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A test of psychological and electrodermal changes immediately after the delivery of 3 analgesic treatment messages

Andrew L. Geers[a,*], Stephanie L. Fowler[b], Suzanne G. Helfer[c], Ashley B. Murray[a]

Abstract

Introduction: Placebo analgesia often results when a pain reduction treatment message is delivered to a patient or research participant. Little information exists regarding the psychological changes that are immediately triggered by the delivery of a treatment message.

Objectives: This experiment tested the impact of 3 different analgesic treatment messages on the expectations, feelings, and electrodermal activity of participants anticipating a pain stimulus.

Methods: In laboratory sessions, healthy participants (N = 138) were randomly assigned to 1 of 4 conditions in a between-subject design. The design included a no treatment message control condition and 3 treatment message conditions: a standard analgesic message, an analgesic treatment with side-effect message, and a double-blind analgesic message. After the treatment message manipulation, measures were taken of: treatment efficacy expectations, pain experience expectations, pretask anxiety, positive affect, negative affect, and electrodermal activity.

Results: Overall, the dependent measures showed relatively few correlations. Furthermore, across all 3 message conditions, treatment-specific expectations were greatly increased compared with the control condition. Finally, participants in the double-blind message condition displayed elevated negative affect.

Conclusion: All 3 analgesic treatment messages produced a stronger immediate influence on treatment efficacy expectations than on the other dependent measures. Treatment messages can alter negative affect along with expectancies. The low correlations found between dependent measures suggest that different patterns of psychological responses may emerge from analgesic treatment messages depending on contextual factors.

Keywords: Placebo, Pain, Expectation, Anticipation, Affect, Treatment message

1. Introduction

In clinical and experimental contexts, placebo analgesia can result when an analgesic treatment message is provided by a practitioner or researcher.[2,9,10] The study of how treatment messages cause placebo analgesia has been growing, with remarkable progress particularly concerning the neurobiological mechanisms. This work is leading to an understanding of the endogenous opioid, cannabinoid, and cholecystokinin systems as well as the specific brain and spinal pathways involved in placebo analgesia.[1,3,9,27] In terms of psychological factors, data from a wide variety of samples and methodologies identify expectations as a key link between analgesic treatment messages and placebo analgesia.[35,46,52] Based on these findings, researchers are now developing expectation interventions so as to incorporate these findings into clinical care.[51]

Although our understanding of placebo analgesia is growing, there is still great opportunity for clarifying the various psychological processes influencing placebo analgesia.[12,23,53] The goal of the present research was to provide a more detailed account of the psychological processes that take place when one is given an analgesic treatment message, but before the delivery of a pain stimulus. This intervening period between a treatment message and a pain stimulus can be referred to as the anticipation phase of placebo analgesia.[50] The present research thus asked the question, when individuals are told they will receive an analgesic treatment, what are the psychological processes that are immediately put in motion by that message? Answering this question will identify the psychological elements in operation when

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[a] Department of Psychology, University of Toledo, Toledo, OH, USA, [b] National Cancer Institute, National Institutes of Health, Bethesda, Maryland, [c] Department of Psychology, Adrian College, Adrian, Michigan

**Corresponding author. Address: Department of Psychology, University of Toledo, Toledo, OH 43606. Tel.: 419-530-8530; fax: 419-530-8479. E-mail address: Andrew.geers@utoledo.edu (A.L. Geers).*

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a placebo analgesic response is taking shape. Neurobiological work finds expectations in this anticipatory phase to predict the brain activities during subsequent pain events, so this anticipatory period is likely to be important to placebo analgesia.[50,60]

Expectations are generally theorized as the key psychological process initiated by treatment messages that elicit placebo analgesia. Research finds treatment messages change expectations during the anticipation phase of placebo analgesia. For example, in one recent study, patients with chronic back pain were told that a sham opioid solution would reduce their pain.[40] These patients displayed lower pain expectations during the anticipation phase of placebo analgesia and subsequently lower acute pain, as compared to a no-message control group. Although there is evidence of expectation changes in the anticipation phase of placebo analgesia, there has been relatively little research comparing different expectations at this time. The present experiment compared 2 types of expectations that may be accessible during this juncture: treatment response expectations and pain experience expectations. First, we assessed whether a message about an analgesic cream alters expectations for a beneficial treatment response, here called "treatment efficacy expectations." Treatment efficacy expectations refer to one's beliefs that a treatment will be successful. These expectations may inform perceptions of treatment events and relate to both short- and long-term outcomes of pain interventions.[13,29] Second, we also measured expectations about the future pain experience, here called "pain experience expectations." These expectations include thoughts directed toward the pain stimulus and the impending pain experience. Treatment efficacy and pain experience expectancies can be viewed as 2 possible variations of what Kirsch has termed response expectancies, defined as the anticipation of nonvolitional responses.[36–38] The key difference between these two is that treatment efficacy expectations relate to the ability of the treatment to reduce pain, whereas pain experience expectations relate to the anticipated level of pain. Thus, the 2 expectancy measures used differ in their focus. For one, attention is on the treatment response in the event. For the other, attention is on the pain experience itself. These may be the same expectation, or it may be that the 2 are unique and differ in the context of placebo analgesia. To the best of our knowledge, the present research is the first to compare how these 2 expectancies are influenced by analgesic treatment messages.

