Topical Review: Placebo Responses and Therapeutic Responses. How Are They Related?

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This article presents a comprehensive review of the topic of placebos, with a special focus on placebo analgesia. It includes a discussion of how placebos work (the placebo effect) and how patients react to them (the placebo response). A literature search was performed to identify relevant literature and publications related to the topic, and a qualitative assessment of papers was undertaken based on accepted rules for scientific evidence. The major finding from this review was that concepts about placebo effects and responses have changed dramatically over the years, especially in more recent years. This has occurred primarily as a result of more sophisticated experimental protocols using placebos in clinical studies of patients in pain, as well as various studies involving normal subjects. Our understanding of the biological and psychological mechanisms underlying placebo effects has expanded significantly due to recent developments in the technology of brain imaging. Based on findings from brain-imaging analyses, we now know that placebo analgesia is definitely a real (ie, biologically measurable) phenomenon. It can be pharmacologically blocked and behaviorally enhanced, and these responses have been demonstrated to be similar to those elicited by administration of "real" analgesic substances. Psychological mechanisms involved in placebo analgesia include expectancy, meaning response, and classical conditioning. This article concludes with an emphasis on understanding therapeutic responses to various treatments for temporomandibular disorders (TMD). Acupuncture and splint therapy can be good examples of powerful placebos in the field of TMD, and both of these are discussed in detail. Present knowledge suggests that every treatment for pain contains a placebo component, which sometimes is as powerful as the so-called "active" counterpart. While the deceptive use of placebos must be considered unethical, every health provider who is treating pain patients must be aware of this important phenomenon in order to harness its huge potential. J OROFAC PAIN 2009;23:93–107

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A placebo is a sham treatment which produces no specific biologic effects on the medical condition or symptoms that a patient is experiencing. Placebos are used in randomized clinical trials (RCTs) to be compared with the supposed activity of a "real" drug, device, procedure, or behavioral manipulation.[1] It has been proposed to use the term "placebo response" when an individual change occurs after a placebo manipulation, and "placebo effect" when such changes occur in a group of subjects.[2]

The construct underlying the use of placebos in clinical trials is the assumption that a supposed active drug or treatment has to be at least superior to a placebo in producing positive outcomes. The implicit assumption of this research design is that placebos have little, if any, efficacy (defined as a specific treatment effect), because they are not targeted at specific symptoms or pathologies. However, recent research has shown that placebos do, in fact, elicit definite biological as well as behavioral responses from patients within a wide variety of medical conditions.

The double-blind controlled RCT, in which neither health providers nor patients know if they are dealing with a sham treatment or with the (supposed) active therapy, has become the gold standard in modern therapeutic research. In its simplest version (balanced placebo), patients are randomly assigned to an active placebo (control) group or to a treatment group, and the collection of the data must be performed by researchers different from those who are providing the treatments.[1,2] The application of this gold standard has enabled the growth of evidence-based treatments, while also demonstrating the ineffectiveness of many traditional treatment modalities. The more RCTs involving the use of placebos have been conducted around the world, the more awareness has been raised about the fact that placebos almost never have a zero effect. Indeed, they sometimes can produce outcomes that can be as large or powerful as the active treatments with which they are being compared. The recognition of this phenomenon has led some researchers to focus directly on analysis of the "placebo effect" in both sick and healthy populations. As a result of those studies, a substantial core of scientific data regarding placebo response mechanisms is now available, and this new evidence has started to influence both treatment research and clinical applications.

The aim in this article is to present a comprehensive review of the most recent relevant advances in both placebo concept evolution and new insights on mechanisms involved in the placebo response. We propose a conceptual model for interpretation of this phenomenon, with a special focus on its implications in the treatment of temporomandibular disorders (TMD).

History of Placebo

The term "placebo" originally had quite a different meaning from its present usage in the field of medicine. Being the initial word of psalm 116:6 "Placebo Domino in regione vivorum" (I will please the Lord in the land of living beings) that was spoken by paid people at the deathbed of wealthy individuals, the term "placebo" initially had a positive connotation. Later, it became synonymous with false or fraudulent action intended to replace the true (prayer).[4]

Before the 19th century, little or no knowledge about treatment mechanisms was available. The empirical and popular applications of various herbs, potions, and folk remedies by court physicians, travelling healers, medicine men, and shamans were the only available form of "medical" treatment. Yet their attempts to treat people sometimes resulted in the accidental discovery of some active chemical compounds such as digitalis, acetylsalicylic acid, quinine, and others. In addition, some empirically developed manipulative or surgical procedures later were found to produce true therapeutic effects.

For this reason, it can be safely concluded that nearly all treatments in the pre-scientific history of medicine were nothing more than placebos, or at least included large doses of placebo. Whether intended or not, the use of colorful pills and potions, as well as a variety of theatrical gestures, often were able to at the least please the patient and divert him/her from excessive attention to ongoing disease. With the publication of Henry Beecher's landmark paper, "The powerful placebo,"[5] and the design of the first randomized trial by Austin Bradford Hill,[6] the placebo effect became a subject for separate analysis and discussion. Initially it was suggested that the "illusionary part" of every treatment could be distinguished or "subtracted" from the supposed active components by evaluating the effects of administering the fake part alone. This construct implied that placebo action is the same regardless of whether it is administrated by itself or embedded in an active treatment (supposed additive action). Later, in conducting randomized placebo-controlled trials of various treatments, it was found that the placebo effect was a much more complex phenomenon.

