Research Paper

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Increasing placebo responses over time in U.S. clinical trials of neuropathic pain

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Abstract

Recent failures of clinical trials of novel analgesics designed to treat neuropathic pain have led to much speculation about the underlying reasons. One often discussed possibility is that the placebo response in these trials has increased in recent years, leading to lower separation between the drug and placebo arms. Whether this has indeed occurred has not yet been adequately addressed. Here, we extracted data from published randomized controlled trials (RCTs) of drugs for the treatment of chronic neuropathic pain over the years 1990 to 2013. We find that placebo responses have increased considerably over this period, but drug responses have remained stable, leading to diminished treatment advantage. This trend has been driven by studies conducted in the United States. Consideration of participant and study characteristics revealed that in the United States but not elsewhere, RCTs have increased in study size and length. These changes are associated with larger placebo response. Analysis of individual RCT time courses showed different kinetics for the treatment vs placebo responses, with the former evolving more quickly than the latter and plateauing, such that maximum treatment advantage was achieved within 4 weeks.

Keywords: Neuropathic, Clinical trials, Placebo, Trends, Geography

1. Introduction

The development of new analgesics to treat neuropathic pain conditions met with early success with clinical trials of gabapentin.[4,29] However, more recent analgesic development efforts have been disappointing. Here, we investigate the possibility that trends in placebo response may be responsible for an increased incidence of failed neuropathic pain trials, as has been proposed.[10] Note that in this article, our use of the term "placebo response" follows colloquial usage and encompasses all factors related to (apparent) analgesia in the placebo arm of a clinical trial (ie, control group), including the placebo effect itself.[26] Nonspecific effects may include social support, attention, and education associated with clinical trials, spontaneous resolution of symptoms (ie, disease natural history), and regression to the mean.

A analysis of study characteristics in neuropathic pain trials identified the magnitude of the placebo response as the most significant factor affecting trial outcome.[16] Decreasing differential effects of drug vs placebo over time have been noted in clinical trials of antipsychotics,[19] antidepressants,[9,21] and statins.[14] This, of course, could be due either to increases in the placebo response itself and/or diminishing efficacy of new drugs. Similar analyses of randomized controlled trials (RCTs) of antipsychotic[1,17,30,32] and antidepressant[6,9,21,28,36] drugs have shown statistically significant increases in placebo response over time.

This study examined whether the placebo responses in neuropathic pain RCTs have increased over the years, and also investigated patient and study characteristics associated with placebo response magnitude. To our knowledge, only 5 studies have considered year of publication as a factor affecting placebo responses in chronic pain RCTs, with 1 reporting increases over time,[15] 1 reporting decreases over time,[23] and 3 articles finding no change.[16,27,35] In addition, we provide a more detailed analysis than existing studies by coding mean pain ratings at all study time points, extracted from tables and graphs presented in published articles, allowing an examination of the time course of placebo and treatment responses.

2. Materials and methods

A search of the MEDLINE, EMBASE, and Cochrane Library databases was conducted on February 17, 2014, with search terms "neuropathic pain AND drug" and the filter term "clinical trial." This search yielded 1899 potential studies (including duplicates) with publication dates before 2014. This list was supplemented with articles featured in a similar previous analysis.[16] The abstracts and texts of all articles were vetted initially by one author (G.J.B.) for adherence to the following inclusion criteria:

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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(1) reported in English;
(2) a randomized, double-blind controlled trial (RCT) design of at least 7 days duration (including a baseline pain measure and a minimum of 1 additional measure ≥7 days after baseline) with
(a) at least 1 inert (placebo) comparator group;
(b) primary outcome was pain intensity as measured by an 11-point numerical rating scale (NRS) or visual analogue scale (VAS);
(c) patients with specific neuropathic conditions: brachial plexus avulsion, cancer-associated neuropathic pain, chemotherapy-induced peripheral neuropathy, chronic low back pain with a neuropathic component, central (poststroke) pain, complex regional pain syndrome (CRPS type I), Guillain–Barré syndrome, HIV-associated neuropathic pain, painful diabetic peripheral neuropathy (PDN), postherpetic neuralgia (PHN), posttraumatic neuralgia (CRPS type II), small fiber neuropathy, or RCTs with mixed neuropathic pain patients with diagnoses including the above; and
(d) published between 1980 and 2013 (we discovered only 1 trial otherwise meeting eligibility outside that range).[38]

Excluded were studies with the following properties:
(1) studies in which the only comparator group(s) received an "active placebo," including a low (presumably nonanalgesic) dose of the treatment being investigated, or if the only comparator group received a known analgesic (ie, superiority trials);
(2) studies with enriched enrollment designs or n = 1 designs;
(3) studies reporting median (vs mean) pain values, or least square means. For studies with 2-way crossover designs, we examined only the data from the first half of the trial (3-way crossover designs were excluded);
(4) studies featuring intrathecal, topical, or transdermal administration; and
(5) studies examining effects in patients with any type of headache (thus excluding migraine as a neuropathic condition) and trigeminal neuralgia.

See **Figure 1** for a PRISMA flow diagram of inclusion and exclusion of articles.

For our secondary aim of examining individual time course curves, a separate inclusion criterion was the presence of at least 3 postbaseline measures.

2.2. Data extraction

Data were extracted by one of the authors (S.T.). Ambiguities were resolved by consensus amongst a subcommittee of the authors (A.H.T., S.T., G.J.B., and J.S.M.).

Baseline and end-of-treatment mean pain ratings were always given in the article's text or primary outcome graph, but mean pain ratings at intermediate time points were usually only presented graphically. Because we were also interested in the temporal profile of placebo and drug response, we extracted means at every study time point using the data extraction software, xyscan (New Haven, CT). We examined the correspondence between graphical and text representation of mean baseline and endpoint ratings in a subsample of 26 articles. The correlation between reported and graphically extracted values was highly significant ($r = 0.99$).

For each included trial, data were recorded for the following variables, where reported: (1) first author, (2) year of publication, (3) clinical condition, (4) pain scale (NRS or VAS), (5) trial design (parallel or crossover), (6) drug(s), (7) trial length in weeks, (8) trial size (ie, number of participants randomized to the placebo group), (9) geographic region (North America, Europe, or Asia), (10) number of trial sites, (11) number of trial arms, (12) mean duration of participants' pain at entry, (13) mean participant age, (14) participant sex ratios, (15) participant race ratios, and (16) methodology to deal with missing data. These variables represent all trial information available from at least 50% of the articles. Of 37 trials performed in North America, 35 were performed exclusively in the United States, 1 exclusively in Canada, 1 in both the United States and Canada, and none in Mexico. Thus, North American trials are referred to henceforth as U.S. trials.

