EFFECTS OF PERSONAL PLACEBO RESPONSE INFORMATION ON FUTURE PLACEBO RESPONSE

By

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The ethics of placebo use has been debated since discovery of the phenomena. However, there has yet to be a study that examines the aftereffect of individuals discovering that they experienced a placebo response on their future ability to experience a placebo response. Seventy-seven participants, 41 female and 36 male undergraduate students from the University of Florida were recruited via flyers and the college undergraduate subject pool and divided into three conditions: placebo informed, placebo uninformed, and repeated baseline. We used a double-placebo design with verbal placebo suggestion and conditioning to induce a placebo response and to examine the effect of providing information about a participant's personal placebo response on their future placebo response. We discovered that there was no difference in future pain responding between participants who were told that they experienced a placebo response versus those who were not. Interestingly, the placebo effect persisted when a second placebo cream was applied even after participants were told that the first cream used in the study was a

placebo. In addition, this study corroborated that revelation of an individual's placebo response does not appear to cause adverse effects on mood. Similar to mood, attitudes about the likelihood of using medical and non-medical treatments for pain, likelihood of participating in future studies, likeability of experimenters and trust of experimenters remained unaffected. Examining the concepts of expectation for pain and the desire for pain relief, we found that desire was a more consistent predictor than expectation in predicting a placebo response. Furthermore, characteristics such as somatic focus may be related to a participant's ability to experience a placebo response, but we found no evidence of any differences in placebo responding between the sexes. These results suggest that placebo use in experimental settings does not have detrimental effects.

CHAPTER 1
INTRODUCTION

Significant progress has been made in placebo research and this progress is most evident in pain research. Hoffman, Harrington & Fields (2005) indicated three possible reasons for this:

> (1) clinically, the placebo-induced pain reduction is probably the best verified instance of this general response; (2) methodologically, the most elegant experimental work on the placebo response has used pain as its paradigm; and (3) conceptually, we have more insight into the brain mechanisms underlying placebo analgesia than we have for any other placebo response.

Definition

There are several terms commonly used in placebo research that are important to define and distinguish. A placebo is an intervention designed to simulate medical therapy, but not believed to be a specific therapy for the target condition (Turner, Deyo, Loeser, Von Korff, & Fordyce, 1994). However, the terms placebo effect and placebo response have been frequently used interchangeably. The placebo effect refers to any average difference between the condition of a group of subjects that has received a placebo treatment, assuming that no change would have been observed in the absence of the placebo administration (Hoffman et al., 2005). In other words, it is the mean placebo response. In contrast, the placebo response refers to the change in an individual caused by a placebo manipulation (Hoffman et al., 2005). This is an important distinction because our focus is the psychology of the placebo response rather than the placebo effect. These definitions will be used for the remainder of the paper.

Discovery of the Placebo

The discovery of the placebo has a serendipitous history. In the 19th century, a leading European neurologist, Jean Martin Charcot became interested in a disorder called hysteria. Symptoms of this mysterious disorder included convulsions, paralysis, tunnel vision, color blindness, patches of anesthesia, incessant coughing, tics, and feelings of choking. While physicians were baffled by this disorder, Charcot took an analytic approach revealing underlying patterns with four completely predictable stages of the disease. It was later revealed that the "universal" physiology and mechanism of this disease was entirely local and only occurred within Charcot's studio. Charcot had been deceived by the subjective experiences of his patients, interpreting them as objective displays of universal significance (Harrington, 2000).

The idea that hysteria was a "made-up" entity was exposed when Hippolyte, a rival of Charcot, showed that he could reproduce, change and extinguish all of the symptoms of hysteria. He claimed that all of these symptoms were a kind of sham: nothing more than effects of a physiological process called suggestion. This finding led to the conclusion that bodily symptoms caused by suggestion are a psychological lie; that those who respond to these types of treatments were not suffering from a real disease at all. In the 1930s and 1940s, the perception of the placebo effect began to change with the discovery of sulfa drugs. The placebo effect began to be perceived as noise, a serious hindrance to medicine's progress (Harrington, 2000).

In 1955, Henry Beecher wrote a seminal article about the history of research on the placebo effect titled, "The Powerful Placebo" (Beecher, 1955). As the title suggested, the paper wanted to demonstrate that the placebo effect was powerful and pervasive. Beecher claimed that approximately 1/3 of patients across a review of 15 clinical trials

experienced a placebo response. Beecher also claimed that the placebo response could produce objectively measurable changes in a patient's physiology, changes that rivaled the effects of the active agent against which the placebo is being compared. Beecher argued that a randomized placebo controlled trial methodology was necessary to protect the active treatment data from the placebo effect.

Subsequently, it became clear that patient expectation or suggestibility was not the only possible confound for researchers. Additional problems included researcher bias, measurement error, statistical regression to the mean, and spontaneous remission. The placebo control group simply became a catch-all for these all of these confounds.

It's Not Nothing

Since the discovery of the placebo effect, placebos have been used as the control arm in randomized placebo control trials. Placebos were perceived as nuisances in the quest to find the actual effect of the "active" treatment. However, what has been ignored until recently is the fact that placebos in itself can affect significant change, sometimes in magnitudes similar to the "active" treatment against which it is being compared.

Recent imaging studies have documented specific brain regions to be associated with a placebo response. A study (Lieberman, Jarcho, Berman, Naliboff, Suyenobu, Mandelkern, & Mayer, 2004) using Positron Emission tomography (PET) with patients with Irritable Bowel Syndrome (IBS) both before and after a 3-week placebo regimen found that increases in ventrolateral prefrontal cortex (RVLPFC) activity from pre-placebo to post-placebo predicted self-reported symptom improvement. Another study (Wager, Rilling, Smith, Sokolik, Casey, Davidson, Kosslyn, Rose, & Cohen, 2004) examined placebo-inducted changes during anticipation and experience of pain using functional magnetic resonance imaging (fMRI). The investigators found that placebo

analgesia was related to decreased brain activity in pain-sensitive brain regions including the thalamus, insula, and anterior cingulate cortex. During anticipation of pain, placebo analgesia was associated with increased activity in the prefrontal cortex. These studies provide not only important insights into the neural mechanisms of placebo analgesia, but also evidence that placebos actually alter the experience of pain.

The placebo response is an extremely complex phenomenon. For example, a placebo analgesic effect can be localized. In a study (Benedetti, Arduino, & Amanzio, 1999), when a placebo analgesic was applied to one index finger and pain stimulation was applied to both index fingers, the placebo response was localized to the finger on which the placebo had been applied. Also, participants receiving placebos can experience improvements in addition to undesirable side effects known as nocebos (Hahn, 1997). Placebos appear to show a dose-response relationship of active agents, for instance, more frequent placebo administration was related to a larger placebo response (De Craen, Moerman, Heisterkamp, Tytgat, Tijssen, & Kleijnen, 1999). The same study found that placebo injections produce stronger effects than placebo capsules and pills (De Craen et al., 1999). These studies collectively demonstrate that placebos produce physiologic as well as psychological changes.

The Placebo Effect

Since Beecher (1955) reported that 35.2% of Participants were placebo responders, it has been assumed that there is a fixed-fraction of placebo responders. However, his examination of 11 studies found large variations in the average number of placebo responders. This idea of placebo-responders were assumed based on a comparison of group differences; however, the same differences could be a result of two scenarios: (1) all individuals in the placebo group exhibiting a moderate response or, (2) a relatively

small subset of individuals exhibiting a large response (Hoffman et al., 2005). Therefore, it has been suggested that it is safer to assume that the fraction varies from 0 to 100% (Benedetti & Amanzio, 1997). Also, it appears that a given subject does not consistently show a placebo response in different situations (Liberman, 1964). Rather, placebo reactivity can be conceptualized as a potential tendency that can be activated under the right situation rather than as trait that only certain people possess (Liberman, 1964). After a survey of placebo literature, Wickramasekera (1985) concluded that (1) only a subset of patients show a significant therapeutic response to placebo substances and procedures in any given study, (2) we cannot identify these participants beforehand, (3) the same subset may not respond in subsequent administrations, (4) the right conditions for a response remains unknown.