In addition to examining cognitive expectancies in the anticipation phase of placebo analgesia, we also assess affective states. First, existing research suggests that anxiety reduction can be important in placebo analgesia,[11,43,55] and anticipatory anxiety has been linked to placebo analgesia.[50] For example, in a sample of patients with irritable bowel syndrome, Vase et al.[59] found that anxiety early in a painful rectal stimulation task was a predictor of placebo effects later in the task. Building from this prior research, we measured whether analgesic treatment messages alter anxiety before an upcoming pain task. In addition to changes in pretask anxiety, there is also evidence suggesting that treatment messages may alter diffuse feeling states immediately after the receipt of a treatment message.[6,18,21] For example, Schmitz et al.[56] found that reading information on treatment leaflets alters momentary negative feeling states. In this study, we separately assessed both positive and negative affect during the anticipation phase of placebo analgesia. Although anxiety and diffuse positive and negative affect may operate similarly, it is also possible that each operates independently in placebo analgesia contexts.[7,25] For example, one possibility is that an analgesic treatment message raises positive affect but does not alter negative affect. To the best of our knowledge, no study has simultaneously assessed pretask anxiety, positive affect, and negative affect immediately after the delivery of a treatment message.

We also assessed electrodermal activity (EDA) during the treatment anticipation period. Electrodermal activity is an indicator of physiological arousal, and physiological arousal often increases during the anticipation of unpleasant or uncertain tasks.[14,16] Furthermore, EDA scores have been changed by treatment instruction manipulations in several studies,[30,57] although in other studies they have not.[17] Based on this earlier research, we included EDA to provide a novel assessment of whether analgesic treatment messages alter physiological arousal during the anticipation phase of placebo analgesia.

Finally, we compared 3 different analgesia treatment messages.[15] The experiment included a no treatment message control condition and 3 treatment message conditions: a standard analgesic message, an analgesic treatment with a side-effect message, and a double-blind analgesic message (no side effects). Our primary hypothesis was that the analgesic treatment messages would increase treatment efficacy expectations and reduce pretask anxiety, pain experience expectations, negative affect, and EDA. As no study has yet compared these 3 treatment messages during the anticipatory phase of placebo analgesia, we did not have set a priori hypotheses regarding difference among the treatment message conditions.

2. Methods

2.1. Participants

To determine sample size, a power analysis was conducted based on 2 prior placebo analgesia studies that measured treatment efficacy expectations in the cold-pressor paradigm.[22,26] The difference on the expectation scale between the no treatment message and analgesic treatment message groups yielded the mean effect size difference of $d = 1.08$ (range = 0.91–1.24). With this effect size estimate and power set to 0.90 ($\alpha = 0.05$), a sample size of 64 participants (16 per condition) would be required. As previous studies had not assessed the full range of dependent measures administered here, we doubled our target enrollment to 32 participants per condition.

One-hundred thirty-eight (76 females and 62 males) healthy students signed up for the study through an online research participation system and completed the experiment in return for partial course credit. Participants ranged in age from 18 to 55 years ($M = 20$, $SD = 4.6$). Seventy-nine self-reported as White, 36 as Black, 7 as Asian, 2 as Middle Eastern, 2 as Native American, 5 as Hispanic, and 5 categorized themselves as another unspecified race/ethnicity. **Table 1** presents age, gender, and ethnicity (percent Caucasian) by experimental condition. Analyses of these characteristics (χ^2 for gender and race and analysis of variance [ANOVA] for age) showed that the characteristics did not significantly differ based on experimental condition, p's > 0.1. On a health history form presented at the beginning of the study session, 4 participants indicated taking anxiolytics/antidepressants and 2 additional participants reported having a diagnosis of chronic depression and another a diagnosis of an anxiety disorder. These participants completed the study and are included in data analyses. Removal of these data does not alter any of the reported results. The only exclusion criterion was prior knowledge of the study. In debriefing, 2 participants reported knowing beforehand that the experiment concerned placebo effects and their data are not included in analyses.

Table 1

Participant characteristics by experimental condition.

	No analgesic message	Analgesic message	Analgesic message with side effects	Double-blind analgesic message
Percent female	52.9	54.3	55.9	48.6
Percent Caucasian	67.4	48.6	73.5	57.1
Mean age	21.24	19.29	19.71	19.29

No significant differences were found in gender, ethnicity, or age by condition (P's > 0.1).

Methods and procedures were approved by the University of Toledo Institutional Review Board and were conducted in compliance with the guidelines of the American Psychological Association and with the policies and principles contained in the Declaration of Helsinki.

