Deceptive and Nondeceptive Placebos to Reduce Pain

An Experimental Study in Healthy Individuals

Tobias Kube, PhD,† Winfried Rief, PhD,* Maj-Britt Vivell, MSc,* N. Leonora Schäfer, BSc,* Teresa Vermillion, MSc,* Karoline Körfer, MSc,* and Julia A. Glombiewski, PhD*†*

Objectives: Recent research has shown that placebos can be effective even if they are openly prescribed to participants. Yet, it is unclear how such "open-label placebos" (OLPs) compare to deceptive placebo (DP) and what the mechanisms of actions are. In this study, we therefore compared 2 versions of OLP to DP and no treatment (NT).

Materials and Methods: Using a standard heat pain paradigm, 117 healthy volunteers underwent a baseline and a posttreatment pain assessment. With the exception of NT, all groups received an inert placebo cream after the first assessment. OLP was administered by either evoking positive expectancies or by raising hope for placebo analgesia, thus distinguishing for the first time conceptually between expectancy and hope in experimental pain research. The primary outcome was pre-post change in pain tolerance.

Results: Increase in pain tolerance was larger in the 3 treatment groups compared with NT, whereas the treatment groups did not differ from each other. Further results showed that participants receiving DP reported a large reduction of subjective pain intensity and unpleasantness, whereas no such reduction was found for the 2 OLP groups. The 2 OLP versions did not differ in terms of their analgesic effects.

Discussion: The study provided evidence for traditional placebo analgesia on the basis of deception. For OLP, we found that OLP indeed increased pain tolerance; however, participants receiving OLP were reluctant to report any subjective analgesic effects. Combined with previous studies, the present findings suggest that the effects of OLP are weaker in healthy volunteers than in clinical samples.

Key Words: placebo effects, open-label placebo, pain, expectancy, hope, heat pain paradigm

(*Clin J Pain* 2020;36:68–79)

Numerous studies have demonstrated that placebo effects contribute substantially to symptom improvement in a variety of medical conditions and mental disorders.[1–4] Although quite widespread,[5,6] the use of deceptive placebos (DPs) in clinical practice has been considered ethically questionable in terms of contradicting key ethical principles such as patient autonomy.[7] Placebos being honestly prescribed to patients (so-called "open-label placebos" = OLPs) might be able to resolve this ethical issue. The idea of administering placebos with full transparency and disclosure, without losing its effectiveness, was until recently considered absurd. Recent studies, however, have demonstrated that OLPs in fact lead to symptom improvement in irritable bowel syndrome,[8] chronic lower back pain,[9] rhinitis,[10] cancer-related fatigue,[11] and attention-deficit hyperactivity disorder.[12,13]

To date, OLPs have mostly been studied in clinical settings in comparison to no treatment (NT). Evidence for the effects of OLP compared with DP is limited so far, as is knowledge about the mechanisms of action of OLP. One recent study using a heat pain paradigm in healthy individuals aimed to fill this gap by comparing 2 versions of OLP to DP and NT[14] and examining whether a plausible rationale of the treatment offered affects pain relief. The authors found that OLP with a rationale was more effective than OLP without a rationale, whereas OLP with a rationale was not different from DP, emphasizing the importance of a convincing rationale. We aimed to develop this idea further by investigating the importance of expectancies and hopes as 2 possible components of such a rationale.

Expectancies represent a well-studied construct in pain and placebo research,[15–19] whereas hope has so far received limited attention. Although there is ongoing debate on the precise definition of hope in different scientific disciplines, most theorists agree that is an inner state referring to the possibility of a desirable future event or experience.[20] The exact overlaps and differences between hopes and expectancies are described in the methods section, but in brief: most researchers in this field agree that expectancies refer to a relatively high (assumed) likelihood of occurrence of the desired, whereas hope can be present even in case of a very low likelihood.[21–25] The interest in the role of hope in placebo research has increased on the basis of the results of qualitative studies. In particular, findings from qualitative studies have shown that many patients from placebo-controlled studies denied having strong treatment expectations; instead, they *hoped* for symptom reduction and were "open to see what happens."[26–28] Therefore, it has been theorized that hope might be an important factor contributing to OLP response beyond expectancy.[29]

The present study is the first to conceptualize hope and expectancies in placebo research and to examine their influence on placebo analgesia. In particular, we compared 4 experimental groups: (1) open-label placebo treatment with

Received for publication June 12, 2019; revised November 6, 2019; accepted November 10, 2019.
From the *Department of Clinical Psychology and Psychotherapy, Philipps-University of Marburg, Marburg; and †Department of Clinical Psychology and Psychotherapy, University of Koblenz-Landau, Landau, Germany.
The authors declare no conflict of interest.
Reprints: Tobias Kube, PhD, Department of Clinical Psychology and Psychotherapy, University of Koblenz-Landau, Ostbahnstraße 10, Landau D-76829, Germany (e-mail: kube@uni-landau.de).
Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website, www.clinicalpain.com.

DOI: 10.1097/AJP.0000000000000781

the induction of hope (OLP-H); (2) open-label placebo treatment evoking expectancies (OLP-E); (3) DP treatment; (4) NT. The primary goal was to compare the 4 groups with respect to their effects on pain perception. We expected that all treatment groups would show greater pain relief than NT. Further, we tested whether DP would elicit more pain relief than the 2 OLP groups. Finally, we explored whether one of the OLP groups would outperform the other one in terms of pain relief. Because of the novelty of separating hopes and expectancies in the present study, a secondary goal was established: to examine whether the induction of hopes and expectancies was successful. Specifically, we hypothesized that participants from the OLP-E group would rate the subjective likelihood of placebo analgesia to be higher than the OLP-H group.

MATERIALS AND METHODS

The study was approved by the local ethics committee (reference number 2017-58v) and was carried out in accordance with ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments. All participants provided written informed consent and were treated in accordance with the ethical guidelines of the German Psychological Society. The study was pre-registered at ClinicalTrials.gov: NCT03517644.

Participants

The sample size was determined by an a-priori power analysis. We estimated the expected effect size on the basis of the results revealed by Locher et al.[14] Accordingly, we expected a small to medium effect size regarding the differences between the experimental groups. Thus, the power analysis (expected effect size $f = 0.20$; power = 0.80; correlation between the first and the second pain assessment: $r = 0.30$) indicated a required sample size of at least 100 participants. We recruited N = 117 participants; this surplus would, if necessary, allow us to exclude participant data due to experimental or statistical issues without substantially losing power. Participants were recruited by email lists and poster in public spaces. In doing so, the study was labeled as "study for the perception of heat pain." The inclusion criteria were as follows: mental and physical health by self-report; at least 18 years old; and sufficient German language skills. The exclusion criteria were: any acute or chronic diseases; skin pathologies; neuropathies or any other sensory abnormality affecting the thermal or tactile modality; the intake of any medication, except for oral contraceptives; currently receiving psychological or psychiatric treatment; consumption of alcohol within the past 12 hours; and studying medicine or psychology. As an incentive for participation, participants were paid €25.

Operationalization of Hopes and Expectancies

Expectations have been defined as future-directed cognitions referring to the incidence or nonincidence of a specific event or experience.[30–32] Specifically, expectancies may relate both to the probability of the occurrence of an event or experience and to the subjective effects associated with it.[33] Although expectations represent a rather cognitive construct, it is widely acknowledged that expectations elicit emotions associated with the anticipated event or experience.[34–39] Expectations are considered to be a core mechanism of placebo effects,[40–43] and positive treatment expectations can boost the effects of pharmacological,[44–46] medical,[47,48] and psychotherapeutic interventions.[49,50]

Finding a consistent definition of hope appears to be nearly impossible in view of its diverging use in in different scientific disciplines (eg, philosophy,[51] psychology,[52] theology,[53] anthropology,[54] and medicine[55]). By 2003, 26 different theories and 54 definitions of hope had been established.[56] Nearly all theorists of hope, however, agree that hope often comprises 2 core components: (1) it refers to a future event or experience, and (2) this event/experience is desirable.[57] As can be seen, at least the first component would also apply to expectancies. Indeed, different scientific disciplines have aimed to answer the question as to whether hopes and expectancies are separable.

