

Focused Review

Placebo and Nocebo in Interventional Pain Management: A Friend or a Foe – Or Simply Foes?

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The present evidence illustrates that the placebo effect depends on a variety of neurochemical and neurophysiological mechanisms, which are measurable and modifiable. However, the placebo response is inexorably tied to the treatment context. All medical treatments take place in a particular context; this context includes the therapist's attitudes, psychosocial factors affecting the therapeutic relationship, and the patient's mindset. Therapeutic efficacy at least in part is attributable to the concordance between the proposed treatment and the patient's belief system. It is this fraction of the therapeutic response that is commonly called the placebo effect. More formally, the placebo effect is defined as that part of the therapeutic response that is not attributable to the properties of active ingredients.

A proposed model of the placebo effect includes a complex reaction with induction, psychophysiological mediators, neurobiological mediators, and actualization of effects. Similarly, nocebo hyperalgesia is also explained by neurobiological mechanisms resulting in anxiety and nocebo hyperalgesia. Functional neuroanatomy of placebo indicates an anticipation phase and modulation phase or placebo response.

In modern medicine it is well recognized that the treatment effect of many active interventions is related to both an active treatment component and the placebo component. Thus, clinical implications are enormous as such placebo analgesia and nocebo hyperalgesia are not simply response biases. Instead, they are the product of neurophysiological processes that modulate the integration of the nociceptive signals throughout the central nervous system. Thus, it has been suggested that clinicians should not try to avoid the placebo effect. On the contrary, they should try to potentiate it, since this is a very important clinical implication.

From the research perspective, the emerging knowledge of placebo continues to cast doubts on the appropriateness of the double-blind placebo-control design in assessing efficacy of treatment - specifically involving interventional techniques or surgery. The research setting itself may introduce nocebo hyperalgesia.

Key words: Placebo, placebo analgesia, placebo treatment, placebo effect, nocebo, nocebo hyperalgesia, psychophysiological mediators, neurobiological mediators, inert agent

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Placebo effect is a widespread and universal phenomenon, which has accompanied the practice of medicine from its very beginnings (1). Similarly, nocebo effects, the development of adverse events or worsening of a condition after the administration of a placebo or a treatment, is also fairly common (2). Historically, placebo and nocebo effects have been thought of as the result of biases in subjective symptom reporting (3). However, this interpretation has now been challenged by increasing evidence that these effects are mediated by specific neural mechanisms (4). All medical treatments take place in a particular context; such a context includes attitudes of the physician, psychosocial factors affecting the therapeutic relationship, and the patient's expectations, desires, and hopes. Accumulating evidence indicates that, at least in some circumstances, therapeutic efficacy is partly attributable to the concordance between the proposed treatment and the patient's belief systems (5). It is this fraction of the therapeutic response that is commonly called the placebo effect. More formally, the placebo effect is defined as the part of the therapeutic response that is not attributable to the properties of active ingredients.

Placebo has been considered as something that stands in the way of "proper medicine" whose rule is only to serve as a foil against which effective ("real") treatment is being tested (6). Thus, placebo remains a poorly understood phenomenon, if not mysterious, mystical, and surrounded by confusing terminology. In clinical trials, placebo is usually considered a nuisance, a tiresome and expensive artifact (7).

The methodologists routinely demand and researchers routinely attempt to include placebo groups in every major clinical trial, without knowing the mechanism of placebo itself and consequently not knowing what happens in the placebo control group. Thus, in clinical practice, placebo has become a much debated issue that provokes discomfort, disillusion, and is often confused with quackery and elicits emotions based on its misinterpretations and applications in clinical medicine (5,8-16).

While placebo analgesia essentially represents a phenomenon when a non-analgesic substance (or action) evokes a reduction in pain sensation, perception, and/or cognitive responses, by contrast, nocebo activity represents a hyperalgesic phenomenon opposite that of placebo analgesia, characteristically considered to be a worsening or consistent lack of change of symptoms after the administration of some agent known to be effective (17).

Placebo effect has been extensively studied with regards to specific mechanisms at the biochemical, cellular, and anatomical levels in different systems and conditions, such as pain, motor disorders, depression, and immune-endocrine responses (4,18-20). However, most of the knowledge about the placebo effect comes from the field of pain, in which both a neuropharmacological approach with opioid antagonists and brain imaging techniques have been used (19). In contrast, the neurobiological mechanisms of the nocebo effect have been less investigated, despite their being as interesting as those of the placebo effect and extremely useful in pain research. In fact, it was shown that gentler, more reassuring words improve the subjective experience during invasive procedures (21).

1.0 HISTORICAL ASPECTS AND DEFINITIONS

The history of placebo effects dates back to 1811 when it was described by Robert Hooper in *Quincy's Lexicon-Medicum* as "an epithet given to any medicine adapted more to please than benefit the patient (22)." The word placebo, Latin for "I shall please," dates back to a Latin translation of the Bible by Jerome (23). It first started to be used in a medicinal context in the 18th century, but in a different sense to that used at present as an ineffective treatment. In 1975 it was defined as a "common place method or medicine" and in 1981 it was defined as "any medicine adapted more to please than to benefit the patient," sometimes with a derogative implication (24), but not with the implication of no effect (25).

Placebos were widespread in medicine until the 20th century and they were sometimes endorsed as necessary deceptions (26). In one of the early descriptions in 1903, Richard Cabot said that he was brought up to use placebos (26), but he ultimately concluded by saying that "I have not yet found any case in which a lie does not do more harm than good (27)." In 1961, the much quoted Henry Beecher, a surgeon (28), found that patients of surgeons he categorized as enthusiasts relieved their patients' chest pain and heart problems more than skeptic surgeons (27,28). In the practice of medicine, many agree with Ambrose Paré who had expressed that a physician's duty was to "cure occasionally, relieve often, console always." However, this philosophy induces placebo effect and invalidates all types of observations and research based on misunderstanding of methodology and the context of placebo effect.

In the 1930s, 2 groups of investigators, using 90 participants in the first study, (29) and 700 in the sec-

ond study, (30) published results which compared the outcomes from the administration of an active drug and a dummy simulator which was termed a placebo in the same trial. Neither experiment displayed any significant difference between drug treatment and placebo treatment causing the researchers to conclude that the drug exerted no specific effects in relation to the conditions being treated.

In 1946, the Yale biostatistician and physiologist, Jellinek (31) was the first to mention either a placebo reaction or a placebo response. He used the words response to placebo, responded to placebo, reaction to placebo, reactors to placebo, placebo response, and placebo reaction, all interchangeably.

