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Placebo Effects: Biological, Clinical and Ethical Advances

Damien G Finniss^a, Ted J Kaptchuk^b, Franklin Miller^c, and Fabrizio Benedetti^d

Damien G Finniss: dfinniss@med.usyd.edu.au; Ted J Kaptchuk: ; Franklin Miller: ; Fabrizio Benedetti:

^aUniversity of Sydney Pain Management and Research Institute, Royal North Shore Hospital, St Leonards, NSW, Australia ^bOsher Research Center, Harvard Medical School, Boston, Massachusetts ^cDepartment of Bioethics, National Institutes of Health, Bethesda, Maryland

^dDepartment of Neuroscience, University of Turin Medical School, and National Institute of Neuroscience, Corso Raffaello 30, I-10125 Turin, Italy

Abstract

For many years, placebos have been conceptualised by their inert content and their use as controls in clinical trials and treatments in clinical practice. Recent research demonstrates that placebo effects are genuine psychobiological phenomenon attributable to the overall therapeutic context, and that placebo effects can be robust in both laboratory and clinical settings. Evidence has also emerged that placebo effects can exist in clinical practice, even if no placebo is given. Further promotion and integration of laboratory and clinical research will allow advances in the ethical harnessing of placebo mechanisms that are inherent in routine clinical care and the potential use of treatments to primarily promote placebo effects.

Introduction

The notion of something called “placebo” started with St. Jerome’s incorrect rendering of the first word of the ninth line of the 116 psalm, where instead of translating the Hebrew “I will walk before the Lord,” he wrote “I will please the Lord.” By the thirteenth century, when hired mourners waited for Vespers for the Dead to begin, they often repetitively chanted the ninth line, and received the name of “placebos” to describe their fake behavior (1). Indeed, in the 14th century, in the *Canterbury Tales*, Chaucer named his sycophant, flattering courtier Placebo. Placebo controls, which entailed administering fake procedures to separate the effects of imagination from reality, began in the 16th century with “progressive” Catholic efforts to discredit “right-wing” exorcisms (2). These controls were then applied in medical experiments, beginning in 1784 with the Franklin commission’s debunking of the psychic force of mesmerism/animal magnetism (3). The use of the word “placebo” in a medical context to describe innocuous treatments to make a patient comfortable dates to at least the end of the 18th century (4). These earlier nefarious connections undoubtedly led to the tainted notion of placebos and placebo effects that has been retained until very recently (1). Mainstream interest in placebo effects only began with the widespread adoption of the placebo controlled randomized controlled trial (RCT) after World War II, as it was quickly noticed that people improved; sometimes dramatically, in placebo control arms (5). Henry Beecher popularized this observation in his famous proto-meta-analysis which claimed that about 35% of patients responded positively to placebo treatment (6). Beecher, however, encouraged an inflated conception of the “powerful placebo” because he failed to distinguish the genuine placebo

response from other confounding factors. Since this time, there has been increasing interest in investigating placebo effects by rigorous research methods, especially in the last ten years.

Conceptual Background

The association of placebo effects with RCTs has caused confusion because the response in the placebo arm is not necessarily a genuine psychosocial response to the simulation of treatment. In fact, the observed response to placebo in RCTs may reflect natural course of disease, fluctuations in symptoms, regression to the mean, response bias with respect to the patient reporting of subjective symptoms and other concurrent treatments. Furthermore, a traditional focus on the “inert” content of a placebo has led to difficulties in defining and understanding placebo effects (7,8), let alone applying them in a clinical research and practice (9).

Much of the controversy surrounding placebo effects relates to how they are conceptualized and then defined. Generally, a placebo is seen as an inert substance or procedure and the placebo effect (or response) is something that follows administration of a placebo. The paradox in this statement lies with the fact that if something is “inert”, it by definition is unable to elicit an effect, and therefore placebos can't elicit placebo effects (7,8). This can be further confused with terminology such as “active” (10), “true” and “perceived” placebos (11), which are all attempts to better conceptualise placebo effects, and other terms such as context effects (12, 13) and meaning responses (7) which have shifted the focus from the use of the word. Nevertheless, the “placebo” terminology, despite its defects, is too engrained in the scientific literature to replace it at this time, especially in the absence of a satisfactory alternative.

