Targeted Use of Placebo Effects Decreases Experimental Itch in Atopic Dermatitis Patients: A Randomized Controlled Trial

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Evidence from pain research shows that the effectiveness of active pharmacological treatments can be enhanced by placebo effects. The “open drug administration” is superior to “hidden drug administration.” In a randomized controlled trial, we aimed to show that the targeted use of placebo effects increases the efficacy of an antihistamine (dimetindene) infusion in participants with atopic dermatitis. We openly infused dimetindene (drug) in full sight with information (intervention group 1: OPEN-DRUG+INST), openly infused drug with an additional classical conditioning learning experience (intervention group 2: OPEN-DRUG+INST+COND) or infused drug without any information or sight (i.e., hidden administration (control group 1: HIDDEN-DRUG)). Control group 2 received a placebo infusion (saline) declared as dimetindene and also experienced the conditioning experience (PLAC+INST+COND). Itch was experimentally induced with histamine via a skin prick test. Outcome was assessed at the subjective (primary end point: experimental itch intensity, numeric rating scale), and objective level (secondary end point: wheal size, mm²). Experimental-induced itch intensity decreased in all groups but at different rates ($P < 0.001$). The groups with the open administration, whether it was dimetindene or placebo, had significantly stronger reductions in itch compared to the HIDDEN-DRUG group (OPEN-DRUG+INST+COND: $P < 0.001$; OPEN-DRUG+INST: $P = 0.009$; and PLAC+INST+COND: $P < 0.001$). Additional drug conditioning mediated via expectation led to a stronger reduction of itching ($P = 0.001$). Results on wheal size were similar ($P = 0.048$), however, no significant difference between the HIDDEN-DRUG group and the PLAC+INST+COND group ($P = 0.967$) was found. We conclude that specifically generated targeted placebo effects can significantly increase the action of a drug (dimetindene) and should be used in clinical practice.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
- Effectiveness of analgesics consist of both a pharmacological and a psychological (placebo effect) component, which complements in an overall drug effect. Until now, there is no randomized controlled trial that investigated this issue in patients with chronic atopic dermatitis.

WHAT QUESTION DID THIS STUDY ADDRESS?
- This study did address the question, whether in patients with chronic atopic dermatitis the targeted application of placebo effects in addition to the pure pharmacological effectiveness of a drug can improve its overall drug action.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?
- By varying the treatment context, additional placebo effects of a drug can be built. Their targeted use can increase drug efficacy in patients with chronic atopic dermatitis.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?
- Treatment context factors should be systematically included in clinical pharmacological studies and the targeted use of placebo effects should be discussed for clinical practice.

Evidence from pain research in nonclinical samples show that drug administration accompanied by tailored information and attention leads to better overall drug outcomes.1–5 These so-called analgesic placebo effects are produced following positive expectancies elicited through verbal suggestions, conditioning and/or social observation.6–8 These placebo effects have the potential to significantly influence pain pathways by triggering physiological changes that could consequently affect not only the

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pain perception but also pharmacological efficacy and clinical outcomes in the context of pain management. The underlying psychological mechanisms of the placebo effect take place in the brain and activate a cascade of endogenous opioids and non-opioids. Placebo effects are closely related to the context in which a medication is given. These contextual factors trigger expectations about treatment outcomes. In this regard, the route of administration of a drug plays an important role in eliciting additional placebo effects: administration in an open perceptible manner by giving positive information about a drug effect and focusing the patients’ perception on positive treatment outcomes (learning experiences) leads to a positive treatment expectation of the patients and thus is important for its efficacy. If a patient receives a drug without any instructions (hidden medication context), no treatment expectation is established. To investigate such components of medication effects, the open-hidden paradigm is a proven placebo research model. However, to date, no studies investigating the treatment of itch with an open-hidden paradigm have been conducted in patients with atopic dermatitis.

Atopic dermatitis is characterized by intense itch, which results in a high psychological burden. The effective pharmacological treatment of itch is limited and has shown a wide range of variation regarding efficacy. This indicates the complexity of itch at the molecular level and suggests a meaningful role of psychological factors. Thus, in this research area in particular, it is of utmost importance to examine the effects of placebo effects on subjective and objective treatment outcomes to test whether they may have different effects on these two outcomes. There are first indications that placebo effects are more likely to raise in subjective than in objective measurements (cf. Kleine-Borgmann et al., 2019). Considering placebo effects based on classical conditioning, there are strong indications for their significant influence also on objective parameters.

There is evidence from placebo-controlled studies that placebo effects are of high relevance in allergy (e.g., allergen-specific immunotherapy). However, only a few studies have investigated placebo responses in patients with atopic dermatitis.

Our aim was to investigate whether the targeted application of placebo effects in addition to the pure pharmacological effectiveness of an antihistamine drug (dimetindene) can improve its overall drug action. For this purpose, we varied the context in which dimetindene was delivered. We compared (i) open drug administration (patients received positive instructions about the medication) and (ii) open drug administration with conditioning (patients received positive instructions about the medication and an itch-reducing experience prior to its administration) to hidden drug administration (patients did not know they received the medication). Furthermore, we controlled for these effects by comparing the open administration (positive instructions/conditioning) of the antihistamine with the administration, ceteris paribus, in a group receiving a placebo.

We hypothesized that both the open administration of antihistamine compared with its hidden administration (targeted use of placebo effects) and compared with a sham-antihistamine are superior in reducing histamine-induced itch and wheal size in participants with atopic dermatitis. Furthermore, we hypothesized that conditioning additional to the open administration of antihistamine (OPEN-DRUG+INST+COND) reveal superior results in reducing histamine-induced itch and wheal size compared to no conditioning (OPEN-DRUG+INST).

**METHODS**

**Approvals, ethics, consent, and permissions**

This study (EudraCT number 2008-008474-31) was conducted in accordance with the Declaration of Helsinki and was approved by the local ethics committee of the Regional Office of Health and Social Affairs Berlin (LaGeSo (Landesamt für Gesundheit und Soziales): Placebo Itching 01, ZS EK 14 301/09) and by the Federal Institute for Drugs and Medical Devices (BfArM: No. 4035425). All patients provided written informed consent.