Although medicine has not always been interested in the placebo effect itself, it has managed to gather a lot of potentially valuable information through 50 years of clinical trials. However, much of the data are confounded by factors other than the placebo effect because of the lack of natural history conditions in most of these studies. The natural histories of pain and the psychological circumstances under which placebo treatments are administered vary widely across different studies. A recent meta-analysis of placebo-controlled clinical trials attempted to assess the magnitude of the placebo effect despite these confounds (Hrobjartsson & Gotzsche, 2001). A total of 114 studies were examined and Hrobjartsson and Gotzsche (2001) were able to estimate the magnitude of the placebo effect. They concluded that these effects are less widespread and weaker than previously believed. Also, they only found a significant effect when studies with continuous data were examined versus those with dichotomous data. However, these

results are a result of combining studies of 40 different conditions such as hypertension, alcohol abuse, anxiety, asthma, and martial discord. This assumes that placebos are effective across all of these different disorders, an assumption that is not held by placebo researchers (Stewart-Williams & Podd, 2004).

There is a major limitation with concluding that the magnitude of the placebo effect is small from the overall results of the Hrobjartsson and Gotzche (2001), meta-analysis. In the meta-analysis, only the condition of pain had a large enough sample for separate analysis. In this condition, the researchers found a small but significant placebo effect. However, there were two major types of studies included in this study: those that were clinical and testing an active drug treatment and those studying actual placebo analgesic mechanisms. The mean effect size was 0.95 (Cohen's d, a large effect) in the 14 studies of placebo mechanisms where strong suggestions for pain relief were typically given (Vase, Riley, & Price, 2002). Also, since Hrobjartsson and Gotzsche's paper, several well-controlled experimental studies about the placebo effect have been published. Stewart-Williams and Podd (2004) reviewed 16 studies and found that 14 demonstrated effect sizes equal or greater than 0.50 standard deviations, a medium effect size.

The Vase et al. (2002) meta-analysis demonstrated the importance of placebo mechanisms in the magnitude of placebo analgesia. While studies inducing placebo analgesia with conditioning or suggestion alone demonstrated effect sizes of 0.83 and 0.85 (Cohen's d), respectively, the magnitude for studies using a combination of conditional and suggestion was 1.45, almost double that of either method alone.

Mechanisms

There are multiple theories regarding the mechanism of placebo. The anxiety theory hypothesizes that the placebo response is due to a reduction of anxiety, which in

turn is associated with a decrease in pain perception. However, this theory does not clarify whether this reduction in anxiety is the cause or consequence of the placebo response (Benedetti & Amanzio, 1997). Two major theories of the placebo response are the conditioning and cognitive or expectancy theories.

Conditioning

The conditioning theory suggests that the placebo response represents a form a classical conditioning. According to this theory, by pairing a neutral stimulus with a stimulus (US) that elicits an unconditioned response (UR), the neutral stimulus becomes a conditioned stimulus (CS) that can also elicit a response similar or related to the UR called the conditioned response (CR). Therefore, stimuli such as a pill or a white lab coat (CS) that may be initially neutral with repeated association with an active drug or procedure (US) that elicits a specific response (UR) could elicit a response similar or related to the active drug or procedure in the absence of this active drug or procedure (CR).

Much of the research in support of the classical conditioning theory has been done on nonhuman animals such as dogs, rats and mice. However, a series of influential studies by Voudouris et al. (1985; 1989; 1990) showed that the placebo response can indeed be conditioned in humans. In their study, after an initial testing session, his participants were divided into two groups and a neutral cream was applied to the skin of both of these groups (Voudouris et al., 1985). However, in one group, the level of nociceptive stimulation was decreased with the administration of the placebo cream while the stimulation was increased in the second group. A final pain testing suggested that placebo responses could be conditioned in the laboratory in both positive and negative directions.

Expectancy

The expectancy theory is the second major theory. According to this theory, a placebo produces an effect because the recipient expects it to (Stewart-Williams & Podd, 2004). In fact, classical conditioning itself may lead to the acquisition of expectancies (Price, 1999). However, expectation can also reflect knowledge about the active agent, the circumstances around administration of the agent, and the condition the agent is treating (Price, 1999). This implies that expectancies can be formed before an initial exposure, contrary to the conditioning theory where an initial association needs to be formed with the active agent.

The expectancy theory has a number of interesting implications. For example, drug advertising may lead to more powerful placebo effects. Another implication is that a drug simply treating the symptoms could treat the underlying disease by affecting expectations that the treatment is working. Listing the possible side effects of a drug may increase the likelihood that patients will experience these effects. Finally, those with hypochondriacal tendencies are at increased risk of developing the physiological or psychological health problems they worry about (Stewart-Williams & Podd, 2004).

Ethics: Experimental Setting

The ethics of placebo use has always been a controversial topic since discovery of the phenomena. The World Medical Association rekindled the debate with the release of a revision of the Declaration of Helsinki in October 2000. Section 29 states

> The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists. (Association, 2004)

This section was particularly seen for its potential to cause substantial difficulties for future development of medical products if it is literally interpreted and universally implemented (Lewis, Jonsson, Kreutz, Sampaio, & van Zwieten-Boot, 2002).

Section 29 was written for the highly admirable purpose of ensuring that patients are not exploited when they take part in clinical trials. This possibility is of particular concern for individuals from less-developed countries who may be involved in research to benefit individuals in more developed countries (Lewis et al., 2002). However, the wording of Section 29 implies ruling out some crucial uses of placebo-controlled trials in areas of medicine where proven prophylactic, diagnostic or therapeutic methods already exist, making no exceptions for possible benefits, adequate patient consent, avoidance of irreversible harm and other precautions against ethically unacceptable consequences (Lewis et al., 2002).

Since then, the Declaration of Helsinki has been clarified with a revision in 2004. The clarification states,

> a placebo-controlled trial may be ethically acceptable, even if proven therapy is available, under the following circumstances: where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method; or where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm. (Association, 2004)

This recent clarification has also been criticized, particularly for the use of the word 'or' linking the two situations. This could be interpreted as scientifically compelling reasons could be used to justify increased risk of serious harm through use of placebo; therefore, perhaps the connector should be 'and' not 'or' (Carlson, Boyd, & Webb, 2004). Also, the use of the word, 'best current' has been questioned since the 'best current' may not be available in a local context (Carlson et al., 2004). In addition, the 'best current' treatment

for some conditions remains controversial without consensus among professionals. Moreover, while it is clear that for some serious conditions where there is often one opportunity for a cure where placebo-controls need to be ruled out, there are other conditions where providing rescue or escape medications are acceptable with adequate patient awareness and consent (Carlson et al., 2004).

Methodologically, the use of placebos is crucial. Researchers, particularly with respect to pain treatment endeavor to determine the efficacy of a specific treatment and why patients improve with treatment (Turner et al., 1994). The randomized controlled trial is the closest that clinical research can get to the experimental situation (Stang, Hense, Jockel, Turner, & Tramer, 2005). The common argument against the use of placebo is that it is unnecessary, that new treatments should be tested against existing treatments (Stang et al., 2005). However, the reality is that "proven effective therapy" is often assumed and fails to show superiority to placebo (Stang et al., 2005). Without a placebo arm, it would not be possible to make the crucial distinction that two drugs are equally ineffective rather than equally effective.