The first use of the term placebo effect is attributed to Henry K. Beecher's 1955 paper "The Powerful Placebo (32)." He was discussing placebo effects when he was contrasting them with drug effects. Subsequently, he also spoke of placebo reactors and placebo non-reactors.

The word "obecalp," placebo spelled backwards, was coined by an Australian physician in 1998 when he recognized the need for a freely available placebo (33). Consequently, this word has been used to make prescribing of fake medicines less obvious to the patient.

Thus, placebo effect is defined as the response of a subject to a substance or to any procedure known to be without any therapeutic effect for the specific condition being treated (34). However, in modern medicine, the placebo effect is defined as the part of the therapeutic response that is not attributable to the properties of active ingredients (5). Further, this is also distinctly different from placebo treatment, since placebo effect or response refer to an outcome, whereas the placebo treatment refers specifically to an inert agent or intervention.

Nocebo is a term loosely used to describe the clinical deterioration that accompanies inert treatments or, in pain research, the effect caused by expectations of hyperalgesia or increased levels of pain (5).

The term nocebo, Latin for "I will harm," was chosen by Walter Kennedy in 1961, to denote the counterpart of one of the more recent applications of the term placebo, Latin for "I will please (26)." It meant that placebo is a drug that produces a beneficial, healthy, pleasant, or desirable consequence in a patient as a direct result of that patient's benefits and expectations.

Thus, nocebo is the phenomenon that is the opposite of placebo (17,34,35). A true nocebo effect is present if a negative effect occurs in expectation of a nega-

tive or harmful occurrence (36). It is also important to note that expected hyperalgesia can develop without the administration of an inert substance. Further, hyperalgesia may also include instances where someone has just been given an unfavorable diagnosis or has just been warned that a painful stimulus is imminent (37).

In addition, in modern medicine nocebo hyperalgesia is also represented as a phenomenon opposite that of placebo analgesia, with worsening or consistent lack of change of symptoms after the administration of some agent known to be effective.

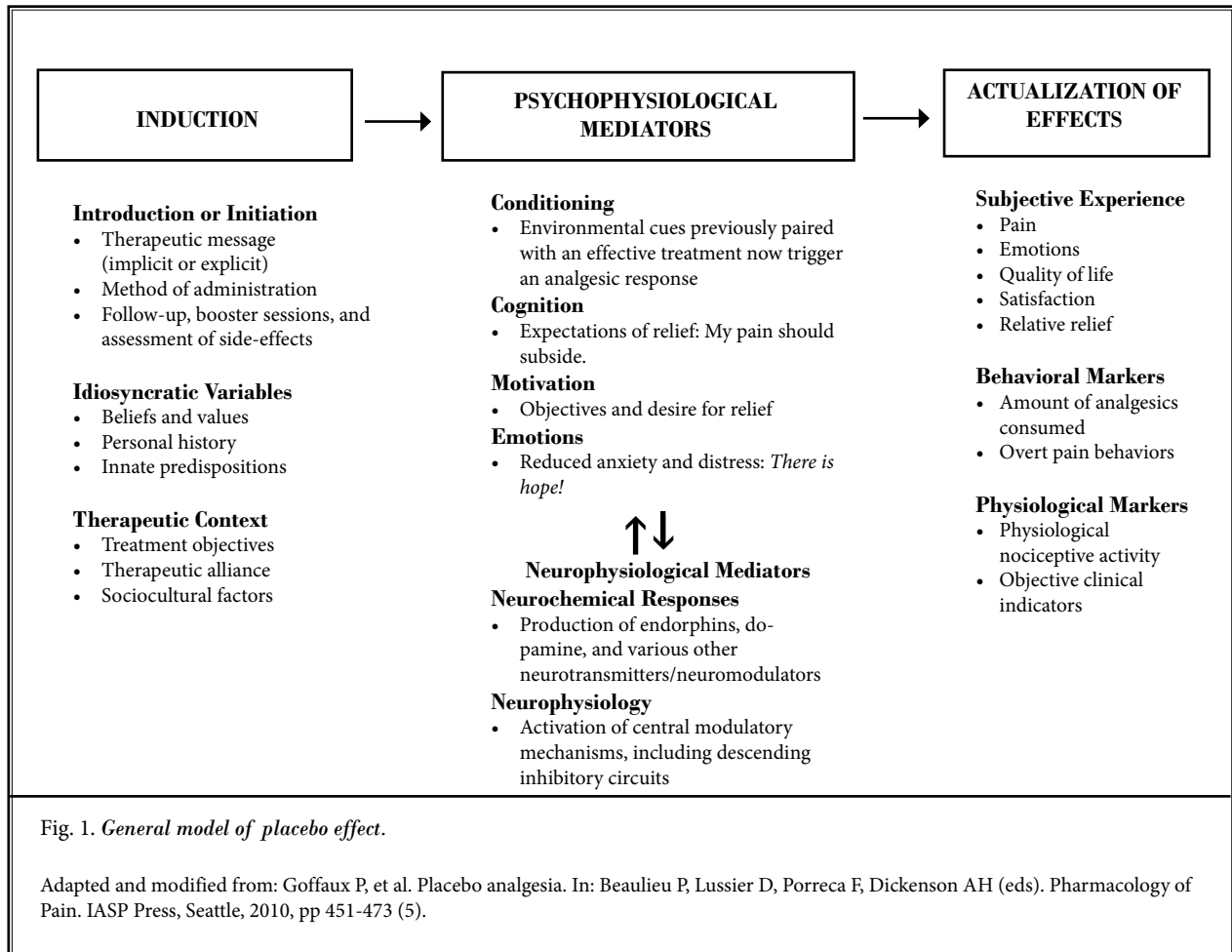
While the term nocebo response originally only meant an unpredictable, unintentional belief-generated injurious response to an inert procedure, subsequent emerging evidence has even labeled some drugs as nocebo drugs, meaning that the terms nocebo drugs and nocebo response have been changed to believe that an intentional, entirely pharmacologically generated and quite predictably injurious outcome has ensued from the administration of an active (nocebo) drug.

2.0 PHYSIOLOGIC MECHANISMS

Placebo and nocebo mechanisms leading to multiple responses are complex, involving psychophysiological and neurobiological mediators and responses. Goffaux et al (5) have established a general model of the placebo effect and also have described modeling of nocebo effects.

