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# Open- and Closed-Label Placebo and Nocebo Suggestions About a Sham Transdermal Patch

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## ABSTRACT

**Objective:** Placebo effects may occur when it is known that an inert substance is given (i.e., open-label placebo). It is not yet clear whether these effects are similar to concealed (i.e., closed-label) placebo effects for itch or whether nocebo effects can be induced under open-label conditions.

**Methods:** Healthy volunteers ($n = 112$) were randomized to an open-label (I) or closed-label (II) positive suggestions group, or an open-label (III) or closed-label (IV) negative suggestions group. Participants were told, as cover story, that a transdermal caffeine patch would be applied that positively influences cognitive abilities and, as a side effect, positively or negatively (depending on group allocation) influences itch. Participants in the open-label groups were given a rationale explaining placebo and nocebo effect mechanisms. Itch (the primary outcome) was induced at baseline and postsuggestions by histamine iontophoresis.

**Results:** Analyses of variance revealed significantly lower itch in the positive compared with the negative suggestions groups for both open- and closed-label contexts (all, $p \leq .008$, Cohen $d \geq 0.47$). Self-rated skin response was less severe after positive versus negative suggestions (all, $p \leq .017$, Cohen $d \geq 0.33$), but no effects on physical skin response were found (all, $p \geq .23$, Cohen $d \leq 0.30$).

**Conclusions:** Itch can be reduced by positive compared with negative suggestions under both open- and closed-label conditions. These findings indicate that open-label suggestions may potentially be a tool to use placebo effects for self-reported outcomes in clinical practice, for example, by explaining the role of expectancy in treatment. It needs to be investigated further under which circumstances an open-label rationale may impact placebo and nocebo effects.

**Trial Registration:** www.trialregister.nl; NTR7174

**Key words:** placebo effects, nocebo effects, expectations, itch, pruritus, open-label placebo.

## INTRODUCTION

**P**lacebo effects are beneficial effects that are not attributable to active treatment components such as pharmacological substances (1,2). Instead, these effects emerge through expectations about treatment outcomes that are shaped by information about a treatment (instructions), learning processes, and environmental and social cues such as a positive patient-clinician interaction (1,3–5). For example, Benedetti and colleagues (6) demonstrated the impact of these processes on the analgesic effects of pain medication in an open-hidden paradigm: when medication was given by a doctor (open), larger analgesic effects were found compared with when it was given automatically by a machine (hidden). Nocebo effects (i.e., adverse treatment outcomes that can be attributed to negative outcome expectations) can be similarly shaped by instructions, learned associations, or social or environmental cues (e.g., negative patient-clinician interaction) (1,7). These effects can emerge not only in medical treatments but also after an inert treatment is provided, which emphasizes the psychological nature of both placebo and nocebo effects (8,9).

Experimental studies have demonstrated that placebo and nocebo effects can be induced in itch (10–12), although some studies show mixed or limited evidence (13–17). In fact, meta-analyses show that greater than 30% of symptom improvement in clinical trials for itch and allergic symptoms can be explained by the placebo effect (18,19). Itch ranks as 1 of the 50 most common interdisciplinary symptoms that affects an estimated one-fifth of the population. It has a debilitating impact on quality of life, whereas existing treatments show limited effects (20–22). Finding ways to enhance existing treatments for itch therefore becomes increasingly

**AN(C)OVA** = analysis of (co)variance, **GLM** = general linear model, **NRS** = Numeric Rating Scale, **PA** = positive affect, **PANAS** = Positive and Negative Affect Schedule, **SS-10** = Sensitive Scale-10, **STAI-S-s** = Spielberger State Trait Anxiety Inventory, State anxiety short scale, **VS** = verbal suggestion

SDC Supplemental Content

important. Potentially, knowledge on their underlying mechanisms could be used to maximize placebo effects in clinical practice and as such facilitate improvement of existing treatments for itch. Likewise, knowledge about the mechanisms underlying nocebo effects may be used to prevent them in clinical practice.

Most studies on placebo and nocebo effects in pain and itch investigated placebo or nocebo effects with covert induction of effects (i.e., hidden or closed administration of an inert treatment, with participants being led to believe an active treatment is given (e.g., Refs. (23,24)). Such an approach does not allow for an easy translation toward clinical practice, as it is simply not ethical to deceive patients (25). In the past decade, accumulating evidence shows that placebo effects can occur when patients are explicitly and openly informed about receiving inert treatment. Providing an inert pill in combination with a rationale on how placebo effects could improve medical conditions was found to lead to symptom improvement. For example, these so-called open-label (i.e., nondeceptive) placebo effects have been found to influence symptoms of irritable bowel syndrome, low back pain, and allergic rhinitis (26–35). Studies with healthy volunteers demonstrate mixed evidence for open-label placebo effects in specific somatic symptoms of itch, nausea, and pain (36–38). It should be noted, though, that the inert treatments that were used in these studies for open-label placebo effect induction differed between symptoms (i.e., placebo pills with and without rationale for pain, peppermint vapor and brain stimulation for nausea, an inert tonic for itch). There is limited literature available on whether an open-label approach can induce placebo effects for itch specifically or how these effects relate to covert (closed-label) placebo effects. Likewise, although we do know that nocebo effects often present as adverse effects to active treatments (e.g., induced by reading the leaflet of a pharmacological substance) (8,39,40), not much is known about whether these effects can also be induced using an open-label approach. A single study investigated open-label and closed-label placebo and nocebo effects induced by verbal suggestions (VSs) about sham cutaneous treatment and found that both open-label and closed-label suggestions influenced itch after, but not during, histamine application on the skin (38).

The current study builds on these previous findings and investigates whether positive and negative outcome expectations, induced by a novel suggestive framework (VSs regarding a transdermal caffeine patch, where positive or negative effects on itch were purported as side effects, provided with either an open-label context or a closed-label context), could influence self-reported itch during an experimental itch induction test using histamine. Secondary outcomes include self-rated and clinical (physical) skin responses to histamine, as well as psychological outcomes, such as well-being. We first examine differences between the combined positive and the combined negative suggestions groups, and next assess effects for open-label and closed-label contexts separately. We expect low itch after positive VSs compared with high itch after negative VSs for both open-label and closed-label contexts.