To obviate these confusions and better understand placebo effects in clinical trials and practice, it is necessary to reconceptualise placebos and placebo effects, shifting the focus from the “inert” content of a placebo or sham procedure to what the placebo intervention, consisting of a simulated treatment and the surrounding clinical context is actually doing to the patient. Accumulated evidence indicates that the placebo effect is a genuine psychobiological phenomenon attributable to the overall therapeutic context (9,14). This psychosocial context surrounding the patient can be comprised of both individual patient and clinician factors, and the interaction between the patient, clinician and treatment environment. The latter represents the many factors involved in a treatment context (such as the specific nature of the treatment and the way it is administered) and the “Doctor-Patient Relationship”, which is a term that encompasses a host of factors that constitute the therapeutic interaction (Panel 2)(12). The placebo intervention is designed to simulate a therapeutic context such that the effect following this intervention, the placebo effect, is attributable to the way in which this context affects the patient brain, body and behaviour (9). When an active treatment is given, the overall response is the result of the treatment itself and the context in which it is given. Such a conceptualization allows for progression in thinking about the many factors which make up the psychosocial context around a patient and how these factors, and the mechanisms by which they operate can be enhanced in clinical practice.

Mechanisms

A key shift in the emerging mechanistic understanding of placebo effects is the recognition that there is not one placebo effect but many (14-16)(Figure 1). These mechanisms can be broadly discussed from psychological and neurobiological viewpoints.

Psychological mechanisms

From the psychological viewpoint, a multitude of mechanisms contribute to placebo effects. These include expectations, conditioning, learning, memory, motivation, somatic focus,

reward, anxiety reduction and meaning (9,17). Whilst there is a growing amount of research into these mechanisms, two principal mechanisms are well supported.

One principal mechanism involves expectancy: expectations of future responses following administration of a placebo (18). Many experiments have used simple verbal cues as modulators of expectancies (19-21). For example, a research subject receiving experimentally induced pain is given a topical placebo cream in the context of two different cues: the first that the cream is inert and will have no effect and the second, that the cream is a powerful pain killer (19). This paradigm demonstrates that such verbal cues can manipulate expectations and mediate placebo effects, including placebo analgesic effects in experimental (21) and clinical pain (22); and placebo induced changes in motor performance in Parkinson's Disease (23,24) and changes in emotions (25) and brain responses in addiction (26). Furthermore, the presence of a conditioning protocol to increase expectations results in larger placebo analgesic responses, demonstrating that expectation can both mediate and modulate placebo effects (20,27,28) as well as interact with other constructs such as desire and emotion (9,22).

Another principal mechanism of placebo effects involves classical conditioning (29). Repeated associations between a neutral stimulus and an active drug (unconditioned stimulus) can result in the ability of the neutral stimulus by itself to elicit a response characteristic of the unconditioned stimulus. Classical conditioning mechanisms have been demonstrated in both animal (30-32) and human studies (27,28,33,34), although it has been difficult to exclude any cognitive component (such as expectancy) in humans (35,36). Despite this issue, conditioning mechanisms in humans are supported by the fact that placebo effects are higher in magnitude after a conditioning protocol (even if an expectation mechanism is present) (20) and have been demonstrated to mediate placebo induced changes in unconscious physiological processes such as hormone secretion (33) and immune responses (34).

The interaction between expectancy and conditioning mechanisms remains an area for further research, which may be particularly relevant to exploring the clinical implications of these mechanisms. Although classical conditioning, manifesting an automatic unconscious mechanism, exists in humans, it can also be conceptualized as a complex process including cognitive components and derived from previous experience of either positive or negative therapeutic outcomes (37). Accordingly, conditioning and expectancy are certainly entangled in the occurrence of placebo effects in clinical practice. The most reasonable interpretation of recent literature is that expectancy is first, conditioning follows and is dependent on the success of the first encounter. This leads to the possibility that the first encounter could be critical for the development of subsequent robust placebo responses: the higher the expectancy, the greater the placebo effect, and, potentially the greater the conditioning effects associated with future drug intake.