**Study design**

This randomized controlled trial (RCT) was performed in adult patients with mild or moderate atopic dermatitis. We used a prospective placebo-controlled, open-hidden medication study design with additional conditioning and repeated measurements (pre, post, and 1 day after intervention). Via simple randomization, urn randomization without replacement, patients were randomly allocated to one of four equally sized treatment groups. They were unaware of their group allocation. A lot of dropout due to not fulfilling inclusion criteria during the baseline measurement or due to withdrawing consent, was replaced by putting their group lot back into the urn. After a lot was drawn by an independent clinician, both healthcare providers (physician and psychologist)—who were also collecting data and assessing outcomes—were informed about the group membership (single-blinded study). A complete masking of the examiners was not meaningful as the study design intended that they should influence the context of the intervention in a targeted way. After baseline measurements, patients were either left ignorant of the treatment (HIDDEN-DRUG), or were informed about receiving the highly effective anti-pruritic drug in the next steps of the examination.

Patients were divided into four groups: (i) open drug administration with verbal instructions emphasizing the positive aspects of the itch-reducing drug dimetindene (OPEN-DRUG+INST group); (ii) optimized open drug administration with the same instructions and an additional classical conditioning learning experience (OPEN-DRUG+INST+COND group); (iii) completely covert administration of the drug to control the influence of the isolated pharmacological effect (control 1: hidden medication, HIDDEN-DRUG group); and (iv) application of a pharmacologically inert, placebo substance with instructions about dimetindene and conditioning to control for the influence of the isolated effect of information and classical conditioning (control 2: PLC+INST+COND group).

This study was carried out in the Department of Dermatology and Allergology at the Charité-University Hospital Berlin and consisted of four trial phases: baseline, intervention, testing after intervention (time point 1: T1) and testing 24 hours after intervention (time point 2: T2).

**Participants**

The participants were 102 patients aged from 18 to 65 years with a severity index (SCORing Atopic Dermatitis (SCORAD)) below 50 points, had no acute eczema on their forearms, were free of past or current psychiatric and neurological disorders, and received neither systemic treatments for skin diseases nor used topical treatments on their arms in the previous 4 and 2 weeks, respectively. Patients with asthma, glaucoma, major cardiovascular diseases, tumors, prostatic hyperplasia, immuno-suppression, and/or serious dysfunction of the liver, kidneys, or thyroid were also excluded. Female participants were required to use sufficient contraception.
Figure 1  Procedure of the entire investigation including all measurements and interventions (2 days). NRS, numeric rating scale.
Procedures

Figure 1 shows the procedure of the entire investigation, including all measurements and interventions (2 days). Patients attended a comprehensive physical examination 1 to 28 days before the study (screening). On day 1 of the experiment (T1), patients underwent a prick test (an experimentally provoked itch sensation via skin prick test with histamine dihydrochloride), and after a 15-minute reaction time, itch intensity ratings on a numeric rating scale (NRS; 0 = no itch, 10 = maximum itch) were assessed every 10 seconds for 10 minutes. Patients were excluded when average ratings were below NRS 3, to avoid floor effects. A blood sample directly after the prick test was checked for abnormal deviations from standard safety laboratory parameters, and, if necessary, the patient was excluded from study participation. Eligible patients were informed that they would participate in a clinical study on the perception of itching and that they would either receive an approved and highly effective itch or placebo medication via infusion. Patients who gave their voluntary informed consent to participate in the study were randomly and blindly allocated to one of four equally sized treatment groups.

The experiment spanned 2 days (T1 and T2) and consisted of four trial phases (baseline, intervention, testing after the intervention (T1), and testing 24 hours after the intervention (T2)). Each trial phase included (i) a 15-minute infusion (dimetindene or saline) followed by (ii) a prick test (prick of histamine dihydrochloride or saline with a subsequent rating of itch perception on the NRS every 10 seconds for 10 minutes). The whole procedure lasted 2 hours each day.

T1, Baseline: Initially, an intravenous infusion of saline followed by a skin prick test with histamine (dihydrochloride) was administered on the same forearm.

T1, Intervention phase: After this baseline measurement, all patients were allocated to one of the four groups (Figure 2) and received their corresponding infusion: either the dimetindene infusion (with or without information) or the placebo infusion (saline) declared as dimetindene. In the subsequent prick test, the two conditioning groups received saline instead of histamine dihydrochloride.

T1, Testing phase: Next, all participants received the same infusion as before in the intervention phase. In the subsequent prick test, all participants received the same pruritogenic substance, histamine dihydrochloride (testing after intervention (T1)).

T2, Testing phase: The testing phase on the second consecutive day of the experiment (24 hours later) was identical to those on T1. A manipulation check was directly performed after study participation to assess patients’ beliefs about their group assignment and their expectations about their treatment.

Outcome assessments

The primary outcome was the average intensity ratings for the experienced itch sensation provoked by histamine dihydrochloride via a skin prick test at the baseline, test phase T1, and test phase T2 measurement points. The secondary outcome was the sizes of wheals due to inflammatory processes via the skin prick test. Both outcomes were assessed at baseline, T1, and T2. The itch intensity of the atopic dermatitis was also assessed by an NRS (0 = no itch, 10 = maximum itch). Wheal sizes were measured in square millimeters by outlining them with an anti-allergenic pen and taking an impression obtained by means of scotch tape, which was subsequently stuck on millimeter paper.22,23 This measurement was conducted by different healthcare providers; the calculation was undertaken by a person masked to the group assignments.

