Biological, clinical, and ethical advances of placebo effects

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For many years, placebos have been defined by their inert content and their use as controls in clinical trials and treatments in clinical practice. Recent research shows that placebo effects are genuine psychobiological events attributable to the overall therapeutic context, and that these effects can be robust in both laboratory and clinical settings. There is also evidence 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 use of placebo mechanisms that are inherent in routine clinical care, and encourage the use of treatments that stimulate placebo effects.

Introduction

The notion of something called "placebo" started with St Jerome's mistranslation of the first word of the ninth line of Psalm 116, when instead of translating the Hebrew "I will walk before the Lord", he wrote "Placebo Domino in regione vivorum" ("I will please the Lord in the land of the living"). By the 13th century, when hired mourners waited for Vespers for the Dead to begin, they often chanted the ninth line, and so were called "placebos" to describe their fake behaviour.[1] Later, in *The Canterbury Tales*, Chaucer named his sycophantic, flattering courtier Placebo. The introduction of placebo controls, which entailed the administration of 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] Individuals "possessed" by the devil were given false holy objects and if they reacted with violent contortions—as if they were genuine relics of the holy cross or consecrated wafers—it was concluded that their possession was in their imagination. This idea of placebo controls was then used in medical experiments, beginning with the Franklin commission's debunking of the psychic force of mesmerism or animal magnetism in 1784.[3]

The use of the word placebo in a medical context to describe innocuous treatments to make a patient comfortable dates from at least the end of the 18th century.[4] The earlier, unsavoury connections undoubtedly led to the tainted reputation of placebos and placebo effects that persisted until very recently.[1] Mainstream interest in placebo effects only began with the widespread adoption of the randomised controlled trial (RCT) after World War II, when it was noticed that people improved—sometimes dramatically—in placebo control groups.[5] Soon after, in his famous proto-meta-analysis, Henry Beecher claimed that about 35% of patients responded positively to placebo treatment.[6] Beecher, however, encouraged an inflated notion of the "powerful placebo" because he failed to distinguish the 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 past 10 years. In this Review, we assess whether advances in understanding of placebo mechanisms in both laboratory and clinical settings could lead to a reconsideration of placebo effects with implications for clinical practice.

Conceptual background

The association of placebo effects with RCTs has caused confusion because the response in the placebo group is not necessarily a genuine psychosocial response to the simulation of treatment. In fact, the reported response to placebo in RCTs might reflect the natural course of disease, fluctuations in symptoms, regression to the mean, response bias with respect to patient reporting of subjective symptoms, or 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] not to mention applying them in clinical research and practice.[9]

Much of the controversy surrounding placebo effects relates to how they are considered and then defined.

Search strategy and selection criteria

We searched the Cochrane Library (2001–09), Medline (1902–2009), PreMedline, and Embase (1966–2009) databases for reports published in English using the search terms "placebo", "placebo effect", "placebo response", "nocebo", "context effect", "patient-therapist interaction", "expectation", and "conditioning". We mainly selected reports published in the past 10 years, but did not exclude frequently referenced and highly regarded older publications, especially those that were pertinent to the history and understanding 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. Reports 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 for older and relevant articles in which a control group was not used.

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 here is that if something is inert, it is by definition unable to elicit an effect.[7,8] This definition can be further confused with terms such as active,[10] true, and perceived placebos,[11] which are all attempts to better understand 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 placebo. 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 resolve these confusions and better understand placebo effects in clinical trials and practice, it is necessary to reconsider 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 suggests that the placebo effect is a genuine psychobiological event attributable to the overall therapeutic context.[9,14] This psychosocial context can consist of individual patient and clinician factors, and the interaction between the patient, clinician, and treatment environment. The treatment environment represents the many factors associated with a treatment context (such as the specific nature of the treatment and the way it is delivered) and the patient–clinician relationship, which is a term that encompasses several factors that constitute the therapeutic interaction (figure 1).[12] The placebo intervention is designed to simulate a therapeutic context such that the effect of the intervention (placebo effect) is attributable to the way in which this context affects the patient's 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 concept allows for progression in understanding of the many factors that make up the psychosocial context surrounding a patient and how these factors, and the mechanisms by which they operate, can be enhanced in clinical practice.

