The contributions of suggestion, desire, and expectation to placebo effects in irritable bowel syndrome patients
An empirical investigation

Lene Vase\textsuperscript{a}, Michael E. Robinson\textsuperscript{b,\*}, G. Nicholas Verne\textsuperscript{c}, Donald D. Price\textsuperscript{d,e}

\textsuperscript{a}Department of Psychology, University of Aarhus, Asylvej 4, 8240 Risskov, Denmark
\textsuperscript{b}Center for Pain Research and Behavioral Health, Department of Clinical and Health Psychology, University of Florida, Health Science Center, Post Office Box 100165-HSC, Gainesville, FL USA
\textsuperscript{c}Malcom Randall VAMC, Research Service (151), 1601 SW Archer Road, Gainesville, FL 32608-1197, USA
\textsuperscript{d}Department of Oral and Maxillofacial Surgery, University of Florida, Health Science Center, Post Office Box 100416, Gainesville, FL 32610-0416, USA
\textsuperscript{e}Department of Neuroscience, University of Florida, Health Science Center, Post Office Box 100416, Gainesville, FL 32610-0416, USA

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Abstract

In order to investigate external factors that may influence the magnitude of placebo analgesia as well as psychological factors that mediate placebo analgesia, 13 irritable bowel syndrome (IBS) patients rated evoked rectal distension and cutaneous heat pain under the conditions of natural history (NH), rectal placebo (RP), rectal nocebo (RN), rectal lidocaine (RL) and oral lidocaine (OL). Patients were given verbal suggestions for pain relief and rated expected pain levels and desire for pain relief for both evoked visceral and cutaneous pain, respectively. Large reductions in pain intensity and pain unpleasantness ratings were found in the RP, RL and OL condition as compared to the natural history condition, whereas no significant difference in pain reduction between the three treatment conditions was found. Ratings during RN and NH were not statistically different. Compared to a previous study, which shows that rectal lidocaine reverses visceral and cutaneous hyperalgesia, these results suggest that adding a verbal suggestion for pain relief can increase the magnitude of placebo analgesia to that of an active agent. Since IBS patients rate these stimuli as much higher than do normal control subjects and since placebo effects were very large, they probably reflect anti-hyperalgesic mechanisms to a major extent. Expected pain levels and desire for pain relief accounted for large amounts of the variance in visceral pain intensity in the RP, RL, and OL condition (up to 81%), and for lower amounts of the variance in cutaneous pain intensity. Hence, the combination of expected pain levels and desire for pain relief may offer an alternative means of assessing the contribution of placebo factors during analgesia.

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1. Introduction

The magnitude of placebo analgesia has been shown to be influenced by the type of suggestion given for pain relief (Pollo et al., 2001; Vase et al., 2002). In clinical trials, there are typically no verbal suggestions for pain relief. However, the informed consent form normally informs the patients that they will receive either an active analgesic agent or a placebo agent. Hence, patients know that there is only a 50% chance or less of getting a pain relieving drug and accordingly are less likely to expect and report high levels of pain relief (Vase et al., 2002). On the other hand, studies that investigate mechanisms of placebo analgesia often give verbal suggestions to enhance placebo analgesia and consequently larger placebo analgesia effects are found (Vase et al., 2002). We have previously conducted a study showing that rectal administration of lidocaine jelly reverses both visceral and cutaneous hyperalgesia found in irritable bowel syndrome (IBS) patients (Verne et al., in press). In that study, no verbal suggestions for pain relief were given, and the pain relief following rectal administration of lidocaine jelly was significantly greater than that following rectal administration of placebo jelly. Yet we also found that placebo jelly produced a somewhat large reduction in evoked rectal pain, thereby suggesting that
this paradigm could serve as a model for analyzing mechanisms of placebo analgesia. Thus, the present study used this same paradigm and modified it by including multiple experimental conditions in which verbal suggestions were given to decrease or enhance pain. The different types of experimental conditions included natural history (NH), rectal placebo (RP), rectal lidocaine (RL), oral lidocaine (OL), and rectal nocebo (RN).