In addition to classical conditioning, other learning processes such as past experiences and social observation have been shown to mediate placebo effects (38). For example, observation of a demonstrator simulating responsiveness to a therapy resulted in placebo effects in subjects that were similar in magnitude to a classical conditioning protocol (39), indicating the presence of multiple placebo effects mediated by expectations and different types of learning.

Neurobiological Mechanisms

Looking at placebo mechanisms from the neurobiological viewpoint further emphasizes the fact that there are multiple placebo effects. It also demonstrates that placebo effects can be manifested in different physiological systems in healthy volunteers and in patients with a host of different clinical conditions (Figure 2).

Most research into the neurobiology of placebo responsiveness has addressed placebo analgesia; accordingly, the neurobiology of placebo effects is commonly considered in terms of opioid and non-opioid mechanisms (40,41). Several studies have demonstrated that placebo effects can be completely (42-44) or partially reversed (45) by the opioid antagonist naloxone, supporting the involvement of endogenous opioids in some placebo analgesic effects (46). Furthermore, placebo analgesic effects are likely to be inhibited by the peptide cholecystokinin (CCK) (44), for they are potentiated when a CCK antagonist is administered (47). Taken together, these studies demonstrate that some placebo mechanisms operate by altering the activity of both CCK and endogenous opioids (48). Interestingly, several studies have demonstrated the bodily region specificity of placebo effects (19,21,49), which are reversed by naloxone (21), indicating highly specific endogenous opioid mediated placebo analgesic responses, rather than a more generalized opioid release, such as increased opioid concentration in the cerebrospinal fluid (50). These results have been confirmed and extended by brain imaging techniques such as positron emission tomography (PET) (51,52) and functional magnetic resonance imaging (fMRI)(53-55), one of which demonstrated placebo induced brain changes which were similar to those seen with opioid drug administration (56). Opioid mediated placebo responses also extend beyond pain pathways. Some studies have found that placebo induced respiratory depression (a conditioned placebo side effect) (57) and decreased heart rate and β -adrenergic activity (58) can be reversed by naloxone, demonstrating the involvement of opioid mechanisms on other physiological processes, such as respiratory and cardiovascular function.

Not all placebo effects are mediated by opioids. Growing evidence illustrates that many placebo effects are mediated by other mechanisms, such as the release of different neurotransmitters and neuromodulators. For example, in one study the placebo response in subjects who had prior conditioning with an opioid drug was reversed by naloxone; however, there was no reversal in those who had a non-opioid drug. Accordingly, completely different placebo mechanisms can be produced depending on the drug used in a conditioning protocol (20).

Although other medical conditions have been investigated from a neurobiological perspective, the placebo mechanisms in these conditions are little understood compared to pain and analgesia. For example, placebo administration to Parkinson patients induces dopamine release in the striatum (23,59), and changes in basal ganglia and thalamic neuron firing (60,61). Changes in metabolic activity in the brain following placebo administration in depression (62) and following expectation manipulations in addiction (26) have also been described.

Less research has been devoted to the nocebo effect, a phenomenon that is opposite to the placebo effect. This is mainly due to ethical limitations, as nocebo administration involves the induction of negative expectations. CCK has been shown to play a key role in nocebo hyperalgesia, and this occurs through anticipatory anxiety mechanisms (63-65). A deactivation of dopamine has also been found in the nucleus accumbens during nocebo hyperalgesia (66), which indicates the involvement of different neurotransmitters. Furthermore, a neuroimaging study of nocebo effects has demonstrated brain activation different from placebo effects, including the hippocampus and regions involved with anticipatory anxiety (67).

