Enhancing Placebo Effects in Somatic Symptoms Through Oxytocin

Aleksandrina Skvortsova, MSc, Diewuwe S. Veldhuijzen, PhD, Henriet Van Middendorp, PhD, Omer Van den Bergh, PhD, and Andrea W.M. Evers, PhD

ABSTRACT

Objective: Placebo effects relieve various somatic symptoms, but it is unclear how they can be enhanced to maximize positive treatment outcomes. Oxytocin administration may potentially enhance placebo effects, but few studies have been performed, and they have had conflicting findings. The study aim was to investigate the influence of positive verbal suggestions and oxytocin on treatment expectations and placebo effects for pain and itch.

Methods: One hundred eight female participants were allocated to one of the following four groups: (1) oxytocin with positive verbal suggestions, (2) placebo with positive verbal suggestions, (3) oxytocin without suggestions, and (4) placebo without suggestions. The administration of 24 IU oxytocin or a placebo spray was preceded by positive verbal suggestions regarding the pain- and itch-relieving properties of the spray or no suggestions, depending on group allocation. Pain was assessed with a cold pressor test, and itch was assessed with histamine iontophoresis.

Results: Positive verbal suggestions induced expectations of lower pain (\(F = 4.77, p = .031\)) and itch (\(F = 5.38, p = .022\)). Moreover, positive verbal suggestions elicited placebo analgesia (\(F = 5.48, p = .021\)) but did not decrease itch. No effect of oxytocin on the placebo effect or on expectations was found.

Conclusions: Positive suggestions induced placebo analgesia but oxytocin did not enhance the placebo effect. Study limitations are that we only included a female sample and a failure to induce placebo effect for itch. Future studies should focus on how oxytocin might influence placebo effects, taken into account the role of sex, dose-dependent effects, and various expectation manipulations.

Trial registration: The study was registered as a clinical trial on www.trialregister.nl (number 6376).

Key words: itch, oxytocin, pain, placebo effect.

INTRODUCTION

The placebo effect, which represents a positive outcome after receiving an inert treatment, has been repeatedly shown to relieve a variety of symptoms or conditions such as pain, depression, anxiety, addiction, and Parkinson disease among others (1–4). An important mechanism that has been suggested to underlie placebo effects is that of positive outcome expectations that are linked to better treatment outcomes (2,5–7).

In experimental or clinical settings, positive outcome expectations can be induced by verbal suggestions regarding the positive effects of a treatment. Placebo effects induced by verbal suggestions of positive outcome expectations have been extensively investigated in the context of placebo analgesia (1,8). Numerous studies demonstrated that mere positive suggestions about the analgesic properties of a placebo treatment may result in decreased pain (9–11). Placebo effects of positive verbal suggestions in the context of itch, a symptom closely related to pain (12), have been less studied. Initial studies have shown that verbal suggestions can increase itch, indicative of a nocebo effect (13), whereas verbal suggestions combined with conditioning, another important proposed mechanism underlying placebo effects, can reduce itch, indicative of placebo effects in itch (14). Inconclusive findings have been reported on the effects of verbal suggestions alone in inducing placebo effects for itch. Bartels and colleagues (13) and Van Laarhoven and colleagues (12) found no decrease in itch after giving participants positive verbal suggestions. However,
Darragh and colleagues (15) used specific verbal suggestions accompanied with a video about the itch-relieving properties of a placebo cream and demonstrated a decrease in subjective ratings of itch induced by histamine iontophoresis.

Despite an increasing body of literature on placebo effects induced by positive verbal suggestions, it is currently not yet clear what exact neurobiological mechanism drives the possible effects of verbal suggestions. Moreover, it is currently unknown how placebo effects can be enhanced to obtain the best therapeutic results.

Enck and Klosterhalfen (16) proposed that oxytocin, a peptide hormone produced in the hypothalamus, might be a facilitator of the placebo effect. Oxytocin is a well-studied hormone that has many positive behavioral effects. Among others, it increases trust (17), empathy, and social learning (16–18). In addition, oxytocin has anxiolytic effects (18–20), and it stimulates the secretion of nitric oxide that has been linked to the relaxation response (21). Oxytocin might therefore maximize positive treatment expectations induced by verbal suggestions or lead to better treatment outcomes by inducing a generally more positive affective state. Few studies have investigated the effect of oxytocin on placebo analgesia, with mixed results. Kessner and colleagues (22) induced placebo analgesia in male participants by giving positive suggestions regarding a placebo cream. Participants who received a 40 IU dose of oxytocin spray demonstrated a higher placebo response to the cream than participants who received a placebo spray. Colloca and colleagues (23) induced placebo analgesia in both male and female participants by giving positive suggestions about pain-relieving effects of a sham electrode. Contrary to Kessner and colleagues (22), they found no effect of 24 IU of oxytocin on placebo analgesia. They however demonstrated that vasopressin, a peptide hormone closely related to oxytocin, enhanced placebo analgesia, but only in women and not in men. In addition to these findings, a few studies have demonstrated that oxytocin itself can influence pain symptoms (24–27); however, this evidence is inconclusive because other studies (22,23,28–30) found no pain-relieving effects of oxytocin. Considering these mixed results, the question remains whether oxytocin can potentially enhance placebo analgesia. Furthermore, no studies to date have examined the effect of oxytocin on placebo effects for other somatic symptoms, such as itch.