Exactly how external factors, such as suggestions for analgesia, influence the magnitude of placebo analgesia is not fully understood at this point. Multiple psychological factors have been suggested to mediate the magnitude of placebo analgesia. These include, for example, hope (Frank, 1965), faith (Bootzin, 1985), anxiety (Gryll and Katahan, 1978; Evans, 1985), conditioning (Wickramasekera, 1980; Voudouris et al., 1985, 1989, 1990), expectancy (Kirsch, 1985, 1990; Montgomery and Kirsch, 1996, 1997; Price et al., 1999) and memory distortion (Price et al., 1999). Two proximal factors that seem to be the most plausible candidates for mediating placebo analgesia include desire or need for pain relief and expectation that a given procedure or agent will relieve pain. Desire relates to the motivational aspect of needing or wanting to obtain pain relief and is associated with hope and faith in a treatment (Price and Barrell, 1984; Price et al., 1985; Price and Fields, 1997). Expectancy is the perceived likelihood of a procedure or an agent bringing significant pain relief and it can be produced by previous experiences, as in conditioning, and via verbal information such as suggestions for pain relief (Price et al., 1985; Kirsch, 1985, 1990, 1999; Price and Fields, 1997). The contribution of expected pain levels to the measured magnitude of placebo analgesia has been documented within experimental pain settings (Montgomery and Kirsch, 1996, 1997; Price et al., 1999; De Pascalis et al., 2002). The potential contribution of desire for pain relief to placebo analgesia, on the other hand, has only been investigated in one experimental study where it did not correlate with the magnitude of placebo analgesia (Price et al., 1999). In that study, however, pain was induced via brief test stimuli. Desire for pain relief may be more of a factor when pain is threatening such as during clinically relevant pain. Therefore, our previous study design where IBS patients were exposed to clinically relevant visceral pain stimuli and clinically irrelevant cutaneous pain stimuli (Verne et al., in press) would present an optimum chance of assessing the contribution of expected pain levels and desire for pain relief to placebo factors during analgesia.

Hence, in the present study, we exposed IBS patients to visceral and cutaneous pain under NH, RP, RL, OL, and RN conditions. We gave patients verbal suggestions for pain relief (placebo) and for pain increase (nocebo) and obtained ratings of expected pain levels and desire for pain reduction to answer the following questions:

1. To what extent do verbal placebo/nocebo suggestions influence evoked rectal pain and evoked cutaneous heat pain in IBS patients? Since IBS patients’ pain ratings of these forms of stimulation reflect a large degree of hyperalgesia (Verne et al., 2001, 2003, in press), this paradigm offers the unique opportunity to determine the effects of placebo and nocebo manipulations on clinically relevant hyperalgesic states.

2. To what extent does expected pain level and desire for pain relief contribute to pain ratings during placebo analgesia?

2. Methods

2.1. Subjects

Thirteen Caucasian pre-menopausal women with IBS participated in the study. The mean age was 30 (± 13) years. The diagnosis of IBS was made by an experienced gastroenterologist based on the ROME II criteria and exclusion of organic disease (Thompson et al., 1999). Twelve of the patients had diarrhea-predominant IBS, whereas one had constipation predominant IBS. The symptoms had lasted for at least 5 years. None of the patients had any symptoms other than those closely related to the IBS and none of the patients were on pain medications, serotonin uptake inhibitors, serotonin antagonists or tricyclic antidepressants at the time of the study. The study was approved by the University of Florida and Gainesville Veterans Administration Institutional Review Boards. All patients signed informed consent prior to the start of the study.

2.2. Setting and materials

The study took place at the Gastroenterology Clinic at the Veteran Administration Hospital, Gainesville. The gastroenterologist who performed the study was the doctor the patients normally consulted in the clinic.