As the RCT paradigm became more popular in research, researchers began to realize that patients' responses to placebos reflected a significant phenomenon, especially in comparison to the outcomes of patients who were enrolled in the no-treatment arm of many studies. This observation led to the paradoxical conclusion that the "non-active" counterpart of any "true" treatment was somehow therapeutic, because of its potential for producing moderate to high levels of positive responses.

Conversely, two recent reviews by Hrobjartsson and Gotzsche[7,8] that evaluated 130 controlled clinical trials and 52 RCTs of placebo versus no treatment did not seem to confirm the power of this response. Instead, their analysis suggested that for both binary and continuous outcomes, no net positive effect at all can be elicited by placebos when standardized conditions are imposed in the experimental setting (except for studies involving placebo analgesia). However, when these skeptical conclusions were discussed by other researchers, it was noted that almost all of the trials included in those reviews were selected to exclude every kind of interaction between health givers and patients, virtually blocking any kind of "contextual" effect.[9]

During the past 10 years, an increasing awareness of contextual effects has lead researchers to the conclusion that they can play a major role in the therapeutic efficacy of every treatment effort and can better explain placebo effects.[9,10] Medical researchers now agree that it is essential to appreciate the contextual factors that surround all therapeutic interactions between doctors and patients, as well as other environmental factors that may affect the course of any medical condition. The contextual factors include a variety of verbal and non-verbal elements, including empathy by doctor and staff, easing of anxiety by proper diagnosis and treatment, and suggesting generic healthy regimens of diet, exercise, rest, and anxiety control.[10] Environmental factors include the natural course of the disease (natural history), which usually includes regression to the mean from a maximal symptom state to a better level.[2] Combinations of these factors come from the beliefs and expectations of the patients, their families, and all parties involved in the medical "gestalt."[1–3,11–13]

Current Understanding of the Placebo Response

Characteristics of Placebos

The term "placebo effect" is often used in the singular form, but in fact there are a variety of placebo responses that have been investigated, leading to the conclusion that they can vary widely from analgesia to physical performance improvements to changes in unconscious phenomena such as heart rate or hormone and neurotransmitter production.[14–20]

All placebos share a number of interesting characteristics, but there are also notable differences between them. For example, when pills are presented to patients, the more colorful, strangely shaped, big or tasteful they are, the more the placebo effect is enhanced.[21] Administration via injections has been shown to have more efficacy than any oral administration,[22] with intramuscular being inferior to intravenous.[23] Medical devices seem to have more therapeutic power than personal clinical interventions.[24] Some types of placebo, notably placebo analgesia, can show somatotopic distribution.[25]

Placebo Responders and Non-responders

It was assumed initially that only a part of the population was placebo-sensitive, but as more studies have been published on this topic, the results suggest that almost all individuals can be, in one situation or another, responders to placebos. The magnitude of the placebo effect is also influenced by contextual factors including conditioning and expectancy[26] and drug-related information that can modify the drug response.[27] Nevertheless, there is little research about consistency of the placebo response. While it is possible to define contextual factors as solid placebo response predictors, it seems difficult to elicit specific personality traits predicting this same response.[28] A pattern of repeated treatment-seeking behavior seems to account for the often-reported short life span of the placebo response. The implications for placebo response modeling are that, according to contextual factors, a clinician may or may not obtain the same type of placebo response each time a chronic pain patient gets a new treatment, whether alternative or mainstream.

Placebo Analgesia

Placebo analgesia is defined as a positive response to the administration of a substance known to be non-analgesic, but the patient strongly believes that he/she received a potent pain killer.[29,30] Placebo analgesia today represents one of the best investigated models of placebo response.[31]

The existence of placebo analgesia is well documented, starting from initial studies using dental postsurgical pain as a model.[32,33] Initially, these researches were criticized for the absence of a "real" treatment group, because it seemed that the patients were receiving no treatment.[34] However, recent advances[30,35] showed clear experimental evidence for the efficacy of placebo analgesia, along with significant correlation to objective findings like respiratory depression.[36] Placebo analgesia can be powerful: subjects induced to believe that a potent painkiller drug has been administered

after a surgical procedure can report a decreased visual analog scale (VAS) score up to 2 to 3 points on a 10-point scale. This produces an efficiency index (pain decrease with placebo/pain decrease with morphine) of 0.56, which means that the placebo is 56 percent as effective as a standard dose of morphine.[29] It has been observed that, if the pharmaceutical industry could introduce on the market a substance with similar analgesic properties, this would surely be considered a major development in the field of pharmacological pain treatment.

Beyond Placebo Analgesia: Other Types of Placebo Responses

For many years, placebo analgesia has been the most common model for investigating the placebo response. However, the more the placebo response is investigated, the more it is evident that this phenomenon involves a wide variety of biological activities beyond analgesia. Recently many papers describing different placebo responses have been published, ranging in several fields including cardiovascular diseases and, notably, immunomodulation responses.[37–41] Different explanatory mechanisms have been proposed for these non-analgesic placebo responses, leading to the suggestion that placebo analgesia is only the very tip of the iceberg; it appears that placebos represent a kind of ubiquitous phenomenon, able to elicit a wide range of biological responses, including but not limited to analgesia in both animals and humans.

The following parts of this review will focus on placebo analgesia, but the reader interested in other placebo responses is invited to read the cited reviews for further details.