2.1 General Model of the Placebo Effect

Goffaux et al (5) modeled the placebo effect according to its induction, psychophysiological mediation, and actualization as illustrated in Fig. 1. The induction phase includes the presence of conditions that favor placebo effects. These include therapeutic message; method of administration; follow-up and booster sessions; assessment of side effects in the introduction or initiation followed by idiosyncratic variables including beliefs and values, personal history, and innate predisposition; as well as therapeutic context involving treatment objectives, therapeutic alliance, and sociocultural factors. The treatment ritual providing a therapeutic message is an excellent example; however, the significance depends on the individual and cultural context. Studies that have examined the importance of such rituals revealed that the administration of a treatment, as well as the message associated with it, shape the magnitude of placebo response. Essentially, a reassuring message such as this treatment is very effective and will bring you quick relief, or this treatment is usually



effective and provides relief for most patients, has been shown to provide positive results (5). In contrast, messages with uncertainty potentially induce hyperalgesia and reduce the desirable impact of placebo effects. This is crucial in conducting randomized double-blind and placebo-controlled trials where participants are informed that they have only a 50% chance of receiving the active treatment, without positive reinforcement (38-40). This certainly will reduce the placebo effect or may even induce the nocebo effect.

In addition, the physical characteristics of a placebo medication, such as its color, size, or quantity, may also contribute to its effectiveness (41,42). By the same token, 2 pills are known to be more effective than one pill (43). Similarly, a "generic" placebo is less effective than a placebo bearing a well-known brand-name analgesic (44). Further, invasive techniques, including the intravenous administration of drugs and surgical treatments,

may produce more pronounced placebo effects than non-invasive treatments, such as topical treatments or oral medications (41,42). Finally, conducting follow-up investigations either as a booster session, or assessment of side effects or effects of toxicity may also contribute to the placebo effect by reinforcing the idea that an active ingredient has been administered (5).

Despite the importance, it is not, in itself, sufficient to assign the entire placebo effect to therapeutic ritual. Multiple variables include that the message has to be directed toward individuals whose characteristics make them amenable to the suggested message, the patient's medical history, and especially his or her previous experience with treatments (5,45). These factors are relevant as the placebo will be more potent if it is congruent with the beliefs, values, and goals adopted by the patient. The treatment history also may affect how the treatment message is interpreted. Thus, the

treatment message must always be interpreted in light of the treatment context and it should be evaluated if the proposed treatment is consistent with the patient's objectives.

The second phase of physiological and psychophysiological responses with a cascade of responses is initiated following the induction (Fig. 1). In this phase, psychophysiological mediators fall into psychological mechanisms and biological mechanisms. Psychological mechanisms include past experience – conditioning effects, expectations regarding treatment, motivational variables – including the desire for relief, and variations in emotional state (e.g., reduction of negative mood). More importantly, these psychological mediators have well-defined neurochemical and neurophysiological intermediaries – biological mechanisms – that are responsible for the emergence of the placebo effect (5).

Once the cascade of physiological responses have taken place, actualization of effects is seen, wherein, placebo responses can be expressed in a large number

of ways and produce quantifiable signs (Fig. 1). These effects include subjective experience including change in pain, emotions, quality of life, satisfaction, and related relief; behavioral markers with amount of analgesics consumed and overt pain behaviors; and physiological markers with physiological nociceptive activity, and objective clinical indicators (5).

2.2 General Model of Nocebo Effect

Multiple hypotheses have been forwarded explaining the nocebo effect including the endogenous substances and psychosocial mediators. Overall, it appears that there is interaction and a link between cholecystokinin (CCK), pain, and anxiety. Based on this philosophy, Goffaux et al (5) illustrated the neurophysiological mechanisms associated with placebo analgesia and nocebo hyperalgesia as illustrated in Fig. 2, based on descriptions of Colloca and Benedetti (20).

Unlike placebo analgesia, which involves the release of endogenous opioids, the nocebo effect acti-

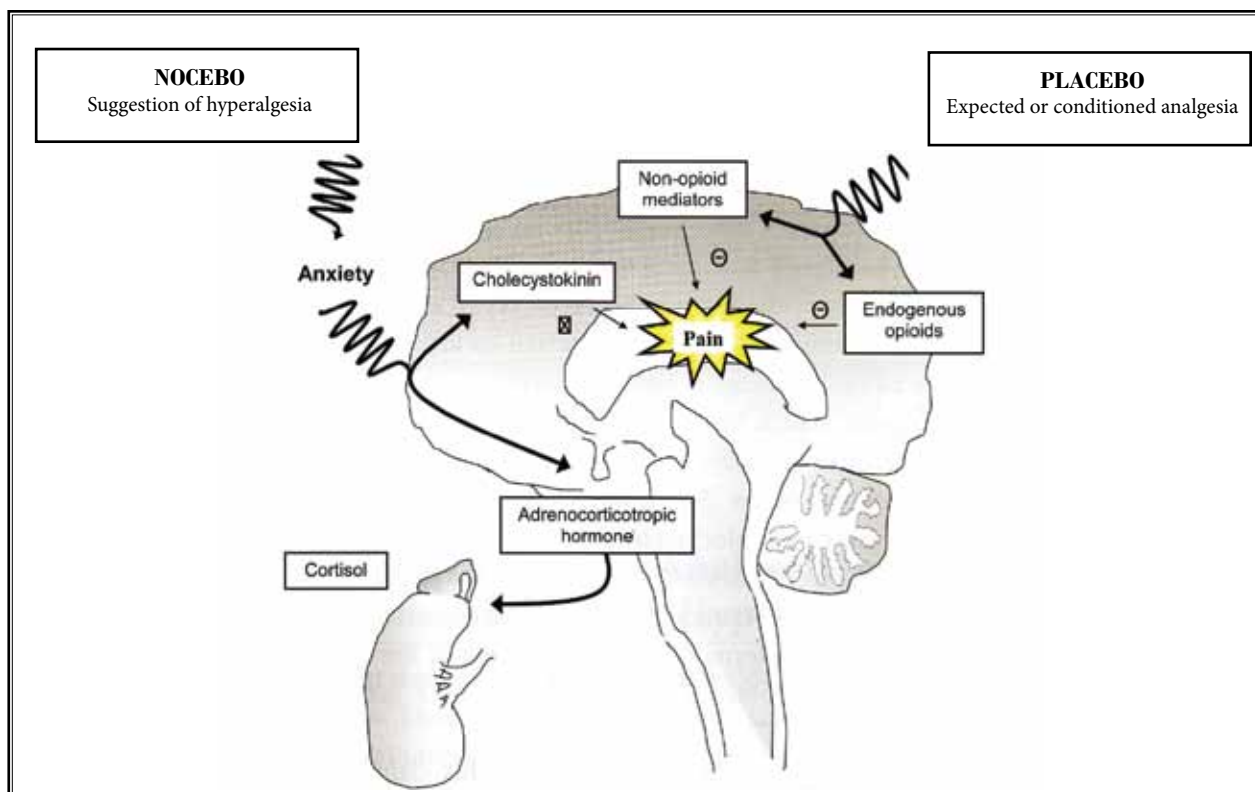


Fig. 2. Neurophysiological mechanisms associated with placebo analgesia and nocebo hyperalgesia.