## METHODS

The study was approved by the Medical Ethics Committee at the Leiden University Medical Center, the Netherlands (NL64502.058.17), and preregistered in the Dutch Trial Register on May 6, 2018 (trial ID: NTR7174). The study was conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent. Data for the study were collected between April 2018 and January 2019.

## Participants

Healthy male and female volunteers were recruited through advertisements on sites of Leiden University and social media. Participants between 18 and 35 years old who had a good understanding of written and spoken Dutch were included. Exclusion criteria consisted of severe somatic or psychological morbidity (e.g., heart and lung diseases, *Diagnostic and Statistical Manual of Mental Disorders* [Fifth Edition] psychiatric disorders); current chronic itch or pain; current use of analgesics, anti-inflammatory drugs, antihistamines, or antibiotics; recent vaccinations; pregnancy; and color blindness. Participants were asked to refrain from caffeine or nicotine consumption and heavy meals 2 hours, exercising 12 hours, and alcohol and drugs 24 hours before participation in the study, which was verified at the start of their appointment.

## Study Design

A between-subject, single-blinded, randomized controlled design was applied. Participants were allocated (by block randomization [$n = 8$/block], online random number generator: www.random.org, Dublin, Ireland) to a) an open-label positive VS, b) closed-label positive VS, c) open-label negative VS, or d) closed-label negative VS group. Allocation was not concealed from the researcher. Participants were invited to a single laboratory session at the faculty of Social and Behavioural Sciences, Leiden University, the Netherlands. Itch was induced at baseline and post-VS by histamine iontophoresis (Figure 1).

## Materials and Measures

### Verbal Suggestions

The study was advertised as a study that investigated the effects of a transdermal caffeine patch on cognitive abilities and sensitivity to physical stimuli.[1] As part of this cover story, cognitive tasks[1] were conducted before and after suggestions. After baseline measurements, participants were told that a) a caffeine-containing patch would be placed on their shoulder; b) caffeine, like nicotine, can be delivered by this method; and c) this would influence both cognitive abilities and sensitivity to physical stimuli such as itch. In the positive VS groups, the following suggestion was then given: "Previous research has shown that itch decreases strongly after applying this patch for most people, i.e., about 95% of people. The caffeine makes your skin less sensitive to physical stimuli. As such, we expect that you will experience less itch, compared with the first test." In the open-label groups, an additional explanation of the placebo effect was given that stressed the following points: a) the patch actually did not contain caffeine; b) the purpose of the study was to test the effects of such positive suggestions; c) previous research has shown that suggestions can reduce itch; d) these effects are due to bodily processes, as the brain responds to information about a treatment in the same manner as to the actual treatment; and e) this may also work when people know that they receive a placebo. For the negative VS groups, positive words were replaced by negative words (i.e., "more itch" instead of "less itch," and "nocebo" instead of "placebo"). A 10 × 10-cm hydrocolloid patch (Medeco B.V., Oud-Beijerland, the Netherlands) was then placed on the nondominant shoulder. More details on the VSs and open-label rationale can be found in the Supplemental Digital Content, http://links.lww.com/PSYMED/A683. The open-label rationale used in the current study differs in content from that of previous studies (e.g., Refs.

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[1] Considering that the VSs were not directly aimed at manipulating the outcomes of the cognitive tasks (but that these were rather included as part of the cover story), the detailed methodology for these tasks, their outcome measures (including related outcomes, e.g., expectations), and their results can be found in the Supplementary Material, http://links.lww.com/PSYMED/A683.
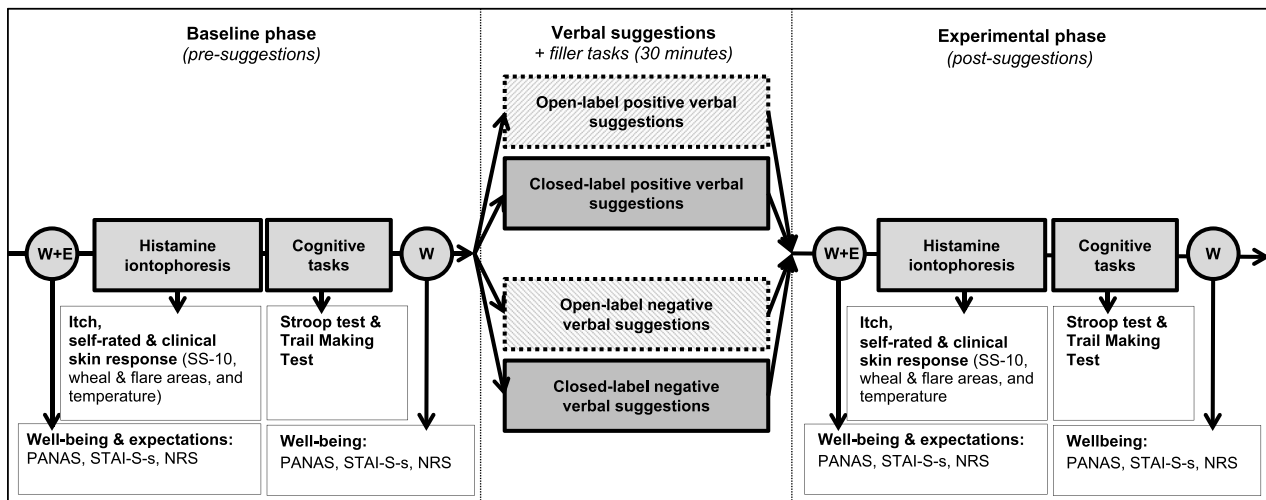
**FIGURE 1.** Overview of study design and measurement schedule for the laboratory session. W = well-being; E = expectations; PANAS = Positive and Negative Affect Schedule (41); STAI-S-s = Spielberger State Trait Anxiety Inventory, State Anxiety Short Scale (42); NRS = Numeric Rating Scale; SS10 = Sensitive Scale-10 (43); Stroop test (44); Trail Making Test (45,46).

(29,47)). For instance, an explanation of conditioning was omitted, as VSs about a patch were used to elicit effects. Likewise, the open-label rationale did not include previous discussion points (on a positive attitude being helpful but not essential and placebo effects being powerful), as this may increase demand bias in the current study design: placebo and nocebo effects were assessed shortly after suggestions were given. In previous studies, effects had always been measured over a longer period (29,47).

