ORIGINAL RESEARCH

Placebo response in neuropathic pain after spinal cord injury: a meta-analysis of individual participant data

Catherine R Jutzeler,[1–3]
Freda M Warner,[1,2]
Jacquelyn J Cragg,[1,3] Jenny
Haefeli,[4] J Scott Richards,[5]
Sven R Andresen,[6] Nanna
B Finnerup,[7,8] Catherine
Mercier,[9] John LK Kramer[1,2]

[1]Faculty of Medicine, ICORD,
University of British Columbia,
Vancouver, BC, Canada; [2]Faculty of
Education, School of Kinesiology,
University of BC, Vancouver, BC,
Canada; [3]Faculty of Medicine, Spinal
Cord Injury Center, University
Hospital Balgrist, University of Zurich,
Zurich, Switzerland; [4]Weill Institute
for Neurosciences, Department
of Neurological Surgery, Brain and
Spinal Injury Center, University of
California, San Francisco, CA, USA;
[5]Department of Physical Medicine
and Rehabilitation, University of
Alabama at Birmingham, Birmingham,
AL, USA; [6]Spinal Cord Injury Centre
of Western Denmark, Department
of Neurology, Regional Hospital of
Viborg, Viborg, Denmark; [7]Danish
Pain Research Centre, Department of
Clinical Medicine, Aarhus University,
Aarhus, Denmark; [8]Department
of Neurology, Aarhus University
Hospital, Aarhus, Denmark; [9]Center
for Interdisciplinary Research in
Rehabilitation and Social Integration,
Québec, QC, Canada

Correspondence: Catherine R Jutzeler
ICORD, University of BC, 818 W
10th Avenue, Vancouver, BC V5Z 1M9,
Canada
Tel +1 604 675 8876
Email catherine.jutzeler@ubc.ca

Background: Understanding factors associated with high placebo responses in clinical trials increases the likelihood of detecting a meaningful treatment effect. The aim of the present study was to identify subject-level factors that contribute to placebo variability in patients with neuropathic pain due to spinal cord injury (SCI).

Methods: Multiple regression analysis of patient data from randomized, double-blind, placebo-controlled trials (duration >4 weeks) involving individuals with SCI was performed. Patient demographics, as well as injury and pain characteristics were examined for their association with changes in pain rating from baseline to the end of the trial (i.e., placebo response). The overall effect of individual predictors was quantified with meta-analysis statistics.

Results: A total of 276 patients with SCI from six studies were included in the analysis. Based on the meta-analysis of subject-level predictors, larger placebo responses were associated with male subjects (β=0.635; standard error [SE]=0.262; p=0.016) and higher baseline pain (β=−0.146; SE=0.073; p=0.044). There were no significant effects for injury characteristics (i.e., severity, level, and time since injury) or pain characteristics (i.e., location and evoked). No significant publication bias was detected.

Conclusion: The current meta-analysis of individual patient data demonstrated the importance of sex and baseline pain intensity on changes in pain ratings in the placebo arm of SCI central neuropathic pain randomized controlled clinical trials. Overall, our findings indicate that placebo responses occur independent of injury characteristics.

Keywords: placebo response, clinical trial, spinal cord injury, neuropathic pain

Introduction

The placebo effect represents a major challenge for the design of clinical trials aimed at relieving chronic pain. The difficulty stems from large changes in pain without an active intervention, which potentially masks meaningful treatment effects. The "placebo problem" is compounded by limited prediction of treatment effects based on preclinical pain models.[1–3] Understanding factors underlying placebo responses has, as a consequence, emerged as an approach to improve the design and interpretation of chronic pain clinical trial outcomes.[4–7]

Central neuropathic pain arises because of damage in the central nervous system (CNS), and is common in individuals with multiple sclerosis, stroke, and spinal cord injury (SCI).[8–10] Interestingly, clinical trials in SCI neuropathic pain report smaller placebo responses relative to other neuropathic pain conditions (e.g., diabetic and HIV neuropathy).[11] This difference raises the possibility that unique factors associated

with central neuropathic pain (e.g., damage in the CNS) contribute to lower placebo responses. A recent meta-analysis identified that longer pain duration and greater between-subject baseline pain variability were associated with a decreased placebo response in patients with central neuropathic pain.[12]

Meta-analyses of published studies are often used to pool effect sizes.[13,14] As an extension of meta-analysis, meta-regression is commonly performed to examine the relationship between effect size and study (e.g., sample size and allocation concealment) and patient-level variables (e.g., age and sex). Conventional meta-regression of pooled study data suffers from major limitations. The most substantial concern is that a correlation observed at the study level may be inversely correlated at the patient level (i.e., ecological fallacy). In addition, study-level meta-regression has limited sensitivity to detect important patient-level factors related to the outcome. To accurately derive these relationships, analysis of individual patient data (IPD) is needed.[15–19] Meta-analyses of IPD are considered the gold standard for systematic reviews.[16,20]

To address factors associated with placebo responses in neuropathic pain, we performed a meta-analysis of patient-level data pertaining to six placebo-controlled randomized trials (RCTs) conducted in the field of SCI. Our primary aim was to examine the effect of subject-level predictors on placebo responses. Specifically, we tested the hypothesis that patient demographics, injury, and pain characteristics contribute to the variability of placebo responses in individuals with neuropathic pain after SCI.

Materials and methods

This study was approved by the University of British Columbia's Clinical Research Ethics Board (H15-00475).

Study selection: search, inclusion, and exclusion criteria

A systematic literature search of English-language articles was performed using PubMed between September 2015 and January 2016. Search terms included "placebo", "spinal cord injury", and "pain". Hand searching was also performed, reviewing reference lists of relevant trials and comprehensive review articles. Additional search terms and combinations were considered to further identify relevant studies (e.g., "neuropathic", "central pain"). We included randomized, placebo-controlled, parallel- or crossover-designed studies for which IPD were available. Only datasets from pharmacologic studies using inert placebos and treatment durations longer

than 4 weeks were included in this analysis. Case studies and open-label clinical trials (i.e., those with no placebo condition) were excluded. Based on this search, corresponding authors were contacted by email to obtain the patient-level data. Contact was also made by email for industry-sponsored studies.

