Conditioning, Expectation, and Desire for Relief in Placebo Analgesia

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The factors that contribute to the magnitude of placebo analgesia have, until recently, been elusive. This review explores the roles of external factors, such as conditioning, and experienced factors, such as expectation and desire for pain reduction, in placebo analgesia. Placebo analgesia effects have been found to reflect decreases in pain beyond that accounted for by the natural history of a pain condition. These effects clearly are influenced by the effectiveness of previous active treatments (ie, conditioning) as well as by environmental factors that provide cues/suggestions for analgesia. However, external factors are effective insofar as they provide expectations for pain reduction and a lowering of desire for relief. Experienced factors, such as expectation and desire for relief, also are integral dimensions of some human emotional states, such as anxiety. We present an explanation of placebo analgesia that suggests that it is the result of mechanisms that also regulate emotional states.

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F or decades, placebo responses mainly were conceptualized as resulting from inert physical agents. Within the last few years, explanations of placebo responses have shifted from emphasis on environmental factors to human meanings and perceptions (see article by Moerman and Harrington in this issue). In this article, we explore the roles of both external and experienced factors in producing placebo analgesia as well as the relationships between them.

The Magnitudes of Placebo Analgesia and the General Contexts That Influence Them

One line of inquiry concerning the causes of placebo analgesia is that of examining placebo effect sizes under different clinical and experimental contexts. If placebo effect sizes vary systematically as a result of different conditions of placebo administration, then this type of information could be useful in at least proposing likely factors that contribute to the magnitude of the placebo effect. In one of the first attempts to make a systematic review of the magnitude of placebo effects, Beecher’s classical meta-analysis showed that 35% ± 2.2% of patients across various illnesses and conditions experience pain relief after placebo treatment.1 However, in these early studies, the level of pain in the placebo group/condition was not compared with the level of pain in a no-treatment group/condition. Therefore, it was not possible to distinguish whether the pain relieving effect resulted from perception of the placebo treatment or from factors related to changes in natural history.2 Thus, these studies did not actually assess placebo analgesia effects. In the 1970s, researchers began to recognize that it was crucial to incorporate a natural history condition (in clinical studies) or a repeated baseline control condition (in experimental studies) to be able to deduce the magnitude of placebo analgesia and to be able to investigate contributing factors.3

Although this study raised considerable controversy, the effect of placebo treatment was compared with a natural history condition in a recent meta-analysis of 29 studies.4 The effect size of placebo analgesia, measured as Cohen’s $d$ (pooled standardized mean difference), was 0.27, reflecting a small effect that is possibly clinically significant. Hrobjartsson and Goetzschel suggested that the small placebo analgesia effect could be the result of con-
founding variables, such as response bias since pain reflects a subjective state. Interestingly, most of the studies (24 of 29) included in the meta-analysis used a clinical trial design in which placebo administration served as the control condition. Verbal suggestions for analgesia typically are avoided in such studies, and the only reference to placebo is made in the consent form in which patients are informed of the possibility of receiving an inert and/or ineffective agent. In most nonresearch clinical settings or in experimental studies of placebo analgesia mechanisms, however, positive suggestions or conditioning with effective agents are likely to enhance placebo analgesia, as will be discussed in this article. Therefore, patients are more likely to expect to receive a pain-relieving medication in experimental studies of placebo analgesia mechanisms, in which strong suggestions for pain relief are given for pain relief. The effect size of placebo analgesia in the studies in which placebo analgesia was induced via either conditioning alone or suggestion alone was 0.83 and 0.85, respectively. However, the magnitude of placebo analgesia was 1.45 (almost twice as high as either factor alone) in the studies in which the placebo analgesia effect was induced via a combination of conditioning and suggestion. Thus, it appears that the effect of external manipulations, such as conditioning and suggestion, are additive, implying that the placebo analgesia effect may be related to how placebo agent is perceived, regardless of the exact external factors that lead to that perception.

