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Antipruritic Placebo Effects by Conditioning H_1-antihistamine

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ABSTRACT

Objective: Allergic rhinitis symptoms can be reduced by behaviorally conditioning antihistamine. It is unclear whether these findings extend to histamine-induced itch or work when participants are informed about the conditioning procedure (open-label conditioning). The current study aims to investigate the efficacy of (open-label) antipruritic behavioral conditioning for histamine-induced itch.

Methods: Healthy participants (n = 92; 84% female) were randomized to I) an open-label conditioned, II) closed-label conditioned, III) conditioned-not-evoked control, or IV) nonconditioned control group. A two-phase conditioning paradigm was used. During acquisition, a conditioned stimulus (CS; distinctively tasting beverage) was repeatedly paired with the H_1-antihistamine levocetirizine (groups I–III). During evocation, the CS was paired with placebo (I, II), or instead of the CS, water was paired with placebo (III). The nonconditioned control group (IV) received CS with placebo in both phases. Itch after histamine iontophoresis and physiological data (i.e., spirometry, heart rate, skin conductance) were assessed. Combined conditioned and combined control groups were first compared, and analyses were repeated for separate groups.

Results: Marginally lower itch was reported in the combined conditioned compared with the control groups ($F(1,88) = 2.10$, $p = .076$, $\eta^2_{partial} = 0.02$); no differences between separate groups were found. No effects on physiological data were found, except for heart rate, which reduced significantly and consistently for control groups, and less consistently for conditioned groups (group by time interaction: $F(7,80) = 2.35$, $p = .031$, $\eta^2_{partial} = 0.17$).

Conclusion: Limited support was found for the efficacy of antipruritic behavioral conditioning, regardless of whether participants were informed about the conditioning procedure. The application of open-label conditioning in patient populations should be further researched.
Trial Registration: www.trialregister.nl; ID NTR5544.

Key words: placebo effects, behavioral conditioning, expectancy, histamine, itch, pruritus.

INTRODUCTION

Placebo effects are beneficial effects that cannot be attributed to active treatment ingredients (1,2). Instead, these effects are ascribed to expectancy mechanisms, with expectations of benefit resulting in improvement of somatic symptoms (e.g., itch and pain (3–6)). The opposite has also been demonstrated, with expectations of deterioration resulting in exacerbation of symptoms or increased adverse effects (i.e., nocebo effects (3,7)). Current evidence shows that placebo and nocebo effects can be induced through multiple pathways, for example, by providing positive or negative information regarding treatments, or through associative learning processes such as conditioning (8–10). In behavioral conditioning, repeated pairing of an initially neutral stimulus (to-be conditioned stimulus [CS]) with an unconditioned stimulus (UCS), which elicits a certain innate response, may lead to the CS eliciting a similar response (conditioned response), even when the UCS is not presented (9,10).

There is evidence that conditioning of allergens to a CS can exacerbate allergic symptoms, upregulate histamine release in animal models of allergy (which has been linked to exacerbation of allergic responses), and adversely influence itch (11–20).

ANCOVA = analysis of covariance, **CS** = conditioned stimulus, **FEV_1** = forced expiratory volume in 1 second, **FVC** = forced vital capacity, **GLM** = general linear model, **HR** = heart rate (in beats per minute), **NRS** = Numeric Rating Scale, **SCL** = skin conductance level, **UCS** = unconditioned stimulus

SDC Supplemental Content

From the Health, Medical and Neuropsychology Unit, Institute Psychology, Faculty of Social and Behavioural Sciences, (Meeuwis, van Middendorp, Pacheco-Lopez, Veldhuijzen, Evers), Leiden University; Leiden Institute for Brain and Cognition (Meeuwis, van Middendorp, Veldhuijzen, Evers), Leiden University Medical Center, Leiden, The Netherlands; Health Sciences Department, Campus Lerma (Pacheco-Lopez), Metropolitan Autonomous University, Lerma, Edo Mex, Mexico; and Departments of Pulmonology (Ninaber), Dermatology (Lavrijsen), and of Psychiatry (van der Wee, Evers), Leiden University Medical Center, Leiden, The Netherlands.

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Moreover, studies indicate that conditioning can also potentially alleviate allergic symptoms by repeatedly pairing a CS (e.g., a novel-tasting beverage) with an H_1-antihistamine (e.g., desloratadine) as UCS (21,22). This has previously resulted in a conditioned basophil response to dust mite allergens (21). However, findings for subjective symptoms were less clear, as these also tended to decrease in the control groups (21,22). Moreover, no study to date has investigated whether conditioning of H_1-antihistamine may influence histamine-induced itch specifically. Because histamine is a modulator of itch not only in allergic conditions but also in other inflammatory conditions such as atopic dermatitis (23,24), demonstrating these effects may provide a basis for new therapeutic approaches aimed at enhancement of placebo responses, reduction of medication use, and minimization of adverse effects (25,26).

Traditionally, a blinded study protocol is used for behavioral conditioning, in which participants do not know whether they receive medication or inert pills (27). This makes direct translation of these effects to clinical practice difficult, as it insinuates that deception is needed to elicit placebo effects, and patients in clinical practice need to be fully informed about treatment (27). However, there is accumulating evidence that placebo effects may also occur when it is known that an inert substance is given (i.e., open-label). Symptoms of allergic rhinitis, irritable bowel syndrome, and chronic low back pain can be reduced when placebo pills are given together with a rationale explaining the placebo effect (28–34). The efficacy of open-label conditioning (i.e., explaining the learning procedure from the beginning) for reduction of symptoms such as itch has not yet been demonstrated.