Predictor variables

The following patient-level information was obtained for all subjects undergoing placebo treatment: age, sex, injury characteristics (i.e., level and severity of injury, time since injury), and pain characteristics (i.e, baseline and post-placebo pain intensity, quality of pain (i.e, evoked). The level and severity of injury were classified using the International Standards for the Neurological Classification of SCI.[21] Level of injury was dichotomized as thoracic or cervical. Completeness of injury was determined according to the American Spinal Injury Association Impairment Scale (AIS) grades. Injury completeness was dichotomized as "complete" (i.e., AIS-A subjects, with no sensory or motor function caudal to the level of injury) or incomplete injuries (i.e., AIS-B to D subjects, with motor and/or sensory sparing).[21]

Statistical analysis

R Statistical Software version 2.15.3 was used for all analyses. Placebo response (dependent variable) was defined as the overall change in rating of the neuropathic pain intensity (i.e., based on 0–10 numeric rating scale) from baseline to the end of the study or the last measurement. As there is a known trial-design effect on placebo response[12] and to enable direct comparison with the parallel-designed studies, only patients who received placebo in the first arm were included for the analysis. A priori studies from the same investigators using similar experimental design (e.g., crossover study) were pooled to increase sample size.[22,23]

In step 1, multivariable regression statistics were used to calculate effect sizes (beta coefficient) and a measure of variance (standard error [SE]). Subject characteristics (age and sex), injury characteristics (plegia, completeness, and duration since injury), and pain characteristics (baseline pain intensity rating) were modeled separately. In an exploratory analysis, the effects of evoked pain (i.e., allodynia) and location of pain (i.e., at-level, below-level, or both) on the placebo response were independently examined.[22–25]

Step 2 of our analysis examined the overall effect size of subject, injury, and pain characteristics across studies (i.e., a pooled effect size). The R package metafor was used to

perform a meta-analysis on the regression coefficients derived from bivariable and multivariable regression models.[26] Forest plots were produced to visualize the results from the random-effect models (R function: forest). Funnel plots were used to assess publication bias (R function: funnel). To assess publication bias by examining asymmetry in the funnel plots, the Egger test was used (R function: regtest).[27]

Results
Study selection and characteristics
The results of the study selection are presented in Figure 1. A total of six placebo-controlled studies met the inclusion criteria and were thus included in the analysis.[22–24,28–30] The data of 276 chronic SCI patients were acquired from the authors of the original studies[22–24,30] or industry sponsors.[28,29] Six patients from one study[24] had to be excluded as not all of the information required for the present study was available in the dataset. Table 1 provides a detailed overview of all the studies included. Ten studies were excluded from the analysis because of the use of an active placebo (n=2),[25,31]

a treatment duration <4 weeks (n=7),[25,31–39] or no access to the IPD (n=1).[39]

Placebo response
Figure 2A illustrates the placebo responses for all studies reviewed (β=–0.622; SE=0.39; p=0.115). Overall, there was no significant placebo response. No significant publication bias was detected by Egger's regression test for funnel plot asymmetry (p=0.674; Figure 2B).

Multivariable regression analyses
All results from the multivariable regression analyses are summarized in Table 2.

### Meta-regression: patient, injury, and pain characteristics
Based on meta-regression statistics of individual patient-level data, sex (β=0.635; SE=0.262; p=0.016; Figure 3A) and baseline pain intensity rating (β=–0.146; SE=0.073; p=0.044; Figure 4) were associated with placebo responses. Males and higher baseline pain intensity ratings were associated with larger placebo responses. No significant publication bias was detected by Egger's regression test for funnel plot asymmetry (sex: p=0.669, baseline pain: p=0.361, placebo response: p=0.673). Age (Figure 3B), injury severity (Figure 5A), level (Figure 5B), and duration (Figure 5C) did not significantly predict placebo responses.

Planned exploratory analysis
In two available trials, evoked pain (β=0.345; SE=1.086; p=0.751; Figure 6A) was not associated with placebo responses. Placebo responses were higher in individuals with below-level compared with below- and at-level neuropathic pain (i.e., both) (Figure 6B). However, this effect was not observed after adjusting for baseline pain (β=0.065; SE=0.481; p=0.893; Figure 6C).

Discussion
Our study examined factors contributing to variable placebo responses in individuals with SCI neuropathic pain. For that purpose, IPD (n=276) derived from six randomized clinical trials were examined. Based on a patient-level meta-approach, sex and baseline pain intensity ratings were the only variables significantly associated with placebo responses. There was a trend toward larger placebo responses in individuals with incomplete injuries (versus complete); however, this effect was not consistent across examined trials. Other neuropathic pain, injury, or subject characteristics were not related to
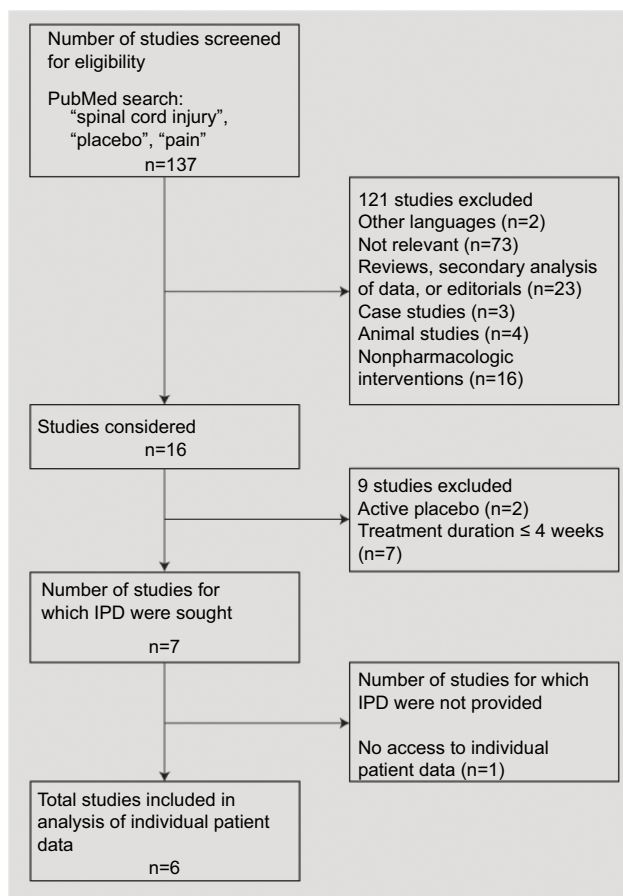
Figure 1 Flow diagram for the selection of randomized placebo-controlled trials.
Abbreviation: IPD, individual patient data.