The Vioxx Gastrointestinal Outcomes Research (VIGOR) provides a concrete example of another potential pitfall of not having a placebo control arm in a clinical study. The VIGOR trial showed a five-fold difference in the incidence of myocardial infarction in the Vioxx (rofecoxib) group compared with the naproxen group (Stang et al., 2005). Unfortunately, without a placebo group, it remained unclear whether there was an increased risk of myocardial infarction with Vioxx or a decreased risk with naproxen (Stang et al., 2005). Four years later, after tens of millions of patients received Vioxx, Merck withdrew the drug from the market because of an increased cardiovascular risk

(Stang et al., 2005). The Declaration of Helsinki (2004) states, "Medical research is only justified if there is reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research." Stang et al. (2005) asserts, "In this case, by trying very hard to be ethical and adhering too rigidly to the anti-placebo dogma, one can end up being unethical."

It is clear that the use of placebo is a hotly contested topic. While there is much debate regarding the ethics of using placebos, it is clear that placebos serve an important function in research and the lack of a placebo control group can have detrimental effects as demonstrated in the Vioxx study. However, much of this debate revolves around the assumption that the placebo effect is somehow not real; that a placebo itself cannot effect true change. There is growing evidence this is not the case. As mentioned earlier, there is mounting evidence from imaging studies that placebos produce real physiologic as well as psychological changes, sometimes similar to that of active treatments. The question then remains, are placebos used in clinical settings and can or should placebos be used in clinical settings?

Clinical Use of Placebo

In 2000, the Sunday New York Times Magazine publicized in a cover article that "the powerful placebo" has come of age and suggested that medicine should make regular use of it (Hoffman et al., 2005). Despite an upsurge of new research into placebo mechanisms and the use of placebos in clinical trials, much remains unknown, especially regarding use of the placebo in the clinical setting. However, a few researchers have attempted to explore this topic.

A team of French researchers (Berthelot, Maugars, Abgrall, & Prost, 2001) interviewed 300 rheumatology inpatients and 100 nurses about their beliefs about the

placebo effect. While all nurses interviewed reported knowing about the placebo effect, only 59% of patients reported knowing about the placebo effect. Regarding the characteristic of placebo responders, all nurses surveyed and 91% of patients believed the placebo effect was dependent on patient personality, while only 63% of nurses and 38% of patients attributed the effect to the personality of the physician. Eighty-three percent of patients and 62% of nurses believed that those who respond well to placebos are psychologically fragile. When asked about the use of placebos in clinical settings, 45% of patients and 66% of nurses reported that physicians should use placebos to treat their patients. Twenty seven percent of patients believed the physician should tell their patients while only 3% of nurses thought the same. Twenty eight percent of patients and 45% of nurses reported that they would agree to take a placebo. It is clear from these results that there is a wide range of knowledge and beliefs about the placebo effect with a lot of ambivalence regarding the topic among patients and nurses (Berthelot et al., 2001).

Focusing more on behaviors rather than beliefs, Nitzan and Lichtenberg (2004) surveyed 89 nurses and physicians from different hospitals, departments and clinics around Israel about the use of placebos in their medical practice. The results were surprising. The authors had assumed that the use of placebo was not widespread and would not exceed 10%. However, they found that 60% admitted using a placebo (53% of doctors and 71% of nurses). No effects of sex or age were revealed. Thirty seven percent of those surveyed reported using a placebo as often as once a month or more. Of those who used a placebo, 94% reported that placebos were generally (33% of respondents) to occasionally (61% of respondents) effective. Also, 68% of those who used a placebo reported telling patients that they were receiving a real medicine, 17% reported saying

nothing at all, and 11% reported telling the patients that they are receiving a non-specific medicine. Only 5% responded that the use of placebos should be categorically prohibited while 75% attributed the effect to purely psychological mechanisms. The authors point out that the retrospective nature of the study may bias frequency estimations; however, the use of placebos or not in a clinical setting is not likely to be forgotten, suggesting that placebos are indeed widely used in clinical practice.

Proposed Study

While the literature on the clinical use of placebos remains limited, it appears that healthcare professionals may routinely use placebos in medical settings. If this is the case, what are the implications of administering placebos to patients? How would people respond if they realized that they experienced a placebo response?

It is possible that knowledge of personally experiencing a placebo response will detrimentally affect the future likelihood of experiencing a placebo response. However, it is also possible that knowledge of personally experiencing a placebo response may enhance the future likelihood of experiencing a placebo response. The primary goal of this study is to test these competing hypotheses. Also, the role of expectation for pain and desire for pain relief will be examined in their ability to predict placebo responses. Next, the effect of knowledge of a personal placebo response on likelihood of participating in future studies and trust and likeability ratings of experimenters will be assessed. Lastly, we will investigate the relationship between somatization and placebo response.

CHAPTER 2
MATERIALS AND METHOD

Participants

Seventy-seven participants, 41 female and 36 male undergraduate students from the University of Florida, were recruited via flyers and the college undergraduate subject pool. Before starting, all participants completed a consent form, which explained the nature of the noxious stimulation. Those with heart conditions, hypertension, diabetes mellitus, asthma, seizures, frostbite, past trauma to hands, lupus erythematosus, arthritis or those on pain medication were excluded from the study. Participants were told that they could withdraw from the experiment at any time.

Apparatus

Medoc Thermal Sensory Analyzer

All thermal stimuli were delivered using a computer-controlled Medoc Thermal Sensory Analyzer (TSA-2001, Ramat Yishai, Israel), which is a peltier-element-based stimulator. The stimuli were a range of temperatures from an adapting temperature of 33^{o}C up to 51^{o}C. Stimuli were applied in a counterbalanced order to the forearm by a contact thermode and were 3 seconds in duration. Multiples sites located on the forearms of both arms were employed. Stimuli presentations were timed such that no site was stimulated with less than a 3-minute interval to avoid sensitization of the site.

Mechanical Visual Analog Scale (VAS)

Participants rated stimuli using a mechanical VAS anchored at the left end by “no pain” the right end by “the most intense pain imaginable.” This method of pain

assessment has been shown to yield ratio scale measurement of clinical pain, which is both internally consistent and provides independent sensory intensity and affective dimensions of experimentally induced pain.

Placebo Cream

The placebo analgesic was in the form of a cream. A simple cold cream was mixed with linalol/oil of thyme in a ratio of 8:1, which gave the cream a distinct smell. The cream was removed with cotton. The control cream was an 8:1 mixture of cold cream and water.

Measures

Demographics Questionnaire

The demographics questionnaire provided information concerning the participants' sex, age, education, race, income, marital status, work status, occupation, height, weight, and pain conditions.

Illness Attitude Scale (IAS)

The IAS (Kellner, Abbott, Winslow, & Pathak, 1987) is a self-report measure designed to measure psychopathology associated with hypochondriasis. The IAS consists of 9 a priori subscales: Worry about Illness, Concerns about Pain, Health Habits, Hypochondriacal Beliefs, Thanatophobia, Disease Phobia, Bodily Preoccupations, Treatment Experience, and Effects of Symptoms. There have been multiple attempts at analyzing the factor structure of the IAS using principal components analysis (Ferguson & Daniel, 1995) (Stewart & Watt, 2000) (Hadjistavropoulos & Asmundson, 1998). Hadjistavropoulos et al. (1999) conducted a exploratory and confirmatory factor analysis and found considerable support for four distinct factors (1) Fear of illness, disease, pain and death, (2) symptom effects, (3) treatment experience, and (4) disease conviction. The

four factor structure was corroborated by Stewart et al. (2000) with a few changes and the factors were renamed fears, behavior, beliefs, and effects.

Pennebacker Inventory of Limbic Languidity (PILL)

The PILL is a self-report measure of the occurrence and frequency of common physical symptoms and sensations. It consists of 54 items, such as coughing, sneezing, racing heart, and headache. Response categories are: have never or almost never experienced the symptom, less than 3 or 4 times per year, every month or so, every week or so, and more than once every week, which are indicated by a five-point Likert scale. This measure asks for generally experienced symptoms over an unspecified time period in the past and assesses a general tendency to experience and report symptoms rather than the actual, everyday symptom experience (Gijsbers van Wijk, van Vliet, & Kolk, 1996). Thus, this trait-like symptom scale is used to assess somatization or a general tendency for reporting physical symptoms (Pennebaker, Hughes, & O'Heeron, 1987). When used with healthy participants, a high score is indicative of somatization. Internal consistency is high (Cronbach's alpha=0.91) (Gijsbers van Wijk et al., 1996). The PILL has sufficient test-retest reliability (0.83) and was found to correlate moderately with comparable symptom scales (Pennebaker, Gonder-Frederick, Stewart, Elfman, & Skelton, 1982).

