Placebo Effects on Itch: A Meta-Analysis of Clinical Trials of Patients with Dermatological Conditions

Antoinette I.M. van Laarhoven[1,2,3], Ineke M. van der Sman-Mauriks[1], A. Rogier T. Donders[4], Mathilde C. Pronk[1], Peter C.M. van de Kerkhof[5] and Andrea W.M. Evers[1,2,3]

Although placebo contributes to the effects of treatment for various symptoms and conditions, its effect on itch has rarely been investigated. In this meta-analysis, the magnitude of the placebo effect on itch was systematically investigated in clinical trials including patients with chronic itch due to atopic dermatitis, psoriasis, or chronic idiopathic urticaria. From searches in four databases, 34 articles were included in the quantitative analyses. Placebo treatment significantly decreased itch (1.3 out of 10, 95% confidence interval 1.02–1.61) compared with baseline itch (effect size 0.55), indicating that placebo effects have a considerable role in these patients' treatment.

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INTRODUCTION

Placebo effects are known to contribute to the effects of treatment for various conditions and symptoms (Benedetti, 2008). Placebo effects have been studied extensively with respect to pain and other conditions—for example, in several meta-analyses that reported on the analgesic effects of placebo in clinical trials. Overall, effect sizes (ESs) vary largely across studies and range from small to large (Vase *et al.*, 2002; Hrobjartsson and Gotzsche, 2004; Vase *et al.*, 2009). The magnitude of the analgesic effect of placebo mainly depends on the study design, being largest in studies investigating placebo mechanisms, when the expectations of pain relief are optimized as much as possible and smaller when placebo effects are minimized (Vase *et al.*, 2009).

In contrast to pain, there is less research on the role of placebo effects in the treatment of chronic itch, the most common symptom of patients with skin disease. A substantial proportion of patients with atopic dermatitis (AD), psoriasis (PSO), and chronic idiopathic urticaria (URT), highly prevalent skin conditions, experience chronic itch (Verhoeven *et al.*, 2007; Weisshaar and Dalgard, 2009; Ständer *et al.*, 2010). It can adversely affect patients' quality of life—e.g., patients experience sleep disturbances, fatigue, and symptoms of psychological distress, such as anxiety and depressive symptoms (Schneider *et al.*, 2006; Ständer *et al.*, 2010). The effect of treatment often varies considerably between patients, in which placebo effects may also have a role.

The effects of placebo on itch have barely been studied. There is only limited experimental evidence, in line with what is known of placebo effects on pain (Colloca *et al.*, 2013), that placebo (and nocebo) effects on itch can be induced experimentally (Van Laarhoven *et al.*, 2011; Bartels *et al.*, 2014). However, the role of placebo effects on itch in the clinical setting has, to our knowledge, not yet been investigated. Therefore the aim of this meta-analysis was to investigate the magnitude of the effect of placebo on itch in randomized controlled trials that investigated the itch-reducing effects of regular pharmacological treatments in highly prevalent chronic dermatological conditions with itch as the main symptom, specifically patients with AD, PSO, or URT. For the purpose of the present study, we were particularly interested in the reduction in itch as evoked in the placebo conditions of these trials. In line with placebo effects on chronic pain, it was hypothesized that placebo effects on itch would occur in clinical trials involving dermatological patients with chronic itch.

RESULTS

Study selection

Of the 11,919 and 33 records retrieved from the initial search in four databases and hand-searching, respectively, 5475 studies were duplicates, 6379 studies were excluded on the basis of screening of the titles/abstracts, and 6 studies that were relevant to read were not available full text (see Supplementary Figure S1 online for the flow diagram of the numbers of studies included in this meta-analysis). The eligibility of 159 studies was assessed in full-text articles. Of these, 89 studies were excluded for various reasons, i.e., because the study was not a randomized controlled trial ($n=7$), no (quantitative) itch scores were measured (mainly PSO), or itch was measured as part of a combined score (e.g.,

[1]*Unit Health, Medical and Neuropsychology, Faculty of Social and Behavioural Sciences, Leiden University, Leiden, The Netherlands;* [2]*Leiden Institute for Brain and Cognition (LIBC), Leiden University, Leiden, The Netherlands;* [3]*Department of Medical Psychology, Radboud University Medical Center, Nijmegen, The Netherlands;* [4]*Department for Health Evidence, Radboud University Medical Center, Nijmegen, The Netherlands and* [5]*Department of Dermatology, Radboud University Medical Center, Nijmegen, The Netherlands*