How Does Placebo Analgesia Work? Explanatory Models

Neurochemical Foundations: Endogenous Opioid and Non-opioid Pathways as Mediators. From a neurochemical standpoint, there is strong evidence that at least a part of the response to placebo analgesia is regulated by endogenous opioid mechanisms.[42–46] Certain specific areas of the brain have been topographically related with the endogenous opioid system, as postulated in early pharmacological studies; this topic will be discussed further in the "Imaging Studies" section below. Various strategies have been used to study the link between the placebo effect and the activity of the endogenous opioid system. The well-known opiate-antagonizing effect of naloxone inhibits placebo analgesia, at least when the placebo is induced via expectancy or via conditioning to opioids.[35,45] The administration of proglumide (which has no anti-pain action in normal conditions) produces a potentiating effect on both placebo and exogenous opiate analgesia. To explain this outcome, it has been hypothesized that proglumide, being an antagonist of the polypeptide cholecystokinin (CCK) which is in turn a potent opiate antagonist, has the net effect of enhancing the opiate system-mediated inhibition of pain processing in the central nervous system (CNS). These data account for the existence of a balance between the endogenous opioid system and CCK in determining placebo analgesia outcomes.[29–31,43–46]

But placebo analgesia is not fully explained by the activation of the endogenous opiate system. For instance, conditioning to non-steroidal anti-inflammatory drugs (NSAIDs) or other drugs appears to be mediated by other unknown mechanisms, since they are naloxone-insensitive.[35,45] There is emerging evidence that the dopaminergic "reward system" or "brain reward circuitry" is also centrally involved and cooperates with the opiate system in developing placebo analgesia. The dopaminergic system has already been linked with expectation of reward in neurological conditions such as Parkinson's disease.[14–20]

In animal models, when the expectancy of a reward reaches the 0.5 probability level (maximum uncertainty), a maximum amount of tonic activation is present in both prefrontal and tegmental dopaminergic neurons which project to the dorsal and ventral striatum.[47]

Also in animal models, the tonic firing of mesolimbic dopamine (DA) cells increases with the expectation of a positive outcome and is reduced when the expected outcome is less prominent than that predicted by initial cues. In other words, mesolimbic DA neurons are thought to be involved in reward expectation and variations from expected outcomes.[48,49]

Interestingly, a human study has demonstrated that subjects who have high expectations of a reward are more prone to experience the effectiveness of a placebo. In other words, people in whom the activation of the dopaminergic reward system is stronger would be more likely to be good placebo responders, accounting for individual differences in placebo response.[50] Another human study has shown that placebo administration increases the activity of dopaminergic cells in the nucleus accumbens, in a similar way to the opiate

system, suggesting that both systems are active in defining placebo response.[51] This study also demonstrated that placebo and nocebo effects are defined by opposite opioid and dopaminergic responses. Nocebo effect, a less-studied phenomenon in which the development of adverse events or worsening of a condition occurs after the administration of a placebo, has been linked to a deactivation of the same dopaminergic and opioid systems, notably in the nucleus accumbens. Another theory proposes that verbal nocebo suggestions are likely to activate anticipatory anxiety that, in turn, activates the descending hypothalamus-pituitary gland axis as well as the CCK-related pro-nociceptive system.[52]

Psychophysiological Foundations: Conditioning Versus Expectancy

Obviously, there is a need for psychophysiologic explanatory models for understanding how placebo analgesia works. To date, the main focus has been on two theoretical mechanisms: classical conditioning and expectancy effect.

Classical Conditioning. This learning model is based on the Pavlovian stimulus substitution concept, in which an unconditioned stimulus causes an unconditioned response. The pairing of an unconditioned stimulus, eg, an aspirin pill, with a conditioned stimulus, ie, shape, color, flavor, taste, consistency of the pill can lead to a conditioned response such as relief from pain, even when the conditioned stimulus is administered by itself.[53]

Expectancy. This theory postulates that the expectation of the patient regarding the effect of the treatment somehow (exact mechanism unknown) triggers the effect.[54] In other words, this seems to be a universal response to any external "intended-to-heal" action,[1] provided that the healing action promotes a symmetrical and complementary endogenous reaction within the patient.

It has been suggested that unconscious conditioning works on unconscious processes such as hormone secretion, while conscious expectancy explains conscious placebo effects such as placebo analgesia.[55] In any case, expectancy appears to be the main drive when both mechanisms are involved.[1] Expectancy and conditioning are not mutually exclusive; a unifying approach based on insights coming from emerging informational and expectancy theories in the classical conditioning mode has been proposed. The informational clue to the patient or subject that the conditioned stimulus is a valid predictor of the unconditioned stimulus leads to associative learning, ie, to the pairing of unconditioned stimulus and conditioned stimulus.[1,55] In other words, what the subject or patient "learns" is the relationship between the unconditioned stimulus and conditioned stimulus, and presumably such learning causes the expectancy of the unconditioned stimulus. This means that, in order to facilitate this association process, the presentation and the pairing must be overt, so it can be perceived by the patient or subject.