Implications for Clinical Practice

Understanding how placebo effects work clinically in relevant patient populations over time has not kept pace with the recent mechanistic research, which mostly has involved laboratory experiments performed over short durations with healthy subjects. In the case of clinical populations, the study of longer-term placebo responsiveness has been limited to RCTs; however, these studies rarely include no-treatment groups to control for natural history and regression to the mean, making it difficult to discern a genuine placebo effect. There have been several meta-analyses which have attempted to address the presence and magnitude of placebo

effects in RCTs, including some studies where no-treatment control groups were used. These analyses concluded that placebo effects are small and limited to subjective outcomes when placebos are used as a control condition in RCTs (68-70). However, placebo effects are much larger in studies which investigate placebo mechanisms (71,72). This finding is not at all surprising given that the mechanistic experiments employ controlled manipulations in verbal instructions and context that may be more representative of normal clinical practice than a clinical trial setting. To this extent, it is important bridge this gap by looking at placebo research from basic science, clinical trial and ethical perspectives in an attempt to better understand how placebo effects operate in the clinical setting.

A three week single blind RCT with irritable bowel syndrome (IBS) patients (n=262), investigated whether placebo effects can be disaggregated into two main components (placebo ritual alone and placebo ritual + supportive patient-practitioner relationship) and then progressively combined to produce clinically significant improvements as compared to no treatment controls (73). The placebo ritual consisted of a validated placebo acupuncture device, which was used in both "treatment" arms (74). Instead of penetrating the skin, the needle telescopes up the shaft of the needle handle. The supportive patient-relationship, used only in one arm, was prospectively scripted and included attention, warmth, confidence and thoughtful silence. At the three week outcome, in the supportive + ritual group, 62% of patients reported adequate relief (AR) on a validated IBS measure, while 44% reported AR with dummy ritual alone and the no treatment group reported 28% AR ($p<0.001$). The results were similar with the other three validated IBS measures used. The effect size of 62% AR was comparable to the improvement seen in RCTs of alosetron for IBS (75). The outcomes were similar after an additional three week follow-up. In addition to demonstrating that genuine placebo effects can be statistically and clinically significant over time in clinical populations, this trial demonstrated that placebo effects can be incrementally added in a manner resembling a graded dose escalation of component factors. Interestingly, in a separate analysis of the study, it was found that patient extraversion, agreeableness, and openness to experience were associated with placebo responses, features only seen in the supportive relationship + ritual treatment arm and not the ritual treatment alone arm (76). Significant practitioner effects were also observed. Future integration of such study designs in clinical RCTs with mechanistic laboratory work will allow for better understanding of these placebo mechanisms and how they can be augmented in practice.

Several RCTs have sought to study whether different vehicles of placebo ritual produce different effects (77). The largest such study compared treatment with placebo acupuncture with treatment with an oral pill in 270 patients with chronic arm pain due to repetitive use (78). At two weeks, the first primary end point, patients taking the pills had greater improvement in ability to function (primarily related to less disturbed sleep because of pain) compared to needle ($p<0.05$) while there was no difference in pain. At the end of the study (6 weeks) those on needle treatment had a significant reduction in pain compared to the pill group ($p<0.001$). Depending on the complaint and the length of time administered, different placebos had different effects. Differential nocebo effects were also observed. Patients in the placebo pill group were told they might have the adverse effects (e.g. drowsiness) of a medication (amitriptyline) and the placebo needle group was informed about the side effects of acupuncture. While 30% of people in both placebo groups reported adverse effects, these effects were entirely different and mimicked the information provided in the informed consent.