A psychological study examining undergraduate students found that participants themselves could distinguish between their hopes and expectations, even though their hopes and expectations were correlated.[58] In the health care context, it has been argued that the main difference between hopes and expectations refers to the subjective probability that individuals expect versus hope to experience certain events.[21] Specifically, it has been theorized that expectations are driven by a *sense of probability*, meaning that expectations are, compared with hope, related to a higher subjective probability; in contrast, the authors have argued that hopes, unlike expectancies, are driven primarily by a *sense of preference*. In fact, research findings emphasize that expectations often refer to the anticipation of negative future events, for example, in the context of mental disorders such as major depression[36,37]; hope, however, almost always refers to desirable events or experiences.[59] An important aspect related to hope and probability is that hope is often closely linked to uncertainty and can be present even if there is very little chance of hope being fulfilled. In particular, the chronic pain literature has shown that hope often coexists with despair and that there is hope for pain relief, even if participants consider the likelihood to be very low.[27,60–62] In these studies, individuals reported on their hopes that things might just become different from the current state. Interestingly, individuals often actively sustain their hope "against the odds"[25(p326)]: a qualitative study on cancer patients revealed that individuals continue to hope for the best as long as there is a subjectively assumed theoretical possibility that things could turn out well at the end.[25] In this study, patients tended to reframe very low probabilities by thinking, for example, "My belief system is that, even if the stats were accurate, I'm the other half of that stat, you know. That's the way I handle the stat. If they tell you that you have one percent, I'll be in that one rather than the one that's—you know—doomed', thus maintaining hope.[25(p325)]

A second aspect used to distinguish hope from expectations is the extent to which cognitive and emotional components are involved.[58] Although expectancies represent a primarily cognitive construct, hope has often been conceptualized as an emotional state[22,63] or even as an existential state.[64] According to Hammelstein and Roth,[63] hope is an emotion resulting from an expectancy. The presence of emotional components in hoping is not least evident by the proximity to despair in the context of clinical populations. Despite these distinctions, there are nevertheless overlaps between hopes and expectations. Hope, for instance, is not necessarily related to low probabilities, and expectancies can also be accompanied by emotional states. Indeed, in 1 study on neuropathic pain, it has been shown that both patients' expectations and positive emotional feelings were associated with placebo-induced reduction in hyperalgesia.[65]

In this study, we aimed to combine these different conceptions to operationalize the possible contribution of hopes and expectancies to placebo analgesia. For this purpose, we have used the following general framework: we have induced an unpleasant state in the participants through painful stimuli and have sought to manipulate experimentally whether they expect or hope to receive pain relief by applying a placebo cream. Specifically, we used the following aspects as distinguishing criteria, acknowledging that a certain overlap still remains: as the main difference, we assumed that expectations, as compared with hopes, might be associated with a higher subjective likelihood of experiencing pain relief after taking a placebo cream. Second, expecting pain relief may reflect a primarily cognitive process, whereas hope represents an emotional state to a greater extent than expectations. The conception of hopes and expectancies is illustrated in Figure 1.

Procedure

To enhance comparability with Locher et al,[14] we decided to use the same pain model and its basic procedures.

Before the beginning of an experimental session, each participant was randomly assigned to one of the 4 conditions. When participants had arrived, they first performed both an objective baseline assessment of heat pain and pain ratings (for further details on the assessment of heat pain, see the section "Heat pain threshold/tolerance and corresponding intensity and unpleasantness ratings").

In the following treatment phase, the OLP-H, OLP-E, and DP groups each received an inert placebo cream (a standard basic cream with oil of thyme produced by a local pharmacy). Although all participants received the same placebo cream, it was provided with different rationales. Participants from the DP group were told, "You are receiving an analgesic cream, which contains the local anesthetic lidocaine. Lidocaine is, for example, the main ingredient of a cream called "Lidocaine-direct" which is commonly used for small burns of the skin or dermatological diseases due to its quick analgesic and antipruritic effects. The effectiveness of lidocaine has been proven in several high quality studies. After applying the cream, you will become less sensitive to painful stimuli compared to in the first trial." Thus, the DP group underwent no conditioning procedure, but received verbal suggestions to lead them to believe that they would receive active medication.

After completing the pretreatment trial, participants from the OLP-H group were told the following: "The cream you are going to receive is a placebo cream that the actual lidocaine cream is compared with. This means that this cream does not contain any pharmacological ingredients. Therefore, it is unlikely that the cream alone will affect your pain perception." The purpose of this statement was to lower the subjective likelihood of occurrence of the desired event (in this case, pain relief) in accordance with the above conceptualization of hope.[22,57,63] Next, the investigator aimed to induce hope by stating that "a few people, especially *women/men of your age*, reported that the placebo cream had a strong analgesic effect when applying it, even though they knew that they were receiving a placebo cream. For instance, a *young woman/man* who participated in the study last week told us that the placebo cream helped her/him to bear the unpleasant heat stimulus and to perceive it as less painful. Therefore, you may become less sensitive to painful stimuli after applying the cream compared to in the first trial." The intention of these positive examples was to make the participants aware of the theoretical possibility that they could also benefit from the cream, analogous to the above interpretation of "I could be the one taking the 1% chance."[25] The sociodemographic information in this explanation was varied with respect to the age and sex of each participant, aimed at increasing the subjective possibility that one could belong to those individuals who are less sensitive after applying the cream, according to Roth and Hammelstein.[22]

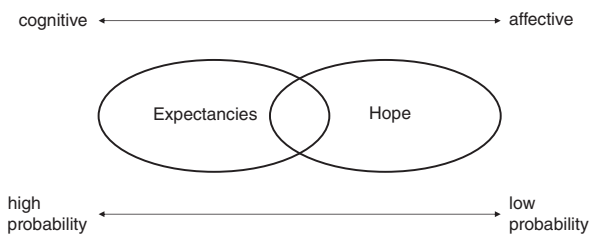

FIGURE 1. Theoretical conceptualization of hope and expectancies in the present study.

To evoke positive treatment expectations in the OLP-E group, we used the instructions recommended by Kaptchuk and colleagues,[8,66] which were very similar to the instructions used by Locher et al[14] in their OLP with a rationale condition. Specifically, participants were told after the baseline measure that they were going to receive an inert placebo cream as described in the OLP-H group. In accordance with Kaptchuk and colleagues[8,66] and Locher et al[14] participants were then informed of the power of placebos by stating, "Several scientific studies have shown that placebos are very effective, even if participants knew that they were going to receive a placebo. In particular, placebo creams lead to substantial pain reduction in ~70% of participants." This information was supposed to make participants aware of the high probability that they could experience pain relief after applying the cream to alter their expectations, as theorized above. Next, participants were informed about the underlying mechanisms of placebo effects, such as classical conditioning, as illustrated by the example of Pavlov's dogs. On the basis of this explanation, participants were subsequently told, "Similar to Pavlov's dogs, a placebo cream that looks like an actual analgesic cream can activate automatic bodily reactions, which in turn may lead to an effective analgesia. Thus, placebos actually affect physical processes, for example, immune parameters. Therefore, you may become less sensitive to painful stimuli after applying the cream compared to in the first trial."

Since a recent study has demonstrated that health care providers' social behavior (in terms of warmth and competence) can influence expectancy effects in placebo research,[67] the 2 OLP conditions were held equivalent in this respect. Specifically, the investigators were trained for the experimental procedure according to a manual for the experimental procedure; this included the instructions for the 4 experimental groups. In doing so, the investigators aimed to be perceived by the participants as both warm and competent. Before applying the placebo cream, participants from the OLP-H and OLP-E groups were asked to complete several measures detailing their hopes and expectations for pain relief.

Participants from the NT group did not receive any treatment. Instead, they were told, "You are in the control group, and you are not going to receive a cream. Thus, we

can directly start with the next trial. Would that be okay with you?"

After the treatment phase, heat pain assessments were repeated. After completing this posttreatment assessment, participants rated several questionnaires through the commercial survey platform Unipark. Finally, all participants were debriefed about the actual aims of the study, and, if appropriate, about the conducted deception. The experimental sessions were conducted by 3 female psychology students (M.-B.V., N.L.S., and T.V.) at a laboratory room of the Philipps-University of Marburg. Data collection lasted from February 2018 to May 2018. Figure 2 shows the design of the study.

Heat Pain Threshold/Tolerance and Corresponding Intensity and Unpleasantness Ratings

To assess pain sensation, we used the suprathreshold method of the Thermo Sensory Analyser (TSA-II), a commonly used device to study pain sensation and analgesic effects. To prevent the effects of sensitization or habituation,[68] the thermode of the TSA-II was fixed on 2 different locations (A and B) on the nondominant forearm, applying a randomly counterbalanced order within each group. Half of the participants started pain assessment with location A for the baseline for the pretreatment measurements, followed by location B for the posttreatment measurements. The other half of the participants started with location B for the baseline assessment, followed by location A in the posttreatment phase.[14] Before starting the measurements, participants were made familiar with the device. In this phase, no painful stimuli were applied.

The pretreatment assessment started with determining participants' heat pain threshold, that is, the point when sensation changes from being warm to being painful. For this purpose, we used the method of limits, starting at 32°C with a rise of 0.5°C every second. That is, participants were asked to stop the increasing heat pain stimulus when the threshold was reached by pressing the space bar of the keyboard placed in front of them. To prevent physical injuries, the measurement would have stopped automatically when the maximum temperature of 52°C was reached. The software automatically decreased temperature immediately to the initial adaptation temperature of 32°C (slope 10°C/s) after termination. After determining their heat pain threshold, participants' heat pain tolerance was assessed; this was also conducted using the method of limits. In doing so, participants were asked to stop when they could not stand the increasing heat any longer. Similar to the assessment of the heat pain threshold, the measurement would have stopped automatically upon reaching 52°C to prevent injuries. Notably, none of the participants reached the maximum temperature of 52°C; that is, the measurement was always stopped before reaching this point. Both pain threshold and tolerance were assessed 3 times to ensure a reliable assessment of pain sensation.