Philosophical Foundations: The Meaning Response

Placebo analgesia can be conceptualized as a particular case of "meaning response," according to Moerman's definition: the physiological or psychological effects of meaning in the treatment of an illness. In this special case, the response is elicited by inert medications or sham procedures.[56] Therefore, a so-called nonactive (placebo) treatment, far from being no therapy at all, produces a therapeutic response because it represents the consequence of the meaning that the treatment has (the meaning response). Drugs, therapeutic manipulations, diagnoses, and other aspects of the doctor-patient relationship can thus be seen as informational vectors of a meaning. As a result, to say that a treatment is not better than placebo does not mean that it does nothing. It simply means that the effectiveness of that treatment was not better than the effect of the context in which the treatment was given (or the effect of meaning that it carried during the study). The meaning of the treatment depends on various factors that are very difficult to rule out in a research study.[57] Not surprisingly, the meaning response is always present in doctor-patient transactions of all kinds, so clinicians need to appreciate that not all positive responses to their treatments are based on the specific qualities of their treatment protocols.

These findings have had a major effect on the design of clinical trials as well as the interpretation of results from placebo-controlled studies. For example, they suggest that an open/hidden protocol (told drug/get drug and told no drug/get drug) plus a natural history (untreated) group can rule out contextual and placebo (meaning) response better than the traditional balanced placebo RCT.

Cultural, Gender, and Psychosocial Foundations

Both cultural and gender differences are well established as important conditions that influence pain experience and response to treatment.[58,59]

In addition, psychosocial factors have an impact on response to both placebo and real therapies.[31]

Culture has been shown to play a specific role, accounting for differences in interpretation and meaning of pain-related physical signs and symptoms. The verbal description of pain experience is deeply influenced by cultural issues, and this has led to the development of different psychometric tools in different countries. Similarly, psychological concerns can be elicited from certain characteristics of verbal pain reports.[60] Culture also influences responses to both real and placebo treatment interventions through complex and powerful biologic predispositions interacting with developmental history.

It has become evident that the study of placebo must include the study of the psychosocial environment that surrounds the placebo response.[31] Hence the biopsychosocial model[61] is particularly appropriate, because it posits an interaction between biologic activity, internal meaning states (eg, psychological states such as depression, anxiety, etc) and socio-cultural concepts of sickness and health. In addition to being the most satisfactory explanatory model for chronic pain, the biopsychosocial model is also suitable for discussing the placebo response. It provides a framework for understanding placebo phenomena at the different levels where they can be observed—eg, functional magnetic resonance imaging (fMRI), cognitive expression, emotional arousal and behavior—and also for appreciating the significance of these interactions between biology and culture.

Other Mechanisms, Top-down Influences

Signal-detection theory, response-appropriate sensation, and reward theory[62] have been proposed as alternative explanations for placebo analgesia. These concepts have not been extensively studied, and although they should not be rejected, it should be understood that different mechanisms are not mutually exclusive, allowing for multimodal interpretations of the placebo response phenomenon.

However, there are other top-down brain influences that should be considered, even though current knowledge about them is limited. Neuroscientists are only at early stages in understanding how pre-existing brain states such as expectancy can shape perceptions, emotions, and behavior, as well as how they can influence the type of pain response or treatment response that will occur in a patient.[63] By analyzing events within this framework, one can understand for instance why the same occlusal splint can produce different outcomes even within the same patient because of his/her previous experiences and beliefs. In other words, the significance of these new data for placebo phenomenology is that the response to a pain stimulus may be better predicted from the non-specific *a priori* state of the brain than from the specific pathophysiologic mechanisms or the specific treatment being provided.

Imaging Studies

One of the problems in quantifying the impact of any therapy for people in pain is the obvious observation that, no matter which mechanisms may be involved (active action, expectancy, conditioning, etc), clinicians ultimately receive nothing more than a subjective report from the patient. The old saying that "pain cannot be measured, since it is a totally personal experience" can be extended to anti-nociceptive properties of drugs (or placebos), because the efficacy of a substance was until recently measured mainly via personal statements (VAS score or similar assessments) as well as the request for more descriptive comments.

Recently this aspect of pain research has been greatly enhanced by the application of several new types of imaging modalities. Two of the most valuable approaches involve Single Photon Emission Computed Tomography (SPECT) and fMRI, both of which allow real-time imaging of brain activity. Another important imaging modality, known as positron emission tomography (PET), has been utilized for studies of brain activity under various conditions. Studies utilizing these modalities represent a totally new "objective" approach to the study of pain analgesia, by "opening a window" on brain activity along the endogenous opiate system both during pain and administration of placebos or active treatments. In addition, researchers are now able to locate with accuracy which groups of neurons sharing the same neurochemistry are active when pain is occurring, or when a supposed anti-pain substance is administered. New data coming from imaging studies have shown where, when, and how brain activity is related to cognitive inputs, such as expectancy of pain relief. Other data coming from neuropharmacologic and neurological studies suggest that cognitive inputs can influence and are capable—via the endogenous opiate system—of modulating physical and emotional states. The combination of all this new information has enabled this research area to become known as the "new mind-body frontier" in imaging and behavioral fields. With placebo analgesia imaging,

we may be able for the first time to see "in vivo" how brain circuitry is able to use cognitive cues to activate certain functional areas.[64,65]