2.2. Design and procedure

In this study, all participants were told they would be taking part in a pain task; however, none of the participants actually completed a pain task. Instead, as our focus was on recording the psychological processes triggered by the delivery of a treatment efficacy message, participants completed a battery of psychological measures after the treatment message manipulation. Otherwise, the study procedures conformed closely to those used in previous placebo analgesia studies with the cold-pressor test.[22,24,55]

The experiment used a between-subject design with participants randomized using the block randomization method, stratifying for participant gender. Participants were assigned to 1 of 4 message conditions: (1) no analgesic message [control group], (2) analgesic message, (3) analgesic with side-effect message, and (4) double-blind analgesic message. In the first message condition, participants received a standard analgesic treatment message in which a (placebo) treatment was described as an analgesic agent. In the second message condition, participants were given the same analgesic message but were further informed that the treatment had 3 side effects. In the third message condition, participants were given a double-blind expectation. That is, they were told they may be receiving an analgesic treatment or they may be receiving a placebo (**Fig. 1**).

The experiment was conducted in the Placebo Effect Laboratory at the University of Toledo, Ohio, USA. The individual sessions took place in a room designed to appear as a medical research laboratory that contained physiological recording equipment. At the beginning of each session, participants completed an informed consent document, a health history form, a mood measure, and a demographic questionnaire. Next, participants relaxed and completed a 5-minute EDA baseline period with the experimenter outside of the room.

After the baseline period, the experimenter returned with a 2.5-gallon container that held water and ice and had a thermometer anchored to the inside. Before entering the room, the experimenter sprayed the outside of the container with water to enhance the perception that the water in the container was exceptionally cold. The experimenter set the container down in the room and informed participants that they would be taking part in the cold-pressor test. Participants were told they will immerse their dominant hand in the container filled with water and crushed ice set at a temperature of 2°C. The experimenter stated that they would be placing their hand in the water up to the wrist, leaving their hand in the water for 2 minutes. The experimenter noted that most participants find this task to be very painful.

At this point in the session, the instructions diverged based on experimental condition. Participants in the *analgesic message condition* were told that the researcher was interested in a new topical, local anesthetic that was being tested for its pain-reducing effects. Participants were told the drug's name was Trivaricane and that this drug had been proven effective in reducing pain in studies at other universities. Participants were

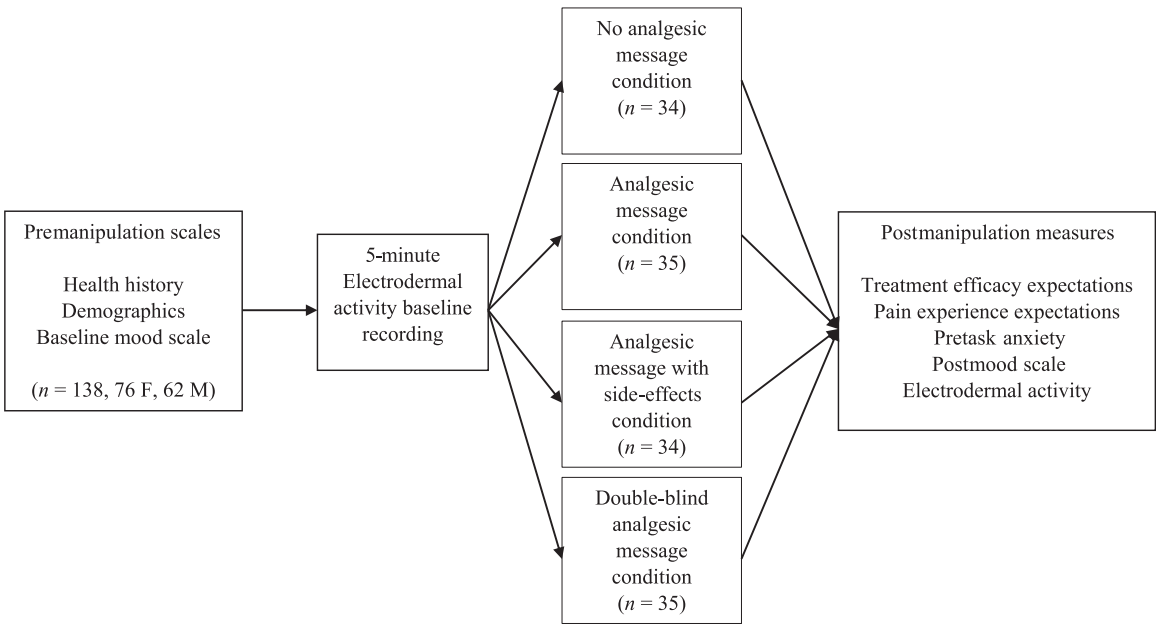

Figure 1. Experiment timeline: Two additional participants with a priori knowledge that the experiment concerned pain expectations are excluded.