Visual Analogue Scales of Mood (VAS - Mood)

Mood was assessed with a mechanical VAS. The negative feelings associated with pain experience assessed were depression, anxiety, frustration, fear, and anger, with end points designated as "none" and as "the most severe imaginable". Visual Analogue Scales (VAS) of pain have been demonstrated to be reliable, internally consistent measures of experimental pain sensation intensity (Price, Bush, Long, & Harkins, 1994).

Procedures

All participants participated in four pain testing stages consecutively. Participants were divided into three groups: placebo informed, placebo uninformed and repeated baseline conditions. Table 2-1 provides a brief overview of the difference in procedures between the three groups. The repeated baseline group was informed that they would be tested using a control cream that does not contain any active agents. On the other hand, both the placebo uninformed and informed groups were told that we are testing the effects of an ointment on pain and given the suggestion of an active agent. Finally, the placebo informed group was told after the first placebo testing stage that the cream used was a placebo while the placebo uninformed group was not told that the first cream used was a placebo. The following paragraphs provide a more detailed description of each stage.

Table 2-1. An overview of the study design.

	Placebo Uninformed	**Placebo Informed**	**Repeated Baseline**
Initial Information	Told we are testing the effects of a cream on pain		Told we will not be testing cream because they are in the control condition
Questionnaire	Same for all groups (counterbalanced)		
Calibration Trials	Same for all groups (testing temperatures determined)		
Baseline	Same 4 trials for all groups		
Conditioning	8 trials, 4 at placebo temp w/ cream, 4 at baseline temp		Also 8 trials, but got placebo temp on all areas
First Placebo	Same 4 trials at Baseline Temp		
Information/ Graph Presentation	Graph Shown and told that the cream worked as expected	Graph Shown and told that they received a placebo and the difference in pain ratings demonstrates a placebo response	Graph shown and told that it represents their pain ratings at 2 time points
Second Placebo	Same 4 trials at the baseline temperature		
Questionnaire	Same for all groups (counterbalanced)		

Stage 1: Baseline

During the first stage, each subject began with the following instructions:

> After filling out several questionnaires about yourself, your attitudes and your mood, you will be asked to participate in four sensory-testing sessions consecutively using a heat thermode where you will receive several brief heat pulses to different areas on your forearms. These pulses will range from undetectable to painful. After the first three sessions, you will be provided with information about your responses during the previous trials. After the information is provided, you will then be asked to participate in the last sensory testing session. After the last session, you will be asked to complete several additional questionnaires.

Half of the participants were randomly assigned to complete a packet of questionnaires including a demographics questionnaire (which will ask for age, sex, education, marital status, ethnicity, occupation/area of study, socioeconomic status), IAS and PILL while the other half were asked to complete the questionnaire at the end of the study. Also, VAS-Mood, likeability of experimenters and trust of experimenters were assessed in all participants before beginning the pain trials.

Next, calibration trials were conducted to control for individual differences in pain perception. An ascending series of trials starting from 43°C increasing by steps of 1°C were completed. The participants rated the pain intensity immediately on a VAS following each trial. On a 0-10 scale, the temperatures at which the patient rated their pain intensity between 0 and 2 (placebo) and between 4-6 (control) were noted. During the first stage after the calibration trials, each subject completed 4 pain-trials at the control stimulus intensity to determine their baseline pain ratings.

Stage 2: Conditioning and Suggestion

In stage 2, the subject in the placebo informed and uninformed conditions were provided with instructions regarding the nature of the experiment. They were told, “The

agent you have just been given is known to significantly reduce pain in some patients". They were also informed that the level of stimulation during this session would remain constant. On counterbalanced selected locations on the arm, each participant received 8 total pain-trials, 4 with the placebo cream at the placebo temperature and 4 at the control temperatures (as determined during the calibration trials) without the placebo cream. Eight trials were used because repeated pairings are necessary for conditioning to occur. The intensity of the stimulus was surreptitiously lowered for the placebo cream to produce the conditioning effect. Participants assigned to the repeated baseline condition were told that they would not receive an active agent during their participation. They were given 8 total pain-trials at the placebo temperature to prevent conditioning. Expected levels of pain intensity, measured on the same scale that was used to rate experimental pain, was assessed from all groups before this session and pain intensity ratings were assessed after each pain trial.

Stage 3: First Placebo

Participants in the placebo informed and uninformed groups were given 4 trials with the placebo cream. Pain intensity ratings were assessed after each pain trial. At the end of this stage, bar graphs of the pain responses were presented to the subject. In this graph, two bars represented the average pain ratings reported with the placebo cream and average ratings without.

Those in the placebo informed group were told that they received a placebo cream and that the reduction in pain ratings with the placebo reflects their placebo response. Those in the placebo uninformed group were told that, as expected, the cream was successful in reducing their pain levels (or unsuccessful if a significant change was not

observed). Those assigned to the repeated baseline condition were also provided with a graph of their pain ratings during the baseline and the first testing stage.

Stage 4: Second Placebo

Those in the placebo informed group were correctly told that they had received a placebo cream and would now receive the actual cream the study is testing. However, they again received the placebo cream. Those in the placebo uninformed group were told that the cream is being tested again, and again received the placebo cream. Those assigned to the repeated baseline condition were told that they would be tested again with the control cream. All groups again participated in 4 trials. Pain intensity ratings were assessed after each pain trial. Mood, trust of experimenters, and likeability of experimenters were assessed from all groups. At the end of this stage, the actual purpose of the experiment was explained to the participants in a debriefing.

CHAPTER 3
RESULTS

Verification of the Placebo Effect

The pain ratings from the repeated baseline group were compared to the pain ratings from the placebo informed and uninformed groups to verify that reductions in pain from the baseline to the first and second placebo testing were the result of the placebo manipulation and not simply habituation with time or repeated testing. To assess this possibility, the pain ratings from the placebo uninformed and informed groups were collapsed and compared with the pain ratings from the repeated baseline group.

A mixed model repeated measures ANOVA, with time as a within subject factor (3) and group as a between subject factor (2) was performed. Results indicated a significant main effect for group ($F(1,75)= 565.957$, $p<0.001$), and for time ($F(2,150)=20.042$, $p<0.001$), and a significant time (baseline, first testing, second testing) by group (placebo informed plus uninformed and repeated baseline) interaction ($F(2, 150)=5.379$, $p=0.006$). Decomposition of the interaction revealed that the main effect for time was not significant for the repeated baseline group ($F(2,32)=2.512$, $p>0.05$, partial eta squared=0.136) whereas it was significant for the collapsed placebo informed and uninformed groups ($F(2,118)=47.417$, $p<0.001$, partial eta squared=0.446), confirming that the change in pain ratings were, for the most part, the result of our manipulation. The effect size (Cohen's d) for the change in pain ratings from the baseline to the first placebo was 0.99 for the collapsed placebo informed and uninformed group whereas it was 0.29 for the repeated baseline group. (Figure 3-1)