A pioneer PET study demonstrated (taking into account the resolution limits of this technique) a large overlapping of brain regions activated during both opioid and placebo analgesia: rostral anterior cingulate cortex (rACC) and orbitofrontal cortex (OrbC).[66] More accurate techniques such as fMRI have shown that during administration of a placebo (with expectation of analgesia), there is a significant co-activity between rACC and rostral ventromedial medulla (RVM), as well as between rACC and periaqueductal gray (PAG), suggesting a top-down rACC/PAG/RVM pain-modulating circuitry involved in placebo analgesia. The activity of other regions such as thalamus, anterior insula (aINS), and the caudal rACC is decreased under placebo, accounting for a reduction in nociceptive activity. Finally, the activation of dorsolateral prefrontal cortex (DLPFC), OrbC, superior parietal cortex, and PAG immediately before the placebo response is consistent with the activation of top-down cognitive-evaluative circuits, as previously discussed.[31,67,68] These brain regions are rich in endogenous opiate mediators; therefore, these imaging studies have confirmed previously described naloxone-based pharmacological studies. Since it is the activation of mu opioid receptors that mediates the activity of this endogenous opiate system, it is not surprising that the availability of these receptors, when marked with radiotracer, is found to be reduced in PET imaging during such conditions.[69] This and other imaging studies[70–72] have given further support to the evidence coming from neuropharmacological and neurological studies that cognitive expectations can directly affect the neurotransmission activity of the endogenous opiate system.

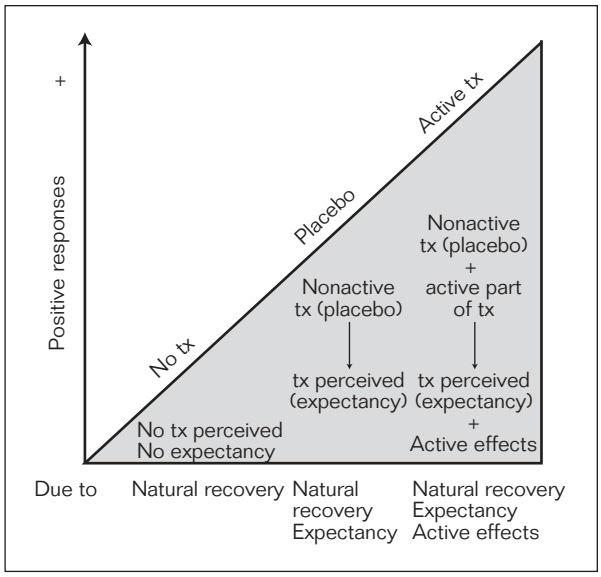

Fig 1 Mechanisms of positive response under three conditions: no treatment (tx), placebo administration, and active treatment administration.

Reconceptualizing the Placebo Response

Implications from Scientific Research

It should be clear from the literature cited throughout this article that placebos can no longer be considered to be "inactive" in the way that sugar pills were characterized many years ago. Indeed, thinking about placebos in this way has been recently described as a misleading prejudice.[1,2] Studies on transplantation of stem cells producing DA in Parkinson's disease patients have demonstrated that even the most "organically driven" RCTs can lead to the surprising results of sham surgery producing positive effects, probably due to the power of expectancy.[17,18] Therefore, it currently is more appropriate to separate therapeutic encounters into:

1. "Real" treatments, which have specific therapeutic mechanisms and clear-cut superiority over sham treatments
2. Placebo treatments, which elicit a variety of generalized (nonspecific) responses
3. No treatment at all (waiting list control group, etc); Fig 1.

The constantly increasing body of evidence regarding expectancy and conditioning processes in triggering placebo analgesia has provided many clues about "when" and under which conditions such phenomena occur. The insights coming from neuropharmacological research and confirmed by brain-imaging studies have increased our understanding of "how" this process develops. And finally, the discovery of biologic mechanisms that are triggered by administration of placebos confirms that something very real is occurring. In the following paragraphs, an explanatory model is proposed to address the gray area of "why" such responses can play an important role in the human body's response to all "sham" and "real" therapeutic interventions.

Endogenous Physiologic Responses: Placebo as a New "Member" of the Group

There are many "embedded" endogenous physiological responses which have significance for self-preservation. These fundamental activities involve autonomic, endocrine, immune, nervous, and cardiovascular systems (among others). Examples of such activities are: healing of fractures, fight-or-flight (stress) responses, cicratization of wounds, and release of endorphins. All these endogenous responses have an obvious strength from an evolutionary standpoint, and it appears that they can be enhanced by ALL therapeutic approaches from outside agents.

Therefore, the placebo response construct can be reconceptualized by including this phenomenon in the above group of "preset" biological conservative responses. While placebo effects have traditionally been described mostly in behavioral terms, it is clear that they also must be considered as part of an inner biological process, reaction, or response. In this conceptual framework, the "placebo response" becomes something that enhances the chance for an organism to respond positively to any external intervention, provided that such interventions have the meaning of (or are viewed as) a cure, a therapy, or a treatment. Being an endogenous response, it is fully mediated by internal psychophysiological mechanisms, involving but not limited to the endogenous opiate system, and it can be enhanced or depressed by many intrinsic and extrinsic factors. For those therapies that are intended to relieve pain, the placebo effect must be distinguished from the net effects of the active treatment in order to determine how powerful that treatment really is. In addition, since placebo and expectancy effects are embedded in each kind of therapy, it should be appreciated that placebos add a non-specific "plus-value" to any conventional or alternative treatment. Some diseases and/or symptoms could be more prone than others to the beneficial effects of placebos as well as real therapies. Ultimately, it would not be unreasonable to describe placebos as an intermediate therapy, ie, one that produces more positive responses than no treatment at all, but less than proven effective therapies.