further told that this topical drug was safe and temporarily deadens the pain receptors in the skin, eliminating a great deal of the pain normally felt during the cold-pressor task. The experimenter (wearing medical examination gloves) then opened up a bottle labeled "Trivaricane: Approved for research purposes only" and applied the placebo cream to the entire hand (from the wrist down) of their dominant arm. The placebo cream was a mixture of iodine, oil of thyme, food coloring, and lotion that created a light brown, medicinal-smelling cream.[48] The procedure for participants in the *analgesic with side-effect message condition* was identical except they were told that the Trivaricane cream had 3 side effects. Specifically, they were told that prior participants reported the drug causes itching, throbbing, and tingling sensations in the hand receiving the application. The procedure for the participants in the *double-blind analgesic message condition* also had one change from the analgesic message condition. For these participants, the experimenter explained that participants in studies on the effects of drugs, such as this one, are randomly assigned to either an active drug condition or a placebo condition. The experimenter stated, as a result, there was a 50% chance they would receive the Trivaricane product and a 50% chance they would receive a placebo that does not reduce pain. Participants in the double-blind analgesic message condition were not told about possible side effects. Finally, participants in the *no analgesic message condition* were given no treatment message. Instead of the analgesic message, they were told that the cream was a hand-cleaning product used in cold-pressor studies. The bottle containing the cream applied to the hand of the no analgesic message condition was labeled "Soft Clean hand cleanser."

After the message manipulation, the procedures were identical for all participants. The experimenter presented participants with a packet of questionnaires and said that they would complete the survey and then place their hand in the ice water immediately on completion. The experimenter left the room while participants responded to the questions. When participants finished the measures, the experimenter returned to the room and informed the participant they would not be taking part in the cold-pressor test. The purpose of the study was explained, and participants were debriefed, thanked, and dismissed. During debriefing, participants were asked whether they had ever submerged an arm or leg in ice water for a long period of time (ie, for more than 1 minute) before the study session. Answers to this query were recorded. Also, in debriefing 4 participants (0.04%) expressed doubt in the analgesic properties of the hand cream. As this occurred after the study's conclusion, it may be that these doubts were prompted because they did not complete the anticipated pain task. These participants are retained in data analyses, and their removal does not alter any of the reported findings.

2.3. Dependent measures

2.3.1. Treatment efficacy expectation scale

Four items, specifically designed for this study, were used to assess expectations about the analgesic ability of the hand cream. Each item was rated on a 1 to 7 scale, with higher scores equating to higher analgesic expectations. These items were: "To what degree do you expect the hand cream to protect your hand from the ice water?" (1 = *not at all* to 7 = *very much*), "How effective do you think the hand cream will be at helping you feel less pain while your hand is in the ice water?" (1 = *not at all* to 7 = *very much*), "What is the likelihood that the hand cream will protect you from pain?" (1 = 0% to 7 = 100%), and "How confident are you that the hand cream will help reduce the pain you feel while your hand is in the ice water?" (1 = *not at all confident* to 7 = *extremely confident*). The 4 items were averaged to form an overall treatment efficacy expectation scale ($\alpha = 0.94$).

2.3.2. Pain experience expectation scale

Four items designed for this study were used to assess pain expectations for the upcoming cold-pressor task. Responses to 2 of the items were made on a 7-point scale, with higher numbers reflecting greater pain. These items were, "How much pain will you experience during the ice water task?" (1 = *no pain* to 7 = *extreme pain*), and "How stressful do you think the pain will be while your hand is in the ice water?" (1 = *not at all stressful* to 7 = *extremely stressful*). The third item read, "How easy will it be to keep your hand in the ice water for the full 2 minutes?" (1 = *not at all easy* to 7 = *extremely easy*). As higher scores on this item reflected greater ease of the pain task, responses were reversed scored. The final item read, "When you put your hand in the ice water, how severe will the pain be?" Participants responded to using a 100-mm visual analogue scale anchored with *not at all severe* on the left side and *very severe* on the right side. As this final item used a different response scale, scores on all 4 items were standardized and averaged to create a pain experience expectation scale ($\alpha = 0.82$).

2.3.3. Pretask anxiety scale

Four items designed for this study were used to gauge participants' anxiety specific to the impending pain task. Responses to all items were made on a 7-point scale, with higher numbers reflecting greater task-specific anxiety. The items were, "How anxious do you feel now, before your hand being in the water?" (1 = *not at all anxious* to 7 = *extremely anxious*), "How much stress do you feel now, before placing your hand in the ice water? (1 = *not at all stressful* to 7 = *extremely stressful*), "How concerned are you now about submerging your hand in ice water?" (1 = *not at all concerned* to 7 = *extremely concerned*), and "How uneasy do you feel about having to submerge your hand in ice water?" (1 = *not at all uneasy* to 7 = *extremely uneasy*). The 4 items were averaged to form a pretask anxiety scale ($\alpha = 0.80$).