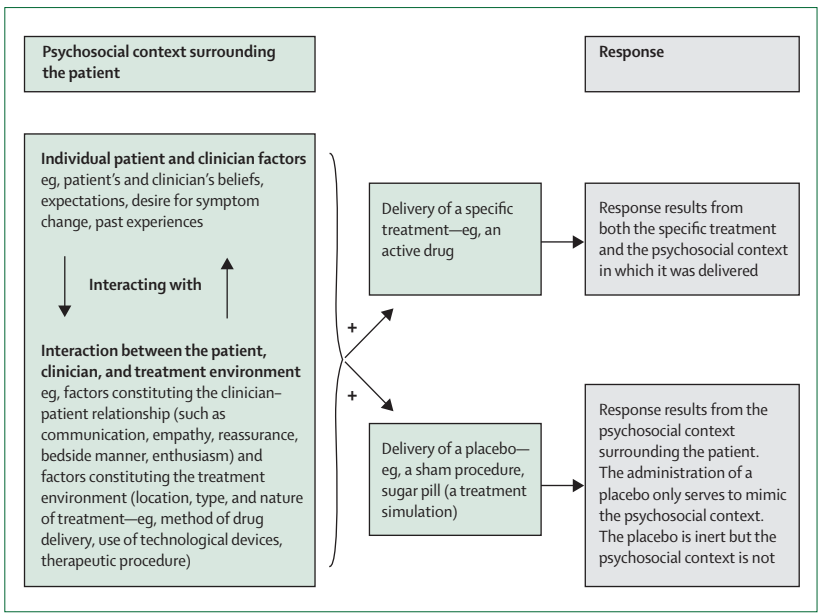

Figure 1: **Contribution of the psychosocial context surrounding the patient (or placebo component of a given treatment) to the overall response**

Mechanisms of placebo effects

Some of the mechanisms that underlie placebo effects are summarised in the table, showing that there is not one placebo effect, but many.[14–16] These mechanisms can be broadly discussed from psychological and neurobiological viewpoints.

Psychological mechanisms

From a psychological viewpoint, there are many mechanisms that contribute to placebo effects. These mechanisms include expectations, conditioning, learning, memory, motivation, somatic focus, reward, anxiety reduction, and meaning.[9,39] Although there is a growing amount of research into these mechanisms, two principal mechanisms are well supported.

The first mechanism involves expectancy: patients given placebo have expectations of future responses.[40] Many experiments have used simple verbal cues as modulators of expectations.[17,33,41] For example, a participant 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.[41] Such verbal cues have been shown to manipulate patients' expectations and mediate placebo effects—eg, placebo analgesic effects in experimental[33] and clinical pain,[42] placebo-induced changes in motor performance in Parkinson's disease,[23,43] changes in emotions,[28] and brain responses in patients with drug addiction.[30] Furthermore, the presence of a conditioning protocol to increase expectations results in larger analgesic responses to placebo, showing that expectation can both mediate and modulate placebo effects,[17,44,45] as well as interact with other constructs such as desire and emotion.[9,42]

A second mechanism underlying placebo effects involves classical conditioning.[46] 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 shown in both animal[34,47,48] and human studies,[35,36,44,45] although it has been difficult to exclude any cognitive component (such as expectation) in human beings.[49,50] Despite this issue, conditioning

	Mechanisms
Pain	Activation of endogenous opioids and dopamine (placebo); activation of cholecystokinin and deactivation of dopamine (nocebo)[17–22]
Parkinson's disease	Activation of dopamine in the striatum and changes in activity of neurons in basal ganglia and thalamus[23–25]
Depression	Changes of electrical and metabolic activity in different brain regions (eg, ventral striatum)[26,27]
Anxiety	Changes in activity of the anterior cingulated and orbitofrontal cortices; genetic variants of serotonin transporter and tryptophan hydroxylase 2[28,29]
Addiction	Changes of metabolic activity in different brain regions[30]
Autonomic responses to deep brain stimulation	Change of neuronal excitability in limbic regions[31]
Cardiovascular system	Reduction of β-adrenergic activity of heart[32]
Respiratory system	Conditioning of opioid receptors in the respiratory centres[33]
Immune system	Conditioning of some immune mediators (eg, interleukin 2, interferon γ, lymphocytes)[34,35]
Endocrine system	Conditioning of some hormones (eg, growth hormone, cortisol)[36]
Physical performance	Activation of endogenous opioids and increased muscle work[37,38]
Alzheimer's disease	Prefrontal executive control and functional connectivity of prefrontal areas[21]

