reduction.

Conclusion: The placebo response varies in trials of neuropathic pain. Standardization of trial design by incorporating flexibility of drug dosing, duration of treatment at least 12 weeks, including a single type of neuropathic pain, and stratifying results by gender may facilitate interpretation and generalizability of trial results. Systematic evidence reviews and meta-analyses should also incorporate consideration of flexibility of dosing, length of treatment, type of neuropathic pain, gender distribution within trials, and baseline levels of pain when pooling studies or comparing drugs across trials with the placebo group as the common comparator.

INTRODUCTION

As part of a systematic review on comparative effectiveness of different drug treatments for neuropathic pain, public comments in response to posting of the review's key questions were solicited (1). One pharmaceutical company commented that reviewers should exercise caution in comparing drugs because the placebo response can vary dramatically between trials. Comparing one drug to another, based on the respective drug's magnitude of improvement over that seen in the corresponding placebo group, can be misleading. This study examines factors which may affect the level of response seen in the placebo groups of neuropathic pain trials and is in response to that comment. Additional analyses focus on the relative treatment effect in neuropathic pain trials, after controlling for the placebo response.

Definition, Epidemiology, and Treatment of Neuropathic Pain

The Neuropathic Pain Special Interest Group of the International Association for the Study of Pain defines neuropathic pain as "pain arising as direct consequence of a lesion or disease affecting the somatosensory system" (2). The pain is often described as burning, tingling, like pins and needles, or like an electric shock. It may be focal (carpal tunnel syndrome, phantom limb pain) or more widespread (diabetic neuropathy or chemotherapy-associated pain affecting the extremities). The pain may be caused by an injury (spinal cord injury-associated neuropathic pain) or by an illness (multiple sclerosis, herpes zoster). The pain may also be characterized as involving the central nervous system (post-stroke pain) or peripheral nervous system (diabetic neuropathy).

The incidence of neuropathic pain in the United States is difficult to determine, given the challenges of data collection from the multitude of competing health care

systems, as well as the lack of data on untreated people (e.g., the large uninsured population). However, a study in the Netherlands of 362,693 individuals contributing over one million person-years (P-Y) of follow-up found the incidence of neuropathic pain to be 8.2 cases per 1,000 P-Y. The incidence of neuropathic pain was highest in mononeuropathy (4.3/1,000 P-Y) and carpal tunnel syndrome (2.3/1,000 P-Y), followed by diabetic neuropathy (0.72/1,000 P-Y) and post-herpetic neuralgia (0.42/1,000 P-Y) (3). A cross-sectional survey of 36 hospital neurology units and 24 primary care centers in Spain found neuropathic pain was the eighth most frequent diagnosis, affecting 2.9 percent of patients in primary care centers and 6.1 percent of patients in hospital neurology units (4). In a French population responding to a postal survey, the prevalence of chronic pain with neuropathic characteristics was reported in 6.9 percent of 23,712 respondents with assessable surveys (5). In the Emergency Department (ED) of a university hospital also in France, 21.4 percent of adults with pain being seen in the ED had neuropathic pain. A review article (6) gave estimates for the prevalence of neuropathic pain of various etiologies (Table 1).

Table 1. Prevalence and range of neuropathic pain

Neuropathic Pain Condition	Prevalence (%)	Population
Painful diabetic neuropathy	15 (11-26)	Diabetics
Postherpetic neuralgia	7-27	Herpes Zoster
HIV-associated	35 (30-63)	HIV+
Phantom limb pain	53-85	Amputees
Carpal tunnel syndrome	2-16	General population
Central post-stroke pain	8-11	Stroke patients
Multiple Sclerosis-associated pain	23 (23-58)	Multiple Sclerosis patients
Spinal cord injury-associated pain	40 (10-80)	Spinal cord injury patients

Based on conservative estimates of those suffering from diabetes or carpal tunnel syndrome, there are over 9 million people living with neuropathic pain in the United States today. Unfortunately, for these individuals, no medication is uniformly effective at providing pain relief. Instead, there are several types of medications that may provide some, but often not total, cessation of pain.

The treatment for neuropathic pain is primarily pharmacological, although interventional therapies such as spinal cord stimulation, or in earlier times frontal lobotomy (7), have been used in extreme cases. Patients today have a variety of medication options to treat their neuropathic pain, including: antidepressants (e.g., tricyclic antidepressants, selective serotonin norepinephrine reuptake inhibitors), sodium channel anti-convulsants (e.g., lacosamide, carbamazepine), calcium channel anti-convulsants (gabapentin, pregabalin), opioid agonists (e.g., morphine, oxycodone, tramadol), nonsteroidal anti-inflammatories (e.g., ibuprofen, aspirin, naproxen sodium) and topical preparations (e.g., lidocaine patch). These medications are often used in combination to reduce pain.

Definition of Placebo and Characteristics Affecting Placebo Response

According to Taber's Medical Dictionary, a placebo is "an inactive substance or treatment given instead of one that has a proven effect" (8). However, physicians may also prescribe active medications even though they are relying on the placebo response for patient improvement. For example, a survey of internists and rheumatologists found that 41 percent had prescribed over-the-counter pain medications, 38 percent had recommended vitamins, 13 percent had prescribed sedatives and 13 percent had prescribed antibiotics primarily for their placebo response (9). Additionally, a placebo

need not be in pill form (or an injectable or topical formulation) but may also be a sham procedure, such as sham surgery or sham acupuncture (10).

Irving Kirsch from the Program in Placebo Studies at Harvard Medical School defines the placebo response as the change in outcome produced by the placebo (11). This is different, he explains, from the placebo effect, which is the difference between the placebo response and the changes observed even without administration of a placebo. He advises considering the one-month remission rates for the common cold in which the placebo response will approximate 100 percent but the placebo effect will be zero. (Similarly, the treatment response is the change observed following treatment versus the treatment effect which is the change in outcome produced by that treatment.)

Studies have shown that the placebo response varies according to certain placebo characteristics. In a study at the University of Cincinnati Medical School, students were told they would receive either a stimulant or a sedative as part of a study of two new drugs, when, in fact, all students were given a placebo (12). Students received either one blue pill, two blue pills, one pink pill, or two pink pills, and then they rated their sleepiness after a lecture. Those who reported the most sedation were those who took the blue pills and those who took two pills.

In a 1987 study of 200 patients who had symptoms but no signs of disease, 50 were given a diagnosis and a pill, 50 were given a diagnosis and no pill, 50 were told "I cannot be certain what is the matter with you" and given a pill, and the remaining 50 told "I cannot be certain what is the matter with you" but were not given a pill (13). Surprisingly, the ones who got better were the patients who were given a definitive diagnosis whether or not they were given a pill ($p<0.001$). Being given a pill, in this case,

made no difference. The author concluded that, “The doctor himself is a powerful therapeutic agent; he is the placebo and his influence is felt to a greater or lesser extent at every consultation.”

Not only can a placebo be a pill or a therapeutic encounter, the placebo can be a sham procedure. A recent systematic review compared the placebo response to oral pharmacological placebos, sham acupuncture, and sham surgery to prevent migraines (10). Reviewers found that the percentage of migraine patients responding to sham acupuncture (38%, 95% CI 30% to 47%) and sham surgery (58%, 95% CI 37% to 77%) were greater than the proportion of patients responding to oral placebos (22%, 95% CI 17% to 28%), with $p<0.01$ for each comparison.

Placebo Response in Neuropathic Pain Trials

Proving that a drug works for neuropathic pain can be challenging. The drug in question must not have such unwelcome side effects that there are high levels of patient dropouts. The drug must also outperform the placebo in randomized controlled trials. In large trials, there will always be patients in the placebo group who improve even though they were not receiving an active drug. The greater the proportion of individuals in the control group who experience pain relief with a placebo, the higher the proportion of individuals in the intervention group who experience pain relief must be, in order to demonstrate the drug superior to placebo. This is the model for most randomized controlled trials conducted today that are designed to demonstrate drug efficacy.

In trials of neuropathic pain, the placebo response has been quite variable. The fraction of those randomized to placebo who experience pain relief may be as low as 3 percent (14) or as high as 43 percent or higher (15). There is not yet a complete

understanding why the placebo response varies, although a few studies in patients with depression or neuropathic pain have suggested possible reasons for this variability (16-21). These reasons include: when the trial was conducted (published), trial duration, sample size, study design, baseline pain levels of the individuals in the study, pain syndrome (e.g., postherpetic neuralgia), and study recruitment rate. Additional studies investigating the placebo response in participants with other conditions (e.g., autism, osteoarthritis) have suggested severity of illness, type of outcome (self-report), gender, patient age, and study location as factors affecting variability of the placebo response (22-27).

This study was conducted to better understand the variables influencing the placebo response in trials of neuropathic pain. Additionally, this study seeks to identify any factors that may affect the relative treatment response after controlling for the placebo response and that therefore should also be considered when comparing drug trials. These factors have implications for trial design, for the interpretation of study evidence and for systematic reviews that synthesize the evidence by conducting indirect or network meta-analyses using the response in the placebo group as the common comparator.

METHODS

This analysis is derived from a systematic review comparing pharmacotherapy for neuropathic pain (1) conducted at the Evidence-based Practice Center, Oregon Health & Science University, and commissioned by the participating organizations (primarily state Medicaid agencies) of the Drug Effectiveness Review Project (DERP). Standard DERP methods for systematic reviews were employed (28). The original systematic review sought to determine the comparative effectiveness and harms of drugs for neuropathic pain and whether or not drug effectiveness or harms differ in certain subgroups of patients (e.g., based on age, race or ethnicity, socioeconomic status).

Inclusion Criteria

The populations, drugs, and research design for studies included in this analysis are outlined below.

Populations

Adults with neuropathic pain due to various conditions including:

- Painful diabetic neuropathy
- Postherpetic neuralgia
- Trigeminal neuralgia
- Central/post-stroke pain
- Phantom limb pain
- Spinal cord injury
- Complex regional pain syndrome (reflex sympathetic dystrophy)
- Peripheral nerve injury

Populations included in the original review but excluded from this analysis are those with cancer-related and HIV-related neuropathic pain, as the etiology of such pain could be due both to the illness and to the medication used to treat the condition.

Drugs

Drugs included in this analysis are:

- Amitriptyline
- Carbamazepine
- Desipramine
- Divalproex/valproic acid
- Doxepin
- Duloxetine
- Gabapentin
- Lacosamide
- Lamotrigine
- Levetiracetam
- Milnacipran
- Nortriptyline
- Oxcarbazepine
- Phenytoin
- Pregabalin
- Protriptyline
- Topiramate
- Venlafaxine

Only oral preparations of these medications are included in this analysis. Topical and injectable preparations of these or other medications are excluded.

Effectiveness Outcomes

The primary outcome variable is the proportion of study subjects with at least a 50 percent reduction in neuropathic pain from baseline to study endpoint. A secondary outcome is the proportion of study subjects with at least a 30 percent reduction in pain from baseline to end of study. Studies reporting only ≥30 percent pain reduction were eligible for inclusion.

Predictor Variables

Covariates eligible for inclusion in meta-regression models included such study-specific variables as: length of treatment with study drug or placebo, location of study, patient population, size of trial, study drug, drug dose, and flexibility of drug dosing. Other included covariates represent patient-specific characteristics averaged or aggregated within each trial (e.g., mean age of patients, percentage of male patients, and average baseline pain level among patients). These types of variables have been included in previous meta-regression analyses (29, 30) including a meta-regression examining the placebo response (22); in the absence of individual patient data these variables are included in this study for their potential to account for between-study heterogeneity.

Study Design

Only randomized, placebo-controlled trials are included. Head-to-head trials (trials comparing one drug with another without a placebo arm) are excluded. Observational studies (e.g., cohort, case-control studies) are also excluded.

Literature Search

To identify relevant citations, Ovid MEDLINE® (1966 to November Week 3 2010), the Cochrane Database of Systematic Reviews® (4th Quarter 2010), the Cochrane Central Register of Controlled Trials® (4th Quarter 2010), and the Database of Abstracts of Reviews of Effects (4th Quarter 2010) were searched, using terms for included drugs, indications, and study designs. Electronic database searches were supplemented by manual searches of reference lists of included studies and reviews. In addition, the US Food and Drug Administration Center for Drug Evaluation and Research, the Canadian Agency for Drugs and Technology in Health, and the National Institute for Health and Clinical Excellence web sites for medical or statistical reviews and technology assessments were searched. Finally, dossiers of published and unpublished studies submitted by pharmaceutical companies were also searched. The MEDLINE search was updated through March 2014 and ClinicalTrials.gov was searched for unpublished studies at the time of the updated search. Except where noted, the inclusion/exclusion criteria were maintained through the updated search.

Study Selection

All citations were reviewed for inclusion using the criteria described earlier. Two of the reviewers (SS, MM, SC, ST, AG) independently assessed titles and abstracts of citations identified from literature searches. Full-text articles of potentially relevant

citations were retrieved, as well as study information from unpublished sources. These were independently assessed for inclusion by two of the reviewers. Disagreements were resolved by consensus. Results published *only* in abstract form (e.g., as a conference proceeding) were not included because they typically provide insufficient detail to perform adequate quality assessment. In addition, results of studies may change substantially between initial presentation at a conference and final journal publication.

Data Abstraction

Data were abstracted by the author and 20 percent of included studies were randomly selected for verification by a second reviewer (AG). Data abstracted included:

- Year of study publication or completion if unpublished
- Trial design (parallel or cross-over)
- Trial duration
- Trial size
- Included drug(s)
- Etiology of neuropathic pain
- Average number of participants enrolled per month
- Fixed versus flexible dosing of study drug (and placebo)
- Trial quality rating
- Location (countries) where the trial was conducted
- Number of study arms
- Whether other non-study drug pain medications were allowed
- Duration of illness
- Duration of pain
- Drug dose
- Baseline pain level
- Numbers achieving 50 percent and 30 percent pain reduction
- Study withdrawal rate

During data abstraction it was observed that the percentage of males in the treatment group occasionally differed by more than 10 percentage points from the percentage of males in the placebo group. Therefore, abstraction included this additional information. As study withdrawal rate is an important element in assessing study validity, overall study withdrawal rates along with treatment and placebo group withdrawal rates were abstracted as well. Preliminary analysis of 25 trials that included patients with

painful diabetic neuropathy (31) indicated little difference between studies for certain variables. Therefore, these variables (e.g., verification of blinding, study funding or sponsorship, use of a run-in period) were not abstracted.

Validity Assessment

Internal validity of each trial was based on use of adequate methods for randomization, allocation concealment, and blinding; similarity of compared groups at baseline; maintenance of comparable groups; adequate reporting of dropouts, attrition, crossover, adherence, and contamination; absence of high or differential loss to follow-up; and use of intent-to-treat analysis. Trials that had a "fatal flaw" were rated "poor quality"; trials that met all criteria were rated "good quality"; the remainder were rated "fair quality." As the fair quality category is broad, studies with this rating vary in their strengths and weaknesses: the results of some fair-quality studies are *likely* to be valid, while others are only *probably* valid. A poor quality trial is not valid—the results are at least as likely to reflect flaws in the study design as the true difference between the compared drugs. A "fatal flaw" was defined as a very serious methodological shortcoming or a combination of methodological shortcomings that is highly likely to lead to biased or uninterpretable results. External validity of trials was assessed based on whether the publication adequately described the study population, how similar patients were to the target population in whom the intervention was applied, and whether the treatment received by the control group was reasonably representative of standard practice. Overall quality ratings for the individual study were based on internal and external validity ratings for that trial. Trials included in the systematic review were

quality rated by two of the independent reviewers (SS, MM, SC, ST, AG) and conflicts resolved by consensus or by utilization of a third reviewer.

Data Analysis

Meta-regression was used for model building, starting with a model to predict the placebo response and then a model to predict the relative treatment effect of study drug on pain reduction while controlling for proportion of participants within each study's placebo group experiencing ≥50 percent or ≥30 percent pain reduction. Univariate analyses were first conducted to determine which predictor variables were individually associated with the placebo response at an $\alpha \leq 0.20$. Predictor variables included study-specific, as well as patient-specific covariates. However, a concern with the inclusion of patient-specific characteristics in meta-regression is that the relationship between patient-specific characteristics across trials may be different from patient characteristics within any given trial (32). For this reason, meta-regression including more conventional study-specific variables was conducted, as well as meta-regression including patient-specific covariates, such as average baseline pain level, when meta-regression with only study-specific variables explained little of the between-study heterogeneity. Redundancy between variables was considered (e.g., number randomized and number analyzed) and only the variable with the lowest p-value was eligible for inclusion in model building. Eligible variables were then entered into a multivariable meta-regression model predicting the placebo response and manual backward elimination was employed. When backward elimination yielded a model that performed poorly (based on the adjusted R-squared statistic and the model p-value), forward selection without an α-cutoff, followed by backward elimination without an α-cutoff was used to suggest feasible alternative

models. Random-effects meta-regression was employed to allow for assessment of residual heterogeneity of between-study variance not explained by the covariates. The I-squared residual statistic, the adjusted R-squared statistic, and the model p-value, along with an effort to minimize loss of data by maximizing the number of observations utilized, guided final model selection. A similar model selection process was used to predict relative treatment response while controlling for placebo response.

One trial randomized participants to amitriptyline, pregabalin, or placebo. Data from this study were entered as two separate studies with the size of the placebo group halved for each study entry while keeping the proportion of participants experiencing pain reduction the same as in the original placebo group. Continuous explanatory variables were centered and scaled as appropriate to improve interpretation of the estimated regression coefficients over a sensible range. Post-estimation probability plots were used to check for outliers and whether the assumption of normality of the random effects was adequate. A funnel plot was used to assess the possibility of publication bias with the Egger test for small study effects. Meta-analysis trim and fill techniques (33) were used and a filled meta-analysis conducted to estimate treatment effects in the absence of potential missing studies. All data analysis was conducted with Stata 10 (34).

RESULTS

Overview

Thirty-nine randomized, placebo-controlled trials (data handled as 40 studies, as described above) reported the proportion of participants experiencing at least 50 percent pain reduction from baseline to study endpoint. (See **Appendices A and B** for characteristics of included studies and stratified forest plots.) Twenty-five studies (including two studies that did not report ≥50 percent pain reduction) specified the proportion of patients who experienced a minimum of 30 percent pain reduction from baseline to study endpoint.

The average number of participants randomized was 271 (range 27 to 469) and studies enrolled participants at an average rate of 24 per month. Thirty-eight trials were parallel group and three were cross-over studies. Thirty-four studies were published and seven were unpublished. All but one trial was rated fair quality (one was rated poor quality). Methodological limitations of studies included unclear randomization techniques, unclear allocation concealment and lack of blinding of study personnel. The single most common type of neuropathic pain was painful diabetic neuropathy (24 studies) followed by postherpetic neuralgia (7 studies). Two additional studies enrolled patients with either painful diabetic neuropathy or postherpetic neuralgia. The study drug most frequently administered was pregabalin (21 studies) followed by duloxetine (5 studies). Pregabalin trials were published (or completed if unpublished) between 2001 and 2012 which was similar to gabapentin trials which were published or completed between 2001 and 2009. Duloxetine trials were published or completed later (between 2005 and 2011). Patients could adjust the dose of study drug or placebo as tolerated in 15

studies. The average length of time participants took the study drug was 10 weeks which included, on average, a 2-week upward drug titration period. Thirteen studies were conducted only in the United States and 27 were conducted in a western country or countries (including the United States). On average, study gender distribution was 54 percent male and 46 percent female, although one study of post-mastectomy patients enrolled no men. The average age of participants was 60 years and in the 24 trials reporting pain duration, the average duration of neuropathic pain was 3.4 years.

Predictors of at Least 50 Percent Reduction in Pain in the Placebo Group

Variables assessed for inclusion into the final model are given in Table 2 along with their univariate p-value and number of included studies in the prediction of ≥50 percent pain reduction in the control group. Bolded variables are those initially considered for multivariable model building.