Visceral pain was evoked by rectal distention. The balloon used for rectal distention consisted of a 500 ml polyethylene bag secured on a rectal catheter (Zinetics Medical, Inc., Salt Lake City, UT) utilizing unwaxed dental floss and paraffilm to ensure a tight seal. Patients were placed in the left lateral decubitus position and the rectal balloon was lubricated (Surgilube, E Fougera and CO, Melville, NY 11747) and placed into the rectum so the attached end of the bag was 4 cm from the anal sphincter. This same lubricant was used in all conditions. A visceral stimulator (Metronics, Minneapolis, MN) was programmed to deliver distension at a rapid rate (14.5 ml/s) to a precise and constant pressure plateau of 35 mmHg, and to simultaneously record pressures and volumes (Whitehead et al., 1990; Mertz et al., 1995). Cutaneous heat pain was evoked in IBS patients by having them immerse their right foot (up to the level of the right lateral malleolus) in a circulating, heated, water bath (Neslab Instrument, Inc., Newington, NH) with a constant temperature of 47°C.
The RL and the OL agent consisted of 300 mg lidocaine jelly (Castra USA, Inc., Westborough, MA) that was presented in a medical looking bottle and administrated to the rectal balloon and in a glass of water, respectively. The RP and the RN agent consisted of sterile surgical lubricant (used in all conditions) that was presented in a similar bottle and administrated on the balloon.

2.3. Measures

Perceived pain intensity and unpleasantness were measured via a mechanical visual analogue scale (M-VAS) (Price et al., 1994). Patients were instructed how to rate both pain sensation intensity and unpleasantness according to standardized written statements described in detail elsewhere (Price et al., 1994). Verbal anchors served to establish the distinction between these two pain dimensions. The VAS sensory scale was anchored at the left by the descriptors ‘no pain sensation’ and at the right by ‘the most intense pain sensation imaginable’. Likewise, the VAS-unpleasantness scale was anchored by the descriptors ‘not at all unpleasant’ and ‘the most unpleasant imaginable’.

Ratings of expectancy and desire were also obtained using M-VAS scales. Expectancy was measured by asking the patients: ‘How do you expect your level of pain intensity to be when this agent takes effect?’ In the NH condition where no agent was administrated, patients were asked: ‘What do you expect your level of pain intensity to be?’ IBS patients were asked about expected rectal pain in the case of balloon distension and expected cutaneous heat pain in the case of water bath stimulation. Similarly, they gave separate ratings for their desire for relief of rectal pain and cutaneous heat pain. Pain expectancy ratings were obtained using the same M-VAS that was used to assess actual pain intensity. Desire for pain relief was measured by asking the patients ‘How strong is your desire for pain relief?’ (for rectal pain and cutaneous heat pain, respectively). In the RN condition, patients were asked: ‘How strong is your desire to avoid pain?’ (for rectal pain and cutaneous heat pain, respectively). Ratings of desire for relief were obtained at M-VAS scales anchored by the descriptors ‘no desire for pain relief’ and ‘the most intense desire for relief imaginable’. These expectancy and desire scales have been validated previously and they have been used in a former study of placebo analgesia (Price and Barrell, 1984; Price et al., 1999).

2.4. Procedure

All patients were asked to fast 12 h before each session. The patients were greeted in the waiting room at the Gastroenterology Clinic, escorted to an examination room and introduced to the study. The patients were told that four drugs that reduced and increased pain in relation to IBS, respectively, were being tested, and that they had been proven effective in preliminary studies.

Each patient’s response to visceral and cutaneous stimuli was tested under five conditions: NH, RP, RL, OL, and RN. NH served as control for RP and RP served as control for RL. OL was included to test different routes of drug administration and RN served as a counterpart to RP. The sessions took place on separate days (5 days between sessions) and the sessions were systematically ordered. Half the patients received RL followed by RP and half the patients received RP followed by RL. The order of OL, NH and RN was randomized across patients. RL and RP conditions were presented in a double blind fashion, so neither the patient nor the doctor, who administrated the pain stimuli and gave the verbal suggestions for pain relief and administrated the agents, knew which drug was given.

Right after the balloon was inserted and the agent was administrated (either on the rectal balloon or orally) the following suggestions were given. In the OL, RL, and RP conditions the patients were told: ‘The agent you have just been given is known to significantly reduce pain in some patients’. Patients were told in the RN condition: ‘The agent you have just been given is known to significantly increase pain in some patients’. Subjects were told that they would receive no treatment in the NH condition.

Immediately after the suggestion was given and before the onset of any active drug effect, the ratings of expectancy and desire were obtained separately for evoked visceral and cutaneous pain. Thereafter, all interactions with the doctor ceased.