The current study investigated whether behavioral conditioning of the antihistaminergic properties of levocetirizine could reduce itch in response to a short-term histamine challenge. Effects of behavioral conditioning on other clinical, physiological, and psychological responses were explored. Moreover, the study aimed to explore the effects of open- versus closed-label conditioning.

MATERIALS AND METHODS

Study Design

Detailed methodology is described in the Methods section in the Supplemental Material, Supplemental Digital Content 1, http://links.lww.com/PSYMED/A581. This study was a block-randomized (1:1:1:1), placebo-controlled crossover study (Dutch Trial Registry ID: NTR5544, registration on October 6, 2015) that was approved by the Medical Ethical Committee at the Leiden University Medical Center, the Netherlands (ID NL52687.058.15) and conducted in concordance with the Declaration of Helsinki (35). All participants provided written informed consent. Data for the study were collected between October 2015 and October 2017.

Conditioning Paradigm and Blinding

In line with previous studies (21,22,36–39), a two-phase conditioning paradigm was applied that consisted of an acquisition phase, in which a distinctively tasting beverage (to-be CS) was combined with a UCS (a capsule containing 5 mg levocetirizine diHCl, an H_1-antihistamine) or an identically looking placebo capsule, and an evocation phase, in which the CS was combined with a placebo capsule. Both phases had three sessions on three consecutive days, and were separated by a 4-day drug washout period. Participants were allocated to I) an open-label conditioned group (acquisition: CS + UCS with an explanation of conditioning and its expected effects; evocation: CS + placebo); II) a closed-label conditioned group (acquisition: CS + UCS; evocation: CS + placebo); III) a conditioned-not-evoked control group (acquisition: CS + UCS; evocation: water + placebo), which was added to control for carryover effects of the conditioning procedure; or IV) a nonconditioned control group (acquisition: CS + placebo; evocation: CS + placebo), which was added to control for the effects of CS only. Block randomization was used to generate a randomization sequence and was managed by an independent party (the Leiden University Medical Center pharmacy that distributed the UCS and placebo capsules). The study was conducted double blinded for the closed-label conditioned group and nonconditioned control group, single blinded for the conditioned-not-evoked group, and nonblinded for the open-label conditioned group. In the conditioned-not-evoked group, the CS was not administered during evocation, and the acquisition phase was conducted by a different experimenter in a different laboratory setting (e.g., location and lighting), to prevent conditioning to the environment. In the open-label conditioned group, the experimenter provided participants with information regarding the conditioning procedure at the start of acquisition (see the Supplemental Material for further details, Supplemental Digital Content 1, http://links.lww.com/PSYMED/A581). Notification of allocation to these two groups by the pharmacy was given to the experimenter after inclusion.

Participants

Healthy male and female volunteers aged between 18 and 35 years were recruited for this study. Inclusion criteria consisted of a good understanding of written and spoken Dutch, and absence of allergic rhinitis or allergic conjunctivitis within 3 months before enrollment in the study. Potential participants were excluded in case of somatic or psychological morbidities that may interfere with the study protocol or participants' safety; allergic rhinitis or conjunctivitis within 3 months before participation; any allergic condition presenting symptoms other than rhinitis or conjunctivitis; recent use of analgesics, antibiotics, antihistamines, or anti-inflammatory medication; recent vaccinations; (intended) pregnancy; or intolerance for any substances used in the study.

Procedure and Study Outcomes

An overview of the study protocol is provided in Figure 1. The study took place at Leiden University and was advertised as a study on the influence of psychological factors on antiallergic medication. Participants were invited for a screening session, and upon inclusion, psychological factors and expected itch were assessed. Well-being was measured through questionnaires (*measurement set A;* i.e., Positive and Negative Affect Schedule (40)), State Trait Anxiety Index–State Anxiety (41)), and Numeric Rating Scales (NRS) for general well-being items). Next, spirometry (forced vital capacity [$FVC_{\%predicted}$], forced expiratory volume in 1 second [$FEV_{1\%predicted}$]) was assessed, and 5-minute measures of heart rate (HR) and skin conductance level (SCL) were taken (*measurement set B*). Itch was induced experimentally through 2.5 minutes of transdermal iontophoresis with a 0.6% diphosphate histamine solution on the volar side of the nondominant forearm. Itch was assessed verbally every 30 seconds during iontophoresis,