Some commentators have suggested that alternative therapies with elaborate rituals and distinct environmental cues can have pronounced and clinically significant placebo effects (79,80). Recent RCTs of acupuncture, while not primarily designed to study placebo effects, provided results that support this hypothesis. A series of large acupuncture trials conducted in Germany compared acupuncture according to traditional Chinese medicine, sham acupuncture

(superficial needling at non-acupuncture points) and either no-treatment (wait list) groups or those receiving usual clinical care. Conditions studied included migraine (81), tension headaches (82), chronic low back pain (83,84) and osteoarthritis of the knee (85). Generally, across the various trials, there was no difference between verum and sham acupuncture, but those in both of these groups experienced substantially greater symptom improvement than no-treatment and usual care control groups (86). Supporting the hypothesis that acupuncture works by means of a placebo effect, Linde et al (2007) showed that in four of these German acupuncture RCTs (n=864) for migraine, osteoarthritis of the knee, migraine and tension headache, for which only one trial showed superiority over placebo, positive expectations influenced analgesic responses, doubling the likelihood of positive outcome (87). These expectancy effects lasted for one year in duration. A more recent study in chronic low back pain (n=640) again showed that eight weeks of tooth pick simulation sham acupuncture plus usual care had clinically meaningful improvements compared to usual care alone, and such effects also lasted one year (88).

Placebo Effects are Inherent in Clinical Practice – even when no placebo is given

Some of the clearest evidence supporting the involvement of placebo effects in clinical care comes in the form of the open-hidden paradigm (Figure 3). In this experimental paradigm a treatment is given in a routine manner (the open administration), where the psychosocial context surrounding treatment administration is present, and a hidden manner, where the treatment is given without the patient's knowledge. In the case of drug therapy, the open administration mimics normal clinical care, where the doctor injects a drug in full view of the patient with verbal and contextual interactions. In the hidden administration, the drug is infused by a computer pump in the absence of the clinician and the therapeutic context. Patients receiving hidden administration are aware that at some stage they will receive a drug but they do not experience the expectation component or other contextual factors surrounding the administration. Because the hidden administration removes the psychosocial context of treatment, this paradigm defines the placebo component as the difference between open and hidden administrations, although no placebo is given (89,90).

The open-hidden paradigm has been used in several clinical settings. In pain, hidden administrations of five commonly used painkillers (morphine, buprenorphine, tramadol, ketorolac, metamizol) have been demonstrated to be markedly less effective than open administrations (89,91,92). This included experiments in healthy volunteers (where pain ratings were higher in the hidden group) and in patients with postoperative pain (where the dose required to reduce pain by 50% was much higher in the hidden administration) (91). These results have been reproduced for drug administration for anxiety and deep brain stimulation for Parkinson's Disease (92,93). A slightly different methodology has been employed in addiction, where the absence of an expectation component with stimulant drug administration results in reduced regional brain glucose metabolism and verbal reports of efficacy (26). Taken together, the open-hidden paradigm demonstrates that the overall outcome of a therapy combines the specific pharmacological or physiological action of the therapy and the psychosocial context in which it is delivered. The latter represents the placebo component, based on expectancy.

The open-hidden paradigm has also provided a means of exploring the interaction between placebo effects and responses to active therapies, something that has not been possible in standard RCT's designed to evaluate treatment efficacy, as in this case one can only compare the response to placebo against the response to the index intervention without understanding the interaction between the two. In this case, it is worth describing a clinical trial performed in 1995, where the cholecystokinin (CCK) antagonist proglumide was shown to be better than placebo, which was in turn better than no-treatment for post-operative pain (47). According to

methodology used in classical clinical trials, these results would indicate that proglumide is a good analgesic which acts on pain pathways, whereas placebo reduces pain by activating placebo analgesic mechanisms (through expectancy pathways). However, this conclusion proved to be erroneous, as a hidden injection of proglumide was completely ineffective. If the drug was an effective modulator of pain pathways, such a difference between open and hidden administration should not be seen. In this instance, the drug achieves a response by interacting with and enhancing placebo mechanisms (expectancy pathways), not by acting on pain pathways, and therefore it is only effective when combined with the placebo mechanisms inherent in the clinical encounter. This is the best example that placebo mechanisms can interact with treatments such as drug therapy, even if no placebo is given, as every therapy is administered in a therapeutic context, rich with potential to activate and modulate placebo mechanisms, many of which can act on similar biochemical pathways to the actual drug (Figure 2).