Statistical analysis

Based on data from a previous study where similar outcome measures (NRS for pain) were used,18 we estimated with G*Power (version 3.1.7; Kiel, Germany) that a sample size of 104 participants would be needed for between- and within-subject comparisons to attain 80% power and a 5% significance level. We determined means, SDs, and proportions to provide descriptive data for every group. Primary treatment effects were estimated using generalized linear models: three repeated measures analyses of variance (ANOVA) with the within-subject factor “phase” (baseline and testing phase T1 and T2) and between-subject factor “group” (HIDDEN-DRUG, OPEN-DRUG+INST, OPEN-DRUG+INST+COND, PLAC+INST+COND); η values were used as measures of effect sizes. Planned comparisons of the interaction effects “phase * group” were conducted via orthogonal contrasts, with r as the effect size. Post hoc pairwise comparisons of treatment groups after the intervention were conducted via independent t-tests, with P = 0.025 as a Bonferroni-corrected criterion for significance. Multiple comparisons within the open-hidden-design were done to identify the magnitude of influencing factors on reduction of itch intensity and wheal size reduction. Difference scores between measurement phases (difference from baseline to T1, and difference from baseline to T2) were calculated and compared via a multivariate analysis of variance (MANOVA) with five a priori nonorthogonal contrasts on factor “group” to estimate the effects of placebo effects (via instruction, via conditioning, via instruction*conditioning, and via instruction*conditioning with a placebo) and the drug on both primary end points. Data for the secondary outcome parameter, clinical (atopic) itch, were not controlled for baseline measurements. Thus, separate analyses were conducted: a MANOVA with planned nonorthogonal contrasts on factor “group” compared the
dependent variable "percentage reduction of itch intensity" (T1-baseline and T2-baseline). The statistical significance in the MANOVA was defined as \( P \) value < 0.01 due to the nonorthogonality of the contrasts. Cohen’s \( d \) was used as effect size to overcome the issue of discrepant group sizes. We report numbers of patients in each analyzed group, treatments effects with their standard errors, significance, effect sizes, and confidence intervals.

To explore the potential mediation role of expectation in driving itch reduction (NRS 0–10; 0 = no itch, 10 = maximum itch) after conditioning, we performed a mediation analysis.24 The variable “conditioning” (yes/no) was treated as the independent variable (cf. Figure 4, predictor, \( X \)), whereas the average delta score of the mean of "itch intensity ratings" of experimental itch stimuli (NRS 0–10) from T1 baseline to T2, testing phase, and after intervention T2, was treated as dependent variable, "itch reduction baseline-T2" (criterion, \( Y \)). Expectations were assessed on day 2 (T2) at the beginning of the experiment (before infusion T2) by asking "Based on your current experience with our experimental itch stimulus, what itch relief on the NRS 0–10 do you expect from the following infusion?" Patients should provide two scores to indicate the expected itch relief. Reinforced expectation (average delta score between the current itch intensity rating and the predicted itch intensity rating with regard to experimental itch stimuli) was treated as the mediator (\( M \)) in mediation models. In this model, we calculated the total effect of conditioning on itch reduction without mediator variable \( c \), the effect of the relationship between conditioning and itch reduction with the additional impact of expectation \( c' \), the direct effect of \( X \) to \( M \) (a), the direct effect of \( M \) to \( Y \) (b), and the indirect effect of \( X \) via \( M \) to \( Y \) (ab). IBM SPSS Statistics 21 software (IBM, Armonk, NY) was used in the per-protocol analysis. For the mediation analyses the macro "PROCESS" 3.5 by Andrew F. Hayes24 was used.

RESULTS

Demographic data and baseline values

Overall, 461 patients were considered during screening. Of these, 295 were excluded (e.g., did not meet inclusion criteria), 166 were randomly assigned to the study groups, of which 60 had to be excluded (i.e., did not reach the baseline itch intensity), 2 had withdrawn for personal reasons and 2 were excluded due to incorrect data collection (Figure S1).

Table 1 shows the patients’ demographic and baseline characteristics. The primary outcome parameters and the clinical characteristics were comparable across the different experimental groups. No significant differences were found with respect to the baseline intensity of the clinical itch.

Experimental itch and wheal size reduction

Table 2 shows the mean scores and SD of experimental itch ratings and mean sizes and SD of the wheals before and after the intervention and related interaction effects. Figure 3a depicts the course of itch reduction from the baseline measurement to T1 and T2. At T2, all study groups showed reduced itch sensations compared with the baseline measurements (HIDDEN-DRUG: −1.64; OPEN-DRUG+INST: −3.16; PLAC+INST+COND: −3.71; and OPEN-DRUG+INST+COND: −5.07) but to different extents, resulting in a significant interaction effect for the “phase * group” \( F \) (6,196) = 7.94, \( P \) < 0.001, \( \eta^2 \) = 0.20; c.f. Supplement S1 for post hoc tests). The PLAC+INST+COND group had a significantly higher itch reduction than the HIDDEN-DRUG and the OPEN-DRUG+INST groups.

Similar results (Figure 3b) were observed for the reduction in wheal size. All study groups showed reduced wheal size compared with the baseline measurements (HIDDEN-DRUG: −8.67; OPEN-DRUG+INST: −14.38; PLAC+INST+COND: −8.81; and OPEN-DRUG+INST+COND: −17.08). In a comparable manner, the interaction between time points and

| Table 1 Baseline characteristics |
|----------------------------------|
| HIDDEN DRUG | OPEN DRUG+INST | OPEN DRUG+INST+COND | PLAC+INST+COND |
| \( n = 24 \) | \( n = 26 \) | \( n = 26 \) | \( n = 26 \) |
| **Demographic characteristics** |
| Age (years) | 32.58 (12.84) | 30.69 (10.77) | 28.81 (9.71) | 30.62 (9.37) |
| Sex: Male | 7 (29.2%) | 9 (34.6%) | 8 (30.8%) | 7 (26.9%) |
| Sex: Female | 17 (70.8%) | 17 (65.4%) | 18 (69.2%) | 19 (73.1%) |
| **Clinical characteristics** |
| Itch intensity of AD * (NRS) | 3.29 (2.87); \( N = 17 \) | 5.47 (3.18); \( N = 15 \) | 4.32 (2.50); \( N = 19 \) | 3.14 (2.98); \( N = 14 \) |
| SCORAD score | 21.97 (7.05) | 27.29 (10.84) | 29.03 (12.46) | 23.18 (8.90) |
| IgE values (LU/mL) | 1286 (3603) | 437 (1122) | 1714 (5863) | 457 (1001) |
| Time to initial AD diagnosis (years), estimated by patients* | 20.86 (13.30) | 22.50 (11.71) | 24.10 (11.02) | 20.86 (9.14) |
| Comorbidity: Allergic rhinitis | 16 (66.7%) | 12 (46.2%) | 17 (65.4%) | 14 (53.8%) |
| Comorbidity: Asthma | 7 (29.2%) | 6 (23.1%) | 8 (30.8%) | 9 (34.6%) |
| DLQI score | 3.42 (2.89) | 6.27 (5.58) | 5.38 (5.15) | 4.46 (5.38) |