### Analyses of Factors That Contribute to the Magnitude of Placebo Analgesia

Given the variability in placebo analgesic effects and the systematic influence of the presence or absence of factors such as previous experience with effective treatments and verbal suggestions, an emerging goal of placebo analgesia research is to identify factors that contribute to the perceived efficacy of a therapeutic intervention. The contribution of placebo analgesia to the effectiveness of analgesic drugs was tested in a clinical study using hidden and open injections of traditional painkillers such as buprenorphine. The patients needed less medication for analgesia when a doctor administrated open injections of painkilling agents with verbal suggestions for pain relief, than when a hidden machine administrated the painkilling agents. Presumably, the difference in analgesic response between open and hidden injections directly reflects the placebo analgesia effect. The difference between open and hidden injections could be eliminated by hidden injections of naloxone in a subsequent experimental study, demonstrating that part of the response variability to analgesic drugs can be attributed to opioid-mediated placebo analgesic effects. It may be particularly useful to explore exactly how subjects experience open injections versus hidden injections to clarify the mediating and moderating factors in placebo analgesia. As discussed below, such an approach is beginning to be applied to placebo analgesic research in general.

### External Factors That Contribute to Placebo Analgesia

#### Conditioning

Previous experiences with pain, the analgesic remedy, and the setting are likely to influence perception of pain treatments. Some investigators propose the idea that placebo effects are based on Pavlovian conditioning. When a patient receives an agent (unconditioned stimulus) that leads to analgesia (unconditioned response), contextual cues such as the medical setting, the white coat, or the pill/syringe (conditioned stimuli) may be associated with pain relief. These contextual factors, which represent the conditioned stimuli, elicit pain relief in the absence of active agents. Crossover studies have supported this hypothesis; the magnitude of placebo analgesia follows the graded doses of the active drug.
when placebo is given as the second drug. Voudouris and colleagues conducted the first studies to investigate the contribution of conditioning with a design that included a repeated baseline control condition. Subjects were tested in 3 sessions: (1) pretest, during which a noxious electrical stimulus was applied to determine the subjects’ threshold, (2) manipulation, during which an inert cream was applied to the skin and the stimulus was surreptitiously reduced to provide an experience of the cream’s analgesic effect, and (3) posttest, during which the “analgesic” cream was applied and the original intensity stimulus was delivered to the same area of the skin. Compared with a group given the cream with no conditioning, the conditioning group showed significant pain reduction by the placebo cream. This result suggests that a previous pairing of reduced stimulus intensity with an inert cream can result in large analgesic effects.

With subjects undergoing ischemic arm pain, the contribution of conditioning also has been tested. On the first day, subjects were tested during a no-treatment session. On the second and third day, a group of 14 subjects was conditioned with the opioid agent morphine, and another group (14 subjects) was conditioned with the nonopioid agent ketorolac. On the fourth day, both groups received open injections of saline and were told that the agent was an antibiotic to test effects of conditioning alone without any effect of overt placebo suggestion. Conditioning in both the morphine and ketorolac groups produced moderate and statistically reliable placebo effects. When the open injection secretly contained naloxone in a subsequent morphine-conditioned group, the placebo effect could be completely prevented. In contrast, the placebo effect was not antagonized by naloxone if ketorolac was used as the conditioning stimulus. Thus, the placebo analgesia effect induced by opioid conditioning (morphine) was mediated by endogenous opioids, whereas the placebo analgesia effect induced by nonopioid conditioning (ketorolac) was not mediated by endogenous opioids.

**Suggestion**

Expectation and belief in future pain relief can be induced by nonverbal and verbal suggestions, and expectations of caregivers can be transferred to patients. For example, the influence of nonverbal suggestions was indirectly tested in a study in which the clinician knew that one group of patients would receive placebo whereas the other group would receive placebo as well as the active analgesic agent fentanyl. The placebo analgesia effect was significantly higher in the second group, indicating that even without intentional or verbal communication, simply the clinician’s belief that a patient may receive a powerful painkiller influences the magnitude of placebo analgesia. Several studies have investigated the influence of verbal suggestions for pain relief.