Expectations can be modulated to improve therapy

A short term experimental trial in 2001 has advanced our understanding of the clinical implications of modulating placebo effects in routine clinical care. In this trial, studying post-operative pain over several days, investigators used intravenous saline (a placebo) as a background infusion in addition to an routine analgesic therapy (buprenorphine on request) (94). One group was told that the administration was simply a rehydrating solution (natural history control group), and another group was told that it was a powerful painkiller (maximized placebo context). Patients received normal analgesic therapy throughout the course of the trial and overall analgesic intake was monitored. The clear differences in the context (primarily expectation of benefit) of the intravenous administration resulted in significant differences in drug intake. The group who believed the solution was assisting in analgesia took 33% less active analgesic for the same pain control, demonstrating an important clinical effect and the potential for using placebo effects in conjunction with an active therapy to reduce overall drug intake. There was also a third group included which followed the same methodology but were given the instructions that “the solution may or may not be a powerful painkiller”, representing the classic double blind instructions characteristic of placebo-controlled trials and adding an element of doubt as to the effectiveness of the therapy. In this group, patients took 20% less analgesic medication, which was not as powerful as the certainty involved in the maximized placebo context.

Similar modulations in short-term placebo effects have also been found in more recent studies in patients suffering from irritable bowel syndrome (22,95). In these studies, patients were exposed to a painful stimulus (rectal distention balloon) under two conditions; local anaesthetic and placebo administration. In one study, patients were told that they “may receive an active or a placebo agent” (95), whereas in the second, they were told that “the agent you have been given is known to significantly reduce pain in some patients” (22). The more subtle changes in instructions and expectations affected the magnitude of placebo responses, whereby in the second trial (more certain instructions) placebo responses were larger.

Physician expectations seem to matter also. One small double-blinded trial conducted some time ago involved administration of a placebo in patients with post-operative dental pain (96). Patients were divided into two groups and were told that they could receive a drug which would increase their pain (naloxone), decrease their pain (fentanyl) or have no effect (placebo). In contrast, the clinicians were told that in one of the groups, there was no chance of administering an active analgesic drug, and to this extent it was the clinicians who were manipulated and not the patients. The placebo response was dramatically less in the group where the clinicians believed that no analgesic therapy could be given, demonstrating that clinicians' beliefs can affect placebo effects. Interestingly, the double-blind nature of the study

suggests that alterations in clinicians' beliefs may have altered the therapeutic context (and placebo effect) in more subtle ways, as the patients were not aware of the different information given to the clinicians.

Loss of placebo mechanisms reduce therapeutic efficacy

Loss of placebo mechanisms has been shown to have significant clinical ramifications. For example, a recent study used an open-hidden design in Alzheimer's Disease (97). It showed that the placebo component (difference between open and hidden administrations) was correlated with cognitive status and functional connectivity between brain regions. Reductions in both cognitive status and functional connectivity correlated to reduced placebo mechanisms and reduced overall analgesic effect, so much so that an increase in dose was required for the same level of analgesia. This signifies the importance of not only attempting to maximize placebo components of therapies, but assessing situations where loss of placebo mechanisms may require increased therapeutic dosage.

Ethical principles of enhancing placebo effects in clinical care

Any ethical evaluation of efforts to promote placebo effects in clinical practice first requires knowledge as to the clinical relevance and significance of placebo effects. The evidence reviewed in the previous section suggests the potential for placebo interventions and the therapeutic context to promote clinically important symptomatic relief. Nevertheless, more studies of placebo effects in specific clinical settings are required before the use of treatments with the primary aim to promote placebo responses can be recommended as evidence-based practice.