In the present study, we investigated whether positive verbal suggestions would induce placebo effects for somatic symptoms of pain and itch and whether oxytocin administration would increase these placebo effects in healthy women. First, we hypothesized that participants who receive positive verbal suggestions would expect and experience less pain and itch in response to validated pain (cold pressor test [CPT]) and itch (histamine iontophoresis [HI]) tests than participants who received no suggestions. Second, we expected that oxytocin would boost the placebo effect induced by positive verbal suggestions and participants who receive oxytocin in combination with suggestions would expect and experience less pain and itch than participants who receive only suggestions or only oxytocin. Similar effects for both pain and itch were expected. We also explored whether oxytocin in combination with verbal suggestions had an effect on the pain unpleasantness after the CPT, skin redness and wheal size, and skin temperature in response to HI. We further studied whether oxytocin reduced pain and itch sensitivity. Questionnaires were administered to control for potential group differences in psychological characteristics such as anxiety, mood, neuroticism, optimism, and extraversion.

METHODS

Study Design

The study design was a randomized controlled trial. It was approved by the medical ethical committee of the Leiden University Medical Center (number NL55922.058.15). The randomization was performed by the Department of Clinical Pharmacy of the Leiden University Medical Center. After the screening, participants were randomly allocated to one of the following groups: (1) oxytocin with positive verbal suggestions, (2) placebo with positive verbal suggestions, (3) oxytocin without verbal suggestions, and (4) placebo without verbal suggestions. Both participants and experimenters were blind regarding the drug condition. One of the two experimenters was aware of the verbal suggestion condition because of the positive verbal suggestions instructions that were given by this experimenter; however, the second experimenter who performed the pain and itch tests was blind regarding allocation of the condition as to avoid influencing the results of the tests.

Participants

Women were eligible to participate when they were healthy and between the age of 18 and 35 years. The exclusion criteria consisted of the following: current use of medication, skin conditions such as eczema, current diagnosis of a mental disorder, Raynaud's syndrome, acute or chronic pain complaints, and (intended) pregnancy. Before the experiment, participants were screened for these exclusion criteria via an online questionnaire in Qualtrics (Provo, UT). Participants were asked to refrain from taking analgesic medication, drinking alcohol, and doing intense physical exercise up to 24 hours before the experiment and drinking caffeine drinks up to 2 hours before the experiment. At the start of the experiment, participants signed an informed consent form and after completion of the experiment they received a monetary compensation.

Procedure

The data were collected between April 2016 and April 2017. The experimental timeline is presented in Figure 1.

The experiment was conducted by a male and a female experimenter. A male experimenter explained the procedure and gave the verbal suggestions, whereas a female experimenter performed the CPT and HI. This consistency was designed to minimize the possible influence of the sex of the laboratory personnel on the pain and itch test outcomes. On the test day, the participant was asked to fill in several baseline questionnaires on a computer. Subsequently, the baseline CPT took place. After the test, positive suggestions were given to participants in the two positive suggestions groups and participants received oxytocin or placebo nasal spray depending on group allocation. During a waiting period of 30 minutes allowing oxytocin to reach peak concentration (31), participants filled in some questionnaires and were offered magazines with neutral content to read. After the waiting period, the HI was performed; no baseline HI was performed to avoid habituation effects that appear during the second HI administration (12). To minimize possible crossover effects of the HI on pain sensitivity, an additional waiting period of 10 minutes was completed. After that, the postintervention CPT took place. At the end of the session, participants were asked about their perceived group allocation, debriefed, and paid for their participation in the study.

Experimental Interventions

Expectation Induction

Positive expectations about the nasal spray were induced in the two groups with positive verbal suggestions. Participants received the following verbal
suggestions: “Now you will receive a nasal spray. This spray contains oxytocin. It has been demonstrated in previous studies that oxytocin decreases pain and itch sensitivity. We expect that after receiving oxytocin, you will also experience less pain during the cold pressor test and less itch during the histamine test.” Participants in the groups without suggestions were told the following: “Now you will receive a spray. This spray contains either oxytocin or placebo”.

**Drug Administration**

Depending on the group allocation, participants received 24 IU of oxytocin (Syntocinon) or placebo nasal spray. Placebo spray looked and tasted identically to oxytocin and was prepared by the Department of Clinical Pharmacy of the Leiden University Medical Center. The nasal spray was administered by the experimenter with two puffs (one puff per nostril) using a MAD Nasal mucosal atomization device (Teleflex, Inc, Research Triangle Park).

**Materials and Questionnaires**

**Cold Pressor Test**

Pain sensitivity was assessed by the CPT. The waterbath consisted of a 2.7 L styrofoam tank with cold water, which was maintained at a fixed temperature of 4°C. Participants were asked to hold their dominant hand in the water for 1 minute (32). During this minute, every 15 seconds their pain levels were assessed on a numerical rating scale (NRS) with a question “How much pain do you have now?” The participant gave an answer on a 0 to 10 scale (0 = no pain, 10 = worst pain ever experienced). In case participants were unable to hold their hand in the water for the entire minute, they could stop the test at any time. The pain intensity scores in response to the baseline and postintervention CPT were calculated as the mean scores of the four pain rating measurement points during each CPT. Before the test, participants were asked whether they experienced any pain and itch and the test was performed only in case of the absence of both. After the test, participants were asked to indicate how unpleasant the test was on a 0 to 10 NRS scale (0 = not unpleasant at all, 10 = very unpleasant).