Correspondence: Antoinette I.M. van Laarhoven, Unit Health, Medical and Neuropsychology, Faculty of Social and Behavioural Sciences, Leiden University, P.O. Box 9555, Leiden 2300 RB, The Netherlands. E-mail: A.vanlaarhoven@fsw.leidenuniv.nl

Abbreviations: AD, atopic dermatitis; ES, effect size; PSO, psoriasis; RCT, randomized controlled trial; URT, chronic (idiopathic) urticaria

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Dermatology Life Quality Index; $n=60$), no patients (with a relevant skin condition) were included or the patient sample was unspecified ($n=9$), >80% of the included patients had another specific diagnosis in addition to the dermatological condition of interest ($n=3$), all patients started with a concurrent treatment in addition to placebo ($n=3$), itch was induced after placebo administration and baseline measurements were not possible ($n=2$), the data had been published previously ($n=3$), or the study was published before 1970 ($n=2$). Of the remaining 70 studies that were included in the qualitative synthesis, 34 were included in the meta-analysis because the required data were available.

Study characteristics

The characteristics of the reviewed studies ($n=70$) are given in Table 1. The review included 12 218 patients with a skin disease, 4141 of whom were included in the placebo conditions—namely, 502 with AD, 1864 with PSO, 1719 with URT, and 56 with MIX (i.e., different dermatological conditions, predominantly AD and URT). In 54 studies (77.1%), systemic placebo treatment was administered orally (pills or solution), in 15 studies (21.4%) by injection, and in 1 study (1.4%) by a combination of both. Sixty-nine studies (98.6%) investigated the effects on clinical itch; 1 study (1.4%) focused on itch-inducing stimuli (Hosogi *et al.*, 2006). Seventeen studies (24%) had a cross-over design; the remaining 53 studies had a parallel-group design (76%). Except for two single-blind studies (Hosogi *et al.*, 2006; Wan, 2009), all were double-blind (97%). Study duration ranged from 1 day to 24 weeks.

Risk of bias within and across studies

The quality of the 70 included studies varied (see Supplementary Figures S2 and S3 online for the authors' risk of bias assessment), and only 6 studies met all 6 validity criteria and thus were of minimal risk of bias. Methods of randomization were adequate in 37% of the studies, 59% did not specify the randomization method, and 4% reported inadequate methods. In 41% of the studies, allocation of participants was adequately concealed, in 51% the concealment was unclear, and in 7% the concealment was inadequate—for example, the article did not report randomization or the study was single-blind. Blinding of participants, personnel, and outcome assessors was rated low in 96% of the studies because of the double-blind design, in 1% of the studies it was unclear (i.e., the study was described as double-blinded but reported inadequate allocation concealment methods), whereas single-blind studies (3%) were characterized as having a high risk of bias. Incomplete outcome data were scored low in 44% of the studies, unclear in 43%, and high in 13% of the studies—e.g., when the reason for missing outcome data was considered to be related to the outcome and drop-outs were not included in the statistical analyses. Selective reporting bias was scored low in 59% of the studies, unclear in 39% of the studies, and high in 3% of the studies, for the reason that the study did not predefine analyses or failed to report primary outcomes for all evaluation moments. With respect to other bias, in 54% of the studies there was a low risk, in 30% of the studies there was insufficient information to assess bias, and in 16% of the studies there was high risk of other bias, mainly because of drop-out rates >40% of the baseline sample size.

Across the studies, there was a substantial heterogeneity, with an overall I^2 of 92%. Inspection of the funnel plot does not indicate publication bias.

Placebo effects on itch

Figure 1 displays the forest plot of the random-effects meta-analysis investigating the magnitude of placebo effects on itch in clinical trials. Overall, there was a mean difference in itch of 1.31 points on a scale from 0 to 10 (95% confidence interval (CI) 1.02–1.61, $I^2=92\%$), with lower levels of itch being reported after placebo treatment than at baseline. This equals a mean reduction of 24% of itch severity, considering that the level of itch at baseline was on average 5.43. The standardized mean difference analysis revealed an overall moderate–large ES of 0.55 (95% CI 0.40–0.70, $I^2=88\%$). The mean decrease in itch in the studies that provided insufficient information to be included in the meta-analysis, but for which the relevant means were available ($n=14$), was 1.59 on a scale from 0 to 10.