Adapted from: Goffaux P, et al. Placebo analgesia. In: Beaulieu P, Lussier D, Porreca F, Dickenson AH (eds). Pharmacology of Pain. IASP Press, Seattle, 2010, pp 451-473 (5). Based on: Colloca L, Benedetti F. Placebos and painkillers: Is mind as real as matter? Nat Rev Neurosci 2005; 6:545-552 (20).

vates cholecystokinin (CCK), a neurohormone found in abundance in the central nervous system (46). Further, Benedetti et al (37) found that expectation-induced hyperalgesia can be blocked by administering proglumide, a CCK-receptor antagonist. Multiple authors have described the role of CCK receptors in the nocebo effect, since these receptors are closely associated with the opioid system, displaying similar spinal and supraspinal distribution patterns (47-49). It is also postulated that increased pain during nocebo treatments could depend on increased brainstem activity within the areas involved in the modulation of nociceptive afferents. It is also well-known that the rostroventral medulla contains pronociceptive efferent circuits triggered by a collection of excitatory cells called "ON" and cells (50). Further, since CCK directly activates "ON" cells (51), it is also postulated that the hyperalgesia reported during the nocebo effect depends on the excitatory bulbospinal circuits which facilitate spinal nociceptive activity.

In addition to the CCK involvement and brainstem activity, it has been suggested that the increased pain observed during a nocebo treatment is primarily the result of increased anxiety (37,52). However, this hypothesis is partly based on results from animal research showing that CCK has anxiogenic properties (53,54). Benedetti et al (19), in an evaluation to clarify the link between CCK, pain, and anxiety, evaluated the effect of a nocebo treatment on the levels of adrenocorticotropic hormone (ACTH) and cortisol-2 hormones that are biological markers of the stress response, showing that: 1) the expectation of hyperalgesia increases both pain and blood levels of ACTH and cortisol, 2) perceptual and hormonal changes are reversed by the administration of diazepam, an anxiolytic, and 3) proglumide blocks the increase in pain, but not the increase in ACTH and cortisol. These findings led the authors to propose a model (Fig. 2) whereby expectations of hyperalgesia increase anxiety levels, which in turn heighten the perception of pain and increase the release of stress hormones. However, the impact of anxiety on pain and stress operates via 2 distinct pathways, with CCK receptors being involved only for pain (5).

3.0 PHARMACOLOGY AND FUNCTIONAL NEUROANATOMY

3.1 Placebo Analgesia and Opioids

Neurophysiological mechanisms associated with placebo analgesia were not described until the 1970s,

with the discovery of endogenous peptides that could bind with opioid receptors (55-58). The increased activity in the dorsal part of the prefrontal area of the brain called the anterior cingulate cortex (ACC), during both placebo and opioid-mediated analgesia has been confirmed by Petrovic et al (59). Amanzio and Benedetti (58) showed that the prefrontal activity observed during opioid-mediated analgesia was greatest in individuals who had strong placebo responses, suggesting a close link between the placebo response and the response to opioids. They also discovered that the increased activity in the prefrontal area was accompanied by increased activity in the periaqueductal gray matter-mesencephalic region containing a large number of opioid neurons, which suggests the prefrontal area is probably involved in the regulation of endogenous opioid activity and response to expectations of relief (58).

In further studies (60,61) the researchers attempted to better identify the regions of the brain responsible for the secretion of opioids. In these studies, using a radioactive μ -opioid receptor tracer, they discovered that during expectations of relief, opioid secretion increased significantly in the structures which are part of a complex limbic and paralimbic circuit, playing a key role in a wide variety of human functions and abilities (5,61-65). These include the perception of pain, the anticipation of future events, the assessment of the affective qualities of a given stimulus, motivation, reinforcement, the selection of motor schemas, and even the expression of empathy for the pain of others (5,62-65).

In addition to the prefrontal, somatosensory, and limbic areas, the periaqueductal gray matter is also activated during the anticipation phase. The periaqueductal gray area contains the cell bodies of the main descending inhibitory pathways, which are anatomically similar to the excitatory pathways responsible for nocebo effect. However, unlike the excitatory pathways, the inhibitory pathways have been shown to reduce the intensity of the nociceptive afferents entering the spine. In a study, Goffaux et al (66) found that expectations of hyperalgesia completely block the analgesic properties of a standard counterirritation procedure, which is known to activate descending inhibitory systems. While anticipatory processes may activate spinal inhibitory circuits, reducing the intensity of pain signals entering the cortex, placebo analgesia also depends on the collection of cortical processes triggered during the experience of pain itself (5,67).

4.0 PSYCHOSOCIAL MEDIATORS

Psychophysiological mediators involve conditioning, cognition, motivation, and emotions. Also involved are interactions between biological mediators with neurochemical responses, as well as the production of endorphins, dopamine, and various other neurotransmitters/neuromodulators. There is also neurophysiological activity with activation of central modulatory mechanisms, including descending inhibitory circuits.

Various psychological factors have been proposed to explain the placebo effect in general and placebo analgesia in particular. Some mediators also have been explained as the basis for nocebo effects. These factors include conditioning, expectation of relief, motivation features, and emotions.

4.1 Conditioning Theory

Conditioning theory suggests that placebo response represents a form of classical conditioning that is based on learning through association, a theory dating back to Pavlov (68-70). However, placebos may exert an expectancy and act through classical conditioning, where a placebo and an actual stimulus are used simultaneously until the placebo is associated with the effect from the actual stimulus (68,69).