**Histamine Iontophoresis**

Ith was induced by means of HI (12). Histamine dihydrochloride (0.5%) was dissolved in a gel of methylcellulose and propylene glycol in distilled water (manufactured by the Department of Clinical Pharmacy, Leiden University Medical Center) and 2.5 mL was placed in a disposable iontophoresis electrode (IOGEL medium, Chattanooga, Hixson). The electrode was placed on the nondominant forearm, 2 cm distal to the lateral epicondyle of the humerus. The reference electrode was applied to the skin on the lateral side of the triceps brachial muscle. The histamine solution was delivered with a dose controller (Chattanooga Ionto, Chattanooga Group, Hixson) for 2.5 minutes at a current level of 0.4 mA. Ith was measured 6 times during 2.5 minutes (immediately and after 30, 60, 90, 120, and 150 seconds from the beginning of the test) by asking the participants the following question: “How much itch do you have now?” The participant gave an answer on an NRS scale ranging from 0 to 10 (0 = no itch at all, 10 = worst itch ever experienced). The itch intensity score was calculated as a mean score of the 6 itch rating measurement points during the HI. Before the test, participants were asked whether they experienced any pain and itch and the test was performed only in case of the absence of both. Upon completion of the test, the size of skin redness and wheal size were measured with a ruler, and skin temperature was measured using a hand-held infrared digital thermometer (held vertically approximately 1 cm above the area; accuracy ± 2.0°C, resolution 0.1°C, BaseTech, Conrad Electronic Benelux BV).

**Questionnaires**

Expectations about pain and itch were measured with questions “How much pain do you expect to experience during the cold pressor test?” and “How much itch do you expect to experience during the histamine test?” Participants gave answers on an NRS from 0 to 10 (0 = no pain/itch at all is expected, 10 = worst pain/itch ever experienced is expected). Participants answered these questions twice: upon coming to the laboratory (baseline expectations) and after receiving the spray with or without the combined suggestions (postintervention expectations).

State anxiety was measured with the short state version of the State Trait Anxiety Inventory (33). The questionnaire consists of six items, and the participants were asked to give the answers on a four-point Likert scale. The score ranges from 6 to 24, with a higher score indicating higher state anxiety. Cronbach’s α in our sample (.80) was similar to previous reports (33).

Positive and negative affect were measured with a short version of the Positive and Negative Affect Schedule (34). The short Positive and Negative Affect Schedule consists of five items for measuring positive affect and five items for measuring negative affect on a five-point Likert scale. The score for both scales ranges from 5 to 25, with higher scores indicating higher positive and higher negative affect, respectively. The Cronbach’s α for positive affect in our sample was .85 and for negative affect .74, which is similar to previous reports (34).

The short version of the Eysenck Personality Questionnaire (35) was used for measuring neuroticism and extraversion. Each scale consists of 12 items, and the participants were asked to use a dichotomous scale for giving the answers (“yes” or “no”). The total score for neuroticism and extraversion ranges from 0 to 12, with higher scores indicating higher neuroticism and higher extraversion, respectively. The Cronbach’s α in this sample was lower than previous reports (35): .74 for neuroticism and .42 for extraversion that reflects low reliability.

The revised Life Orientation Test (36) was used to measure dispositional optimism. The questionnaire consists of three positive, three negative, and four filler items and answers are given on a five-point Likert scale. The total score ranges from 0 to 24, with higher score indicating higher optimism. In this sample, Cronbach’s α was .66.

**Statistical Analysis**

The data analysis was performed using SPSS Statistics Version 21 (IBM Corporation) with a two-tailed significance level of α value of less than .05. The power calculation was based on two studies: a study on the effect of oxytocin on placebo analgesia (22), which reported an effect size of 0.18 and another study on the effect of oxytocin on cold pressor pain (24), which reported an effect size of 0.2.
analyses yielded a sample size of 23 persons per group to obtain a power of .80 at an α level of .05. Taking into account 15% of potential dropouts due to among others technical problems, the total sample size was adjusted to a more conservative number of 108 participants.

The data were screened for univariate outliers using z-scores. No z-scores above 3.29 or below −3.29 were found indicating the absence of univariate outliers. Skewness and kurtosis and Shapiro-Wilk test were calculated and indicated normality of distribution of all variables. Homogeneity of variances was checked with Levene’s tests that indicated homogeneity of variances in the groups. Baseline characteristics (baseline CPT pain score, baseline CPT pain unpleasantness, expected pain, expected itch, state anxiety, mood, neuroticism, extraversion, and optimism) of the participants were compared between the groups with a one-way between-subject analysis of variance (ANOVA). Baseline CPT and postintervention CPT pain scores were compared with a paired-sample t-test.

The effects of oxytocin and positive verbal suggestions on the pain and itch expectations were analyzed by using two 2 × 2 factorial ANOVAs with spray (placebo, oxytocin) and positive verbal suggestions (with, without) as between-group factors and pain and itch postintervention expectations, respectively, as dependent variables in separate analyses.