The data are presented as the means (SD) or n (%).
AD, atopic dermatitis; DLQI, Dermatology Life Quality Index; NRS, numeric rating scale; SCORAD, SCORing Atopic Dermatitis.

* Data were not available for all randomized patients.
Table 2: Mean scores and SD of experimental itch ratings, and mean sizes and SD of wheals after the intervention

| Mean scores and SDs of itch intensity ratings and wheal sizes after intervention | Interaction effects and group differences |
|---|---|
| HIDDEN DRUG | OPEN DRUG+INST | OPEN DRUG+INST+COND | PLAC+INST+COND | OPEN DRUG+INST | OPEN DRUG+INST+COND | PLAC+INST+COND |
| Mean (SD) | Mean (SD) | Mean (SD) | Mean (SD) | Mean (SD) | Mean (SD) | Mean (SD) |
| (n = 24) | (n = 26) | (n = 26) | (n = 26) | vs. HIDDEN DRUG | vs. OPEN DRUG+INST | vs. HIDDEN DRUG |
| Experimentally provoked pruritus intensity rating (NRS 0–10) |
| Phase*group (B–T1) | ----- | ----- | ----- | ----- | ----- | ----- |
| Phase*group (T1–T2) | ----- | ----- | ----- | ----- | ----- | ----- |
| Baseline | 5.27 (1.62) | 5.91 (1.37) | 6.10 (1.68) | 5.77 (1.60) | ----- | ----- | ----- |
| T1 | 4.20 (2.19) | 3.19 (2.02) | 2.28 (2.27) | 2.64 (1.91) | 0.097A (d = 0.24) | 0.130A (d = 0.21) | 0.010A (d = 0.36) |
| T2 | 3.63 (2.10) | 2.75 (1.82) | 1.03 (1.32) | 2.06 (1.76) | 0.118A (d = 0.22) | 0.000A (d = 0.48) | 0.006A (d = 0.38) |
| Wheal size (mm²) |
| Phase*group (B–T1) | ----- | ----- | ----- | ----- | ----- | ----- |
| Phase*group (T1–T2) | ----- | ----- | ----- | ----- | ----- | ----- |
| Baseline | 30.21 (6.56) | 29.27 (11.14) | 29.88 (15.07) | 32.42 (13.38) | ----- | ----- | ----- |
| T1 | 18.71 (7.69) | 13.69 (5.64) | 16.85 (10.75) | 23.50 (10.25) | 0.011A (d = 0.36) | 0.191A (d = 0.18) | 0.069A (d = 0.26) |
| T2 | 21.54 (7.44) | 14.88 (5.52) | 12.81 (6.71) | 23.62 (8.48) | 0.001A (d = 0.46) | 0.229A (d = 0.17) | 0.364A (d = 0.13) |

Interaction effects after intervention and differences between groups. Interaction effects of phases by treatment group were tested using a priori-defined comparison contrasts in general linear models. Differences between groups were estimated via post hoc or exploratory analyses with adjusted confidence intervals (A 97.5%, Bonferroni-corrected). *Effect sizes are $\eta^2$ unless otherwise indicated.
groups was significant, although its effect size was lower ($F_{(6,196)} = 2.17$, $P = 0.048$, $\eta^2 = 0.06$). Moreover, the OPEN-DRUG+INST+COND group had a significant different course ($P = 0.021$, $\eta^2=0.10$) from T1 to T2 compared to the OPEN-DRUG+INST group, who showed a significant deterioration to T2. Compared with the HIDDEN-DRUG group the course of OPEN-DRUG+INST was not significant different (B- T1: $P = 0.175$, $\eta^2=0.04$; T1– T2: $P = 0.452$, $\eta^2 = 0.01$). In addition, results on wheal size showed no significant difference between the HIDDEN-DRUG group and the PLAC+INST+COND group (B- T1: $P = 0.485$, $\eta^2 = 0.10$; T1– T2: $P = 0.342$, $\eta^2 = 0.02$).

Instructions and conditioning make a sham-dimethindene infusion (placebo) more effective than the drug

We compared the HIDDEN-DRUG group (pure pharmacological drug component) to the PLAC+INST+COND group (pure context, placebo component: instructions and conditioning). The PLAC+INST+COND group showed more successful symptom relief than the HIDDEN-DRUG group. A priori planned comparisons (Table 2) between these groups showed that the groups differed between the time points for itch sensation (group*time [baseline-T2]: $F_{(2,96)} = 9.89$, $P < 0.001$, $\eta^2 = 0.17$). In both groups, itch reduction occurred primarily between baseline and T1 ($F_{(1,48)} = 15.47$, $P < 0.001$, $\eta^2 = 0.49$), whereas itch sensations from T1 were maintained through T2 ($F_{(1,48)} = 0.00$, $P = 0.988$, $\eta^2 = 0.00$). At the end of the study, the group receiving a placebo together with context factors that rated the induced pruritus as less intense than that of the group exposed to the pharmacological effect ($-1.57, t_{(48)} = -2.87, P = 0.006, d = 0.38; 97.5\%$ confidence interval (CI) $-2.86$ to $-0.31$).