A conditioned pain reduction can be totally removed when its existence is explained (71). It has been demonstrated that in a placebo-controlled trial of antidepressants, once the trial was over, the patients who had been given placebos quickly deteriorated (72). It has also been shown that if a placebo is described as a muscle relaxant, it will cause muscle relaxation, and if described as the opposite, it will cause muscle tension (73). A placebo presented as a stimulant will have this effect on heart rhythm and blood pressure, but when administered as a depressant, the opposite effect occurs (74). It has been shown that alcohol placebos can cause intoxication and sensory motor impairment (75,76). Patients with headache taking regular aspirin (unconditioned stimulus) can associate the shape, color, and taste of aspirin (conditioned stimulus) with decreases in pain. After several associations, pain decreases when patients are given a placebo that looks and tastes like aspirin (34). Tachycardia has been reported when a conditioned stimulus was substituted for glyceryl trinitrate (77). In 3 studies, placebo responders were conditioned to a neutral cream following conditioning trials in which the cream was associated with pain relief (78-80).

Wickramasekera (69,81,82) described that classical conditioning occurs not only with pharmacological

agents, but also various other aspects of medical care including doctors' offices, physicians, nurses, syringes, and physical examination. Further, it has been shown that the strength of the conditioned response increases with the increasing number of paired associations (83).

It also has been described that human conditioning occurs without the individual knowing it and it does not involve cognition (5,8,34,69,82). Consequently, it is expected that the response to any unconditioned stimulus will necessarily come to involve an unconditioned response - a placebo response. This response will depend on the individual's learning history, also called the "response generalization." According to such a model, the unexplained variability in placebo response within individuals is due to their past medical history and their differences and learning history with a particular treatment, in a particular environment (82).

Similar to the placebo effect, the nocebo effect can also be conditioned through an association with negative stimuli. It has been demonstrated that drug-related information generates both placebo and nocebo responses that modify the drug response (73). In descriptions of the role of learning, nocebo and placebo effects have been described (84). The authors found that verbal suggestions alone, without prior conditioning, turn tactile stimuli into pain as well as low-intensity painful stimuli into high-intensity pain. A conditioning procedure produced similar effects, without significant differences. Therefore, they concluded that, in contrast to placebo analgesia, whereby a conditioning procedure elicits larger effects compared to verbal suggestions alone, learning seems to be less important in nocebo hyperalgesia.

Placebo analgesia has been shown to be induced by social observational learning (85) and multiple conditioning sessions induced robust placebo and nocebo responses to both non-painful and painful stimuli that persisted over the entire experiment (86).

4.2 Expectance Theory

The expectance theory postulates that placebo response is related to a patients' expectations of improvement, which are connected to the change that takes place (87-90). The expectancy theory was developed by Goldstein in 1962 (91). The expectancy effect can be enhanced through factors such as enthusiasm of the doctor, differences in size and color of placebo pills, or the use of other interventions. In one study, the response to placebo increased from 44% to 62% when the doctor treated them with "warmth, attention, and confidence" (92).

Expectancy effects have been found to occur over a range of substances when patients who think that a treatment will work display stronger placebo effect than those who do not. It has been shown that placebo alcohol produced increased sexual arousal to erotic stimuli (93), increased aggressive behavior (94), and increased craving for alcohol (95). In addition, Volkow et al (96) found that patients who expected to receive treatment showed more significant changes in brain metabolic activity than those patients who expected to receive placebo, although both groups were given an active drug. Further, it has been shown that expectancies can even override the pharmacological effect of a drug (97,98). Because placebos are dependent upon perception and expectation, various factors which change the perception can increase the magnitude of the placebo response. Studies have shown that the color and size of the placebo pill make a difference, with "hot colored" pills working better as stimulants while "cool colored" pills work better as depressants. Further, capsules, rather than tablets, seem to be more effective, and size can make a difference (99).

When evaluating the reproducibility of placebo analgesia, it is a challenge to identify the factors and personality traits that contribute to variability and expectations (100). While early placebo studies failed to identify a placebo-prone psychological profile, several studies since then have noted that some attributes, such as psychopathology, dispositional optimism, and social desirability, are associated with placebo response, although evidence is often contradictory (100). Of these factors, dispositional optimism seemed a likely personality trait to influence expectations regarding the treatment effect because higher levels of optimism are associated with a greater response to positive expectations. It has been concluded that high dispositional optimism and low state anxiety were found to be significant predictors of placebo response.

It has been described that optimism and pessimism both have positive and negative effects on placebo and nocebo responses. Several lines of research converge to show that optimists often shift their focus away from adversity to the more positive features of the situation - especially when dealing with adversity that is out of their control (101). It has been shown that optimists can beat early stage breast cancer or improve substantially with coronary by-pass surgery compared to pessimistic patients. It has been shown that optimists were more likely to focus on their recovery and less likely to dwell on their post-surgery negative effects than pessimists

(102). In the study of dispositional optimism predicting placebo analgesia, the authors concluded that dispositional optimism was associated with a lower pain rating. Thus, dispositional optimism can alter placebo response to laboratory pain (102).

4.3 Motivation Theory

While the expectation of relief is an important contributor to placebo response, there are various other psychological mediators, including motivation. Thus, a patient's desire for relief explains a large part of the placebo response. A study by Price et al (103) measured pain before and after the application of a placebo cream, which was accompanied by verbal suggestions. The authors suggested that the lack of effect was attributable to the relatively low desire for relief in experimental studies compared to clinical studies, and that desire for relief, therefore, plays a more important role in pain when it signals potentially life-threatening illness.

In another study, Vase et al (104) illustrated that desire for pain relief helped to predict the magnitude of a placebo response in a group of patients with irritable bowel syndrome exposed to a clinically relevant painful stimulus. However, this desire had no productive value for the placebo response when pain was evoked at the left foot using a hot water bath. The motivation failed to predict the placebo effect for one type of pain; it failed to do so for a different type of pain illustrating variance.

4.4 Emotions Theory

Among all the emotions related to placebo, anxiety has been the major psychological mediator. Anxiety has been reduced with administration of a placebo treatment. While commonly elevated levels of stress produce increased levels of pain and distress, in some circumstances, they may also produce analgesia, known as stress-induced analgesia. The administration of a placebo treatment may reduce the distress associated with pain, but not its level of intensity (5). Thus, based on this premise, a larger reduction in pain unpleasantness than in pain intensity is expected (105,106). While stress-induced analgesia has been described, it appears unlikely that anxiety is a mediator for all analgesic or placebo responses, because its effects are likely to be general and do not explain the evidence of localized pain relief (107,108). Further, even though it is always believed that anxiety effects are the cause of increased levels of pain, it is not yet clear whether anxiety effects

are the cause or the consequence of placebo response (34). However, in a study conducted by Aslaksen and Flaten (109), it was shown that when a patient receives information that a pain killer is administered (i.e., a placebo treatment), stress and anxiety are reduced, along with subjective pain scores and cardiac indicators of sympathovagal activity. Further, in a series of stepwise regressions, it was revealed that only subjective decreases in stress were a significant predictor of placebo analgesia. They indicated that reduced stress is a possible mechanism by which placebos lead to reductions in subjective pain scores.