To test the effects of oxytocin and positive verbal suggestions on the postintervention CPT pain intensity ratings, a factorial 2 × 2 Analysis of Covariance was performed, with spray and suggestions as between-group factors and the baseline CPT pain intensity rating as a covariate. A similar analysis was conducted to examine the effects of oxytocin and positive verbal suggestions on the postintervention CPT unpleasantness rating, including the baseline CPT unpleasantness rating as a covariate.

To assess the effects of oxytocin and positive verbal suggestions on itch induced by the HI, a factorial 2 × 2 ANOVA was performed with spray and suggestions as between-group factors. Three additional 2 × 2 ANOVAs were performed to evaluate the effects of the spray and suggestions on the size of skin redness, wheal size, and the skin temperature after the HI.

To check whether the groups differ in their perceived group allocation, χ² test was performed. Finally, to assess whether oral contraception use influenced the results of the analyses, the same analyses were performed with pill intake as a covariate. Because the analyses did not change the results, these results are not reported further.

As an effect size measure, partial η² was calculated for analyses on the primary and secondary outcomes.

### RESULTS

#### Demographics and Baseline Characteristic

A total of 108 participants (age 22.1 ± 2.4; 57.7% taking oral contraceptives) were equally assigned to the four groups (n = 27 per group). Baseline characteristics of the groups are presented in Table 1. There were no significant differences between the four groups in any of the baseline characteristics. The baseline CPT (M = 4.6, SD = 2.1) was experienced significantly as less painful than the postintervention CPT (M = 5.0, SD = 2.2; t(107) = −4.5, p < .001).

#### The Effect of Verbal Suggestions and Oxytocin on Expected Pain

Expected pain scores are presented in Table 2 and Figure 2A. A significant main effect of the positive verbal suggestions on expected pain was found (F(1, 104) = 4.77, p = .031, η² = .04): participants in the positive verbal suggestions groups expected significantly less pain than those in the groups that did not receive suggestions. However, neither a significant main effect of the spray (F(1, 104) = 0.03, p = .86, η² = .001) nor a significant interaction between the spray and the positive verbal suggestions (F(1, 104) = 0.19, p = .66, η² = .002) on expected pain was found, indicating that oxytocin did not influence the expected pain of the participants.

#### The Effect of Verbal Suggestions and Oxytocin on Expected Itch

Expected itch scores are presented in Table 2 and Figure 2B. There was a significant main effect of the positive verbal suggestions on the expected itch (F(1, 104) = 5.38, p = .022, η² = .05), indicating that participants in the positive verbal suggestions groups expected less itch in comparison with the groups that did not receive suggestions. However, neither the spray (F(1, 104) = .04, p = .84, η² = .001) nor the interaction between the spray and the positive

### Table 1. Baseline Characteristics

|                      | Oxytocin With Positive Suggestions (n = 27) | Placebo With Positive Suggestions (n = 27) | Oxytocin Without Suggestions (n = 27) | Placebo Without Suggestions (n = 27) | F(1; 104) | p   |
|----------------------|-------------------------------------------|-------------------------------------------|--------------------------------------|-------------------------------------|----------|-----|
| Age                  | 22.2 (2.5)                                | 21.9 (2.4)                                | 22.2 (2.4)                           | 22.2 (2.2)                          | .10      | .96 |
| Baseline expected pain| 4.7 (1.8)                                 | 4.6 (2.3)                                 | 4.8 (2.5)                            | 5.7 (2.1)                           | 1.35     | .26 |
| Baseline CPT pain intensity| 4.7 (2.3)                              | 4.4 (2.0)                                 | 4.6 (2.1)                            | 4.5 (2.2)                           | .12      | .95 |
| Baseline CPT unpleasantness | 5.9 (2.4)                              | 6.1 (2.2)                                 | 6.2 (2.1)                            | 5.6 (2.6)                           | .33      | .80 |
| Baseline expected itch | 4.9 (2.2)                                | 5.8 (2.5)                                 | 5.6 (2.3)                            | 5.8 (2.3)                           | .10      | .40 |
| State anxiety (STAI-S) | 9.8 (2.4)                                 | 9.0 (2.1)                                 | 9.0 (1.7)                            | 9.8 (2.3)                           | 1.21     | .31 |
| Positive mood (PANAS) | 27.1 (6.1)                                | 27.2 (6.2)                                | 29.7 (5.0)                           | 27.7 (7.0)                          | 1.07     | .36 |
| Negative mood (PANAS) | 12.6 (2.3)                                | 11.3 (1.9)                                | 12.7 (3.8)                           | 13.0 (2.4)                          | 2.23     | .089|
| Neuroticism (EPQ-RSS) | 4.5 (2.9)                                 | 3.7 (2.6)                                 | 3.48 (2.5)                           | 4.2 (2.7)                           | .08      | .50 |
| Extraversion (EPQ-RSS) | 8.0 (1.6)                                 | 8.0 (1.9)                                 | 8.3 (1.6)                            | 8.0 (1.9)                           | .21      | .89 |
| Optimism (LOT-R)     | 22.6 (3.0)                                | 22.2 (3.6)                                | 22.2 (3.0)                           | 21.9 (3.2)                          | .18      | .91 |

CPT = cold pressor test; STAI-S = State Train Anxiety Inventory, State Version; PANAS = Positive and Negative Affect Schedule; EPQ-RSS = Eysenck Personality Questionnaire short version; LOT-R = The revised Life Orientation Test.