Instructions significantly increase drug efficacy

Significant differences ($F_{(1,48)} = 11.10$, $P = 0.002; \eta^2 = 0.19$) in itch intensity reduction were recorded for the effects of instructions between the HIDDEN-DRUG group and the OPEN-DRUG+INST group from baseline to T1 (c.f. Table 2). Post hoc analyses (cf. Table 3) indicated that instructions regarding the subsequent medical treatment led to a higher itch reduction (baseline to T1, 1.65, $99\%$ CI 0.14 to 3.16, $P = 0.005$; and baseline to T2, 1.52, $99\%$ CI 0.02 to 3.03, $P = 0.009$) than no instructions (HIDDEN-DRUG). However, if both groups are compared only with T1 and T2, respectively, and the interaction with time is not taken into account, no significant differences are found (T1: $t_{(48)} = -1.69$, $P = 0.097; d = 0.24$; T2: $t_{(48)} = -1.59$, $P = 0.118$).

The analyses of the wheal sizes (Table 2) showed that similar instructions led to smaller wheal sizes in the OPEN-DRUG+INST group (Bonferroni-corrected T1: $-5.02$, $t_{(48)} = -2.65$, $P = 0.011; d = 0.36, 97.5\%$ CI $-9.40$ to $-0.63$; Bonferroni-corrected T2: $-6.66$, $t_{(48)} = -3.61$, $P = 0.001, d = 0.46, 97.5\%$ CI $-9.85$ to $-2.54$).

Instructions and classical conditioning make a drug more effective than instructions alone

The combination of instructions and classical conditioning had a higher impact on treatment efficacy than instructions alone. Our data (Table 2) from the OPEN-DRUG+INST+COND group revealed a significantly lower itch intensity over time after itch elicitation and conditioning compared with that of the OPEN-DRUG+INST group (group*time [baseline-T2]: $F_{(2,100)} = 6.41$, $P = 0.002, \eta^2 = 0.11$). The contrast analyses did not reach significance, but the post hoc comparisons for T2 showed that conditioning led to significantly lower itch intensity
Table 3 Multiple comparisons of reduction effects within the open-hidden design: influence of instruction, conditioning, and medication on the changes of itch sensation and wheal sizes

| Comparison                                | Mean diff (99% CI) | P   | d   | Mean diff (99% CI) | P   | d   | Mean diff (99% CI) | P   | d   | Mean diff (99% CI) | P   | d   | Mean diff (99% CI) | P   | d   |
|-------------------------------------------|--------------------|-----|-----|--------------------|-----|-----|--------------------|-----|-----|--------------------|-----|-----|--------------------|-----|-----|
| Itch intensity reduction of experimentally provoked pruritus (NRS 0–10) |                    |     |     |                    |     |     |                    |     |     |                    |     |     |                    |     |     |
| From baseline to T1                      | 1.65               | 0.005 | 0.94 | 2.75               | < 0.001 | 1.33 | 2.07               | < 0.001 | 1.12 | 1.10               | 0.053 | 0.51 | 0.68               | 0.233 | 0.30 |
| (0.14 to 3.16)                           | (1.24 to 4.26)     |      |     | (0.56 to 3.58)     |      |     | (−0.38 to 2.58)    |      |     | (−0.80 to 2.15)    |      |     | (0.05 to 2.15)     |      |     |
| From baseline to T2                      | 1.52               | 0.009 | 0.77 | 3.43               | < 0.001 | 1.75 | 2.08               | < 0.001 | 0.95 | 1.91               | 0.001 | 1.03 | 1.35               | 0.018 | 0.65 |
| (0.02 to 3.03)                           | (1.93 to 4.93)     |      |     | (0.58 to 3.58)     |      |     | (−0.43 to 3.38)    |      |     | (−0.12 to 2.83)    |      |     | (0.98 to 2.83)     |      |     |
| From T1 to T2                            | −0.12              | 0.797 | −0.09 | 0.68               | 0.001 | 0.153 | 0.001              | 0.81 | 0.086 | 0.47               | 0.68 | 0.014 | 0.35               |      |     |
| (−1.37 to 1.12)                          | (−0.56 to 1.93)    |      |     | (−1.24 to 1.25)    |      |     | (−0.42 to 2.03)    |      |     | (−0.55 to 1.90)    |      |     | (−0.55 to 1.90)    |      |     |
| Wheal size reduction (mm²)                |                    |     |     |                    |     |     |                    |     |     |                    |     |     |                    |     |     |
| From baseline to T1                      | 4.08               | 0.282 | 0.39 | 1.54               | 0.684 | 0.12 | 2.58               | 0.496 | 0.20 | 2.54               | 0.494 | −0.19 | 4.16               | 0.268 | 0.26 |
| (−5.83 to 13.98)                         | (−8.37 to 11.44)   |      |     | (−12.48 to 7.33)   |      |     | (−12.24 to 7.17)   |      |     | (−5.59 to 13.82)   |      |     | (−5.59 to 13.82)   |      |     |
| From baseline to T2                      | 5.72               | 0.093 | 0.53 | 8.41               | 0.014 | 0.72 | 0.14               | 0.967 | 0.01 | 2.69               | 0.417 | 0.21 | 8.27               | 0.014 | 0.64 |
| (−3.14 to 14.57)                         | (−0.44 to 17.26)   |      |     | (−7.81 to 8.99)    |      |     | (−5.98 to 11.37)   |      |     | (−4.00 to 16.94)   |      |     | (−4.00 to 16.94)   |      |     |
| From T1 to T2                            | 1.64               | 0.521 | 0.21 | 6.87               | 0.008 | 0.81 | 2.72               | 0.289 | 0.27 | 5.23               | 0.039 | 0.66 | 4.15               | 0.099 | 0.41 |
| (−5.05 to 8.34)                          | (0.18 to 13.57)    |      |     | (−3.98 to 9.41)    |      |     | (−1.33 to 11.79)   |      |     | (−2.41 to 10.71)   |      |     | (−2.41 to 10.71)   |      |     |
| Itch intensity reduction of atopic pruritus (%) |                    |     |     |                    |     |     |                    |     |     |                    |     |     |                    |     |     |
| From baseline to T1                      | 25.08              | 0.185 | 0.52 | 30.92              | 0.083 | 0.67 | 29.39              | 0.129 | 0.52 | 5.84               | 0.745 | 0.15 | 1.54               | 0.933 | 0.03 |
| (−24.79 to 74.95)                        | (−15.81 to 77.66)  |      |     | (−21.55 to 80.32)  |      |     | (−41.86 to 53.55)  |      |     | (−47.28 to 50.36)  |      |     | (−47.28 to 50.36)  |      |     |
| From baseline to T2                      | 9.26               | 0.592 | 0.17 | 16.73              | 0.303 | 0.32 | 25.51              | 0.152 | 0.46 | 7.47               | 0.651 | 0.23 | −8.78              | 0.604 | −0.26 |
| (−36.86 to 55.17)                        | (−26.29 to 59.75)  |      |     | (−21.39 to 72.41)  |      |     | (−36.45 to 51.39)  |      |     | (−53.73 to 36.17)  |      |     | (−53.73 to 36.17)  |      |     |