Table 2. Predictor variables for 50 percent pain reduction in placebo group

Variable	# of studies	p-value
Enrolls only patients with PDN	40	**<0.001**
Diagnosis	40	**0.002**
Enrolls only patients with PHN	40	**0.009**
Baseline pain level in placebo group	34	**0.015**
Drug Category: 5 categories	40	**0.020**
Drug Category: 3 categories	40	0.031
Length of treatment	40	**0.033**
Enrolls only patients without PDN or PHN	40	**0.046**
Study design	40	**0.047**
Number of patients randomized	40	**0.050**
Number of patients analyzed	40	0.087
Length of treatment (maintenance period		

Table 2. Predictor variables for 50 percent pain reduction in placebo group (continued)

Variable	# of studies	p-value
only)	40	0.102
Drug	40	0.108
Average enrollment per month	27	**0.153**
Study conducted in the U.S.	36	0.247
Percent males in study	40	0.313
Duration of neuropathic pain	22	0.330
Percent males in placebo group	38	0.335
Study conducted in western country(ies)	35	0.389
Mean age of study participants	40	0.398
Average proportion achieving maximum study dose	34	0.420
Total study withdrawal rate	39	0.451
Withdrawal rate in treatment group	39	0.460
Number of months study enrolled patients	27	0.474
Year of publication or study completion (unpublished)	40	0.540
Enrolls only patients with PDN or with PHN	40	0.584
Withdrawal rate in placebo group	39	0.665
Study has two treatment arms	40	0.711
Difference in % males in treatment and placebo groups	38	0.752
Enrolls patients with a variety of pain etiologies	40	0.782
Drug dosing flexibility	40	0.801

Abbreviations: PHN=postherpetic neuralgia; Drug Category-5: pregabalin, gabapentin, tricyclic antidepressants, antiepileptic drugs; selective norepinephrine reuptake inhibitors; Drug Category-3: Antiepileptic drugs (including pregabalin and gabapentin), tricyclic antidepressants, and selective norepinephrine reuptake inhibitors; Bolded p-values represent variables entered into initial model

Because only 22 studies (55%) reporting 50 percent pain reduction included information on pain duration, pain duration was considered ineligible for further inclusion in order to maximize data available for model building. The model containing all bolded variables explained 35 percent of the between-study variance with the included covariates and was not significant. The model p-value was 0.226 indicating that a test of the null hypothesis that the coefficients of the covariates are all zero could not be rejected (there is no evidence of association of any covariate with the outcome). The amount of the residual variation due to between-study heterogeneity (as opposed to within-study sampling variability) was 68 percent. Using backward elimination, at an $\alpha \leq 0.20$ for inclusion into the model, resulted in a model containing the predictor variables study design, having or not having postherpetic neuralgia, and baseline pain level in the placebo group. However, this model only accounted for 47 percent or the between-study heterogeneity. To improve upon the model, forward selection without restricting the p-value (variables could be entered into the model even if their univariate p-value was >0.20) was employed and resulted in a model that explained 70 percent of the between-study variance with the covariates. To validate the model, backward elimination was again used but without restricting the univariate p-value. This resulted in a somewhat better model that explained 74 percent of the between-study variance (model p-value <0.001; I-squared residual=48%; n=34). Predictor variables included in the final model were flexibility of dosing, having or not having painful diabetic neuropathy, the proportion of males enrolled in the study, and the level of baseline pain in the placebo group. Even though dosing flexibility and proportion of males enrolled were not variables initially entered into backward elimination, their addition improved the model based on

the adjusted-R squared statistic. On average, the placebo response was greater in studies with fixed medication dosing, studies enrolling patients with painful diabetic neuropathy (as opposed to other types of neuropathic pain), studies with smaller percentages of males, and studies with lower average baseline levels of pain in the placebo group (Table 3). Baseline pain level in the placebo group was centered on the value 6.3 (on a 0-10 numerical rating scale). The proportion of males was centered on 50 percent.

Table 3. Coefficients in final model predicting 50 percent pain reduction in placebo group

Variable	Est. Effect (95% CI)	p-value
Flexible dosing:		
No?		
Yes?	0.093(0.040 to 0.145)	0.001
Diabetic Nerve Pain:		
No?		
Yes?	0.129(0.078 to 0.180)	<0.001
Males:		
For every 1 percentage point increase in males	-0.003(-0.005 to -0.001)	0.001
Baseline pain:		
For every 1 point increase in pain score	-0.078(-0.142 to -0.013)	0.020
Constant:	0.133(0.089 to 0.179)	<0.001

Keeping all other factors the same, flexible dosing was associated with a 9.2 (95% CI 4 to 14) percentage point increase in the proportion of participants that experience ≥50 percent reduction in pain in the placebo group. Having diabetic nerve pain increased the response (of those with ≥50 percent reduction in pain) by 12.9 (95% CI 7.8 to 18)

percentage points. Similarly each 1 unit increase in baseline pain was associated with a 7.7 (95% CI 1.3 to 14) percentage point drop in response.

To determine the ability of using only conventional, study-specific covariates to predict the proportion of patients in the placebo group with at least 50 percent reduction in pain in meta-regression, backward elimination and forward selection model building were conducted without inclusion of patient-specific variables. Length of treatment was the sole remaining predictor variable regardless of model building strategy but it accounted for only 13 percent of the between-study variance (model p-value=0.03). For every 1 week increase in treatment length, the placebo response increased by 0.7 (95% CI 0.06 to 1.4) percentage points.

In this instance, the inclusion of patient-specific characteristics as predictor variables greatly improved our understanding of factors influencing the heterogeneity between studies. However, in order to avoid the ecological fallacy (32, 35), it is imperative to remember that the unit of analysis is the study, not the individual. The previous model (with baseline pain level and proportion of males) includes variables that represent the average for each study. We cannot make statements that suggest that being female or having a lower baseline level of pain is associated with increased placebo response. We can only say that across included neuropathic pain studies, those with greater proportions of females or with lower levels of pain tend to have higher placebo responses. In order to draw conclusions regarding the association between such characteristics as a patient's baseline pain level or gender and the placebo response, analysis using individual patient data is needed (36).

Predictors of Relative Risk of at Least 50 Percent Pain Reduction after Controlling for Placebo Response

The same variables that were assessed for ≥50 percent pain reduction in the placebo group were eligible for inclusion in model building of treatment response while controlling for the placebo effect. Their associated univariate p-values are shown in Table 4. In univariate analysis, the length of time patients were treated with the study drug (or placebo) accounted for 100 percent of the remaining between-study variance after adjusting for the placebo response with 100 percent of the within-study sampling variability also accounted for (I-squared residual=0%) and model p<0.001. Since this model could not be improved upon, no further model building was attempted.

Table 4. Predictor variables for 50 percent pain reduction controlling for placebo response

Variable	# of studies	p-value
Length of treatment	40	0.001
Difference in % males in treatment & placebo groups	38	0.002
Drug Category: 5 categories	40	0.019
Drug Category: 3 categories	40	0.028
Enrolls only patients with PHN	40	0.037
Mean age of study participants	40	0.049
Year of publication or study completion (unpublished)	40	0.067
Number of patients randomized	40	0.077
Enrolls only patients without PDN or PHN	40	0.099
Diagnosis	40	0.113
Drug	40	0.122
Length of treatment (maintenance period only)	40	0.193
Study design	40	0.224

Table 4. Predictor variables for 50 percent pain reduction controlling for placebo response (continued)

Variable	# of studies	p-value
Enrolls patients with a variety of pain etiologies	40	0.321
Percent males in treatment group	39	0.353
Enrolls only patients with PDN or with PHN	40	0.383
Average proportion achieving maximum study dose	34	0.461
Baseline pain level in placebo group	34	0.541
Study conducted in the U.S.	36	0.597
Percent males in placebo group	38	0.678
Number of months study enrolled patients	27	0.701
Number of patients analyzed	40	0.710
Enrolls only patients with PDN	40	0.724
Withdrawal rate in treatment group	39	0.782
Withdrawal rate in placebo group	39	0.782
Average enrollment per month	27	0.786
Total study withdrawal rate	39	0.787
Percent males in study	40	0.802
Drug dosing flexibility	40	0.883
Study has two treatment arms	40	0.910
Study conducted in western country(ies)	35	0.931

Abbreviations: PDN=painful diabetic neuropathy; PHN=postherpetic neuralgia; Drug Category-5: pregabalin, tricyclic antidepressants, antiepileptic drugs; selective norepinephrine reuptake inhibitors; Drug Category-3: Antiepileptic drugs (including pregabalin and gabapentin), tricyclic antidepressants, and selective norepinephrine reuptake inhibitors

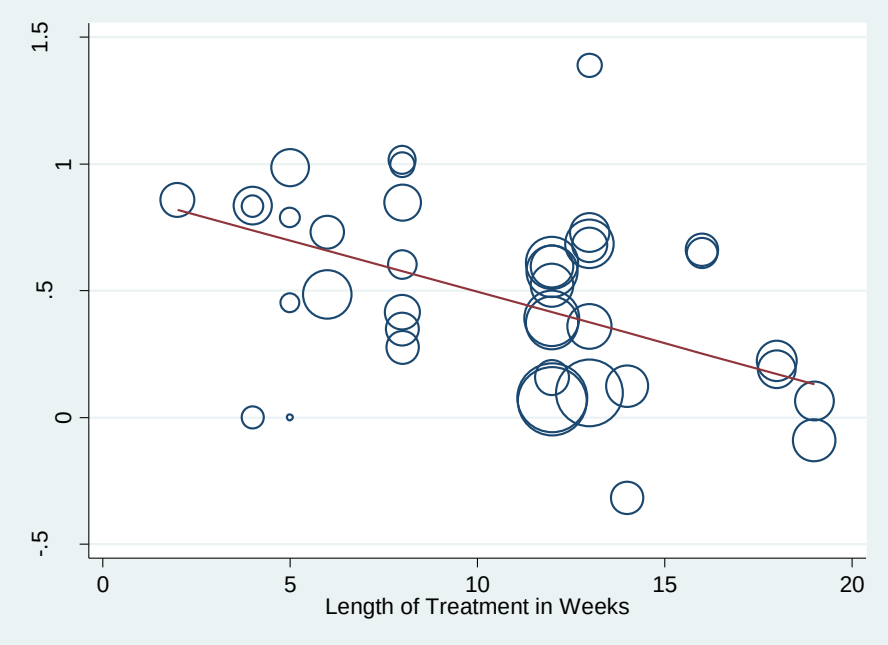
With the model including treatment length and controlling for the placebo response, a 10 percentage point increase in placebo response is associated with an 18 percent reduction in relative risk (Table 5). Additionally, a one week increase in treatment length is associated with a 3 percent reduction in relative risk.

Table 5. Model predicting 50 percent pain reduction after controlling for placebo response

Variable	Est. Effect (95% CI)	p-value
Placebo Rate:		
10 percentage point increase	0.822 (0.765 to 0.884)	<0.001
Treatment Length:		
For every 1 week increase in length	0.968 (0.950 to 0.986)	0.001

The relationship between length of treatment in weeks and relative treatment effect is displayed in Figure 1 (size of circles corresponds to the precision of the estimate or inverse of its within-study variance, larger circles imply greater variance). Figures 2 and 3 display the relationship between length of treatment and placebo and treatment response, respectively.

Figure 1. Log RR of treatment response by length of treatment



This decrease in relative effect is due to an increase in the placebo effect (Figure 2) as there is little change in treatment effect as length of treatment increases (Figure 3).

Figure 2. 50 percent pain reduction by length of treatment in placebo group

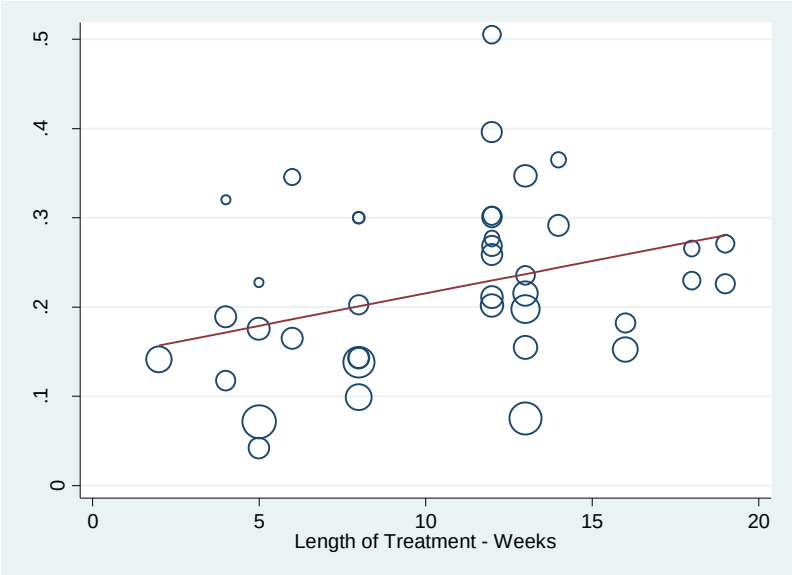
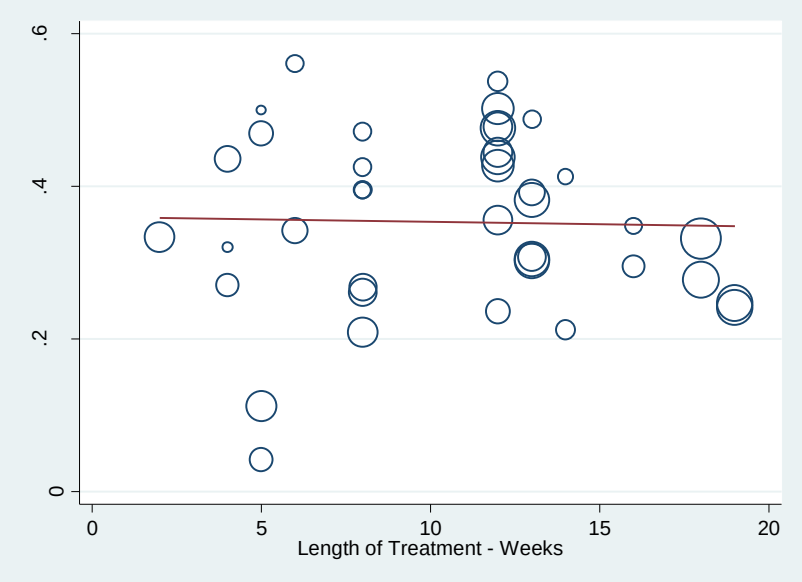


Figure 3. 50 percent pain reduction by length of treatment in treatment group



Predictors of at Least 30 Percent Reduction in Pain in the Placebo Group

In a study of patients with complex regional pain syndrome, successful pain reduction occurred in patients who reported at least a 50 percent reduction in pain (37). Pain relief was considered unsuccessful when pain reduction was less than or equal to 13 percent. In our analysis we included ≥30 percent pain reduction as a secondary outcome as it likely represents a clinically meaningful improvement in pain, although perhaps insufficient pain relief for patients to regard the treatment as totally successful. Twenty-five studies reported this outcome; 23 of these studies also reported 50 percent pain reduction. As expected, the correlation between the placebo response for 50 percent and 30 percent pain reduction was high ($r=0.93$, $p<0.001$). Using the predictor variables from the final model predicting ≥50 percent pain reduction in the placebo group (flexibility of drug dosing, having painful diabetic neuropathy, the proportion of males in the study, and the baseline pain level in the placebo group), resulted in a model with a significant p-value (0.025) and covariates that accounted for 41 percent of the between-study variance (versus 74 percent in the model predicting ≥50% pain reduction). This difference may be due to fewer studies reporting the proportion of patients experiencing at least a 30 percent reduction in pain and the possibility that achieving 30 percent pain reduction is easier with placebo than is achieving 50 percent pain reduction with placebo. With 30 percent pain reduction as the dependent variable and using backward elimination and forward selection, a slight improvement on the model was achieved with the predictor variables: diagnosis (type of neuropathic pain) and study design (parallel or cross-over) that accounted for 53 percent of the between-study heterogeneity (model p-value 0.004), although study design was just shy of achieving statistical significance in the model

(p=0.07). See **Appendix C** for univariate p-values for ≥30 percent pain reduction in the placebo group.

Predictors of Relative Risk of at Least 30 Percent Pain Reduction after Controlling for Placebo Response

Length of treatment was the sole predictor variable needed to predict the relative treatment effect after controlling for the proportion of participants with ≥50 percent pain reduction (**Appendix C**). With the proportion of patients experiencing at least 30 percent pain reduction as the dependent variable, and continuing to control for the placebo response, the model including length of treatment again accounted for 100 percent of the between-study variance, p<0.001. No further model building was attempted.

Sensitivity Analyses

The model predicting ≥50 percent pain reduction (predictor variables: flexibility of dosing, painful diabetic neuropathy, proportion of males enrolled, and baseline pain level in placebo group) accounted for 74 percent of the between-study variance and did well in various sensitivity analyses. When this model was applied to only parallel group studies (32 observations) the covariates accounted for 79 percent of the variance. When the model was applied to only trials of pregabalin (17 observations), the model also performed well and explained 63 percent of the between-study variance. In published studies (34 observations), the same covariates accounted for 73 percent of the variance.

The model predicting relative risk for proportion of patients experiencing ≥50 percent pain reduction, while adjusting for the placebo rate of each individual study, contained only the predictor variable length of treatment and accounted for all of the between-study variance (adjusted R-squared=100%). This model continued to account for

100 percent of between-study variance in both published and unpublished studies, in parallel group studies, in trials enrolling only participants with painful diabetic neuropathy, in studies of people who do not have diabetes, in pregabalin trials, in non-pregabalin studies, and trials rated fair-quality (there were no trials rated good quality and only one trial rated poor quality). There were insufficient observations to test the model in crossover studies and studies rated other than fair quality.

Tests for Normal Random Effects

Normal probability plots of standardized shrunken residuals for both the null and full model for relative risk of treatment effect are found in **Appendix D**. Also included in **Appendix D** are normal probability plots for predicting the placebo response. All plots indicate that the assumption of normal random effects is adequate with no notable outliers.

Publication Bias

In a meta-analysis of included studies, the relative risk for 50 percent pain reduction was 1.57, 95% CI 1.42 to 1.75, I-squared=53%) (Figure 4). See **Appendix B** for random effects forest plots stratified by various predictor variables. (These stratifications were performed to assess patterns in the data.) Funnel plot analysis indicated the possibility of additional unpublished studies with fewer studies to the left of the pooled estimate (data from known unpublished studies are included in the funnel plot) (Figure 5). Egger's bias coefficient of 1.76 (p=0.01) strongly indicates the presence of funnel plot asymmetry and publication bias (38).

Trim and fill method of estimating and inserting potentially missing studies resulted in a random effects pooled estimate of 1.40, 95% CI 1.25 to 1.56 (as compared to 1.57) based on the addition of 10 studies (n=50) (**Appendix E**).

Figure 4. Random effects forest plot of relative risk for 50 percent pain reduction

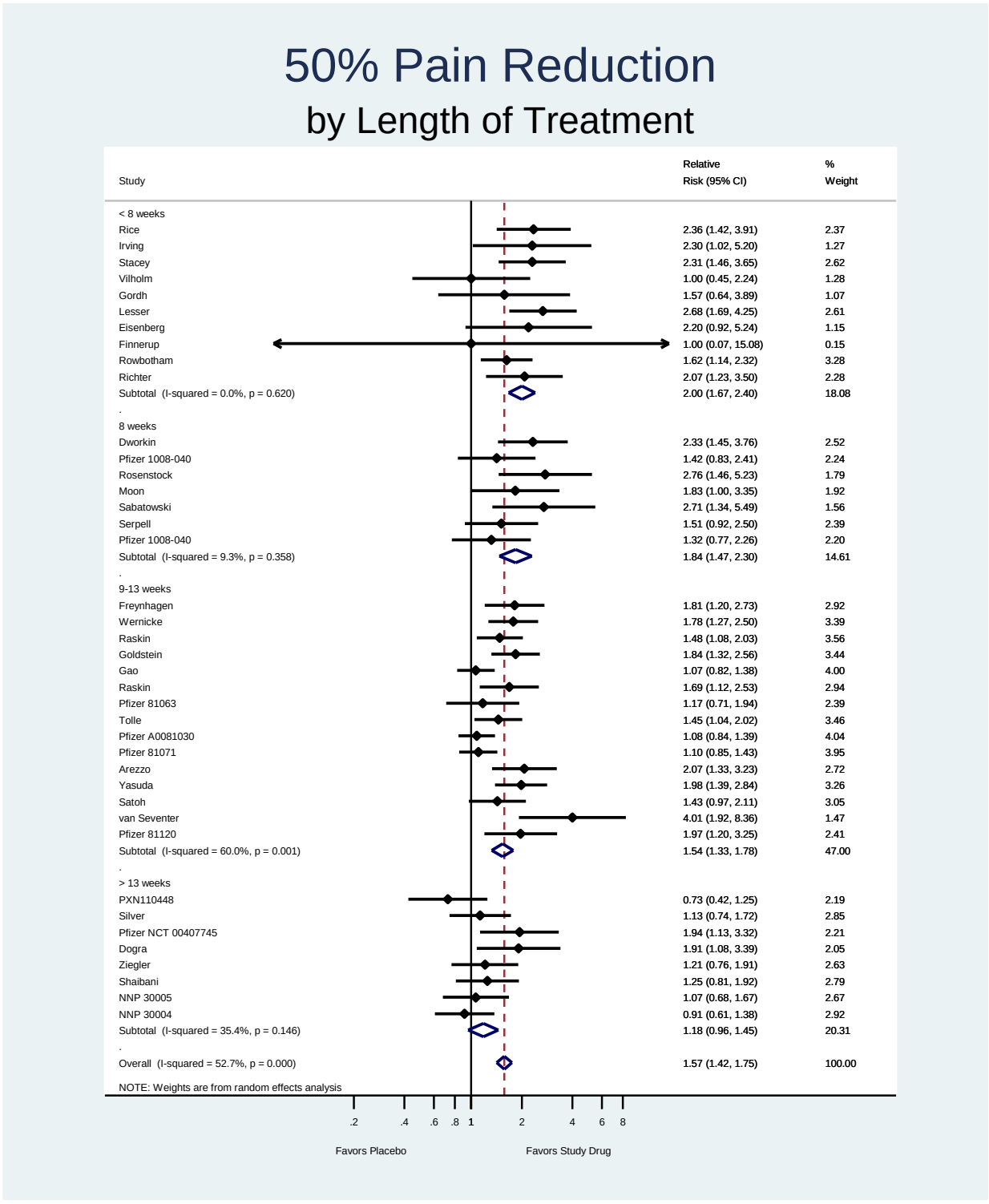
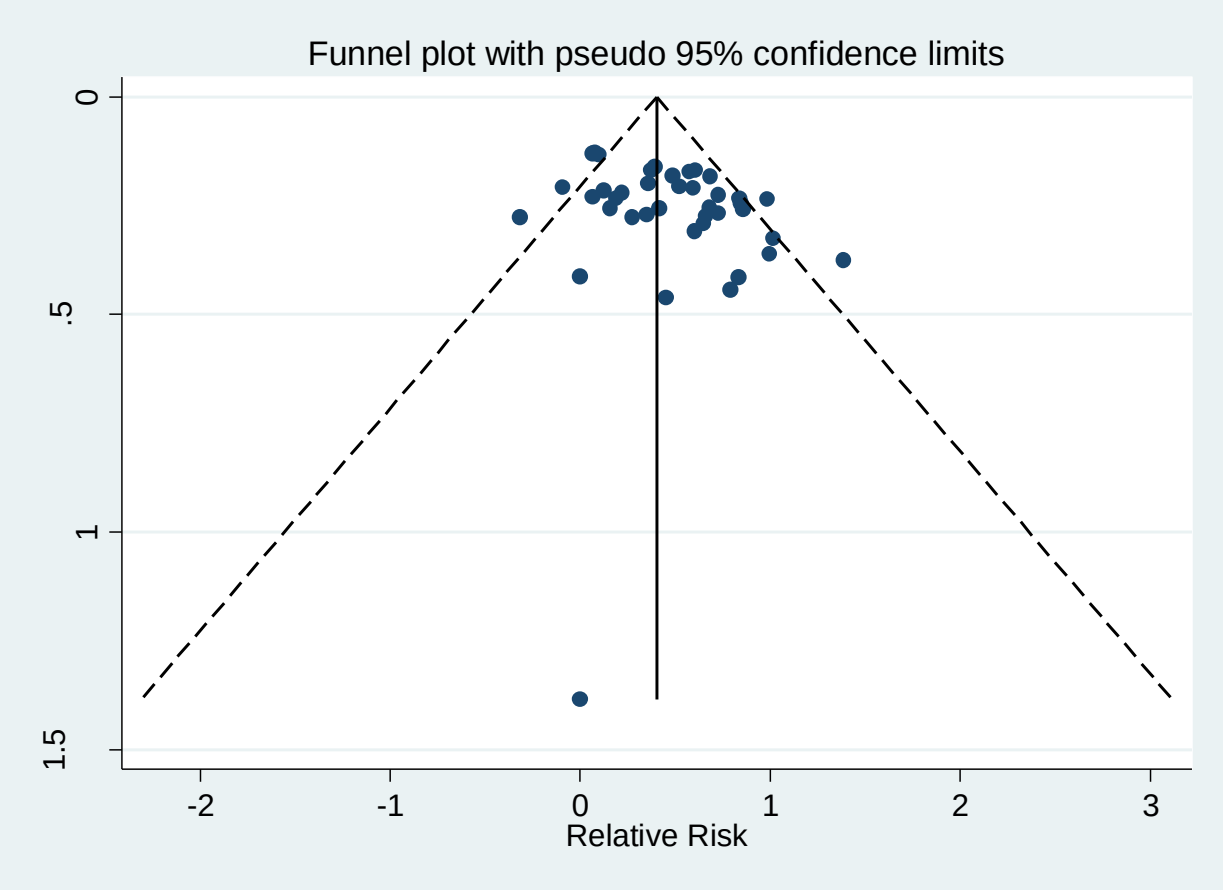


Figure 5. Funnel plot to assess publication bias in studies reporting 50 percent pain reduction



DISCUSSION

Summary

Model building using conventional study-specific variables resulted in length of treatment as the sole predictor variable for ≥50 percent reduction in pain among participants randomized to the placebo group. Unfortunately, this model (although significant) accounted for only 13 percent of the heterogeneity between the 40 studies. Therefore, model building including patient-specific covariates, as well as study-specific covariates was performed in an attempt to better explain between-study heterogeneity.