5.0 PLACEBO ANALGESIA

The magnitude of placebo analgesia effects has been shown to be highly variable and depends on several contextual factors (110). Various meta-analyses have found different magnitudes of placebo analgesia (38-40). Meta-analyses based on studies in which placebo is used only as a controlled condition, generally find a low magnitude of placebo analgesia as indicated by a small effect size. However, meta-analyses based on studies that investigate placebo analgesia mechanisms found a large magnitude of placebo analgesia as indicated by a larger effect size. This difference is not surprising as the psychosocial context in the 2 types of studies differs, for example by the verbal suggestions given for pain relief. However, the findings that the magnitude of placebo analgesia is high in studies of placebo analgesia mechanisms has been debated and strongly questioned.

The direct comparison of placebo effects on clinical and experimental pain showed an important reduction in placebo analgesia in low back pain after single pre-exposure to the ineffective control treatment, suggesting that additional involvement of highly flexible mechanisms may counteract the pro-analgesic effects of expectations (111). In an evaluation of categories of placebo response in the absence of site-specific expectation of analgesia (85), the authors concluded that there were at least 2 patterns of placebo responses. Some individuals showed a site-specific response while others showed a more generalized response.

6.0 IMPLICATIONS OF PLACEBO IN CLINICAL TRIALS

The placebo effect makes it more difficult to evaluate new treatments and prove the effectiveness of existing treatments (112-114). Apparent benefits of a new treatment, usually a drug, may not derive from the treatment but from placebo effect. This is particularly likely

given that new therapies seem to have greater placebo effects. The participants in such trials are blinded as to whether they received the treatment or a placebo. Often clinical trials are double-blinded and placebo-controlled, so that the researchers also do not know which participants are receiving the active or placebo treatment. Consequently, the placebo effect in such clinical trials is weaker than in normal therapy since participants are not certain whether the treatment they are receiving is active or not (115,116). Beecher (32) published "The Powerful Placebo," in which he showed that 35% of the cases of placebo treatment induced a therapeutic effect. In 2001, an article was published in *The New England Journal of Medicine* entitled "Is the Placebo Powerless" (3). Subsequently, the authors updated the review and in both instances came to the same conclusion: that of the 10 clinical conditions investigated in 3 trials or more, placebo had a statistically significant pooled effect only on pain or phobia on continuous scales (117). Further, neurobiologic mechanisms have confirmed endogenous opioid as well as dopaminergic mechanisms.

While placebo inclusion in pain medicine trials is appropriate, inclusion in interventional pain management techniques is difficult due to a lack of understanding. Consequently, the results are uniformly misinterpreted.

Since the publication of Beecher's (32) "The Powerful Placebo" in 1955, the phenomenon has been considered to have clinically important effects (3,28). However, Beecher's (32) view was challenged subsequently in a systematic review in 2001 (3). Goffaux et al (5) also wanted to dispel one of the most commonly held misconceptions regarding placebos, namely that around 30% of individuals will respond to a placebo procedure, or that 30% of any treatment effect is attributable to non-specific or placebo effects, derived from Beecher's manuscript (32). They commented that Beecher's conclusions are heavily contested today because the author did not take into account factors such as expectations and motivation.

In a Cochrane Review (38) on placebo studies, the authors did not find that placebo interventions have important clinical effects in general. However, in certain settings, placebo interventions can influence patient-reported outcomes, especially pain and nausea, though it is difficult to distinguish patient-reported effects of placebo from biased reporting. The effect on pain varied, even among trials with low risk of bias, from negligible to clinically important. Variations in the effect of placebo were partly explained by variations in how trials were conducted and how patients were informed.

The contradictory literature on placebo effects indicates on average the effect to be present in 30% of patients and short-lived. There are proponents with clinical reports that placebo effects can last for over 2 months for panic disorder (118), 6 months for angina pectoris (119), and 30 months for rheumatoid arthritis (120). Further, placebo effects after verbal suggestion for mild pain have been reported to be robust and still exist after being repeated 10 times, even if they have no actual pharmacological analgesic action (71). In painful conditions it has been stated that placebo analgesia is more likely to work with proportional response to severity of pain (121).

Thus, contrary to long-held beliefs, placebo analgesia and nocebo hyperalgesia are not simply response biases. Instead, they are the product of neurophysiological processes that modulate the integration of the nociceptive signals throughout the central nervous system. An important clinical implication surrounding the use of placebos concerns the potentiation of treatment effects. Clinicians should not try to avoid the placebo effect; on the contrary, they should try to potentiate it (5). Goffaux et al (66) were able to either increase or block the effect of genuine analgesic procedure merely by manipulating expectations. Thus, clinically, the treatment efficacy increases when both the clinician and the patient take a positive attitude toward treatment, and, conversely, the treatment efficacy is jeopardized if the prevailing attitude is negative. The objective is not to create false or exaggerated expectations where patients would risk experiencing disappointment, but rather to be confident in the proposed treatment. Further, special care should also be taken to avoid creating expectations of hyperalgesia with an erroneous negative prognosis or expectations of no effect from the proposed treatment, which would hamper the effectiveness of future treatments.

Further, even if the treatment message seems to be a critical component underlying placebo analgesia, it is important to incorporate the medical context and the patient's history. It was also shown that the effectiveness of placebo analgesia was greatest when individuals were first exposed to the placebo than when they were first exposed to the control condition (105). It has been stated that current practices, where physicians start with low analgesic doses before gradually ramping up to larger doses, exposes patients to an initial barrage of inefficacy, which increases the likelihood of experiencing subsequent treatment failures.

7.0 OPEN-HIDDEN PARADIGM

Generally the gold standard in clinical trial design is the double-blind placebo-controlled trial with 2 arms: an active group and a placebo group. When outcomes in the active group are better than the placebo group, the conclusion is that treatment is effective. However, considering the multiple inadequacies of the above model, a different model has been developed known as the "open-hidden" paradigm.