2.3.4. Positive and negative affect scales

Before and after the treatment message manipulation, participants completed the Brief Mood Introspection Scale.[44] The Brief Mood Introspection Scale is a widely used measure of transient affect that is highly correlated with other mood scales and variables associated with mood, such as the frequency of chronic illness and the natural recall of positive and negative memories.[5,45,47,49] For this measure, participants assessed their current feelings with 8 positive feeling descriptors (eg, happy and content) and 8 negative feeling descriptors (eg, sad and fed up). Each descriptor is rated on a scale ranging from 1 (*definitely do not feel*) to 4 (*definitely feel*). The 8 positive affect items completed before the experimental manipulation were averaged to create a baseline positive affect scale ($\alpha = 0.79$), and the 8 negative affect items from the beginning of the experiment were averaged to create a baseline negative affect scale ($\alpha = 0.73$). Similarly, the 8 positive affect items and the 8 negative affect items completed after the treatment message manipulation were

averaged separately to create a post positive affect scale (α = 0.80) and a post negative affect scale (α = 0.73).

2.3.5. Electrodermal activity

Using the Biopac mp150 System (Biopac, Santa Barbara, CA), finger electrodes were positioned on the middle and ring fingers of the participant's nondominant hand. These electrodes were used to measure tonic skin conductance level (SCL) with a GSR100C amplifier with silver/silver chloride electrodes filled with SignaGel electrode gel. The sampling rate was set at 200 Hz. Participants relaxed and completed a 5-minute EDA baseline period with the experimenter outside of the room. The task period was 3 minutes. Analyses were conducted on the average SCL of the 5-minute baseline period and the average SCL during the 3-minute task period.

2.4. Statistical analyses

Means and SDs were calculated for all dependent measures. Bivariate correlations between the dependent measures were calculated. For the measures with both a baseline and postmanipulation measurement (ie, positive affect, negative affect, and EDA), a change score was computed and correlated with the other measures. To determine the influence of the message manipulation on the treatment efficacy expectation scale, the pain experience expectation scale, and the anxiety scale, scores on these measures were submitted to separate 4-level (message condition) one-way ANOVAs. The positive affect scale, negative affect scale, and EDA measures each had baseline scores. To verify that these variables did not differ across conditions before randomization, the baseline scores were first submitted to separate 4-level (message condition) one-way ANOVAs. To determine the influence of the message manipulation on positive affect, negative affect, and EDA scores, the postmanipulation scores were then submitted to separate 4-level one-way analyses of covariance (ANCOVAs). In each of these ANCOVAs, we controlled for a measure's own baseline score. If any omnibus F test violated the assumption of homogeneity of variance, the Welch ANOVA test,[61] which does not assume equal variance, was conducted. Effect size was estimated in the omnibus tests using partial eta squared (η_p^2).

If an omnibus F test was significant, post hoc comparisons were performed. If the assumption of homogeneity of variance was not violated, the Tukey honestly significant difference test was used to compare conditions[58] and Cohen's *d* was used to estimate effect size.[8] If the assumption of homogeneity of variance was violated, the Games–Howell post hoc test for unequal variances was used[19] and effect size was estimated with Glass's Δ,[28] which accounts for unequal variances. All significance tests were two-tailed with α set at 0.05.

Finally, exploratory analyses were conducted to determine whether the effect of condition on the dependent measures varied due to whether participants reported in debriefing that they had submerged an arm or leg in ice water for a long period of time before the study session.

3. Results

3.1. Descriptive statistics and bivariate correlations

Table 2 presents the bivariate correlations between measures. The treatment efficacy expectation scale was only correlated with the pain experience expectation scale. This correlation was negative and modest in magnitude ($r = -0.19$). The pain experience expectation scale was moderately correlated with the pretask anxiety scale ($r = 0.52$) and modestly and negatively correlated with an increase in positive affect from baseline ($r = -0.18$). Finally, an increase in positive affect from baseline was also modestly and negatively correlated with both pretask anxiety ($r = -0.21$) and an increase in negative affect from baseline ($r = -0.21$). No other correlations reached statistical significance.

3.2. Influence of the treatment messages on treatment efficacy expectations

Treatment efficacy expectation means and SDs across the 4 conditions are presented in **Table 3**. When the scores were submitted to the ANOVA, the analysis violated the assumption of homogeneity of variance, the Levene test,[42] $F(3, 134) = 5.06$, $P = 0.002$. The Welch ANOVA test was then conducted. This ANOVA produced a significant effect of condition, $F(3, 71.52) = 28.55$, $P < 0.0001$, $\eta_p^2 = 0.33$. The Games–Howell post hoc test among the conditions indicated that participants not given the analgesic message had lower expectations for the hand cream to reduce pain than participants in the analgesic message condition ($P < 0.00001$, confidence interval [CI]: 1.38–2.82, Glass's $\Delta = 2.60$), the analgesic with side-effect message condition ($P < 0.00001$, CI: 1.08–2.51, Glass's $\Delta = 2.21$), and the double-blind analgesic message condition ($P < 0.0001$, CI: 0.64–1.92, Glass's $\Delta = 1.58$). Participants in the analgesic message condition also had higher efficacy expectations for the hand cream than participants receiving the double-blind analgesic message condition ($P < 0.05$, CI: 0.02–1.63, Glass's $\Delta = 0.61$).