A model containing four predictor variables (dosing flexibility, having or not having painful diabetic neuropathy, proportion of males versus females enrolled in a study, and baseline pain level in the placebo group on an 11-point numerical rating scale) accounted for 74 percent of the between-study variance among 34 of 40 included studies. The placebo effect was lower in trials where participants were randomized to a fixed study dose (although the dosing effect was very mild), in studies where participants were comprised of patients with neuropathic pain conditions other than painful diabetic neuropathy, in trials that enrolled a higher proportion of males, and in trials where placebo patients had higher levels of baseline pain. Recruitment rate, sample size, number of treatment groups and year of study publication or (or completion if unpublished) have previously been suggested as playing a role in the placebo response (17, 20, 39, 40) but did not in this study.

The slight decrease in placebo response with fixed dosing of study medication could possibly be explained by a decreased sense of control relative to flexible dosing where participants can choose to take more or fewer pills as needed, as the placebo dose

is titrated up or down to tolerability and effect. Although patients receiving the study drug on a fixed dosing schedule may also experience a decreased sense of control, perhaps the ability to titrate the "drug" up or down has a greater effect in the placebo group. The placebo response was also increased when the study was comprised of patients with painful diabetic neuropathy, similar to the findings by Cepeda and colleagues (21), who reported a lower placebo response in patients with postherpetic neuralgia compared with diabetic nerve pain, and in patients with higher baseline pain levels in the placebo groups. In this study, the baseline pain level in studies of patients with postherpetic neuralgia was 6.56 compared to 6.25 in studies of patients with painful diabetic neuropathy without the condition ($p=0.08$). In studies with a >21 percent placebo response, the mean baseline pain rating in the placebo group was 6.22 and in studies with a lower placebo response rate, the mean baseline pain rating was 6.44 ($p=0.049$). Perhaps the more severe the pain, the less likely a placebo will make it noticeably better. This is not unlike the finding that a greater placebo response was demonstrated by children and adolescents with more severe versus less severe autism symptoms (24). Enrolling a higher proportion of males in the study was associated with a slightly lower placebo response. Several studies have found no differences between males and females in response to placebo (41, 42). However, one included study found no difference in mean change in pain rating from baseline to endpoint for females in the placebo group compared to the duloxetine group (mean change in numerical rating scale for females in placebo group = -2.58; mean change in numerical rating scale for females in duloxetine group = -2.25, $p=0.11$), whereas for males the mean change in pain rating from baseline to endpoint was significantly different between the placebo and the duloxetine groups

(-2.04, -3.10, respectively, p=0.02). This suggests an increased placebo response in females compared to males (43). The exact mechanism of any gender difference, whether real or artifactual remains unclear, although it has been suggested that different mechanisms may be at work in males and females and produce the same result (44).

After controlling for the placebo response, the length of time taking study medication (upward titration and maintenance of dose) explained 100 percent of the remaining between-study variance. Longer trials were associated with reduced relative treatment effect. Length of treatment also explained 100 percent of remaining between-study variance in multiple sensitivity analyses. This is especially true in trials of 12 weeks or longer (model p=0.001) but in trials less than 12 weeks in duration the model did not perform as well (model p=0.10) due to decreased statistical heterogeneity for which the addition of covariates is no longer necessary to explain between-study variance. In general, longer exposure to the placebo results in an increase in the placebo response and decreased relative treatment effect. This may be due partly to regression to the mean at which point pain rated at higher levels of intensity may naturally decrease if enough time is allowed and the subsequent pain relief is attributed to taking the placebo medication. Since, on average, a greater proportion of participants experience pain relief in the active drug arm than the placebo arm, there is greater room for regression to the mean to differentially benefit the placebo group. Additionally, the average length of treatment in trials of postherpetic neuralgia (which had a lower average placebo response) was only seven weeks whereas in other populations the average length of treatment was 11 weeks (p=0.05).

Strengths of this Report

Strengths of this study are the rigor with which the initial systematic review was conducted, following the precise methods of the Drug Effectiveness Review Project regarding search strategy, study selection, and quality rating of studies (28). Additionally, to the author's knowledge, this is the first study of neuropathic pain trials to examine the effects of gender distribution, average patient age, dosing flexibility, study location, and number of treatment arms on both the placebo response and on the relative treatment effect after adjusting for the placebo response. In addition, numerous sensitivity analyses were conducted based on study outcome, trial design, study drug, neuropathic pain condition, and study publication status. The model predicting relative treatment response, while adjusting for placebo response, was equally valid when only parallel group trials were included, as well as when only published studies or unpublished studies were included. The validity of the model was also unchanged when including only trials of patients with painful diabetic neuropathy, trials of pregabalin, or trials in which the outcome measured was the proportion of patients experiencing a 30 percent, instead of 50 percent, pain reduction.

Limitations of this Report

We recognize several potential limitations in our analysis. While we examined the effect of a specific set of medications on neuropathic pain in use over the past two decades, our analysis did not include recently approved agents (e.g., desvenlafaxine) nor were opioids or non-steroidal anti-inflammatory drugs included. Also, although an effect of study design was evident, the data on cross-over designs was limited (n=3). In addition, due to sparse data, it was difficult to come to firm conclusions regarding the

effect of tricyclic antidepressants or the effect of overall study quality on the proportion of study participants in the placebo group experiencing at least a 50 percent reduction in pain. We examined study withdrawals (mean 22%, range 7.4% to 45%) as a predictor of the placebo response and of relative treatment effect, as it is an important element of study quality, but found little evidence of an effect (p-values 0.45 and 0.79, respectively). Also, the proportion of patients leaving the study did not differ based on dosing flexibility (22% with flexible dosing versus 21% with fixed dosing, p=0.91). Another limitation of this study is that we could not examine the effects of having concomitant anxiety or depression or of taking psychotropic medication on the placebo response as this information was often not reported in neuropathic pain trials.

Implications for Health Research and Quality Improvement

Systematic evidence reviews and meta-analyses are essential tools for our understanding of the efficacy and effectiveness of therapies. The presence of the placebo effect and its quantification appears to be dependent on design features of clinical trials. We explored these features in one domain, the pharmaceutical control of neurogenic pain. Our findings have implications for systematic reviews of drug therapy for neuropathic pain that employ indirect or network meta-analysis with the placebo response as a common comparator. Accounting for differences in the placebo response between trials is necessary. This could be accomplished by simultaneously adjusting for characteristics influencing the placebo response (flexibility of drug dosing, gender, etiology of neuropathic pain, and severity of baseline pain) or only comparing trials with similar characteristics. Treatment length should also be considered as it may affect relative treatment effect. Failure to take trial differences into account could misrepresent one drug

as superior to another drug in treating neuropathic pain when, in reality, they have similar effects or drug superiority is reversed.

Our findings also have implications for standardization of study design in neuropathic pain trials. For example, since the etiology of pain is an important factor in pain reduction, we recommend that trials be conducted in patients with the same type of neuropathic pain rather than mixing types of pain (i.e., including spinal cord injury patients and patients with painful diabetic neuropathy in the same trial). We also recommend that trials be parallel, rather than cross-over in design, due to increased potential for patients correctly guessing whether they are receiving active drug or placebo when exposed to more than one treatment as in cross-over studies. Because dosing flexibility helped to predict the placebo response, we suggest trials either include both a fixed-dose arm and a flexible-dose arm (provided upward titration is recommended for the particular study drug), or including only flexible dosing since this more closely approximates real-world practice. We also recommend that trial length be a minimum of 12 weeks to allow for better assessment of a drug's pain reduction capabilities over an extended period since most patients with neuropathic pain may remain on the medication indefinitely. We also recommend a sensitivity analysis if both genders are included in a study and suggest pooling results by sex only if gender does not predict either treatment or placebo response. With rare exception, neuropathic pain trials all require patients to report similar levels of baseline pain to meet study eligibility criteria and we recommend no changes to current methods. However, standardizing other aspects of trial design will not only help demonstrate whether or not a drug controls pain in a study environment that

approximates a real-world setting, but will also maximize the utility of drug-drug comparisons.

Other possible variations on trial design, not addressed by this study, but which may influence the placebo response are the waiting list control design (in addition to a placebo group, to assess effects of no treatment), covert randomization (patients consent to an observational study and then are covertly randomized, thereby escaping belief in the possibility of being in a placebo group), and cluster randomization (informed consent may not be required so patients may not know they are in a study) as suggested by Dieppe (45). Another trial design that could control the placebo response is the sequential parallel comparative design, in which placebo non-responders are re-randomized with half each receiving study drug and placebo; this approach increases study power and thus the likelihood of achieving a positive relative treatment effect (46). Within a study, controlling patient expectations for receiving active treatment, using biomarkers instead of self-reported outcomes, increasing medication adherence, and ensuring adequate blinding are other methods to reduce the placebo response (47).

Future Research Needs

This study focused on the proportion of patients experiencing at least 50 percent reduction in pain from baseline to study endpoint, which is a binary outcome (patients either did or did not experience a 50% pain reduction) with an easily calculable relative risk for treatment response. This research did not examine placebo or relative treatment response using a continuous outcome measure. Examples of continuous outcomes frequently used in neuropathic pain trials are pain ratings on an 11-point numerical rating scale and pain ratings on a 0-100 visual analogue scale. Neuropathic pain trials often

utilize numerous outcome measures, both binary and continuous (and possibly report only favorable outcomes). An important step in understanding the placebo response will be to verify that the response is similar regardless of outcome measure used, particularly if pain relief as measured on a continuous scale is similar to a binary pain measurement.

This study also focused on patients with painful diabetic neuropathy, postherpetic neuralgia, traumatic nerve injury, and central nerve pain such pain experienced due to having a stroke (post-stroke pain). Omitted from these populations are patients with chemotherapy-related and HIV-related neuropathic pain. These types of pain are complicated because while the conditions themselves may cause pain, neuropathic pain may also develop secondary to pharmacologic treatment for cancer and HIV. Verifying that the model explains the between-study heterogeneity in trials of patients with cancer and HIV would also be useful.

Additionally, experimenting with alternative study designs to differentiate the response due to natural history from the placebo response using a no treatment control group in addition to a placebo group would facilitate our appreciation of the true magnitude of the placebo response.

CONCLUSION

The placebo response varies in trials of neuropathic pain. Standardization of trial design by incorporating flexibility of drug dosing, duration of treatment at least 12 weeks, including a single type of neuropathic pain, and stratifying results by gender may facilitate interpretation and generalizability of trial results. Systematic evidence reviews and meta-analyses should also incorporate consideration of flexibility of dosing, length of treatment, type of neuropathic pain, gender distribution within trials, and baseline levels of pain when pooling studies or comparing drugs across trials with the placebo group as the common comparator.

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APPENDICES

A. Characteristics of Included Studies

B. Forest Plots of Random Effects Model of Relative Risk for 50 Percent Pain Reduction (Various Stratifications)

C. Predictor Variables for 30 Percent Pain Reduction and Their P-Values

D. Normal Probability Plot and Stata Commands

E. Meta Trim and Fill Results and Metabias Test for Small Study Effects

Appendix A: Characteristics of Included Studies

Author	Year	Drug and Dose (mg)	N	Length	% Males	Age	Pain Type	50% Pain Reduction	30% Pain Reduction
Arezzo(48)	2008	Pregabalin 600	167	13	61.68	58.30	PDN	40/82 vs 20/85	Not Reported
Dogra(49)	2005	Oxcarbazepine 300-1800	146	16	58.22	60.12	PDN	24/69 vs 14/77	31/69 vs 22/77
Dworkin(50)	2003	Pregabalin 300,600	173	8	46.80	71.50	PHN	42/89 vs 17/84	56/89 vs 21/84
Eisenberg (51)	2001	Lamotrigine 25-400	59	5	62.30	55.20	PDN	12/24 vs 5/22	Not Reported
Finnerup (52)	2009	Levetiracetem 1000-3000	36	5	80.60	52.80	SCI	1/24 vs 1/24	3/24 vs 4/24
Freynhagen (53)	2005	Pregabalin 300,153-600	338	12	54.10	62.20	PDN/PHN	137/273 vs 18/65	171/273 vs 24/65
Gao(43)	2010	Duloxetine 60-120	215	12	47.00	59.26	PDN	57/106 vs 55/109	74/106 vs 67/109
Goldstein (54)	2005	Duloxetine 20,60,120	457	12	61.50	60.10	PDN	158/332 vs 29/112	Not Reported
Gordh(55)	2008	Gabapentin 300-2400	120	5	46.70	48.80	TNI	11/98 vs 7/98	29/98 vs 10/98
Guan(56)	2011	Pregabalin 150-600	309	8	46.40	60.10	PDN/PHN	Not Reported	130/203 vs 53/102
Irving(57)	2009	Gabapentin 1800	158	4	46.80	70.00	PHN	29/107 vs 6/51	49/107 vs 16/51
Lesser(58)	2004	Pregabalin 75,300,600	260	5	61.39	59.50	PDN	76/162 vs 17/97	Not Reported
Moon(59)	2010	Pregabalin 150-600	241	8	48.80	59.70	Multiple	42/161 vs 11/77	68/161 vs 27/77
NNP 3004 (60)	2007	Lamotrigine 200,300,400	360	19	53.25	60.28	PDN	63/225 vs 23/85	87/255 vs 32/85
NNP 3005 (60)	2007	Lamotrigine 200,300,400	360	19	54.10	59.93	PDN	61/253 vs 19/84	87/255 vs 25/84
P 1008-040 (61)	2007	Pregabalin 600	168	8	57.00	60.00	PDN	34/86 vs 12/40	Not Reported
P 1008-040 (61)	2007	Amitriptyline 75	169	8	57.00	60.00	PDN	37/87 vs 12/40	Not Reported

Appendix A: Characteristics of Included Studies (continued)

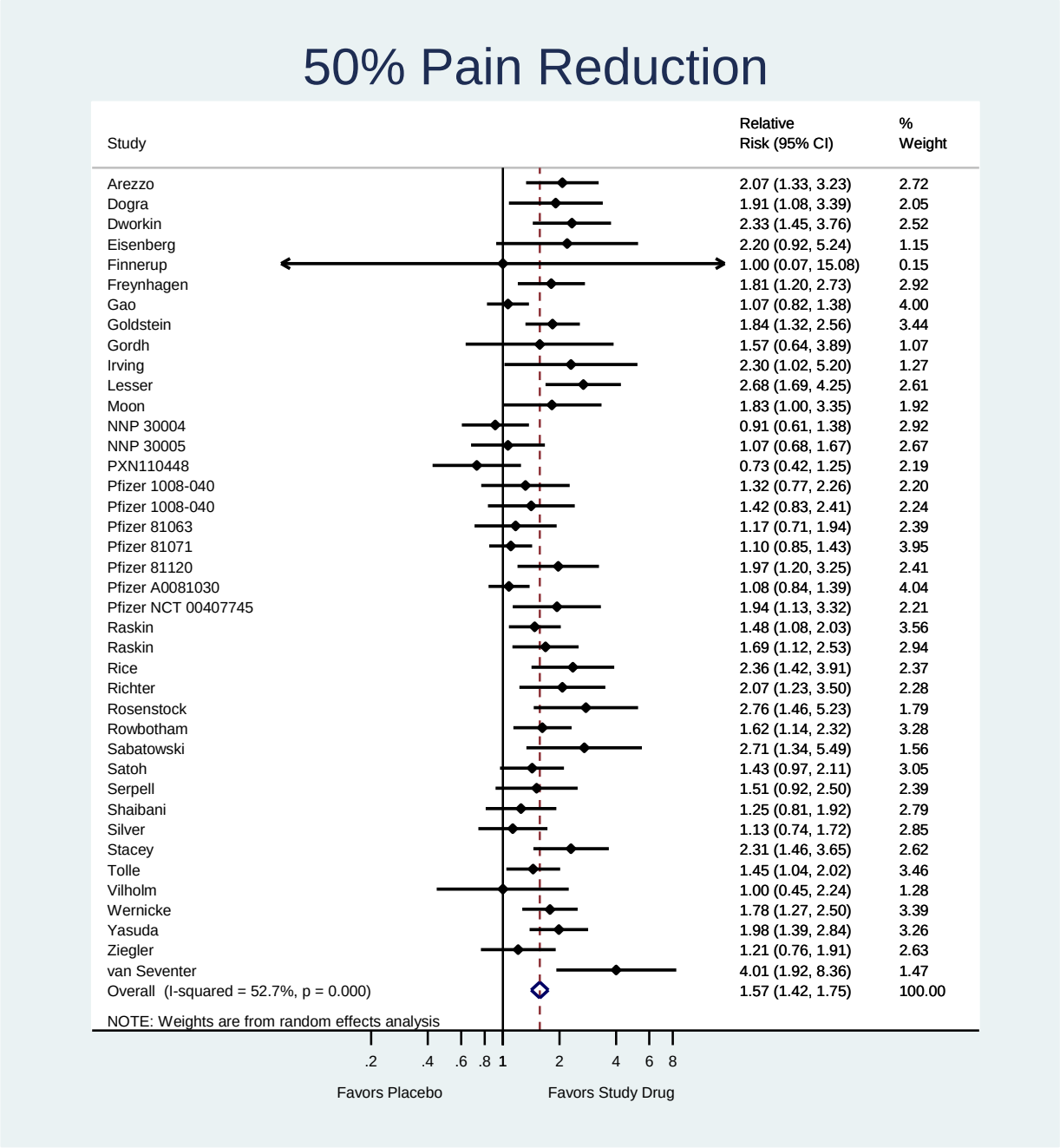
Author	Year	Drug and Dose (mg)	N	Length	% Males	Age	Pain Type	50% Pain Reduction	30% Pain Reduction
P 81063(62)	2008	Pregabalin 150-600	220	12	62.60	58.00	Post Stroke	26/110 vs 22/109	48/110 vs 35/109
P 81071(63)	2007	Pregabalin 300,600	462	13	56.40	59.40	PDN	115/301 vs 52/150	181/301 vs 78/150
P 81120(64)	2009	Pregabalin 150,300,600	372	13	53.40	70.10	PHN	83/272 vs 15/97	Not Reported
P 81030(65)	2007	Pregabalin 150-600	412	12	39.16	57.20	PDN	114/267 vs 53/134	172/267 vs 73/134
P 00407745 (66)	2012	Pregabalin 150-600	220	16	80.40	45.90	SCI	31/105 vs 16/105	48/105 vs 33/105
PXN110448 (67)	2009	Pregabalin 300	421	14	60.70	58.90	PDN	14/66 vs 35/120	28/66 vs 57/120
Raskin(68)	2004	Topiramate 400	323	12	49.50	59.20	PDN	74/208 vs 23/209	103/208 vs 37/109
Raskin(69)	2005	Duloxetine 60,120	348	12	46.60	58.80	PDN	101/227 vs 34/113	Not Reported
Rice(70)	2001	Gabapentin 1800,2400	334	2	41.30	75.32	PHN	71/213 vs 15/106	Not Reported
Richter(71)	2005	Pregabalin 150,600	246	6	60.57	57.07	PDN	55/161 vs 14/85	Not Reported
Rosenstock (72)	2004	Pregabalin 300	146	8	56.20	59.70	PDN	30/76 vs 10/70	Not Reported
Rowbotham (73)	2004	Venlafaxine 75,150-225	244	6	59.00	59.00	PDN	46/82 vs 28/81	Not Reported
Sabatowski (74)	2004	Pregabalin 150,300	238	8	44.96	72.14	PHN	42/157 vs 8/81	Not Reported
Satoh(75)	2011	Pregabalin 300,600	317	13	75.50	61.40	PDN	55/179 vs 29/135	Not Reported
Serpell(76)	2002	Gabapentin 900-2400	307	8	46.23	56.90	Multiple	32/153 vs 21/152	Not Reported
Shaibani (77)	2009	Lacosamide 200,400,600	469	18	56.50	59.80	PDN	129/389 vs 17/64	221/389 vs 29/64
Silver(78)	2007	Lamotrigine 200,400,600	223	14	53.50	60.20	Multiple	26/63 vs 27/74	37/63 vs 45/74
Stacey(79)	2008	Pregabalin 300, 150-600	270	4	55.76	67.37	PHN	78/179 vs 17/90	115/179 vs 28/90