In contrast to the clinical trial with active and placebo arms, in an open-hidden paradigm, the experiment is reversed. The specific effect of the treatment is maintained, but the context of the treatment is eliminated by using a preprogrammed computer-controlled infusion pump to administer the intravenous drug infusion. The pump is hidden from the patient and there are no doctors or nurses in the room. Thus, the patient does not know when he or she is receiving the treatment. By eliminating the context of the treatment, it is believed that most of the clinical response (i.e., pain relief) that the participants experience is attributed to the specific effect of the drug and not the placebo effect. In contrast, when open injections are given in full view of the patient, clinical changes experienced are believed to be the result of both the specific effect of the drug and the context effect. Thus, the difference between the open and hidden may be taken as a measure of the context effect.

Benedetti et al (110), in 1995, ran a classic double-blind randomized trial that showed that the CCK and antagonist proglumide was better than placebo, and placebo was better than no treatment, for relieving pain in a group of 93 post-thoracotomy patients.

According to the classical clinical trial methodology, the conclusion that can be drawn is that proglumide is an effective analgesic acting on pain pathways; however, this conclusion was proved to be wrong when the authors repeated the experiment by using the open-hidden paradigm (6). It was shown that the hidden injection of proglumide (the context and the result of the placebo effect are eliminated) produced no analgesic effect at all. Consequently, the whole effect the proglumide produced in the classical trial was considered as placebo effect. Thus, it was assumed that proglumide acts only in expectation pathways, not in pain pathways. This also has been described as an uncertain principle in clinical trials (6). In summary, the uncertainty in clinical trials cannot be resolved by using the classical trial design. Thus, the open-hidden paradigm may offer a way to address the uncertainty by eliminating the context (meaning of

a treatment), hence, rendering the expectation pathways silent. It has been recommended that, to avoid or overcome ethical problems, the design may consist of unknown temporal sequences of drug administration where the participant knows that a pain killer will be administered but does not know when (111). This is based on the philosophy that if a drug is really effective, pain reduction will correlate with the time that the drug is administered. This paradigm offers a way to assess context effect without using a placebo group at all, thus potentially solving the debate on the use of placebo in clinical trials (112). Consequently, it may provide an excellent alternative to placebo-controlled trials and also would be consistent with the World Medical Association's declaration of Helsinki Ethical Guidelines (6). Overall, the hidden procedure is easy to carry out in the postoperative phase in which the patient is connected to several intravenous lines such as for antibiotic therapy or blood transfusions; however, it is not feasible in chronic pain management with interventional techniques.

8.0 PLACEBO AS A TREATMENT MODALITY

Placebo as a treatment modality has been discussed as an interesting but also a practical concept. Essentially placebo research not only emphasizes the crucial role of non-specific effects of treatment and expectations in the outcomes of a treatment, but also offers a means to make use of the non-specific effects of treatment and expectations in order to increase the placebo response and the effect of therapy (6). Consequently, multiple aspects of increasing the expectancies have been described which include credibility of the physician, therapist, therapeutic setting, the treatment, administrative ritual, and the nature of the relationship between the patient and the physician (82). However, the most important expectancies are probably related to the nature of the patient-physician relationship, the physician's attitudes and behaviors toward the patient, and the enthusiasm for the treatment being recommended (6). Neurobiology of the doctor-patient relationship and the mechanism on how the appropriate words could activate the endogenous opioids or dopamine system has been described which in essence improves the outcomes of a treatment (113).

Utilizing placebo agents as treatment has been prohibited in the United Kingdom; however, studies have shown that approximately 24% of physicians would prescribe a placebo simply because the patient wanted treatment, whereas 58% would not, and for the remaining 18%, it would depend on circumstances (114).

9.0 IMPLICATIONS IN INTERVENTIONAL TECHNIQUES

The misunderstanding of placebo and its role in interventional techniques is not only limited to researchers and methodologists, but also clinicians, despite overwhelming literature illustrating the role of placebo and active control (9-17,122-177). There are numerous difficulties related to placebo groups and interventional techniques. Thus, an active control study utilizing local anesthetics is considered appropriate. However, local anesthetic is not a placebo.

In recent years, evidence-based specialists have devoted significantly more attention to placebo effect, particularly as it relates to the experience of analgesia; however, methodologists have been ignoring the poorly understood and complex mechanisms of placebo analgesia and nocebo hyperalgesia. In fact, in a study in patients undergoing interventional procedures (17), sodium chloride solution, midazolam, and fentanyl produced placebo effects in 13% to 15%, 15% to 20%, and 18% to 30% of the patients respectively. However, surprisingly a nocebo effect was seen in 5% to 8% of the patients in the sodium chloride group, 8% of the patients in the midazolam group, and 3% to 8% of the patients in the fentanyl group. Consequently, it is essential to focus on not only the methodological aspects, but also other aspects wherein positive and negative effects may be seen either with placebo or active agents in 13% to 30% of patients (17).

Designing a placebo study in interventional techniques is an extremely difficult task. Many believe that comparing the impact of an intervention with the natural course of the disease in a randomized, blinded fashion can only be achieved when the comparator group receives a placebo. This placebo, in the case of interventional treatment, would be a sham intervention, and represents the first obstacle for randomized controlled trials (RCTs) in interventional pain management. During the patient information session, the clinician must inform the patient about the potential risks and benefits of the treatment that will be studied, but the clinician also must explain to the patient that he or she may have perhaps a 50% chance of receiving an intervention with no active component, with an automatic reduction of the placebo effect and initiation of nocebo hyperalgesia. Considering that interventional pain management techniques are only offered when conservative treatment fails, researchers face a patient population that has a highly pronounced wish for improvement and is often reluctant to accept the potential receipt of a

placebo therapy. This results in a high rate of patients refusing to participate in a study and subsequent withdrawals if they do participate. Similarly, the referring physician may negatively influence the inclusion rate. Both factors essentially compromise the inclusion rate of patients very seriously to an extent that the study may have to be cancelled or cannot be performed. This effect is seen not only with placebo-controlled trials, but also with active-controlled trials. Further, the effect will not actually reveal the true effect of the lack of treatment since all patients who are suffering with chronic pain are not enrolled in the study, and are not receiving the same attention, evaluation, explanation, and so-called placebo treatment. Finally, a well designed study must be a true placebo trial.