The major dependent measure of our analyses was the change in pain ratings from baseline to end of treatment, expressed in percentage terms compared with the baseline value. Visual

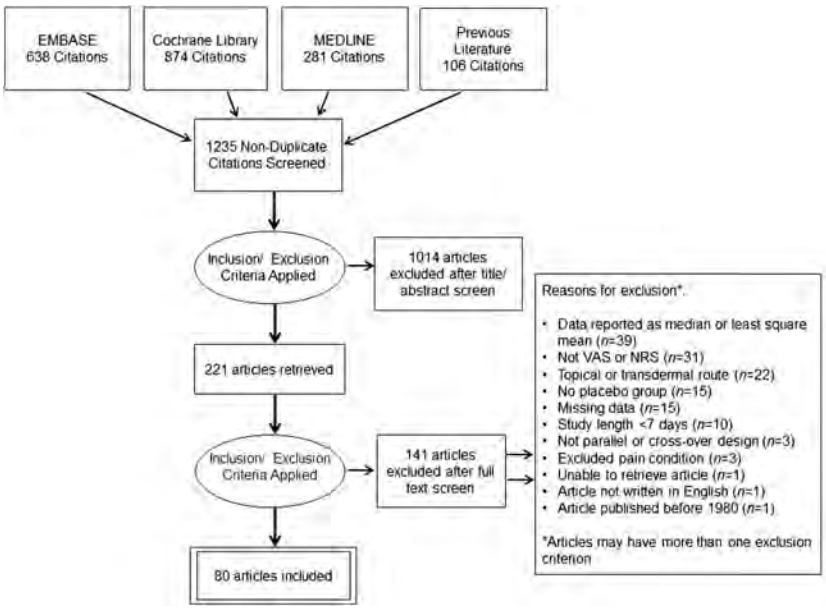

Figure 1. PRISMA flow diagram.

analogue scale scores reported from 0 to 100 were converted to 0 to 10. Analyses performed on absolute (untransformed) ratings change scores and slope data yielded virtually equivalent results (not shown).

Trials were categorized as successful if at least 1 drug or drug dose featured a statistically significant ($P < 0.05$) difference from the placebo control group at the end of treatment in the primary outcome measure.

2.3. Statistical analyses

A criterion $\alpha = 0.05$ was adopted for all analyses. Differences between groups were evaluated using Student *t* test or analysis of variance as appropriate, followed by Tukey Honestly Significant Difference post hoc test. Simple linear trends were investigated using linear regression; significance was established by comparing slopes to zero by F test. Because all dependent measures were normally distributed, univariate correlations were calculated using Pearson *r* statistic. Multivariable regression model selection used backwards selection with variables dropped if $P > 0.05$. Interaction terms were dropped first until all remaining interactions were statistically significant, followed by first-order terms dropped until all were statistically significant.

Because the main dependent measure here was a single outcome, the placebo response itself, and sample size was an independent variable in our analyses, meta-analytic statistical approaches were not appropriate. This study was intended as exploratory in nature, without a prespecified analysis protocol, and as such both Bonferroni-corrected and uncorrected significance levels are provided.

3. Results

Our search yielded 84 individual clinical trials in neuropathic pain patients (contained in 80 articles published from 1990 to 2013), in which 92 different drugs were compared with placebo. These trials and their characteristics are listed in **Table 1**. Full reference information of these articles is provided as Supplementary Table 1 (available online as Supplemental Digital Content at http://links.lww.com/PAIN/A155).

3.1. Drug and placebo responses over time

Baseline pain ratings of patients randomized to the placebo condition in the 84 neuropathic pain trials in our analysis were in a fairly restricted range (3.6-8.4; mean: 6.4; SD: 0.9). Baseline pain ratings did not change over the 23-year period examined (slope compared with zero: $F_{1,82} = 0.004$, $P = 0.95$) (**Fig. 2A**).

For the whole 23-year period, the average placebo response in these studies—defined as the percentage decrease in pain ratings from baseline to the reported end of treatment in the control arm—was an 18.3% decrease in ratings compared with baseline (95% confidence interval [CI]: 15.2%-21.4%) over the whole period. The magnitude of the placebo response increased significantly over time ($F_{1,82} = 9.6$, $P = 0.002$) (**Fig. 2B**).

Drug responses—defined as the percentage decrease in pain ratings from baseline to the end of treatment in the drug arm—averaged a 34.7% decrease from baseline (95% CI: 31.2%-38.2%) and were stable over time ($F_{1,90} = 0.2$, $P = 0.67$) (**Fig. 2C**).

On average, drugs produced 16.5% more analgesia than placebo (95% CI: 13.4%-19.6%), the equivalent of approximately 1.0 point (on an 11-point scale) better than placebo assuming a starting pain rating of 6.4; this treatment advantage decreased significantly over time ($F_{1,90} = 14.3$, $P = 0.0003$), such that by 2013, drugs produced only 8.9% more analgesia than placebo compared with 27.3% in 1996 (**Fig. 2D**).

3.2. Effects of study characteristics—categorical variables

Effects of categorical study characteristics on placebo response, drug response, and treatment advantage are shown in **Table 2**. Of the 92 drug responses tested in these RCTs, 62% were statistically superior to placebo. Whether the trial succeeded or failed was not associated with the size of the placebo response ($t_{82} = 0.4$, $P = 0.72$), although obviously drug responses ($t_{90} = 4.8$, Bonferroni-corrected $P < 0.001$) and treatment advantage ($t_{90} = 6.4$, Bonferroni-corrected $P < 0.001$) were significantly higher in positive trials.

Over the entire period taken as a whole, geographical region did not affect placebo response ($F_{2,67} = 0.3$, $P = 0.76$) or treatment advantage ($F_{2,75} = 2.4$, $P = 0.10$), but strongly affected drug responses ($F_{2,75} = 5.6$, $P = 0.005$; Bonferroni-corrected $P = 0.03$), with trials conducted in Asia showing stronger drug responses compared with those in the United States (Tukey $P = 0.02$) or Europe (Tukey $P = 0.005$).