Appendix A: Characteristics of Included Studies (continued)

Author	Year	Drug and Dose (mg)	N	Length	% Males	Age	Pain Type	50% Pain Reduction	30% Pain Reduction
Tolle(80)	2008	Pregabalin 150,300,600	396	12	55.40	58.61	PDN	131/299 vs 29/96	Not Reported
v.Seventer (81)	2010	Pregabalin 150-600	254	8	49.20	51.50	Post Trauma	Not Reported	50/126 vs 32/126
v.Seventer (82)	2006	Pregabalin 300,600,1200	370	13	45.70	70.70	PHN	83/275 vs 7/93	121/275 vs 16/93
Vilholm(83)	2008	Levetiracetem 3000	27	4	00.00	60.00	Mastectomy	8/25 vs 8/25	Not Reported
Wernicke (84)	2006	Duloxetine 60,120	334	12	61.10	60.70	PDN	108/226 vs 29/108	149/226 vs 45/108
Yasuda(85)	2011	Duloxetine 40,60	339	13	75.70	60.80	PDN	67/171 vs 33/137	98/171 vs 59/167
Ziegler(86)	2010	Lacosamide 400,600	357	18	51.50	57.90	PDN	78/281 vs 17/74	130/281 vs 26/74

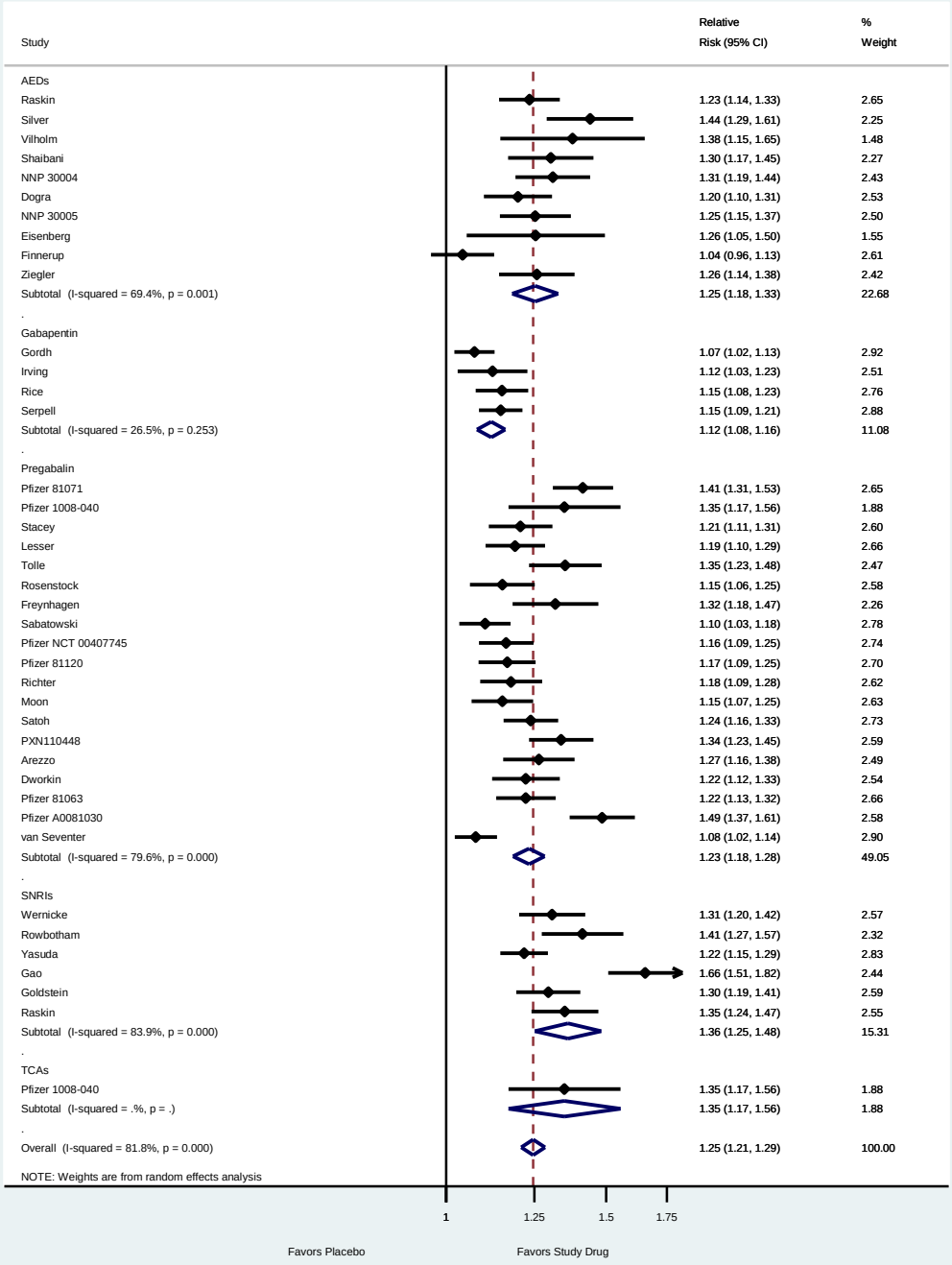
Abbreviations: PDN=painful diabetic neuropathy; PHN=postherpetic neuralgia; SCI=spinal cord injury; P=Pfizer

Appendix B. Forest Plots and Heterogeneity Statistics for 50 Percent Pain Reduction in the Placebo Group



50% Pain Reduction - Placebo Group

by Drug Category



Test(s) of heterogeneity:

	Heterogeneity statistic	degrees of freedom	P	I-squared**	Tau-squared
AEDs	29.39	9	0.001	69.4%	0.0058
Gabapentin	4.08	3	0.253	26.5%	0.0004
Pregabalin	88.22	18	0.000	79.6%	0.0062
SNRIs	31.04	5	0.000	83.9%	0.0091
TCAs	0.00	0	.	.%	0.0000
Overall	214.13	39	0.000	81.8%	0.0076

** I-squared: the variation in ES attributable to heterogeneity)

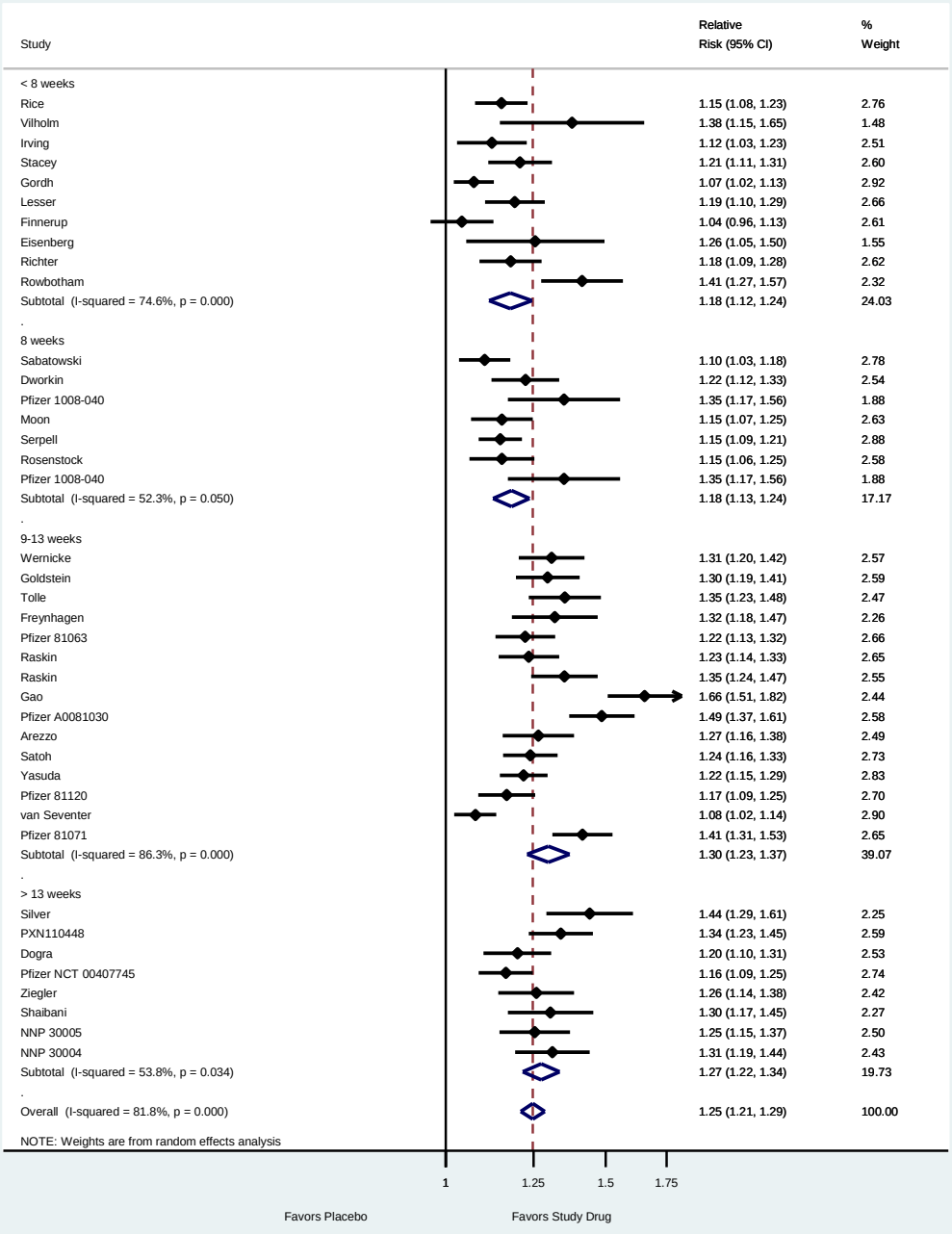
Note: between group heterogeneity not calculated;
only valid with inverse variance method

Significance test(s) of ES=1

AEDs	z= 7.63	p = 0.000
Gabapentin	z= 6.14	p = 0.000
Pregabalin	z= 10.28	p = 0.000
SNRIs	z= 7.21	p = 0.000
TCAs	z= 4.14	p = 0.000
Overall	z= 14.22	p = 0.000

50% Pain Reduction - Placebo Group

by Length of Treatment



Test(s) of heterogeneity:

	Heterogeneity statistic	degrees of freedom	P	I-squared**	Tau-squared
< 8 weeks	35.45	9	0.000	74.6%	0.0052
8 weeks	12.58	6	0.050	52.3%	0.0019
9-13 weeks	102.02	14	0.000	86.3%	0.0097
> 13 weeks	15.17	7	0.034	53.8%	0.0024
Overall	214.13	39	0.000	81.8%	0.0076

** I-squared: the variation in ES attributable to heterogeneity)

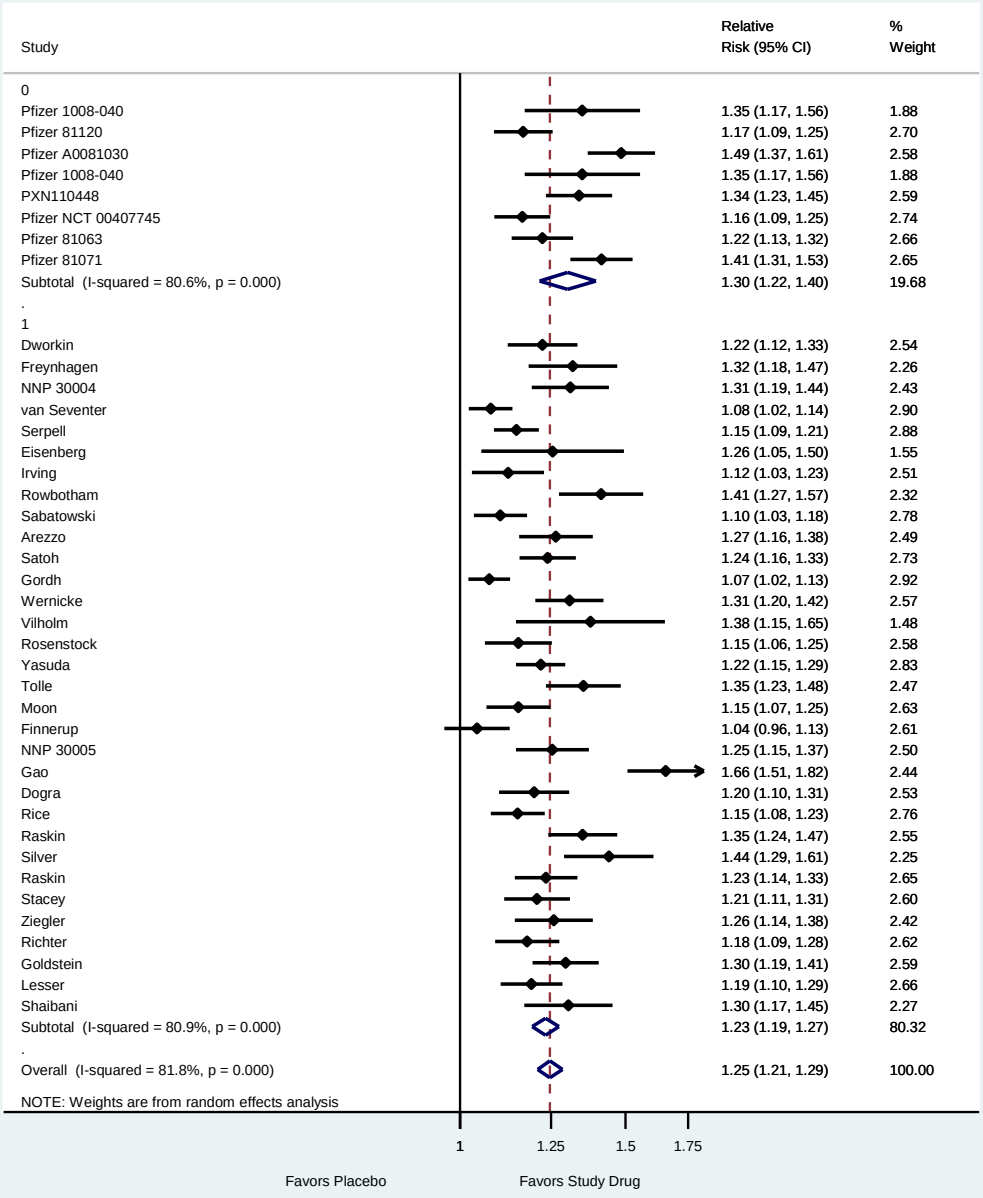
Note: between group heterogeneity not calculated;
only valid with inverse variance method

Significance test(s) of ES=1

< 8 weeks	z= 5.99	p = 0.000
8 weeks	z= 7.09	p = 0.000
9-13 weeks	z= 9.45	p = 0.000
> 13 weeks	z= 10.11	p = 0.000
Overall	z= 14.22	p = 0.000

50% Pain Reduction - Placebo Group

by Publication Status



Test(s) of heterogeneity:

	Heterogeneity statistic	degrees of freedom	P	I-squared**	Tau-squared
0	36.07	7	0.000	80.6%	0.0077
1	162.65	31	0.000	80.9%	0.0070
Overall	214.13	39	0.000	81.8%	0.0076

** I-squared: the variation in ES attributable to heterogeneity)

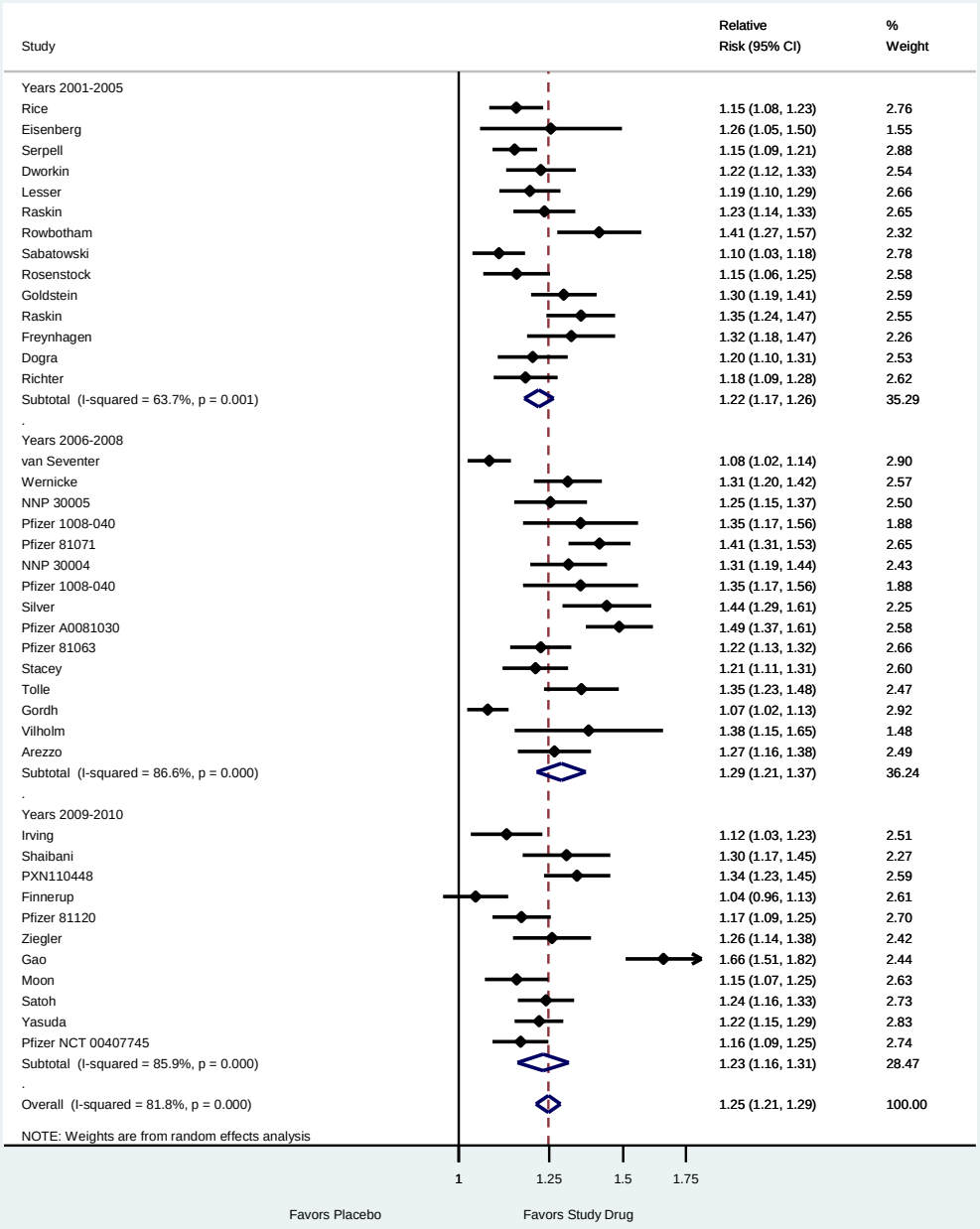
Note: between group heterogeneity not calculated;
only valid with inverse variance method

Significance test(s) of ES=1

0	z= 7.49	p = 0.000
1	z= 12.47	p = 0.000
Overall	z= 14.22	p = 0.000

50% Pain Reduction - Placebo Group

by Year of Publication/Completion



Test(s) of heterogeneity:

	Heterogeneity statistic	degrees of freedom	P	I-squared**	Tau-squared
Years 2001-2005	35.77	13	0.001	63.7%	0.0029
Years 2006-2008	104.47	14	0.000	86.6%	0.0118
Years 2009-2010	71.09	10	0.000	85.9%	0.0099
Overall	214.13	39	0.000	81.8%	0.0076