### Itch Induction: Histamine Iontophoresis
Itch was induced experimentally by histamine iontophoresis (see Meeuwis et al. (16) for detailed methodology). Briefly, itch was induced for 2.5 minutes on the volar side of the forearm. After 2.5 minutes, iontophoresis electrodes were removed, after which a 3-minutes follow-up period commenced. Baseline iontophoresis was conducted on the dominant forearm and post-VS iontophoresis on the nondominant forearm (handedness was assessed by a general inquiry on the participant's predominant hand).

### Outcome Measures

#### Expected Itch and Expected Patch Efficacy for Skin Sensitivity
Before each itch induction, participants rated expected itch on a Numeric Rating Scale (NRS) from 0 ("no itch") to 10 ("worst imaginable itch"). In addition, participants rated (post-VS, but before iontophoresis) the extent to which they believed the patch would influence skin sensitivity during the itch induction test on a NRS (0 "no effect," 10 "very effective").

#### Self-Rated Itch
Self-rated itch was assessed every 30 seconds during both iontophoresis tests and their follow-up period, using the same NRS as was used for expected itch. Participants were asked to rate mean itch experienced during iontophoresis (the primary study outcome) immediately upon removal of the iontophoresis electrodes. Correlations between mean itch assessed after iontophoresis and itch scores assessed every 30 seconds during iontophoresis were calculated to assess reliability of the primary outcome: self-rated mean itch (as assessed directly after the test) was significantly associated with all other itch measurements during iontophoresis for both baseline and post-VS measurements (all, $r \geq 0.35$; all, $p \leq .001$).

#### Self-Rated and Clinical Skin Response to Histamine
As a measure of self-rated skin response, participants were asked to fill in a version of the Sensitive Scale-10 (SS-10) questionnaire (43) that was

adjusted for use with histamine iontophoresis (see also Ref. (16)). In the current study, Cronbach $\alpha$ values for the postiontophoresis SS-10 were .85 and .86, respectively. Wheal size and flare response to histamine were assessed after both iontophoresis tests by tracing the outer edges on a transparent, 1-cm$^2$ gridded sheet. Images were uploaded and retraced in ImageJ (48), and wheal and flare areas were calculated (in centimeters squared). In addition, skin temperature measurements were taken with a handheld infrared digital thermometer preiontophoresis and postiontophoresis. Rise in skin temperature due to iontophoresis ($\Delta$-temperature) was calculated as an outcome measure by subtracting the preiontophoresis from postiontophoresis measurements.

### Well-Being: Positive and Negative Affect Schedule
To assess the effects of suggestions on well-being, participants filled out the Positive and Negative Affect Schedule (PANAS; (41)) at four moments during the laboratory session (Figure 1). In the current study, Cronbach $\alpha$ ranged from .88 to .91 for the PANAS positive affect (PA) scale. Considering the scores on negative affect were very low at all measurement points ($M_{range} = 11.49–12.32$, with variances between 4.09 and 9.60, whereas the scale ranges from 10 to 50), group differences for this scale were not analyzed. Two additional scales for well-being were assessed at the same moments as the PANAS and are discussed in the Supplemental Digital Content, http://links.lww.com/PSYMED/A683.

### Procedure
Before participation, volunteers filled out an online screening questionnaire. Eligible volunteers were invited for a single 2-hour laboratory session at the research site of the Faculty of Social and Behavioural Sciences, Leiden University, the Netherlands. Upon arrival, the general procedures were explained and participants provided written informed consent (for the online screening questionnaire, separate online consent was given). Briefly, the inclusion and exclusion criteria were checked and adherence to lifestyle rules was verified. Next, the baseline phase started and participants filled out questionnaires for well-being and expectations. Demographics and personality factors were assessed (the latter were not related to the current study purpose and will be reported elsewhere). Histamine iontophoresis was conducted on the dominant arm, during and after which participants rated itch. Clinical and self-rated skin responses were assessed, followed by cognitive tests and assessment of well-being. VSs were given (depending on group allocation) and the inert patch was placed on the participant's shoulder. Participants were asked to perform some neutral filler tasks (i.e.,

Sudokus, word and picture search puzzles) with a two-fold purpose: a) to minimize carryover effects in itch and b) to further reinforce the cover story of testing effects of the patch on cognitive tasks. During these filler tasks, the researcher temporarily left the room. Participants were told that they could always call the researcher back, for example, in case of questions (to not interrupt provider-participant interaction, as this may contribute to open-label placebo effects) (49). Thirty minutes after the baseline phase ended, the researcher returned, and well-being and expectations were assessed. Histamine iontophoresis was conducted on the nondominant forearm, followed by the cognitive tests and well-being questionnaires. Finally, participants filled out a closing questionnaire that contained items on, for example, familiarity with methodology, and where participants could fill in their thoughts pertaining to the purpose of the study. They were debriefed on the true purpose of the study (in the open-label groups, the study purpose was reconfirmed) by the researcher. Participants received a compensation of €20 for the laboratory session.

## Statistical Analysis

Power analysis was conducted in G*Power (50) to determine the optimal sample size for detecting between-group differences in mean itch, adjusted for baseline. The estimated effect size was based on a meta-analysis of open-label placebo (47), which found an average effect of $d = 0.88$ for open-label placebo effect induction in patient samples, compared with a no-treatment control group. Because the current study investigated effects in healthy volunteers rather than patients, a more conservative effect size of $d = 0.78$ was used. An a priori power analysis for analysis of covariance (ANCOVA), with $\alpha = .05$ and $\beta = 0.80$, indicated that, taking into account an additional 5% missing data rate, 28 participants per group were needed to detect differences between the positive and negative VS groups (for separate analysis of open-label and closed-label contexts).