Impact of the pharmacological effect and of the different manipulations of instruction and conditioning (leading to a placebo effect) on experimental itch intensity, wheal size reduction and a topic itch intensity were tested via contrast analyses in multivariate analyses (a priori contrasts of two groups, respectively, on difference values between baseline and T1, and baseline and T2; adjusted confidence intervals: 99%, Bonferroni corrected). CI, confidence interval.
Patients’ expectations

Examination of the patients’ expectations showed that they believed the description they were provided. Overall, 76.5% of the HIDDEN-DRUG group expected, as intended, that there was no pharmacological treatment; 94.7% of the OPEN-DRUG+INST+COND group, 93.8% of the OPEN-DRUG+INST group, and all patients of the PLAC+INST+COND group expected, as intended, that they received the itch-reducing drug treatment.

To further elucidate the mediation between conditioning and expectations with respect to itch sensation, we performed a mediation analysis to explore the potential mediation role of expectation in driving effects in itch sensation after conditioning. We analyzed whether conditioning predicts itch reduction from baseline to T2 (cf. Figure 4), and whether the direct path would be mediated by reinforced expectation. We included only OPEN-DRUG+INST+COND, OPEN-DRUG+INST, and PLAC+INST+COND (n = 48) in this mediation analysis because we had not assessed expectations in the HIDDEN-DRUG group. We had decided not to ask patients in this group about their expectation of infusion to avoid possible expectation by such a survey.

With regard to itch reduction from baseline to T2 we also observed a direct effect of conditioning, c = 1.920, P = 0.0003 (cf. Figure 4). However, we found that the relationship between conditioning and itch reduction baseline to T2 was not fully explained by conditioning, but partially mediated also by reinforced expectation since the addition of the variable “reinforced expectation” to the test model suppressed the significant effect of conditioning on itch reduction baseline to T2, c = 1.271, P = 0.057. We found that this relationship was fully mediated by reinforced expectation, as the indirect effect was significant ab = 0.649, 95% CI 0.110 to 1.343.

**Difference between placebo effects on subjective and objective treatment outcome measures**

Table 3 demonstrates all multiple comparisons of reduction with effect sizes within the open-hidden design for the experimental itch intensity reduction (subjective), the clinical itch intensity reduction (subjective), and wheal size reduction (objective). Considering the significant post hoc tests and comparing certain groups, placebo effects occur more frequently and with higher effect sizes on the subjective outcome measure “experimental itch intensity.” The comparison between the groups OPEN-DRUG+INST+COND vs. HIDDEN-DRUG, between OPEN-DRUG+INST+COND vs. OPEN-DRUG+INST, and between OPEN-DRUG+INST+COND vs. PLAC+INST+COND showed that placebo effects occur on both levels, the subjective (experimental itch intensity) as well as on objective outcome measures (“wheal size”), however, with higher effect sizes on the subjective level. Significant placebo effects resulting from OPEN-DRUG+INST and PLAC+INST+COND in comparison to HIDDEN-DRUG only occur on the subjective level.

**DISCUSSION**

This RCT investigated how targeted placebo effects, induced by instructions and conditioning, impacted the action of a drug (dimetindene) on experimental (histamine-induced) itch in patients with atopic dermatitis. Our findings showed that the openly administered dimetindene combined with placebo effects significantly and clinically reduced itch more than the hidden administered dimetindene. Even the openly administered placebo (saline: PLAC+INST+COND) combined with instructions and conditioning resulted in superior effects on experimental itch than the hidden administration of dimetindene (HIDDEN-DRUG). Overall, we found in our mediation analyses including the conditioned groups OPEN-DRUG+INST+COND, PLAC+INST+COND, and the OPEN-DRUG+INST group without conditioning, that conditioning and expectation play an important role for augmented dimetindene itch reducing effects. Expectation was significantly formed by conditioning and the indirect effects of conditioning on itch reduction via patients’ expectation was significant.

Additionally, these placebo effects were reflected in more objective parameters. Combining instructions and conditioning (OPEN-DRUG+INST+COND) led to a greater decrease in wheal size than that for instructions alone (OPEN-DRUG+INST). The
instructions alone did not significantly affect the reduction in wheal size, corroborating evidence that, even if expectations are successfully manipulated, the objective reactions differ from the subjective perceptions.25

Our findings suggested that the route of drug administration plays a critical role in its efficacy. Regarding the open-hidden paradigm,3,13,26 our data revealed similar results to those reported by previous studies on placebo analgesia.1,26 The efficacy of dimethindene significantly increased when openly administered. According to the literature concerning placebo mechanisms,5,6,8,27–29 it was possible to elicit this phenomenon via instructions and learning experiences (conditioning). Boosting the pharmacological effectiveness via instruction is of great importance.12 This manipulation can improve the effects produced by a medication and, from an ethical perspective, should not be withheld from patients.