Rectal distension (35 mmHg) was applied twice for 30 s, followed by a 60 s inter-stimuli rest. Following each stimulus, the patients rated the perceived pain intensity and unpleasantness and the mean values for pain intensity and unpleasantness were recorded. Then the right foot was immersed in the 47°C water bath for 20 s and pain intensity and unpleasantness ratings were obtained. This protocol was repeated at 5, 15, 20, 40 and 50 min after administration of the agent. The patients were debriefed after all of the sessions were completed.

2.5. Statistical analysis

Repeated measures analyses of variance (ANOVA) were conducted on pain ratings at 5, 15, 20, 40 and 50 min. Separate analyses were run for visceral pain intensity, visceral pain unpleasantness, cutaneous pain intensity and cutaneous pain unpleasantness ratings. In all analyses, condition (NH, RP, RL, OL and RN) and time of testing served as within subject factors. Omnibus F-tests were followed by simple contrasts as indicated.

To examine the a priori hypotheses about the effects of pain expectation and desire for pain relief on placebo responding, hierarchical multiple regressions were conducted with expectancy and desire entered in the first block and with the interaction of expectancy and desire entered in the second block. Separate regressions were conducted for pain intensity ratings for both visceral pain and cutaneous
pain. To reduce the number of regressions, the average rating for the placebo condition was calculated for time periods from 5 to 50 min and regressions were only conducted on pain intensity ratings. These averages served as the predicted variable in each regression. Separate regressions were run for visceral pain intensity and cutaneous pain intensity.

3. Results

Overall, the results showed large reductions in pain intensity and unpleasantness as a result of placebo manipulations and lidocaine administration, as illustrated in Fig. 1. Much smaller changes resulted from nocebo suggestion. The results for each form of stimulation and pain dimension will be presented in turn.

3.1. Visceral pain intensity

(Fig. 1a) Results of the ANOVA for visceral pain intensity indicated significant main effects for condition \(F(4,44) = 15.4, P < 0.001, \eta^2 = 0.58\), time \(F(4,44) = 6.9, P < 0.001, \eta^2 = 0.38\) and condition by time interaction \(F(16,176) = 3.8, P < 0.001, \eta^2 = 0.25\). Simple contrasts indicate that compared to the NH condition, the RP, RL and OL conditions all had much lower mean pain intensity ratings. Mean pain sensation ratings were higher but not statistically different in the RN condition as compared to the NH condition. Additional contrasts indicated that there were no statistically significant differences in mean pain ratings between RP, RL and OL conditions. Effects were largest at the later time periods. These relationships are illustrated in Fig. 1a.

3.2. Visceral pain unpleasantness

(Fig. 1b) Results of the ANOVA for visceral pain unpleasantness mirrored results of the intensity ratings. This analysis indicated significant main effects for condition \(F(4,44) = 11.9, P < 0.001, \eta^2 = 0.52\), time \(F(4,44) = 3.9, P < 0.009, \eta^2 = 0.26\) and condition by time interaction \(F(16,176) = 3.3, P < 0.001, \eta^2 = 0.23\). Simple contrasts indicate that compared to the NH condition, the RP, RL, and OL conditions all had much lower mean pain unpleasantness ratings. Again, mean ratings were higher but not statistically different in the RN condition as compared to the NH condition. Additional contrasts indicated that there were no statistically significant differences between RP, RL, and OL. Effects were largest at the later time periods. These relationships are illustrated in Fig. 1b.

3.3. Cutaneous pain intensity

(Fig. 1c) Results of the ANOVA for cutaneous pain intensity indicated significant main effects for condition
Cutaneous intensity

Table 1
Rectal placebo

<table>
<thead>
<tr>
<th>Model</th>
<th>$R^2$ change</th>
<th>$F$</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visceral intensity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Expect$^+$ desire</td>
<td>0.64</td>
<td>9.1</td>
<td>0.006</td>
</tr>
<tr>
<td>Expect X desire</td>
<td>0.12</td>
<td>5.0</td>
<td>0.05</td>
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<tr>
<td>Total model</td>
<td>0.77</td>
<td>10.2</td>
<td>0.003</td>
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<tr>
<td>Cutaneous intensity</td>
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<td></td>
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<tr>
<td>Expect + desire</td>
<td>0.35</td>
<td>2.65</td>
<td>0.12</td>
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<tr>
<td>Expect X desire</td>
<td>0.01</td>
<td>0.22</td>
<td>0.65</td>
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<td>Total model</td>
<td>0.36</td>
<td>1.7</td>
<td>0.24</td>
</tr>
</tbody>
</table>

$^a$ Denotes significant beta weight.