The use of NRS over VAS showed nominally (ie, uncorrected for multiple comparisons) significantly larger placebo responses ($t_{82} = 2.1$, $P = 0.04$); scale use did not significantly affect drug responses ($t_{90} = 1.7$, $P = 0.09$) or treatment advantage ($t_{90} = 1.3$, $P = 0.20$).

Parallel designs showed nominally larger placebo responses compared with crossover designs ($t_{82} = 2.2$, $P = 0.03$), but design did not affect drug responses ($t_{90} = 0.4$, $P = 0.72$); as a result, crossover designs showed nominally higher treatment advantage ($t_{90} = 2.2$, $P = 0.03$). The use of fixed vs escalating dose schedules had no impact on placebo response, drug response, or treatment advantage (data not shown).

Patients with PDN exhibited nominally higher placebo responses than patients with PHN ($t_{44} = 2.3$, $P = 0.03$) as has been previously reported,[7,11] but no significant differences were observed in drug responses ($t_{48} = 0.9$, $P = 0.34$) or treatment advantage ($t_{48} = 1.1$, $P = 0.29$).

Whether last observation carried forward (LOCF) imputation or intent-to-treat (ITT) analysis was used to handle missing outcome data did not affect placebo responses ($t_{52} = 0.2$, $P = 0.83$), drug responses ($t_{54} = 0.6$, $P = 0.64$), or treatment advantage ($t_{54} = 1.3$, $P = 0.19$).

Placebo response sizes were not obviously affected by drug class ($F_{14,69} = 1.1$, $P = 0.40$), and neither were drug responses ($F_{15,76} = 1.6$, $P = 0.11$) or treatment advantage ($F_{15,76} = 1.1$, $P = 0.33$) (see Supplementary Fig. 1, available online as Supplemental Digital Content at http://links.lww.com/PAIN/A156).

Analysis of these factors' effects on placebo response over time revealed some interesting linear trends. Placebo response size has remained constant over time in positive (ie, with a statistically significant treatment advantage) trials ($F_{1,52} = 1.5$, $P = 0.24$), but has significantly increased over time in negative trials ($F_{1,28} = 12.7$, $P = 0.001$). Although all tended to increase over time, no significant trends over time were observed in trials using VAS ($F_{1,38} = 2.8$, $P = 0.10$) or NRS ($F_{1,42} = 3.5$, $P = 0.07$) or in crossover design trials ($F_{1,19} = 3.3$, $P = 0.08$). Parallel design trials showed a nominally significant increase in placebo responses over time ($F_{1,61} = 5.2$, $P = 0.03$). No significant trends over time were observed in either PDN ($F_{1,30} = 2.6$, $P = 0.11$) or PHN ($F_{1,12} = 0.02$, $P = 0.88$) trials. Trials using the LOCF method showed a nominally significant increase in placebo response size over time ($F_{1,24} = 4.5$, $P = 0.04$); trials using ITT did not ($F_{1,33} = 0.4$, $P = 0.53$).

Table 1

Characteristics of the 84 clinical trials analyzed.

Year	First author	Disease	Drug	Region	Success?
1990	Panerai AE	CP	CMI, nortryptiline	Europe	Yes
1996	Chiou-Tan FY	SCI	Mexiletine	USA	No
1997	Oskarsson P	PDN	Mexiletine	Europe	Yes
1997	Wright JM	PDN	Mexiletine	USA	No
1998	Backonja M	PDN	GBP	USA	Yes
1998	Eisenberg E	PHN	Memantine	Other	No
1998	Ertas M	PDN	Levodopa	Asia	Yes
1998	Kemper C	HIV	Mexiletine	USA	No
1998	Rowbotham M	PHN	GBP	USA	Yes
1999	McCleane G	Mixed	Lamotrigine	Europe	No
2000	Galer BS	Mixed	Riluzole (2 trials)	USA	No
2000	Wallace MS	Mixed	Mexiletine	USA	No
2001	Eisenberg E	PDN	Lamotrigine	Other	Yes
2001	Rice AS	PHN	GBP	Europe	Yes
2001	Semenchuk MR	Other	Bupropion SR	USA	Yes
2001	Simpson DA	PDN	GBP	USA	Yes
2002	Bone M	PLP	GBP	Europe	Yes
2002	Pandey CK	Guillain–Barré	GBP	Asia	Yes
2002	Raja SN	PHN	MOR + nortryptaline	USA	Yes
2002	Serpell MG	Mixed	GBP	Europe	Yes
2002	Wallace MS	Mixed	GV196771	USA	No
2002	Wallace MS	Mixed	4030W92	USA	No
2003	Boureau F	PHN	Tramadol	Europe	Yes
2003	Karst M	Mixed	CT3	Europe	Yes
2003	Watson CP	PDN	CR oxycodone	USA	Yes
2004	Berman JS	BPA	GW 1000 02	Europe	No
2004	Caraceni A	Cancer	GBP	Europe	Yes
2004	Kochar DK	PDN	SV	Asia	Yes
2004	Raskin P	PDN	Topiramate	USA	Yes
2004	Rosenstock J	PDN	PGB	USA	Yes
2004	Thienel U	PDN	Topiramate (3 trials)	USA	Yes
2004	van de Vusse AC	CRPS	GBP	Europe	Yes
2005	Atli A	PDN	Zonisamide	USA	Yes
2005	Dogra S	PDN	Oxcarbazepine	USA	Yes
2005	Goldstein DJ	PDN	Duloxetine	USA	Yes
2005	Kochar DK	PHN	Divalproex sodium	Asia	Yes
2005	Raskin J	PDN	Duloxetine	Other	Yes
2005	Rog DJ	CP	THC + CBD	Europe	Yes
2006	Grosskopf	PDN	Oxcarbazepine	Other	No
2006	Schifitto G	HIV	Memantine	USA	No
2006	Sindrup SH	PDN	TKA731	Europe	No
2006	van Seventer R	PHN	PGB	Other	Yes
2006	Wernicke JF	PDN	Duloxetine	USA	Yes
2007	Arbaiza D	Cancer	Tramadol	Other	Yes
2007	Freeman R	PDN	Tramadol + ACET	USA	Yes
2007	Nurmikko TJ	Mixed	Sativex	Europe	Yes
2007	Rauck RL	PDN	Lacosamide	Other	Yes
2007	Silver M	Mixed	Lamotrigine + GBP	USA	No
2007	Vinik AI	PDN	Lamotrigine (2 trials)	USA	No
2007	Youle M	HIV	Acetyl-L-carnitine (ALCAR)	Other	No
2008	Gordh TE	PTN	GBP	Europe	No
2008	Ranoux D	PHN	Botox	Europe	Yes
2008	Rao RD	CIPN	Lamotrigine	USA	No
2008	Vranken JH	CP	PGB	Europe	Yes
2009	Agrawal	PDN	SV + GTN	Asia	Yes
2009	Chen JY	PHN	Vitamin C	Asia	Yes
2009	Irving G	PHN	GBP ER	USA	Yes
2009	Rowbotham MC	PDN	ABT 594	USA	Yes
2009	Shackelford S	PHN	GW406381	Other	No
2009	Shaibani A	PDN	Lacosamide	USA	Yes
2009	Yuan RY	PDN	Botox	Asia	Yes
2010	Moon DE	Mixed	PGB	Asia	Yes
2010	Selvarajah D	PDN	Sativex	Europe	No
2010	Simpson DM	HIV	PGB	USA	No
2010	van Seventer R	PHN	PGB	Asia	Yes