Secondary analyses

For the individual dermatological conditions, the mean decrease in itch within the placebo condition was 0.75 (95% CI 0.12–1.39, $I^2=79\%$) for AD, 1.04 (95% CI 0.54–1.53, $I^2=88\%$) for PSO, and 1.71 (95% CI: 1.28–2.15, $I^2=93\%$) for URT, showing larger ES for URT 0.71 (95% CI 0.50–0.91, $I^2=86\%$) and PSO 0.45 (95% CI 0.23–0.66, $I^2=86\%$) than for AD 0.30 (95% CI 0.05–0.56, $I^2=64\%$). The mean difference in itch was significant across conditions ($P=0.03$). There was no significant difference between the effect of oral (mean difference 1.41; 95% CI 0.87–1.94, $I^2=94\%$) versus injected (mean difference 1.21; 95% CI 0.75–1.68, $I^2=85\%$) placebo treatment ($P=0.60$). In the explorative analyses, which only included studies that were published the past 20 (since 1994) and 10 years (since 2004), the overall mean difference in itch was 1.49 (95% CI 1.19–1.78, $I^2=92\%$) and 1.70 (1.29–2.12, $I^2=95\%$), respectively.

Sensitivity analyses

Sensitivity analyses testing the stability of the effects in relation to the correlation coefficient imputed for the SDs at baseline and at the end of placebo treatment ($r=0.5$) yielded a maximum variance of 2.2% of the main outcome (mean difference in itch ranging from 1.32 to 1.38). Sensitivity analyses after exclusion of the separate studies that had a high risk of bias for one of the risk of bias categories resulted in a maximum variance of 3.8% of the main outcome (mean difference in itch ranging from 1.31 to 1.36; I^2 range 92–93%). Exclusion of all studies that had a high risk of bias in one of the categories at once resulted in a mean decrease in itch of 1.57 (95% CI 1.23–1.92, $I^2=93\%$). After exclusion of the small studies (fewer compared with 25 patients in the placebo condition; $n=15$), the overall mean difference in itch was 1.47 (95% CI 0.99–1.94, $I^2=95\%$), indicating that placebo effects were smaller for the studies with smaller sample sizes.

Table 1. Study and patient characteristics of randomized controlled trials comparing an itch-reducing agent with a placebo included in the meta-analysis

No.	Study[a]	Sample size placebo (analyzed)[b]	Gender	Category of active treatment	Placebo administration route	Placebo treatment duration (weeks)	Study design	Blinding	Origin of itch
Atopic dermatitis									
1.	Berth-Jones and Graham-Brown, 1989	28 (24)	Unclear	Antihistamine	Oral	1	Cross-over	Double-blind	Clinical
2.	Berth-Jones and Graham-Brown, 1990	50 (45)	M + F	Natural component of opium	Oral	4	Cross-over	Double-blind	Clinical
3.	**Berth-Jones *et al.*, 2002**	28 (28)[c]	M + F	Immunomodulator	Oral	12	Cross-over	Double-blind	Clinical
4.	Ebata *et al.*, 1998	10 (10)	M + F	Benzodiazepine	Oral	1	Cross-over	Double-blind	Clinical
5.	Friedmann *et al.*, 2007	30 (29)[c]	M + F	Leukotriene receptor antagonist	Oral	8	Parallel	Double-blind	Clinical
6.	Frosch *et al.*, 1984	18 (16)	M + F	Antihistamine	Oral	4	Cross-over	Double-blind	Clinical
7.	**Hosogi *et al.*, 2006**	14 (14)	M + F	Antihistamine	Oral	0.1	Cross-over	Single-blind	Experimental: Histamine
8.	Kavli and Larsen, 1981	Unclear (9)	M + F	Antihistamine	Oral	12	Cross-over	Double-blind	Clinical
9.	Leung *et al.*, 1990	52 (45)	M + F	Immunomodulator	Injection	6	Parallel	Double-blind	Clinical
10.	**Lintu *et al.*, 2001**	40 (39)	M + F	Anti-fungal	Oral	4	Parallel	Double-blind	Clinical
11.	**Malekzad *et al.*, 2009**	20 (18)	M + F	Opioid receptor antagonist	Oral	2	Parallel	Double-blind	Clinical
12.	Meggitt *et al.*, 2006	21 (20)[c]	M + F	Immunomodulator	Oral	12	Parallel	Double-blind	Clinical
13.	**Munro *et al.*, 1994**	24 (10)	M + F	Immunomodulator	Oral	8	Cross-over	Double-blind	Clinical
14.	**Oldhoff *et al.*, 2005**	23 (22)	M + F	Immunomodulator	Injection	2	Parallel	Double-blind	Clinical
15.	**Pittler *et al.*, 2003**	15 (15)[c]	M + F	Autologous blood therapy	Injection	5	Parallel	Double-blind	Clinical
16.	Shupack *et al.*, 1991	11 (unclear)	M + F	Natural component of opium	Oral	2	Parallel	Double-blind	Clinical
17.	Sowden *et al.*, 1991	16 (12)	M + F	Immunomodulator	Oral	8	Cross-over	Double-blind	Clinical
18.	**Stiller *et al.*, 1994**	19 (17)	M + F	Immunomodulator	Injection	12	Parallel	Double-blind	Clinical
19.	Van Joost *et al.*, 1994	23 (23)	M + F	Immunomodulator	Oral	6	Parallel	Double-blind	Clinical
20.	**Wahlgren *et al.*, 1990a**	24 (24)	M + F	Antihistamine	Oral	1	Cross-over	Double-blind	Clinical
21.	**Wahlgren *et al.*, 1990b**	10 (10)	M + F	Immunomodulator	Oral (solution)	10	Cross-over	Double-blind	Clinical
22.	Wolff *et al.*, 2005	26 (26)[c]	M + F	Immunomodulator	Oral	12	Parallel	Double-blind	Clinical
Psoriasis									
23.	Bissonnette *et al.*, 2006	41 (41)[c]	M + F	Immunomodulator	Oral	12	Parallel	Double-blind	Clinical
24.	Bushmakin *et al.*, 2013	50 (34)	M + F	Immunomodulator	Oral	12	Parallel	Double-blind	Clinical
25.	Feldman *et al.*, 2005	166 (166)	M + F	Immunomodulator	Injection	12	Parallel	Double-blind	Clinical
26.	**Gordon *et al.*, 2014**	38 (38)[c]	M + F	Immunomodulator	Oral	12	Parallel	Double-blind	Clinical
27.	**Gordon *et al.*, 2003**	187 (187)[c]	M + F	Immunomodulator	Injection	12	Parallel	Double-blind	Clinical
28.	**Krueger *et al.*, 2005**	193 (193)[c]	M + F	Immunomodulator	Injection	12	Parallel	Double-blind	Clinical