Table 1 Details of reviewed studies

Study details	Study 1	Study 2	Study 3	Study 4	Study 5	Study 6
Publication, author, year	Finnerup et al,[22] 2009[a]	Finnerup et al,[23] 2002[a]	Siddall et al,[29] 2006	Cardenas et al,[28] 2013	Richards et al,[24] 2015	Andresen et al,[30] 2016
Study design	Crossover	Crossover	Parallel	Parallel	Parallel	Parallel
Intervention	Levetiracetam	Lamotrigine	Pregabalin	Pregabalin	Venlafaxine XR	Palmitoylethanolamide
Duration of placebo, days						
Mean (SD)	29.4 (11.6)	61.1 (2.5)	61.9 (30.5)	171.6 (9.6)	81.8 (9.4)	82.3 (22.3)
Subject characteristics						
Number	18	12	67	106	39	34
Sex, n (%)						
Male	15 (83.3)	10 (83.3)	54 (80.6)	91 (85.8)	33 (84.6)	29 (85.3)
Female	3 (16.7)	2 (16.7)	13 (19.4)	15 (14.2)	6 (15.4)	5 (14.7)
Age, years						
Mean (SD)	56.6 (10.9)	41.5 (10.7)	49.8 (14.2)	45.3 (14.0)	42.7 (11.1)	54.4 (11.2)
Injury characteristics						
ASIA Impairment Scale[b], n (%)						
A: Complete	6 (33.3)	5 (41.7)	34 (50.7)	57 (53.8)	23 (59.0)	10 (29.4)
B: Incomplete	1 (5.6)	1 (8.3)	7 (10.4)	10 (9.4)	6 (15.4)	3 (8.8)
C: Incomplete	1 (5.6)	2 (16.6)	7 (10.4)	7 (6.6)	5 (12.8)	9 (26.5)
D: Incomplete	10 (55.6)	4 (33.3)	19 (28.4)	32 (30.2)	5 (12.8)	12 (35.3)
Cause of SCI, n (%)						
Violence (e.g., gunshot)	–	0 (0)	0 (0)	8 (7.5)	14 (35.9)	0 (0)
Accident (e.g., fall, vehicular)	–	8 (66.7)	59 (88.1)	81 (76.5)	21 (53.8)	22 (64.7)
Other	–	4 (33.3)	8 (11.9)	17 (16)	4 (10.3)	12 (35.3)
Time since injury, years						
Mean (SD)	4.6 (4.1)	13.0 (9.5)	10.4 (9.8)	10.6 (10.3)	16.7 (13.0)	11.7 (11.1)
Plegia, n (%)						
Paraplegia	10 (55.6)	7 (58.3)	38 (56.7)	56 (52.8)	15 (38.5)	20 (58.8)
Tetraplegia	18 (44.4)	5 (41.7)	29 (43.3)	50 (47.2)	24 (61.5)	14 (41.2)
Pain characteristics						
Baseline pain score						
Mean (SD)[c]	6.8 (1.3)	5.3 (1.7)	6.7 (1.4)	6.5 (1.4)	7.0 (1.8)	6.2 (1.1)
Location, n (%)						
At level of SCI	1 (5.6)	2 (16.7)	–	25 (23.7)	–	7 (20.6)
Below level of SCI	6 (33.3)	5 (41.7)	–	53 (50.0)	–	14 (41.2)
Both	11 (61.1)	5 (41.7)	–	28 (26.3)	–	13 (38.2)

Notes: [a]As there is a known trial-design effect on placebo response and to enable direct comparison with the parallel-designed studies, only patients who received placebo in the first arm were included for the analysis. [b]American Spinal Injury Association (ASIA) Impairment Scale: A, no sensory or motor function is preserved; B, sensory function is preserved below the level of the injury, but there is no motor function; C, sensory and motor functions are preserved below the neurologic level, and more than half of the key muscles below the neurologic level have a muscle grade of <3; D, sensory and motor functions are preserved below the neurologic level, and at least half of the key muscles below the neurologic level have a muscle grade of >3. [c]Baseline pain levels were assessed using a 11-point Numeric Rating Scale (0=no pain, 10=worst possible pain).
**Abbreviation:** SCI, spinal cord injury.

placebo responses. Overall, placebo responses among individuals with neuropathic pain due to SCI were small and difficult to predict at the subject level.