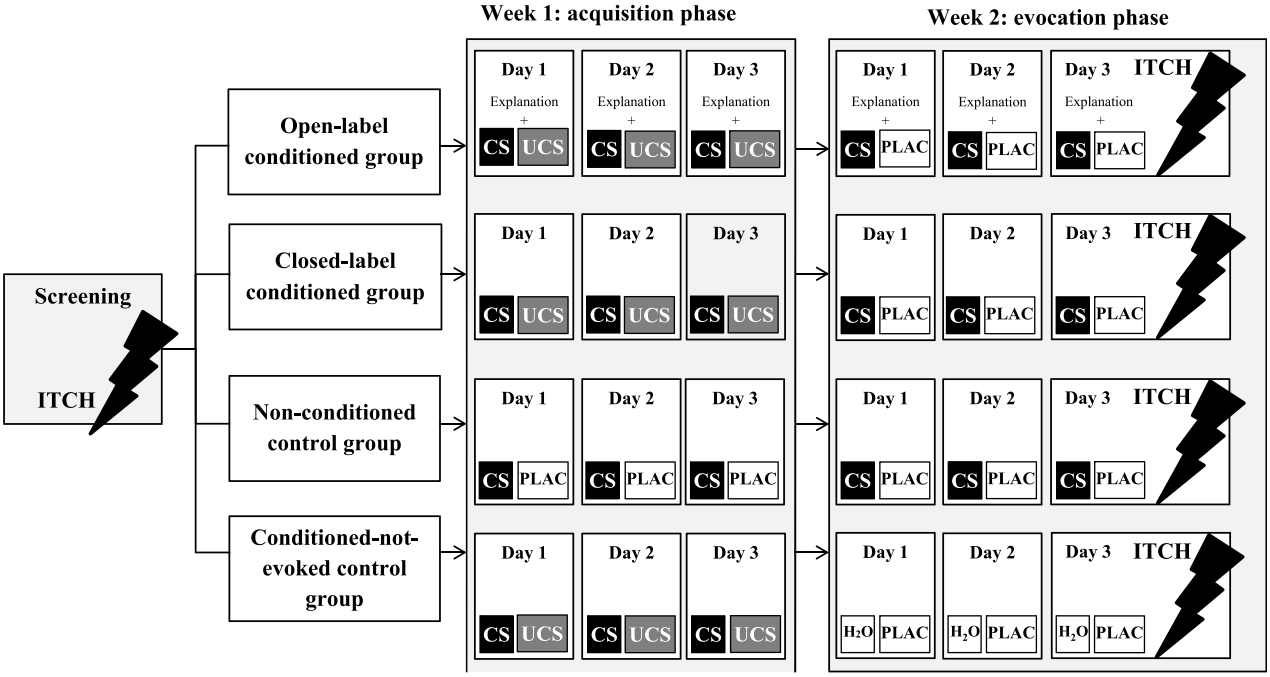

FIGURE 1. Overview of the study protocol. A conditioned stimulus (CS; distinctively tasting drink) was combined with an unconditioned stimulus (UCS; levocetrizine) or placebo capsule (PLAC) during acquisition. During evocation, the CS was combined with PLAC, and for the conditioned-not-evoked group, PLAC was provided with water (H_2O). Histamine iontophoresis (ITCH) was conducted at baseline and in the final evocation session.

and the self-rated and clinical skin response to histamine was measured (*measurement set C*). Finally, participants indicated how much itch they expected to experience during the final evocation session, and blood samples were taken to assess eosinophil profile and immunoglobulin E response to aeroallergens. In the next week, participants were invited for the acquisition sessions. For each of the three acquisition sessions, measurement set A was assessed before the CS was administered with the UCS or placebo pill. After a 4-day drug washout, participants were invited for the evocation sessions. During evocation, measurement sets A + B were assessed pre-CS, and +30 and +60 minutes post-CS administration, with an additional +90-minute post-CS assessment for the final session. Measurement set C (histamine iontophoresis) was reassessed in the final session between +60 and +90 minutes post-CS. At the start of the final session, expected itch, remembered itch, and expected medication efficacy were assessed. Finally, participants filled in a closing questionnaire in which they indicated whether they suspected to have received placebo or active medication, and compared the itch experienced during both tests. Participants rated the pleasantness of the CS taste in each session on an NRS. Participation was reimbursed by €150. An overview of the measurement schedule is provided in Figure 2.

Power Calculation and Statistical Analysis

A detailed description of the statistical analyses can be found in the Methods section in the Supplemental Material, Supplemental Digital Content 1, http://links.lww.com/PSYMED/A581. An a priori power calculation using 1000 simulated data sets at a power level of $\beta = 0.85$, an α level of $\alpha = .05$, and an assumed effect size of $\Delta/\sigma = 1/1$ indicated that 92 participants were needed to find differences between the four groups. All analyses were performed using SPSS 23.0 for Windows (IBM SPSS Inc., Chicago, Illinois). As described in the a priori plan for the statistical analyses, differences in mean itch during iontophoresis in the evocation phase between the combined open- and closed-label conditioned groups and the combined control groups were assessed using a one-sided general linear model (GLM) analysis of covariance (ANCOVA), including baseline itch as covariate. Secondarily, a GLM ANCOVA was conducted two-sided to explore effects between the separate groups. In case of significant group effects, Bonferroni post hoc tests were conducted. These analyses were repeated for the secondary parameters itch expectation and other iontophoresis-related outcomes (measurement set C). For well-being and physiological outcomes (measurement sets A + B), mixed between-within-subject repeated-measures analysis of variance (RMAs) were conducted. In case of significant effects, within-subject RMAs were conducted post hoc to assess changes from baseline for individual groups. The groups were compared on the closing questionnaire items by χ^2 tests. Relations between suspected medication intake and the primary outcome of itch were assessed by GLM ANCOVAs. Because the open-label group received information on medication administration, analyses for the closing questionnaire items were repeated without this group. Assumptions were checked before analyses, and all analyses were conducted with $\alpha = .05$. As an effect size, $\eta^2_{partial}$ was calculated for each analysis. All values in the Results section represent mean (standard deviation, or M [SD]), unless stated otherwise.

RESULTS

Participants

Ninety-nine participants were included in the study, of whom seven dropped out of the study after inclusion for various reasons.