All analyses were conducted in SPSS 23.0 for Windows (IBM SPSS Inc, Chicago, IL) with an $\alpha$ level of .05. Normal distribution of the variables, baseline differences, and assumptions were checked before data analysis. As was a priori determined, open-label and closed-label groups were first combined to detect differences between the effects of positive VSs and negative VSs and to increase power for these analyses. General linear model ANCOVAs were conducted for each outcome measure of itch expectations, mean itch, and self-rated and clinical skin response, controlled for baseline measures. Within-group baseline–to–post-VS change was explored for each group by paired-sample $t$ tests (Bonferroni corrected: $\alpha/2 = .025$) to assess the impact of each type of VSs on itch, and self-rated and clinical skin response. Effects of group on well-being were explored by mixed between-within repeated-measures analysis of variance (ANOVA). For expected patch efficacy for itch, general linear model ANOVA was used. As an effect size, Cohen $d$ was calculated from (covariate adjusted) group means (M) and standard deviations (SDs), with the following categories for interpretations: 0.2, small effect; 0.5, medium effect; and 0.8, large effect (51). All analyses were repeated for the separate open-label groups and the separate closed-label groups, as has been done in a previous study (38). This approach was chosen based on previous indications that placebo effect sizes are similar in open- and closed-label contexts (38) and the subsequent issues with generating adequate power for statistical models (52). As expected, an ANOVA revealed no significant difference in the main outcome mean itch between open-label and closed-label contexts ($F(1,108) = 0.39$, $p = .53$, Cohen $d = 0.13$; $F_{pos}$ $(1,52) = 0.75$, $p = .39$, Cohen $d = 0.24$; $F_{neg}$ $(1,53) = 0.01$, $p = .91$, Cohen $d < 0.001$).

For secondary analyses, a Bonferroni correction for multiple comparisons was applied ($\alpha/2 = .025$ for ANCOVA and $(\alpha/2)/2 = .0125$ for further within-group $t$ tests). Data of one participant were excluded from the analyses, as technical issues with the iontophoresis device prevented a baseline measurement of itch. Group means are described as mean [SD], unless stated otherwise.

## RESULTS

### Participants

In total, 236 potential participants expressed interest in the study, of whom 79 volunteers refrained from participating for reasons unknown (e.g., no response after invitation), and of whom 43 were excluded (30 for somatic and/or psychological conditions, 7 for medication use, and 6 for having trouble understanding Dutch). Two participants dropped out during the laboratory session, resulting in a final sample of 112 participants (16.1% male) aged between 18 and 31 years ($M_{age}$ [SD] = 21.88 [2.77]). No group differences were found for demographic factors, baseline itch expectations, and baseline iontophoresis outcome parameters for either the combined open- and closed-label groups (all, $p \geq .16$) or separate groups (all, $p \geq .060$; Table 1).

### Expected Itch and Expected Patch Efficacy for Skin Sensitivity

Expected itch during iontophoresis (adjusted for baseline) was significantly lower after suggestions in the combined positive VS groups (M [SD] = 4.00 [1.87]) compared with the combined negative VS groups (M [SD] = 5.69 [2.16]; $F(1,108) = 18.00$, $p < .001$, Cohen $d = 0.82$). When analyses were repeated for open-label and closed-label contexts separately, group differences in the same direction as for the combined groups were found (open-label: $M_{pos}$ [SD] = 4.17 [1.86] versus $M_{neg}$ [SD] = 5.93 [1.51]; closed-label: $M_{pos}$ [SD] = 3.84 [1.91] versus $M_{neg}$ [SD] = 5.44 [2.66]), with larger effect sizes found for the open-label rather than closed-label context (open-label: $F(1,52)$ =10.36, $p = .002$, Cohen $d = 0.89$; closed-label: $F(1,53) = 8.10$, $p = .006$, Cohen $d = 0.78$; Figures 2A, B). Expected patch efficacy for skin sensitivity was somewhat lower in the combined positive VS groups (M [SD] = 3.43 [2.11]) compared with the combined negative VS groups (M [SD] = 4.28 [2.55]); however, effects were marginal and small ($F(1,109) = 3.64$, $p = .059$, Cohen $d = 0.36$). When groups were separated for open-label and closed-label context, no differences were found (both, $p \geq .13$; Table 1 and Figures 2C, D).

### Self-Rated Mean Itch

Self-rated mean itch during iontophoresis was significantly lower in the combined positive VS groups (M [SD] = 3.29 [1.53] compared with the combined negative VS groups (M [SD] = 4.21 [1.96]; $F(1,108) = 17.14$, $p < .001$, Cohen $d = 0.51$), controlled for baseline. Similar group differences were found when analyses were repeated for open-label and closed-label contexts separately (open-label: $M_{pos}$ [SD] = 3.34 [1.66] versus $M_{neg}$ [SD] = 4.24 [1.76]; closed-label: $M_{pos}$ [SD] = 3.25 [1.42] versus $M_{neg}$ [SD] = 4.19 [2.17]), with medium-sized differences for the closed-label context ($F(1,53) = 9.02$, $p = .004$, Cohen $d = 0.54$) and small-to-medium-sized differences for the open-label context ($F(1,53) = 7.62$, $p = .008$, Cohen $d = 0.47$; Figures 3A, B). Within-group analysis of baseline–to–post-VS change for itch indicated that mean itch reduced significantly after positive VS (both combined and separate groups: all, $p \leq .007$), whereas it did not change in the negative VS groups (all, $p \geq .22$; Table 2).

**TABLE 1.** Means (SDs) and AN(C)OVA Outcomes for both the Combined and Separate Open- and Closed-Label Positive and Negative VS Groups