3.3. Influence of the treatment messages on pain experience expectations

Pain experience expectation means and SDs across the 4 conditions are displayed in **Table 3**. When these scores were submitted to the 4-level ANOVA, the analysis did not yield a significant effect of condition, $F(3, 132) = 1.60$, $P = 0.19$, $\eta_p^2 = 0.04$.

3.4. Influence of the treatment messages on pretask anxiety

Pretask anxiety means and SDs across conditions are provided in **Table 3**. When pretask anxiety scores were submitted to the 4-level ANOVA, the analysis did not yield a significant effect of condition, $F(3, 132) = 0.91$, $P = 0.44$, $\eta_p^2 = 0.02$.

3.5. Influence of the treatment messages on negative and positive affect

Baseline negative affect scores were first submitted to a one-way ANOVA (see **Table 3** for means and SDs). This analysis found no differences between groups before the message manipulation, $F(3, 132) = 0.11$, $P = 0.96$, $\eta_p^2 < 0.01$. Next, post negative affect scores were submitted to a 4-level ANCOVA, controlling for baseline negative affect scores. Three participants did not complete the post affect scale, thus reducing the sample for this analysis. The analysis violated the assumption of homogeneity of variance, the Levene test, $F(3, 129) = 4.09$, $P = 0.008$. The Welch ANOVA test was then conducted on the negative affect change scores (ie, post negative affect scores − baseline negative affect scores). This ANOVA produced a significant effect of condition, $F(3, 70.17) = 3.32$, $P = 0.02$. The Games–Howell post hoc test among the conditions indicated

Table 2

Correlations among treatment efficacy expectations, pain experience expectations, pretask anxiety, negative affectivity change, positive affectivity change, and changes in EDA.

	Treatment efficacy expectation	Pain experience expectation	Pretask anxiety	Negative affectivity change	Positive affectivity change	EDA change
Treatment efficacy expectations	—	–0.192*	–0.013	–0.024	–0.021	0.073
Pain experience expectations	—	—	0.521**	0.148	–0.175*	0.034
Pretask anxiety	—	—	—	0.094	–0.209*	0.139
Negative affectivity change	—	—	—	—	–0.206*	0.106
Positive affectivity change	—	—	—	—	—	–0.003

*$P < 0.05$, **$P < 0.01$.
EDA, electrodermal activity.

that participants in the double-blind message condition reported a larger increase in negative affect than participants in the analgesic side-effect message condition ($P < 0.05$, CI: 0.02–1.63, Glass's $\Delta = 0.76$). No other comparisons reached statistical significance.

A 4-level ANOVA on the baseline positive affect scores found no a priori differences between conditions, $F(3, 132) = 1.34$, $P = 0.27$, $\eta_p^2 = 0.03$ (see **Table 3** for means and SDs). Also, the ANCOVA on post positive affect scores yielded no effect of message condition, $F(3, 131) = 0.84$, $P = 0.47$, $\eta_p^2 = 0.02$.

3.6. Influence of the treatment messages on electrodermal activity

There was a malfunction with the EDA recording for 1 participant, resulting in 137 participants for the EDA analyses. A 4-level ANOVA on the baseline EDA scores found no a priori differences between conditions, $F(3, 131) = 1.48$, $P = 0.22$, $\eta_p^2 = 0.03$. Also, the ANCOVA on post-EDA scores yielded no effect of message condition, $F(3, 130) = 1.85$, $P = 0.14$, $\eta_p^2 = 0.04$ (see **Table 3** for means and SDs).

3.7. Exploratory analyses with prior cold-water immersion exposure

In debriefing, 91 (66%) of the participants reported having immersing an arm or leg in cold water for longer than 1 min on a previous occasion. To explore whether such prior exposure altered responses in this experiment, we reran our analyses, this time, including prior exposure (yes or no) as an additional independent variable. Analyses with all the dependent variables revealed only 2 main effects of prior exposure. First, participants with prior exposure reported less anxiety ($M = 2.48$) about the pain task than those without prior exposure ($M = 3.09$), $F(1, 130) = 7.31$, $P = 0.008$, $\eta_p^2 = 0.05$. Second, there was also a main effect of prior exposure on the pain experience expectation scale. Specifically, participants with prior exposure reported lower pain experience expectations ($M = -0.11$) than those without prior exposure, ($M = 0.19$), $F(1, 130) = 4.23$, $P = 0.04$, $\eta_p^2 = 0.03$. There were no main effects of prior exposure on the other dependent measures, and prior exposure did not significantly interact with experimental condition on any of the dependent measures (all P's > 0.05).