($F(4, 44) = 9.7$, $P < 0.001$, $\eta^2 = 0.47$), time ($F(4, 44) = 3.5$, $P < 0.014$, $\eta^2 = 0.24$) and condition by time interaction ($F(16, 176) = 1.7$, $P = 0.045$, $\eta^2 = 0.14$).

3.4. Cutaneous pain unpleasantness

(Fig. 1d) Results of the ANOVA for cutaneous pain unpleasantness ratings indicated a significant main effect for condition ($F(4, 44) = 9.1$, $P < 0.001$, $\eta^2 = 0.45$). The main effect for time was not significant ($F(4, 44) = 1.9$, $P = 0.13$, $\eta^2 = 0.146$). The condition by time interaction was also significant ($F(16, 144) = 1.97$, $P = 0.02$, $\eta^2 = 0.15$). Simple contrasts indicated similar results for the condition comparisons with RP, RL, and OL conditions differing from NH and RN conditions. Fig. 1d illustrates these relationships.

3.5. Prediction of pain ratings during the rectal placebo condition

Results of the regression analyses relating desire and expected pain intensities to pain ratings during the RP condition are summarized in Table 1. Expectancy and desire ratings predicted 77% of the variance in the average intensity ratings of rectal distension in the RP condition. Examination of beta weights indicated that only expectation contributed uniquely to the model. The interaction between expectancy and desire approached but just failed to reach statistical significance, although it accounted for 12% of the variance in pain scores. For the cutaneous water stimulation, expectancy and desire ratings did not reliably predict intensity ratings and only accounted for about 36% of their variance.

3.6. Prediction of pain ratings during the rectal lidocaine condition

Results of the RL predictions are summarized in Table 2. Expectancy and desire ratings predicted 81% of the variance in visceral pain intensity ratings. Examination of the beta weights indicates that only expected pain level significantly contributed to pain intensity ratings, although both expectancy and desire are positively related to pain ratings. The interaction of expectancy and desire was not predictive of pain ratings. For the cutaneous stimulation, expected pain levels, desire for relief, and the interaction between expected pain level and desire were not reliably predictive of pain intensity scores.

3.7. Prediction of pain ratings during the oral lidocaine condition

The regression model predicted 71% of the variance in rectal distension ratings (Table 3). Although the combination of expectation and desire accounted for a significant amount of variance, the interaction between these factors was not significant. Examination of beta weights indicated that only expectation was a positive predictor. For cutaneous pain intensity ratings, the regression model predicted 72% of the variance in pain scores. Again, the interaction of expectation and desire did not account for a significant amount of variance and only expectation rating was a significant contributor.

The regressions suggest that the placebo pain ratings may be at least partly a result of expectations of pain and desire for pain relief, but that the large majority of this effect is the result of expected pain levels. Examination of expectancy and desire ratings in the NH and RP conditions support this hypothesis. A T-test of the difference between mean ratings of expected pain during NH and RP conditions was significant ($t = 2.2$, $P = 0.048$, df = 12) in the case of evoked rectal pain, as shown in Fig. 2. A T-test for the difference in desire ratings between NH and RP conditions approached but did not quite achieve statistical significance ($t = 2.1$, $P = 0.059$) (Fig. 2). Similar analyses for comparisons between NH and RL indicated lower pain expectancy

Table 2
Rectal lidocaine

<table>
<thead>
<tr>
<th>Model</th>
<th>$R^2$ change</th>
<th>$F$</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visceral intensity</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Expect$^+$ desire</td>
<td>0.81</td>
<td>21.5</td>
<td>0.001</td>
</tr>
<tr>
<td>Expect X desire</td>
<td>0.006</td>
<td>0.28</td>
<td>0.61</td>
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<tr>
<td>Total model</td>
<td>0.81</td>
<td>13.3</td>
<td>0.001</td>
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<tr>
<td>Cutaneous intensity</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Expect + desire</td>
<td>0.29</td>
<td>2.0</td>
<td>0.18</td>
</tr>
<tr>
<td>Expect X desire</td>
<td>0.0</td>
<td>0.10</td>
<td>0.98</td>
</tr>
<tr>
<td>Total model</td>
<td>0.29</td>
<td>1.2</td>
<td>0.75</td>
</tr>
</tbody>
</table>