(*continued on next page*)

Table 1 (*continued*)

Year	First author	Disease	Drug	Region	Success?
2010	Xiao L	PHN	Botox	Asia	Yes
2011	Anand P	PTN	Dilmapimod	Other	Yes
2011	Backonja MM	PHN	GBP enacarbil	USA	Yes
2011	Kim JS	CP	PGB	Other	No
2011	Vranken JH	CP	Duloxetine	Europe	No
2011	Yasuda H	PDN	Duloxetine	Asia	Yes
2012	Heij L	SFN	ARA 290	Europe	No
2012	Jenkins TM	PTN	PGB	Other	Yes
2012	Mishra S	Cancer	PGB	Asia	Yes
2012	Shaibani AI	PDN	DMQ	USA	Yes
2013	Langford RM	CP	THC + CBD	Other	No
2013	Ostenfeld T	PTN	Losmapimod	Europe	No
2013	Rauck R	PDN	GBP enacarbil	USA	No
2013	Smith EM	CIPN	Duloxetine	USA	Yes
2013	Yousef AA	CLBP	Magnesium	Other	Yes

Formulations are not shown.

Regions labelled "Other" indicate either that the trial occurred at multiple sites on different continents and/or that trial occurred on a continent other than North America, Europe, or Asia.

ACET, acetaminophen (paracetamol); AMI, amitriptyline; Botox, botulinum toxin; BPA, brachial plexus avulsion; Cancer, cancer-associated neuropathic pain; CIPN, chemotherapy-induced peripheral neuropathy; CLBP, chronic low back pain (neuropathic); CMI, chlorimipramine; CP, central (poststroke) pain; CRPS, complex regional pain syndrome (type 1); DMQ, dextromethorphan + quinidine; ER, extended release; GBP, gabapentin; GBS, Guillain–Barré Syndrome; GTN, glyceryl trinitrate; HIV, HIV-associated peripheral neuropathy; Mixed, patients with >2 types of diagnoses included; MOR, morphine; PDN, painful diabetic (poly)neuropathy; PGB, pregabalin; PHN, postherpetic neuralgia; PTN, posttraumatic neuralgia (CRPS, type II); SFN, small fiber neuropathy; SR, sustained release; SV, sodium valproate; THC + CBD, tetrahydrocannabinol + cannabidiol.

Most intriguingly, the increase in placebo response magnitude over the 23-year period seemed to be driven solely by trials conducted in the United States ($F_{1,35} = 16.4$, $P = 0.0003$, Bonferroni-corrected $P = 0.002$), with no changes over time in either European ($F_{1,19} = 1.2$, $P = 0.29$) or Asian ($F_{1,10} = 0.4$, $P = 0.52$) trials (**Fig. 3A**).

3.3. Effects of study characteristics—continuous variables

Intercorrelation of quantitative study characteristics with placebo response and each other is shown in **Table 3**. No correlation between baseline pain level and placebo response was observed ($r = 0.07$, $P = 0.55$). Mean participant age ranged only from 42 to 75 years, and a nonsignificant trend ($r = 0.22$, $P = 0.19$) was observed such that placebo responses were larger in older subjects. The mean duration of pain in the most of these trials was <6 years; placebo responses tended to be lower ($r = -0.26$, $P = 0.07$) in trials featuring longer pain durations. Sex did not affect placebo responses ($r = -0.06$, $P = 0.61$), but placebo responses tended to be higher in trials with non-Caucasian participants ($r = 0.33$, uncorrected $P = 0.04$).

Study design parameters had larger effects on placebo response size than participant characteristics. A particularly

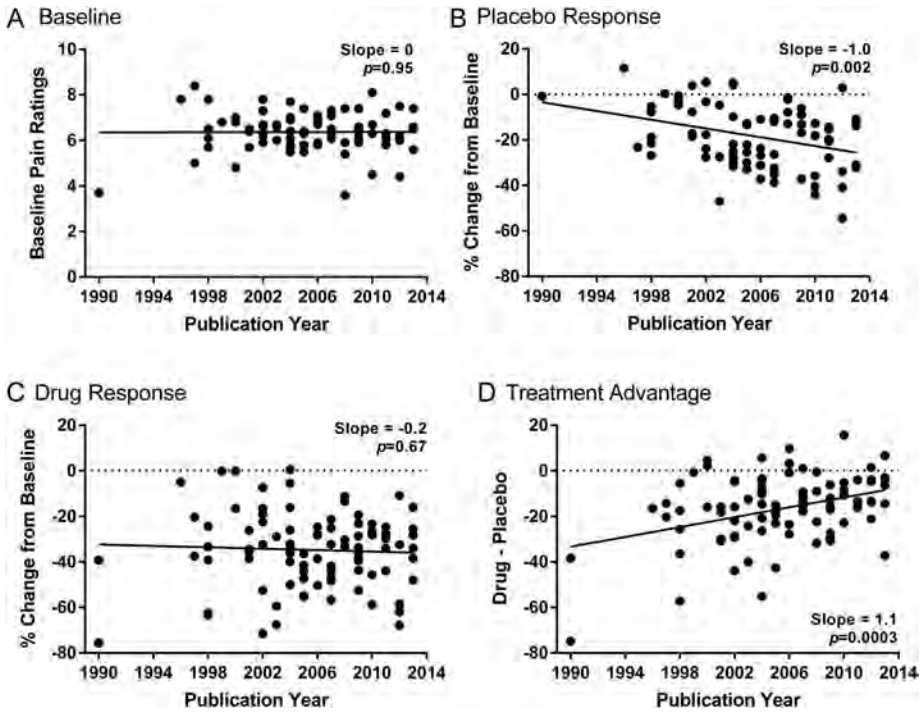

Figure 2. Trends in neuropathic pain trials over the period 1990 to 2013. (A) No change over time was observed in baseline (predrug) pain ratings. Placebo response increased significantly over time (B), but treatment (drug) response (C) did not. Treatment advantage (drug–placebo) decreased significantly over time (D). All *P* values are uncorrected but, in graphs (B) and (D), remain highly significant after Bonferroni correction for multiple comparisons.