The same paradigm of ischemic tourniquet pain tolerance was used to test whether suggestion in itself was enough to produce placebo analgesia. After the first day’s no-treatment session, on the second day, patients were given an open injection of saline and told that the agent was a powerful painkiller. A small but statistically reliable placebo effect was produced by this placebo treatment. When the experiment was repeated with an open injection of naloxone instead of an open injection of saline on the second day, the placebo analgesia effect was entirely eliminated, indicating that suggestion induces a placebo analgesia effect that is mediated by endogenous opioids. Recent studies have shown that both direct and indirect suggestions for pain relief lead to placebo analgesia of large magnitudes. Additionally, several studies have shown that verbal suggestions can lead to reduction of pain in highly specific areas of the body and that these specific placebo effects may be mediated by endogenous opioids.

Most of the studies presented so far have shown that conditioning in itself or suggestion in itself may lead to placebo analgesia. However, in most studies and especially in most clinical settings, previous exposure to analgesic agents and verbal suggestions for pain relief combine to produce placebo analgesia. The combination of morphine conditioning and verbal suggestions for inducing placebo analgesia also was examined in the study by Amanzio and Benedetti. The magnitude of this placebo analgesia effect was approximately twice the size of the placebo effect induced via either conditioning or suggestion alone. Interestingly, this large placebo effect could be completely prevented by naloxone. Thus, even though conditioning and suggestion may make separate contributions to placebo analgesia effects, they are likely to both activate a common opioid analgesia network. A recent study suggests that conditioning and suggestion both influence conscious phenomena (eg, pain) through expectations, whereas conditioning without conscious expectations can influence unconscious physiological processes such as cardiovascular responses and hormonal secretions.

**Experienced Factors That Contribute to Placebo Analgesia**

Patients are likely to perceive external factors, such as conditioning and suggestion, in different ways. Therefore, it is important to examine how these environmental factors and factors within the human experience relate to each other during placebo analgesia.

**Expectancy**

In pain studies, expectancy (the experienced likelihood of an outcome or an expected effect) can be measured by asking people about the level of pain they expect to experience. One of the first studies to directly measure and manipulate expected pain levels used a design in which subjects were conditioned with reduced stimulus intensity (cutaneous electrophoresis) in the presence of an inert cream, similar to studies by Voudouris. Subjects rated expected pain levels immediately after the conditioning trials. Pain ratings were noticeably reduced by the conditioning procedure in a group of subjects that did not know about the stimulus manipulation (ie, the placebo analgesic effect). However, regression analyses showed that expected pain levels mainly accounted for this effect. Thus, expectancy accounted for 49% of the
variance in postmanipulation pain ratings. Furthermore, when another group of subjects was informed about the experimental design and learned that the cream was inert, their expected pain levels did not differ from expected pain levels during the baseline condition and the placebo analgesia effect disappeared. Thus, although conditioning can lead to placebo analgesia, it appears to be mediated by conscious expectations.

Using a similar paradigm, the extent to which expectations of pain relief can be graded and related to specific areas of the body was further tested. In this study 3 “strengths” of placebo cream were applied to the subjects’ forearms and external manipulations were performed to perpetuate the belief that that cream A was a strong analgesic, cream B a weak analgesic, and cream C a control agent on 3 adjacent areas of the arm. Conditioning was accomplished by surreptitiously lowering the heat stimuli in areas A (large reduction) and B (small reduction) but not C (no reduction), after the creams were applied. After these manipulation trials, subjects were asked to rate their expected pain levels for the next series of trials. The conditioning trials led to graded levels of expectancy for the 3 creams C, B, and A (of successively less intense pain). When identical stimulus intensities were applied during the postmanipulation trials, subjects rated pains in areas C, B, and A as progressively less intense, demonstrating a graded placebo effect. In this study, expected pain levels accounted for between 25% and 36% of the variance in postmanipulation pain ratings. These results provide further evidence for the somatotopic specificity of the placebo analgesic effect, given that these placebo effects were induced on three immediately adjacent areas of the arm.