Similar to the concept of placebo analgesia,20,28 the results of our study show that itch-reducing placebo effects can also occur with pharmacological treatment in patients with atopic dermatitis. In line with Benedetti et al.,27 this suggests that the effect of an antipruritic medication consists of two components: one pharmacological and one psychological. The latter, the placebo effect, can be considered “additive”12 (i.e., supplementing and enhancing the itch-reducing medication beyond the isolated pharmacological effect). Our results show that the highest clinical efficacy was obtained through a combination of the drug, instructions, and conditioning. As explained under “Limitations,” within our study design we cannot answer how these drug and psychological effects are combined, whether they are additive or interactive. However, a placebo administered under the same context conditions produced almost similar clinical efficacy. Moreover, it achieved even better results than the administration of the drug with instructions only. This indicated the strong influence of psychological variables (e.g., context factors in which a drug is given).

Our results showed that placebo effects were stronger reflected on the subjective outcome “itching intensity” than on the objective outcome “wheal-size.” The difference between PLAC+INST+COND and HIDDEN-DRUG was significant for itch intensity, but not for wheal size. This result is in line with the study of ref, 30. Kleine-Borgmann et al. (2019), who investigated placebo effects in a study of patients with low back pain. They found significant placebo effects in subjective pain ratings but not in objective mobility parameters. In contrast to our study, the placebo agent in this study was an open-label placebo and not an add-on placebo effect on a pharmacological substance. Our results also suggest that placebo effects are more likely to be reflected in centrally mediated subjective experience than in peripherally mediated objective measurements. Basically, it is helpful here to distinguish between the noxious processing in the periphery (inflammatory process in the periphery) and the processing of these stimuli at central level. One reason that the PLAC+INST+COND group showed no changes in objective measures (periphery: wheal sizes) could be that for various reasons the centrally triggered descending inhibitory itch/inflammatory modulation was too weak. Comparable hypothetical models have been described in the field of pain research.31 It could be that our conditioning procedure was too weak, because we have not preconditioned the NaCl with the drug. Thus, no conditioning of an isolated pharmacological or other centrally mediated response as a result of a sensory stimulus could be performed. Our conditioning procedure only included an association of the physiological status “no itching” with the NaCl infusion. Presumably, a pharmacological or other centrally mediated trigger for a change in physiological processes in the periphery (in our case wheals) is required to initiate such a process at the physiological level, which can then be triggered by a conditioned stimulus (cf. Dworkin, 1993).32 In fact, more research is needed to substantiate this statement.

We found clinically significant treatment effects (baseline-T2) for itch reduction via the administration of an antihistamine (30.42%–83.45%) and a placebo (62.07%). Compared with clinical trials of allergen-specific immunotherapy,4 which have shown a wide range of placebo effects,19 the placebo effect in our study was remarkably high. Our results are compatible with a number of meta-analyses that have demonstrated that the efficacy of targeted placebo analgesia (24%) was much higher than the placebo effect in a placebo-controlled clinical trial.33,34 We also obtained a greater placebo effect than that found in a recent meta-analysis of placebo effects on itch sensation in clinical trials.19 In contrast to placebo-controlled clinical trials, where the patients believe that the chance of receiving the active substance is only 50%,34,35 patients in our study were provided with the information that their chance of receiving the drug was 100%. This certainty seems to be important for the formation of the placebo effect.

Our data showed a stable placebo effect in experimentally induced itch in all groups on day 2 of the experiment. Previous studies of placebo analgesia have shown that placebos can exhibit long-lasting efficacy (e.g., for psychological treatments46 and acupuncture).38 However, to assess the long-term clinical relevance of such results in patients with atopic dermatitis, further studies are required.

Recently, placebo effects have been suggested to boost analgesic drug effects, and a specific and reproducible placebo response has been expected.4,28,38,39 In contrast, pharmacological substances are less effective outside a therapeutic setting.40 Placebo responses are the result of complex interactions of cognitive factors, such as expectations, beliefs, trust, desires, and emotional factors,4,41 and ultimately the patient’s personal experience in the context of the medication administration.42 Similar to analgesic placebo effects,4,42,38,39,43,44 the placebo effects in the clinical practice of itch can be used to provide patients with an additional placebo-based benefit. Here, to exploit placebo effects does not need deception. The goal would be to integrate the placebo effects into therapeutic concepts of itch management to optimize dermatology treatment outcomes, not only by pharmacological pain treatment. According to the concept of open medication,5,8,13,26 it is advisable to enhance patient–physician communication, for example, by placing emphasis on positive drug effects, avoiding an overemphasis on side effects and to enhance learning components by applying analogies in an open manner, and to include many sensory aspects to increase analgesic effectiveness.28 Well-balanced information about a medication in a valued and
trusting atmosphere to facilitate patient-physician communication can increase efficacy.

Limitations of the study
The selection of study groups was clinically and feasibility oriented. We chose those interventions which, purely theoretically, can also be used meaningfully in clinical practice. Due to the feasibility of the study, we decided not to use the group PLAC+INST (placebo group without conditioning). We assumed that this group would also have achieved an effect, but expected a rather small effect compared to the drug groups. For the question, how do the effects of treatment expectation combine with the effects of a pharmacological treatment, are these additive or interactive—potentially synergistic, this decision was unfavorable. The additional group PLAC+INST in our design could have answered this question. For ethical reasons, we decided not to use the natural history group. The multiple histamine prick-test application without any treatment seemed to us not justifiable.

Outlook
Our data indicate that a targeted application of placebo effects is possible and can significantly improve the overall drug action of a drug (dimetindene) in addition to its pure pharmacological effectiveness. Our results show that a variation of the context in which the drug is delivered is of utmost importance. An open drug administration, where patients receive positive instructions about the medication, reveals significant better results than a drug which is applied without information or care. These context factors are critical involved in patients’ expectation about their medication and influence their treatment outcome. Future research in the field of anti-itch agents should consider the results of our studies. This means to include a precise description of the instructions and the context of administration. Further studies should use fully balanced designs (additional group PLAC+INST) to investigate, how these placebo effects combine with the effects of a pharmacological treatment, whether they are combined in an additive or interactive—potentially synergistic manner. The management of patients’ expectations in this way should be specifically applied in clinical practice.