Low placebo response hallmarks SCI clinical trials

According to our meta-analysis, individuals with SCI and neuropathic pain have no significant placebo response in clinical trials testing pharmacologic interventions lasting 4 weeks or longer. This finding is in agreement with the small effect we previously reported,[12] but is in stark contrast to the majority of other chronic pain conditions.[40–46] Emerging

clinical trial data have further substantiated our observation of limited placebo response in SCI patients. In a recent trial demonstrating the efficacy of botulinum toxin type A (BTXA), fewer than 10% of SCI patients administered saline achieved a meaningful reduction in pain (i.e., >30%).[47] Comparatively, approximately almost half of the patients with myofascial pain in a similarly designed BTXA clinical trial (i.e., also 4 weeks in duration, parallel design) responded (i.e., >30% reduction in pain) to the administration of saline.[48] In a BTXA clinical trial, large placebo responses are expected, given the invasiveness of the intervention compared with conventional pharmacologic studies.[49,50]
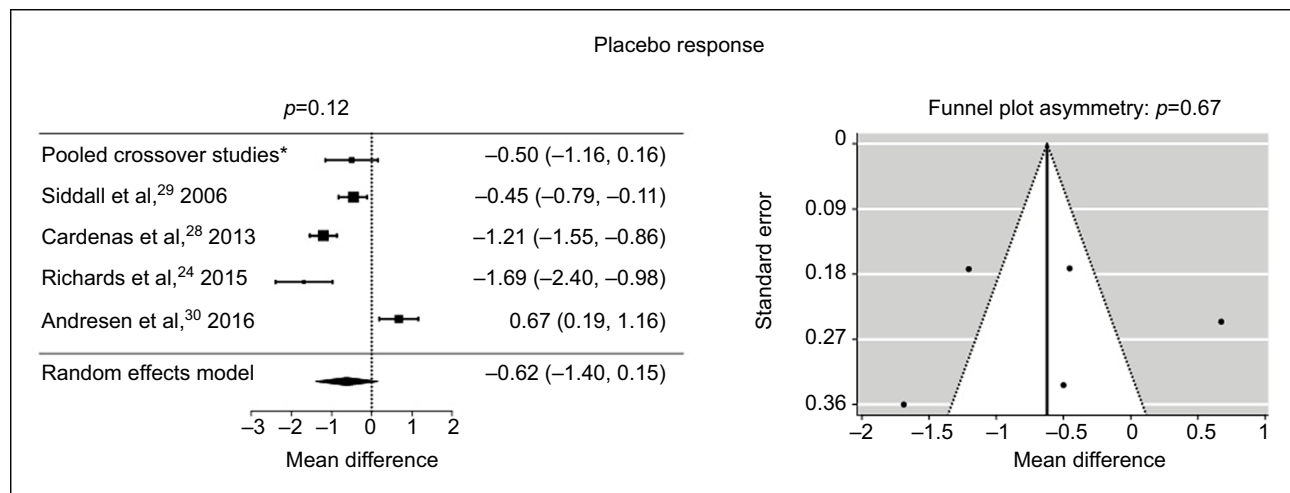
Figure 2 Change in pain intensity in the placebo group for all studies.
Notes: A negative mean difference indicates a reduction in pain score after placebo treatment. Funnel plot: standard error against mean change in pain intensity for the placebo group for all studies. *Finnerup 2002 and Finnerup 2009:[22,23] cross-over designed studies. As there is a known trial-design effect on placebo response and to enable direct comparison with the parallel-designed studies, only patients who received placebo in the first arm were included for the analysis. To increase the sample size these two studies were pooled.

While there was no overall significant placebo response, three trials demonstrated average reductions in pain intensity ratings with placebo. The largest placebo response was reported in a recent trial conducted in the USA.[24] Comparatively, the most recent trial conducted in Europe reported no discernible placebo response.[30] Collectively, these observations correspond with findings that indicate that placebo responses are increasing in American neuropathic pain clinical trials.[51] However, the high placebo response in the American trial[24] should be interpreted with caution as the study was focused on depression, which may confound the results; the placebo response rate in depression consistently falls between 20% and 40% (e.g., improvement on the 29-item modified Hamilton Depression Scale).[52–55]

The presence of damage in the CNS represents the most distinguishing physiologic/anatomical feature that could explain small placebo responses in individuals with SCI. In principle, damage in the spinal cord disrupts normal physiology involved in generating placebo analgesia, thereby reducing the capacity to experience placebo response.[56–58] Our subject-level meta-analysis indicates a trend to this effect, namely, that individuals with more complete injuries tended to exhibit smaller placebo responses than individuals with incomplete injuries (Figure 7). Comparatively, level of injury (i.e., para versus tetra) had no discernible impact on placebo responses. The impact of injury severity on individual placebo responses was not, however, consistent enough across trials to yield an overall effect. A variable effect of injury severity on placebo responses may be related to a number of factors, including that a clinical measure of damage in the spinal cord

(i.e., AIS grades) is insufficient to characterize the extent of pathology in spinal pathways involved in placebo analgesia. From a pragmatic perspective, injury completeness may only have a subtle effect, while other factors play a much larger role in placebo (e.g., expectation).[5,59–62]

Predictors of placebo response

Reductions in pain were predicted by baseline ratings, insofar as patients with higher ratings demonstrated larger placebo responses. This is consistent with the notion that enrollment in clinical trials occurs when pain intensity is at its peak, and that a follow-up measurement is biased to decrease (i.e., regression toward the mean).[63] Our observations also indicate that male patients have larger placebo responses than females. With regard to sex-related differences, other studies have reported similar observations[64–66] or no effect of sex.[67] Caution interpreting the effect of sex is warranted on the basis that the vast majority of subjects examined herein were male, consistent with the typical demographics of SCI.[68]

If not related to damage in the spinal cord, what factors unique to SCI explain markedly low placebo responses (i.e., no significant response across all trials)? SCI neuropathic pain is commonly regarded as a chronic condition refractory to treatment.[69,70] This, in turn, could decrease expectation of benefit and drive lower placebo responses.[71] The unique complexities of neuropathic pain, including that pain symptoms arise from other secondary health complications (e.g., infections, spasticity, and pressure ulcers to name a few), may also contribute to low placebo responses. Finally, all of the IPD included in our meta-analysis are all from preapproval trials