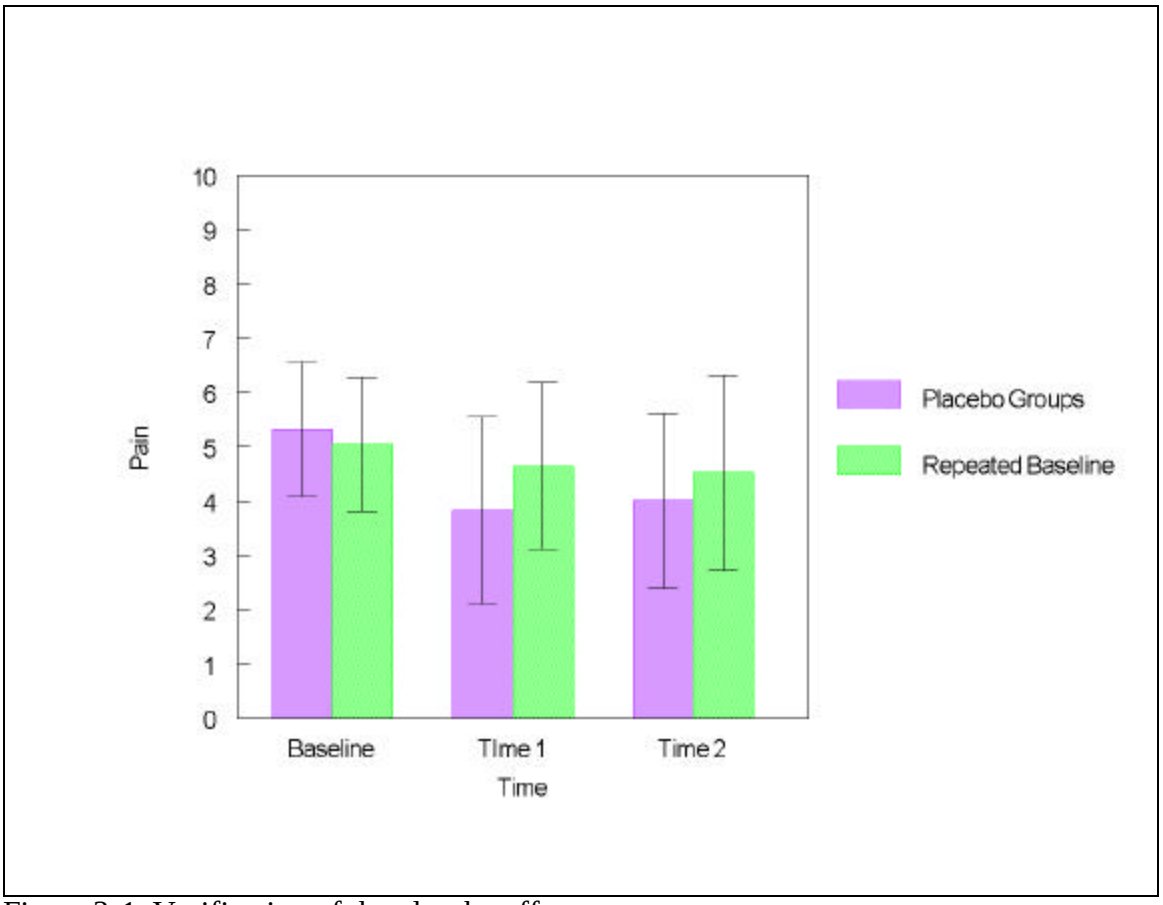

Figure 3-1. Verification of the placebo effect.

The level of a participant's placebo response was calculated by subtracting their pain ratings at the first placebo testing from their pain ratings at baseline. Only those who demonstrated a placebo response (i.e., difference scores > 0) were included in the following analyses. Fifty participants out of the total 60 tested in the placebo informed and uninformed conditions fit this requirement.

Pain Ratings

We wanted to determine whether there was a difference in the placebo effect between the placebo informed and uninformed groups at the first placebo (after conditioning) and second placebo testing (after placebo response information presentation). A repeated measures mixed-model ANOVA revealed a non-significant group (placebo informed and uninformed) by time (baseline, first placebo, and second

placebo) interaction (F(2,96)=0.218, p>0.05). Test of within-subjects effects revealed a significant main effect across the three time points (F(2,96)=99.699, p<0.001). The pain ratings from baseline (M=5.253, SD=1.283) to first placebo (M=3.289, SD=1.297) decreased significantly (F(1,48) =135.136, p<0.001) whereas the ratings between first placebo and second placebo (M=3.600, SD=1.457) significantly increased (F(1,48)=7.643, p=0.008). The test of between-subject effects showed that there was no significant overall difference between the two information groups (F(1,48)=0.528, p>0.05). (Figure 3-2)

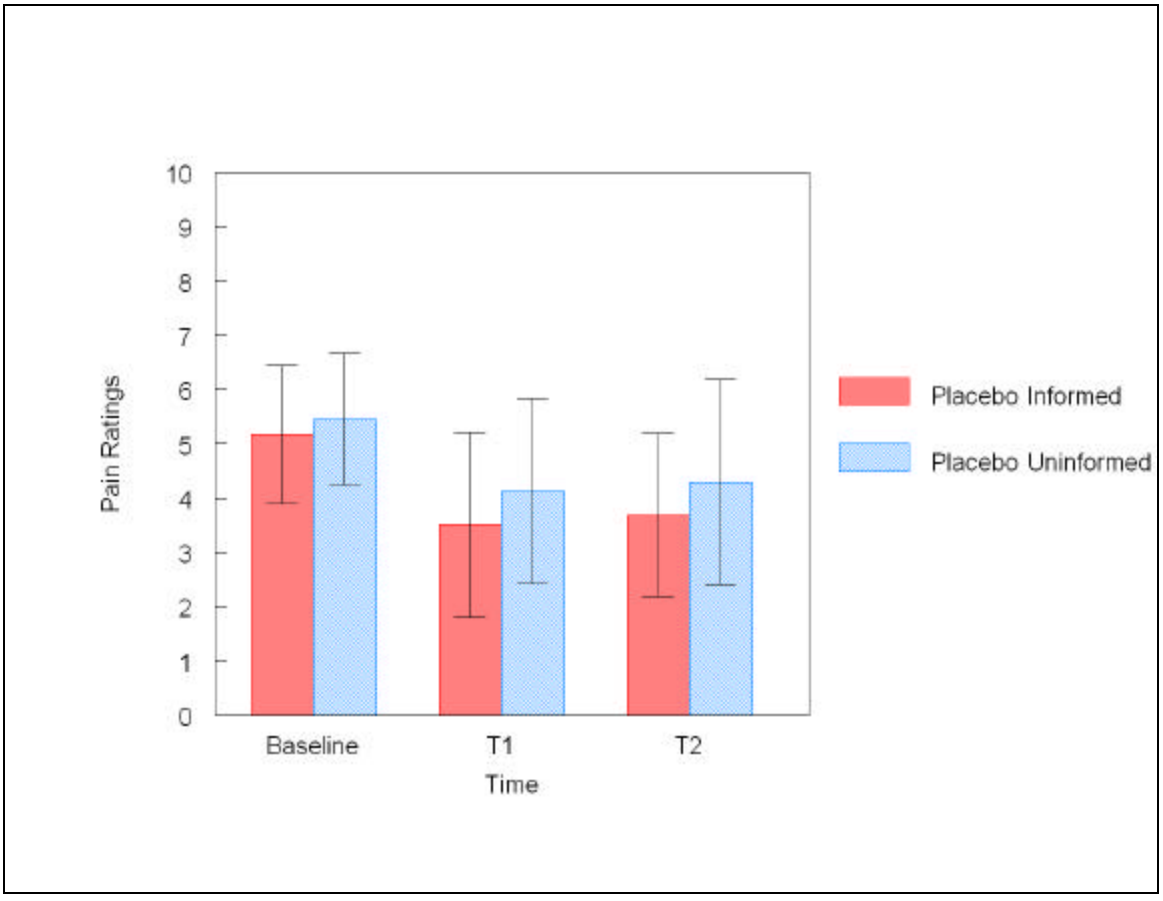

Figure 3-2. Pain ratings at baseline, time 1 and time 2 for the placebo informed and uninformed groups.