4. Discussion

The goal of the present experiment was to provide a more detailed account of the psychological processes that immediately follow the provision of 3 different analgesic treatment messages. The clearest outcome was that treatment efficacy expectations were more strongly influenced by the treatment messages than all other dependent variables. Scores on this variable significantly differed between the no-message control condition and all 3 treatment message conditions. Furthermore, treatment efficacy expectations differed between the treatment message condition and the double-blind message condition. Taken together, these data provide further evidence for the importance of studying treatment efficacy expectations in placebo analgesia. Notably, these findings are congruent with many existing accounts of

Table 3

Means and SDs on all dependent measures by experimental condition.

	No analgesic message	Analgesic message	Analgesic message with side effects	Double-blind analgesic message
Treatment efficacy expectation	1.68 (0.81)	3.79 (1.35)	3.48 (1.36)	2.96 (1.15)
Pain experience expectation	0.21 (0.80)	–0.17 (0.85)	–0.13 (0.67)	0.03 (0.85)
Pretask anxiety	2.42 (1.26)	2.88 (1.26)	2.60 (1.18)	2.77 (1.28)
Baseline negative affectivity	1.81 (0.51)	1.85 (0.45)	1.87 (0.41)	1.85 (0.48)
Post negative affectivity	1.83 (0.56)	1.82 (0.41)	1.80 (0.43)	1.99 (0.44)
Baseline positive affectivity	2.97 (0.61)	3.08 (0.47)	3.18 (0.39)	3.00 (0.46)
Post positive affectivity	2.97 (0.48)	3.03 (0.48)	3.01 (0.47)	2.90 (0.45)
Baseline EDA	0.35 (0.49)	0.26 (0.37)	0.23 (0.14)	0.20 (0.15)
Post EDA	0.48 (0.60)	0.51 (0.51)	0.39 (0.27)	0.36 (0.29)

Scores on the treatment efficacy expectation scale and pretask anxiety scale range from 1 to 7 with higher scores equating to greater efficacy and anxiety, respectively. As the items of the pain experience expectation scale had different ranges, scores on this measure were standardized, with higher scores equating to expectations of greater pain. Scores on the positive and negative affect scales range from 1 to 4.
EDA, electrodermal activity.

placebo analgesia that place considerable emphasis on efficacy expectations generated by treatment messages.[2,12,37]

One interesting finding was that the measures used were, in general, not highly related. This outcome is congruent with findings in other literature. That is, as was found here, in many other domains affective and cognitive variables measured in the same context often do not correlate,[39,41] and positive and negative affect measures are often only weakly associated.[7,25] In the present context, the prospect that there are multiple and separable psychological processes after a treatment message suggests this variation should be given greater attention. One somewhat unexpected finding was that the treatment efficacy expectation scale and that pain experience expectation scale were only modestly correlated. The fact that these 2 expectation scales were not highly related is notable, as researchers have not often distinguished between these 2 types of expectancies. However, in the current study, treatment efficacy expectations were more strongly altered by the message manipulation than pain experience expectations. On a practical level, this finding suggests that when testing expectations as a mediator of placebo analgesia, researchers would be well advised to measure treatment efficacy expectations. Relatedly, the results suggest that in clinical encounters, analgesic treatment messages could be of greater benefit when they target efficacy responses rather than changes in pain experience. That is, when feasible, practitioners could place more attention on building treatment efficacy expectations than on pain experience expectations.

It is interesting to consider the superiority of the treatment efficacy expectation scale over the pain experience expectation scale from the perspective of response expectancy theory.[36–38] Response expectancy theory differentiates between response expectancies (anticipations of one's own nonvolitional responses) and stimulus expectancies (anticipation of external events), and argues that response expectancies are the more consequential expectancy in treatment analgesic contexts.[37,38] From this approach, the weaker results on the pain experience expectation scale may have occurred because, when completing that scale, participants' thoughts pertain to both one's own responses and thoughts about the pain stimulus itself. As such, the scores may reflect a blend of response and stimulus expectancies, with the stimulus thoughts perhaps being less influenced by the treatment message manipulation.

The other psychological variable influenced by the message manipulation was negative affect. Specifically, there was greater negative affect in the double-blind expectation condition as compared to treatment with side-effect message condition. This result may reflect greater feelings of discomfort and potential disappointment that can arise from knowing that one may not have been given a useful treatment.[4,62] This finding indicates that analgesic treatment messages do not only alter expectations. Rather, the same treatment message can simultaneously change expectancies and feeling states. This result is notable, as when researchers test for psychological changes after a treatment message manipulation, they frequently only measure expectations.[23] These data suggest that it may also be valuable to measure feeling changes in future placebo analgesia studies. Finally, as negative affect was elevated in the double-blind message condition, this result suggests it would be prudent for researchers to examine how negative feelings are involved in randomized clinical trials, in which participants are given double-blind instructions. It is notable that negative feelings from double-blind treatment messages could be greater in randomized clinical trials, as the disappointment from potentially not receiving the active treatment is likely much greater than for healthy volunteers.