Table 2

Effects of categorical study characteristics on placebo response, drug response, and treatment advantage in neuropathic pain clinical trials.

Variable	Levels*	n	Placebo†	Drug†	Advantage†	Slope‡
Trial success	Positive	57	18.7 (1.8)	40.7 (1.9)¶#	23.0 (1.6)¶#	−0.5
	Negative	35	17.6 (2.8)	25.0 (2.8)	6.0 (2.0)	−1.7#‖
Trial location	USA	39	18.3 (2.4)	33.3 (2.6)	15.4 (2.1)	−1.8#‖
	Europe	23	16.2 (3.2)	29.6 (3.7)	15.0 (3.8)	−0.7
	Asia	16	20.0 (4.5)	47.1 (3.9)#‖	24.6 (3.8)	−0.8
Pain scale	NRS	47	21.3 (1.9)§	37.6 (1.9)	14.6 (1.5)	−0.8
	VAS	45	15.0 (2.3)	31.7 (3.0)	18.5 (2.7)	−0.8
Trial design	Parallel	65	20.2 (1.6)§	34.3 (1.8)	14.4 (1.6)	−0.8§
	Crossover	27	12.5 (3.6)	35.7 (4.3)	21.6 (3.3)§	−1.1
Pain condition	PDN	35	24.5 (1.9)§	39.9 (2.0)	16.7 (2.3)	−0.7
	PHN	15	16.4 (3.1)	36.3 (3.4)	20.9 (2.7)	−0.1
Missing data	ITT	36	19.8 (1.9)	34.0 (2.4)	15.4 (2.1)	−0.3
	LOCF	20	20.5 (3.1)	32.3 (2.7)	11.2 (2.0)	−1.5§

* All variable levels with n ≥ 10 are shown. n's are based on number of drugs tested.

† Values are mean placebo response, drug response, or treatment advantage (drug–placebo) over the full 23-year period, expressed as percent decrease from baseline values. Values in parentheses are SEM.

‡ Values represent the slope of the linear regression of the placebo response only over the 23-year period. Negative slopes indicate placebo responses increasing over time.

§ $P < 0.05$ compared to all other levels (uncorrected).

‖ $P < 0.01$ compared to all other levels (uncorrected).

¶ $P < 0.001$ compared to all other levels (uncorrected).

# $P < 0.05$ compared to all other levels (Bonferroni-corrected).

ITT, intent-to-treat; LOCF, last observation carried forward; NRS, numerical rating scale; PHN, postherpetic neuralgia; PDN, painful diabetic peripheral neuropathy; VAS, visual analog scale.

robust effect of study size was observed, with placebo responses increasing with sample size of the control group ($r = 0.42$, Bonferroni-corrected $P = 0.001$). Also significant after Bonferroni correction was the correlation between placebo response and study length ($r = 0.34$, $P = 0.05$). Study size, number of study sites, study length, and number of study arms were all highly positively intercorrelated ($r = 0.28$-0.75).

3.4. Geographic specificity of effects

Changes in study size and duration in the United States vs elsewhere over the selected 23-year period and effects of those parameters on placebo responses stratified by geographical region are shown in **Figure 3**. Over time, clinical trials of neuropathic pain have become larger ($F_{1,35} = 15.8$, $P = 0.0003$) and longer ($F_{1,35} = 8.0$, $P = 0.008$) in the United States, but not in the rest of the world ($F_{1,40} = 0.2$, $P = 0.23$, $F_{1,40} = 1.4$, $P = 0.24$, respectively) (**Fig. 3B and C**). Furthermore, a strongly significant relationship between study size and magnitude of placebo response ($F_{1,35} = 32.1$, $P < 0.0001$) and study length and magnitude of placebo response ($F_{1,35} = 34.8$, $P < 0.0001$) was evinced in the United States but not elsewhere ($F_{1,40} = 1.1$, $P = 0.31$, $F_{1,40} = 0.0$, $P = 0.91$, respectively) (**Fig. 3D and E**).

3.5. Multivariable analyses

To identify independent contributions of these factors to placebo responses, we performed multivariable linear regression analysis. Geographical region was given a dummy variable: 1 for U.S. trails and 0 for non-U.S. trials (n = 79 trials; excluded were 5 trials that occurred both in the United States and outside it). In addition to the geographical region variable, we included the following variables because they were significantly ($P < 0.05$) associated with placebo response on their own (**Table 3**): (1) number of sites, (2) study size, (3) study duration, (4) number of study arms, and (5) year of publication. Our modeling strategy was to fit a model with all of these variables including all interactions with the geographical region variable. The final model included geographical region, sample size, study duration, and an interaction term of geographical region with study duration (**Table 4**). The interpretation of this model is that the placebo response increases with sample size. In the United States, but not in the rest of the world, the placebo response increases with greater study duration. The fact that study duration has increased over the years may underlie the increasing placebo response in the United States.