After each pain threshold and tolerance assessment, participants were asked to rate the corresponding pain intensity and unpleasantness using a Numerical Analogue Scale, ranging from 0 (no pain sensation/not unpleasant at all) to 100 (the most intense pain sensation imaginable/the most unpleasant imaginable).[19,69] The distinction between pain intensity and unpleasantness is commonly used to assess the cognitive (intensity) and affective dimensions of pain (unpleasantness) separately.[70]

Randomization and Blinding

Before each experimental session, participants were assigned by the investigators (M.-B.V., N.L.S., and T.V.) to 1 of the 4 conditions. In doing so, the investigator drew a

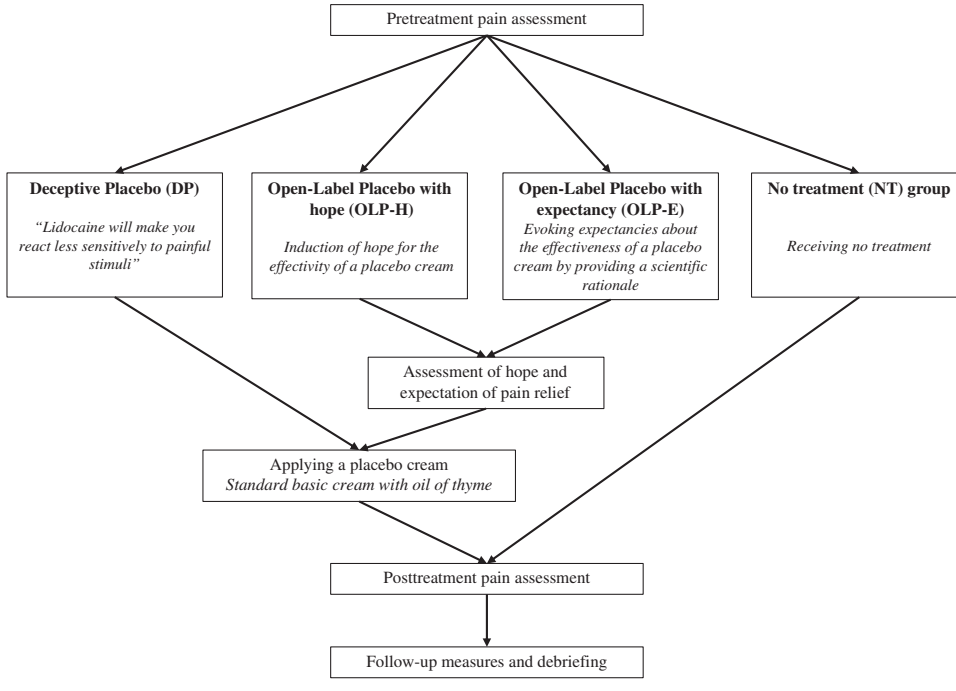

FIGURE 2. Illustration of the study design.

number (1 = OLP-H, 2 = OLP-E, 3 = DP, 4 = NT) out of a concealed envelope before the participants arrived at the laboratory room. Furthermore, before each experimental session, block randomization was used in terms of the location of the heat pain stimuli on the forearm in such a way that an equal number of participants followed the same location sequence in each group. Because of the study design, investigators were aware of the allocation code of each participant at the start of the trial, and only participants from the DP condition were masked.

Measures and Questionnaires

Hopes and Expectancies

To assess hopes and expectancies in terms of the efficacy of the placebo cream in the 2 OLP conditions, several measures were used. According to the above conceptualization, the most important distinguishing criterion between hopes and expectancies in the present study is the subjective likelihood of placebo analgesia. Therefore, we asked participants to specify the subjective likelihood (using a Numerical Analogue Scale from 0% to 100%), by which they believed the placebo cream would help them.

As secondary indicators, we aimed to assess the extent to which participants cognitively believed in placebo analgesia (expectancy) versus whether they were in a positive emotional state toward the placebo application (hope). Because the present study was, to the best of our knowledge, the first to examine the possible contributions of hopes versus expectancies to placebo analgesia, no appropriate questionnaire for the assessment of these constructs was available. We therefore developed 2 brief questionnaires to assess participants' hopes and expectancies for pain relief. Both scales comprised 6 items. Items were presented in German, and were translated into English for this article. Aiming to assess hope as a positive emotional state before applying the placebo cream, we used rather affective words/terms to construe the hope scale, for example, "I have the feeling that the cream could help me to better cope with the painful stimulus." Furthermore, to take into account that hope is often associated with uncertainty about what will happen, we used verbs such as "could," "would," and "might," for example, "Since placebos have already been effective in other people, I hope that the cream could also make me less sensitive to pain." The items of this scale were rated on a 5-point Likert scale. Internal consistency of this scale was $\alpha = 0.91$.

For the construction of the expectations scale, we used rather cognitive terms, such as "I assume that the cream will make me less sensitive to the pain." In addition, we consequently used the will-future to express a high certainty, for example, "The cream will help me deal with the pain." Also, we aimed to assess the specific rationale of placebo effects that was provided only in the OLP-E group, but not in the OLP-H group; the item was "Through learning mechanisms such as classical conditioning, the cream will make me less sensitive to pain." Like the hope scale, items of the expectancy scale were rated on a 5-point Likert scale. Internal consistency of this scale was $\alpha = 0.93$. Both the 6-item hope scale and the 6-item expectancy scale are presented in their entirety in the Appendix (Supplemental Digital Content 1, http://links.lww.com/CJP/A605).

In the end, we asked participants whether their possible confidence that the cream would help them was based more on expectancies or more on hopes. This question could be answered on a 6-point Likert scale ranging from 1 (hope) to 6 (expectancy). The mean in the OLP-H group was 2.12 (SD = 1.86) and the mean in the OLP-E group was 3.12 (SD = 1.97); the effect size of the difference between the groups was medium, but did not reach significance ($t_{48} = -1.850$, $P = 0.070$, $d = 0.522$).

To avoid participants becoming irritated by answering fairly similar items immediately after one another, we added 5 distractor items after the hope scale/before the expectations scale (eg, "The temperature in this room is comfortable," "The light conditions in this room are appropriate" and "I do not feel bothered by loud noise"). As hopes and expectancies were of interest only in the 2 OLP conditions, the measures described above were used only in these 2 experimental groups.

Pain Expectancy

After the treatment phase and before the beginning of the second heat pain procedure, we used a Numerical Analogue Scale to assess to what degree participants expected the stimuli in the posttreatment phase to be painful (0 = "no pain at all," 100 = "most intense pain imaginable").

Credibility of the Treatment

To assess the credibility of the treatment, we used the same questions as Locher et al.[14] In particular, participants from the 2 OLP conditions were asked to rate whether they believed they had received a placebo (Likert scale from 1 = "I was sure that I received a placebo cream," 2 = "I doubted whether I received a placebo cream," and 3 = "I did not believe that I received a placebo cream"). Participants from the DP group were asked to rate whether they believed they had received an analgesic cream (Likert scale from 1 = "I was sure that I received an analgesic cream," 2 = "I doubted whether I received an analgesic cream," and 3 = "I did not believe that I received an analgesic cream"). Similar to the previous study,[14] participants were excluded from analyses if they did not believe that they had received a placebo cream or an analgesic cream (ie, scoring 3 on the Likert scale). Finally, participants from the OLP groups were asked to rate their familiarity with the term placebo (Likert scale from 1 = "I have heard of the term placebo and I can describe it with my own words," 2 = "I have heard of the term placebo but I do not know what it is," and 3 = "I have never heard of the term placebo before").

Other Measures

To assess any possible confounding variables, we measured the Big-Five personality traits neuroticism and openness to experiences (NEO Five-Factor Inventory) and beliefs about medicine (Beliefs about Medicines Questionnaire). These variables were chosen because personality traits such as neuroticism and openness have been shown to influence the placebo response,[71,72] and beliefs about medicine have been shown to predict adherence to medications.[73] In addition, we assessed resilience (Resilience Scale) and depressive symptoms (Patient Health Questionnaire 9 [PHQ-9]) to examine whether these variables affected the results. All of these measures are described in more detail in the Supplementary Material (Supplemental Digital Content 2, http://links.lww.com/CJP/A606). In addition, sociodemographic variables, including age, sex, and education level, were assessed using a brief self-report questionnaire.

Pilot Study

According to the conceptualization of hopes and expectancies, participants from the OLP-E group were expected to rate the subjective likelihood of pain relief to be higher than participants from the OLP-H group. To examine whether the respective instructions indeed led to differences in the subjective likelihood of pain relief, we carried out a pilot study. In a brief online survey, in which a convenience sample (N = 95) was used, participants were provided with the written instructions that the investigators planned to use for the OLP groups during the main experiment. Participants received either the OLP-H or the OLP-E instructions. Results of the pilot study indicated that the 2 groups indeed differed in their subjective likelihoods ($t = -2.257$, $P = 0.026$, $d = 0.474$), with lower ratings among participants who received the hope instructions ($M = 36.7$, SD = 21.75) than participants who received the expectancy instructions ($M = 47.87$, SD = 24.87).

Statistical Analyses

First, we performed data screening according to the suggestions made by Tabachnick and Fidell,[74] and tested the assumptions of analyses of variance (ANOVAs). There were no missing values due to the study design (participants could only continue if they entered all values). Univariate outliers were inspected by standardized values of measured variables and their histograms.[75] Multivariate outliers were identified by Mahalanobis distance and Cook distance (with $\alpha = 0.5-$ quantile of the F distribution), as suggested by both Cohen et al[76] and Stevens.[77] Following the recommendations of Stevens, participants were excluded as outliers in cases of conspicuous values on the dependent variables (DVs) to ensure that the analyses reflected the majority of the data and were not influenced by highly influential/errant data points. Like Locher et al,[14] we defined heat pain tolerance and the corresponding intensity and unpleasantness ratings as primary outcomes. Heat pain threshold and the corresponding subjective ratings, and the pain expectancy ratings, were considered as secondary outcomes.