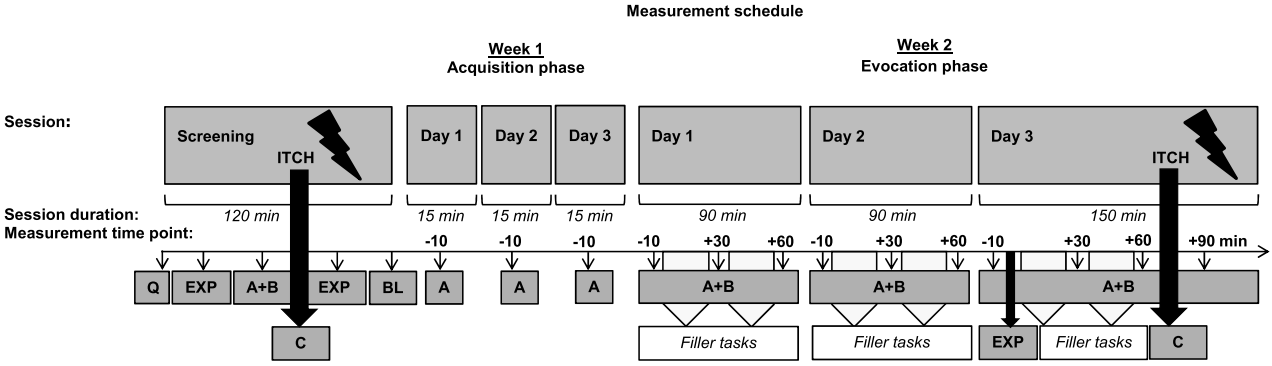

FIGURE 2. Overview of the measurement schedule. Numbers on the timeline are deducted from CS administration, with −10 representing pre-CS, and +30, +60, and +90 representing post-CS measurements. Personality questionnaires (Q); expected itch (EXP); measurement sets for well-being (A); spirometry, heart rate, and skin conductance (B); and histamine iontophoresis (e.g., itch; C) and blood samples (BL) were taken. Filler tasks consisted of neutral magazines, Sudokus, and puzzles.

For a complete overview of participants' flow, see Supplemental Figure 1, Supplemental Digital Content 1, http://links.lww.com/PSYMED/A581. The final sample consisted of 92 participants (M_{age} [SD], 22.1 [2.5] years; 84% female) randomized to the open-label conditioned group (n = 23), the closed-label conditioned group (n = 24), the conditioned-not-evoked control group (n = 23), or the nonconditioned control group (n = 22). Participants did not differ significantly between groups on demographic factors (see Table 1 [combined groups] and Supplemental Table 1 [separate groups], Supplemental Digital Content 1, http://links.lww.com/PSYMED/A581).

Group Differences at Baseline and During the Acquisition Phase

Participants randomized to the combined open- and closed-label conditioned groups showed a larger wheal area after baseline histamine iontophoresis (M [SD], 12.3 [3.1]) compared with the combined control groups (M [SD], 10.6 [3.6]; $F(1,88) = 6.14$, $p = .015$, $\eta^2_{partial} = 0.07$). A marginal overall difference between the separate groups was found for positive affect on the second acquisition day ($F(3,88) = 2.61$, $p = .057$, $\eta^2_{partial} = 0.08$; Bonferroni post hoc tests: $p > .31$). No other differences were found between groups at baseline, or at the pre-CS measurements during the acquisition and evocation sessions (all, $p > .09$). Groups did not differ in their rating of the pleasantness of the taste of the CS (all, $p > .20$), which was generally rated as unpleasant (M_{rating} [SD], 3.8 [1.5]).

Expected Itch

No differences in expected itch, remembered itch, or expected medication efficacy were found between the combined conditioned groups and the control groups (all, $p > .11$). When effects of separate groups were explored, a medium-sized effect on expected itch was demonstrated ($F(3,86) = 2.96$, $p = .037$, $\eta^2_{partial} = 0.09$), with post hoc Bonferroni tests illustrating that the open-label conditioned group expected borderline significantly less itch (M [SD], 3.2 [2.2]) compared with the conditioned-not-evoked group (M [SD], 4.6 [1.6]; $p = .050$; Figure 3 and Supplemental Table 1, Supplemental Digital Content 1, http://links.lww.com/PSYMED/A581).

Mean Self-reported Itch

As illustrated in Figure 4, a marginal small-sized conditioned effect was demonstrated for mean itch ($F(1,88) = 2.10$, $p = .076$, $\eta^2_{partial} = 0.02$), with the combined conditioned groups reporting lower itch compared with the combined control groups in response to iontophoresis during evocation ($M_{difference}$, −0.34; standard error, 0.24). A nonsignificant difference in itch was found when analyses were repeated for the separate groups ($F(3,86) = 1.47$, $p = .23$, $\eta^2_{partial} = 0.05$).

Self-rated and Clinical Skin Response to Histamine Iontophoresis

No effects on self-rated skin response to iontophoresis were demonstrated for both the combined ($F(1,88) = 0.47$, $p = .25$, $\eta^2_{partial} = 0.01$) and separate group analyses ($F(3,86) = 0.53$, $p = .66$, $\eta^2_{partial} = 0.02$). Moreover, no effects were detected for the clinical skin response parameters (all, $p > .21$; see also Table 1 [combined groups] and Supplemental Table 1 [separate groups], Supplemental Digital Content 1, http://links.lww.com/PSYMED/A581).

Spirometry

No significant group by time interactions were found for $FVC_{\%predicted}$ or $FEV_{1\%predicted}$ during the course of the evocation sessions for both the combined and separate group analyses (all, $p > .32$), indicating that conditioning did not evoke changes in spirometry over time. In addition, no main effect of group on spirometry parameters was found (all, $p > .13$; Supplemental Tables 2 and 3, Supplemental Digital Content 1, http://links.lww.com/PSYMED/A581).