** I-squared: the variation in ES attributable to heterogeneity)

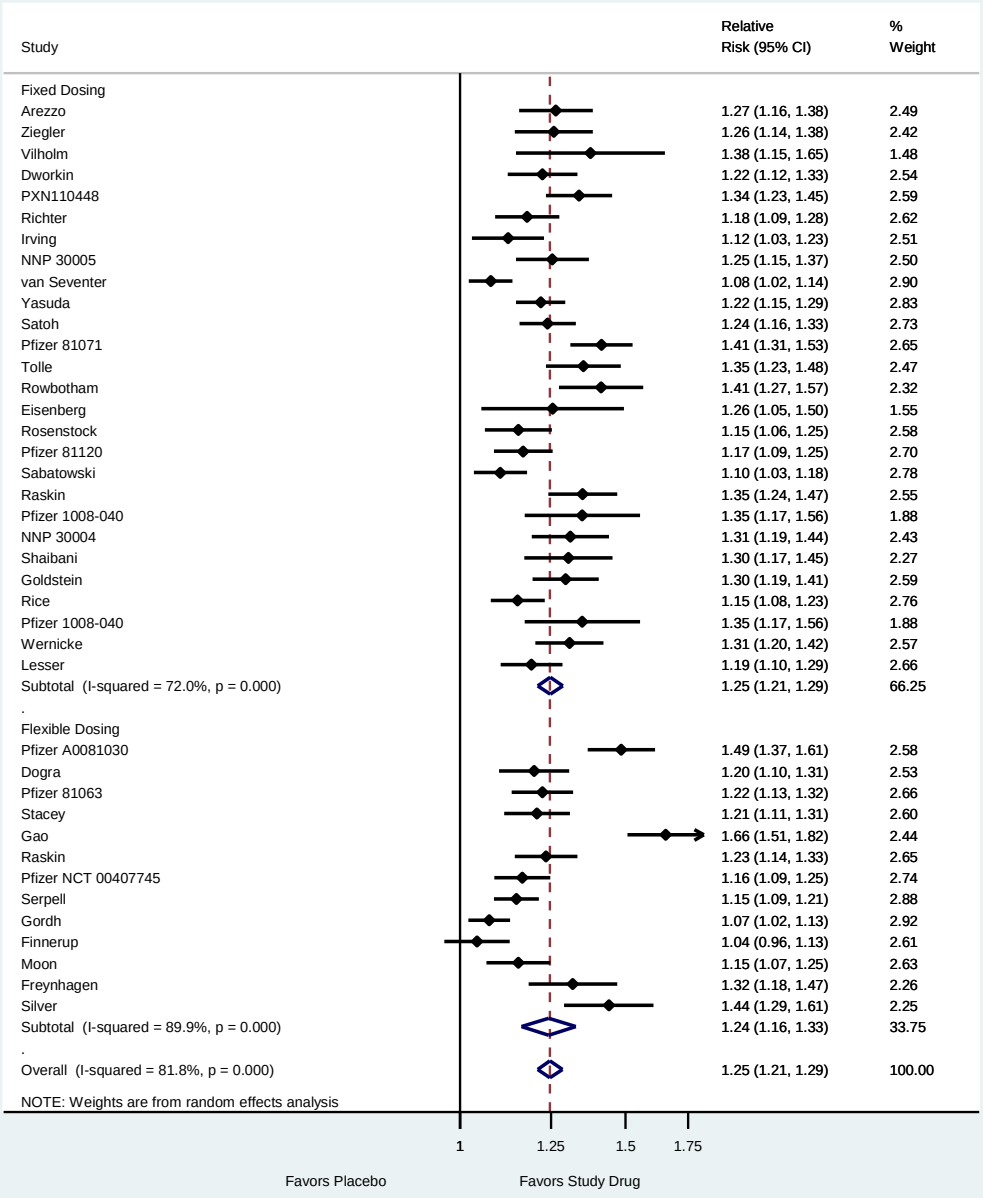
Note: between group heterogeneity not calculated;
only valid with inverse variance method

Significance test(s) of ES=1

Years 2001-2005	z= 10.67	p = 0.000
Years 2006-2008	z= 8.19	p = 0.000
Years 2009-2010	z= 6.41	p = 0.000
Overall	z= 14.22	p = 0.000

50% Pain Reduction-Placebo Group

by Flexibility of Dosing



Test(s) of heterogeneity:

	Heterogeneity statistic	degrees of freedom	P	I-squared**	Tau-squared
Fixed Dosing	92.72	26	0.000	72.0%	0.0046
Flexible Dosing	119.28	12	0.000	89.9%	0.0134
Overall	214.13	39	0.000	81.8%	0.0076

** I-squared: the variation in ES attributable to heterogeneity)

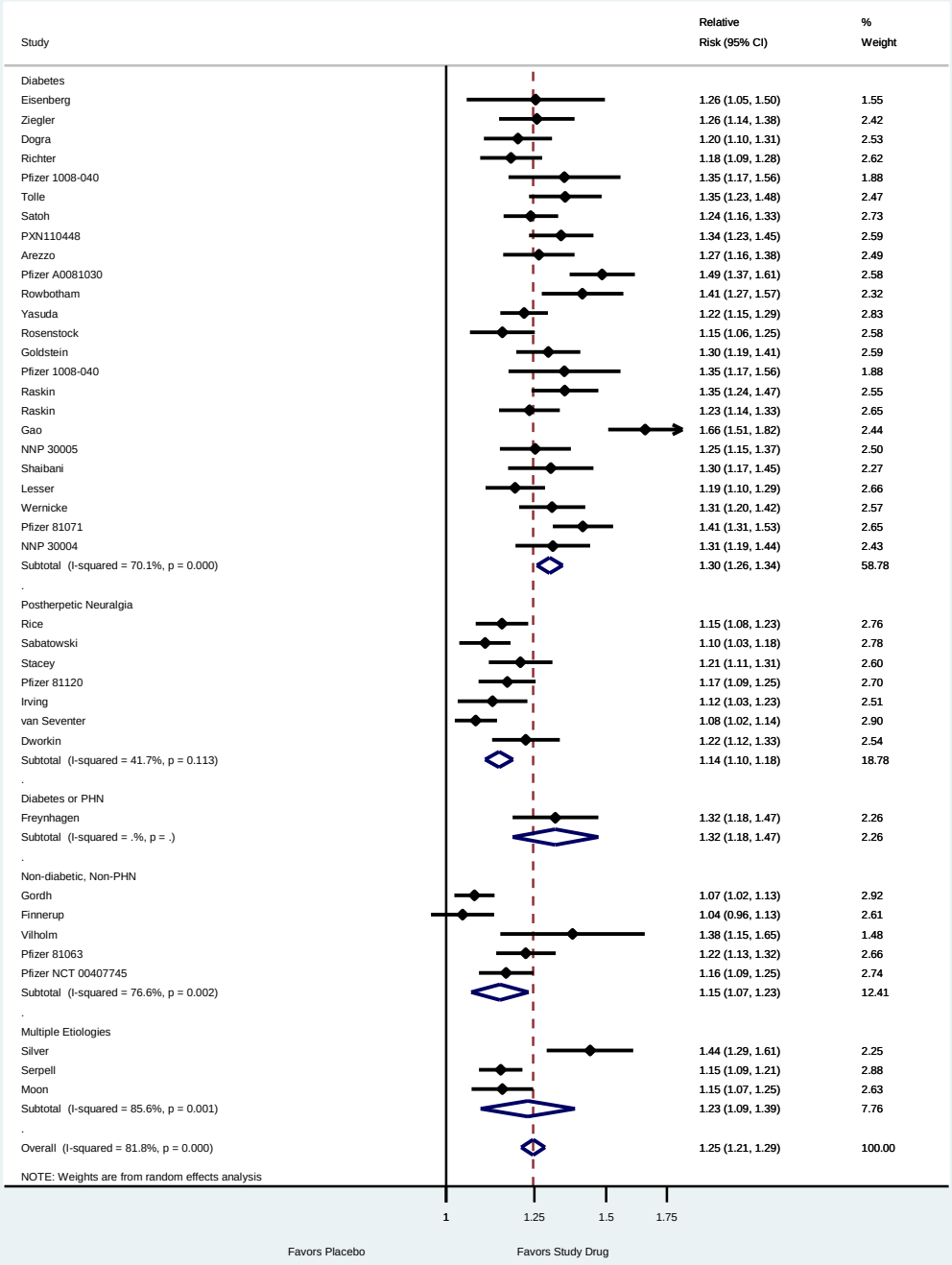
Note: between group heterogeneity not calculated;
only valid with inverse variance method

Significance test(s) of ES=1

Fixed Dosing	z= 13.94	p = 0.000
Flexible Dosing	z= 6.38	p = 0.000
Overall	z= 14.22	p = 0.000

50% Pain Reduction - Placebo Group

by Etiology of Pain



Test(s) of heterogeneity:

	Heterogeneity statistic	degrees of freedom	P	I-squared**	Tau-squared
Diabetes	76.90	23	0.000	70.1%	0.0046
Postherpetic Neuralg	10.29	6	0.113	41.7%	0.0009
Diabetes or PHN	0.00	0	.	.%	0.0000
Non-diabetic, Non-PH	17.10	4	0.002	76.6%	0.0049
Multiple Etiologies	13.87	2	0.001	85.6%	0.0094
Overall	214.13	39	0.000	81.8%	0.0076

** I-squared: the variation in ES attributable to heterogeneity)

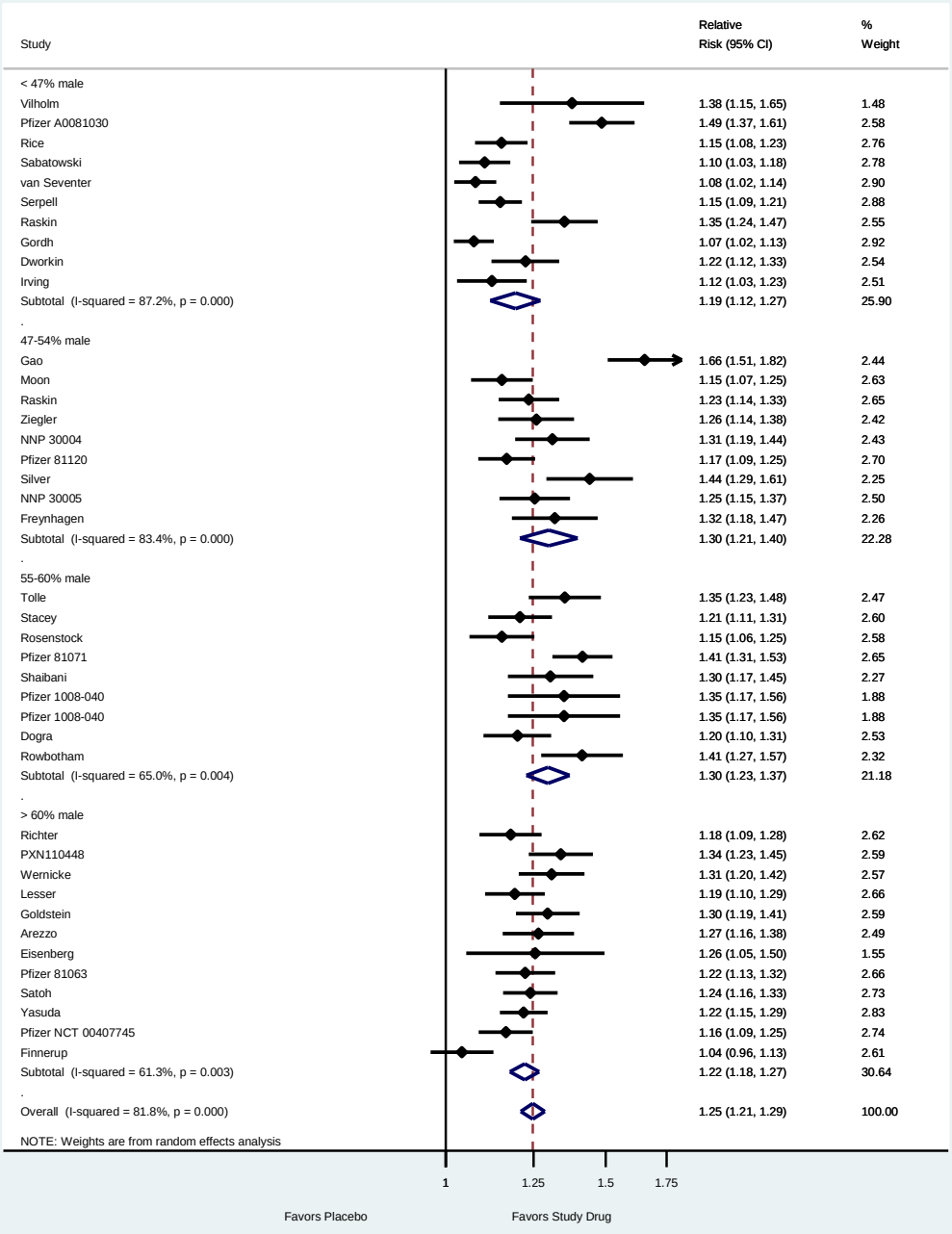
Note: between group heterogeneity not calculated;
only valid with inverse variance method

Significance test(s) of ES=1

Diabetes	z= 15.56	p = 0.000
Postherpetic Neuralg	z= 7.42	p = 0.000
Diabetes or PHN	z= 4.99	p = 0.000
Non-diabetic, Non-PH	z= 3.69	p = 0.000
Multiple Etiologies	z= 3.40	p = 0.001
Overall	z= 14.22	p = 0.000

50% Pain Reduction - Placebo Group

by Percent Male



Test(s) of heterogeneity:

	Heterogeneity statistic	degrees of freedom	P	I-squared**	Tau-squared
< 47% male	70.34	9	0.000	87.2%	0.0087
47-54% male	48.22	8	0.000	83.4%	0.0103
55-60% male	22.85	8	0.004	65.0%	0.0044
> 60% male	28.41	11	0.003	61.3%	0.0025
Overall	214.13	39	0.000	81.8%	0.0076

** I-squared: the variation in ES attributable to heterogeneity)

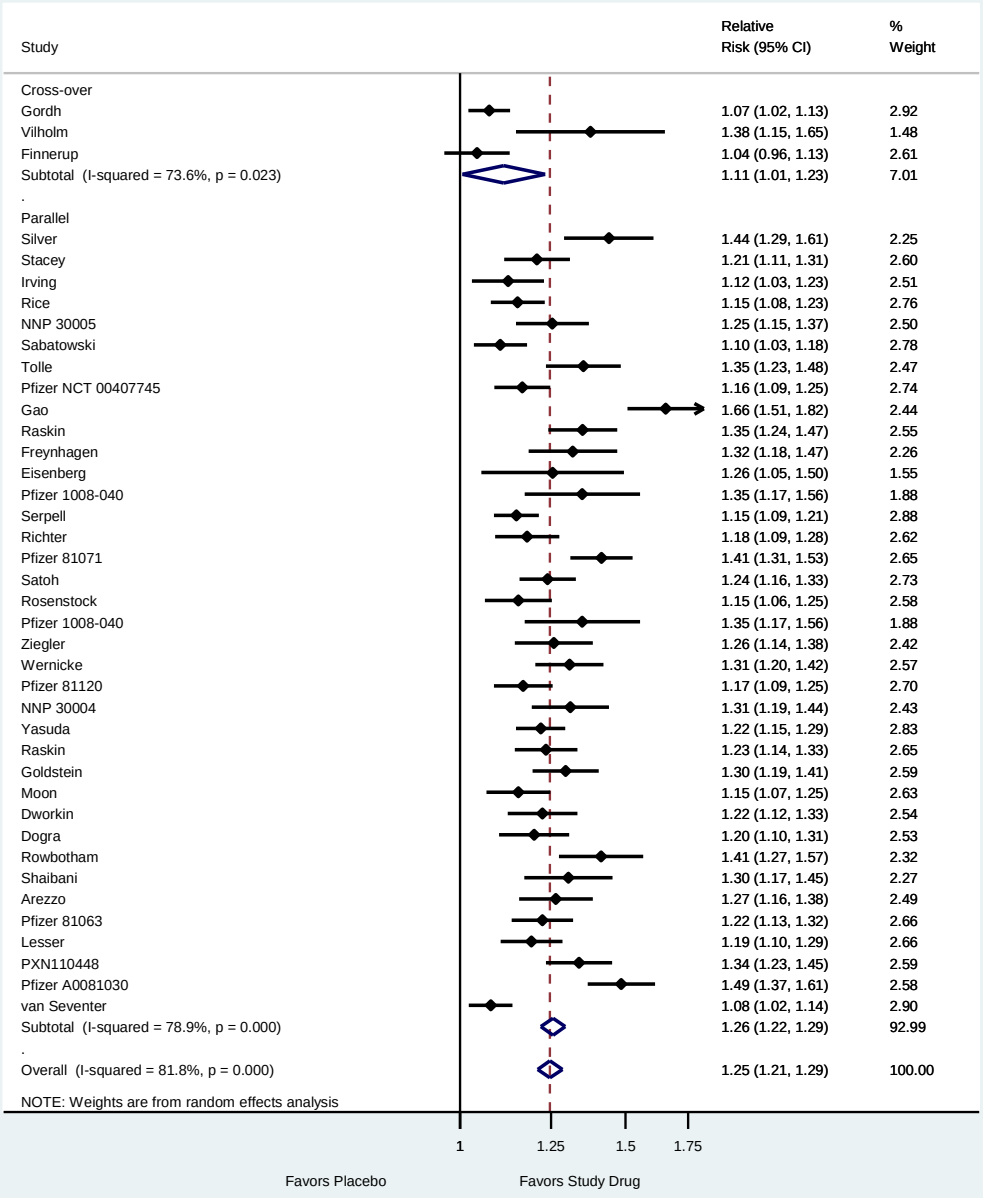
Note: between group heterogeneity not calculated;
only valid with inverse variance method

Significance test(s) of ES=1

< 47% male	z= 5.48	p = 0.000
47-54% male	z= 7.03	p = 0.000
55-60% male	z= 9.29	p = 0.000
> 60% male	z= 10.58	p = 0.000
Overall	z= 14.22	p = 0.000

50% Pain Reduction - Placebo Group

by Study Design



Test(s) of heterogeneity:

	Heterogeneity statistic	degrees of freedom	P	I-squared**	Tau-squared
Cross-over	7.58	2	0.023	73.6%	0.0054
Parallel	170.74	36	0.000	78.9%	0.0064
Overall	214.13	39	0.000	81.8%	0.0076

** I-squared: the variation in ES attributable to heterogeneity)

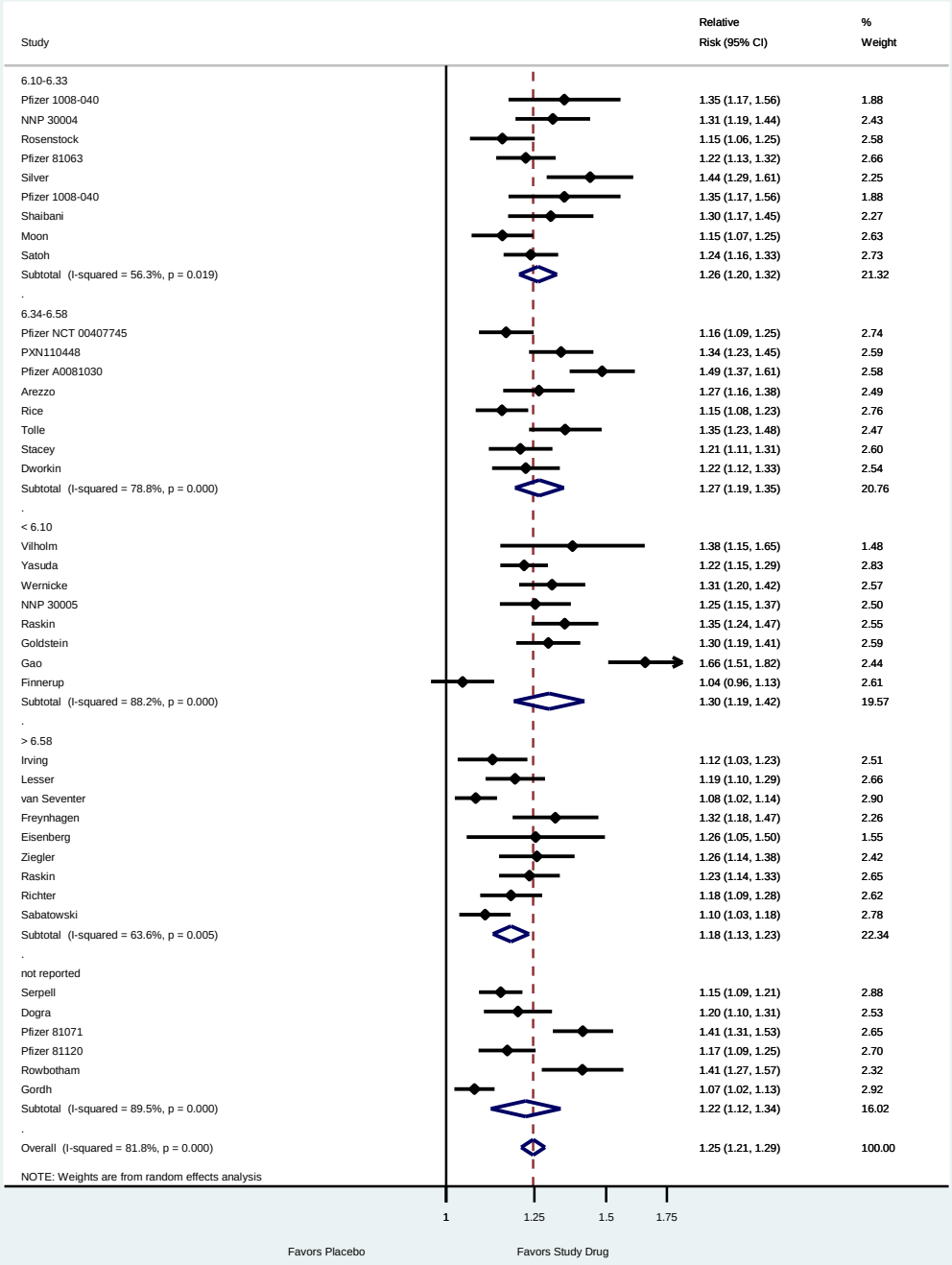
Note: between group heterogeneity not calculated;
only valid with inverse variance method