Means and standard deviations are given for all variables.
verbal suggestions (F(1, 104) = .041, p = .84, η_p^2 < .001) had a significant effect on the expected itch.

The Effect of Verbal Suggestions and Oxytocin on Pain Outcomes
The pain intensity scores of CPT administration are presented in Figure 3A. There was a significant main effect of positive verbal suggestions on pain (F(1, 103) = 5.48, p = .021, η_p^2 = .05): participants who received positive verbal suggestions reported less pain in response to the postintervention CPT in comparison with participants who did not, while controlling for baseline CPT levels. However, neither the main effect of the spray (F(1, 103) = 0.78, p = .38, η_p^2 = .01) nor the interaction between the spray and the positive verbal suggestions on pain scores (F(1, 103) = 0.60, p = .44, η_p^2 = .01) were significant. In addition, the results of the factorial Analysis of Covariance indicated a significant main effect of suggestions on the unpleasantness ratings of the CPT (F(1, 103) = 15.43, p = .002, η_p^2 = .09): participants in the positive verbal suggestions group rated the postintervention CPT as less unpleasant compared with the groups that received no suggestions, while controlling for baseline unpleasantness scores for the CPT. However, neither the main effect of the spray (F(1, 103) < .001, p > .99, η_p^2 < .001) nor the interaction between the spray and the positive verbal suggestions (F(1, 103) = 1.55, p = .33, η_p^2 = .01) were significant.

The Effect of Verbal Suggestions and Oxytocin on Itch Outcomes
The itch intensity scores of the four groups are presented in Figure 3B. No main effect of the positive verbal suggestions (F(1, 104) = 0.93, p = .34, η_p^2 = .009), the spray (F(1, 104) = 1.11, p = .30, η_p^2 = .01), or the interaction between the spray and the positive verbal suggestions (F(1, 104) = 0.21, p = .65, η_p^2 < .001) were found for itch. Three factorial 2 × 2 ANOVAs indicated also no significant main effects of the positive verbal suggestions and the spray on the size of skin redness, wheal size, and skin temperature after the HI (Table 2).

TABLE 2. Somatic Symptom Outcome Parameters

|                        | Oxytocin With Positive Suggestions (n = 27) | Placebo With Positive Suggestions (n = 27) | Oxytocin Without Suggestions (n = 27) | Placebo Without Suggestions (n = 27) |
|------------------------|---------------------------------------------|------------------------------------------|---------------------------------------|--------------------------------------|
| Pain                   |                                             |                                          |                                       |                                      |
| Postintervention expected pain | 5.3 (2.5)                                  | 5.4 (2.0)                                | 6.0 (1.9)                             | 6.2 (2.3)                            |
| Postintervention CPT pain intensity | 5.1 (2.2)                                  | 4.5 (1.7)                                | 5.4 (1.9)                             | 5.2 (2.4)                            |
| Postintervention CPT pain unpleasantness | 6.1 (2.4)                                  | 5.9 (2.4)                                | 6.8 (2.1)                             | 6.5 (2.3)                            |
| Pre- and postintervention difference score | -0.4 (1.0)                                 | -0.1 (1.2)                               | -0.7 (1.3)                            | -0.7 (0.9)                           |
| Itch                   |                                             |                                          |                                       |                                      |
| Postintervention expected itch | 4.2 (2.3)                                  | 4.4 (2.3)                                | 5.4 (2.6)                             | 5.4 (2.2)                            |
| Postintervention HI itch intensity | 3.2 (1.7)                                  | 3.1 (1.5)                                | 3.7 (1.7)                             | 3.2 (1.6)                            |
| Redness size, mm       | 93.9 (15.1)                                 | 94.5 (18.4)                              | 94.8 (16.8)                           | 99.1 (17.2)                          |
| Wheal size, mm         | 58.6 (4.8)                                  | 58.8 (5.4)                               | 60.5 (6.7)                            | 58.9 (4.6)                           |
| Skin temperature, °C   | 31.3 (1.5)                                  | 31.1 (1.7)                               | 30.9 (1.4)                            | 31.0 (1.3)                           |

CPT = cold pressor test; HI = histamine iontophoresis.
Means and standard deviations are given for all variables.

FIGURE 2. Postintervention pain (A) and itch (B) expectation scores for all groups. Error bars indicate standard errors.
Perceived Group Allocation
The four groups did not differ in their perceived group allocation ($\chi^2(3, N = 108) = .49, p = .92$).

DISCUSSION
This is one of the first studies that investigated the influence of oxytocin and positive verbal suggestion on the placebo effects for both pain and itch. The study findings demonstrate that positive verbal suggestions were successful in inducing expectations of lower pain and itch, and subsequently were able to elicit small but significant placebo analgesia, but did not decrease itch sensitivity. However, oxytocin did not influence the placebo effects induced by positive verbal suggestions of pain or itch and also did not affect pain or itch sensitivity.