$^a$ Denotes significant beta weight.
for the RL condition compared to the NH condition ($t = 4.3, P = 0.001, df = 12$) (Fig. 2). For the OL condition, expected pain was lower than NH ($t = 3.2, P = 0.008, df = 12$). Compared to the NH condition, desire for pain relief in RL ($t = -1.4, P = 0.18, df = 12$) and OL ($t = -0.45, P = 0.66, df = 12$) did not differ significantly (Fig. 2).

Similar analyses for differences in desire and expected pain levels between NH and treatment conditions during cutaneous heat pain were all non-significant (all $P > 0.05$).

### 4. Discussion

#### 4.1. The influence of verbal suggestions on pain levels

These results indicate large placebo analgesic effects for visceral and cutaneous pain intensity and pain unpleasantness. Expected pain levels and desire for pain relief accounted for large amounts of the variance in visceral pain intensity and smaller amounts of the variance in cutaneous pain intensity.

In our previous study where no suggestions for pain relief were given, the results were like those of a clinical trial. Thus, the effect of RL was significantly greater than the effect of RP and the effect of RP was of moderate size and significant, as shown in Fig. 3 (left) (Verne et al., in press).

In our previous study, analysis of the visceral pain intensity ratings 20 min after administration of RP as compared to administration of RL showed a difference score of 2.0 VAS units and an effect size of 1.43 (Cohen’s $d$). The difference score between the RP and the NH condition was 1.6 VAS units and the effect size of this difference was 0.89. In the present study, however, where suggestions for pain relief were given, the effect of RP was increased to an extent that eliminated the difference in effects between RL and RP, as shown in Fig. 3 (right) and also in Fig. 1. Thus, at 20 min after the beginning of treatment, the difference score between the RP and the NH condition was 3.0 VAS units and the effect size of this difference was 2.0, approximately twice as large as that found in our previous study. Hence, these results suggest that adding a suggestion for pain relief can increase the magnitude of placebo analgesia to approximately the same level as that produced by an active agent such as lidocaine. Similar to RP, RL produced significant and large pain relieving effect at 5 and 15 min after administration (see Fig. 1). At these time points, OL is unlikely to have produced active effects as systemic

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Table 3

<table>
<thead>
<tr>
<th>Oral lidocaine</th>
<th>$R^2$ change</th>
<th>$F$</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visceral intensity</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Expect + desire</td>
<td>0.71</td>
<td>11.1</td>
<td>0.004</td>
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<tr>
<td>Expect * desire</td>
<td>0</td>
<td>0</td>
<td>0.98</td>
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<tr>
<td>Total model</td>
<td>0.71</td>
<td>6.6</td>
<td>0.015</td>
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<tr>
<td>Cutaneous intensity</td>
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<tr>
<td>Expect + desire</td>
<td>0.72</td>
<td>11.7</td>
<td>0.003</td>
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<tr>
<td>Expect * desire</td>
<td>0</td>
<td>0.1</td>
<td>0.74</td>
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<tr>
<td>Total model</td>
<td>0.72</td>
<td>7.1</td>
<td>0.012</td>
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* Denotes significant beta weight.

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![Fig. 2. Comparisons of expected pain levels and desire for pain relief for natural history vs. rectal placebo, natural history vs. rectal lidocaine, and natural history vs. oral lidocaine conditions. All measures are reported prior to administration of visceral and cutaneous stimuli.](image)
absorption of OL has been shown not to take place until at least 20 min after administration (de Boer et al., 1979). Hence, the effect in the OL condition is likely the predominant result of a placebo analgesia effect, thereby demonstrating that adding placebo suggestions are effective for both oral and rectal routes of placebo administration.