Significance test(s) of ES=1

Cross-over	z= 2.08	p = 0.038
Parallel	z= 15.13	p = 0.000
Overall	z= 14.22	p = 0.000

50% Pain Reduction - Placebo Group

by Baseline Pain Level in Placebo Group



Test(s) of heterogeneity:

	Heterogeneity statistic	degrees of freedom	P	I-squared**	Tau-squared
6.10-6.33	18.31	8	0.019	56.3%	0.0029
6.34-6.58	33.02	7	0.000	78.8%	0.0062
< 6.10	59.49	7	0.000	88.2%	0.0142
> 6.58	21.97	8	0.005	63.6%	0.0029
not reported	47.59	5	0.000	89.5%	0.0106
Overall	214.13	39	0.000	81.8%	0.0076

** I-squared: the variation in ES attributable to heterogeneity)

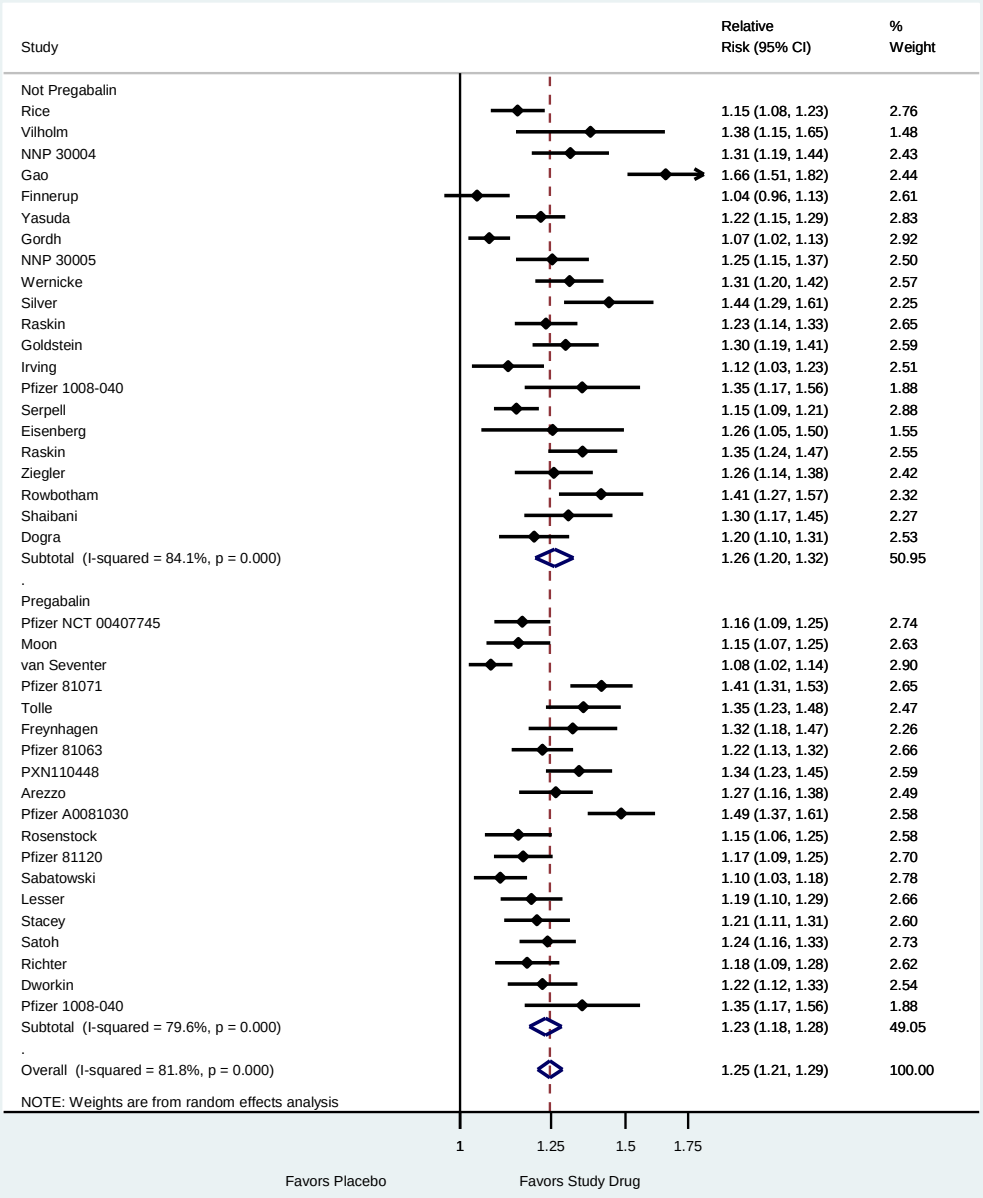
Note: between group heterogeneity not calculated;
only valid with inverse variance method

Significance test(s) of ES=1

6.10-6.33	z= 9.56	p = 0.000
6.34-6.58	z= 7.54	p = 0.000
< 6.10	z= 5.74	p = 0.000
> 6.58	z= 7.04	p = 0.000
not reported	z= 4.49	p = 0.000
Overall	z= 14.22	p = 0.000

50% Pain Reduction - Placebo Group

Pregabalin vs Not Pregabalin



Test(s) of heterogeneity:

	Heterogeneity statistic	degrees of freedom	P	I-squared**	Tau-squared
Not Pregabalin	125.64	20	0.000	84.1%	0.0096
Pregabalin	88.22	18	0.000	79.6%	0.0062
Overall	214.13	39	0.000	81.8%	0.0076

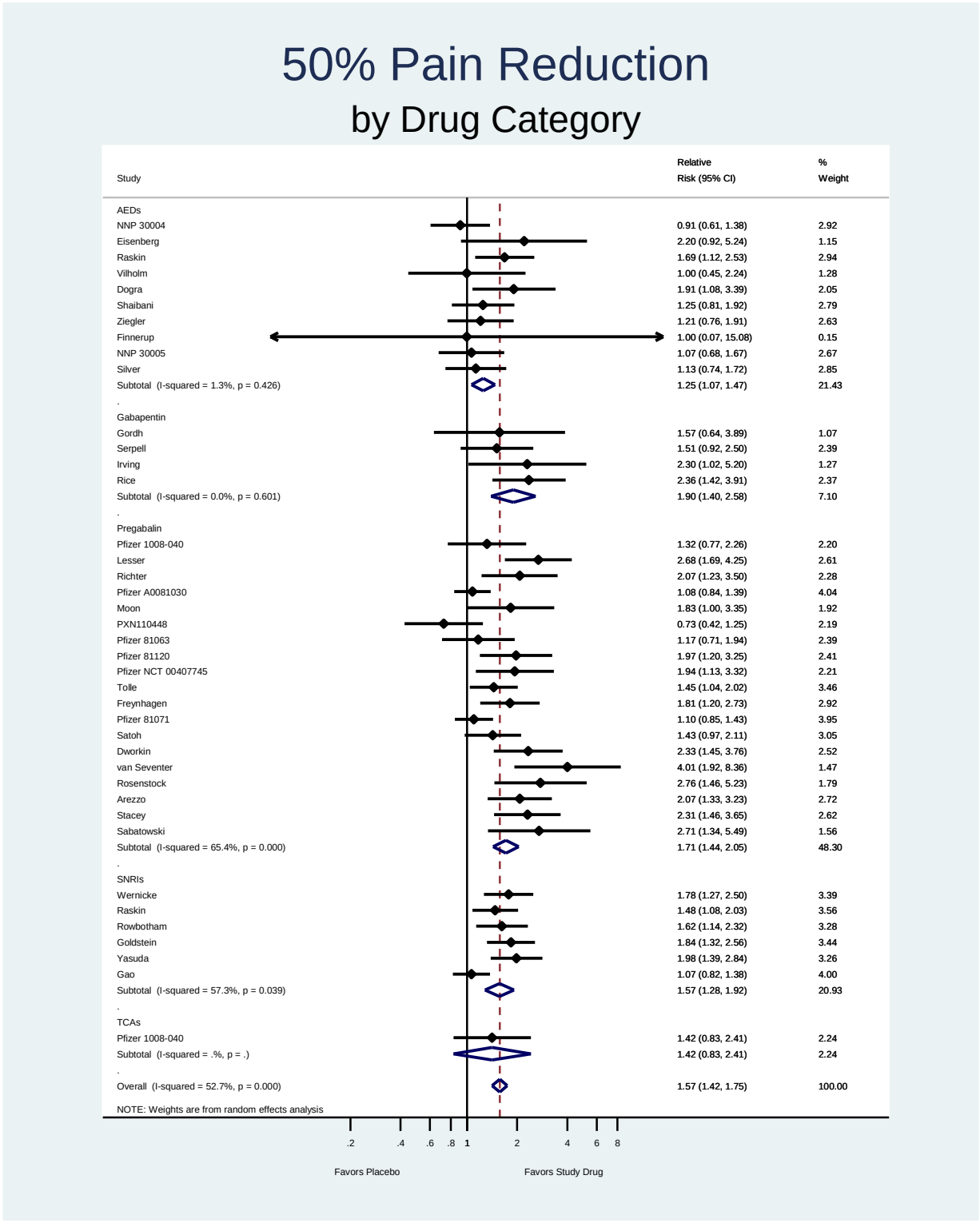
** I-squared: the variation in ES attributable to heterogeneity)

Note: between group heterogeneity not calculated;
only valid with inverse variance method

Significance test(s) of ES=1

Not Pregabalin	z= 9.70	p = 0.000
Pregabalin	z= 10.28	p = 0.000
Overall	z= 14.22	p = 0.000

Appendix B. Forest Plots and Heterogeneity Statistics for 50 Percent Pain Reduction (Relative Risk)



Test(s) of heterogeneity:

	Heterogeneity statistic	degrees of freedom	P	I-squared**	Tau-squared
AEDs	9.12	9	0.426	1.3%	0.0009
Gabapentin	1.86	3	0.601	0.0%	0.0000
Pregabalin	52.07	18	0.000	65.4%	0.0945
SNRIs	11.72	5	0.039	57.3%	0.0363
TCAs	0.00	0	.	.%	0.0000
Overall	82.39	39	0.000	52.7%	0.0550

** I-squared: the variation in ES attributable to heterogeneity)

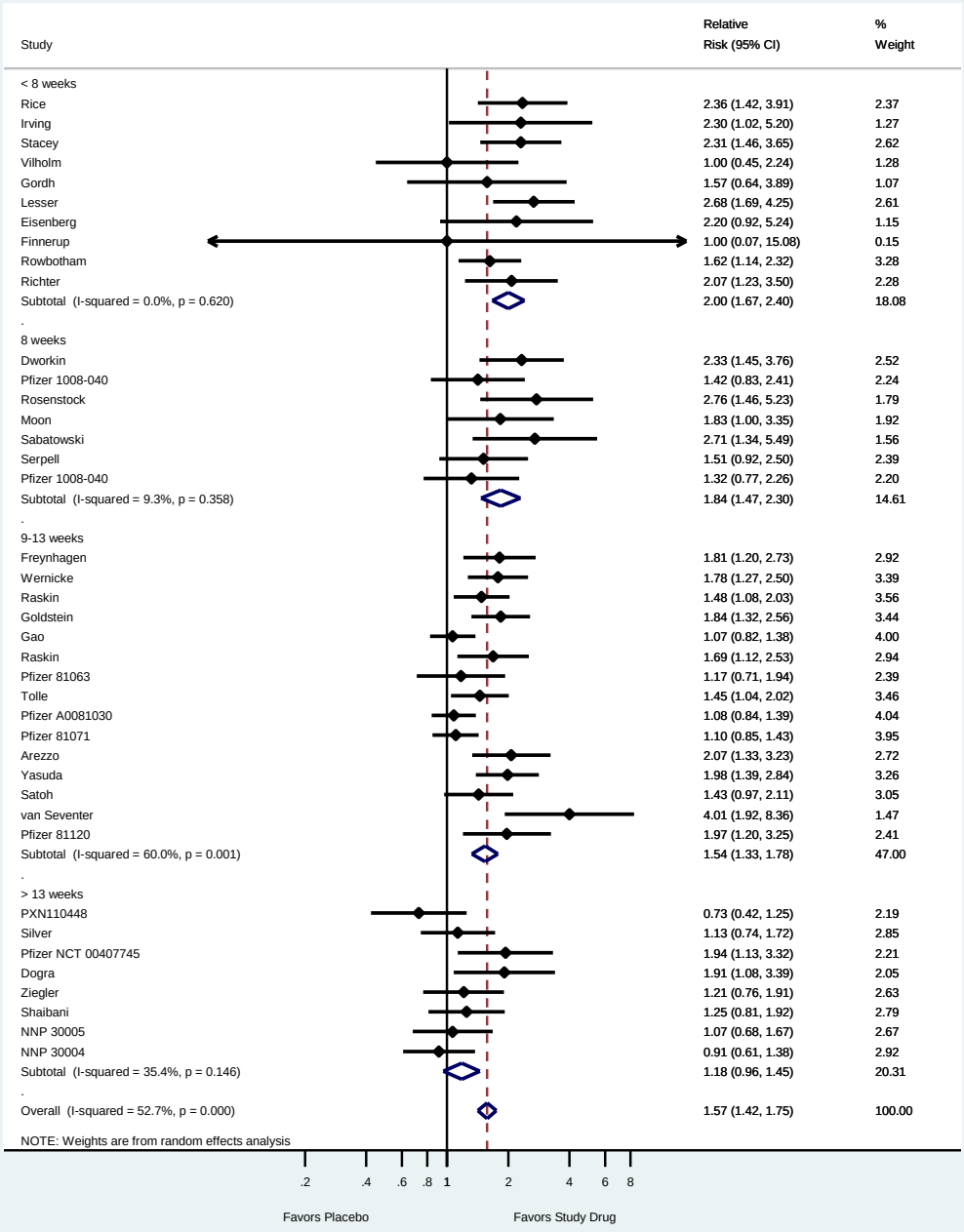
Note: between group heterogeneity not calculated;
only valid with inverse variance method

Significance test(s) of ES=1

AEDs	z= 2.73	p = 0.006
Gabapentin	z= 4.10	p = 0.000
Pregabalin	z= 5.97	p = 0.000
SNRIs	z= 4.36	p = 0.000
TCAs	z= 1.28	p = 0.199
Overall	z= 8.44	p = 0.000

50% Pain Reduction

by Length of Treatment



Test(s) of heterogeneity:

	Heterogeneity statistic	degrees of freedom	P	I-squared**	Tau-squared
< 8 weeks	7.16	9	0.620	0.0%	0.0000
8 weeks	6.62	6	0.358	9.3%	0.0084
9-13 weeks	35.01	14	0.001	60.0%	0.0482
> 13 weeks	10.84	7	0.146	35.4%	0.0315
Overall	82.39	39	0.000	52.7%	0.0550

** I-squared: the variation in ES attributable to heterogeneity)

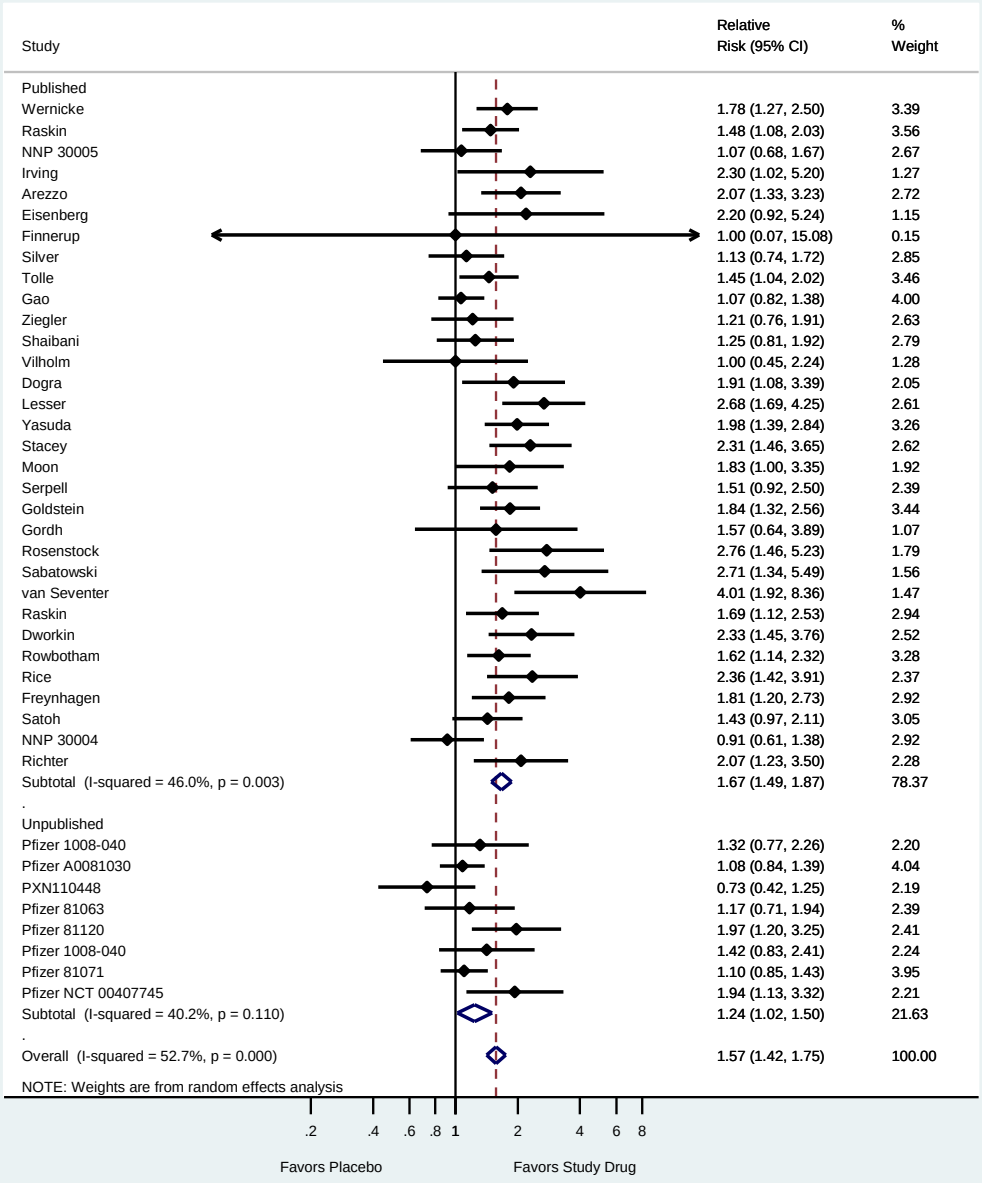
Note: between group heterogeneity not calculated;
only valid with inverse variance method

Significance test(s) of ES=1

< 8 weeks	z= 7.53	p = 0.000
8 weeks	z= 5.38	p = 0.000
9-13 weeks	z= 5.70	p = 0.000
> 13 weeks	z= 1.57	p = 0.116
Overall	z= 8.44	p = 0.000

50% Pain Reduction

by Publication Status



Test(s) of heterogeneity:

	Heterogeneity statistic	degrees of freedom	P	I-squared**	Tau-squared
Published	57.36	31	0.003	46.0%	0.0445
Unpublished	11.71	7	0.110	40.2%	0.0294
Overall	82.39	39	0.000	52.7%	0.0550

** I-squared: the variation in ES attributable to heterogeneity)

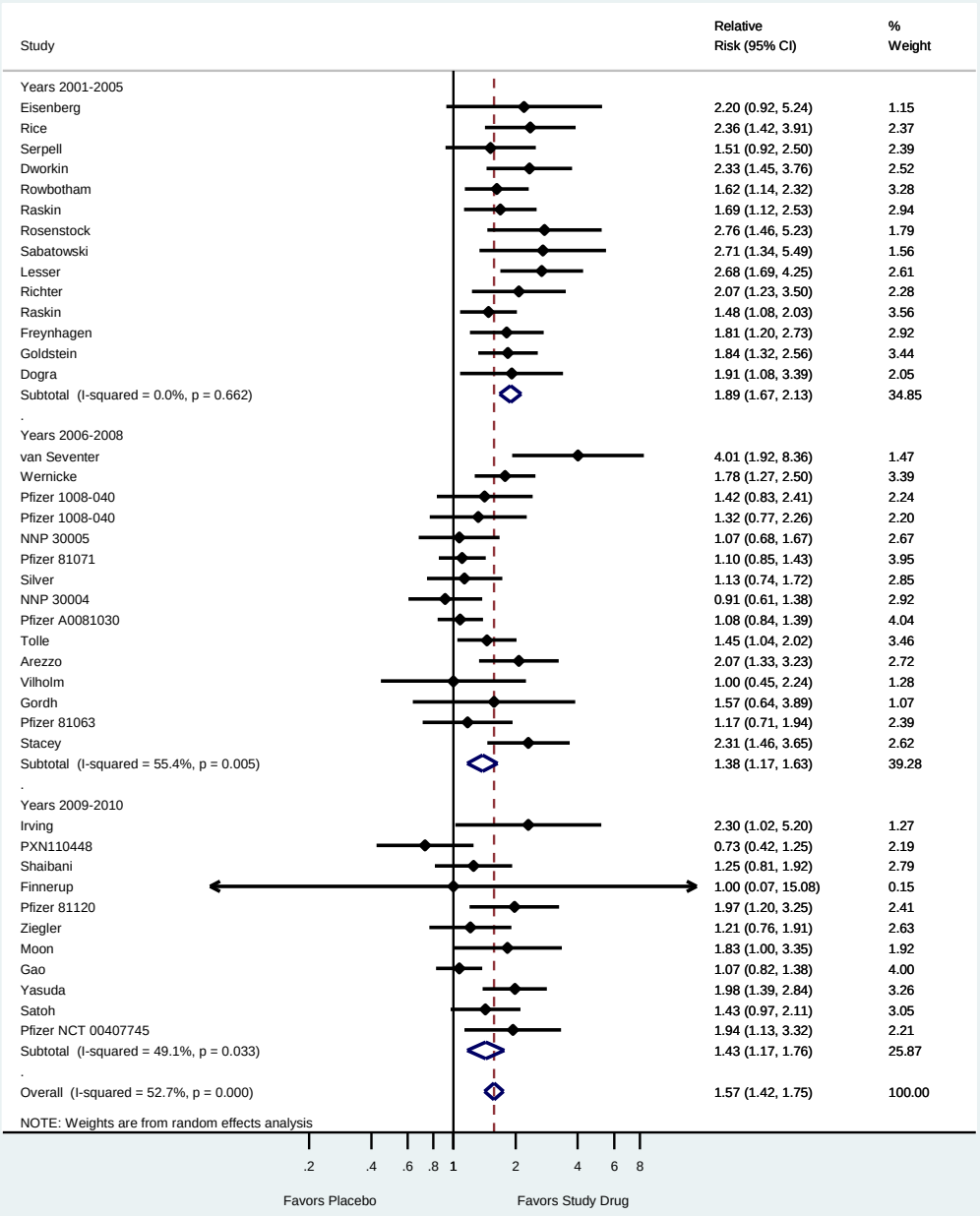
Note: between group heterogeneity not calculated;
only valid with inverse variance method