A second important ethical consideration relates to whether and how placebo effects can be promoted without deception. Since it has been demonstrated that placebo effects are inherent in routine clinical care, and that the psychosocial context surrounding the patient (including the patient-Doctor interaction and the therapeutic ritual) can be augmented to improve these placebo effects, it is ethically sound, not to mention clinically relevant, to provide a supportive clinical encounter that relieves anxiety and promotes positive expectations along with honest disclosure of the expected benefits of a medically indicated therapy. To this extent, routine conscious attempts to identify and exploit features of the clinical encounter to augment placebo effects represent one ethical (non-deceptive) means of applying the understanding of placebo mechanisms to improving clinical outcomes.

Whether it is ethical to recommend a treatment primarily to produce a placebo effect is a more complicated and controversial question. Most studies of the placebo effect have employed deception in the administration of "inert" placebos as a key element of experimental design. Whereas the use of deception in research poses its own ethical issues (98), the problem of deception in clinical practice raises even stronger concerns. To recommend or administer a placebo intervention to a patient presented deceptively as a therapy with specific efficacy for the patient's condition violates informed consent and threatens the trust that is central to clinical practice (99). Recent data indicate that the administration of sugar pills and saline injections is in fact very low (100,101), but that clinicians commonly prescribe various active treatments with the primary intent of promoting a placebo response or complying with the wishes of the patient. The available evidence suggests that the practice of disclosure to patients regarding such placebo treatments is deceptive or at least not sufficiently transparent.

Can the recommendation for a treatment intended to promote the placebo effect be made without deception and also without undermining its therapeutic potential? Consider, for example, the case of a clinician who recommends treatment with acupuncture for a patient with chronic low back pain who has not been helped by standard medical therapy. Aware of the

results of the recent acupuncture trials, described above, this clinician thinks that acupuncture may work by promoting a placebo response. The clinician might provide the following disclosure to the patient: “I recommend that you try acupuncture. Several large studies have shown that traditional acupuncture is not better than a fake acupuncture treatment, but that both of these produce considerably greater symptom improvement in patients with chronic low back pain condition as compared with those patients who receive no treatment or conventional medical therapy. Although the specific type of needling doesn't appear to make any difference, it is likely that acupuncture works by a psychological mechanism that promotes self-healing, known as the placebo effect.” On its face, this disclosure appears honest. A patient who received this disclosure and subsequently got better after undergoing acupuncture might nonetheless develop a false belief about why it worked. This does not mean, however, that the patient has been deceived by his physician.

Can it be ethical for clinicians to prescribe “inert” placebos with a disclosure that the treatment being administered (a placebo) “has been shown to be effective by altering pain transmission in similar ways to other treatments”? As is the case with most of the studies of the placebo effect (98), an element of deception is involved, and in this example the element of deception relates to a lack of full disclosure of the content of the placebo and the complete reason for why it is being given: that is, not only to modulate pain transmission but to do so through a placebo effect. Therefore, as is the case with the example of acupuncture, completely eliminating deception would involve additional disclosure that the placebo had no active medicine in it and would be working through psychological mechanisms that promote self healing. It is not known how such disclosure might affect placebo responses, and with the exclusion of two small trials in patients with various mild psychiatric symptoms (and without a no-treatment control group) (102,103) there has been no research to answer this important question. It is therefore important for clinicians who are recommending treatments for the primary intention of maximizing placebo effects to be aware of the ethical implications of different types of disclosure and the potential for deception. Clinically-focused research is needed to explore non-deceptive techniques for administering treatments aimed at promoting placebo effects.

Conclusions

It is evident that placebo effects are real and that they have therapeutic potential. Laboratory evidence supports the existence of numerous placebo mechanisms and effects in both healthy volunteers and patients with a variety of medical conditions. Furthermore, clinically relevant evidence demonstrates that placebo effects can have meaningful therapeutic effects, by virtue of magnitude and duration, in different patient populations. Although substantial progress has been made in understanding placebo effects, considerable scientific work remains to be done in both laboratory experiments and translational clinical trial research, with the ultimate aim of harnessing placebo effects to improve patient care.