SUPPORTING INFORMATION
Supplementary information accompanies this paper on the Clinical Pharmacology & Therapeutics website (www.cpt-journal.com).

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CONFLICT OF INTEREST
The authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS
A.S., M.W., and R.K. wrote the manuscript. R.K., F.B., L.S.G., and M.W. designed the research. A.S., L.S.G., and T.S.B performed the research. A.S., M.W., T.S.B., and R.K. analyzed the data. M.W., F.B., A.S., and R.K. contributed analytical tools.
22. Bousquet, J. et al. Practical guide to skin prick tests in allergy to aeroallergens. *Allergy* **67**, 18–24 (2012).
23. Rueff, F. et al. Skin tests for diagnostics of allergic immediate-type reactions. Guideline of the German Society for Allergology and Clinical Immunology. *Pneumologie* **85**, 484–495 (2011).
24. Hayes, A.F. *Introduction to Mediation, Moderation, and Conditional Process Analysis, Second Edition* (Methodology in the Social Sciences). 2nd ed. (Guilford Press, New York, NY, 2018).
25. Darragh, M., Booth, R.J., Koschwanez, H.E., Sollers, J. & Broadbent, E. Expectation and the placebo effect in inflammatory skin reactions: a randomised-controlled trial. *J. Psychosom. Res.* **74**, 439–443 (2013).
26. Colloca, L., Lopiano, L., Lanotte, M. & Benedetti, F. Overt versus covert treatment for pain, anxiety, and Parkinson’s disease. *Lancet Neurol.* **3**, 679–684 (2004).
27. Benedetti, F. Mechanisms of placebo and placebo-related effects across diseases and treatments. *Annu. Rev. Pharmacol. Toxicol.* **48**, 33–60 (2008).
28. Klinger, R., Colloca, L., Bingel, U. & Flor, H. Placebo analgesia: clinical applications. *Pain* **155**, 1055–1058 (2014).
29. Price, D.D., Finniss, D.G. & Benedetti, F. A comprehensive review of the placebo effect: recent advances and current thought. *Annu. Rev. Psychol.* **59**, 565–590 (2008).
30. Kleine-Borgmann, J., Schmidt, K., Hellmann, A. & Bingel, U. Effects of open-label placebo on pain, functional disability, and spine mobility in patients with chronic back pain: a randomized controlled trial. *Pain* **160**, 2891–2897 (2019).
31. Chapman, C.R. & Vierck, C.J. The transition of acute postoperative pain to chronic pain: an integrative overview of research on mechanisms. *J. Pain* **18**, 359–e1 (2017).
32. Dworkin, B.R. *Learning and Physiological Regulation* (The University of Chicago Press, Chicago, IL, 1993).
33. Vase, L., Petersen, G.L., Riley, J.L. & Price, D.D. Factors contributing to large analgesic effects in placebo mechanism studies conducted between 2002 and 2007. *Pain* **145**, 36–44 (2009).
34. Vase, L., Riley, J.L. & Price, D.D. A comparison of placebo effects in clinical analgesic trials versus studies of placebo analgesia. *Pain* **99**, 443–452 (2002).
35. Kotsis, V., Benson, S., Bingel, U., Forsting, M., Schedlowski, M. & Giezewski, E.R. Perceived treatment group affects behavioral and neural responses to visceral pain in a deceptive placebo study. *Neurogastroenterol. Motil.* **24**, 935–e462 (2012).
36. Flor, H., Haag, G., Turk, D.C. & Koehler, H. Efficacy of EMG biofeedback, pseudotherapy, and conventional medical treatment for chronic rheumatic back pain. *Pain* **17**, 21–31 (1983).
37. Haake, M., Müller, H.H., Schade-Brittinger, C., Basler, H.D., Schafer, H. & Maier, C. German Acupuncture Trials (GERAC) for chronic low back pain: randomized, multicenter, blinded, parallel-group trial with 3 groups. *Arch. Intern. Med.* **167**, 1892–1898 (2007).
38. Klinger, R., Kothe, R., Schmitz, J., Kamping, S. & Flor, H. Placebo effects of a sham opioid solution: a randomized controlled study in patients with chronic low back pain. *Pain* **158**, 1893–1902 (2017).
39. Klinger, R., Stuhreyer, J., Schwartz, M., Schmitz, J. & Colloca, L. Clinical use of placebo effects in patients with pain disorders. *Int. Rev. Neurobiol.* **139**, 107 (2018).
40. Benedetti, F. The placebo response: science versus ethics and the vulnerability of the patient. *World Psychiatry* **11**, 70–72 (2012).
41. Petersen, G.L., Finnerup, N.B., Grosen, K., Pilegaard, H.K., Tracey, I. & Benedetti, F. Expectations and positive emotional feelings accompany reductions in ongoing and evoked neuropathic pain following placebo interventions. *Pain* **155**, 2687–2698 (2014).
42. Klinger, R. & Flor, H. Clinical and ethical implications of placebo effects: enhancing patients’ benefits from pain treatment. *Handb. Exp. Pharmacol.* **225**, 217–235 (2014).
43. Finniss, D.G. & Benedetti, F. Mechanisms of the placebo response and their impact on clinical trials and clinical practice. *Pain* **114**, 3–6 (2005).
44. Klinger, R. Das Potenzial des analgetischen Plazeboeffektes – S3-Leitlinien–Empfehlung zur Behandlung akuter und perioperativer Schmerzen. The potential of the analgetic placebo effect – [S3-guideline recommendation on the clinical use for acute and perioperative pain management]. *Anesthesiol. Intensivmed. Notfallmed. Schmerzther.* **45**, 22–29 (2010).