| | Combined Open- and Closed-Label Contexts (n = 111) | | | | Open-Label Context Exclusively (n = 55) | | | | Closed-Label Context Exclusively (n = 56) | | | |
| | Positive VS (n = 55) | Negative VS (n = 56) | AN(C)Ova p | AN(C)Ova Cohen d | Positive VS (n = 27) | Negative VS (n = 28) | AN(C)Ova p | AN(C)Ova Cohen d | Positive VS (n = 28) | Negative VS (n = 28) | AN(C)Ova p | AN(C)Ova Cohen d |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Demographics** | | | | | | | | | | | | |
| Sex (male), n (%) | 8 (14.55) | 10 (17.86) | .64 | | 4 (14.81) | 5 (17.86) | .76 | | 4 (14.29) | 5 (17.86) | .72 | |
| Age, y | 21.89 (2.49) | 21.93 (3.02) | .94 | 0.01 | 21.67 (2.60) | 22.29 (3.10) | .43 | 0.22 | 22.11 (2.39) | 21.57 (2.95) | .46 | 0.20 |
| **Baseline itch expectation** | | | | | | | | | | | | |
| Expected itch | 4.93 (1.91) | 5.37 (1.99) | .24 | 0.23 | 4.80 (1.89) | 5.81 (2.02) | .060 | 0.53 | 5.05 (1.95) | 4.92 (1.89) | .80 | 0.06 |
| **Baseline histamine iontophoresis** | | | | | | | | | | | | |
| Mean itch | 3.98 (1.43) | 4.00 (1.73) | .94 | 0.01 | 3.89 (1.35) | 4.01 (1.70) | .78 | 0.08 | 4.06 (1.53) | 3.99 (1.78) | .87 | 0.04 |
| Self-rated skin response (SS-10)[a] | 30.92 (13.26) | 29.79 (12.90) | .65 | 0.09 | 30.40 (13.38) | 32.53 (13.99) | .57 | 0.16 | 31.43 (13.37) | 27.05 (11.31) | .19 | 0.35 |
| Wheal area, cm² | 8.92 (3.38) | 9.28 (3.87) | .61 | 0.10 | 9.15 (3.71) | 8.95 (3.52) | .84 | 0.06 | 8.70 (3.08) | 9.60 (4.24) | .47 | 0.24 |
| Flare area, cm² | 43.36 (15.70) | 42.17 (13.01) | .19 | 0.08 | 42.25 (15.69) | 42.48 (12.54) | .95 | 0.02 | 44.44 (15.92) | 41.87 (13.70) | .52 | 0.17 |
| Change in skin temperature, °C[b,c] | 1.39 (1.15) | 1.68 (1.00) | .16 | 0.27 | 1.02 (1.05) | 1.44 (1.00) | .13 | 0.41 | 1.76 (1.15) | 1.93 (0.95) | .56 | 0.16 |
| **Post-VS expectation outcomes for itch** | | | | | | | | | | | | |
| Expected itch | 4.00 (1.87) | 5.69 (2.16) | <.001 | 0.82 | 4.17 (1.86) | 5.93 (1.51) | .002 | 0.89 | 3.84 (1.91) | 5.44 (2.66) | .006 | 0.78 |
| Expected patch effectiveness for skin sensitivity | 3.43 (2.11) | 4.28 (2.55) | .059 | 0.36 | 2.70 (2.12) | 3.71 (2.75) | .13 | 0.41 | 4.13 (1.89) | 4.84 (2.24) | .20 | 0.34 |
| **Post-VS histamine iontophoresis** | | | | | | | | | | | | |
| Mean itch | 3.29 (1.53) | 4.21 (1.96) | <.001 | 0.51 | 3.34 (1.66) | 4.24 (1.76) | .008 | 0.47 | 3.25 (1.42) | 4.19 (2.17) | .004 | 0.54 |
| Self-rated skin response (SS-10)[a,d] | 23.60 (11.88) | 27.56 (12.71) | <.001 | 0.39 | 23.37 (11.73) | 29.07 (12.68) | .017 | 0.33 | 23.82 (12.22) | 26.00 (12.80) | .010 | 0.45 |
| Wheal area, cm² | 8.19 (3.18) | 7.92 (3.42) | .24 | 0.15 | 8.15 (3.27) | 7.83 (3.02) | .75 | 0.06 | 8.23 (3.15) | 8.01 (3.84) | .17 | 0.25 |
| Flare area, cm² | 41.66 (13.33) | 41.71 (13.82) | .65 | 0.05 | 41.25 (11.84) | 42.21 (12.28) | .90 | 0.02 | 42.09 (14.88) | 41.22 (15.41) | .50 | 0.09 |
| Change in skin temperature, °C[c,e] | 1.20 (1.19) | 1.20 (1.09) | .39 | 0.14 | 1.19 (1.48) | 1.07 (1.09) | .23 | 0.30 | 1.21 (1.12) | 1.34 (1.10) | .92 | 0.02 |

SD = standard deviation; AN(C)OVA = analysis of (co)variance; VS = verbal suggestion; SS-10 = Sensitive Scale-10.

[a] Misery and Jean-Decoster (43).

[b] n = 1 missing due to technical difficulties with the infrared thermometer.

[c] Calculated as postiontophoresis temperature − preiontophoresis temperature.

[d] n = 1 missing on the post-VS SS-10.

[e] n = 1 missing due to technical difficulties with the infrared thermometer.
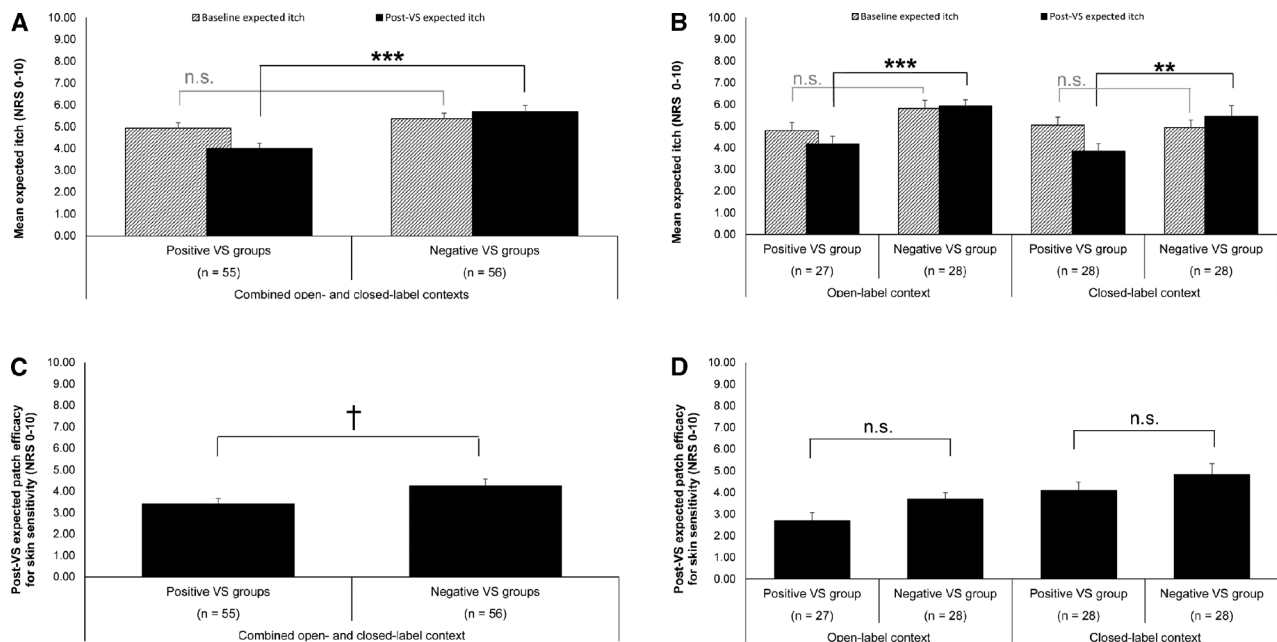
**FIGURE 2.** Mean Numeric Rating Scale (NRS) score with the standard error of the mean (SEM) for the baseline and postverbal suggestions (VSs) itch expectation in the combined open- and closed-label positive and negative VS groups (A) and the separate open-label and closed-label positive and negative VS groups (B), and mean NRS with SEM for post-VS expected patch efficacy for skin sensitivity in the combined open- and closed-label positive and negative VS groups (C) and the separate open-label and closed-label positive and negative VS groups (D). *** $p < .001$, ** $p < .01$, † $p < .10$. n.s. = nonsignificant.