HR and SCL

A medium-sized significant group by time interaction was demonstrated in the combined groups for HR (Wilk $\lambda = 0.83$, $F(7,80) = 2.35$, $p = .031$, $\eta^2_{partial} = 0.17$). Separate-group RMAs demonstrated an overall reduction in HR compared with baseline for both conditioned and control groups (both, Wilk $\lambda > 0.25$; both, $p < .001$). Post hoc comparisons over time demonstrated that in the combined conditioned groups, HR was significantly reduced compared with baseline for only three of seven post-CS measures ($p \leq .001$). In the combined control groups, HR was significantly

TABLE 1. Means, SDs and Analyses of (Co)Variance Results for the Combined Conditioned Groups Versus the Combined Control Groups

			ANCOVA Results: Effects of Group on Outcome Parameter	
	Combined Open- and Closed-Label Conditioned Groups (n = 46)	Combined Conditioned-Not-Evoked and Nonconditioned Control Groups (n = 45)	p	$\eta^2_{partial}$
Demographic factors				
Age[a], M (SD)	22.59 (3.00)	21.44 (1.80)	.15	
Body mass index[b], M (SD)	23.53 (3.29)	22.90 (3.35)	.37	
Sex (male), n (%)	9 (19.6)	6 (13.3)	.42	
Ethnicity (white), n (%)[c]	41 (93.2)	41 (95.3)	.51	
Allergy, anamnesis (yes), n (%)	14 (30.4)	14 (31.1)	.94	
Allergy, IgE response (positive), n (%)[d]	16 (34.8)	18 (41.9)	.49	
Eosinophilic profile (within reference range), n (%)	45 (97.8)	42 (93.3)	.39	
History of antihistamine use[e]	12 (26.1)	8 (17.8)	.34	
Preconditioning histamine iontophoresis (baseline), M (SD)				
Process measure				
Expected itch before iontophoresis	4.27 (2.06)	4.17 (2.04)	.83	<0.01
Expected itch after iontophoresis	3.79 (1.87)	3.92 (1.93)	.75	<0.01
Primary outcome measure				
Mean self-reported itch	3.66 (1.94)	3.39 (1.66)	.48	<0.01
Secondary outcome measures				
Subjective skin response	24.19 (14.22)	24.62 (11.79)	.88	<0.01
Wheal area (cm^2)[f]	12.33 (3.05)	10.63 (3.55)	.02	0.07
Flare area (cm^2)[f]	47.98 (12.46)	46.90 (10.63)	.66	<0.01
Skin temperature change (°C)[g]	1.66 (1.57)	1.64 (1.83)	.96	<0.01
Postconditioning histamine iontophoresis (evocation)				
Process measure				
Expected itch[h]	3.79 (2.25)	4.25 (1.71)	.15	0.02
Remembered itch from baseline	3.96 (2.12)	3.90 (1.99)	.90	<0.01
Expected medication efficacy	4.60 (2.33)	3.81 (2.40)	.11	0.03
Primary outcome measure				
Mean self-reported itch[h]	2.88 (1.96)	3.02 (1.54)	.08	0.02
Secondary outcome measures				
Subjective skin response[h]	23.81 (14.28)	25.39 (11.37)	.50	<0.01
Wheal area (cm^2)[i]	11.03 (3.09)	10.00 (3.41)	.66	<0.01
Flare area (cm^2)[i]	45.29 (12.82)	45.31 (12.18)	.45	<0.01
Skin temperature change (°C)[g]	1.33 (1.71)	1.06 (1.47)	.42	<0.01

ANCOVA = analysis of covariance; M (SD) = mean (standard deviation); IgE = Immunoglobulin E.

[a] As tested by nonparametric Mann-Whitney test (analysis of variance assumptions were violated).

[b] n = 1 missing.

[c] n = 4 missing.

[d] n = 1 missing.

[e] Not within the past 2 months and an extensive history of levocetirizine use was considered ground for exclusion.

[f] Analysis corrected for the amount of time passed between histamine iontophoresis and measurement of the variable.

[g] Calculated as posthistamine iontophoresis skin temperature (control).

[h] Analysis corrected for preconditioning (baseline) variable.

[i] Analysis corrected for preconditioning (baseline) variable, as well as for the amount of time passed between histamine iontophoresis and measurement of the variable.