3.6. Time courses

Our strategy of coding pain ratings at every time point allowed us, for the first time, to look at the temporal evolution of placebo and treatment responses. Individual time course curves of placebo responses in all 44 studies featuring at least 3 postbaseline measures are shown in **Figure 4A**. Of these studies, 15 (34%) featured 3 to 4 measures, 16 (36%) featured 5 to 10 measures, and 13 (30%) featured 12 weekly measures. In addition, 5 studies (11%) featured biweekly measures, 4 (9%) featured monthly measures, and 35 (80%) featured weekly measures. Most individual curves could be fit with straight line or 1-phase exponential decay curves with approximately equal goodness-of-fit (not shown). Note the almost complete absence of any large increases in pain ratings at any time point. Mean placebo and drug responses over time are displayed in **Figure 4B**. Both displayed impressive goodness-of-fit to a 1-phase exponential decay curve ($r^2 = 0.96$ and 0.99, respectively). Significant differences in the half-life of the curves were observed; placebo group pain scores decayed with a half-life of 3.7 weeks (95% CI: 2.4-7.5), whereas drug group pain scores decayed much more quickly, with a half-life of 1.7 weeks (95% CI: 1.5-2.0). As a result, treatment advantage reached a maximum at 4 weeks and reached a plateau or even slightly declined thereafter (**Fig. 4C**).

3.7. Funnel plot of treatment advantage

A funnel plot of the relationship between treatment advantage and study sample size is provided as **Figure 5**.

4. Discussion

We show here that placebo responses in RCTs of chronic neuropathic pain have increased over time and treatment

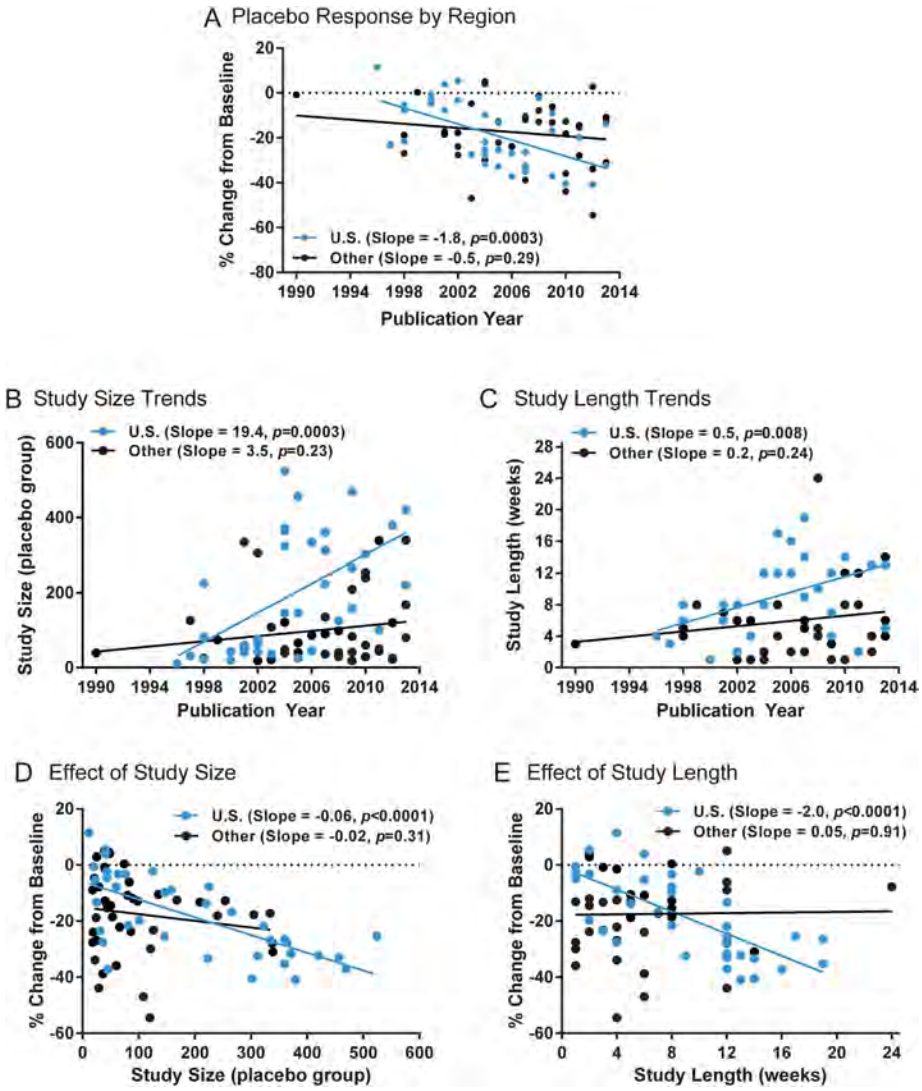

Figure 3. Comparison of placebo response parameters between U.S. trials and trials conducted elsewhere in the world. "Other" refers to all non-U.S. trials; trials including both U.S. and non-U.S. study sites are omitted. (A) Placebo response increased significantly over time in the United States only. Study size (B) and study length (C) similarly increased in U.S. trials only. Furthermore, study size (D) and study length (E) only affect placebo responses in U.S. trials.

advantage over placebo has decreased over the period 1990 to 2013, a trend wholly specific to trials conducted in the United States. Moreover, over this period, U.S. clinical trials have become larger and longer, changes that have not occurred elsewhere. Multivariate analysis suggests that it is study size and duration (interacting with geographical region)—increases that

Table 3

Intercorrelations between placebo response and continuous variables in neuropathic pain trials.

	Placebo	Participant characteristics					Study characteristics			
		BL	Age	Duration	% male	% white	Size	Sites	Length	Arms
Placebo	—									
BL	0.07	—								
Age	0.22	0.01	—							
Duration	−0.26	−0.06	−0.38	—						
% male	0.06	0.01	0.03	0.10	—					
% white	−0.33	0.08	0.05	0.29	−0.48	—				
Size	**0.42**	0.15	0.31	0.12	0.02	−0.09	—			
Sites	0.35	0.29	0.28	0.00	0.08	−0.20	**0.75**	—		
Length	**0.34**	0.19	0.07	0.12	0.11	0.32	**0.53**	0.36	—	
Arms	0.22	0.14	0.35	0.08	0.09	0.02	**0.61**	**0.49**	0.28	—

Bolded correlations are significant at $P \leq 0.05$ after Bonferroni correction for multiple comparisons; underlined correlations are significant at $P \leq 0.001$ after Bonferroni correction.

% male, percentage of male trial participants randomized to the placebo arm; % white, percentage of Caucasian (as reported by authors) trial participants randomized to the placebo arm; Age, average age of trial participants randomized to the placebo arm; Arms, number of study arms including placebo; BL, baseline pain score; Duration, average pain duration of trial participants randomized to the placebo arm; Length, total length of trial in weeks; Placebo, placebo response expressed as percent change from baseline at the end of the study; Sites, total reported number of study sites; Size, total number of trial participants randomized to the placebo arm.