Clinical Implications of New Placebo Concepts

This modern understanding of placebo effects and placebo responses should not be used to justify the indiscriminate use of all sorts of treatment modalities, while defending them by saying that "everything seems to work." Advocates of so-called alternative medicine have generally been unable to demonstrate therapeutic effects; however, the same observation is equally relevant to advocates of many of the unfounded treatments currently offered by mainstream dental and medical practitioners for pain management generally, and for TMD pain more specifically. Similarly, clinicians who use ineffective or, even worse, excessive treatments will have a certain level of "positive" outcomes, but the price paid by patients both physically and financially may be too high. Therefore, the scientific community still should demand empirical proof before recognizing any alternative or radical procedures as being validated. In the following sections, two examples are provided to demonstrate how our new understanding of placebos has influenced clinical thinking. First, a new look at how acupuncture works as a treatment for pain will be presented. Second, the impact of placebos in the management of TMD will be considered.

Acupuncture: Real and Sham (Placebo) Effects

Acupuncture is probably the best-known and most widely used alternative medicine procedure for the treatment of pain. Its status as an alternative technique is based on its ancient Eastern origins, which were based on either anatomic speculations or empirical testing of so-called "acupuncture points and meridians." However, since its introduction into the world of Western (allopathic) medicine, it has been subjected to a variety of placebo-controlled trials and, in addition, has been studied with the brain-imaging techniques discussed earlier in this article.

Modern investigators have attempted to explain acupuncture in terms of Western science. They have suggested that the mechanical action of needling activates receptors in peripheral tissues so that neural impulses are conducted to the CNS, which act on ascending pathways to higher levels of the brain and cause the release of neurotransmitters that subsequently modulate pain processing in the CNS. This Western theory of the mechanism of acupuncture, which clearly is quite different from the Eastern flow of energy theory, is based on studies that have used acupuncture to treat pain as well as studies of normal subjects in pain-provoking experiments.[73–82] Several studies have also suggested that acupuncture-induced analgesia is mediated by the release of endogenous opioids.[83] Results from human and animal studies, with the help of PET and fMRI, support these conclusions.[84–87]

Nevertheless, culture and expectancy are two issues that need to be evaluated in acupuncture studies. It has been argued that acupuncture therapy is different from most Western medical treatments because it views the patient in a holistic way. Viewing the patient "holistically" is associated with a medical philosophy originating from certain Asian cultures. Therefore, "Western" therapeutic research using placebo controls may undermine a large part of the effectiveness of acupuncture. There are problems with double blinding, as it is impossible for the acupuncturist not to know which subject is receiving "real" or sham acupuncture. It is also difficult for subjects to be blinded, especially if they have had acupuncture previously and can recognize the feeling of acupuncture needles penetrating their skin. Nevertheless, some clever types of sham acupuncture procedures have been developed, including the use of retractable needles as well as applying real needles to "incorrect" locations. The behavioral aspects of sham acupuncture treatments should be similar to their real treatment counterparts, assuming that the investigators conduct the experiments properly. However, to date there seems to be little information about many of the other complex interactions between acupuncture, placebo, patient, doctor, and setting, so all studies of this phenomenon suffer from that deficiency.

Although scientific evidence supports a physiological basis for acupuncture analgesia, the true efficacy of acupuncture for pain relief in humans remains in question, since both specific and nonspecific factors may play a role in acupuncture therapy for pain. Many acupuncture trials have shown little or no superiority of correctly performed (true) acupuncture over placebo/sham controls, in spite of the fact that both seem to be clinically effective. For example, research comparing acupuncture to sham acupuncture (placing a needle into a non-acupoint and just barely penetrating the skin) has shown that both treatments decreased the pain response to a pressure algometer applied to the masseter muscle in a group of myofascial pain patients.[75]

The study of real and placebo acupuncture has been enhanced recently by the recognition of the expectancy and meaning-response phenomena discussed elsewhere in this article. By manipulating the patient's expectations and other behavioral variables, some remarkable outcomes have been obtained. For example, Pariente et al used PET to examine the cerebral consequences of needling and expectation in a study utilizing real acupuncture, placebo acupuncture, and a skin-prick that the patient was told would have no therapeutic effect. Real acupuncture activated pain centers in the brain more than placebo acupuncture, but both real and placebo acupuncture (with the same expectation of a therapeutic effect as real acupuncture) caused greater activation of pain centers in the brain than the skin-prick.[88]

Kong et al utilized a well-established expectancy manipulation model which was combined with a novel placebo intervention, ie, a validated sham acupuncture needle, to investigate the brain network involved in placebo analgesia. Their complicated experimental protocol involved 24 subjects who received heat stimuli to various areas of the forearm, while deliberately confusing them by suggesting different scenarios to expect. Their results suggest that placebo analgesia may be configured through multiple brain pathways and mechanisms.[72] Another study[89] investigated how a subject's perception of what kind of acupuncture treatment they received affected their outcome responses. In that study, a group of myofascial TMD patients showed improvement in their subjective complaints based on how they perceived which treatment they received. Those who believed they got real acupuncture reported significant decreases in their subjective pain reports after acupuncture treatment, regardless of whether the actual treatment was real or sham.