Table 2 Prediction of change in pain rating (placebo response)

|		Subject characteristics			Injury characteristics				Pain characteristics	
		Constant	Sex	Age	Constant	Plegia[b]	Completeness[c]	Duration of SCI	Constant	Baseline pain
Study 1 and 2 pooled[a]	β	−2.263	0.500	0.050	0.603	−1.187	−0.642	0.001	4.323	−0.377
	95% CI	−5.193, −0.668	−0.970, −2.530	0.001, −0.010	−1.620, −2.827	−2.285, −1.000	−2.777, −0.402	−0.092, −0.094	0.825, −7.821	−0.779, −0.024
	SE	1.428	0.853	0.024	1.082	0.773	0.799	0.045	1.705	0.196
	p-value	0.125	0.369	0.049	0.582	0.137	0.429	0.977	0.017	0.064
Study 3 (Siddall et al,[29] 2006)	β	−1.384	0.533	0.006	0.145	0.069	−0.552	0.001	0.083	−0.005
	95% CI	−3.050, −0.281	−0.341, −1.408	0.019, −0.030	−1.047, −1.340	−0.625, −0.762	−1.239, −0.136	−0.001, −0.004	−1.937, −2.103	−0.253, −0.244
	SE	0.834	0.438	0.012	0.598	0.344	0.347	0.001	1.011	0.124
	p-value	0.102	0.228	0.632	0.809	0.114	0.844	0.294	0.935	0.971
Study 4 (Cardenas et al,[28] 2013)	β	−2.516	0.586	0.018	−1.609	0.292	0.064	0.002	1.542	−0.212
	95% CI	−4.035, −0.997	−0.383, −1.556	0.007, −0.043	−2.314, −0.903	−0.456, −1.039	−0.683, −0.812	−0.001, −0.006	−0.670, −3.755	−0.457, −0.179
	SE	0.766	0.488	0.013	0.355	0.377	0.377	0.002	1.116	0.123
	p-value	0.001	0.233	0.161	<0.001	0.865	0.441	0.165	0.170	0.148
Study 5 (Richards et al,[24] 2015)	β	−0.396	1.158	−0.034	−0.139	−0.663	−0.673	−0.062	−0.126	−0.227
	95% CI	−3.594, −2.801	−0.762, −3.079	−0.113, −0.036	−1.854, −1.576	−2.164, −0.839	−2.331, −0.985	−0.124, −0.001	−7.041, −6.790	−0.662, −0.207
	SE	1.578	0.948	0.034	0.846	0.740	0.817	0.031	3.413	0.214
	p-value	0.803	0.229	0.333	0.870	0.377	0.416	0.052	0.971	0.296
Study 6 (Andresen et al,[30] 2016)	β	0.222	0.754	−0.004	0.473	−0.127	0.276	0.007	0.732	0.0304
	95% CI	−2.525, −2.970	−0.696, −2.204	−0.050, −0.043	−1.161, −2.107	−1.298, −1.045	−1.010, −1.564	−0.042, −0.056	−2.933, −4.398	−0.463, −0.524
	SE	1.347	0.611	0.023	0.800	0.574	0.630	0.024	1.794	0.242
	p-value	0.870	0.297	0.878	0.559	0.827	0.664	0.780	0.686	0.901