We would like to stress that the lack of difference between lidocaine and placebo conditions, need not be interpreted as a lack of effect for lidocaine. Traditionally, placebo conditions have been used as control conditions, employing an ‘inactive’ intervention or agent. This study suggests that placebo expectation might be better conceptualized as another active agent. With this conceptualization, results of this study indicate that the placebo and lidocaine conditions resulted in equivalent (and large) effects, not that the lidocaine effects were ‘just placebo’.

There appeared to be a consistent enhancement of pain sensory intensity and unpleasantness in the predicted direction in the RN condition (Fig. 1) but mean pain ratings in the RN condition were not significantly different from the NH condition. Interestingly, however, the overall difference in mean visceral pain intensity ratings between RN and RP conditions at 20 min after administration of the agents was 3.9 VAS units and the effect size of this difference was 2.27. These results demonstrate that suggestions for pain relief and pain increase can powerfully modulate the hyperalgesia present in IBS patients. Moreover, these changes in pain levels increased over time and lasted the entire 50 min of the session, suggesting stable modification of pain levels.

In addition to the verbal suggestions, there may have been a number of interpersonal and contextual factors that contributed to the manipulation of pain levels. First, in both the previous and the present study, the doctor who performed the experiment was the doctor that the patients normally consulted in the clinic and with whom the majority of the patients had a good relationship. In the present study, the doctor took time to talk with each patient before the experiment, which may have contributed to an enhancement of the magnitude of placebo analgesia (Gracely and Katahn, 1978; Thomas, 1987). Second, the doctor wore a white coat, which traditionally has been believed to increase credibility (Guess et al., 2002). Third, the study was performed in the hospital setting where the patients normally were treated. Therefore, previous experiences with pain relief in the hospital setting may have influenced the experience of pain reduction (Voudouris et al., 1985, 1989, 1990).

In contrast to the findings of Gracely et al. (1978) but in accordance with the findings of Montgomery and Kirsch (1997), Price (1999) and De Pascalis et al. (2002), these external factors are likely to have influenced not only the affective-motivational dimension but also the sensory-discriminative dimension of pain. Effects on both dimensions would be consistent with a descending control mechanism involving a cerebral cortical–brainstem–spinal cord pathway (Price and Soerensen, 2002). Inhibition at this level of the dorsal horn would be expected to reduce both pain dimensions because these dimensions are not differentially represented at this level.

4.2. The contribution of expected pain levels and desire for pain relief to pain reduction

The external factors could exert their effects by changing the perception of the placebo agent, for example by inducing expectations for lowered pain levels and desires for pain relief (Vase et al., 2002). In both the rectal placebo and the rectal lidocaine conditions, expected pain levels and desire for pain relief accounted for large amounts of the variance in visceral pain intensity but only for lower and statistically non-significant amounts of the variance in cutaneous pain intensity ratings. The prospect of experiencing evoked visceral pain is likely to be more threatening and/or clinically relevant for IBS patients than that of experiencing cutaneous heat pain and therefore may activate placebo-related factors to a greater extent. Hence, desires and expectations for pain relief are likely to be directed toward visceral pain to a higher extent than toward cutaneous pain. On the other hand, desire and expectation ratings accounted for 71–72% of the variance in both visceral and cutaneous pain ratings in the case of oral lidocaine. Thus, oral administration of lidocaine may have influences on desires and expectations different from those associated with RL or RP administration. Since OL makes the tongue numb, patients may expect that OL will relieve pain in their entire body, whereas they may expect that RP and RL bring pain relief to their rectum and colon only. This interpretation is supported by our regression analyses but not by the t-tests showing that differences in desire ratings and expected heat pain levels across the NH and OL conditions were not statistically

![Fig. 3. Comparisons of natural history, rectal placebo and rectal lidocaine scores on visceral pain intensity ratings (VAS) during a 50-min session](image)
significant. Thus, the role of these factors in the OL is somewhat questionable.