Table 1. (Continued)

No.	Study[a]	Sample size placebo (analyzed)[b]	Gender	Category of active treatment	Placebo administration route	Placebo treatment duration (weeks)	Study design	Blinding	Origin of itch
29.	Leonardi *et al.*, 2012	27 (26)[c]	M + F	Immunomodulator	Injection	16	Parallel	Double-blind	Clinical
30.	**Mamolo *et al.*, 2013**	50 (43)[c]	M + F	Immunomodulator	Oral	12	Parallel	Double-blind	Clinical
31.	Ortonne *et al.*, 2005	264 (262)	Unclear	Immunomodulator	Injection	12	Parallel	Double-blind	Clinical
32.	Papp *et al.*, 2012	88 (88)[c]	M + F	Immunomodulator	Oral	16	Parallel	Double-blind	Clinical
33.	**Revicki *et al.*, 2008**	53 (53)[c]	M + F	Biologic + DMARD	Oral + Injection	16	Parallel	Double-blind	Clinical
34.	**Revicki *et al.*, 2007**	397 (347)[c]	M + F	Biologic	Injection	16	Parallel	Double-blind	Clinical
35.	Tyring *et al.*, 2006	309 (307)	M + F	Immunomodulator	Injection	1	Parallel	Double-blind	Clinical
Chronic idiopathic urticaria									
36.	**Abu Shereeah *et al.*, 1998**	9 (8)	M + F	Antihistamine	Oral	3	Parallel	Double-blind	Clinical
37.	Bernstein and Bernstein, 1986	27 (24)	M + F	Antihistamine	Oral	8	Parallel	Double-blind	Clinical
38.	Breneman *et al.*, 1995	63 (61)	M + F	Antihistamine	Oral	4	Parallel	Double-blind	Clinical
39.	**Bressler *et al.*, 1989**	9 (7)	M + F	Calcium channel antagonist	Oral	4	Cross-over	Double-blind	Clinical
40.	**Brostoff *et al.*, 1996**	28 (28)[c]	M + F	Antihistamine	Oral	4	Parallel	Double-blind	Clinical
41.	**Camarasa *et al.*, 2001**	20 (18)[c]	M + F	Antihistamine	Oral	3	Parallel	Double-blind	Clinical
42.	Di Lorenzo *et al.*, 2004	40 (5)	M + F	Antihistamine + Leukotriene receptor antagonist	Oral	6	Parallel	Double-blind	Clinical
43.	**Dubertret *et al.*, 1999**	80 (80)[c]	M + F	Antihistamine	Oral	4	Parallel	Double-blind	Clinical
44.	Dubertret *et al.*, 2007	69 (69)[c]	M + F	Antihistamine	Oral	4	Parallel	Double-blind	Clinical
45.	Ferguson *et al.*, 1985	Unclear (14)	M + F	Antihistamine	Oral	2	Cross-over	Double-blind	Clinical
46.	**Finn *et al.*, 1999**	95 (90)[c]	M + F	Antihistamine	Oral	4	Parallel	Double-blind	Clinical
47.	Fox *et al.*, 1986	26 (26)[c]	M + F	Antihistamine	Oral	8	Parallel	Double-blind	Clinical
48.	Gibson *et al.*, 1984	20 (20)	M + F	Antihistamine	Oral	0.7	Cross-over	Double-blind	Clinical
49.	**Gimenez-Arnau *et al.*, 2007**	111 (111)[c]	M + F	Antihistamine	Oral	6	Parallel	Double-blind	Clinical
50.	Goh *et al.*, 1991	32 (28)	M + F	Antihistamine	Oral	1	Cross-over	Double-blind	Clinical
51.	**Juhlin and Arendt, 1988**	30 (30)	M + F	Antihistamine	Oral	2	Cross-over	Double-blind	Clinical
52.	Kailasam and Mathews, 1987	24 (23)	M + F	Antihistamine	Oral	8	Parallel	Double-blind	Clinical
53.	Kalivas *et al.*, 1990	74 (68)	Unclear	Antihistamine	Oral	4	Parallel	Double-blind	Clinical
54.	**Kaplan *et al.*, 2013**	84 (83)[c]	M + F	Immunomodulator	Injection	12	Parallel	Double-blind	Clinical
55.	**Kaplan *et al.*, 2005**	92 (92)[c]	M + F	Antihistamine	Oral	4	Parallel	Double-blind	Clinical
56.	Kapp and Pichler, 2006	85 (85)[c]	M + F	Antihistamine	Oral	4	Parallel	Double-blind	Clinical
57.	**Kosnik and Subic, 2011**	24 (22)	M + F	Leukotriene receptor antagonist	Oral	2	Cross-over	Double-blind	Clinical
58.	**Magerl *et al.*, 2013**	26 (26)[c]	M + F	Lipid raft modulator	Oral	4	Parallel	Double-blind	Clinical