An unexpected outcome of the experiment was a lack of other changes on the battery of dependent measures. For example, anxiety, sometimes discussed as a factor that can reduce placebo analgesia, was not altered by the treatment messages. Similarly, positive affect has also been discussed as a factor that might increase placebo analgesia but was not changed by the treatment messages. In this study, these 2 variables, as well as pain experience expectations and EDA scores, were not altered by any of the 3 treatment message manipulations. It may be that these variables play a much smaller role in responding to placebo analgesic messages than treatment efficacy expectations. It is also possible that aspects of the current experimental design dampened effects on these variables. For instance, it may be that pretask anxiety would have been reduced if this was a patient rather than a volunteer sample. Relatedly, pretask anxiety may have changed if the type or duration of the pain stimulus was more uncertain to participants.[50,54] In addition, it is possible that some of these variables, such as EDA, only change once contact with the pain stimulus has occurred. These issues should be explored in future research.

This experiment uncovered only one difference between the 3 treatment message conditions. As noted, this was the significant difference in negative affect between the double-blind and treatment with side-effect conditions. It is possible that the side-effect condition did not differ more from the other treatment message conditions because the side effects introduced were mild. Had more severe side effects been stated, perhaps additional changes would have been observed. One explanation for the overall lack of message condition differences comes from the robust effect found on the treatment efficacy expectation scale. Specifically, in this experiment, all 3 analgesic messages produced a robust change in treatment efficacy expectations. Because this effect was strong in magnitude, this treatment efficacy knowledge may have overwhelmed all other information (eg, the side effect and double-blind instructions) that was provided in conjunction with the messages. If this is the case, future experiments could find greater variation in responses to these treatment messages, and perhaps effects of individual differences, if a weaker treatment efficacy expectation is induced. This possibility, as well as other explanations for this outcome, should be explored in subsequent studies.

Finally, exploratory analyses were conducted to assess the potential influence of prior exposure with cold-water immersion. In this study, participants' reports of prior exposure did not affect response to the 3 analgesic treatment messages. We did, however, find 2 main effects of prior exposure. Specifically, participants with prior cold-water immersion exposure reported less anxiety and lower pain experience expectations than participants without this experience. In some respects, these findings appear inconsistent with clinical and laboratory research on nocebo effects, in which pain experience increases pain reports.[1,2,10] On the other hand, the results are congruent with clinical and laboratory research showing that familiarity and accurate knowledge about an impending pain stimulus can reduce distress and pain.[31–34] Based on the present results, it may be that the participants without prior exposure had, overall, greater uncertainty and elevated concern about engaging the cold-water task than those who had familiarity from a past event.[32] Although we find these data intriguing, it is important to note that these analyses were exploratory and the total number of participants reporting prior exposure was greater than the number of participants reporting not having prior exposure. Furthermore, prior exposure was recorded at the end of the study session, which may have altered participants' recollections of past experiences. Additional research is needed to clarify the role of prior exposure in the anticipation phase of placebo analgesia.

4.1. Limitations

It is important to acknowledge the limitations of this research. First, the experiment was conducted in a laboratory context and the sample consisted of healthy college student volunteers. It would be enlightening to administer these same dependent measures to clinical samples in medical contexts to find out whether the same psychological activities are taking place.[35] Second, although we attempt to measure 5 different psychological constructs, there are others we did not include that can be examined in future studies. For example, motivation, desire, and hope should be included in future studies,[59] and treatment side effects should also be assessed. It would also be valuable to assess the extent to which participants actively thought about the treatment message during this anticipation phase.[20] Third, in this experiment, we included only a single measure of each of our psychological processes. To further verify that the results are due to differences in these processes, rather than to the specific measures, future studies should use other measures of these processes. Fourth, the sample size was determined based on prior placebo analgesia studies using a treatment efficacy expectation measure. This effect was the largest observed between conditions in this study, and as a consequence, it may be that differences would have emerged on the other measures if the sample size was larger. That said, the effect sizes on the other dependent measures were quite modest, suggesting only a very large sample would allow for potential differences to emerge. Finally, the 3 treatment message manipulations could also be altered in subsequent studies to determine the specific message features that trigger different psychological responses. For example, researchers could test whether describing very severe side effects results in significant changes in anxiety or EDA in this anticipatory phase of placebo analgesia.

5. Conclusions

In summary, this experiment manipulated 3 types of analgesic messages to determine the immediate psychological and EDA changes initiated by these messages. Across all 3 message conditions, treatment efficacy expectations were increased. Also, participants in the double-blind message group reported an increase in negative affect. The psychological and EDA measures showed relatively low interrelations, suggesting that there may be no single coordinated immediate psychological response to an analgesic treatment message. Rather, different patterns of psychological responses could manifest depending on the context.

Disclosures

The authors have no conflict of interest to declare.

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