Some excellent review papers have been published recently that deal with the issue of patient expectancy as it affects therapeutic research. Linde et al examined the pooled analysis of four randomized controlled acupuncture trials comprising a total of 864 patients. These trials found a significant association between better improvement and higher outcome expectations, again showing that the patients who considered acupuncture an effective or highly effective therapy did better than the patients who were more skeptical.[90] Lewith et al reviewed the literature on the effect of acupuncture on brain activation as measured by fMRI and PET.[91] They concluded that pain involves a complex psychophysiologic matrix that is intimately intertwined with expectation. Acupuncture clearly affects this matrix in both a specific and non-specific manner that is consistent with its specific clinical effects, as well as the effects of expectation on pain relief. From a cultural standpoint, these studies suggest that for a treatment such as acupuncture to be effective, even if it comes from a culture different from that of the provider/patient, a common cultural layer/background must exist, allowing both the provider and the patient to share a common set of expectations or beliefs. Beliefs/expectations are, of course, pre-existing mental/brain states and their

top-down non-specific influence on pain experience is well known.

In conclusion, it appears that both real and placebo acupuncture can produce significant pain relief for many people. A recent German study showed that both of them were more effective than a traditional conservative care regimen for treating back pain patients.[92] This kind of result suggests that acupuncture is at the very least an elegant-type of placebo, similar in many ways to occlusal appliances (see below), and therefore it should be viewed as a low-risk and high-prudence procedure[93] for successfully treating various types of pain patients.

Applying Present Knowledge About Placebo Effects and Placebo Responses to TMD Treatments

The history of placebo utilization in TMD treatment studies goes back more than 40 years. Schwartz and his colleagues at Columbia University used a placebo pill in a simple study of the effects of carisiprodol in 1958,[94] but it was not until the 1960s and 1970s that placebos became more widely used in this field. In a series of clinical studies conducted by Laskin and Greene and their group of colleagues at the University of Illinois in Chicago, various types of placebos were provided to TMD patients who were involved in treatment outcome studies. These included dummy pills dispensed double-blind in some scenarios,[95] but in others they were dispensed by prescription in order to see how much the doctor-patient relationship might augment the placebo response.[96] In other studies, a placebo (non-occluding) splint was used as a control in a study of oral appliances[97]; fake biofeedback was used as a comparison to real biofeedback[98]; inert physical therapy devices were used in comparisons with real devices[99]; and finally, a group of myofascial pain patients received mock equilibrations instead of real ones.[100]

The initial rationale offered by the Chicago group for utilizing these diverse placebos in their studies was not only the necessity of having experimental comparisons or controls, but also the need to challenge existing biases in the field. Unlike some other medical conditions, TMD seemed to be very responsive to a variety of untested therapies, many of which were irreversible, invasive, and expensive. Despite having many papers published about the dento-skeletal etiology and mechanistic treatment of these disorders during the first two thirds of the 20th century,[101–103] nobody had critically challenged their underlying assumptions. The natural (untreated) course of most TMD had never been properly studied, and the possibility of conservative treatment being sufficient for most TMD patients had not been seriously considered. Furthermore, the possibility that psychosocial factors could play an important role in both the etiology and management of TMD pain was only beginning to be recognized.[104,105] Therefore, the use of placebos in clinical studies became a valuable tool for challenging the strong positive biases of certain clinicians, as well as a means for evaluating whether a conservative biopsychosocial treatment approach might be more appropriate than a mechanistic one.

The outcomes from this series of placebo studies had significant impact on the direction of subsequent TMD research and treatment. Not only did many of the placebo-treated patients respond very positively but, in addition, long-term follow-up studies showed that most of them continued to do well for years afterward.[106–110] The "blinded" placebo groups in typical controlled studies responded much as Beecher's classic paper[5] had concluded, ie, about one third of the patients reported considerable or total pain relief. However, when the placebos were augmented by writing prescriptions, positive commentaries by the doctors, or elaborate treatment procedures, these numbers sometimes went as high as two thirds positive outcomes. Finally, the discovery that both placebos and conservative treatment modalities could produce as much or more clinical success for the majority of TMD patients than more aggressive procedures became the basis for a gradual (and still ongoing) transformation: the evolution from a dental model to a medical model.[111]

Today we find that TMD treatments offered to patients in the community of dental practitioners around the world can include a wide variety of modalities, ranging from mechanical dental and surgical treatments to conservative physical modalities and cognitive-behavioral interventions.[93,112] Also, a sizeable number of patients report the use of alternative and complementary medicine approaches.[113,114] Many of these approaches claim to be successful, and in some cases these claims are backed up by limited evidence of efficacy in clinical trials.[115–117] Nevertheless, no therapy available for TMD at pres-ent shows evidence of clear-cut efficacy, nor has any one demonstrated net superiority over others when matched with placebos in controlled trials. A classical example of these studies[118] proved in a RCT setting that splints with only palatal coverage (and consequently no possi-

ble mechanical effect on occlusion and/or temporomandibular joint and muscle function) were as effective as the supposed "active" splints in diminishing signs and symptoms of myofascial pain. While several other studies[119–123] have reported similar outcomes, a Swedish series of studies by Ekberg, Vallon, and Nilner have shown superiority of real splints over placebo versions, but these authors have acknowledged that both types produced high percentages of positive responses.[122–127]

In the discussion section of their comprehensive review paper about splint therapy for TMD, Dao and Lavigne[128] have offered an interesting observation which may tie together much of the previous discussion in this paper about our new understanding of placebo responses. They separate the terms "efficacy" and "effectiveness" by defining the first as a real therapeutic impact, while the second term explains the subjective impact of a successful treatment experience. They then recommended that, despite their lack of true efficacy, splints should be employed as a treatment modality for TMD because they are effective treatments and they are harmless when properly utilized. Obviously, this implies that so long as clinicians stay in the domain of conservative and reversible care, there will be a variety of other effective treatments available in addition to splints that are likely to be helpful in treating their TMD patients. Combined with a cognitive-behavioral education of patients and an awareness of important psychosocial factors (especially in chronic pain patients), this approach should lead to "effective" treatment protocols and the avoidance of aggressive ones. A practical checklist of contextual factors that can increase or decrease the subjective effectiveness of any treatment is shown in Table 1.