First, we aimed to study whether positive verbal suggestions about nasal spray would change the expectations of participants about pain and itch and elicit placebo effect. The results demonstrated that the verbal suggestions successfully influenced expectations about pain and itch and elicited placebo analgesia. These findings are in line with studies that also showed that positive verbal suggestions can induce placebo analgesia (e.g., 9–11). We were however unable to demonstrate that these verbal suggestions can induce itch reduction, corresponding to previous research (13,14,32). The fact that participants performed a baseline pain test but no baseline itch test could explain the difference in the results between these two outcome measures. It might be that to exhibit a placebo effect, people need to experience the symptom before the suggestions of the improvement are given. This baseline exposure to the symptom might be a reference point that plays an essential role in the expectations of the participants regarding the effects of the treatment. In line with this hypothesis, Darragh and colleagues (15) found placebo effect for itch and wheal size only after participants experienced a baseline itch-inducing test. Finally, sex differences in the effects of oxytocin might play an important role. It was shown that oxytocin has an opposite effect on brain activation patterns (41) and social interactions (42,43) in men and women. Possibly, oxytocin enhances placebo analgesia more in men than women (22) although different findings have been found as well (23). Various factors might possibly underlie sex differences such as, for example, varying levels of oxytocin and other hormones in women during the cycle (44), sex difference in the baseline levels of gonadal hormones that were shown to modulate oxytocin receptor expression (45), and differences in the brain structure of men and women (46). Future research should focus on sex differences in the effects of oxytocin on outcomes such as trust, anxiety, treatment expectations, and the placebo response.

As an additional finding, there was also no evidence that oxytocin influences pain or itch ratings directly. The literature about the analgesic effects of oxytocin is contradictory, whereas the effects of oxytocin on itch have not been studied so far. It remains

FIGURE 3. Subjective pain (A) and itch (B) intensities scores after the cold pressor test and histamine iontophoresis, respectively, for all groups. Error bars indicate standard errors.
unclear what underlies these contradictory findings. Some studies found that oxytocin can decrease experimentally induced pain (24–27), whereas others did not (22,23,28–30). A recent study by Tracy and colleagues (30) found pain-enhancing effects of oxytocin in women with chronic pain but no effects of oxytocin on pain sensitivity in healthy men and women. Most studies that found significant effects of oxytocin included male participants (24,25,27); however, there are also studies in men that found no analgesic results of oxytocin (22,23,30). The research about the effects of oxytocin on the pain sensitivity in women is scarce, and it is not possible to state whether sex differences might play a role in this relationship.

This study has several unique features. Our research design allows investigating the separate effects of verbal suggestions and oxytocin on pain and itch sensitivity and their interaction. Moreover, it was the first study to research the effect of oxytocin on pain and itch expectations. Besides these strong points, this study also has several limitations. First, as only women were included in this study, it is not possible to generalize the results to men. Second, we observed a placebo effect for pain but not for itch. Because no placebo effects for itch were found, this makes it impossible to generalize the results of the lack of oxytocin effects to itch. Moreover, even though the placebo effect for pain was found to be statistically significant, this effect was quite small and possibly would not be perceived by patients in clinical settings. Future studies should focus on ways to strengthen placebo effects by, for example, combining positive verbal suggestions with conditioning. In addition, as the postintervention expectations were measured after the baseline CPT, our pain and itch expectation measures might be not identical. It is recommended that future research either includes two separate sessions or uses other methods of itch induction that can be repeated twice. In addition, in contrast to studies in which placebo effects were induced by giving positive verbal suggestions about a placebo cream (22) or a sham electrode (23), we gave positive verbal suggestions about the nasal spray itself. This procedure does not require an extra placebo treatment and might be clearer for the participants. However, future studies need to compare different placebo applications to find out which of the methods are more effective. Furthermore, the administration of a nasal spray with a particular taste and smell might have elicited a placebo response in both groups regardless of the verbal suggestions. Another limitation is that menstrual cycle phase was not measured in this study. Cycle phase can have an effect on the experience of pain (47). However, as we controlled for the baseline pain sensitivity that was measured at the same day, we expect these possible effects of the menstrual cycle to be negligible. Also only one dosage of oxytocin was administered in this study. Future studies should preferably compare the influence of different dosages of oxytocin on the placebo effect. Finally, a general limitation of oxytocin research is the lack of knowledge of the underlying mechanisms of the intranasal oxytocin effects. There is an ongoing debate in the literature about how the intranasal oxytocin reaches the brain and via what pathways, central or peripheral, it influences behavior (48).

To conclude, we found that positive verbal suggestions can modify the expectations regarding pain and itch and induce small but significant placebo analgesia; however, oxytocin does not seem to influence expectations or the placebo effect for pain in healthy women. Future studies should investigate the effects of oxytocin on placebo effect at various methods of placebo effect induction and different doses for both sexes. This will advance our knowledge of the role of oxytocin in placebo effect and the possible ways to maximize the placebo effect in clinical settings.

Source of Funding and Conflicts of Interest: This study is funded by a European Research Council Consolidator Grant (ERC-2013-CoG-617700, granted to A. Evers). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the article. The authors report no conflicts of interest.

REFERENCES

1. Benedetti F, Pollo A, Lopiano L, Lanotte M, Vighetti S, Rainero I. Conscious expectation and unconscious conditioning in analgesic, motor, and hormonal placebo/nocebo responses. J Neurosci 2003;23:4315–23.