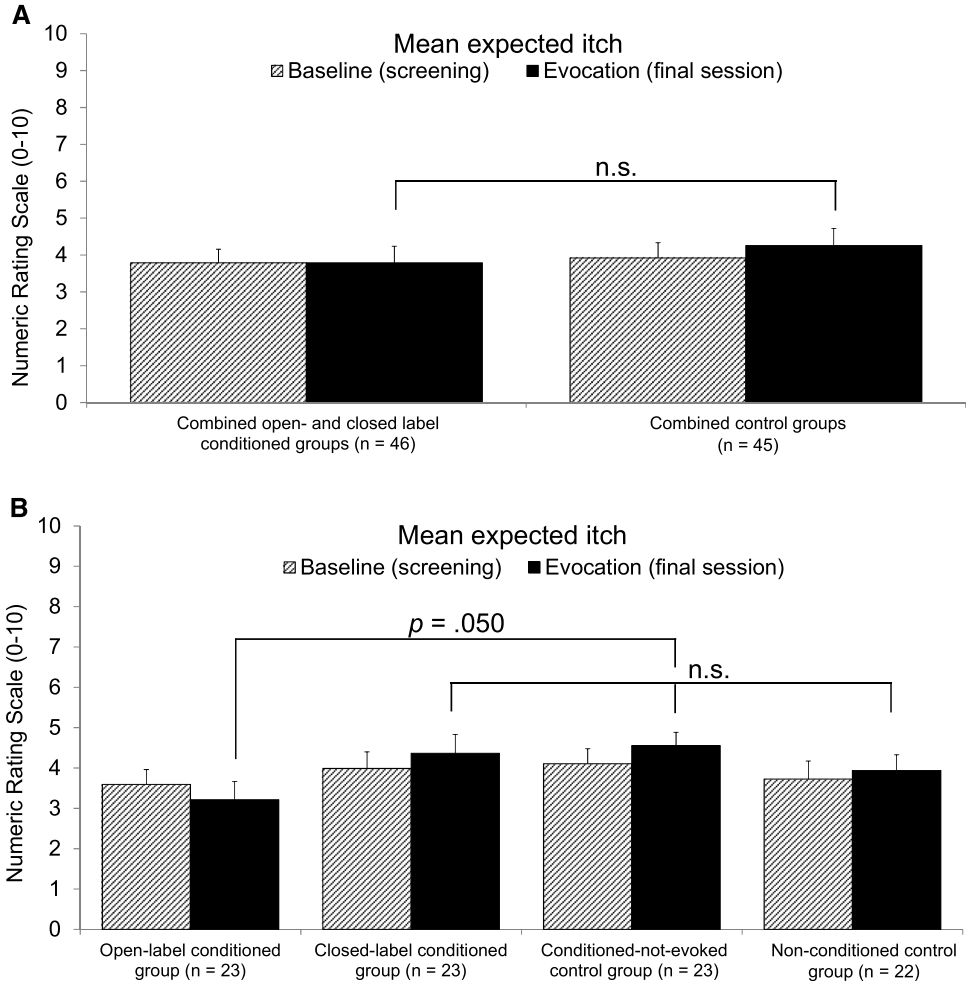

FIGURE 3. Means and standard errors of expected itch, with (A) the effects of the combined conditioned groups and the combined control groups on expected itch, controlled for baseline expected itch as measured postiontophoresis during the screening, and (B) the effects of the separate groups on expected itch.

reduced compared with baseline for six of seven post-CS measures ($p \leq .001$) and marginally reduced for the other (1/7) post-CS measure ($p = .075$). When analyses were repeated for the four (noncombined) groups, a similar medium-sized group by time interaction was found (Wilk $\lambda = 0.64$, $F(21,225) = 1.79$, $p = .021$, $\eta^2_{partial} = 0.14$). Post hoc separate-group RMAs and pairwise comparisons demonstrated significant HR reduction in line with the patterns for the combined groups. No group by time interactions (both, $p > .44$) or main effects of group (both, $p > .43$) were found for SCL in analyses with combined or separate groups. An overview is provided in Supplemental Tables 2 and 3, Supplemental Digital Content 1, http://links.lww.com/PSYMED/A581.

Well-being

No group by time interactions (all, $p > .23$) or main effects of group (all, $p > .11$) were demonstrated for the Positive and Negative Affect Schedule positive affect, State Trait Anxiety Index–State Anxiety, or NRS general well-being measures for both the combined and separate group analyses (see Supplemental Table 2 and 3, Supplemental Digital Content 1, http://links.lww.com/PSYMED/A581).

Closing Questionnaire: Suspected Medication Intake and Its Association With Mean Itch and Other Iontophoresis-Related Outcomes

No differences between groups were found when participants compared baseline and evocation itch in the closing questionnaire (all, $p > .15$). The groups differed marginally to significantly in suspected medication intake for all sessions (all, $p < .066$), except for the first evocation session. When the open-label conditioned group was excluded from the analysis, no differences were found (all, $p > .11$). Participants who suspected taking active medication during the final evocation session had reported less itch during iontophoresis as compared with those who suspected taking placebo (open-label conditioned group included: $F(1,88) = 3.82$, $p = .054$, $\eta^2_{partial} = 0.04$; open-label conditioned group excluded: $F(1,65) = 6.09$, $p = .016$, $\eta^2_{partial} = 0.09$) and also reported lower subjective skin response (open-label conditioned group included: $F(1,88) = 5.95$, $p = .017$, $\eta^2_{partial} = 0.06$; open-label conditioned