## Self-Rated and Clinical Skin Response to Histamine

Participants in the combined positive VS groups rated their skin response as less severe compared with the combined negative VS groups, as indicated by small-to-medium-sized significantly lower scores on the SS-10 in the positive VS groups (M [SD] = 23.60 [11.88]) compared with the negative VS groups (M [SD] = 27.56 [12.72]; $F(1,107) = 13.58$, $p < .001$, Cohen $d = 0.39$). When open-label and closed-label contexts were separated, similar group differences were found, with somewhat larger effects found for the closed-label context (closed-label: $F(1,52) = 7.23$, $p = .010$, Cohen $d = 0.45$; open-label: $F(1,52) = 6.09$, $p = .017$, Cohen $d = 0.33$; Table 1). No differences were found for clinical skin response outcomes of wheal and flare area, or skin temperature change between the combined positive and combined negative VS groups (all, $p \geq .24$) or between the separate open- and closed-label groups (all, $p \geq .23$). An overview of the within-group baseline–to–post-VS change for each variable is provided in Table 2. In short, no significant within-group changes were found for clinical skin response in the combined groups (all, $p \geq .063$), except for wheal area and skin temperature change in the combined negative VS groups, which decreased significantly from baseline (both, $p \leq .001$). When open-label and closed-label contexts were separated, similar decreases were demonstrated in the negative VS groups (all, $p \leq .009$), except for change in skin temperature in the open-label context ($p = .071$).

## Well-Being: PA

No effect of the combined-group by time interaction on PA was found ($p = .81$), indicating that VSs did not influence affect during the laboratory session. No main effect of group was found ($p = .51$), but PA changed significantly over time ($p < .001$; Figure S1, Supplemental Digital Content, http://links.lww.com/PSYMED/A683). Post hoc Bonferroni tests indicated that PA after baseline iontophoresis was significantly higher compared with all other measurements (all, $p \leq .002$), whereas the other measurement moments did not differ significantly from each other over time (all, $p \geq .99$). Next, analyses were separated for open-label and closed-label contexts. In the open-label context, PA after baseline iontophoresis was higher compared with the two subsequent measurements (all, $p \leq .001$), whereas in the closed-label context, PA after baseline iontophoresis was higher compared with the first and third (post-VS) measurements (all, $p \leq .017$; Figure S1, http://links.lww.com/PSYMED/A683). Results for two additional well-being scales are discussed in Supplemental Digital Content, http://links.lww.com/PSYMED/A683.

## DISCUSSION

The current study investigated whether positive and negative VSs regarding a sham transdermal patch for both open-label and closed-label contexts were able to influence self-reported itch during an experimental histamine test. Overall, the study findings illustrate that both open- and closed-label positive suggestions are able to influence expectations for itch and mean itch experienced during an experimental itch induction test compared with negative suggestions. The effects on itch expectations seem larger for the open-label context, whereas for self-rated perceived itch assessed after iontophoresis, the effects were larger when suggestions were given in the closed-label context. Secondary within-group analyses indicated that mean itch decreased significantly after positive suggestions for both open-label and closed-label contexts, but that negative suggestions failed to increase itch compared with baseline. No effects on clinical skin response were found, but participants
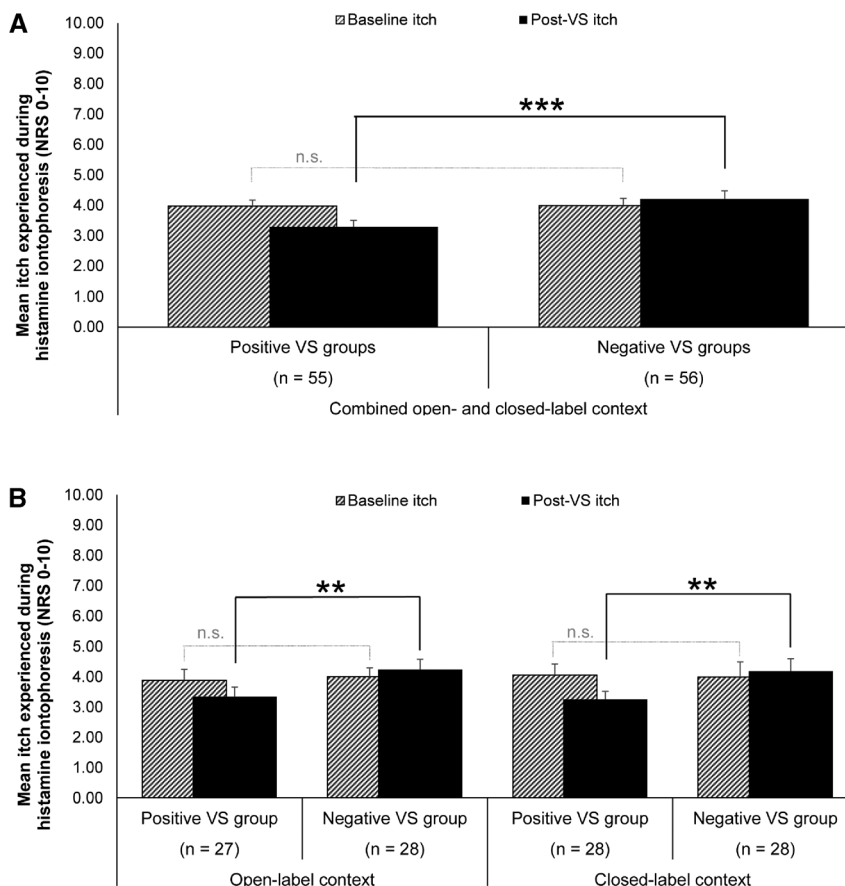
**FIGURE 3.** Mean Numeric Rating Scale (NRS) score for itch experienced during histamine iontophoresis for the baseline and postverbal suggestions (VSs) measurements, with the standard error of the mean (SEM) for the combined open- and closed-label positive and negative VS groups (A) and the separate open-label and closed-label positive and negative VS groups (B). *** $p < .001$, ** $p < .01$. n.s. = nonsignificant.

rated their own skin response as less severe after positive compared with negative suggestions for both open-label and closed-label contexts.