Table 1. (Continued)

No.	Study[a]	Sample size placebo (analyzed)[b]	Gender	Category of active treatment	Placebo administration route	Placebo treatment duration (weeks)	Study design	Blinding	Origin of itch
59.	**Maurer *et al.*, 2011**	22 (22)[c]	M + F	Immunomodulator	Injection	24	Parallel	Double-blind	Clinical
60.	**Maurer *et al.*, 2013b**	79 (79)[c]	M + F	Immunomodulator	Injection	12	Parallel	Double-blind	Clinical
61.	Monroe *et al.*, 2003	110 (75)[c]	M + F	Antihistamine	Oral	6	Parallel	Double-blind	Clinical
62.	**Nelson *et al.*, 2000**	79 (79)[c]	M + F	Antihistamine	Oral	4	Parallel	Double-blind	Clinical
63.	Pacor *et al.*, 2001	17 (17)	M + F	Antihistamine + Leukotriene receptor antagonist	Oral	4	Parallel	Double-blind	Clinical
64.	**Peremans *et al.*, 1981**	17 (16)	M + F	Antihistamine	Oral	5	Parallel	Double-blind	Clinical
65.	Ring *et al.*, 2001	95 (95)[c]	M + F	Antihistamine	Oral	6	Parallel	Double-blind	Clinical
66.	**Saini *et al.*, 2011**	21 (21)[c]	M + F	Immunomodulator	Injection	4	Parallel	Double-blind	Clinical
67.	Wan, 2009	30 (17)	M + F	Antihistamine + Leukotriene receptor antagonist	Oral	4	Parallel	Single-blind	Clinical
68.	**Zuberbier *et al.*, 2010**	184 (181)[c]	M + F	Antihistamine	Oral	4	Parallel	Double-blind	Clinical
Mixed population (AD and URT)									
69.	Henz *et al.*, 1998	47 (11 + 28)	M + F	Antihistamine	Oral	2	Parallel	Double-blind	Clinical
70.	Monroe, 1989	17 (17)	Unclear	Opioid receptor antagonist	Oral	1	Parallel	Double-blind	Clinical

Abbreviations: DMARD, disease-modifying anti-rheumatic drug; F, female; M, male.

[a]Studies in bold have been included in the quantitative meta-analysis.

[b]Sample size placebo at start (numbers analyzed).