Table 4

Multivariable linear regression model.

Variable	β	SE (β)	*P*
Study size	−0.034	0.013	0.012
Study duration	0.23	0.42	0.58
Geographical region	15.74	5.16	0.003
Geographical region × duration	−1.55	0.60	0.012

are in turn associated with increased placebo responses—that are responsible for the temporal trend observed. Stable patient characteristics such as age, sex, baseline pain scores, and pain duration were not associated with placebo response magnitude.

4.1. Comparison with similar analyses in trials in depression and schizophrenia

Placebo responses have also been shown to be increasing over time in RCTs of antidepressants and antipsychotics, which like studies of chronic pain rely on subjective outcome measures. In some of these meta-analyses, changing participant characteristics have been proposed to be responsible for the trend.[1,6,9,13,18,21] In general, this study did not uncover strong evidence that patient characteristics were related to placebo response magnitude.

Meta-analyses of placebo responses in antidepressant and antipsychotic RCTs have also provided evidence that changing study characteristics drive trends in placebo response. These include (1) number of trial arms[21,30,31]; (2) study duration/number of trial visits[1,24,37]; (3) study size[6]; (4) number of study sites[1,6]; (5) the nature of the study sites[9]; and (6) trial location.[8,9,17]

4.2. Comparison with previous analyses of analgesia trials

To our knowledge, only 5 relevant analyses of RCTs of chronic pain treatments have been published, one of osteoarthritis trials,[39] one of trials in fibromyalgia and PDN,[15] one of irritable bowel syndrome trials,[23] and 2 of neuropathic pain trials.[16,27]

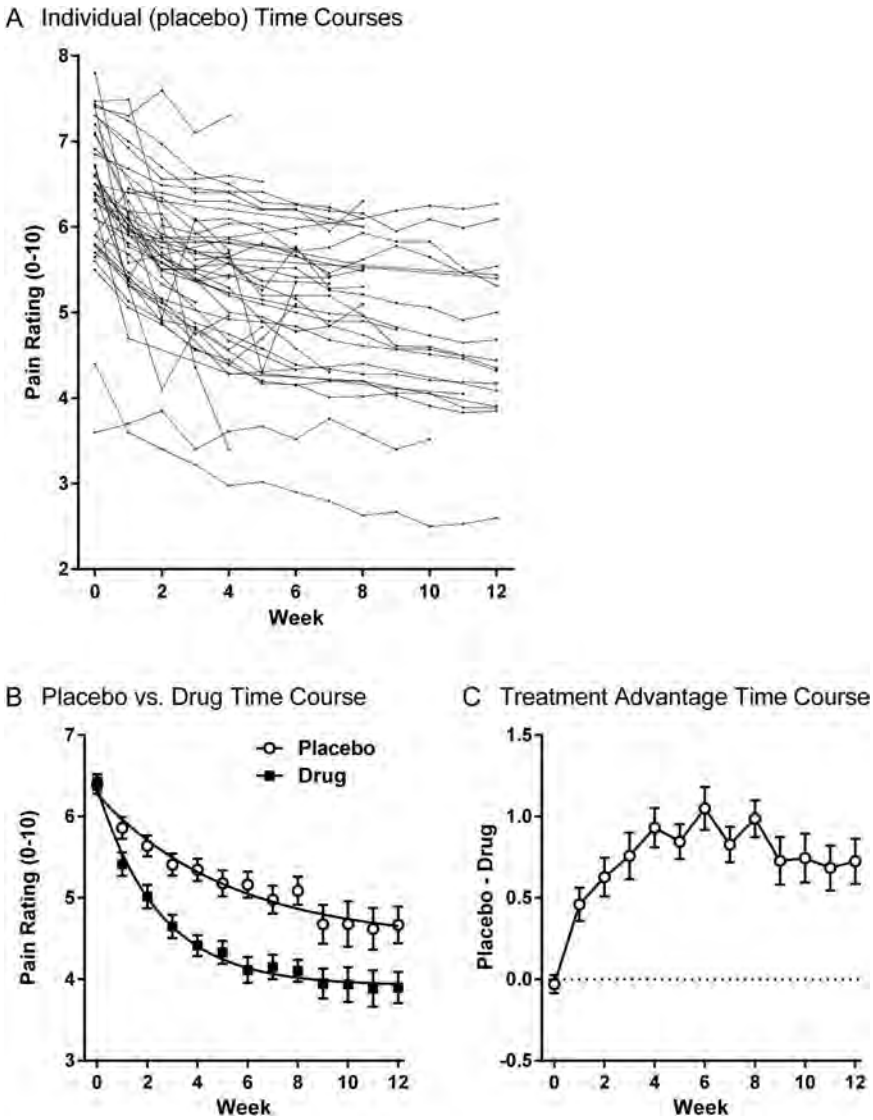

Figure 4. Week-by-week temporal evolution of placebo responses, drug responses, and treatment advantage in neuropathic pain trials. (A) Individual placebo response time courses from all studies featuring at least 3 postbaseline measurements (n = 44). Symbols represent pain scores in the placebo arm. (B) Placebo and drug responses by week. Bars represent mean ± SEM pain scores. Curves are fit based on a 1-phase exponential decay function. (C) Treatment advantage by week. Bars represent mean ± SEM difference scores (drug–placebo).

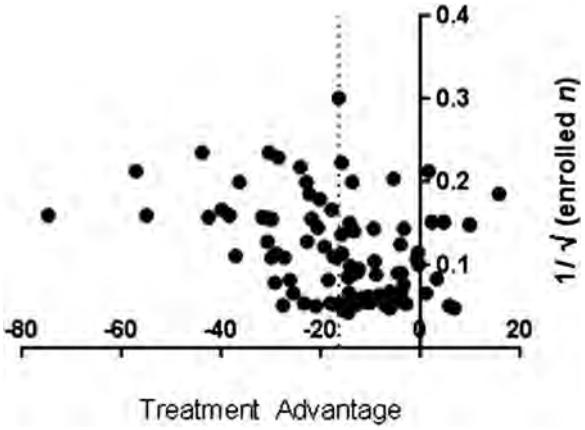

Figure 5. Funnel plot of treatment advantage (drug–placebo). Asymmetry of effect sizes around the mean treatment effect (dotted line) may suggest publication bias in favor of studies showing large effects. n = sample size of placebo arm.