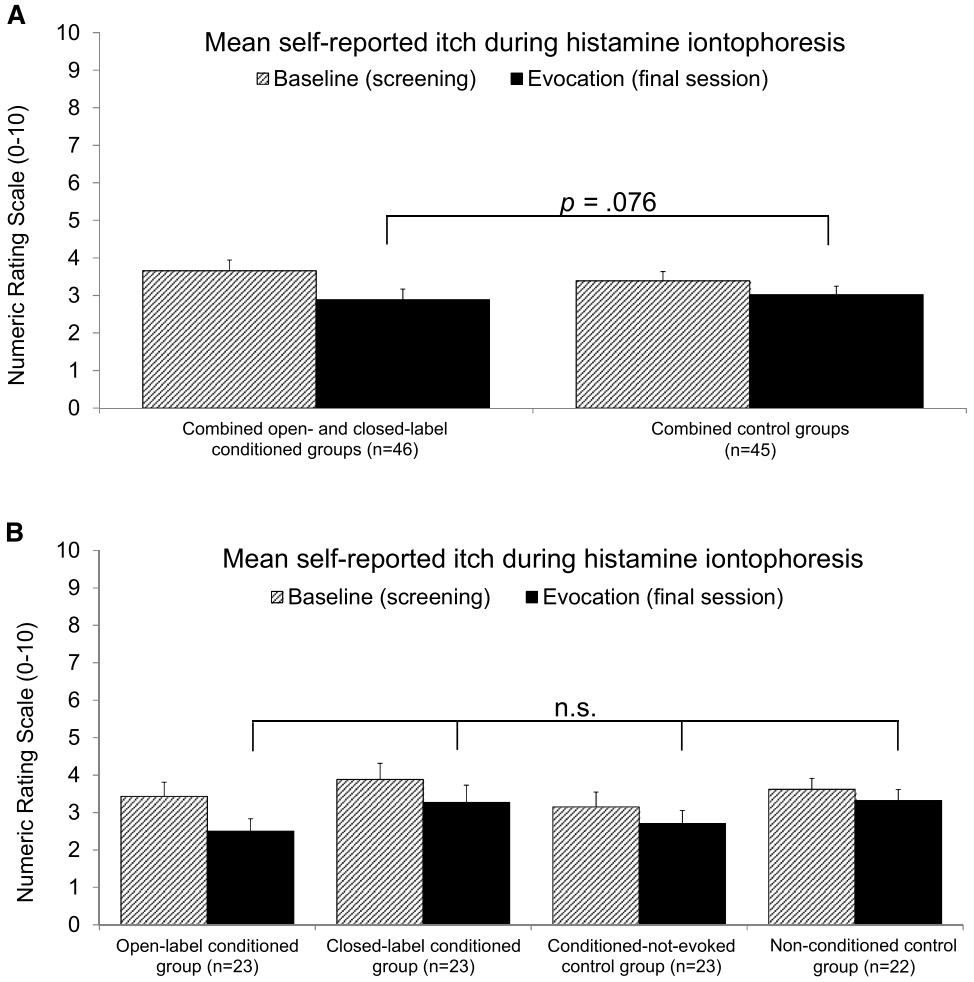

FIGURE 4. Means and standard errors of the mean for itch during iontophoresis in the final evocation session, with (A) mean itch for the combined conditioned and the combined control groups, and (B) mean itch for the separate groups.

group excluded: $F(1,65) = 4.92$, $p = .030$, $\eta^2_{partial} = 0.07$; Supplemental Tables 4 and 5, Supplemental Digital Content 1, http://links.lww.com/PSYMED/A581).

DISCUSSION

The current study investigated whether behavioral conditioning of the antihistaminergic properties of levocetirizine could reduce itch and other clinical, physiological, and psychological responses to histamine, under both open-label (i.e., with participants knowing about the conditioning procedure) and closed-label conditions. Conditioning was found to be marginally effective in reducing itch when the combined conditioned groups were compared with the combined control groups. However, no effects of conditioning were found for self-rated or clinical skin responses to histamine. Marginal antipruritic effects occurred regardless of whether participants were informed about the procedure, implying that, if further optimized, open-label behavioral conditioning might be suitable for future applications in clinical practice.

These findings show that conditioning, albeit only marginally, influenced self-reported itch, which is in line with previous findings that show that associative learning mechanisms can influence itch and allergic symptoms (11,14,21,22). Most studies have investigated conditioned exacerbation of allergic responses, whereas evidence for alleviation of itch through associative learning mechanisms is more limited and has only so far been examined in allergic patients (21,22). In patients, it may be especially difficult to ascribe findings exclusively to behavioral conditioning because external influences on learning may also be relevant. For example, natural fluctuations in symptom severity during acquisition of the conditioned response may affect conscious expectancy, due to these fluctuations being interpreted as medication effects. This in turn could influence symptom reporting within both the conditioned and control groups. Resultantly, to reduce the influence of such external factors on conditioning, the current study sought to investigate whether antipruritic effects could be conditioned in healthy volunteers.

Goebel and colleagues (21) had previously found a unique conditioned response for basophil activation in allergic patients, but symptoms reduced regardless of group allocation. Vits and colleagues (22) confirmed these findings and demonstrated symptom reduction for the conditioned and sham-conditioned (placebo) patient groups, compared with a natural history group. This led them to conclude that other cognitive processes, for example, patients' expectations of benefit, may be relevant. Likewise, the current

study provides only limited evidence for the role of conditioning in reducing histamine-induced itch. Some differences between the current study and previous studies can be noted. In the studies of Goebel and colleagues (21) and Vits and colleagues (22), patients reported symptoms at the time of enrollment in the study. In the current study, the sample consisted of nonallergic participants, or allergic participants who had not experienced symptoms for some time before enrollment. Potentially, this may have elicited smaller conditioned responses, as the pharmacological effects of levocetirizine during acquisition may not have been clearly perceived as much as they would be when allergic symptoms were present. Moreover, itch was induced in the final evocation session, to prevent that histamine iontophoresis—which entails the introduction of a foreign chemical substance to the skin (42)—interfered with measurements of conditioned responses for other study outcomes. Although literature indicates that conditioned immunological responses can persist for multiple—potentially even up to 14—evocation moments (39,43,44), it may be possible that some extinction in the conditioned response was already present in the second and third evocation sessions. Future research could investigate whether conditioned effects for itch are stronger at earlier evocation moments, for example, when participants are for the first time reexposed to the CS after the acquisition phase. Alternatively, it may be possible that the antipruritic effects of levocetirizine were too small for experimental histamine-induced itch to be effectively conditioned. Indeed, in the current study, itch reduced from baseline in general, with only marginal differences between the conditioned and control groups (21.3% reduction of itch from baseline in the conditioned groups versus 10.9% reduction in the control groups). Previous evidence dispels the notion that this small difference between groups may be due to failure of the UCS to suppress itch though, because it is demonstrated that levocetirizine has a suppression rate for itch that lies between 62% and 94% (45–47). A similar suppression rate would be expected for levocetirizine in the current study. Future research, however, may want to include a drug control group to confirm this notion and to be able to directly compare conditioned with nonconditioned responses.