2. Benedetti F. Mechanisms of placebo and placebo-related effects across diseases and treatments. Annu Rev Pharmacol Toxicol 2008;48:33–60.

3. De La Fuente-Fernandez R, Stoeloe AJ. The placebo effect in Parkinson’s disease. Trends Neurosci 2002;25:302–6.

4. Volkow ND, Wang G-J, Ma Y, Fowles JS, Zhou W, Maynard L, Telang F, Vaska P, Ding YS, Wong C, Swanson JM. Expectation enhances the regional brain metabolism and the reinforcing effects of stimulants in cocaine abusers. J Neurosci 2003;23:11461–8.

5. Finniss DG, Kaptchuk TJ, Miller F, Benedetti F. Biological, clinical, and ethical advances of placebo effects. The Lancet 2010;375:686–95.

6. Auer CJ, Glombiewski JA, Doering BK, Winkler A, Laferton JA, Broadbent E, Rief W. Patients’ expectations predict surgery outcomes: a meta-analysis. Int J Behav Med 2016;23:49–62.

7. Mondloch MV, Cole DC, Frank JW. Does how you do depend on how you think you’ll do? A systematic review of the evidence for a relation between patients’ recovery expectations and health outcomes. CMAJ 2008;179:1155–63.

8. Atlas LY, Wager TD. How expectations shape pain. Neurosci Lett 2012;520:140–6.

9. Amazigo M, Benedetti F. Neuropharmacological dissection of placebo analgesia: expectation-activated opioid systems versus conditioning-activated specific sub-systems. J Neurosci 1999;19:484–94.

10. Whalley B, Hyland ME, Kirsch I. Consistency of the placebo effect. J Psychosom Res 2008;64:537–41.

11. Voudouris NJ, Peck CL, Coleman G. The role of conditioning and verbal expectancy in the placebo response. Pain 1990;45:121–8.

12. Van Laarhoven AI, Walker AL, Wilder-Smith OH, Kroeze S, Van Riel PL, Van de Kerkhof PC, Kraaimaat FW, Evers AW. Role of induced negative and positive emotions in sensitivity to itch and pain in women. Br J Dermatol 2012;167:1115–8.

13. Bartels DJ, van Laarhoven AI, Haverkamp EA, Wilder-Smith OH, Doners AR, van Middendorp H, Van de Kerkhof PC, Evers AW. Role of conditioning and verbal suggestion in placebo and nocebo effects on itch. PLoS One 2014;9:e91727.

14. van Laarhoven AI, Vogelaar ML, Wilder-Smith OH, van Riel PL, van de Kerkhof PC, Kraaimaat FW, Evers AW. Induction of nocebo and placebo effects on itch and pain by verbal suggestions. Pain 2011;152:1486–94.

15. Darragh M, Chang JW, Booth RJ, Consedine NS. The placebo effect in inflammatory skin reactions: the influence of verbal suggestion on itch and weal size. J Psychosom Res 2015;78:489–94.

16. Enck P, Klösterhalsen S. The story of O-is oxytocin the mediator of the placebo response? Neurogastroenterol Motil 2009;21:347–50.

17. Kovfeld M, Heinrichs M, Zaks PJ, Fischbacher U, Fehr E. Oxytocin increases trust in humans. Nature 2005;435:673–6.

18. Cardoso C, Ellenbogen MA, Orlando MA, Bacon SL, Jober R. Intranasal oxytocin attenuates the cortisol response to physical stress: a dose–response study. Psychoneuroendocrinology 2013;38:399–407.

19. Ditzen B, Schaer M, Gabriel B, Bodenmann G, Ehret H, Heinrichs M. Intranasal oxytocin increases positive communication and reduces cortisol levels during couple conflict. Biol Psychiatry 2009;65:726–31.

20. Heinrichs M, Baumgartner T, Kirschbaum C, Ehret H. Social support and oxytocin interact to suppress cortisol and subjective responses to psychosocial stress. Biol Psychiatry 2003;54:1398–99.

21. Fredriech G, Stefano GB. Placebo neural systems: nitric oxide, morphine and the dopamine brain reward and motivation circuits. Med Sci Monit 2005;11:MS54–65.

22. Kessner S, Sprenger C, Wrobel N, Wieck H, Bingel U. Effect of oxytocin on placebo analgesia: a randomized study. JAMA 2013;310:1733–5.

23. Colloca L, Pine DS, Emms M, Miller FG, Grillon C. Vasopressin boosts placebo analgesic effects in women: a randomized trial. Biol Psychiatry 2016;79:794–802.
24. Rash JA, Campbell TS. The effect of intranasal oxytocin administration on acute cold pressor pain: a placebo-controlled, double-blind, within-participants cross-over investigation. Psychosom Med 2014;76:422–9.

25. Zunhammer M, Geis S, Busch Y, Eichhammer P, Greenlee MW. Pain modulation by intranasal oxytocin and emotional picture viewing - a randomized double-blind fMRI study. Sci Rep 2016;6:31606.

26. Louvel D, Delvaux M, Felez J, Fieramonti J, Bueno L, Lazarthe Y, Frexinos J. Oxytocin increases thresholds of colonic visceral perception in patients with irritable bowel syndrome. Gut 1996;39:741–7.