For all ANOVAs, the independent variable was the experimental condition (OLP-H vs. OLP-E vs. DP vs. NT). We carried out a multivariate analysis of variance (MANOVA) to examine any possible baseline differences between the 4 experimental conditions' samples on initial heat pain threshold, tolerance, and the corresponding intensity and unpleasantness ratings, respectively. The significant effects, as indicated by the MANOVA, were further explored by post hoc paired-samples t tests. In addition, we performed 2 separate χ^2 tests, with sex and education level as categorical DV. In terms of a manipulation check, we performed another MANOVA to examine whether the OLP-H group and the OLP-E group differed in their ratings of hopes and expectancies for the effectiveness of the placebo cream (DVs: subjective likelihood of placebo analgesia; sum score hope scale; and sum score expectancy scale).

For our main analysis, that is, the pre to post changes in heat pain tolerance and the corresponding intensity and unpleasantness ratings, we carried out 3 separate 1-way ANOVAs with the respective pre to post change scores (heat pain tolerance, intensity, and unpleasantness) as DVs. For all 3 primary outcome ANOVAs, we tested 3 orthogonal contrasts: (c1) NT versus treatment groups (OLP-H, OLP-E, DP) (1 tailed), (c2) DP versus OLP groups (OLP-H, OLP-E) (2 tailed), and (c3) OLP-H versus OLP-E (2 tailed). Like Locher et al,[14] we decided to use planned contrasts instead of post hoc tests to reduce the risk of type-1 errors according to Price and colleagues.[19,78] Furthermore, when defining the contrasts, we followed the recommendation of Field[79] when first comparing all of the treatment groups with the NT group. The same contrasts were tested for the secondary outcome (ie, heat pain threshold, including the corresponding intensity and unpleasantness ratings). Furthermore, using analysis of covariance, we examined whether group differences in pain perception were influenced by personality traits (neuroticism and openness), beliefs about medicine, resilience, and depressive symptoms. We also computed the correlations of these measures with changes in pain perception. Type-1 error levels were set at 5%. All analyses were carried out using IBM SPSS Statistics, Version 25.

RESULTS

Sample Characteristics

After data screening, 6 participants had to be excluded because they did not believe that they had received a placebo cream (n = 5) or an "analgesic" cream (n = 1), respectively. Although participants were informed that studying medicine was defined as an exclusion criterion, 2 participants indicated after completing the posttreatment assessment that they were studying medicine: these 2 participants were also excluded. Similarly, although participants were aware that acute or chronic illnesses were defined as exclusion criteria, 5 participants had to be excluded because they reported various diseases after the posttreatment assessment (asthma [n = 2], scoliosis [n = 1], golf elbow syndrome [n = 1], and inflammation of the lumbar spine [n = 1]). A further 3 participants were identified as statistical outliers and were therefore excluded according to Stevens.[77] Thus, subsequent analyses are based on data from 100 participants (n = 25 for each of the 4 conditions). The excluded participants did not differ from participants left in the analyses in terms of age, sex distribution, education level, and pain perception (all $P > 0.380$).

The mean age of the participants was 24.82 years (SD = 5.92 y), and 52% of the participants were female. Most participants were students (92%) and 55% of the participants had a high school degree. The mean sum score of the PHQ-9 was 5.13 (SD = 3.54), indicating that, on average, participants reported minimal depressive symptoms according to Kroenke et al.[80]

Examination of Baseline Differences Between the Groups

A MANOVA indicated that participants from the 4 experimental groups did not differ in their baseline heat pain threshold ($F_{3,96} = 0.420$, $P = 0.739$; $\eta^2_P = 0.013$), the corresponding intensity ($F_{3,96} = 1.364$, $P = 0.259$; $\eta^2_P = 0.041$), and unpleasantness rating, ($F_{3,96} = 1.689$, $P = 0.174$; $\eta^2_P = 0.050$), heat pain tolerance ($F_{3,96} = 0.541$, $P = 0.655$; $\eta^2_P = 0.017$), the corresponding intensity ($F_{3,96} = 1.094$, $P = 0.355$; $\eta^2_P = 0.033$), and unpleasantness rating ($F_{3,96} = 2.541$, $P = 0.061$; $\eta^2_P = 0.074$). In addition, the MANOVA indicated that the 4 groups did not differ on age ($F_{3,96} = 1.207$, $P = 0.312$; $\eta^2_P = 0.036$), or depressive symptoms ($F_{3,96} = 1.617$, $P = 0.191$; $\eta^2_P = 0.048$). The distribution of male and female participants did not significantly differ across the 4 groups ($\chi^2 = 5.769$, $P = 0.123$), nor did the distribution of education level ($\chi^2 = 13.125$, $P = 0.360$). All sociodemographic values of the sample are shown in Table 1.

TABLE 1. Sample Characteristics of the Study Participants

Variables	OLP-H (n = 25)	OLP-E (n = 25)	DP (n = 25)	NT (n = 25)
Age, mean (SD) (y)	26.12 (8.32)	24.20 (3.57)	23.60 (4.81)	24.92 (5.76)
PHQ-9 sum score, mean (SD)	6.56 (3.50)	4.24 (3.84)	4.84 (3.13)	4.96 (3.28)
Sex, n (%)				
Male	6 (24.0)	13 (52.0)	13 (52.0)	16 (61.5)
Female	19 (76.0)	12 (48.0)	12 (48.0)	10 (38.5)
Educational level, n (%)				
No educational degree	0	0	0	0
Vocational training	2 (8.0)	2 (8.0)	1 (4.0)	0
High school degree	10 (40.0)	14 (56.0)	16 (64.0)	16 (61.5)
University degree	13 (52.0)	9 (36.0)	8 (32.0)	10 (38.5)

DP indicates deceptive placebo; NT, no treatment; OLP-E, open-label placebo with expectancy induction; OLP-H, open-label placebo with hope induction; PHQ-9, Patient Health Questionnaire 9 for the measurement of depressive symptoms.

Manipulation Check

The MANOVA indicated that participants from the OLP-H group rated the subjective likelihood of placebo analgesia to be significantly lower than participants from the OLP-E group ($F_{1,48} = 6.052$, $P = 0.018$), reflecting a medium to large effect ($d = 0.700$). Moreover, the MANOVA indicated that participants from the OLP-E group had higher total scores on both the hope scale ($F_{1,48} = 6.566$, $P = 0.014$) and the expectancies scale ($F_{1,48} = 6.167$, $P = 0.017$) compared with the OLP-H group, both reflecting medium to large differences ($d = 0.701$ and 0.669, respectively). The total scores of the hope scale and the expectancies scale highly correlated with each other ($r = 0.902$, $P < 0.001$). The descriptive values for the manipulation check are presented in Table 2.

Primary Results: Pain Tolerance

Heat Pain Tolerance

Planned contrasts indicated that the increase in heat pain tolerance was significantly larger in the 3 treatment groups compared with the NT group (c1: $t_{96} = 1.677$, $P = 0.048$, $d = 0.413$). Further contrasts indicated that the 3 treatment groups did not significantly differ from each other (c2: $t_{96} = 0.350$, $P = 0.727$, $d = 0.085$, c3: $t_{96} = 0.284$, $P = 0.777$, $d = 0.073$). The group means for heat pain tolerance and the corresponding intensity and unpleasantness ratings are presented in Table 3. Results for change in pain tolerance are shown in Figure 3A.

TABLE 2. Results of the Manipulation Check Regarding the Induction of Hope and Expectancies in the Open-label Placebo Conditions

	Mean (SD)		
Variables	OLP-H (n = 25)	OLP-E (n = 25)	Group Differences
Subjective likelihood of placebo analgesia*	31.08 (21.09)	47.16 (24.69)	$F_{1,48} = 6.132$, $P = 0.017$
Hope scale sum score†	17.36 (6.39)	21.48 (5.31)	$F_{1,48} = 6.150$, $P = 0.017$
Expectancy scale sum score‡	15.00 (5.80)	18.88 (5.80)	$F_{1,48} = 5.601$, $P = 0.022$

*Ranging from 0% to 100%.
†Ranging from 6 to 30.
‡Ranging from 6 to 30.
OLP-E indicates open-label placebo with expectancy induction; OLP-H, open-label placebo with hope induction.

Corresponding intensity and unpleasantness ratings. Change in the corresponding intensity and unpleasantness ratings also differed across the 4 groups. With respect to pain intensity ratings, planned contrasts indicated that the 3 treatment groups (OLP-H, OLP-E, DP) reported significantly larger reduction in pain intensity than the NT group (c1: $t_{96} = -3.429$, $P < 0.001$, $d = 0.854$). Further, the DP group showed significantly larger reduction in pain intensity than the 2 OLP conditions (c2: $t_{96} = 4.625$, $P < 0.001$, $d = 1.004$). The 2 OLP conditions, however, did not significantly differ in their change in pain intensity (c3: $t_{96} = 0.007$, $P = 0.994$, $d = 0.002$). The results for pain intensity are shown in Figure 3B.