Speculatively, the marginal antipruritic conditioned effect in the current study could have emerged through peripheral neurobiological mechanisms, for example, immune-mediated inhibition of pruriceptor neurons (48–50). Such mechanisms have been proposed to underlie systemic behaviorally conditioned immunosuppression (8,51). Alternatively, effects may have emerged through top-down central nervous system antipruritic mechanisms, for example, in case of itch with a neuropathic and psychogenic origin (23,52,53). As an example of central nervous system–mediated itch, itch has been found to be socially contagious in both patients and healthy volunteers (54–56). Future research may aim to clarify through which pathways antipruritic conditioned effects are established.

No conditioning effects were found for spirometry parameters. Literature indicates that pulmonary conditions such as asthma are sensitive to placebo responding (57,58), and antihistamines have been found to have bronchodilatory properties, as shown by their impact on spirometry parameters such as FEV_1 (59–62). As such, we explored whether conditioning of antihistamines could affect these parameters as well. The missing data rate in the current study likely affected the findings, however, and the study may have been underpowered for small effects. Moreover, as the sample consisted of healthy volunteers, conditioned responses may be very small because lung function may have already been optimal for a large number of participants. It may be interesting for future research to test the effects of conditioning with antihistamines by experimentally inducing bronchoconstriction, for example, through embedding a histamine bronchial provocation test. No conditioned responses were found for the secondary parameter SCL. HR reduced significantly during evocation for the combined control groups. The time that participants spent sitting in the laboratory was relatively inactive, which likely explains the decrease in HR. For the conditioned groups, HR did not decrease as much in the second and final evocation sessions. Levocetirizine is considered safe for use, and studies show no effects on cardiac safety parameters (63); however, subclinical cardiac effects are often not reported. Moreover, H_1-antihistamines—including cetirizine, from which levocetirizine is derived—have been associated with tachycardia and other cardiac adverse effects (64–66). As such, the difference in HR change over time between the conditioned and control groups might speculatively be the result of a conditioned response, although this should be further investigated. In addition, future research may aim to investigate how to enhance the learning process exclusively for the itch-suppressive effects of antihistamines, while avoiding conditioning of adverse effects.

Following the open-label rationale, significantly lower itch was expected during evocation in the open-label group compared with the conditioned-not-evoked group. However, although findings were in the expected direction, itch expectations in the open-label group did not significantly differ from those in the closed-label conditioned and nonconditioned groups. That an open-label rationale may potentially influence expectancy is in line with studies that found that inert pills combined with an open-label rationale can reliably induce placebo effects (28–34). It has also been shown that an open-label rationale regarding the role of expectations in eliciting placebo effects for itch can, in an experimental setting, result in lower expected itch even without providing inert pills (67). The current study extends these findings by preliminary showing an effect of an open-label rationale for a conditioning framework. Potentially, these expectations may help strengthen placebo effects induced by conditioning, although this needs to be investigated more extensively. Demonstrating the efficacy of open-label conditioning could lead toward new therapeutic possibilities and help facilitate utilization of placebo effect mechanisms in clinical practice. It should be noted, though, that the open-label rationale in the current study consisted of multiple components (e.g., an explanation of the conditioning procedure, a suggestion that effects may be as large as the effects of the medication, and a suggestion of reduced itch). Future research may clarify which of these components are essential for inducing expectations of reduced itch, and investigate what other factors help optimize these effects. For example, higher likability and competence of a health care provider have been shown to enhance placebo effects for allergic responses (68). It may be worthwhile to investigate to which extent factors such as likability and competence may influence the efficacy of an open-label rationale as well.

Some limitations of the current study should be considered. Because participants were mostly women, a sex bias cannot be excluded. The experimenter was blinded to group allocation only for the closed-label conditioned and the nonconditioned groups, but

not for the open-label conditioned and conditioned-not-evoked groups, because of the differences in the protocol for these latter two groups. Future research may consider having a second, blinded experimenter performing measurements, to prevent that the experimenters' own expectations influence measurement of the outcome parameters. Second, participants underwent histamine iontophoresis only twice, to prevent interference of histamine application on the conditioned response. As a result, it was not possible to assess conditioned effects for itch on the first and second evocation days, or to assess whether extinction may have taken place. In addition, no drug control group was included in the current study. Moreover, effects of antihistamine administration were not assessed in the acquisition phase because this could influence participants' conscious expectancy and thus the conditioning procedure. Because the efficacy of levocetirizine for inhibiting the response to histamine has been described in previous literature (45–47,63), we did not directly compare the magnitude of conditioned effects with those of levocetirizine. Future research may consider measuring the response to histamine on multiple testing days and including a drug control group. Finally, all groups received some form of intervention (either conditioning or placebo throughout the study). This may complicate an estimation of a true placebo response, as the idea of receiving an intervention may already influence study outcomes. Moreover, itch was induced twice. Although unlikely to have largely affected study findings—given that the itch stimulus was of short duration and inductions were spaced over 2 weeks apart—habituation cannot be ruled out. Future research may also consider adding a natural history group to control for this.

In conclusion, the current study provides preliminary support for behavioral conditioning of antipruritic effects. In addition, the findings suggest that conditioning may be effective when it is known that a learning paradigm is used. Future research may aim to clarify under which circumstances and on which evocation moments conditioning can be successful in reducing itch. Demonstrating the efficacy of (open-label) conditioning of antipruritic effects may lead toward new therapeutic possibilities. Moreover, further investigation of the content of the open-label rationale may help facilitate utilization of placebo effect mechanisms in clinical practice.

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