Significance test(s) of ES=1

Published	z= 8.91	p = 0.000
Unpublished	z= 2.16	p = 0.030
Overall	z= 8.44	p = 0.000

50% Pain Reduction

by Year of Publication/Completion



Test(s) of heterogeneity:

	Heterogeneity statistic	degrees of freedom	P	I-squared**	Tau-squared
Years 2006-2008	31.38	14	0.005	55.4%	0.0558
Years 2001-2005	10.39	13	0.662	0.0%	0.0000
Years 2009-2010	19.66	10	0.033	49.1%	0.0535
Overall	82.39	39	0.000	52.7%	0.0550

** I-squared: the variation in ES attributable to heterogeneity)

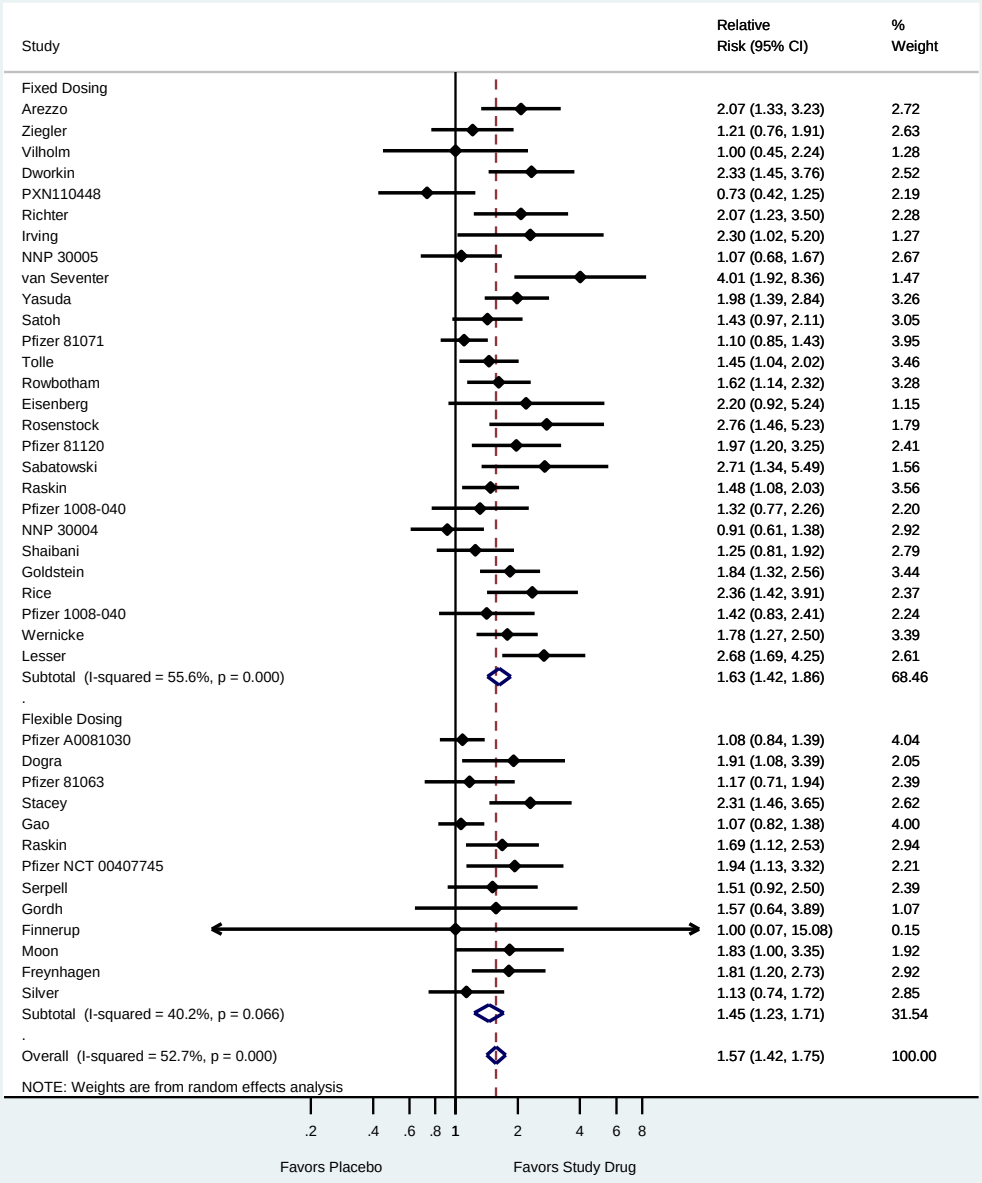
Note: between group heterogeneity not calculated;
only valid with inverse variance method

Significance test(s) of ES=1

Years 2006-2008	z= 3.75	p = 0.000
Years 2001-2005	z= 10.29	p = 0.000
Years 2009-2010	z= 3.43	p = 0.001
Overall	z= 8.44	p = 0.000

50% Pain Reduction

by Flexibility of Dosing



Test(s) of heterogeneity:

	Heterogeneity statistic	degrees of freedom	P	I-squared**	Tau-squared
Fixed Dosing	58.61	26	0.000	55.6%	0.0632
Flexible Dosing	20.08	12	0.066	40.2%	0.0336
Overall	82.39	39	0.000	52.7%	0.0550

** I-squared: the variation in ES attributable to heterogeneity)

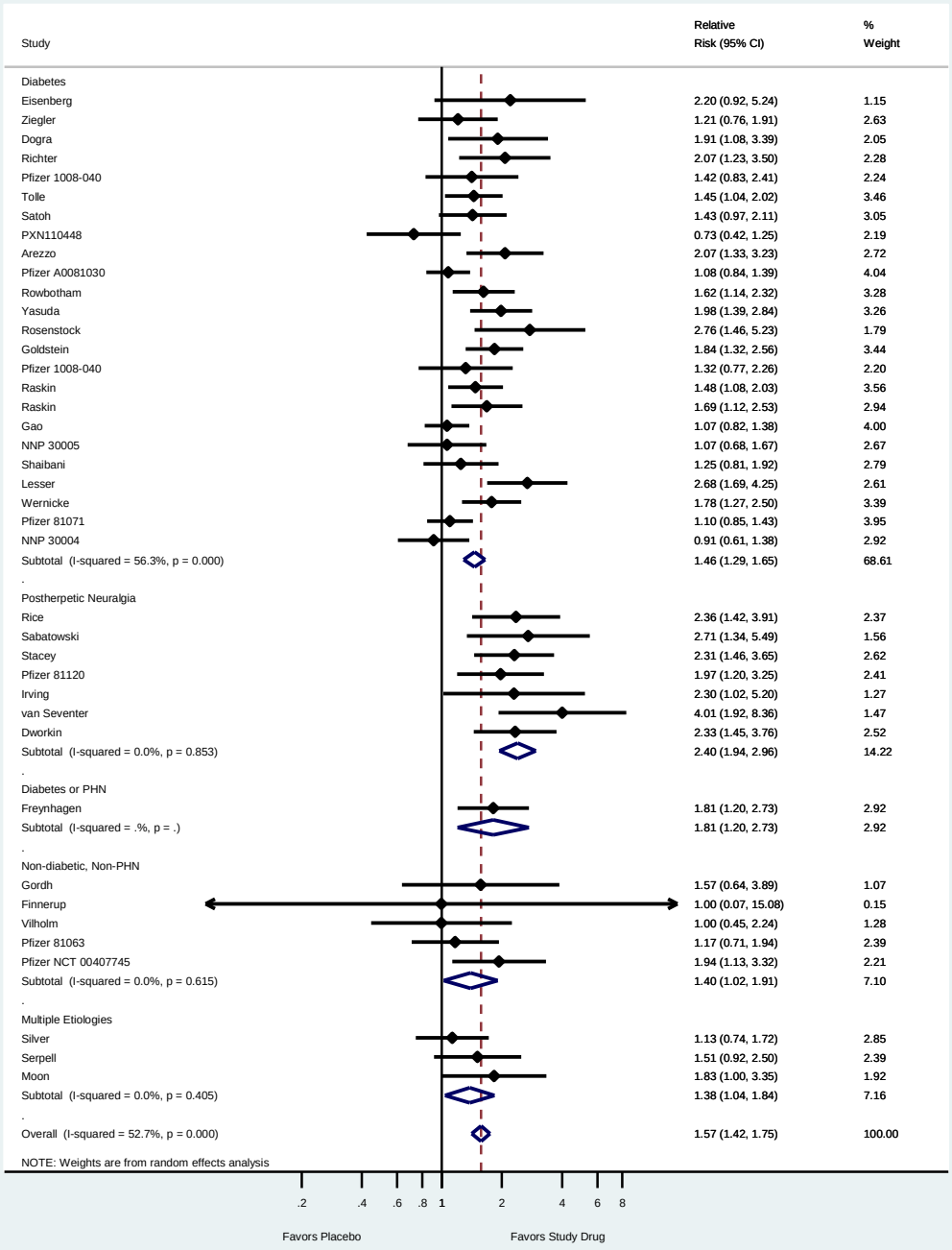
Note: between group heterogeneity not calculated;
only valid with inverse variance method

Significance test(s) of ES=1

Fixed Dosing	z= 7.21	p = 0.000
Flexible Dosing	z= 4.40	p = 0.000
Overall	z= 8.44	p = 0.000

59% Pain Reduction

by Etiology of Pain



Test(s) of heterogeneity:

	Heterogeneity statistic	degrees of freedom	P	I-squared**	Tau-squared
Diabetes	52.58	23	0.000	56.3%	0.0502
Postherpetic Neuralg	2.64	6	0.853	0.0%	0.0000
Diabetes or PHN	0.00	0	.	.%	0.0000
Non-diabetic, Non-PH	2.67	4	0.615	0.0%	0.0000
Multiple Etiologies	1.81	2	0.405	0.0%	0.0000
Overall	82.39	39	0.000	52.7%	0.0550

** I-squared: the variation in ES attributable to heterogeneity)

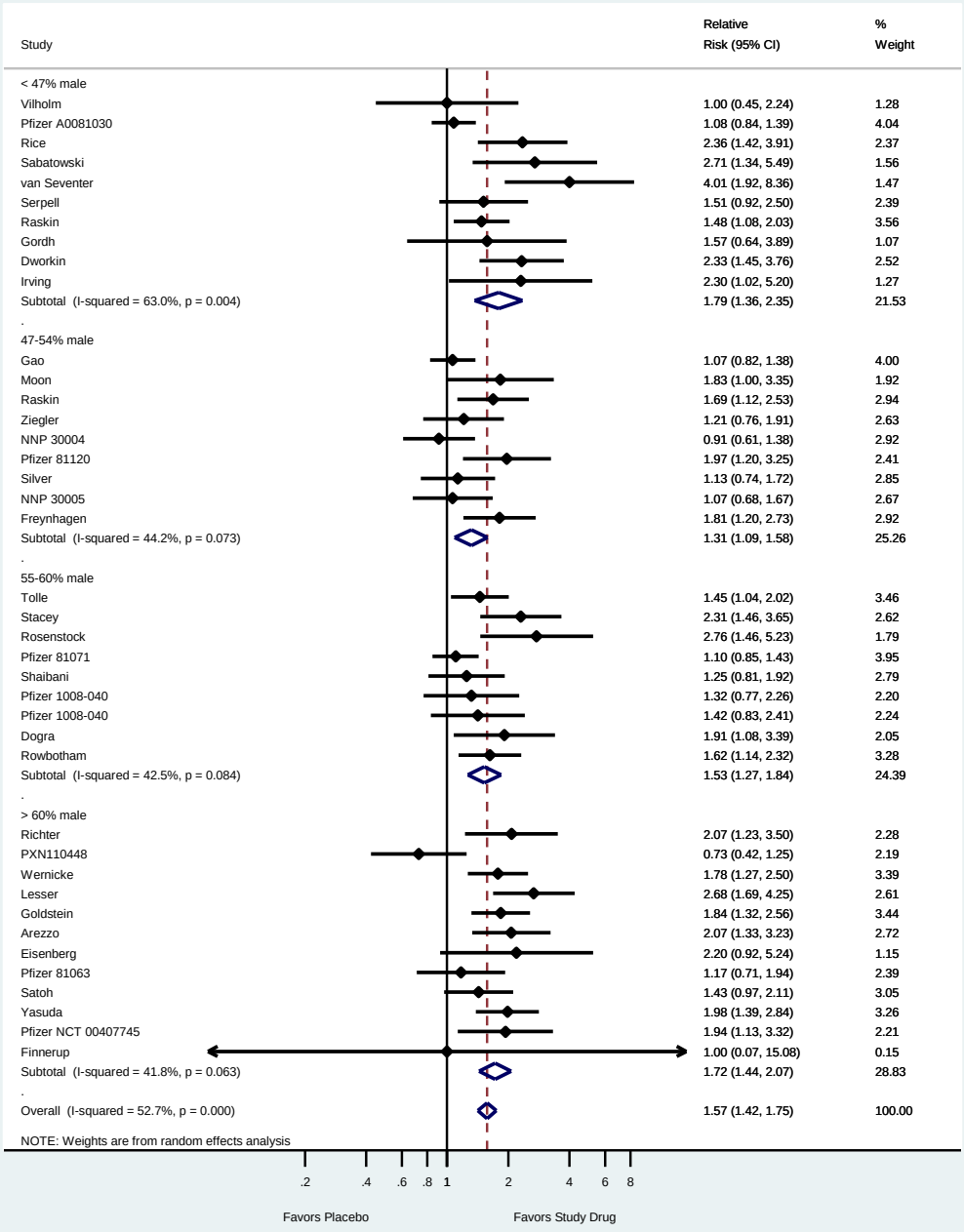
Note: between group heterogeneity not calculated;
only valid with inverse variance method

Significance test(s) of ES=1

Diabetes	z= 6.00	p = 0.000
Postherpetic Neuralg	z= 8.10	p = 0.000
Diabetes or PHN	z= 2.84	p = 0.005
Non-diabetic, Non-PH	z= 2.11	p = 0.035
Multiple Etiologies	z= 2.22	p = 0.026
Overall	z= 8.44	p = 0.000

50% Pain Reduction

by Percent Males



Test(s) of heterogeneity:

	Heterogeneity statistic	degrees of freedom	P	I-squared**	Tau-squared
< 47% male	24.36	9	0.004	63.0%	0.1074
47-54% male	14.33	8	0.073	44.2%	0.0349
55-60% male	13.91	8	0.084	42.5%	0.0335
> 60% male	18.90	11	0.063	41.8%	0.0400
Overall	82.39	39	0.000	52.7%	0.0550

** I-squared: the variation in ES attributable to heterogeneity)

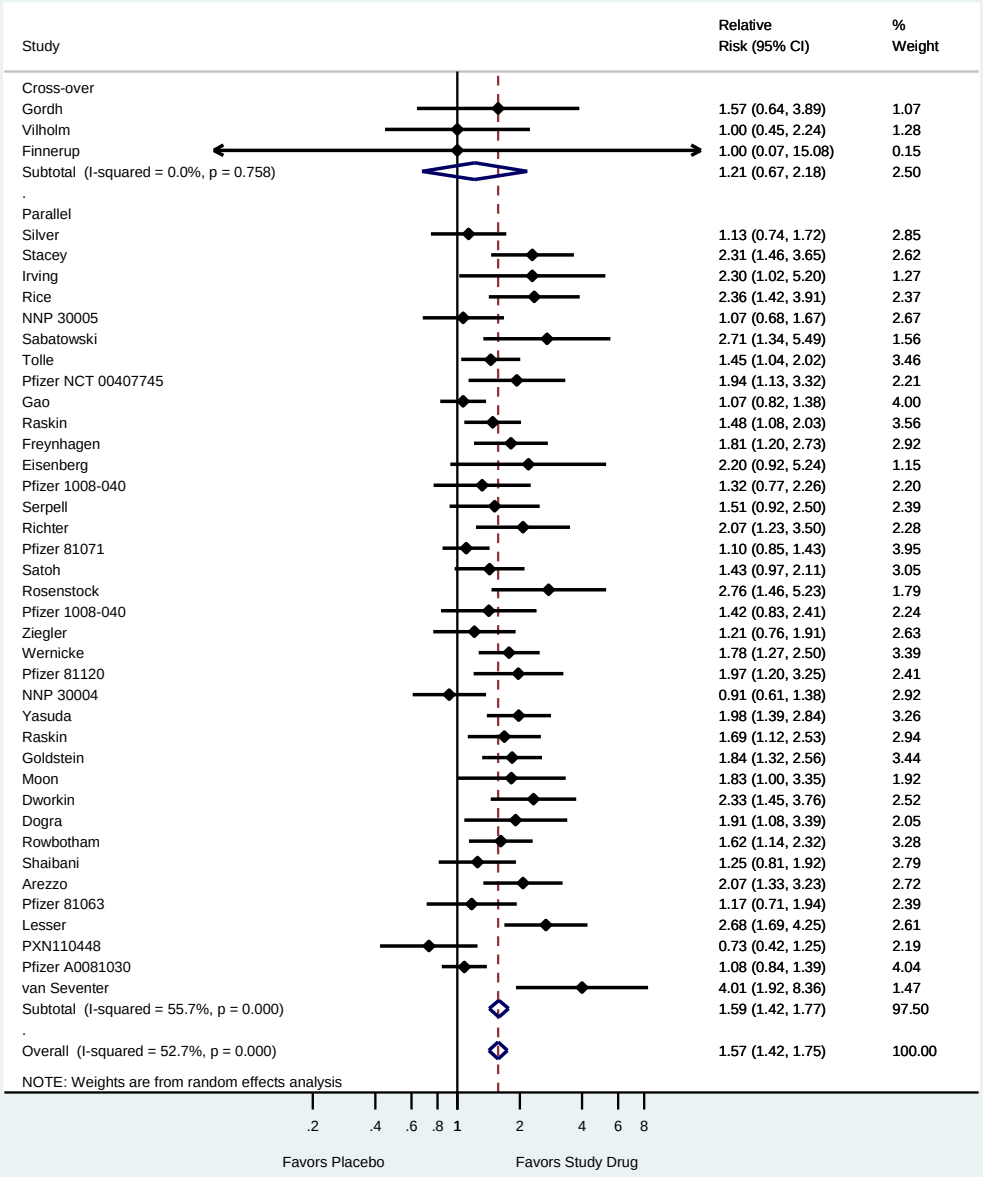
Note: between group heterogeneity not calculated;
only valid with inverse variance method

Significance test(s) of ES=1

< 47% male	z= 4.19	p = 0.000
47-54% male	z= 2.87	p = 0.004
55-60% male	z= 4.41	p = 0.000
> 60% male	z= 5.88	p = 0.000
Overall	z= 8.44	p = 0.000

50% Pain Reduction

by Study Design



Test(s) of heterogeneity:

	Heterogeneity statistic	degrees of freedom	P	I-squared**	Tau-squared
Cross-over	0.55	2	0.758	0.0%	0.0000
Parallel	81.33	36	0.000	55.7%	0.0583
Overall	82.39	39	0.000	52.7%	0.0550