With respect to change in unpleasantness ratings, planned contrasts indicated that the 3 treatment groups (OLP-H, OLP-E, DP) reported significantly larger reduction in pain unpleasantness than the NT group (c1: $t_{96} = -1.745$, $P = 0.042$, $d = 0.398$). The DP group showed significantly larger reduction in pain unpleasantness than the 2 OLP conditions (c2: $t_{96} = 3.806$, $P < 0.001$, $d = 0.874$). The 2 OLP conditions did not significantly differ in their change in pain unpleasantness (c3: $t_{96} = -0.965$, $P = 0.337$, $d = 0.378$). The results for pain unpleasantness are shown in Figure 3C.

Secondary Results: Pain Threshold

Heat Pain Threshold

Planned contrasts indicated that change in heat pain threshold did not differ across the 4 groups (c1: $t_{96} = 0.900$, $P = 0.185$, c2: $t_{96} = -0.836$, $P = 0.405$, c3: $t_{96} = 0.585$, $P = 0.560$).

Corresponding Intensity and Unpleasantness Ratings

In contrast to changes in heat pain threshold, changes in the corresponding subjective intensity ratings did differ across the 4 groups. Although the first contrast indicated that the 3 treatment groups (OLP-H, OLP-E, DP) did not report significantly larger reduction in pain intensity than the NT group (c1: $t_{96} = -1.496$, $P = 0.069$, $d = 0.355$), the second contrast indicated that the DP group showed significantly larger reduction in subjective pain intensity than the 2 OLP conditions (c2: $t_{96} = 2.252$, $P = 0.027$, $d = 0.549$). The 2 OLP conditions did not significantly differ in their changes in pain intensity (c3: $t_{96} = 1.804$, $P = 0.074$, $d = 0.502$).

With respect to changes in subjective pain unpleasantness ratings, planned contrasts indicated no significant group differences (c1: $t_{96} = -0.317$, $P = 0.376$, c2: $t_{96} = 1.308$, $P = 0.194$, c3: $t_{96} = 0.137$, $P = 0.891$). The group means for

Copyright © 2019 Wolters Kluwer Health, Inc. All rights reserved.

TABLE 3. Heat Pain Tolerance and the Corresponding Intensity and Unpleasantness Ratings

	Mean (SD)			
Variables	**OLP-H (n = 25)**	**OLP-E (n = 25)**	**DP (n = 25)**	**NT (n = 25)**
Baseline				
Heat pain tolerance (°C)	48.08 (1.47)	48.43 (1.43)	48.37 (0.81)	48.52 (1.33)
Heat pain intensity*	83.92 (12.32)	81.29 (15.31)	78.56 (13.72)	77.42 (14.07)
Heat pain unpleasantness†	82.31 (12.68)	79.52 (16.55)	72.93 (20.67)	70.08 (20.08)
Posttreatment				
Heat pain tolerance (°C)	48.33 (1.38)	48.62 (1.57)	48.53 (0.84)	48.44 (1.26)
Heat pain intensity*	83.95 (11.36)	81.31 (15.37)	71.27 (13.23)	80.12 (13.76)
Heat pain unpleasantness†	80.75 (14.45)	80.51 (15.75)	63.95 (23.66)	70.65 (18.69)
Pain expectancy‡	75 (16.76)	64.56 (18.8)	49.72 (21.57)	70.48 (18.87)

*Rated on a Visual Analogue Scale with the poles 0 = not intense at all and 100 = most intense pain sensation imaginable.
†Rated on a Visual Analogue Scale with the poles 0 = not at all unpleasant and 100 = the most unpleasant imaginable.
‡Rated on a Visual Analogue Scale with the poles 0 = I expect no pain at all and 100 = I expect the most intense pain sensation imaginable.
DP indicates deceptive placebo; NT, no treatment; OLP-E, open-label placebo with expectancy induction; OLP-H, open-label placebo with hope induction.

pain threshold and the corresponding intensity and unpleasantness ratings are presented in Supplementary Table 5 (Supplemental Digital Content 3, http://links.lww.com/CJP/A607).

Pain Expectancy Ratings

The MANOVA indicated that the 4 groups significantly differed in pain expectancy ($F_{3,96} = 8.328$, $P < 0.001$; $\eta_P^2 = 0.207$). Paired-samples post hoc t tests showed that participants from the OLP-H group expected significantly higher levels of pain compared with the OLP-E group ($t_{48} = 2.073$, $P = 0.044$, $d = 0.586$), and the DP group ($t_{48} = 4.627$, $P < 0.001$, $d = 1.308$). The OLP-H group differed from the NT group in its pain expectancy ($t_{48} = 0.896$, $P = 0.375$, $d = 0.253$). The OLP-E group did not differ from the NT group either ($t_{48} = -1.111$, $P = 0.272$, $d = 0.314$), but did expect higher levels of pain than the DP group ($t_{48} = 2.593$, $P = 0.013$, $d = 0.733$). Finally, pain expectancy in the DP group was significantly lower than in the NT group ($t_{48} = -3.622$, $P = 0.001$, $d = 1.024$). Pain expectancy ratings significantly correlated with the measures of hoped ($r = -0.396$, $P = 0.004$) and expected pain relief ($r = -0.354$, $P = 0.012$). The results for pain expectancy ratings are presented in Table 3.

Personality and Psychological Variables

When measures of personality traits (neuroticism and openness to experiences), beliefs about medicine, resilience, and depressive symptoms were included as covariates, the pattern of results for change in heat pain tolerance (and threshold, respectively) and its corresponding intensity and unpleasantness ratings did not significantly change. None of these variables had unique effects on the DVs, and their inclusion did not change the significance of any of the other effects. Effect sizes in the analyses of covariance were similar to those in the ANOVAs for the effects of most interest, that is, the between-participant effects.

In Table 4, we report the correlations of the above-mentioned personality/psychological variables with changes in pain perception. As can be seen in this table, there was a significant correlation between openness to experience and reduction in the subjective pain unpleasantness for pain threshold ($r = -0.248$; $P = 0.013$); that is, the more open a person was, the greater the

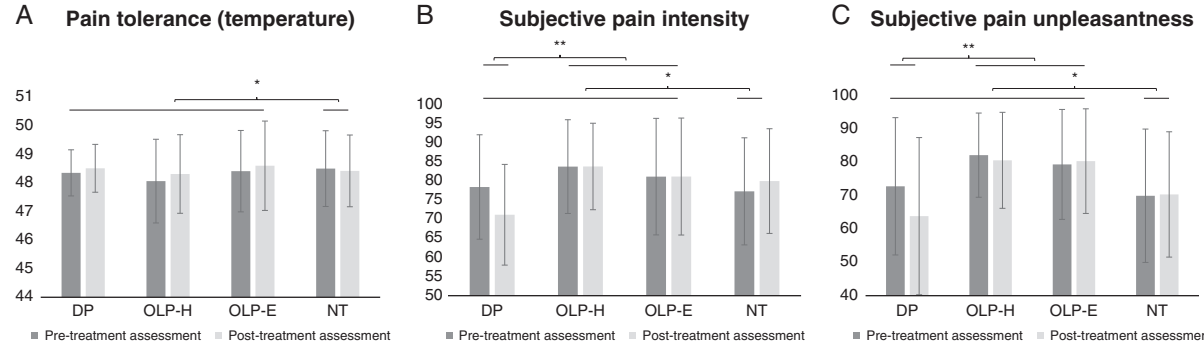

FIGURE 3. Illustration of the results for change in pain tolerance and the corresponding intensity and unpleasantness ratings. A, Planned contrasts indicated that the 3 treatment groups reported a larger increase in pain tolerance compared with the NT group. The 3 treatment groups did not significantly differ in change in pain tolerance. B, Planned contrasts indicated that the 3 treatment groups reported a larger reduction of subjective pain intensity compared with the NT group. Further, changes in subjective pain intensity were larger in the DP group than in the 2 OLP groups. The 2 OLP groups did not differ from each other. C, Planned contrasts indicated that the 3 treatment groups reported a larger reduction of subjective pain unpleasantness compared with the NT group. Further, changes in subjective pain unpleasantness were larger in the DP group than in the 2 OLP groups. The 2 OLP groups did not differ from each other. *$P < 0.05$; **$P < 0.001$; error bars reflect the SD. DP indicates deceptive placebo; NT, no treatment; OLP, open-label placebo; OLP-E, open-label placebo with expectancy induction; OLP-H, open-label placebo with hope induction.

TABLE 4. Correlations of Psychological Constructs With Pre-Post Changes in Pain Perception

	Pain Tolerance			Pain Threshold		
	Changes in Temperature	Changes in Subjective Pain Intensity	Changes in Subjective Pain Unpleasantness	Changes in Temperature	Changes in Subjective Pain Intensity	Changes in Subjective Pain Unpleasantness
Neuroticism	−0.099	0.054	0.119	0.096	0.027	0.116
Openness to experience	0.113	−0.102	−0.011	−0.025	−0.045	−0.248*
Beliefs about medicine	−0.141	0.054	0.053	−0.038	−0.045	0.007
Resilience	0.072	−0.104	−0.089	−0.033	−0.097	−0.065
Depressive symptoms	−0.049	0.145	0.118	0.001	0.103	0.089

*$P < 0.05$.

reported decrease in subjective pain unpleasantness. All other correlations were nonsignificant. Interestingly, the correlation of openness to experience with the reduction in subjective pain intensity ($r = -0.548$; $P = 0.005$) and unpleasantness ($r = -0.363$; $P = 0.075$) for pain threshold was particularly pronounced in participants receiving OLP with the hope instruction.