Notes: [a]Finnerup 2002 and Finnerup 2009: crossover designed studies.[22,23] As there is a known trial-design effect on placebo response and to enable direct comparison with the parallel-designed studies, only patients who received placebo in the first arm were included for the analysis. To increase the sample size these two studies were pooled. [b]Categories: tetra- or paraplegia, reference. [c]Complete: AIS A and B, incomplete: AIS C and D.
Abbreviations: AIS, Association Impairment Scale; SCI, spinal cord injury; SE, standard error.
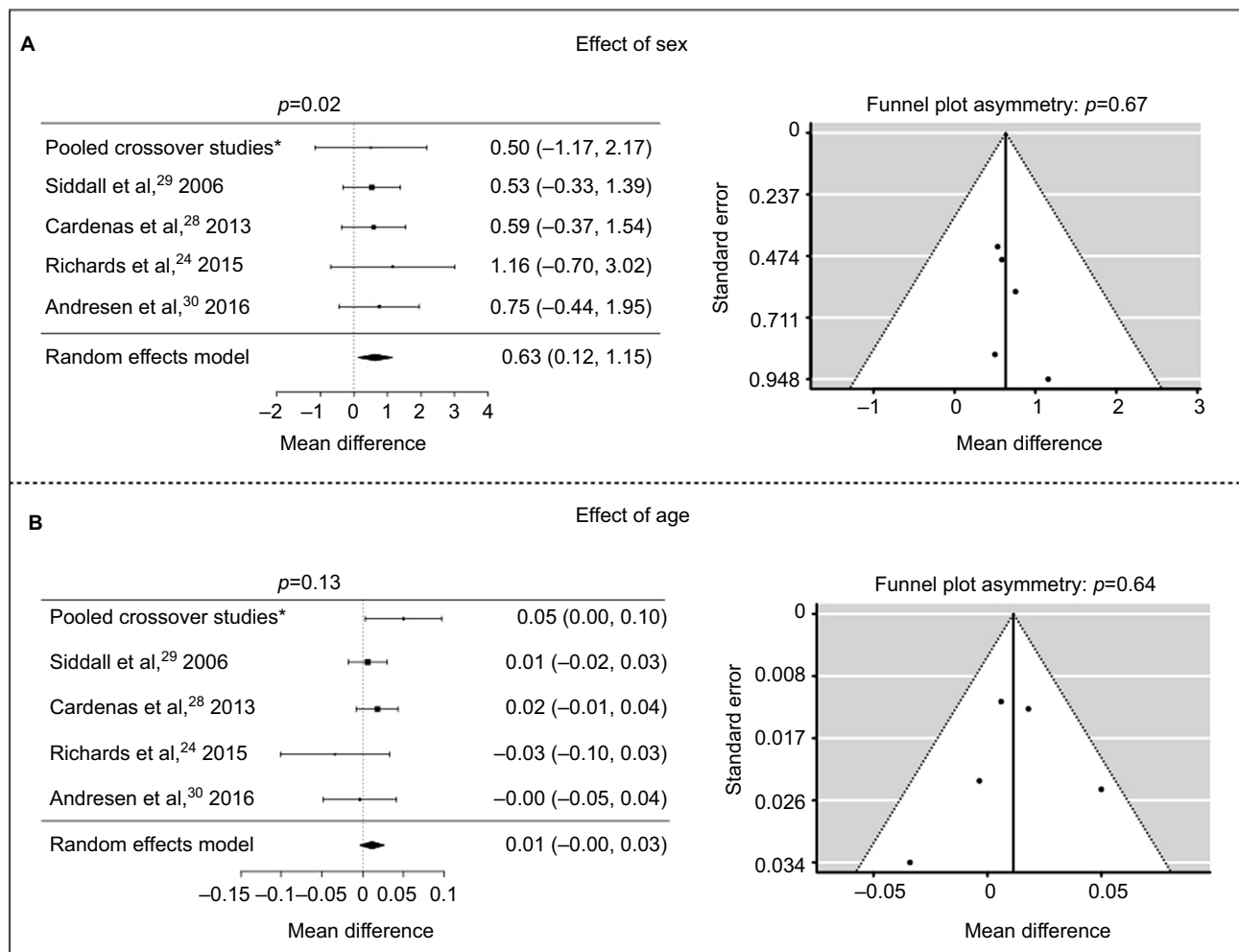
Figure 3 Effect of patients' characteristics on the placebo response.
Notes: (**A**) Age had no modulatory effect on the placebo response. (**B**) There was a significant main effect of sex. That is, being male was associated with higher placebo response. A negative mean difference indicates a reduction in pain score after placebo treatment. *Finnerup 2002 and Finnerup 2009:[22,23] cross-over designed studies. As there is a known trial-design effect on placebo response and to enable direct comparison with the parallel-designed studies, only patients who received placebo in the first arm were included for the analysis. To increase the sample size these two studies were pooled.
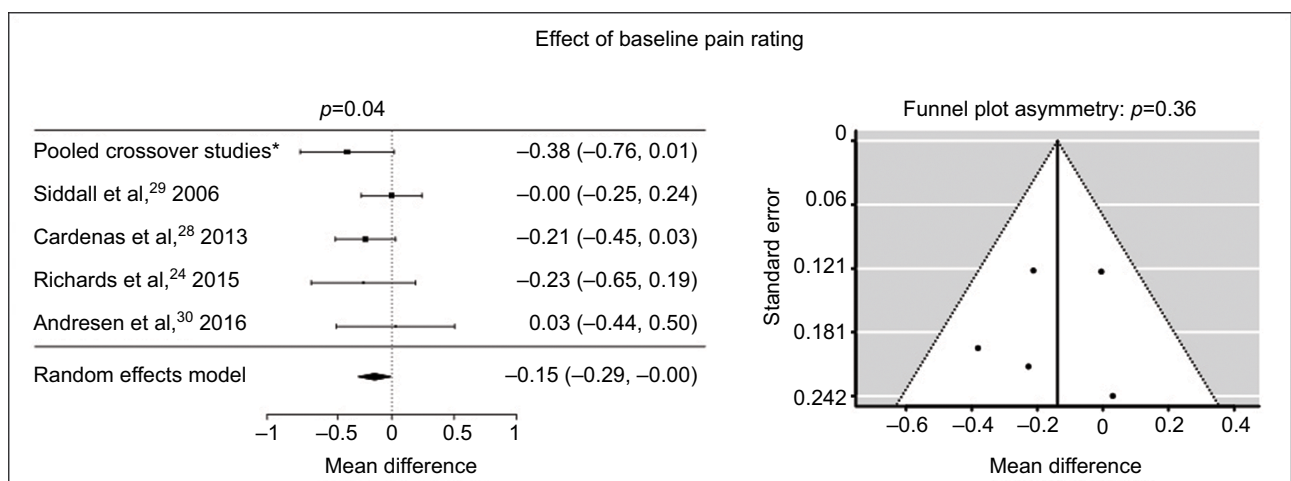
Figure 4 Effect of baseline pain intensity and duration of placebo treatment.
Notes: Higher baseline pain ratings at baseline were associated with greater placebo responses. A negative mean difference indicates a reduction in pain score after placebo treatment. *Finnerup 2002 and Finnerup 2009: cross-over designed studies.[22,23] As there is a known trial-design effect on placebo response and to enable direct comparison with the parallel-designed studies, only patients who received placebo in the first arm were included for the analysis. To increase the sample size these two studies were pooled.
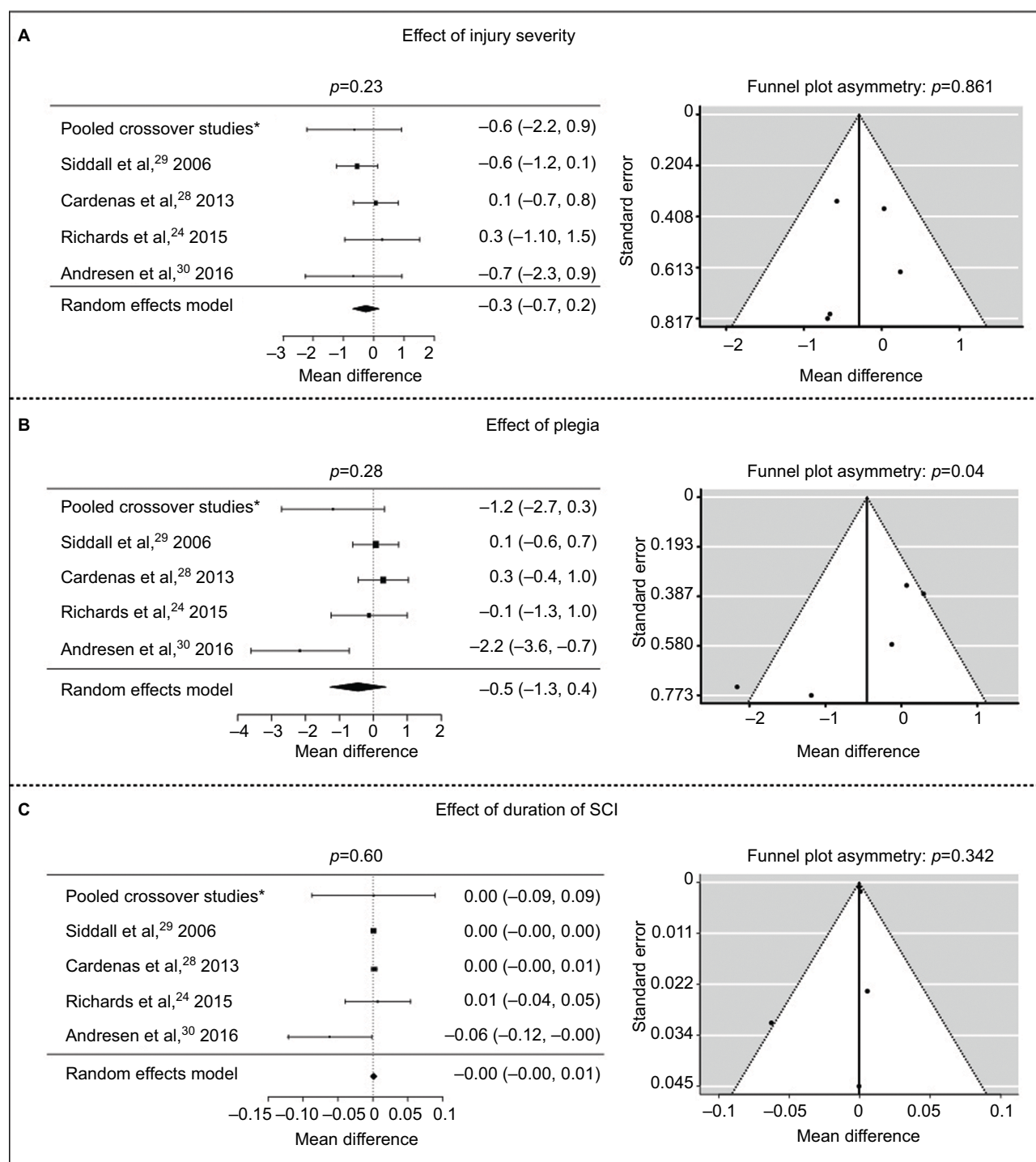
Figure 5 Effect of injury characteristics on the placebo response.
Notes: The placebo response was not affected by (**A**) injury completeness, (**B**) type of plegia (i.e., para- or tetraplegia), and (**C**) duration of spinal cord injury (SCI). A negative mean difference indicates a reduction in pain score after placebo treatment. *Finnerup 2002 and Finnerup 2009:[22,23] Cross-over designed studies. As there is a known trial-design effect on placebo response and to enable direct comparison with the parallel-designed studies, only patients who received placebo in the first arm were included for the analysis. To increase the sample size these two studies were pooled.
Abbreviation: SCI, spinal cord injury.