**Desire for Pain Reduction**

Although expectancy appears to be an important psychological mediator of the placebo analgesia, it is unlikely to work alone. Because motivation is known to influence perception, desire (the experiential dimension of wanting something to happen or wanting to avoid something happening) is also likely to be involved in placebo analgesia. In the study just described, the subjects’ level of desire for pain reduction also was manipulated. In one group, presenting them the prospect of receiving a large number of painful stimuli successfully increased their desire for pain relief. In a second group, informing them that only a few stimuli would be presented decreased desire. Interestingly, ratings of desire for pain relief were not significantly associated with the magnitudes of placebo analgesia. One possible reason for this lack of association may be because pain was induced via brief heat stimuli in this experimental setting. Desire for pain relief may be more of a factor in clinical pain where the pain is threatening or has an uncertain duration, therefore likely inducing fear or anxiety. Consequently, it is important to investigate the contribution of expectations and desire for pain relief in more clinically relevant settings.

**Memory of Pain**

This same study also showed that distorted memory of recent pain also contributes to the placebo effect. The placebo analgesia effect was assessed in 2 ways, on concurrent ratings of pain obtained immediately after the stimuli were applied and on retrospective ratings of pain obtained approximately 2 min after the stimuli were applied. Based on retrospective ratings, the magnitude of placebo analgesic effects was three to four times greater than the effect based on concurrent ratings. The main reason for this difference was that subjects remembered their baseline pain intensity as being much larger than it actually was. Similar to placebo analgesia effects based on concurrent ratings, the placebo effects based on remembered ratings were strongly correlated with expected pain intensities (r = 0.5-0.6). In fact, there was a stronger correlation between expected pain and remembered pain than between expected pain and actual pain. Consequently, it is important to measure placebo analgesia effects with concurrent ratings since it may be distorted by remembered pain. Moreover, since remembered pain and expected pain are closely related, these factors appear to interact. These effects of distorted memory on placebo analgesia have been replicated.

**Predicting Placebo Analgesia**

Two similarly designed studies further explain how factors within and external to human experience may relate in placebo analgesia. In both studies, patients diagnosed with irritable bowel syndrome (IBS) were exposed to rectal distention via a balloon barostat (a type of visceral stimulation that simulates their clinical pain) and tested under natural history, rectal placebo, and rectal lidocaine conditions. Both pain intensity and unpleasantness were rated immediately after each stimulus. In the first study, a standard clinical trial was conducted in which the patients were given an informed consent form stating that they “may receive an active pain reducing medication or an inert placebo agent” the rectal lidocaine had a significant pain relieving effect compared with rectal placebo (P < 0.001), and the rectal placebo had a significant pain relieving effect compared with the natural history condition (Fig. 1, left panel). On the basis of meta-analyses discussed earlier, the second study added a suggestion to the placebo condition and lidocaine condition. Patients of the second study were told at the beginning of each treatment condition that “the agent you have just been given is known to significantly reduce pain in some patients” (rectal placebo, rectal lidocaine). A much larger placebo analgesic effect was found in the second study. In fact, the magnitude of placebo analgesia was so high that there was no longer a significant difference between the magnitude of rectal lidocaine and rectal placebo (Fig. 1, right panel). Therefore, these 2 studies indicate that it is possible to increase the magnitude of placebo analgesia to a level that matches an active agent by adding an overt suggestion for pain relief.