A reevaluation of TMD therapy literature in light of our new understanding of placebo response suggests that, once all the confounding factors are accounted for, the capability to elicit a positive endogenous response is the common feature of many TMD pain treatments that have been demonstrated to be more effective than no treatment. This interpretation also accounts for the differences frequently observed between the no-treatment group (negative control) and the placebo control group in many TMD pain studies. In addition, it explains better than the placebo/active treatment paradigm why outcomes such as those produced in studies of sham versus true acupuncture as a treatment for TMD and other painful conditions turn out the way they do.[75,92]

Placebo Responses and Treatment of Pain Disorders: Ethical Issues

The American Pain Society (APS) published a major position paper in 2005 on the use of placebos in both clinical research and patient care.[129] Based on a combination of scientific findings and ethical considerations, they offered the following conclusions:

1. The deceptive use of placebos and the misinterpretation of the placebo response to discredit the patient's pain report are unethical and should be avoided
2. The ethical use of placebos is justified only as part of [therapy] studies…and not as the ongoing treatment when the trial is over
3. Health-care providers, when using placebos, have an ethical obligation to ensure that placebos are not used for the punishment, deception, or long-term under-treatment of patients with pain

Nothing in this article is in disagreement with those guidelines. However, in a field where there are no definitive treatments, and with few treatments directed precisely at underlying tissue pathophysiology, and also with no clearly superior treatment modalities, clinicians have to make practical choices within these limitations.[93] Fortunately, both the natural course of most non-chronic TMD as well as the patients' tendencies to respond to treatment interventions are very positive compared to many other medical conditions. The authors are not recommending the deliberate use of placebo modalities in treating TMD patients, but rather think it is essential for clinicians to be aware of the hidden (but powerful) impact of the placebo effects that are embedded in all of their therapeutic interactions. They should also recognize that every intervention, whether pharmacological, mechanical, psychological, or surgical, can elicit the expectancy responses described earlier. Therefore, they can enhance the likelihood of good outcomes by learning how to elicit trust and promote positive expectations in their patients (see Table 1).

Finally, we agree with the position of the APS that, from both an ethical and a semantics point of view, the term placebo should not be used in the typical office setting, nor should the sham version of any therapy be prescribed. Instead, discussions between doctors and their patients should focus on enhancing natural healing responses and providing pain relief during that process ("make people feel better while they get better"). By staying on the conservative and reversible side of the therapeutic

Table 1 Will It Work? A Checklist Table of 30 Specific Contextual Factors Influencing Effectiveness of a Treatment

Clinician		Treatment		Patient	
+	–	+	–	+	–
Good communicator explains the treatment	Poor communicator, expects the treatment to work by itself	New, innovative, technical	Same as usual (traditional)	No previous experience with the proposed treatment	Previous negative experiences with the same treatment
Bona fide believer in the treatment	Minimal confidence in the treatment	Looks like a powerful treatment (shape and color of pills, hands-on manipulations, mechanical devices, injections, etc)	No features evoking a sense of powerfulness	External influences: advertisements, opinions of friends and colleagues, reputation of the clinician	External influences: nobody knows the treatment, negative opinions collected, clinician unknown
Good "healer actor" skills (ability to show feelings of empathy, commitment, support, etc)	Feels empathy, commitment, support, but does not show it (shyness, busyness, etc)	Background of the treatment (philosophical, scientific, according to patient beliefs)	Background of the treatment (contrary to patient beliefs)	Inner attitudes: ability to "think positive," good coping skills, locus of control	Inner attitudes: "the glass is always half empty," depression, secondary gains, illness behavior
Good office environmental setting (colors of the walls, noisy office, busy clinician, nurses' attitude toward patient, etc)	Bad office environmental setting	Treatment makes sense and seems to be scientific	Treatment seems to be complex, scary, unproven	Appreciates healing efforts, compliant with treatment, involved in self-care	Self-focused, passive, non-compliant, unrealistic expectations
Ability to enhance the amount of positive outcome (and minimize the negative)	Focused on unsuccessful outcome, concerned about future treatment	Branded (well established, familiar, good track record)	Unbranded (experimental, not widely used, unfamiliar)	Signal detection: positive response bias in judging treatment/pain relief	Signal detection: negative response bias in judging treatment/pain relief

+ ENHANCE meaning response, expectancy, placebo effect.
– DEPRESS meaning response, expectancy, placebo effect.

universe, clinicians can choose among several well-studied and safe modalities, and they can also encourage their patients to become engaged in the self-care processes that facilitate healing. Clearly, this is the modern ethical approach to the management of pain disorders.

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