27. Paley A, Krahé C, Maltezos S, Williams S, Howard M, Fotopoulou A. The analgesic effect of oxytocin in humans: a double-blind, placebo-controlled cross-over study using laser-evoked potentials. J Neuroendocrinol 2016;28.

28. Goodin BR, Anderson AJ, Freeman EL, Bulls HW, Robbins MT, Ness TJ. Intranasal oxytocin administration is associated with enhanced endogenous pain inhibition and reduced negative mood states. Clin J Pain 2014;31:757–67.

29. Marmeli S, Pisanu GM, Sardo S, Marchi A, Pili A, Carboni M, Minerva L, Trincas G, Carta MG, Melis MR, Agabio R. Oxytocin nasal spray in fibromyalgic patients. Rheumatol Int 2014;34:1047–52.

30. Tracy LM, Laboschagne I, Georgiou-Karistianis N, Gibson SJ, Giummarra MJ. Sex-specific effects of intranasal oxytocin on thermal pain perception: a randomised, double-blind, placebo-controlled cross-over study. Psychoneuroendocrinology 2017;83:101–10.

31. Striepens N, Kendrick KM, Hanking V, Landgraf R, Willner U, Maier W, Hurlemann R. Elevated cerebrospinal fluid and blood concentrations of oxytocin following its intranasal administration in humans. Sci Rep 2013;3:3440.

32. Peerdeman KJ, van Laarhoven AI, Donders AR, Hopman MT, Peters ML, van der Meulen RJ, Ditzen B, Pagnoni G, Rilling JK. Oxytocin and vasopressin effects on the neural response to social cooperation are modulated by sex in humans. Brain Imaging Behav 2015;9:754–64.

33. Marteau TM, Bekker H. The development of a six-item short-form of the state scale of the Spielberger State-Trait Anxiety Inventory (STAI). Br J Clin Psychol 1994;33:132.

34. Watson D, Clark LA, Tellegen A. Development and validation of brief measures of positive and negative affect: the PANAS scales. J Pers Soc Psychol 1988;54:1063–70.

35. Sanderman R, Arrindell WA, Ranchor AV. Eysenck personality questionnaire (EPQ). Noordelijk Centrum voor Gezondheidsvraagstukken: Groningen; 1991.

36. Scheier MF, Carver CS, Bridges MW. Distinguishing optimism from neuroticism (and trait anxiety, self-mastery, and self-esteem): a reevaluation of the Life Orientation Test. J Pers Soc Psychol 1994;67:1063–78.

37. Paul F, Endefelder E, Lang AG, Buchner A. G² Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav Res Methods 2007;39:175–91.

38. Van IJzendoorn MH, Bhandari R, Van der Veen R, Grewen KM, Bakermans-Kranenburg MJ. Elevated salivary levels of oxytocin persist more than 7 h after intranasal administration. Front Neurosci 2012;6:174.

39. Legros JJ. Inhibitory effect of oxytocin on corticotropin releasing hormone in humans: are vasopressin and oxytocin ying-yang neurohormones? Psychoneuroendocrinology 2001;26:649–55.

40. Schlosser A, Almeida O, Patchev V, Yassouridis A, Elaoud J. Oxytocin-stimulated release of adrenocorticotropic from the rat pituitary is mediated by arginine vasopressin receptors of the V1b type. Endocrinology 1994;135:2058–63.

41. Feng C, Hackett PD, DeMarco AC, Chen X, Stair S, Haroon I, Ditzen B, Pagnoni G, Rilling JK. Oxytocin and vasopressin effects on the neural response to social competition are modulated by sex in humans. Brain Imaging Behav 2015;9:754–64.

42. Fischer-Sholly M, Levkovitz Y, Shamay-Toory S. Oxytocin facilitates accurate perception of competition in men and kinship in women. Soc Cogn Affect Neurosci 2012;8:313–7.

43. Rilling JK, DeMarco AC, Hackett PD, Chen X, Gautam P, Stair S, Haroon E, Thompson R, Ditzen B, Patel R, Pagnoni G. Sex differences in the neural and behavioral response to intranasal oxytocin and vasopressin during human social interaction. Psychoneuroendocrinology 2014;39:237–48.

44. Salonia A, Nappi RE, Pantaleo M, D’Anci L, Brancati A, Fabini F, Zanni G, Rigatti P, Montorsi F. Menstrual cycle-related changes in plasma oxytocin are relevant to normal sexual function in healthy women. Horm Behav 2005;47:164–9.

45. Insel TR. The challenge of translation in social neuroscience: a review of oxytocin, vasopressin, and affiliative behavior. Neuron 2010;65:768–79.

46. Ruigrok AN, Salimi-Khorshidi G, Lai MC, Baron-Cohen S, Lombardo MV, Tait RJ, Suckling J. A meta-analysis of sex differences in human brain structure. Neurosci Biobehav Rev 2014;39:54–50.

47. Hellström B, Lundberg U. Pain perception to the cold pressor test during the menstrual cycle in relation to estrogen levels and a comparison with men. Int J Psychophysiol 2005;55:231–41.

48. Leng G, Ludwig M. Intranasal oxytocin: myths and delusions. Biol Psychiatry 2016;79:243–50.