Correlations of Hope and Expectancy with Changes in Pain Perception

The sum score of the hope scale did not significantly correlate with changes in pain tolerance ($r = 0.047$; $P = 0.747$) and pain threshold ($r = -0.135$; $P = 0.352$). Also, there were no significant correlations of the hope scale and the corresponding subjective intensity (tolerance: $r = -0.146$; $P = 0.311$; threshold: $r = -0.156$; $P = 0.279$) and unpleasantness ratings (tolerance: $r = -0.157$; $P = 0.277$; threshold: $r = -0.265$; $P = 0.063$). Similarly, the expectancy scale correlated neither with changes in pain tolerance ($r = -0.058$; $P = 0.690$) nor pain threshold ($r = -0.166$; $P = 0.250$). There were no significant correlations among the expectancy scale and the corresponding pain intensity (tolerance: $r = 0.016$; $P = 0.910$; threshold: $r = -0.125$; $P = 0.387$) and unpleasantness (tolerance: $r = -0.076$; $P = 0.598$; threshold: $r = -0.250$; $P = 0.080$) ratings either.

DISCUSSION

In recent years, research has shown that placebos can lead to symptom reduction among patients with medical conditions even if they are provided with full transparency and disclosure.[8,9,11,81] However, it has remained subject to debate what particular mechanisms the effects of OLPs are based on and whether the potential of OLPs also applies to healthy individuals. The present study aimed to fill this gap by investigating hopes and expectancies as 2 possible underlying mechanisms of OLPs in a healthy sample. In doing so, the present study was, to our knowledge, the first to operationalize hopes and expectancies as 2 separate constructs. Our results indicate that pain tolerance in the 3 treatment groups (OLP-H, OLP-H, DP) increased to a significantly larger degree than in the NT group. The treatment groups did not differ from each other in their changes in pain tolerance. With respect to the corresponding subjective intensity and unpleasantness ratings, results showed that placebo analgesia occurred only in the DP group, whereas no such reduction in pain intensity or unpleasantness could be observed in the OLP groups. A very similar pattern of results was found for changes in pain threshold.

Thus, the primary hypothesis of the study, assuming that the 3 treatment groups would report a greater amount of pain relief than the NT group, could be confirmed for pain tolerance. With respect to the corresponding intensity and unpleasantness ratings, this hypothesis could be confirmed as well according to the first planned contrast; however, further contrasts revealed that the significant difference between the treatment groups and the NT was driven by the large reduction of pain intensity and unpleasantness in the DP. With respect to OLP, the present findings thus imply that although participants receiving an OLP cream did not report any analgesic effects of the cream, they did show a significant increase in their pain tolerance. This might support the notion of Kaptchuk,[29,82] arguing that the main part of the OLP response might occur on the basis of unconscious learning mechanisms. Future studies could address this by continuing a promising line of experimental research carried out by Jensen[83–85] demonstrating that subliminal healing cues unconsciously evoked placebo effects.

The present findings raise questions about the potential of OLP in healthy volunteers. Similar to the present study, Locher et al,[14] using a healthy sample, too, found no differences between NT and 2 versions of OLP in the post-treatment subjective pain intensity and unpleasantness. Thus, although studies using clinical samples (such as individuals with irritable bowel syndrome,[8] chronic lower back pain,[9] rhinitis,[10] or cancer-related fatigue[11]) found substantial symptom improvement for OLP, both Locher et al[14] and the present study found much weaker effects of OLP in healthy samples. Hence, it is conceivable that OLP carries more potential among clinical samples because individuals with clinically relevant symptom impairment might be open to any new treatment approach, whereas healthy individuals, in the absence of real suffering, might be more skeptical to receive a placebo. This interpretation is supported by a recent meta-analysis suggesting that patients with clinically relevant conditions benefit more from analgesic placebo treatments than healthy individuals.[86] In addition, it is possible that differences between healthy and clinical samples in terms of their learning history or comorbidity (eg, depressive symptoms[87,88]) influence the efficacy of OLPs in chronic pain versus healthy samples. The role of openness in the context of OLP is also supported by the additional finding of the present study suggesting that openness to new experience is associated with greater subjective pain relief, particularly among those participants who underwent the hope induction.

It is noteworthy that to interpret the current findings with respect to differences between DP and OLP, it may also be helpful to consider the results of studies using the

balanced placebo design,[89] in which both the actual treatment (verum vs. placebo) and the information about the treatment (verum vs. placebo) are varied, thereby allowing a comparison between a placebo prescribed as a placebo (=OLP) and a placebo prescribed as drug/verum (=DP). In line with the results of the present study, most studies (albeit not all[44]) using the balanced placebo design found significant differences between OLP and DP.[90–93]

With respect to the secondary goal of the current study, that is, the analysis of the contribution of hopes versus expectancies, further results indicate that the study was only partly successful in differentially manipulating hopes and expectancies. On the one hand, we found that participants from the OLP-H group rated the subjective likelihood of placebo analgesia, as hypothesized, to be significantly lower than participants from the OLP-E group. On the other, participants from the OLP-E group scored higher not only on a measure of expectancies but also on a measure of hope. One possible interpretation for this group difference is that, overall, the OLP-E rationale was more convincing than the OLP-H instruction. Another interpretation of the higher hope scores in the OLP-E group is that although the 2 instructions were successful in inducting different cognitive-affective states in the OLP-H versus OLP-E group (as indicated by the different likelihood ratings), the hope and expectancy scales were not able to capture these differences. In fact, the extremely high inter-correlation of the hope and the expectancy scale suggests that the assessment tools of the present study failed to differentially measure hopes versus expectancies. Notably, although participants in the OLP-E group had stronger expectancies for pain relief compared with the OLP-H group, they did not report greater pain relief, thus questioning the relative contribution of expectancies to placebo analgesia in this study. An alternative explanation, however, could be that the OLP-H group had an unmeasured active ingredient that might have compensated the weaker expectancies in the OLP-H group.

Notwithstanding the methodological problems of assessing hope versus expectancy in the present study, further research into these concepts might provide implications for the treatment of chronic pain in clinical practice. Although it is widely acknowledged that optimizing patients' expectations through psychological interventions can improve treatment of patients with medical conditions (see Kube et al[94] for a review), including chronic pain[95–99] it is less clear for clinicians how to take hope into account. Because not sufficiently considering patients' hopes seems to go along with the risk of negatively affecting patients' well-being,[100–102] further research into the delicate balance between providing realistic information and preventing patients from becoming hopeless is warranted. With respect to the optimization of placebo effects, the current findings on DP underscore the potential of harnessing the effects of an inert treatment when provided with a convincing rationale and a credible medical setting. For OLP, too, available evidence suggests that its effectiveness might be enhanced if it is provided with a plausible rationale.[14] This is in line with the partly significant results of both OLP versions used in the present study, both of which were administered with a rationale.

The present findings also have ethical implications. Previous researchers providing evidence for the efficacy of OLPs drew the conclusion from their findings that the necessity of deception in traditional placebo studies is to be questioned. Even though this conclusion is to be supported from an ethical point of view,[7] it might be somewhat premature, given that OLPs in the present study were less effective in eliciting subjective placebo analgesia than DPs.

Limitations

One limitation refers to the assessment of hopes and expectancies in the OLP groups. Given the novelty of the distinction between hopes and expectancies in experimental pain research, there were no validated measurement tools available, leading to the necessity to use novel self-developed measures. This limits the validity of evaluations on group differences in the OLP-H and OLP-E groups. Furthermore, although the instruction used in the OLP-H group was successful in evoking a lower subjective probability of placebo analgesia compared with the OLP-E condition, we cannot safely state that the instruction was also successful in inducing hope in terms of an affective state. To further investigate this issue, future studies may use validated measurements for positive and negative mood, such as the Positive and Negative Affect Schedule.[103] Moreover, it should be noted that the study investigators delivered the instructions for the experimental conditions. Therefore, experimenter bias cannot be ruled out; however, to address this issue, manualized instructions were provided, and when practicing the provision of the instructions, particular effort was put into appearing equally warm and competent in all groups because these attributes have been shown to affect the placebo response.[67] Furthermore, it is possible that the cream applied in the treatment groups accounts for changes in these groups compared with NT. To rule this alternative explanation out, future studies may consider including an additional group receiving the inert cream without the provision of any rationale.

Concluding Remarks

The present study compared deceptive and non-DPs in terms of their effectivity in reducing experimentally induced heat pain. In doing so, we examined hopes and expectancies as 2 possible mechanisms of OLP analgesia. Although expectancies represent a well-studied construct in pain research, hope has so far mostly been studied in qualitative studies, and our study was the first to operationalize it in placebo research. Results indicate that participants from the 2 OLP groups and the DP group showed a larger increase in pain tolerance than participants from the NT group. However, subjective analgesic effects in both open-label conditions were less pronounced compared with the DP condition. Thus, more research examining the potential and the underlying mechanisms of OLPs in both clinical and healthy samples is needed.