(i.e., none were performed after a drug had been approved for use in SCI neuropathic pain). Larger responses are associated with postapproval trials.[72] Future studies trialing pregabalin (i.e., a drug now approved for use in SCI neuropathic pain) could expect larger placebo responses than reported here.

Limitations of the study

There are some limitations of our analysis. The low number of trials limits the results of our IPD meta-analysis. Despite many advantages compared to conventional group-level meta-analyses,[15] individual patient-level meta-analysis will remain limited
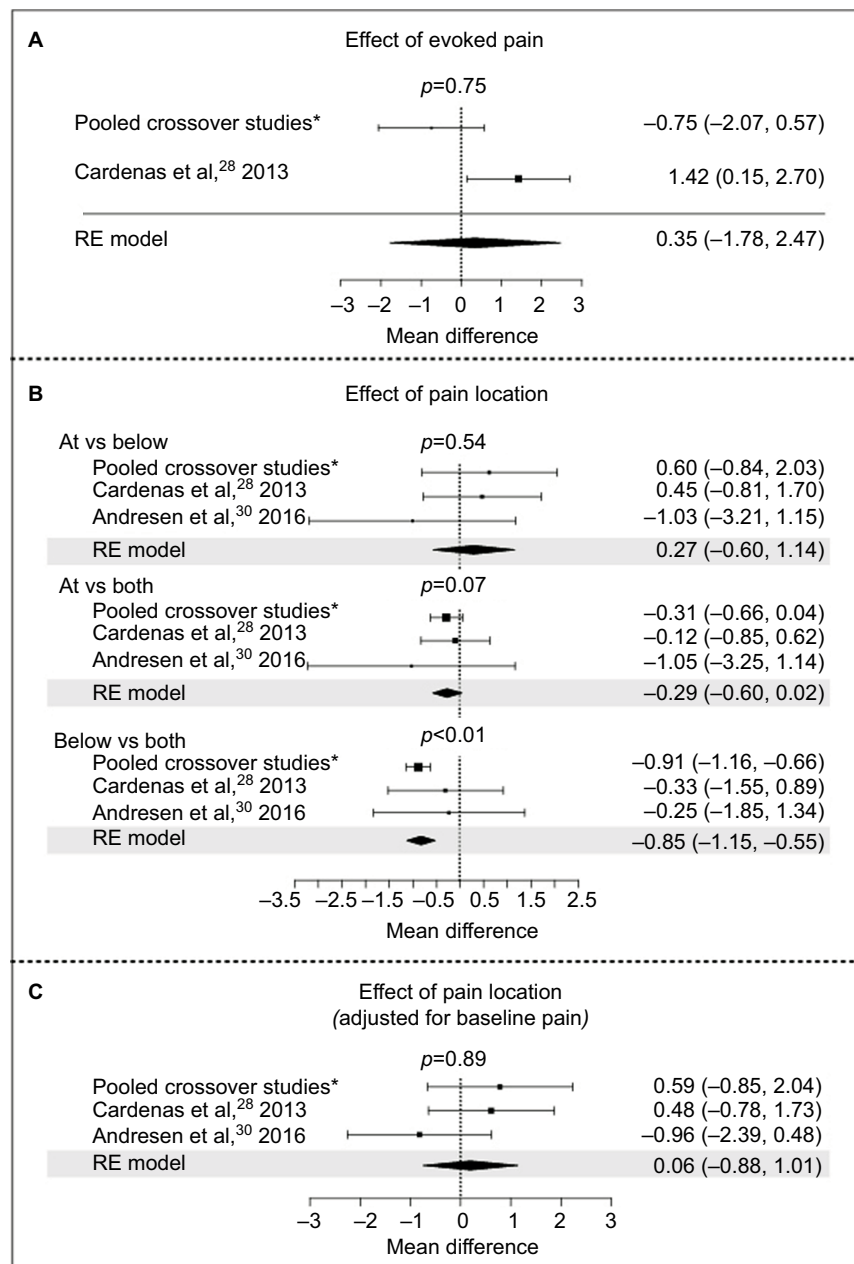
Figure 6 Effect evoked pain and pain location of pain (i.e., at level, below level, or both) on the placebo response.
Notes: A negative mean difference indicates a reduction in pain score after placebo treatment. (**A**) The presence of evoked pain had no modulatory effect on the placebo response. (**B**) No difference in placebo response was detected between patients with at-level pain and patients with below level pain or both. Patients with below pain exhibited higher placebo responses compared to those who had at- and below level pain (i.e., both). (**C**) However, this effect of location was diminished when adjusting for baseline pain rating. Thus, the effect was only related to the baseline pain being higher. *Finnerup 2002 and Finnerup 2009:[22,23] Cross-over designed studies. As there is a known trial-design effect on placebo response and to enable direct comparison with the parallel-designed studies, only patients who received placebo in the first arm were included for the analysis. To increase the sample size these two studies were pooled.
Abbreviation: RE, random effects.