[c]Indicates that the numbers of patients were analyzed on the basis of modified intention to treat—e.g., including all randomized patients who received at least one dose of the study drug and/or for whom at least one postbaseline value was available.

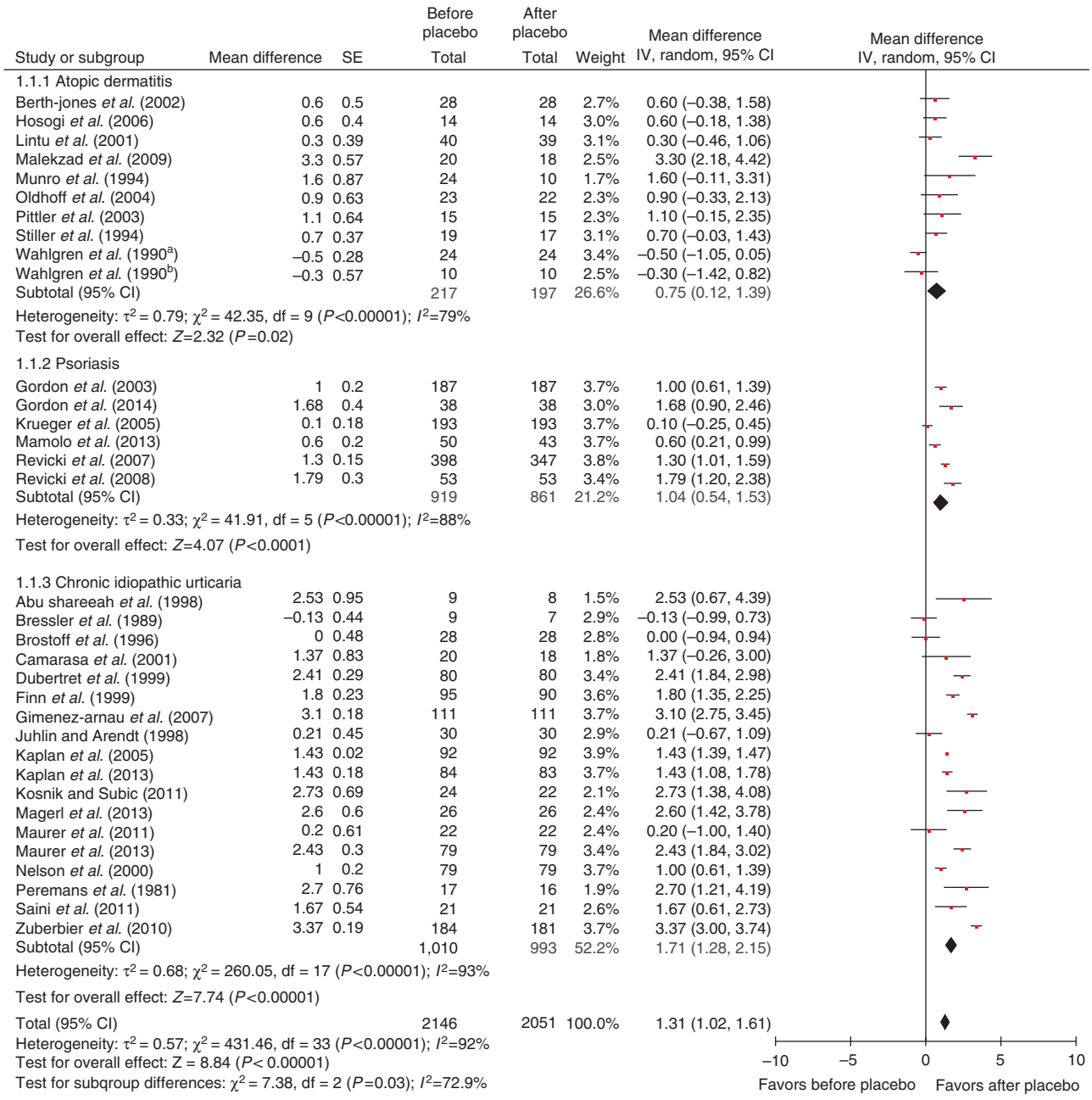

Figure 1. Forest plot of the random effects meta-analysis of the studies included in the quantitative analysis. CI, confidence interval.

DISCUSSION

This meta-analysis investigated the effect of placebo on itch in patients with chronic itch due to AD, PSO, or URT, who participated in clinical trials investigating regular pharmacological treatment for their skin condition and who were blindly randomized to the placebo-control condition. Overall, itch was significantly reduced by 24% from baseline. The ES (0.55) was medium to large, indicating that itch can be considerably reduced by placebo effects. Placebo effects on itch were largest in patients with URT, followed by patients with PSO and AD. The route of administration did not significantly influence the effect of placebo.