Table: **Mechanisms for placebo effects in medical conditions and physiological systems**

mechanisms in human beings are substantiated by the fact that placebo effects are higher in magnitude after a conditioning protocol (even if an expectation mechanism is present).[17] Additionally, conditioning mechanisms mediate placebo-induced changes in unconscious physiological processes such as hormone secretion[36] and immune responses.[35]

The interaction between expectation and conditioning mechanisms remains an area for further research, which might be particularly relevant to exploring the clinical implications of these mechanisms. Although classical conditioning, manifesting an automatic unconscious mechanism, exists in human beings, it can also be regarded as a complex process consisting of cognitive components and derived from previous experience of either positive or negative therapeutic outcomes.[51] Accordingly, conditioning and expectation are certainly entangled in the occurrence of placebo effects in clinical practice. The most reasonable interpretation of recent publications is that conditioning follows expectation and is dependent on the success of the first encounter. This notion leads to the possibility that the first encounter is crucial for the development of subsequent robust placebo responses: the higher the expectation, 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 mediate placebo effects.[52] For example, participants who observed a demonstrator simulating responsiveness to a therapy had placebo analgesic responses that were similar in magnitude to those in patients who received a classical conditioning procedure.[53]

Neurobiological mechanisms

Looking at placebo mechanisms from the neurobiological viewpoint further emphasises that there are several placebo effects. Placebo effects can occur in different physiological systems in healthy volunteers and in patients with many different clinical conditions (figure 2).

Most research into the neurobiology of placebo responsiveness has addressed placebo analgesia; accordingly, the neurobiology of placebo effects is usually considered in terms of opioid and non-opioid mechanisms.[54,55] Several studies have shown that placebo effects can be completely[18,19,56] or partly reversed[57] by the opioid antagonist naloxone, supporting the involvement of endogenous opioids in some placebo analgesic effects.[58] Furthermore, placebo analgesic effects are likely to be inhibited by the peptide cholecystokinin,[19] since such effects are potentiated in patients treated with cholecystokinin antagonist.[59,60] Several studies have shown that placebo effects can occur at specific body regions.[33,41,61] This body-region specificity is reversed by naloxone,[33] suggesting that analgesic responses to placebo involve highly specific endogenous opioid release, rather than a more generalised opioid release (such as increased opioid concentration in the cerebrospinal fluid).[62] These results have been substantiated and extended by brain imaging techniques such as PET[63,64] and functional MRI.[65–67] In one PET study, brain changes in response to placebo were reported to be similar to changes seen after treatment with opioid drug.[68] Opioid-mediated placebo responses also extend beyond pain pathways. Some studies have shown that placebo-induced respiratory depression (a conditioned placebo side-effect)[69] and decreased heart rate and β-adrenergic activity[32] can be reversed by naloxone.

Many placebo effects are mediated by non-opioid mechanisms, such as the release of different neurotransmitters and neuromodulators. In one study, the placebo response in participants who had previous conditioning with an opioid drug was reversed by naloxone; however, there was no reversal in those who had conditioning with a non-opioid drug.[17] Therefore, completely different placebo mechanisms can be produced depending on the drug used in the conditioning protocol.

Although other medical disorders have been investigated from a neurobiological perspective, the placebo mechanisms in these conditions are little understood compared with those for pain and analgesia. For example, in patients with Parkinson's disease, administration of placebo led to dopamine release in the striatum[23,70] and resulted in changes in basal ganglia and thalamic neuron firing.[24,25] Studies have also shown changes in metabolic activity in the brain after administration of placebo in patients with depression[26] and after manipulation of expectations in patients with drug addiction.[30]