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DISEASE/SYSTEM	MECHANISMS	REFERENCES
Pain	Activation of endogenous opioids and dopamine (placebo). Activation of CCK and de-activation of dopamine (nocebo)	Levine et al 1978, Benedetti 1996, Amanzio and Benedetti 1999, Benedetti et al 1997, 2006; Scott et al 2008
Parkinson's disease	Activation of dopamine in the striatum and changes in activity of neurons in basal ganglia and thalamus	de la Fuente-Fernandez et al 2001 Benedetti et al 2004, 2009
Depression	Changes of electrical and metabolic activity in different brain regions, e.g. ventral striatum	Leuchter et al 2002, Mayberg et al 2002
Anxiety	Changes in activity of the anterior cingulate and orbitofrontal cortices. Genetic variants of serotonin transporter and tryptophane hydroxylase 2	Petrovic et al 2005 Furmark et al 2008
Addiction	Changes of metabolic activity in different brain regions	Volkow et al 2003
Autonomic responses to DBS	Change of neuronal excitability in limbic regions	Lanotte et al 2005
Cardiovascular	Reduction of β -adrenergic activity of heart	Pollo et al 2003
Respiratory	Conditioning of opioid receptors in the respiratory centres	Benedetti et al 1999
Immune system	Conditioning of some immune mediators (e.g., IL-2, IFN- γ , lymphocytes)	Ader et al 1975 Goebel et al 2002
Endocrine system	Conditioning of some hormones (e.g., growth hormone, cortisol)	Benedetti et al 2003
Physical performance	Activation of endogenous opioids and increased muscle work	Benedetti et al 2007 Pollo et al 2008
Alzheimer's disease	Prefrontal executive control and functional connectivity of prefrontal areas	Benedetti et al 2006

Figure 1.
The principal placebo mechanisms that have been unraveled across different medical conditions and systems/apparatuses

Figure 2.

Social stimuli around the treatment may activate, through expectation and/or conditioning mechanisms, a number of receptorial pathways in different diseases and therapeutic interventions (the involvement of 5-HT receptors in hormonal responses and depression is not definitive). These receptors are the same to which different drugs bind, thus indicating that psychosocial factors are capable of modulating the action of drugs. This interference has profound implications for our understanding of drug action: when a drug is given, the very act of administering it (i.e., the psychosocial context) may perturb the system and change the response to the drug. From : Benedetti (2008) *Annu Rev Pharmacol Toxicol*

Figure 3.

In routine clinical practice, any treatment has a specific and a non-specific effect. The non-specific effect may come from the mere knowledge that a treatment is being given. The effectiveness of the active treatment can be assessed either by eliminating its specific effect (placebo study) or by eliminating the non-specific effects (hidden treatment). From: Colloca et al. (2004) *Lancet Neurol*

AIM:

The aim of this paper was to review the literature on the placebo effect to ascertain whether advances in understanding of placebo mechanisms in both laboratory and clinical settings could lead to a reconceptualisation of placebo effects with implications for clinical practice.

SEARCH STRATEGY:

We searched the Cochrane Library (2001-2009), MEDLINE 1902-2009, PREMEDLINE, EMBASE (1966-2009). We used the search terms placebo, placebo effect, placebo response, nocebo, context effect, patient-therapist interaction, expectation, conditioning.

We largely selected publications in the last ten years, but did not exclude commonly referenced and highly regarded older publications, particularly those that were pertinent to the history and conceptualization of placebo effects. We also searched the reference lists of articles identified by this search strategy, particularly the reference lists of systematic reviews and meta-analyses, and selected those we judged relevant, including review articles and book chapters.

Papers were included if they studied or discussed the history, ethics and mechanisms of placebo use and placebo effects both in experimental and clinical settings. In the case of mechanistic and clinical trials, trials were only included if they were controlled, however, rare exceptions were made in older and relevant papers where a control group was not employed. This literature was synthesized into the most appropriate and relevant reference list for the purposes of this review.

Panel 1.

Panel 2.

Contributions of the psychosocial context surrounding the patient (or placebo component of a given therapy) to the overall response