The present results are generally in line with those for meta-analyses of the effect of placebo in patients with chronic pain—e.g., in patients with fibromyalgia pain decreased by 1.4 points out of 10 (Hauser *et al.*, 2011), and in patients with osteoarthritis an ES of 0.51 was found (Zhang *et al.*, 2008) but the ES was higher than in other meta-analyses involving patients with various (acute) pain conditions (0.15–0.27) (Vase *et al.*, 2002; Hrobjartsson and Gotzsche, 2004; Vase *et al.*, 2009). The majority of the patients included in the current meta-analysis had long-term itch that was resistant to treatment, and itch was one of the main symptoms of their dermatological condition. The relatively

large effect of placebo on itch may be explained by the fact that itch is highly susceptible to suggestion, as supported by experimental research (Papoiu *et al.*, 2011; Van Laarhoven *et al.*, 2011).

From a clinical point of view, the magnitude of the placebo effect on itch (overall itch reduction of 24%) is considered a minimally important difference in patients with URT, for whom a cutoff for itch improvement of 4.5–5 out of 21 has been reported (Mathias *et al.*, 2012). It is also somewhat less compared with the clinically important difference of $\geqslant$30% defined for PSO (Mamolo *et al.*, 2014). In clinical trials of pain, a decrease of 24% would be characterized as a minimally to moderately important clinical improvement (Dworkin *et al.*, 2009). Furthermore, the effect of placebo on itch differed by skin condition, being largest in patients with URT, followed by PSO and AD. The smaller effect of placebo in patients with AD is probably because these patients generally receive topical treatment or phototherapy (Eichenfield *et al.*, 2014; Sidbury *et al.*, 2014), whereas systemic treatment is preferred for patients with PSO or URT (Menter *et al.*, 2009; Maurer *et al.*, 2013a). Consequently, patients' expectations of the treatment may have been more positive in the patients with PSO and URT than in the patients with AD. Moreover, the magnitude of the placebo effect on itch was greater in the more recent and higher quality studies, more often involving patients with PSO and URT, because of improvements in study quality and in the effectiveness of the active treatments over time, which might increase patients' positive expectations of treatment, and hence the reduction in itch caused by placebo (Colloca and Miller, 2011).

Although the underlying mechanisms of AD, PSO, and URT and associated itch are largely unknown, it is clear that the clinical manifestation, underlying pathophysiology, and effectiveness of treatments differ across these conditions (e.g., Guttman-Yassky *et al.*, 2011; Saini, 2014). However, placebo effects can, depending on the patient's expectations and specific context, affect a wide range of brain regions and biochemical pathways (e.g., Pollo *et al.*, 2011). For example, it has been shown that antinociceptive pathways can be activated in pain and that dopamine can be released in Parkinson's disease (Benedetti, 2008; Pollo *et al.*, 2011). Similarly, it is also likely that various itch-pathways—e.g., mediated by histamine or substance P—can be affected by placebo effects. More research to the mechanisms underlying placebo effects in (different types of) itch is warranted.

The study had some limitations. First, it compared the levels of itch at the end of placebo treatment with the levels of itch at baseline. A no-treatment control condition would have been a better comparator compared with the baseline levels of itch, to exclude the possibility that the reduction in itch was due to regression to the mean or natural course of disease (Barnett *et al.*, 2005; Miller and Rosenstein, 2006). However, with the clinical trials currently available, the present approach is the best way to investigate the effects of placebo on itch. Second, although heterogeneity across studies was high, secondary and sensitivity analyses did not reveal one major source of heterogeneity—e.g., skin condition or study quality. The random-effects model was selected to take into account the expected heterogeneity (Hedges and Vevea, 1998). Third, although relevant data for the placebo condition were not fully available for several studies, we found no indications for publication bias in the funnel plot. Moreover, potential publication bias would probably be in favor of active treatment conditions, so that the present study might have underestimated the magnitude of placebo effects on itch. Finally, earlier studies of the analgesic effect of placebo have shown that placebo effects are stronger in mechanistic studies than in clinical trials (Vase *et al.*, 2002), probably because of the certainty of the suggestions given, suggesting that the current study does reflect a rather conservative indication of the magnitude of placebo effects on itch. Future clinical studies would be recommended to report on the underlying pathophysiology, as well as the extent to which the itch-reducing effects of the treatment had been emphasized.