** I-squared: the variation in ES attributable to heterogeneity)

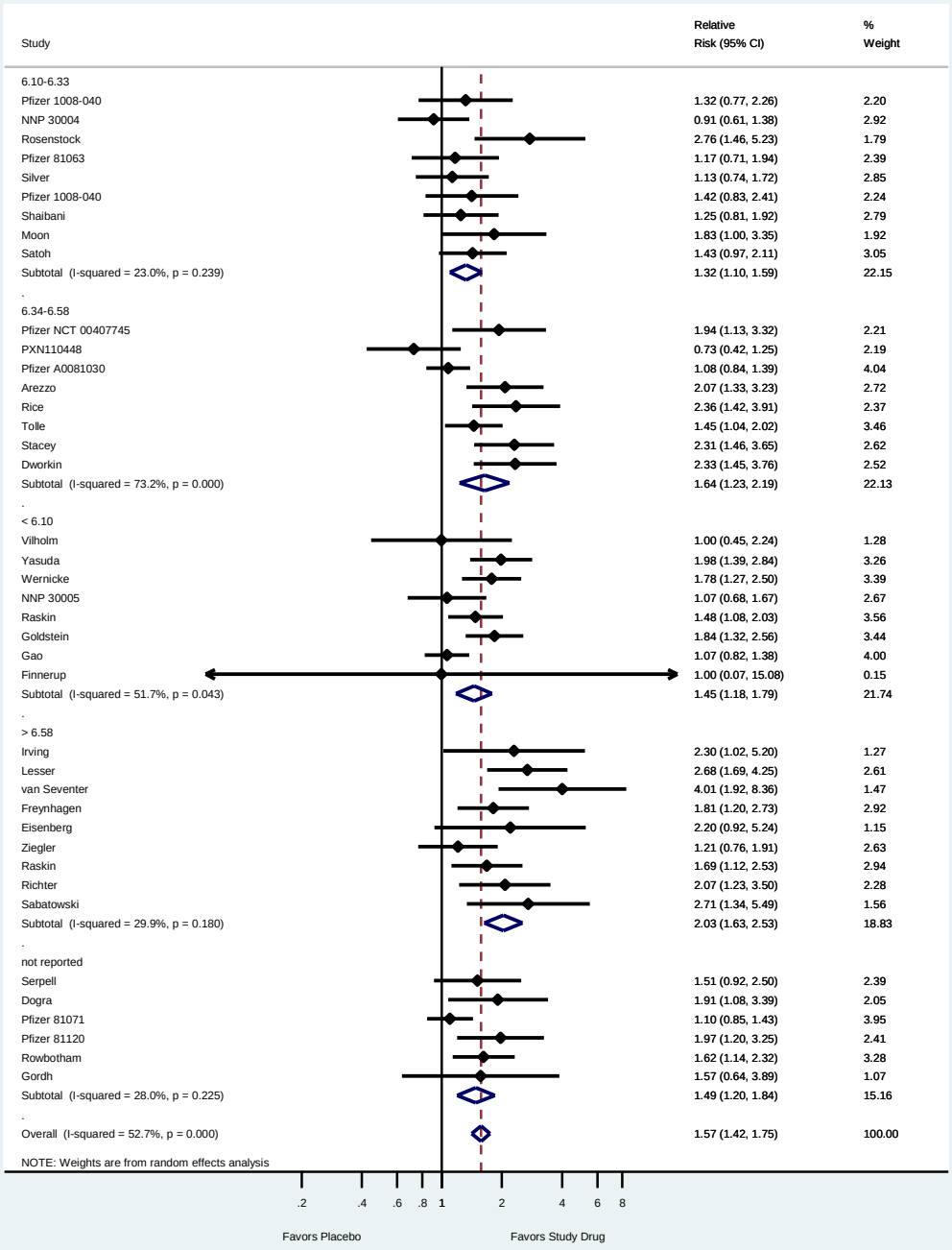
Note: between group heterogeneity not calculated;
only valid with inverse variance method

Significance test(s) of ES=1

Cross-over	z= 0.64	p = 0.525
Parallel	z= 8.34	p = 0.000
Overall	z= 8.44	p = 0.000

50% Pain Reduction

by Baseline Pain Level in Placebo Group



Test(s) of heterogeneity:

	Heterogeneity statistic	degrees of freedom	P	I-squared**	Tau-squared
6.10-6.33	10.39	8	0.239	23.0%	0.0179
6.34-6.58	26.09	7	0.000	73.2%	0.1207
< 6.10	14.49	7	0.043	51.7%	0.0413
> 6.58	11.41	8	0.180	29.9%	0.0324
not reported	6.94	5	0.225	28.0%	0.0198
Overall	82.39	39	0.000	52.7%	0.0550

** I-squared: the variation in ES attributable to heterogeneity)

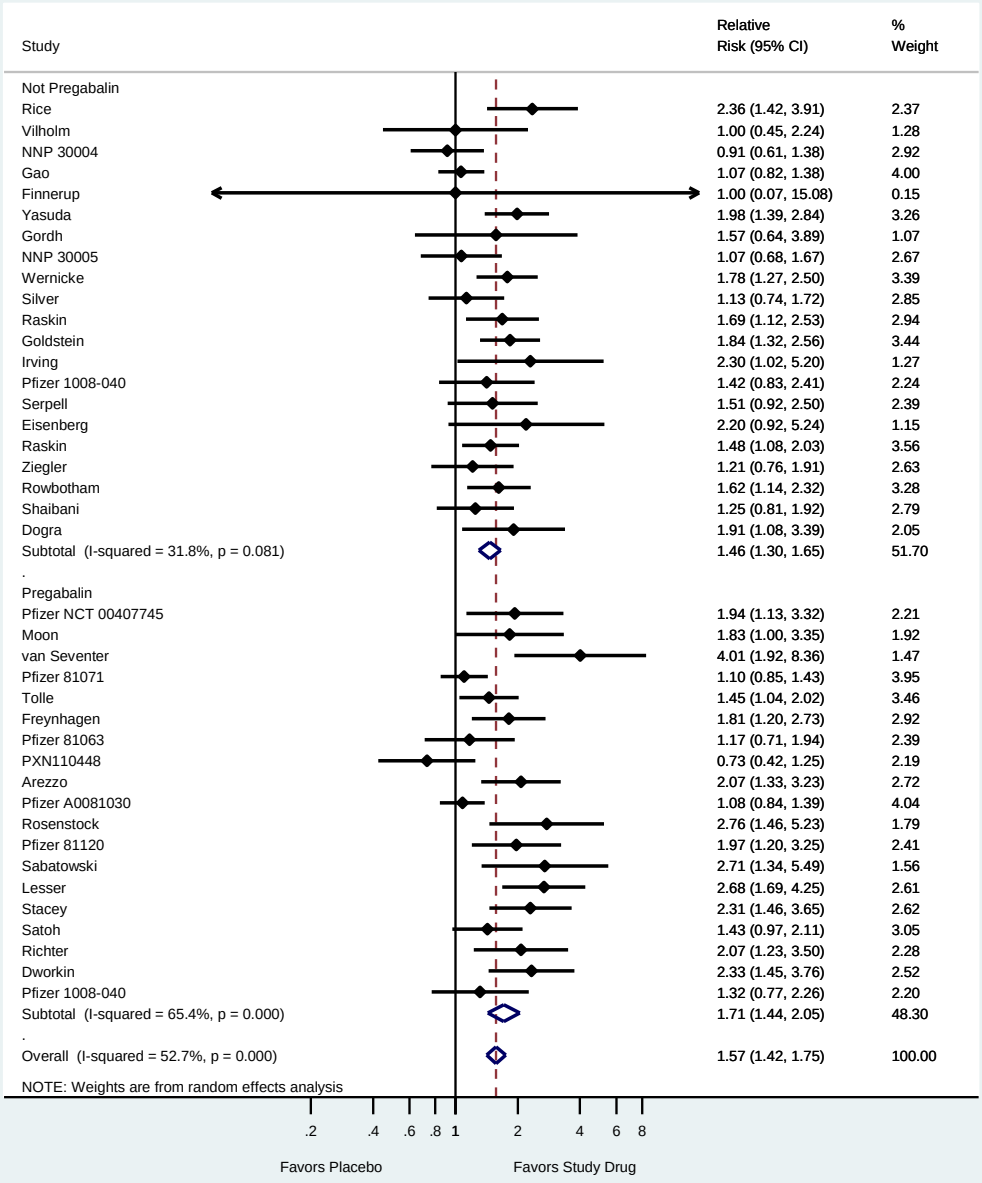
Note: between group heterogeneity not calculated;
only valid with inverse variance method

Significance test(s) of ES=1

6.10-6.33	z= 3.00	p = 0.003
6.34-6.58	z= 3.38	p = 0.001
< 6.10	z= 3.54	p = 0.000
> 6.58	z= 6.35	p = 0.000
not reported	z= 3.60	p = 0.000
Overall	z= 8.44	p = 0.000

50% Pain Reduction

Pregabalin vs Not Pregabalin



Test(s) of heterogeneity:

	Heterogeneity statistic	degrees of freedom	P	I-squared**	Tau-squared
Not Pregabalin	29.35	20	0.081	31.8%	0.0234
Pregabalin	52.07	18	0.000	65.4%	0.0945
Overall	82.39	39	0.000	52.7%	0.0550

** I-squared: the variation in ES attributable to heterogeneity)

Note: between group heterogeneity not calculated;
only valid with inverse variance method

Significance test(s) of ES=1

Not Pregabalin	z= 6.20	p = 0.000
Pregabalin	z= 5.97	p = 0.000
Overall	z= 8.44	p = 0.000

Appendix C. Predictor Variables for 30 Percent Pain Reduction and Their P-Values

Table C1. Predictor variables for 30 percent pain reduction

Variable	# of studies	p-value
Diagnosis	25	0.007
Study design	25	0.008
Enrolls only patients without PDN or PHN	25	0.011
Number of patients randomized	25	0.018
Enrolls only patients with PDN	25	0.035
Number of patients analyzed	25	0.063
Enrolls only patients with PHN	25	0.090
Baseline pain level in placebo group	22	0.114
Study conducted in western country(ies)	21	0.116
Length of treatment	25	0.132
Drug Category: 3 categories	25	0.178
Drug Category: 5 categories	25	0.188
Enrolls patients with a variety of pain etiologies	25	0.218
Average enrollment per month	19	0.289
Percent males in placebo group	25	0.357
Enrolls only patients with PDN or with PHN	25	0.373
Drug	25	0.378
Difference in % males in treatment & placebo groups	25	0.384
Length of treatment (maintenance period only)	25	0.398
Percent males in study	25	0.457
Study conducted in the U.S.	21	0.467
Year of publication or study completion (unpublished)	25	0.475
Average proportion achieving maximum study dose	18	0.477
Number of months study enrolled patients	19	0.580

Table C1. Predictor variables for 30 percent pain reduction (continued)

Variable	# of studies	p-value
Total study withdrawal rate	24	0.606
Withdrawal rate in placebo group	24	0.614
Duration of neuropathic pain	16	0.720
Withdrawal rate in treatment group	24	0.755
Mean age of study participants	25	0.799
Study has two treatment arms	25	0.884
Drug dosing flexibility	25	0.958

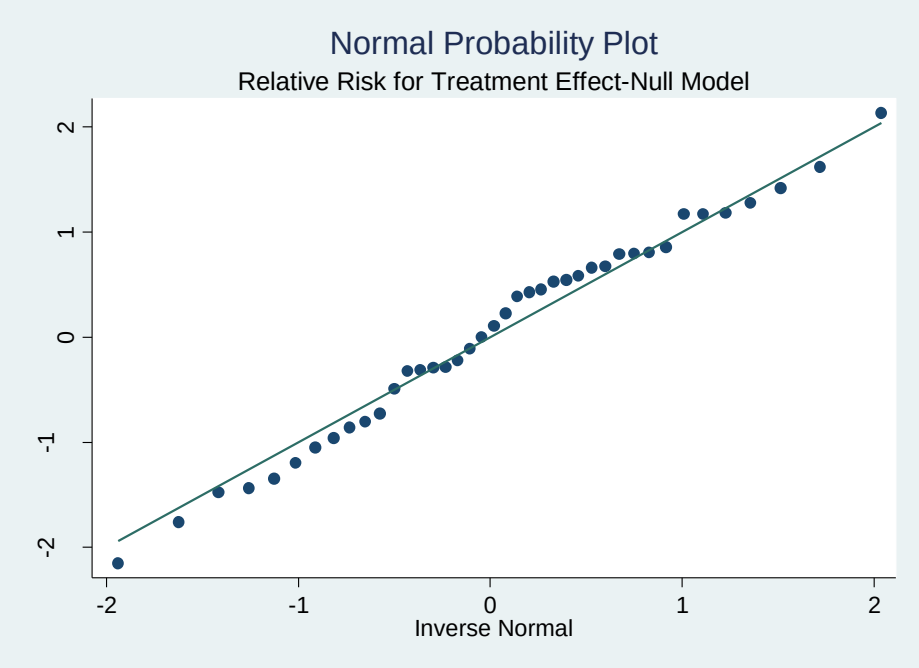
Table C2. Predictor variables for 30 percent pain reduction controlling for placebo response

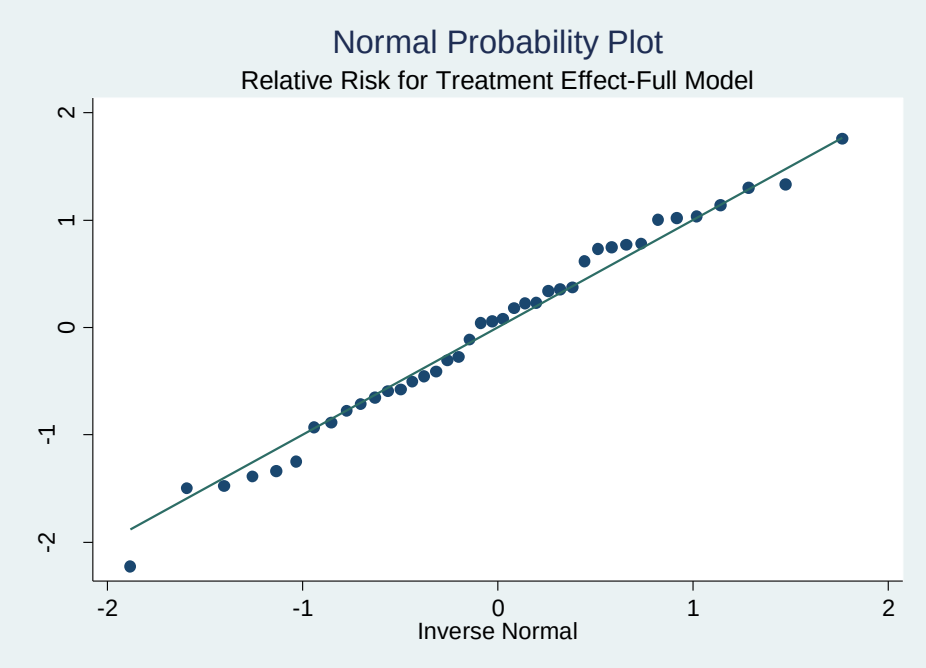
Variable	# of studies	p-value
Length of treatment	25	0.012
Enrolls only patients with PHN	25	0.017
Drug Category: 5 categories	25	0.078
Study conducted in the U.S.	21	0.083
Mean age of study participants	25	0.083
Drug Category: 3 categories	25	0.105
Diagnosis	25	0.123
Difference in % males in treatment & placebo groups	25	0.190
Drug	25	0.222
Average proportion achieving maximum study dose	18	0.283
Duration of neuropathic pain	16	0.305
Enrolls only patients with PDN	25	0.328
Length of treatment (maintenance period only)	25	0.338
Percent males in placebo group	25	0.350
Enrolls patients with a variety of pain etiologies	25	0.360
Year of publication or study completion (unpublished)	25	0.392
Enrolls only patients with PDN or with PHN	25	0.400
Withdrawal rate in placebo group	24	0.402
Study conducted in western country(ies)	21	0.413
Percent males in study	25	0.472
Drug dosing flexibility	25	0.472
Average enrollment per month	19	0.475
Enrolls only patients without PDN or PHN	25	0.483
Number of patients randomized	25	0.483
Withdrawal rate in treatment group	24	0.589

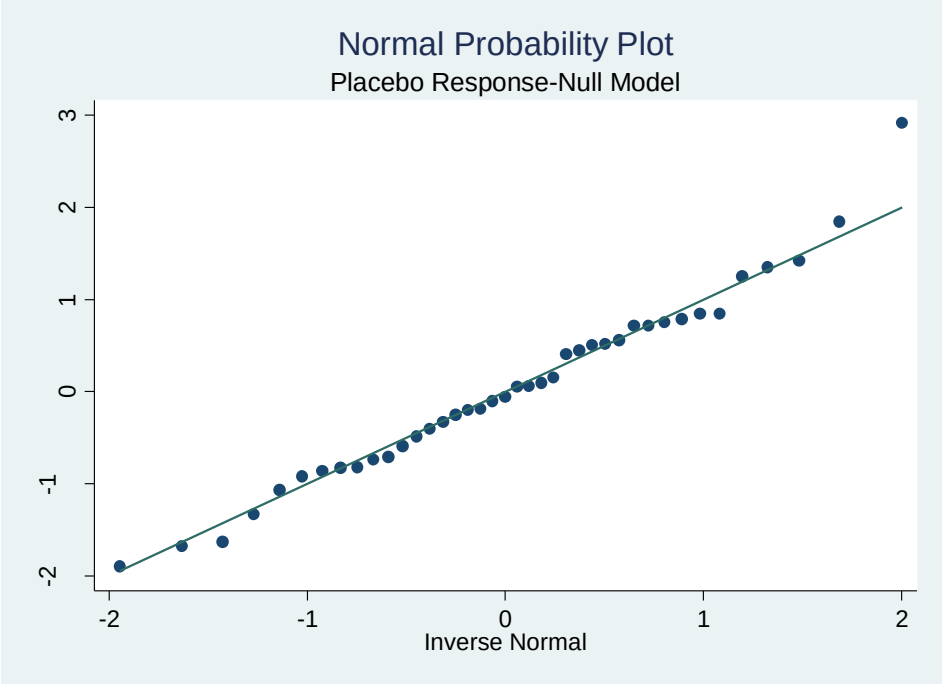
Table C2. Predictor variables for 30 percent pain reduction controlling for placebo response (continued)

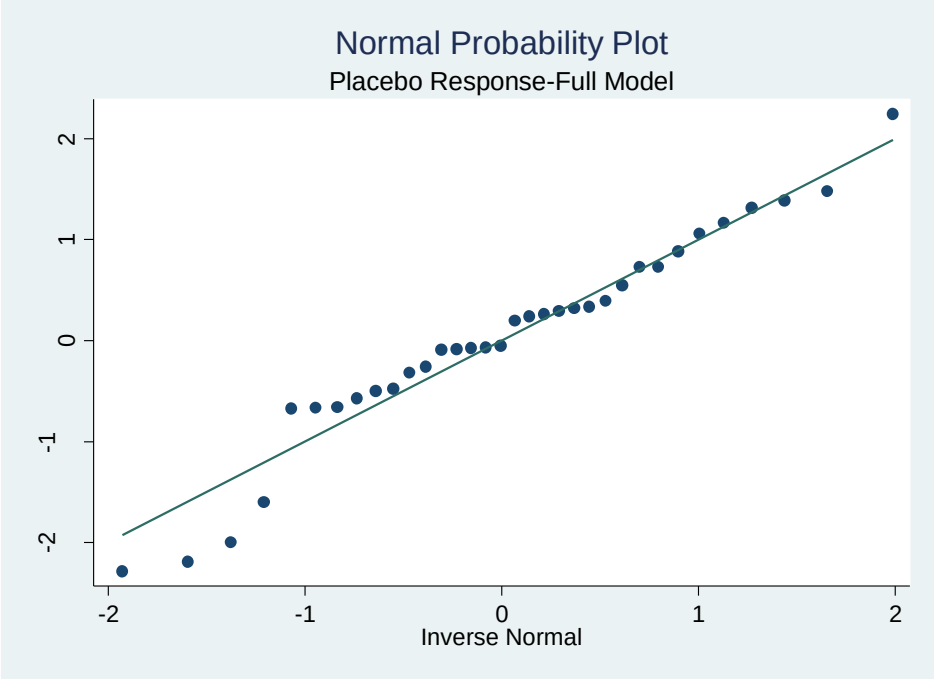
Variable	# of studies	p-value
Total study withdrawal rate	24	0.592
Number of patients analyzed	25	0.656
Number of months study enrolled patients	19	0.672
Study has two treatment arms	25	0.687
Baseline pain level in placebo group	22	0.708
Study design	25	0.813

Appendix D. Normal Probability Plots






Normal Probability Plot
Placebo Response-Null Model
3
2
1
0
-1
-2
-2
-1
0
1
2
Inverse Normal


Normal Probability Plot
Placebo Response-Full Model
2
1
0
-1
-2
-2
-1
0
1
2
Inverse Normal

Appendix E. Meta Trim and Fill Results and Metabias Test for Small Study Effects

```
metatrim logRR selogRR, eform

Note: default data input format (theta, se_theta) assumed.

Meta-analysis

       |  Pooled      95% CI         Asymptotic      No. of
Method |     Est   Lower   Upper  z_value  p_value   studies
-------+-----------------------------------------------------
Fixed  |   0.403   0.335   0.472   11.550    0.000     40
Random |   0.453   0.348   0.558    8.439    0.000

Test for heterogeneity: Q= 82.391 on 39 degrees of freedom (p= 0.000)
Moment-based estimate of between studies variance =  0.055

Trimming estimator: Linear
Meta-analysis type: Fixed-effects model

iteration |  estimate    Tn    # to trim     diff
----------+-----------------------------------
    1     |    0.403    500         5         820
    2     |    0.358    562         8         124
    3     |    0.331    594         9          64
    4     |    0.328    598        10           8
    5     |    0.320    607        10          18
    6     |    0.320    607        10           0

Filled
Meta-analysis (exponential form)

       |  Pooled      95% CI         Asymptotic      No. of
Method |     Est   Lower   Upper  z_value  p_value   studies
-------+-----------------------------------------------------
Fixed  |   1.376   1.291   1.468    9.778    0.000     50
Random |   1.397   1.250   1.560    5.915    0.000

Test for heterogeneity: Q= 131.246 on 49 degrees of freedom (p= 0.000)
Moment-based estimate of between studies variance =  0.091


. metabias logRR selogRR, egger

Note: data input format theta se_theta assumed.

Egger's test for small-study effects:
Regress standard normal deviate of intervention
effect estimate against its standard error

Number of studies =  40                                  Root MSE      =   1.347
------------------------------------------------------------------------------
     Std_Eff |      Coef.  Std. Err.     t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       slope |   .0355038   .1432237     0.25   0.806    -.2544374     .325445
        bias |   1.763459   .6482372     2.72   0.010      .451171    3.075746
------------------------------------------------------------------------------

Test of H0: no small-study effects          P = 0.010
```

Filled funnel plot with pseudo 95% confidence limits