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

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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.,

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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.