In conclusion, placebo would appear to have a substantial effect in the treatment of itch in dermatological patients with chronic itch. As it is recognized that both the certainty of the suggestions given along with treatment and conditioning principles affect the efficacy of that treatment (Vase *et al.*, 2002; Pacheco-Lopez *et al.*, 2006), making use of the placebo effect in an open manner and under strict ethical conditions (Colloca and Miller, 2011; Rief *et al.*, 2011) might improve the efficacy of itch-reducing treatments in clinical dermatological practice.

METHODS

Protocol and registration

The meta-analysis was performed according to the PRISMA Statement (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) (Moher *et al.*, 2009) and the recommendations of the Cochrane Collaboration (Higgins and Green, 2009) (www.cochrane-handbook.org), within the (word) limitations of the journal. The study protocol has been published in the Prospero registry (CRD42013006053).

Information sources and searches

The databases Pubmed, PsycInfo, Embase, and the Cochrane Library were searched from inception until 6th July 2014 by the first author, using the following key terms: ''itch'' or ''pruritus'' and ''placebo'', ''sham'' or ''dummy/ies''; animal studies were excluded. In the Supplementary Table S1 online, the specific MeSH terms and Boolean operators used for Pubmed are shown (for the other three databases, comparable terms, e.g., MeSH and EMTREE, were used). In addition, the references of eligible studies and studies that cited the eligible studies were hand-searched for relevant articles.

Eligibility criteria

The titles and abstracts of the identified studies were screened by the first author according to the following criterion: the study had to be an original randomized placebo-controlled trial investigating regular systemic medication in patients with a chronic dermatological condition associated with chronic itch—namely, AD, PSO, or URT. The eligibility criteria are described in more detail in the Supplementary Material online.

Study selection

The full text of potentially eligible studies, including those for which there was any doubt about the eligibility based on the abstract, was

retrieved via online university libraries or the authors. The eligibility of the full-text articles was evaluated by the first author; a second reviewer assisted if there was doubt about article eligibility. Discrepancies were resolved by discussion with a third reviewer.

Data collection process and data items

The following data were extracted from the included studies by the use of a standardized form, developed prior to the meta-analysis: population and participant demographics; details of the active and placebo interventions; details of the study design; itch outcome measures; and relevant data for meta-analysis—i.e., sample size, mean, and SD of the (change of the) measurements before and after placebo. The data were extracted by two review members. Ambiguities were identified and rechecked, and consensus was achieved through discussion. If needed, a third review member reviewed the data to reach consensus. Missing data were requested from study authors.

Risk of bias in individual studies and across studies

The quality of all included studies was assessed using the Cochrane risk of bias tool version 5.0.2. The following categories were evaluated for each study: Sequence generation, Allocation concealment, Blinding of participants, personnel, and outcome assessors (as one category), Incomplete outcome data, Selective outcome reporting, and Other sources of bias (with a main focus on drop-out rate, baseline differences across treatment groups). These categories were scored with yes (i.e., low risk of bias), no (i.e., high risk of bias), or unclear risk of bias. Two review members independently assessed the quality of the included studies using this tool. Disagreements for particular studies were resolved through discussion, with the involvement of a third review member where necessary. Poor-quality studies (i.e., for which at least one risk of bias category was scored high) were identified, for which sensitivity analyses were conducted (see section Sensitivity analyses). In order to assess the risk of bias across studies, the funnel plot was inspected for the presence of publication bias.

Summary measures

The change (with SD or SE) in itch score from baseline to the end of placebo treatment was the preferred outcome to be collected. If not available, the itch scores at baseline as well as at the end of placebo treatment were retrieved. If multiple outcome data for itch were reported, the measurement that included the relevant data for the meta-analysis was selected, with a preference for actual itch scores obtained in the clinic (i.e., actual itch scores) over retrospective self-report or diary assessments. If only experimentally induced itch was investigated, then preference was given to data for itch induced at lesional skin with a commonly used stimulus such as histamine. In cross-over trials, only data from patients randomized first to the placebo condition were included (see also Vase *et al.*, 2002). Scientifically admissible numerical data were recorded by the first author and then checked for completeness and correctness by another author. Data displayed in graphs were extracted by two review authors. If relevant data could not be extracted from the publication, the authors of that study were asked to provide the remaining data. The authors of 36 studies were contacted and contact details of 5 authors were unavailable. Requested information could be provided from four studies.

Analyses

The exact procedures for the synthesis of results and main analysis, as well as secondary and sensitivity analyses, are described in the Supplementary Material online.

CONFLICT OF INTEREST

The authors state no conflict of interest.

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SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at http://www.nature.com/jid

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