by the inclusion of "accessible" study data. While accessibility is undoubtedly improving, open access data repositories with sufficient information to perform secondary data analyses are urgently needed.[73] In addition to accessing data, important variables, such as a measure of expectation (e.g., whether a patient accurately predicted if they were in the placebo group), were not examined. As a surrogate of expectation, we did consider duration of injury. That duration had no effect on placebo responses may reflect that only chronic subjects were included (>4.6 years postinjury on average, see Table 1). Future studies should aim to systematically address expectation in both the placebo and active treatment groups.[59–62,74–76]
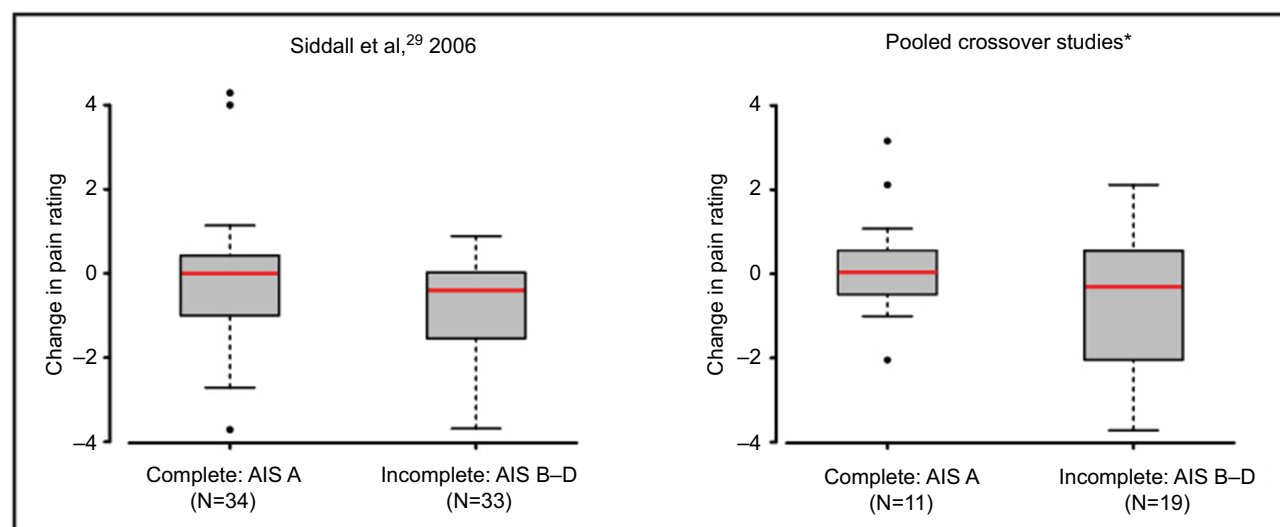
Figure 7 Effect of injury completeness on placebo response.

Notes: There was a trend towards larger placebo responses in individuals with incomplete injuries (versus complete). A negative change in pain rating indicates a reduction in pain score after placebo treatment. *Finnerup 2002 and Finnerup 2009:[22,23] Cross-over designed studies. As there is a known trial-design effect on placebo response and to enable direct comparison with the parallel-designed studies, only patients who received placebo in the first arm were included for the analysis. To increase the sample size these two studies were pooled

Abbreviation: AIS, Association Impairment Scale.

Conclusion

Our meta-analysis of IPD demonstrates that low placebo responses are a hallmark of neuropathic pain in RCTs of individuals with chronic SCI. Contrasting the hypothesis that disease-specific factors contribute to lower placebo responses, injury and pain characteristics were not predictive of changes in pain rating. All identified predictors – baseline pain and sex – are not disease-specific and, thus, poorly explain a reduced capacity to report placebo. These factors, however, still remain crucial to consider when designing clinical trials.

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Disclosure

The authors report no conflicts of interest in this work.

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