REFERENCES

1. Kirsch I, Moore TJ, Scoboria A, et al. The emperor's new drugs: an analysis of antidepressant medication data submitted to the US Food and Drug Administration. *Prev Treat*. 2002;5:23.
2. Rief W, Nestoriuc Y, Weiss S, et al. Meta-analysis of the placebo response in antidepressant trials. *J Affect Disord*. 2009;1:1–8.
3. Zhang W, Robertson J, Jones A, et al. The placebo effect and its determinants in osteoarthritis: meta-analysis of randomised controlled trials. *Ann Rheum Dis*. 2008;67:1716–1723.
4. Schedlowski M, Enck P, Rief W, et al. Neuro-bio-behavioral mechanisms of placebo and nocebo responses: implications for clinical trials and clinical practice. *Pharmacol Rev*. 2015;67:697–730.
5. Hróbjartsson A, Norup M. The use of placebo interventions in medical practice—a national questionnaire survey of Danish clinicians. *Eval Health Prof*. 2003;26:153–165.
6. Bostick NA, Sade R, Levine MA, et al. Placebo use in clinical practice: report of the American Medical Association Council on Ethical and Judicial Affairs. *J Clin Ethics*. 2008;19:58–61.
7. Blease C, Colloca L, Kaptchuk TJ. Are open-label placebos ethical? Informed consent and ethical equivocations. *Bioethics*. 2016;30:407–414.

8. Kaptchuk TJ, Friedlander E, Kelley JM, et al. Placebos without deception: a randomized controlled trial in irritable bowel syndrome. *PLoS One*. 2010;5:e15591.
9. Carvalho C, Caetano JM, Cunha L, et al. Open-label placebo treatment in chronic low back pain: a randomized controlled trial. *Pain*. 2016;157:2766–2772.
10. Schaefer M, Harke R, Denke C. Open-label placebos improve symptoms in allergic rhinitis: a randomized controlled trial. *Psychother Psychosom*. 2016;85:373–374.
11. Hoenemeyer TW, Kaptchuk TJ, Mehta TS, et al. Open-label placebo treatment for cancer-related fatigue: a randomized-controlled clinical trial. *Sci Rep*. 2018;8:2784.
12. Sandler AD, Bodfish JW. Open-label use of placebos in the treatment of ADHD: a pilot study. *Child Care Health Dev*. 2008;34:104–110.
13. Sandler AD, Glesne CE, Bodfish JW. Conditioned placebo dose reduction: a new treatment in attention-deficit hyperactivity disorder? *J Dev Behav Pediatr*. 2010;31:369–375.
14. Locher C, Nascimento AF, Kirsch I, et al. Is the rationale more important than deception? A randomized controlled trial of open-label placebo analgesia. *Pain*. 2017;158:2320–2328.
15. Atlas LY, Wager TD. How expectations shape pain. *Neurosci Lett*. 2012;520:140–148.
16. Peerdeman KJ, van Laarhoven AIM, Keij SM, et al. Relieving patients' pain with expectation interventions: a meta-analysis. *Pain*. 2016;157:1179–1191.
17. Vase L, Robinson ME, Verne GN, et al. The contributions of suggestion, desire, and expectation to placebo effects in irritable bowel syndrome patients: an empirical investigation. *Pain*. 2003;105:17–25.
18. Vase L, Robinson ME, Verne GN, et al. Increased placebo analgesia over time in irritable bowel syndrome (IBS) patients is associated with desire and expectation but not endogenous opioid mechanisms. *Pain*. 2005;115:338–347.
19. Price DD, Milling LS, Kirsch I, et al. An analysis of factors that contribute to the magnitude of placebo analgesia in an experimental paradigm. *Pain*. 1999;83:147–156.
20. Webb D. Modes of hoping. *Hist Hum Sci*. 2007;20:65–83.
21. Leung KK, Silvius JL, Pimlott N, et al. Why health expectations and hopes are different: the development of a conceptual model. *Health Expect*. 2009;12:347–360.
22. Roth M, Hammelstein P. Hope as an emotion of expectancy: first assessment results. *Psychosoc Med*. 2007;4:Doc05.
23. Bruininks, Malle BF. Distinguishing hope from optimism and related affective states. *Motiv Emot*. 2005;29:324–352.
24. Little M, Sayers E-J. While there's life… hope and the experience of cancer. *Soc Sci Med*. 2004;59:1329–1337.
25. Thorne S, Hislop TG, Kuo M, et al. Hope and probability: patient perspectives of the meaning of numerical information in cancer communication. *Qual Health Res*. 2006;16:318–336.
26. Kaptchuk TJ, Shaw J, Kerr CE, et al. "Maybe I made up the whole thing": placebos and patients' experiences in a randomized controlled trial. *Cult Med Psychiatry*. 2009;33:382–411.
27. Eaves ER, Ritenbaugh C, Nichter M, et al. Modes of hoping: understanding hope and expectation in the context of a clinical trial of complementary and alternative medicine for chronic pain. *Explore (NY)*. 2014;10:225–232.
28. Di Blasi Z, Crawford F, Bradley C, et al. Reactions to treatment debriefing among the participants of a placebo controlled trial. *BMC Health Serv Res*. 2005;5:1–8.
29. Kaptchuk TJ. Open-label placebo: reflections on a research agenda. *Perspect Biol Med*. 2018;61:311–334.
30. Olson JM, Roese NJ, Zanna MP. *Expectancies, in Social Psychology: A Handbook of Basic Principles*. New York, NY: Guilford Press; 1996:211–238.
31. Kube T, D'Astolfo L, Glombiewski JA, et al. Focusing on situation-specific expectations in major depression as basis for behavioural experiments—Development of the Depressive Expectations Scale. *Psychol Psychother*. 2017;90:336–352.
32. Laferton JAC, Kube T, Salzmann S, et al. Patients' expectations regarding medical treatment: a critical review of concepts and their assessment. *Front Psychol*. 2017;8:233.
33. Kirsch I. Response expectancy as a determinant of experience and behavior. *Am Psychol*. 1985;40:1189–1202.
34. Wilson TD, Gilbert DT. Affective forecasting. *Adv Exp Soc Psychol*. 2003;35:345–411.
35. Catanzaro SJ. Negative mood regulation expectancies, emotional distress, and examination performance. *Pers Soc Psychol Bull*. 1996;22:1023–1029.
36. Horwitz AG, Berona J, Czyz EK, et al. Positive and negative expectations of hopelessness as longitudinal predictors of depression, suicidal ideation, and suicidal behavior in high-risk adolescents. *Suicide Life Threat Behav*. 2017;47:168–176.
37. Kube T, Siebers VHA, Herzog P, et al. Integrating situation-specific dysfunctional expectations and dispositional optimism into the cognitive model of depression—A path-analytic approach. *J Affect Disord*. 2018;229:199–205.
38. Backenstrass M, Schwarz T, Fiedler P, et al. Negative mood regulation expectancies, self-efficacy beliefs, and locus of control orientation: moderators or mediators of change in the treatment of depression? *Psychother Res*. 2006;16:250–258.
39. Beck AT, Rush A, Shaw B, et al. *Cognitive Therapy of Depression*. New York, NY: Guilford Press; 1979.
40. Rief W, Bingel U, Schedlowski M, et al. Mechanisms involved in placebo and nocebo responses and implications for drug trials. *Clin Pharmacol Ther*. 2011;90:722–726.
41. Enck P, Bingel U, Schedlowski M, et al. The placebo response in medicine: minimize, maximize or personalize? *Nat Rev Drug Discov*. 2013;12:191–204.
42. Rutherford BR, Wall MM, Brown PJ, et al. Patient expectancy as a mediator of placebo effects in antidepressant clinical trials. *Am J Psychiatry*. 2017;174:135–142.
43. Schwarz KA, Pfister R, Buchel C. Rethinking explicit expectations: connecting placebos, social cognition, and contextual perception. *Trends Cogn Sci*. 2016;20:469–480.
44. Schenk LA, Sprenger C, Geuter S, et al. Expectation requires treatment to boost pain relief: an fMRI study. *Pain*. 2014;155:150–157.
45. Bingel U, Wanigasekera V, Wiech K, et al. The effect of treatment expectation on drug efficacy: imaging the analgesic benefit of the opioid remifentanil. *Sci Transl Med*. 2011;3:70ra14.
46. Kube T, Rief W. Are placebo and drug-specific effects additive? Questioning basic assumptions of double-blinded randomized clinical trials and presenting novel study designs. *Drug Discov Today*. 2017;22:729–735.
47. Benson S, Hagen S, Hoffmann O, et al. Can a brief psychological expectancy intervention improve postoperative pain? A randomized, controlled trial in breast cancer patients. *Pain*. 2019;160:1562–1571.
48. Rief W, Shedden-Mora MC, Laferton JAC, et al. Preoperative optimization of patient expectations improves long-term outcome in heart surgery patients: results of the randomized controlled PSY-HEART trial. *BMC Med*. 2017;15:4.
49. Price M, Anderson P, Henrich CC, et al. Greater expectations: using hierarchical linear modeling to examine expectancy for treatment outcome as a predictor of treatment response. *Behav Ther*. 2008;39:398–405.
50. Greenberg R, Constantino M, Bruce N. Are patient expectations still relevant for psychotherapy process and outcome? *Clin Psychol Rev*. 2006;26:657–678.
51. Bloch E. *Das Prinzip Hoffnung* [The Principle of Hope]. Frankfurt, Germany: Suhrkamp; 1959.
52. Snyder CR. Hope theory: rainbows in the mind. *Psychol Inq*. 2002;13:249–275.
53. Carrigan RL. Where has hope gone? Toward an understanding of hope in pastoral care. *Pastoral Psychol*. 1976;25:39–53.
54. Good MJD, Good BJ, Schaffer C, et al. American oncology and the discourse on hope. *Cult Med Psychiatry*. 1990;14:59–79.
55. Thorne S, Oglov V, Armstrong E-A, et al. Prognosticating futures and the human experience of hope. *Palliat Support Care*. 2007;5:227–239.
56. Lopez SJ, Snyder CR, Pedrotti T. Hope: many definitions, many measures. In: Lopez SJ, Snyder CR, eds. *Positive*