The within-group itch reduction from baseline to postsuggestions indicates that placebo effects were likely induced after positive suggestions, although caution is needed in interpreting these findings (as other factors, such as order effects, may have impacted changes from baseline). That positive suggestions may be able to reduce itch is in line with findings of some but not all previous studies (11,13–15,17). The discrepancies in study findings in the literature could potentially be explained by the strength and duration of VSs. Most of the studies on placebo effects in itch induce positive expectations by using brief suggestions of low or reduced itch (14,15,17). In line with this, Bartels et al. (13) demonstrated that a combination of learning and suggestions was able to induce placebo effects, but brief suggestions alone could not. On the other hand, Darragh et al. (11) combined VSs with an information leaflet, which may have contributed to the strength of suggestions. The current study combined positive suggestions about itch with the cover story that a caffeine patch would influence cognitive abilities. That caffeine is able to impact, for example, focus and attention may be commonly accepted knowledge, which may in turn have contributed to the believability of the suggestions for itch. Negative VSs did not seem to increase experienced itch from the baseline to postsuggestions test. This may indicate that the VSs

failed to elicit nocebo effects, which would not be in line with previously conducted research (10,12,53–55). However, previous studies have induced nocebo-like effects by giving suggestions directly about the itch elicitation methods. Potentially, suggestions regarding a sham treatment method may not elicit equally strong nocebo effects. A previous study, in which suggestions were given about a sham topical treatment, likewise failed to elicit significant increases in itch after negative suggestions (38). Moreover, most participants were unfamiliar with the itch induction method, which may have resulted in higher itch scores during the baseline test. This may complicate the estimation of the nocebo response, as the suggestions could have negated a naturally occurring decrease in itch. Future research may consider adding a no-suggestion (natural history) group to control for such effects and to more explicitly evaluate the size of placebo and nocebo effects.

Self-rated skin response was rated as less severe after both open-label and closed-label positive suggestions compared with negative suggestions. Indications that suggestions may be able to influence self-rated skin response have been found in previous research (16) and are further supported here. Clinical—or physical—skin response to histamine on the other hand was generally not influenced by VSs, which is in line with existing literature (11,16,56). Wheal area and skin temperature change decreased significantly in the negative VS groups. No differences between

**TABLE 2.** Within-Group Baseline–to–Post-VS Changes on Histamine Iontophoresis Outcomes for both the Combined and Separate Open- and Closed-Label Positive and Negative VS Groups

| | Positive VS Groups | | | | Negative VS Groups | | | |
|---|---|---|---|---|---|---|---|---|
| | n | Mean Change | t | p | n | Mean Change | t | p |
| Combined open- and closed-label groups | | | | | | | | |
| Mean itch | 55 | −0.68 | 4.97 | <.001 | 56 | 0.22 | −1.24 | .22 |
| Self-rated skin response (SS-10)[a] | 55 | −7.32 | 6.92 | <.001 | 55 | −2.29 | 2.48 | .016 |
| Wheal area, cm² | 55 | −0.73 | 1.90 | .063 | 56 | −1.35 | 4.64 | <.001 |
| Flare area, cm² | 55 | −1.25 | 1.14 | .26 | 56 | −0.46 | 0.44 | .66 |
| Change in skin temperature, °C[b,c] | 54 | −0.19 | 1.18 | .25 | 56 | −0.47 | 3.46 | .001 |
| Open-label context | | | | | | | | |
| Mean itch | 27 | −0.55 | 3.11 | .004 | 28 | 0.24 | −1.02 | .32 |
| Self-rated skin response (SS-10)[a] | 27 | −7.03 | 5.38 | <.001 | 28 | −3.46 | 2.74 | .011 |
| Wheal area, cm² | 27 | −1.00 | 1.73 | .095 | 28 | −1.12 | 2.82 | .009 |
| Flare area, cm² | 27 | −0.16 | 0.09 | .92 | 28 | −0.27 | 0.19 | .86 |
| Change in skin temperature, °C[b,c] | 27 | 0.17 | −0.67 | .51 | 28 | −0.37 | 1.88 | .071 |
| Closed-label context | | | | | | | | |
| Mean itch | 28 | −0.81 | 3.87 | .001 | 28 | 0.20 | −0.74 | .46 |
| Self-rated skin response (SS-10)[a] | 28 | −7.60 | 4.54 | <.001 | 27 | −1.09 | 0.81 | .42 |
| Wheal area, cm² | 28 | −0.47 | 0.91 | .37 | 28 | −1.12 | 3.69 | .001 |
| Flare area, cm² | 28 | −2.34 | 1.89 | .37 | 28 | −0.65 | 0.42 | .68 |
| Change in skin temperature, °C[b,c] | 27 | −0.55 | 3.14 | .004 | 27 | −0.58 | 3.03 | .005 |

VS = verbal suggestion; SS-10 = Sensitive Scale-10.

Mean change was calculated as post-VS score − baseline score, with negative values, indicating a decrease from baseline, and positive scores, indicating an increase from baseline.

[a] Misery and Jean-Decoster (43).

[b] n = 1 missing due to technical difficulties with the infrared thermometer.

[c] Calculated as postiontophoresis temperature − preiontophoresis temperature.

positive and negative suggestion groups were found, however; making it unlikely that these decreases were related to the manipulation used in the current study. Evidence exists that handedness and physiological differences (e.g., in permeability of the stratum corneum) between application sites may influence the physiological response to histamine iontophoresis (e.g., wheal size) (57,58), which may have affected the findings of the current study. A single previous study showed medium-sized increases in skin temperature after negative suggestions (38), but these findings could not be replicated here. Overall, the findings further support the notion that VSs may be more likely to impact subjective sensations such as pain or itch, whereas learning (i.e., conditioning) may be needed in addition to instructions to induce placebo effects for physical parameters such as clinical skin response (e.g., wheal, flare).