Mood

A series of mixed-model ANOVAs was conducted to examine the time (pre and post) by group (placebo informed and uninformed) interaction and main effects for group and time for mood. No significant interactions were found for depression, anxiety, frustration, anger, or fear. A test of within-subjects effects revealed no significant changes for time in depression and anger from pre to post. However significant improvements (main effects for time) were found for anxiety, frustration, and fear. In addition, the main effects for group (placebo informed and uninformed) were not significant for depression ($F(1,48)=0.052$, $p>0.05$), anxiety ($F(1,48)=0.415$, $p>0.05$), frustration ($F(1,48)=0.955$, $p>0.05$), anger ($F(1,48)=0.596$, $p>0.05$), and fear ($F(1,48)=0.799$, $p>0.05$). These results show there were significant general improvements over time for anxiety, frustration and fear, but there were no significant group differences for any of the mood variables. (Table 3-1)

Table 3-1. Mood mixed-model ANOVA results.

Mood	Time by condition interaction	Pre-post change (within subjects)	Pre	Post	Pre-post change (Cohen's d)
Depression	$F(1,48)=0.761$ $p>0.05$	$F(1,48)=0.322$ $p>0.05$	M=0.733 SD=1.630	M=0.690 SD=1.559	0.027
Anxiety	$F(1,48)=0.501$ $p>0.05$	$F(1,48)=10.701$ $p=0.002$*	M=2.078 SD=2.293	M=1.514 SD=1.952	0.265
Frustration	$F(1,48)=0.076$ $p>0.05$	$F(1, 48)=6.693$ P=0.013*	M=1.696 SD=2.389	M=1.114 SD=1.917	0.269
Anger	$F(1,48)=0.006$ $p>0.05$	$F(1,48)=.896$ $p>0.05$	M=0.783 SD=2.006	M=0.639 SD=1.732	0.077
Fear	$F(1,48)=1.667$ $p>0.05$	$F(1,48)= 8.194$ $p=0.006$*	M=0.997 SD=1.863	M=0.538 SD=1.463	0.274

Attitudes

A series of mixed-model ANOVAs were conducted to examine the time (pre and post) by group (placebo informed and uninformed) interaction and main effects for group

and time for the different attitude variables (the participants' likelihood of using medical treatments to treat pain, likelihood of using non-medical treatments to treat pain, likelihood of future participation in studies in general, likelihood of future participation in studies conducted in our lab, likeability of experimenters in general, likeability of experimenters in our lab, trust of experimenters in general, and trust of experimenters in our lab). No significant time by group interactions were found for any of the attitude variables. Moreover, a test of within-subjects effects revealed no significant main effects for time. Similarly, a test of between-subjects effects found no main effects for group in the participants' likelihood of using medical treatments to treat pain ($F(1,48)=1.004$, $p>0.05$), likelihood of using non-medical treatments to treat ($F(1,48)=1.758$, $p>0.05$), likelihood of future participation in studies in general ($F(1,48)=0.539$, $p>0.05$), likelihood of future participation in studies conducted in our lab ($F(1,48)=1.342$, $p>0.05$), likeability of experimenters in general ($F(1,48)=1.345$, $p>0.05$), likeability of experimenters in our lab ($F(1,48)=2.704$, $p>0.05$), trust of experimenters in general ($F(1,48)=1093$, $p>0.05$), and trust of experimenters in our lab ($F(1,48)=3.427$, $p=0.07$). (Table 3-2)

Table 3-2. Attitude mixed-model ANOVA results.

Variable	Time by condition interaction	Pre-post change (within subjects)	Pre	Post
participants' likelihood of using medical treatments to treat pain	F(1,48)=0.423 p>0.05	F(1, 48)=0.929 p>0.05	M=3.907 SD=2.954	M=4.196 SD=2.826
likelihood of using non-medical treatments to treat pain	F(1,48)=1.357 p>0.05	F(1,48)=3.251 p>0.05	M=2.110 SD=2.881	M=2.528 SD=3.096
likelihood of future participation in studies in general	F(1,48)=1.067 p>0.05	F(1,48)=0.371 p>0.05	M=6.450 SD=2.594	M=6.312 SD=2.588
likelihood of future participation in studies conducted in our lab	F(1,48)-0.155 p>0.05	F(1,48)=1.897 p>0.05	M=5.641 SD=2.985	M=6.086 SD=2.922

likeability of experimenters in general	F(1,48)=0.403 p>0.05	F(1,48)=0.882 p>0.05	M=6.747 SD=2.226	M=6.926 SD=2.393
likeability of experimenters in our lab	F(1,48)=0.003 p>0.05	F(1,48)=0.456 p>0.05	M=7.915 SD=1.889	M=7.721 SD=2.047
trust of experimenters in general	F(1,48)=0.016 p>0.05	F(1,48)=.827 p>0.05	M=6.555 SD=2.400	M=6.367 SD=2.477
trust of experimenters in our lab	F(1,48)=0.914 p>0.05	F(1,48)=2.213 p>0.05	M=7.752 SD=1.941	M=7.472 SD=2.018

Expectation

Expected pain levels were rated before the baseline, first test, and second test. A repeated measures mixed-model ANOVA revealed a non-significant group (placebo informed and uninformed) by time (baseline, before first placebo, and before second placebo) interaction ($F(2,96)=2.273$, $p>0.05$). The main effect for group was also not significant ($F(1,48)=1.148$, $p>0.05$). However, the main effect for time showed significant change over time ($F(2,96)=88.626$, $p<0.001$). Expectation for pain decreased significantly from baseline ($M=4.866$, $SD=1.082$) to the first placebo ($M=2.376$, $SD=1.326$; $F(1,49)=144.855$, $p<0.001$) and decreased significantly from baseline to the second placebo ($M=2.804$, $SD=1.328$; $F(1,49)=136.710$, $p<0.001$), but significantly increased from the first placebo to the second placebo ($F(1,49)=5.974$, $p=0.018$). (Figure 3-3)

Simple linear regressions were employed to determine whether changes in expected pain levels from baseline to the first placebo test and from baseline to the second placebo test predicted the first or second placebo responses (baseline minus first placebo pain testing ratings) and second (baseline minus second placebo pain testing ratings) placebo response. Change in expected pain intensity from baseline to the first test (baseline expectation minus pre-first test expectation) did not significantly predict the first placebo response ($F(1,48)=2.659$, $p>0.05$, $r^2=0.052$) or the second placebo response

(F=(1,48)=2.732, p>0.05, r^2=0.026). However, change in expectation from baseline to the second test (baseline expectation minus pre-second test expectation) did significantly predict the second placebo response (F(1,48)=6.098, p=0.017, std. beta=0.161, r^2=0.113), but not the first placebo response (F=(1,48), F=3.305, p>0.05, r^2=0.045).