Psychological Assessment. Washington, DC: American Psychological Association; 2003:91–107.
57. Kube T, Blease C, Ballou SK, et al. Hope in Medicine—applying multidisciplinary insights. *Perspect Biol Med*. 2019; 62:591–616.
58. Montgomery GH, David D, DiLorenzo T, et al. Is hoping the same as expecting? Discrimination between hopes and response expectancies for nonvolitional outcomes. *Pers Individ Dif*. 2003;35:399–409.
59. Simpson C. When hope makes us vulnerable: a discussion of patient–healthcare provider interactions in the context of hope. *Bioethics*. 2004;18:428–447.
60. Corbett M, Foster NE, Ong BN. Living with low back pain—Stories of hope and despair. *Soc Sci Med*. 2007;65:1584–1594.
61. Eaves ER, Sherman KJ, Ritenbaugh C, et al. A qualitative study of changes in expectations over time among patients with chronic low back pain seeking four CAM therapies. *BMC Complement Altern Med*. 2015;15:1–10.
62. Eaves ER, Nichter M, Ritenbaugh C. Ways of hoping: navigating the paradox of hope and despair in chronic pain. *Cult Med Psychiatry*. 2016;40:35–58.
63. Hammelstein, Roth M. Hoffnung–Grundzüge und Perspektiven eines vernachlässigten Konzeptes [Hope–Basics and Perspectives of a Neglected Concept]. *Zeitschrift für Differentielle und Diagnostische Psychologie*. 2002;23:191–203.
64. Mattingly C. *The Paradox of Hope: Journeys Through a Clinical Borderland*. Berkeley, CA: University of California Press; 2010.
65. Petersen GL, Finnerup NB, Grosen K, et al. Expectations and positive emotional feelings accompany reductions in ongoing and evoked neuropathic pain following placebo interventions. *Pain*. 2014;155:2687–2698.
66. Ballou S, Kaptchuk TJ, Hirsch W, et al. Open-label versus double-blind placebo treatment in irritable bowel syndrome: study protocol for a randomized controlled trial. *Trials*. 2017;1:1–15.
67. Howe LC, Goyer JP, Crum AJ. Harnessing the placebo effect: exploring the influence of physician characteristics on placebo response. *Health Psychol*. 2017;36:1074–1082.
68. Emerson NM, Zeidan F, Lobanov OV, et al. Pain sensitivity is inversely related to regional grey matter density in the brain. *Pain*. 2014;155:566–573.
69. Petersen GL, Finnerup NB, Norskov KN, et al. Placebo manipulations reduce hyperalgesia in neuropathic pain. *Pain*. 2012;153:1292–1300.
70. Price DD. Neuroscience—Psychological and neural mechanisms of the affective dimension of pain. *Science*. 2000;288:1769–1772.
71. Davis C, Ralevski E, Kennedy SH, et al. The role of personality-factors in the reporting of side-effect complaints to moclobemide and placebo—a study of healthy male and female volunteers. *J Clin Psychopharmacol*. 1995;15:347–352.
72. Hyland ME, Whalley B, Geraghty AWA. Dispositional predictors of placebo responding: a motivational interpretation of flower essence and gratitude therapy. *J Psychosom Res*. 2007;62:331–340.
73. Horne R, Weinman J, Hankins M. The beliefs about medicines questionnaire: the development and evaluation of a new method for assessing the cognitive representation of medication. *Psychol Health*. 1999;14:1–24.
74. Tabachnick BG, Fidell LS. *Using Multivariate Statistics*, 6th ed. Harlow, UK: Pearson; 2014.
75. Kline RB. *Principles and Practice of Structural Equation Modeling*, 2nd ed. New York, NY: Guilford Press; 2005.
76. Cohen J, Cohen P, West SG, et al. *Applied Multiple Regression/Correlation Analysis for the Behavioral Sciences*, 3rd ed. Mahawah, NJ: Erlbaum; 2003.
77. Stevens J. *Applied Multivariate Statistics for the Social Sciences*, 2nd ed. Hillsdale, NJ: Erlbaum; 2002.
78. Ruxton GD, Beauchamp G. Time for some a priori thinking about post hoc testing. *Behav Ecol*. 2008;19:690–693.
79. Field A. *Discovering Statistics Using SPSS*. London, UK: Sage Publications; 2009.
80. Kroenke K, Spitzer RL. The PHQ-9: a new depression diagnostic and severity measure. *Psychiatr Ann*. 2002;32:509–515.
81. Kam-Hansen S, Jakubowski M, Kelley JM, et al. Altered placebo and drug labeling changes the outcome of episodic migraine attacks. *Sci Transl Med*. 2014;6:218ra5.
82. Ongaro G, Kaptchuk TJ. Symptom perception, placebo effects, and the Bayesian brain. *Pain*. 2019;160:1–4.
83. Jensen KB, Kaptchuk TJ, Kirsch I, et al. Nonconscious activation of placebo and nocebo pain responses. *Proc Natl Acad Sci USA*. 2012;109:15959–15964.
84. Jensen KB, Kaptchuk TJ, Chen X, et al. A neural mechanism for nonconscious activation of conditioned placebo and nocebo responses. *Cereb Cortex*. 2014;25:3903–3910.
85. Jensen K, Kirsch I, Odmalm S, et al. Classical conditioning of analgesic and hyperalgesic pain responses without conscious awareness. *Proc Natl Acad Sci USA*. 2015;112:7863–7867.
86. Forsberg JT, Martinussen M, Flaten MA. The placebo analgesic effect in healthy individuals and patients: a meta-analysis. *Psychosom Med*. 2017;79:388–394.
87. Banks SM, Kerns RD. Explaining high rates of depression in chronic pain: a diathesis–stress framework. *Psychol Bull*. 1996; 119:95–110.
88. Fishbain DA, Cutler R, Rosomoff HL, et al. Chronic pain-associated depression: antecedent or consequence of chronic pain? A review. *Clin J Pain*. 1997;13:116–137.
89. Rohsenow DJ, Marlatt GA. The balanced placebo design: methodological considerations. *Addict Behav*. 1981;6:107–122.
90. Atlas LY, Whittington RA, Lindquist MA, et al. Dissociable influences of opiates and expectations on pain. *J Neurosci*. 2012;32:8053–8064.
91. Kong J, Kaptchuk TJ, Polich G, et al. An fMRI study on the interaction and dissociation between expectation of pain relief and acupuncture treatment. *Neuroimage*. 2009;47:1066–1076.
92. Lund K, Vase L, Petersen GL, et al. Randomised controlled trials may underestimate drug effects: balanced placebo trial design. *PLoS One*. 2014;9:e84104.
93. Hammami MM, Al-Gaai EA, Alvi S, et al. Interaction between drug and placebo effects: a cross-over balanced placebo design trial. *Trials*. 2010;11:1–10.
94. Kube T, Glombiewski JA, Rief W. Using different expectation mechanisms to optimize treatment of patients with medical conditions—A systematic review. *Psychsom Med*. 2018;80:535–543.
95. Glombiewski JA, Holzapfel S, Riecke J, et al. Exposure and CBT for chronic back pain: an RCT on differential efficacy and optimal length of treatment. *J Consult Clin Psychol*. 2018;86:533.
96. Leeuw M, Goossens ME, van Breukelen GJ, et al. Exposure in vivo versus operant graded activity in chronic low back pain patients: results of a randomized controlled trial. *Pain*. 2008;138:192–207.
97. Linton SJ, Boersma K, Jansson M, et al. A randomized controlled trial of exposure in vivo for patients with spinal pain reporting fear of work-related activities. *Eur J Pain*. 2008;12:722–730.
98. Vlaeyen JW, De Jong J, Leeuw M, et al. Fear reduction in chronic pain: graded exposure in vivo with behavioral experiments. In: Amundsen GJG, Vlaeyen JW, Crombez G, eds. *Understanding and Treating Fear of Pain*. Oxford, UK: Oxford University Press; 2004:313–343.
99. Woods MP, Asmundson GJG. Evaluating the efficacy of graded in vivo exposure for the treatment of fear in patients with chronic back pain: a randomized controlled clinical trial. *Pain*. 2008;136:271–280.
100. Oliffe J, Thorne S, Hislop TG, et al. "Truth telling" and cultural assumptions in an era of informed consent. *Fam Community Health*. 2007;30:5–15.
101. Pergert, Lützén K. Balancing truth-telling in the preservation of hope: a relational ethics approach. *Nurs Ethics*. 2012;19:21–29.
102. Eliott J, Olver I. The discursive properties of "hope": a qualitative analysis of cancer patients' speech. *Qual Health Res*. 2002;12:173–193.
103. Tellegen A. Development and validation of brief measures of positive and negative affect: The PANAS Scales. *J Pers Soc Psychol*. 1988;54:1063–1070.