In addition, a very new study analyzes individual patient placebo data from 9 industry trials of osteoarthritis and chronic low back pain.[35] Of these, one reported that increased sample size predicted larger placebo response.[39] One reported a trend towards longer trial duration predicting larger placebo response,[27] and another demonstrated a positive relationship between number of face-to-face visits (positively correlated with trial duration) and placebo response.[35] Both sample size and trial duration were significantly associated with placebo response magnitude in the univariate analyses of Katz et al.,[16] but not in their final multiple regression model. Four of the studies reported that the size of the placebo response could be predicted by the size of the active treatment response.[15,16,35,39] We noted this as well because the correlation between placebo response and (maximum) treatment response across studies was $r = 0.58$ ($P < 0.001$). Although this relationship may simply represent a statistical artefact,[20] the correlation between the placebo response and (maximum) treatment response across studies may be related to underlying nonspecific factors. These nonspecific factors could include patients' perception of the intervention, the relationship with the health care provider and expectations of treatment effect, which in turn could be influenced by trial size and duration. We found no evidence whatsoever that baseline pain level affected placebo response, in contrast to others.[15,34,35,38]

4.3. Influence of trial size and length on placebo response

Over the period analyzed, neuropathic pain RCTs have become bigger, longer, and conducted at more sites in the United States, but not elsewhere in the world. Furthermore, our multivariate analysis suggests that it is this increase in trial size and duration that is most associated with increasing placebo response magnitudes in the United States. Whether or not these associations indicate a causal effect is unknown. The positive relationship between trial duration and the magnitude of the placebo response might be explained by a positive feedback mechanism by which initially perceived pain reduction leads to increasing analgesia over the course of the trial. The mechanism might be similar to demonstrated effects of successful analgesia on subsequent placebo analgesia responses.[2] Longer trials may also feature more nonspecific therapeutic effects, for example, more opportunities for, and ultimately richer, social support, attention from trial staff, and education. Larger trials may feature relaxed eligibility criteria, resulting in different patient characteristics.

The reason(s) for the change in the United States alone is not known. As to trial duration, the U.S. Food and Drug Administration requires that phase III clinical trials for analgesics to treat chronic pain be at least 12 weeks long. However, this requirement was first promulgated in 1992; all but one of the studies in our sample was conducted afterwards, and many were not phase III studies. It may be that an important difference between clinical trials in the United States and elsewhere concerns the more common use of contract research organizations (CROs) in the former. In an analysis of placebo responses in antidepressant clinical trials, Dunlop et al.[9] observed that treatment advantage was larger in trials with higher percentages of patients enrolled from academic sites and that the participation of academic sites had declined from 1992 to 2012. The authors pointed to several differences between academic and private trial sites, including financial incentives, personnel turnover, stringency of training, and the possibility that academic centers enroll a greater proportion of patients referred by other physicians because of poor treatment response. It is also possible that recruitment methods relying principally on advertising are more popular in the United States than elsewhere (especially in large trials), resulting in differing patient characteristics in U.S. studies.

4.5. Time course issues

Analysis of time course data of neuropathic pain RCTs—performed for the first time in this study—reveals that responses in both the drug and placebo arms increase over several weeks and then plateau. However, the plateau is generally reached sooner in the drug arm than the placebo arm, with a full 2-week difference in estimated half-lives of the curves. Maximum treatment advantage is reached by 4 weeks after trial start and plateaus at that level for 8 to 12 weeks. These temporal courses were seen regardless of study date. It is noteworthy that no study found a reversal of the placebo response, ie, a sustained return towards baseline pain level, even in studies lasting for 3 months.

Our current understanding of the placebo effect is based on classical conditioning theory or expectancy theory.[22,34] But a conditioned or expectancy response is not self-sustaining, in the absence of reward (reinforcement) both extinguish. Thus, one might expect that the placebo response would be transient; this was not seen in any of the studies we analyzed. Why does the analgesic placebo response endure? Brain imaging studies show that experimental placebo analgesia is characterized by decreases in activity in pain-processing regions of the brain that seem to be similar to or identical with the decreases that one sees when the intensity of the pain stimulus is decreased.[3] Thus, perceived pain reductions with placebos are likely caused by reduced activation in pain-processing regions resulting from inhibition of early stage nociceptive processing in the spinal cord[12] and the thalamus[25] by endogenous pain inhibitory mechanisms. Thus, the analgesia obtained with placebo matches the expectations and predictions of the individual. The achieved pain relief likely induces a sense of reward, which is analgesic in and of itself,[5] thereby sustaining a positive feedback loop maintaining pain reductions in placebo arms over long periods.

Our data are consistent with the possibility that the mechanism (s) that produces the large early-onset component of the placebo response are replaced by or augmented by other mechanisms that sustain the placebo response. The presence of such late-onset mechanisms may be associated with the correlation between placebo magnitude and study duration, for example,

longer trials having more clinic visits that involve more social interactions between patients and study staff.[2,9]

4.6. Limitations

Our inclusion criteria limited the number of trials analyzed herein. Trials using intrathecal, topical, or transdermal drug administration were excluded because of the suspicion that route of administration has a strong effect on placebo responding. Trials in fibromyalgia were excluded because of our uncertainty as to whether this condition should be categorized as neuropathic pain. Our limited sample limits generalizations as to the cause(s) of failed trials. Our study results are of course potentially influenced by trends in study quality and/or publication bias, such that the placebo response in failed trials is likely undersampled. Visual inspection of **Figure 5** is suggestive of an asymmetry that could be explained by a publication bias against studies showing smaller treatment advantage, which suggest the following alternative interpretation of the findings. In the past, small studies were conducted. If they had a large placebo response, they did not show a positive treatment advantage and therefore they were not published. In contemporary U.S. studies, trials are typically large enough to detect positive treatment advantage despite large placebo responses, and therefore reported placebo responses seem to have increased. Of course, it is not at all clear that there really is asymmetry here, and a growing body of research has indicated that interpretation of funnel plots is subjective and problematic.[33]

Conflict of interest statement

The authors declare that they have no conflicts of interest.

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A. H. Tuttle and S. Tohyama have contributed equally.

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Appendix A. Supplemental Digital Content

Supplemental Digital Content associated with this article can be found online at http://links.lww.com/PAIN/A155; http://links.lww.com/PAIN/A156.

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