Although open-label suggestions seem particularly effective in inducing expectations for itch in the current study, effects on experienced itch as assessed directly after iontophoresis were somewhat lower than for the closed-label context, albeit still medium-sized. It may be possible that the open-label rationale, in which the role of expectations in placebo or nocebo effects was emphasized, could have made participants more conscious of their own expectations and could have resulted in more extreme reports of expectations. Alternatively, considering that smaller effects for experienced itch were induced in the open-label context (compared with those in the closed-label context), these findings may imply that stronger expectation effects need to be induced in an

open-label context to reach similarly sized effects in itch. More research is necessary to investigate how open-label explanations of placebo and nocebo effects could influence their emergence in somatic symptoms such as itch.

It should be noted that a calculated mean itch score during iontophoresis, derived from the itch measurements taken every 30 seconds (data shown in Supplementary Material, http://links.lww.com/PSYMED/A683), demonstrated significant medium-to-large effects of suggestions when open-label and closed-label groups were combined. Similar medium-to-large effects were found for the separate open-label context during iontophoresis, and marginal effects were found for the closed-label context. However, effects for the closed-label context lasted into the follow-up period after iontophoresis, whereas for the open-label context, effects of suggestions went extinct immediately after iontophoresis. Future research should investigate how these differences may have occurred, for example, whether effects of VSs on itch may be stronger but last for a shorter period under open-label conditions, as well as the role of potentially confounding factors such as memory recall or confirmation bias.

The current study is one of the first to investigate similar VSs for both an open-label and a closed-label context (32,36,38). A previous study showed mixed evidence for the effects of open-label and closed-label suggestions on itch, but effect sizes did indicate that VSs had lower efficacy for itch in an open-label context as well (38). Findings of the current study show similar

effect sizes to those in other studies that investigate open-label placebo effects in laboratory settings with healthy participants (32,36,38). Most open-label studies in clinical populations report higher effect sizes than those reported in the current study, though (47). A range of different expectations may exist in clinical populations that could potentially influence efficacy of open-label placebo and that are absent in healthy populations (e.g., high desire for symptom relief and increased expectations of benefit). Generally, previous studies on open-label placebo effects have used a rationale in which these effects were explained as learned Pavlovian responses (26–35). The rationale in the current study differs from the one used previously, as only placebo and nocebo effects induced by positive or negative information (suggestions) and conscious expectancy were explained. These differences in rationale may as a consequence impact expectations in a different manner. Moreover, the open-label rationale in the current study was added onto a concealed positive or negative VS (i.e., that the patch contained caffeine that would impact perception of itch, whereas in truth the patch contained no caffeine). This differs from previous work: open-label rationales have either been provided immediately and without prior concealed suggestions (26–35), or have been added as an extended explanation of mechanisms onto a very succinct suggestion about to-be-expected effects (38). Potentially, such a "placebo-reveal" (i.e., explaining that you provided deceptive information first) may have resulted in smaller placebo responses in the open-label context compared with the closed-label (concealed) context. It has been shown that conditioned analgesia persists after it is revealed that individuals are in fact receiving a placebo (59). A similar mechanism (i.e., first a placebo effect induction, which persists after the open-label rationale) may have played a role in the current study. In clinical settings, part of the efficacy of treatment may be attributed to placebo responses that are caused by information provided by a clinician about treatments. Investigating whether and how an explanation of placebo effects may interact with these processes could have implications for clinical practice. Moreover, investigating the impact of an open-label rationale on previously formed placebo effects (and expectations) is relevant, as patients in clinical practice will likely have formed expectations about treatment, and consequently, placebo responses may have occurred, long before an open-label rationale may be given.

Future research could aim to investigate how variations in the open-label rationale could impact its efficacy, for example, by immediately integrating the open-label rationale in the suggestions or by investigating the efficacy of various open-label explanations of the placebo effect. Alternatively, participants may have responded differently to the negative suggestions, when they are given under concealed (closed-label) or open-label conditions. This may explain differences in effect size found under the open-label and closed-label contexts in the current study. There is evidence that information framing can influence the size of nocebo effects, with positive framing reducing the occurrence of (nocebo) adverse effects compared with negative framing (40). Hypothetically, explaining nocebo effects may likewise impact how nocebo effects are formed, although this cannot be concluded exclusively based on data of the current study. Rather, future research may aim to clarify this relation. If it can be shown that open-label information can impact the formation of nocebo effects, this may be a potential method to prevent nocebo effects occurring in clinical practice. Moreover, an open-label rationale and suggestions may then be used

to enhance placebo effects and inhibit nocebo effects simultaneously, for example, by providing an explanation on the role of expectancy and context in treatment of medical conditions.

Some limitations need to be taken into account for the current study. The study sample consisted of young predominantly female healthy volunteers, which may challenge generalization of study findings to the general population. The study was conducted single-blinded, with the researcher giving the suggestions also being the one that conducted the tests. Potentially, this may have (unconsciously) impacted the participants' rating of itch during iontophoresis. Future research might consider using a double-blinded approach, for example, by having iontophoresis performed by a second researcher who is blinded to allocated conditions. Second, participants received histamine iontophoresis twice within 2 hours, which may have caused habituation. However, the itch stimuli were relatively short (2.5 minutes) and presented almost 1 hour apart. Moreover, by design, baseline iontophoresis took place on the dominant arm and postsuggestions iontophoresis on the nondominant arm. There are indications that handedness may affect sensory threshold and pain sensitivity, with the nondominant arm being more sensitive (60,61). It is likely that differences between both arms in sensitivity to itch would have negated habituation effects. Regardless, future research may aim to further control for these factors, including handedness. The lack of a no-treatment group in the current study complicates an estimation of the true placebo or nocebo response, as itch may have changed from baseline to post-VS regardless of suggestions. Including a no-treatment group, or counterbalancing the baseline and postsuggestion tests, may be a valuable contribution in future research to more explicitly evaluate placebo and nocebo effect sizes.

In short, the current study provides evidence that positive VSs regarding a sham transdermal patch for both open-label and closed-label contexts can influence expectations, itch experienced during, and self-reported skin response after an experimental histamine test in comparison with negative VSs. Future research may aim to investigate how variations in open-label rationale may impact the efficacy of positive and negative suggestions for itch. Potentially, open-label rationales may then be used to enhance placebo effects and inhibit nocebo effects in clinical practice, for example, by explaining role of expectancy in treatment.

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