Very few studies have applied true placebo or so-called sham interventions. Many of those claiming to be placebo-controlled are actually active interventions with injection of active agents. True placebo would only be injection of an inactive agent into an inactive location away from the epidural space or facet joint nerves, or facet joints themselves. Even the injections of sodium chloride solution and dextrose have been shown to yield different results (178). The experimental and clinical findings from the investigations of the electrophysiological effects of 0.9% sodium chloride and dextrose 5% in water solution have illustrated multiple variations of neural stimulation. The potential inaccuracy created by 0.9% sodium chloride solution versus 5% dextrose has been described in the literature (178-180). Further, injection of sodium chloride into the disc, facet joint, or paraspinal muscles produces similar, yet variable results (180,181). There are also studies showing the lack of inertness of sodium chloride solution when injected into a closed space (182,183). Sodium chloride itself has been injected to treat low back pain and sciatica (183).

In addition to the injection of placebo, placement of the needle itself and injection of any solution with adhesiolysis effects, as well as the neurolytic effects of the needle and various solutions injected, along with mechanical pressure, and dilution of inflammatory substances, all play a substantial role in understanding the placebo effect or its lack thereof (134,136).

Clinical aspects, as well as placebo and nocebo, have to be taken into consideration. The rules which apply for oral medications may not apply whenever there is an intervention. Even if local anesthetic is considered to be a placebo, or if the placebo actually helps, it may be worthwhile to provide patients with such a placebo

treatment for them to improve. Otherwise, the patients who have long-term chronic pain may continue to suffer. Also, when evaluating a placebo effect, one should consider the role of repeat interventions over a period of as long as 2 years with continued positive results in a high percentage of the patients similar to the other intervention.

10.0 ETHICAL CONSIDERATIONS

Ethical implications of placebo affect the practice of medicine as well as research. The use of placebo in research has been a subject of heated debate. The literature is replete not only with the importance of placebo research but also with nocebo effects and numerous adverse consequences. In a review of 109 phase one trials, it was illustrated that 10% of volunteers in the placebo arm experienced adverse events (184). Further, some argue that using a placebo arm in a research study amounts to deception, and therefore raises a number of ethical issues. This may in essence induce nocebo effects of not only the placebo, but also the treatment itself.

To resolve the ethical dilemma of placebo arms in research, the American Psychological Association (185) allows investigators to deceive "subjects" in 4 situations: when the study is expected to have significant social and scientific values, when any equally effective non-deceptive approach is not feasible; when participants are not deceived about any aspect of the study that would affect their willingness to participate, and when deception is explained to participants at the conclusion of the study.

The American Pain Society (186) recommends the use of placebo in clinical trials when there is limited harm to patients from delayed treatment, when the alternative active treatment is unproven, and when there is a substantial potential benefit to future patients in establishing the efficacy of a treatment, and/or avoiding side effects of a treatment.

Others have described placebo-controlled trials as authorized deception (187). Participants are informed of the deception and asked to consent to it without being informed of the nature of the deception. The supporters of authorized deception have justified this by arguing that investigators can still obtain valid consent as long as they do not deceive about any aspect of the study that would affect their willingness to participate.

Stein and Ray (188) concluded that ethical guidelines for research emphasize minimizing risks and protecting the individual patient, rather than obtaining benefits for society at the cost of serious preventable

harm to some. Because several drugs that materially decrease the risk of fractures in patients with osteoporosis are currently available, they believe that placebo-controlled studies with fracture endpoints in patients with osteoporosis will nearly always be unethical. Such trials cannot be justified by regulatory preferences for placebo-controlled studies, the approval of local institutional review boards, or informed consent from the participants. The alternative-design control trials, such as active control, generally will be required, even though such trials are more complex and expensive, usually require larger sample sizes, and have more methodologic complexities than placebo-controlled trials. However, these challenges should not be considered an ethical justification for administering placebo to some patients, which would result in potentially preventable fractures.

Rosen and Khosla (189) also advised that placebo-controlled trials in osteoporosis must proceed with caution, and concluded that trial design and implementation should not supersede patient welfare or underestimate the potential for harm. To be ethical, the trial design first must answer the question being asked; it should also provide potential participants with a high and clear standard of informed consent, including active review by an institutional review board and an independent data and safety monitoring board, with shared decision-making being a centerpiece of the process. The Declaration of Helsinki states that placebo trials are permissible when no major harm could be expected to participants as a result of delaying treatment, and this must remain a major guideline for investigators (190). It has been described that it may be considered unethical to not be empathetic in medicine. In describing a neurobiological perspective of empathy in medicine (191), it has been shown that not only physiological concordance correlating with patient perception of physician empathy exists, but also neurobiological correlates exist, as shown by neuroimaging studies of empathy.

The ethical appropriateness of clinical research depends on protecting participants from excessive risks (192). However, no systematic framework has been developed to assist researchers, and as a result, investigators, funders, and review boards rely only on their intuitive judgements. Intuitive judgements of risk are subject to well-documented cognitive biases, thus raising concerns that research participants are not being adequately protected. Systematic evaluation of research

risks (SERR), which evaluates the risks of research interventions by comparing these interventions with the risks of comparator activities that have been deemed acceptable, has been developed.

SERR involves a 4-step process: identify the potential harms posed by the proposed research intervention, categorize the magnitude of the potential harms into one to 7 harm levels on a harm scale, quantify or estimate the likelihood of each potential harm, and compare the likelihood of each potential harm from the research intervention with the likelihood of harms of the same magnitude occurring as a result of inappropriate comparator activity.

11.0 CONCLUSION

This manuscript clearly illustrates that placebo analgesia and nocebo hyperalgesia are not simple response biases. Instead, they are the product of neurophysiological processes that modulate the integration of the nociceptive signs throughout the central nervous system (5). Clinicians should not try to avoid the placebo effect, but should try to potentiate it. By the same token, the objective should not be to create false or exaggerated expectations, but rather to be confident in the proposed treatment. Special care should be taken to avoid creating negative influences and expectations of hyperalgesia or expectations of no effect from proposed treatment.

The literature is replete with the presence of placebo effects in almost all clinical interventions – occasionally it can be very powerful. Understanding that the placebo effect depends on a variety of neurochemical and neurophysiological mechanisms, which are measurable and modifiable, researchers should treat the placebo effect as a nuisance and clinicians should embrace the placebo effect in order to increase the effectiveness of proposed treatments. Methodologists should improve their understanding of placebo analgesia, nocebo hyperalgesia, and active treatment models and utilize appropriate methodology in evaluating related studies.

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