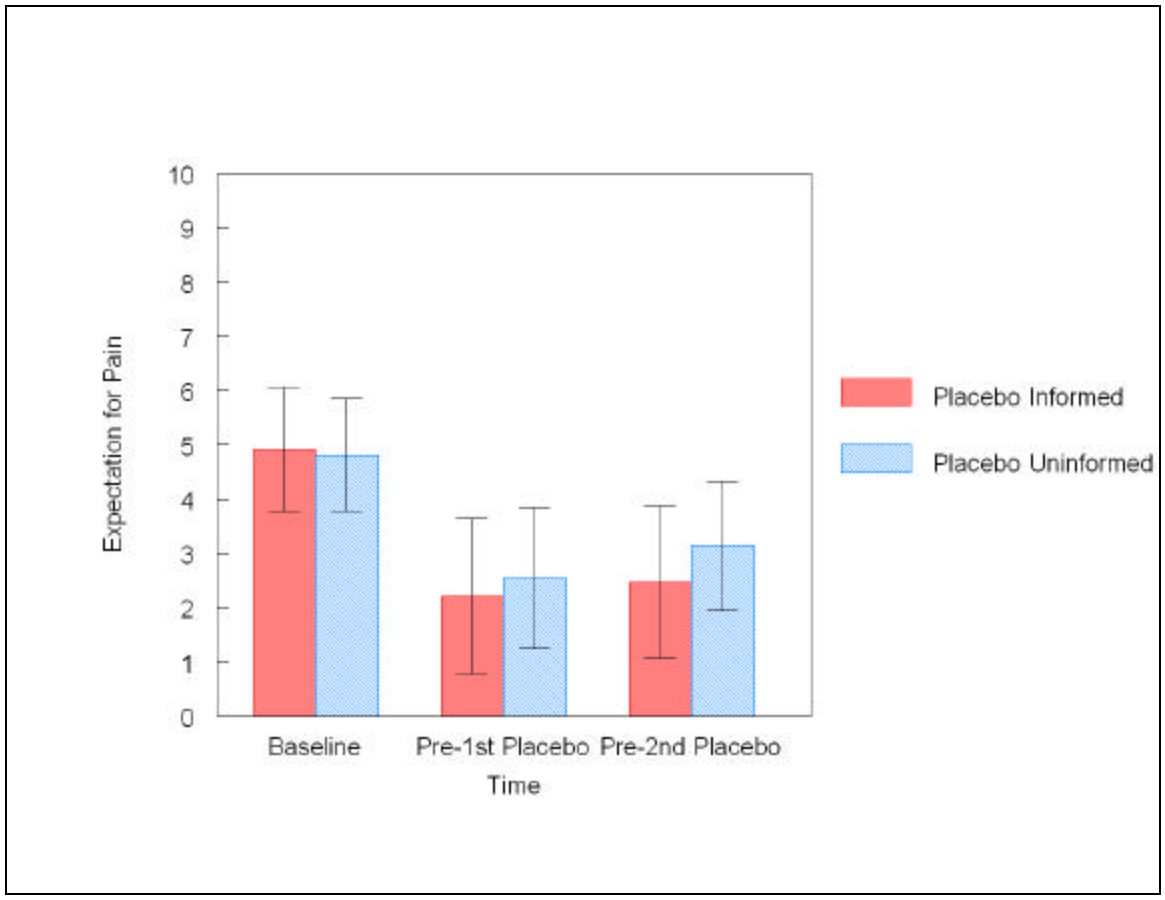

Figure 3-3. Expectation for pain ratings at baseline, pre-first placebo and pre-second placebo for the placebo informed and uninformed groups.

Desire for Pain Relief

Desire for pain relief was assessed at two time points. The first was just before the conditioning trials and the second was just after showing pre to post first placebo pain ratings to the participants and just prior to administering the second placebo. A mixed-model ANOVA revealed a non-significant group (placebo informed and uninformed) by time (before conditioning, and before second placebo) interaction (F(1,47)=1.074,

p>0.05). Additionally, the main effect for group was also not significant (F(1,47)=0.634, p>0.05). However, there was a significant main effect for time (F(1,47)=7.652, p=0.008) from pre-conditioning (M=5.9776, SD=2.670) to pre-second testing (M=5.259, SD=2.989). (Figure 3-4)

Simple linear regressions were employed to determine whether the change in desire predicted the first (baseline minus first placebo pain testing ratings) and second (baseline minus second placebo pain testing ratings) placebo responses. The change in desire significantly predicted the first (F(1,47)=6.791, p=0.012, std. beta=0.355, r^2=0.126) and second (F(1,47)=9.168, p=0.004, std. beta=0.404, r^2=0.163) placebo response.

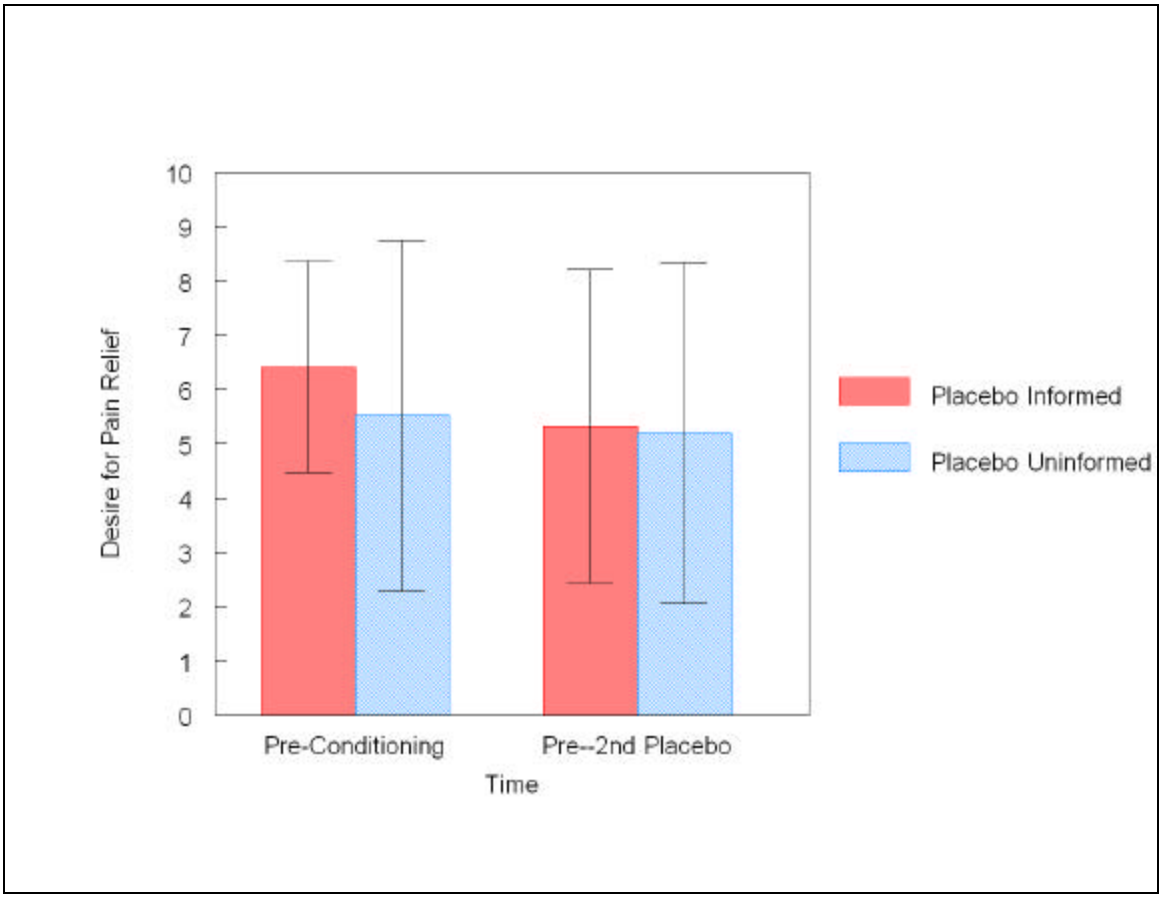

Figure 3-4. Desire for pain relief at pre-conditioning and pre-second placebo for the placebo informed and uninformed groups.

Expectation and Desire Interaction

To predict the first placebo effect, the change in expectation and desire from pre-conditioning to just prior to the 2nd placebo were entered together in the first step of a hierarchical regression. In the first model, both changes in expected pain intensities (t=2.233, std. beta=0.260, p=0.030) and desire (t=3.436, std. beta=0.400, p=0.001) significantly predicted the first placebo effect both independently and together ($F(2,56)=17.826$, $p<.001$, $r^2=0.264$). When the expectation and desire interaction (i.e., product) was added in the final model of the hierarchical regression, the interaction was not significant (t=-0.365, std. beta= -0.045, p>0.05); however, the complete model ($F(3,55)=11.965$, $p=0.001$, $r^2=0.265$) and both expectation (t=2.238, std. beta=0.263, p=0.029) and desire (t=3.358, std. beta=0.414, p=0.001) remained significant.