Patients were asked to rate their expected pain level and desire for pain relief immediately after the agent was administered (before the onset of its effects) in both studies. In the second study, the combination of expected pain levels and desire for pain relief accounted for 77% of the variance in postplacebo pain ratings (see Table 2); how-
ever, expected pain levels have accounted for between 25
to 49% of the variance in postplacebo pain ratings in pre-
vious studies. Therefore, it is possible that the combina-
tion of expected pain level and desire for pain relief ac-
counts for a greater amount of the variance in post placebo
pain ratings than either factor alone. Nevertheless, al-
though the interaction between expected pain level and
desire for pain relief seems to have contributed, the ma-
jority of the contribution came from the expected pain
level (Table 2). Interestingly, the combination of expected
pain level and desire for pain relief accounted for 81% of
the variance in pain ratings during the rectal lidocaine
condition. These findings further support the conclusion
that placebo factors make strong contributions to the effi-
cacy of active treatments.

Calculating Placebo Analgesia

Thus far, studies of placebo analgesia have examined the
placebo effect and the extent to which factors such as ex-
pected pain level and desire for pain relief predict the vari-
ance in post placebo pain ratings. Although these findings are
important, predictive relationships are not necessarily pre-
dictions of the placebo effect; they are simply predictions of
pain ratings in a given condition. In the study presented
previously, expected pain ratings from each condition (nat-
ural history, rectal placebo, and rectal lidocaine) were all
predictive of pain, but not necessarily that of the placebo
effect.21 Because the placebo effect is the difference between
pain intensity in a no-treatment and a placebo condition, it
can be reasoned that a difference score between the natural
history condition/group ratings and placebo condition/group
ratings should be used for both the predicted (pain ratings)
and the predictor (eg, expected pain ratings) variable. In this
way, the change from natural history or baseline in response
to the placebo condition can be predicted. Also, this allows
examination of how trait factors such as personality styles or
relationships to health care providers or more dynamic fac-
tors such as changes in expected pain levels predict the pain
reduction with placebo treatment. Nocebo effects can be
computed with a similar approach.

The data from the 2 studies presented previously were
combined and re-analyzed to determine whether such an

Table 2 The Contribution of Expectancy and Desire to Rectal
Placebo Analgesia (From Vase et al[21])

<table>
<thead>
<tr>
<th>Model</th>
<th>(R^2) change</th>
<th>(F)</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expectancy* + desire</td>
<td>0.64</td>
<td>9.1</td>
<td>0.006</td>
</tr>
<tr>
<td>Expectancy (\times) desire</td>
<td>0.12</td>
<td>5.0</td>
<td>0.05</td>
</tr>
<tr>
<td>Total model</td>
<td>0.77</td>
<td>10.2</td>
<td>0.003</td>
</tr>
</tbody>
</table>

*Denotes significant beta weight.
Table 3 The Contribution of Changes in Expectancy and Desire to Rectal Placebo Analgesia

<table>
<thead>
<tr>
<th>Model</th>
<th>R² change</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Δ Expectancy + Δ desire</td>
<td>0.16</td>
<td>0.17</td>
</tr>
<tr>
<td>Δ Expectancy × Δ desire</td>
<td>0.22</td>
<td>0.02</td>
</tr>
<tr>
<td>Total model</td>
<td>0.38</td>
<td>0.02</td>
</tr>
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approach can reliably predict placebo analgesia effects and the results are shown in Table 3. For each of the 23 subjects, the placebo effect (natural history pain intensity minus rectal placebo pain intensity), change in expected pain (natural history pain expectation minus rectal placebo pain expectations), and change in desire for pain relief (natural history desire minus rectal placebo desire) were calculated. The changes in expectation, changes in desire, and their interaction (centered to reduce multicollinearity) were entered into a regression equation with the placebo effect as the predicted variable. Change scores for desire and expected pain were entered into the model first. This component accounted for sixteen percent of the variance in placebo effects (Table 3); however, this was not statistically significant. A second component (change in desire X change in expectation) was then entered into the regression equation after statistically controlling for the first component (Table 3). This accounted for an additional twenty-two percent of the variance in the placebo effect, which was statistically significant. The entire model accounted for 38% of the variance in the placebo effect (Table 3).