Previous studies have shown that expected pain levels account for between 25 and 49% of the variance in pain ratings following administration of placebo (e.g. Montgomery and Kirsch, 1997; Price et al., 1999). However, by combining expected pain levels and desire for pain relief in the present study, it was possible to account for 77% of the variance in pain ratings following administration of rectal placebo (see Table 1). The large majority of the contribution came from expected pain levels, but the interaction between expected pain level and desire for pain relief also seemed to have contributed to a small extent at least in the case of RP. Desire alone did not contribute any unique variance during RP. However, neither desire nor the interaction between desire and expected pain level contributed to unique amounts of variance in pain ratings during the other treatment conditions. The small to negligible contribution from desire intensity is consistent with results of a previous study that used only brief heat stimuli (Price et al., 1999). Contrary to their prediction, desire did not seem to have a significant overall contribution to the more clinically relevant form of placebo analgesia studied in the present experiment. Further studies in which desire for pain relief is manipulated are needed to test the role of this factor in placebo analgesia.

The combination of expected pain levels and desire for pain relief also accounted for up to 81% of the variance in the RL condition (see Table 2). Hence, a large part of the variance in pain ratings in the RL condition seems to be mediated by placebo factors. These findings are in agreement with the study by Amanzio et al. (2001), which shows that part of the response variability to analgesics in experimental as well as clinical pain is mediated by placebo factors.

4.3. Placebo analgesia as an anti-hyperalgesia effect

Many previous studies on placebo analgesia have employed brief experimental pain such as that produced by 5-s heat stimuli or electric shock (see references in Price et al., 1999) and/or clinical pain such as post-operative pain (e.g. Amanzio et al., 2001). Most experimental forms of pain are likely the result of nociception without hyperalgesia. The present study utilized a form of evoked rectal pain for which IBS patients demonstrate marked hyperalgesia. Thus, IBS patients previously have been shown to rate this form of stimulation as much more painful (5–6 on VAS) than do normal controls (1–2 on VAS) (Mertz et al., 1995; Naliboff et al., 1997; Verne et al., 2001; Dunphy et al., 2003; Verne et al., 2003, in press). IBS patient’s ratings of pain stimuli employed in the present study were very similar in magnitude (Ca 5 on VAS; see Fig. 3) to those of previous studies and thereby reflect a large degree of hyperalgesia. Therefore, the large magnitudes of placebo analgesia found in this study are likely to have resulted largely from anti-hyperalgesic effects (Price, 1999). This possibility is supported by the large reductions in evoked rectal pain in these patients (Fig. 1) and by the fact that the post-placebo pain ratings of our IBS subjects were very similar in magnitude to those of normal control subjects (< 2.0 on VAS). Thus, placebo manipulations did not eliminate all evoked rectal pain but mainly that which was related to hyperalgesia. Anti-hyperalgesic effects of placebo can be quite large, as seen in the present study, and are consistent with the observation that placebo administration has larger effects on temporal summation of second pain than on first pain evoked by brief heat stimuli (Price et al., 2002). Temporal summation of second pain (i.e. windup) is considered to reflect a mechanism integral to central sensitization and hyperalgesic states (Price et al., 2002).

4.4. Implications of the findings

By illuminating some of the factors that mediate the variability in pain ratings following administration of placebo analgesia, it may be possible to enhance the utilization of placebo analgesia factors in clinical practice as well as to improve the measurement of placebo analgesia. The present data suggest that verbal suggestion for pain relief may increase the magnitude of placebo analgesia to that produced by an active agent. However, the combination of an active agent and a suggestion for pain relief did not increase the analgesic effect beyond either factor given alone, most likely due to a floor effect. Nevertheless, the combination of the two factors would probably be the optimal treatment as it assures a greater chance of benefit than either factor by itself. The verbal suggestion was a statement of a true fact in the present study since RP showed a large and significant pain relieving effect as compared to the NH condition in our previous study (Verne et al., in press). Hence, verbal suggestions for pain relief need not be deceptive and thereby ethically problematic. Also, as the combination of expected pain levels and desire for pain relief accounted for large amounts of the variance in post-treatment ratings, these two factors may constitute additional or alternative measures of placebo factors during analgesia. The possibility of measuring the placebo effect without inclusion of a placebo group may be both feasible and desirable, especially in view of growing concern about inclusion of placebo groups in clinical trial studies (Price, 2001; Guess et al., 2002).

In future studies it would be important to further investigate how psychological factors, such as suggestions for pain relief, expected pain levels and desire for pain relief, interact with physiological factors, such as release of endogenous opioids, during analgesia. Such an approach could result in a refined understanding of the ways in which placebo treatments as well as active treatments contribute to analgesia.
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References