Predicting the second placebo effect, again the change in expectation and desire from pre-conditioning to the 2nd placebo were entered together in the first step of a hierarchical regression. In the first model, both changes in expectation (t=2.847, std. beta=0.320, p=0.006) and desire (t=3.598, std. beta=0.405, p=0.001) significantly predicted the first placebo effect both independently and together ($F(2,56)=17.212$, $p<0.001$, $r^2=0.312$). When the expectation and desire interaction was added in the final model of the hierarchical regression, the interaction was not significant (t=-0.609, std. beta=-0.072, p>0.05); however, the complete model ($F(3,55)=11.645$, $p<0.001$, $r^2=0.316$) and both expectation (t=2.871, std. beta=0.326, p=0.006) and desire (t=3.593, std. beta=0.427, p=0.001) remained significant.

Somatization

Two measures of somatization were administered, the PILL and the IAS. The total scores of the measures were found to be significantly correlated (r=0.392, p=0.007) with

each other. The PILL ($F(1,46)=4.215$, $p=0.046$) was predictive of a participant's first placebo response explaining 8.4% of the variance. However, the PILL was not predictive of a participant's second placebo response ($F(1,46)=3.671$, $p>0.05$) when entered in a regression.

The IAS total score was not predictive of a participant's first ($F(1,48)=0.758$, $p>0.05$) or second ($F(1,48)=0.161$, $p>0.05$) placebo response. Given the multifactorial nature of the IAS, the 4 factors proposed by Stewart et al. (2000) were independently entered in a regression. The factors fear ($F(1,48)=0.708$, $p>0.05$), behavior ($F(1,48)=0.284$, $p>0.05$), beliefs ($F(1,48)=1.480$, $p>0.05$) and effects ($F(1,48)=1.119$, $p>0.05$) did not significantly predict a participant's first placebo response. In addition, fear ($F(1,48)=1.119$), $p>0.05$), behavior ($F=1,48)=3.328$, $p>0.05$), beliefs ($F(1,48)=0.766$, $p>0.05$) and effects ($F(1,48)=0.444$, $p>0.05$) did not significantly predict a participant's second placebo response.

Sex Differences

A 2x2 ANOVA was used to analyze whether there were any significant differences between men and women in their ability to get a first or second placebo response. The interaction between sex and information condition ($F(1,46)=0.119$, $p>0.05$) in the participant's ability to get a first placebo response was not significant. Additionally, there was neither a main effect for sex ($F(1,46)=0.779$, $p>0.05$) nor information group ($F(1,46)=0.411$, $p>0.05$). Similarly, the interaction between sex and information condition in the participant's ability to get a second placebo response was also non-significant ($F(1,46)=0.134$, $p>0.05$). Also, the main effects for sex ($F(1,46)=1.499$, $p>0.05$) and information condition ($F(1,46)=0.428$, $p>0.05$) were both not significant.

CHAPTER 4
DISCUSSION

The ethics of placebo use has been debated since discovery of the phenomena. Under the heading, "No place for placebos when treating pain," Dr. Sullivan (2004) wrote, "this deception of the patient is damaging and unjustified." Alternatively, Dr. Oh (1994) concludes, "in appropriate patients, doctors might consider giving a placebo when active treatment is both costly and likely to confer only marginal or transient benefit." While neither extreme may be the answer, this debate has persisted without a good understanding of the result of placebo use. There has yet to be a study that examines the aftereffect of individuals discovering that they experienced a placebo response on their future ability to experience a placebo response. The main goal of this study was to explore the effect of such information on pain response.

We discovered that there was no difference in future pain responding between participants who were told that they experienced a placebo response versus those who were not. Interestingly, the placebo effect persisted when a second placebo cream was applied even after participants were told that the first cream used in the study was a placebo. Although the strength of that second placebo was slightly reduced, approximately 84% of the original placebo effect remained. Next, we wanted to explore the effect of feedback of personal placebo information on mood.

A previous pilot study (Chung, Price, Verne, Perlstein, Craggs, & Robinson, 2006) found no detrimental effects when information was revealed to patients with irritable bowel syndrome about their pain reduction from a placebo. We replicated this finding in

a more general population. This study corroborated that revelation of an individual's placebo response does not appear to cause adverse effects on mood. While we found no change in depression and anger; curiously, we found that participants' anxiety, frustration and fear improved at the end of the study regardless of the information provided during the study. Since there were no differences between the two information groups, it is possible the improvement is a result of repeated testing or related to the participants' reaction to simply completing the study. If the improvements were related to procedures or information provided in the study, the exact nature and mechanism remains unknown. Nevertheless, the lack of worsening mood is notable.

Similar to mood, attitudes about the likelihood of using medical and non-medical treatments for pain, likelihood of participating in future studies, likeability of experimenters and trust of experimenters were assessed both before and after the study. Despite the level of deception involved in participating in the placebo information condition, there were no differences between the placebo informed and uninformed groups in their attitudes. This suggests that participants may not change their attitudes about pain treatment, research participation or feelings toward experimenters after participating in a study involving placebo use with experimental pain. Moreover, attitudes seem unaffected by learning that the pain reduction reflected a placebo response.

Given that previous mood, attitudes, and pain responding do not appear to be affected by placebo information, what role does expectation and desire for pain relief have on the placebo effect in the context of providing personal placebo information? Similar to the findings regarding pain ratings, there were no differences between the two information groups in their expected pain intensities. The change in expected pain

intensities from baseline to the first test was not related to the first or second placebo response. However, the change in expectation from baseline to the second test was significantly predictive of the second placebo response, but not the first placebo response. Examining the concept of desire, similar to expectation, there were no differences between the two groups in their desire for pain relief. However, the change in desire for pain relief from before the conditioning session did significantly predict a participant's first and second placebo response. In addition, the interaction between desire and expectation did not significantly predict the first or second placebo effect.

Previous studies have suggested that desire for pain relief may be more of a factor in clinical pain where pain is threatening or has uncertain duration. Furthermore, Price et al. (Price, Milling, Kirsch, Duff, Montgomery, & Nicholls, 1999) found that expectation for pain but not desire was associated with the magnitude of placebo analgesia. However, although our study was conducted in an experimental setting where the participants were informed about the number of pain testing stages (potentially increasing predictability), desire was a more consistent predictor of the placebo response than expectation. It will be important to further explore the relationship between expectation, desire and pain responding in future studies.

Next, we examined the role of personal characteristics, somatization and sex, in participants' placebo responses and maintaining those the response after feedback about their placebo responses. Two measures of somatization, the PILL and the IAS were used to examine this relationship. While the IAS was not significantly predictive of placebo responding at any level, the PILL did predict participants' first placebo responses, but not the second placebo responses. We can speculate why the two measures may have

produced different results. The IAS is a face valid measure that asks about worries, behaviors and beliefs about illnesses. On the other hand, the PILL is a symptom checklist that asks participants about their experience with various symptoms. While it is assumed that the PILL measures an element of somatic focus, exactly what the questionnaire measures remains unknown. The PILL may be measuring something more than somatization (such as anxiety) that enhanced its sensitivity to predict placebo responders. Further studies are needed to explore the relationship between PILL and the ability to experience a placebo response.

Finally, we examined sex differences in the ability to experience a placebo response. We found no differences between men and women's first or the second placebo response. These results suggest that characteristics such as somatic focus may be related to a participant's placebo response, but we found no evidence of any differences in placebo responding or the effect of placebo response information between the sexes.

Conclusions and Future Directions. The lack of differences in pain responding and in worsening mood has noteworthy implications for future placebo studies. These results suggest that placebo use in experimental settings may not result in detrimental effects. While our study demonstrated that a double placebo design is feasible to examine the role of a placebo use on a second placebo administration, we do not know if our findings will generalize to clinical setting. Future studies should examine the effect of placebo use with clinical populations. Furthermore, we found that the placebo effect significantly decreased during the second placebo administration regardless of the assigned information condition. The reason for this is unclear. One possibility is that any information decreases the placebo effect. It is also possible that with time, the placebo

effect will be reduced. If so, it would be important to explore the rate of decay and the variables related to this decay. Such information may assist in the development of protocols that maximizes the magnitude and longevity of placebo effects.

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