There are at least 2 implications to the re-analysis using the change score approach. First, it suggests that the change score approach is a better reflection of placebo analgesia effects. Thus, future studies should include the change score analysis in addition to more standard analyses. Second, it suggests that a main factor is the interaction between changes in desire and changes in expectation. The importance of this interaction is consistent with Price and Barrell’s desire–expectation model of emotional feelings as well as value-expectancy models. It suggests that placebo analgesia effects occur within the context of emotions.

**Placebo Analgesia as an Emotional Response**

More recently, the role of emotion in placebo analgesia has been examined in a number of studies. Interactions between desire and expectation account for magnitudes of positive and negative feelings during hypothetical emotional situations and emotional feelings during actual events. These same interactions also can account for direction and strength of choices during instances of decision making. Table 3 extends the list of phenomena associated with the desire–expectation model in showing that interactions between desire for relief and expected pain levels account for large and significant amounts of the variance in the placebo response. Placebo effects may change over time as a consequence of changes in emotional states. Similar to the aforementioned studies on patients with IBS, 26 patients with IBS were exposed to rectal distension under natural history, rectal placebo, and rectal lidocaine conditions and ratings were obtained of expected pain, desire for pain relief, anxiety, and actual pain during each experimental condition (Vase and coworkers, 2005, in press). In this study, however, ratings of expected pain levels, desire for pain relief, and anxiety were obtained at 2 time points, at the onset of placebo administration (early) and midway through the 40-min observation period (late). Ratings of these 3 factors decreased from early to late time points as did pain ratings within the placebo condition. Decreases in these 3 factors across natural history versus placebo conditions accounted for 11% (not significant) of the variance in placebo responses (pain in natural history minus pain in placebo condition) at the onset of placebo administration and for 58% (significant at P < 0.001) of the variance in placebo responses in the late period of observation. These results suggest that the placebo effect can increase over time as a function of decreases in expected pain levels, desire for relief, and negative emotions such as anxiety. These findings support the view that placebo effects may be at least partly mediated by changes in emotional states. Equally interesting is that similar results occurred for the lidocaine condition, providing further evidence that placebo effects and the factors that evoke them are embedded in active treatments.

Placebo treatments can initiate a more positive or less negative emotional state for a patient. It is possible that the placebo analgesia effect can at least partly result from decreases in negative emotions or increases in positive emotions. This possibility is supported in part by the studies just described and also by a study, which shows that pain, unpleasantness and pain intensity may be reduced by evoking positive emotions or increased by evoking negative emotions. Because this study was not about placebo effects, it provides an independent line of evidence that emotional feelings modulate pain. If placebo manipulations alter pain, they may do so by altering emotional states. Alternatively, it is possible that desire and expectation are merely factors that are common to both placebo mechanisms and emotions. In a recent study, it was found that low desire for pain relief decreased pain intensity and unpleasantness, whereas a high desire for pain relief increased pain unpleasantness but not pain intensity, suggesting that a decrease in desire may actually lower pain intensity. These results are consistent with placebo studies described above.

**Conclusions and Future Directions**

Whereas past explanations of placebo analgesia focused mainly on environmental factors and classical conditioning models, modern explanations focus more on human meanings, conscious expectations, and emotions as mediators or moderators of this phenomenon. This shift in emphasis is exciting because it suggests that the placebo analgesic response can be understood as a mind-body interaction and as
a phenomenon of human consciousness, which has parallels within pain-regulating areas of the brain. Thus, future studies that combine brain imaging with analyses of dimensions of human experience should provide important neuroscientific and psychological insights into the mechanisms of placebo effects, with both significant scientific benefits and consequent improvements in the care of patients with pain.

References