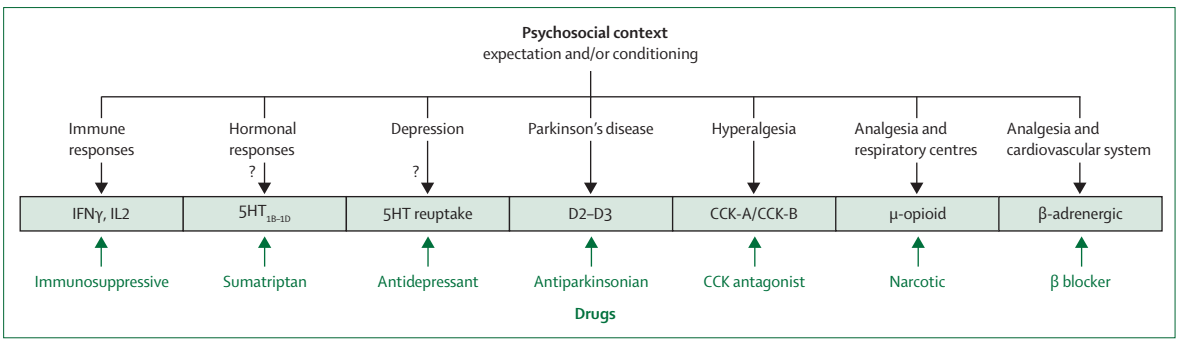

***Figure 2*: Receptor pathways activated by both psychosocial context and drugs**
Social stimuli around the treatment might activate, through expectation or conditioning mechanisms, several receptor pathways in different diseases and therapeutic interventions (the involvement of serotonin [5-hydroxytryptamine; 5HT] receptors in hormonal responses and depression is not definitive). These receptors are the same to which different drugs bind, suggesting that psychosocial factors are capable of modulating the action of drugs. This interference has implications for our understanding of drug action: when a drug is prescribed, the very act of giving it to a patient (ie, the psychosocial context) might affect the system and change the response to the drug. Reproduced with permission from reference 39. IFNγ=interferon γ. IL2=interleukin 2. CCK=cholecystokinin.

Less research has been concerned with the nocebo effect, an occurrence that is opposite to the placebo effect. The reason for the paucity of data is mainly because of ethical limitations, since nocebo administration involves the induction of negative expectations. Cholecystokinin has a key role in nocebo hyperalgesia, which occurs through anticipatory anxiety mechanisms.[20,21,37] Deactivation of dopamine release has also been found in the nucleus accumbens during nocebo hyperalgesia,[22] which suggests the involvement of different neurotransmitters. Furthermore, a neuroimaging study has shown that nocebo affects brain activation differently from placebo, including in the hippocampus and regions involved with anticipatory anxiety.[71]

Implications for clinical practice

Understanding how placebo effects work clinically in relevant patient populations over time has not kept pace with the recent research into mechanisms of placebo effects, which has mainly involved laboratory experiments done over short durations with healthy participants. In the case of clinical populations, the study of long-term placebo responsiveness has been limited to RCTs. However, these studies rarely included groups of participants receiving no treatment to control for natural history and regression to the mean, making it difficult to discern a genuine placebo effect. Several meta-analyses have attempted to address the presence and magnitude of placebo effects in RCTs, including some studies in which 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.[72–74] However, placebo effects are much larger in studies that investigate placebo mechanisms.[75,76] This finding is not at all surprising given that the mechanistic experiments use controlled manipulations of verbal instructions and context that might be more representative of normal clinical practice than a clinical trial setting. It is therefore important to 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 single-blind RCT in 262 patients with irritable bowel syndrome investigated whether placebo effects can be disaggregated into two main components (placebo ritual alone and placebo ritual plus supportive patient–clinician relationship) and then progressively combined to produce clinically significant improvements compared with no treatment.[77] The placebo ritual consisted of a validated placebo acupuncture device, which was used in both treatment groups.[78] Instead of penetrating the skin, the needle retracts into the needle handle. The supportive patient–clinician relationship, used only in one group, was prospectively scripted and consisted of attention, warmth, confidence, and thoughtful silence. At the 3-week outcome, adequate relief on a validated measure for irritable bowel syndrome was reported by 62% of participants in the placebo ritual plus supportive care group, 44% in the placebo ritual alone group, and 28% in the no-treatment group ($p<0·001$). The results were similar with three other validated measures for irritable bowel syndrome used in the study. The effect size of 62% adequate relief was similar to the improvement seen in patients treated with alosetron in RCTs of irritable bowel syndrome.[79] Outcomes were similar after an additional 3 weeks of follow-up. In addition to showing that genuine placebo effects can be statistically and clinically significant over time in clinical populations, this trial showed that placebo effects can be incrementally added in a manner resembling a graded dose escalation of component factors. In a separate analysis of the study, patient extroversion, agreeableness, and openness to experience were found to be associated with placebo responses in the placebo ritual plus supportive care group but not in

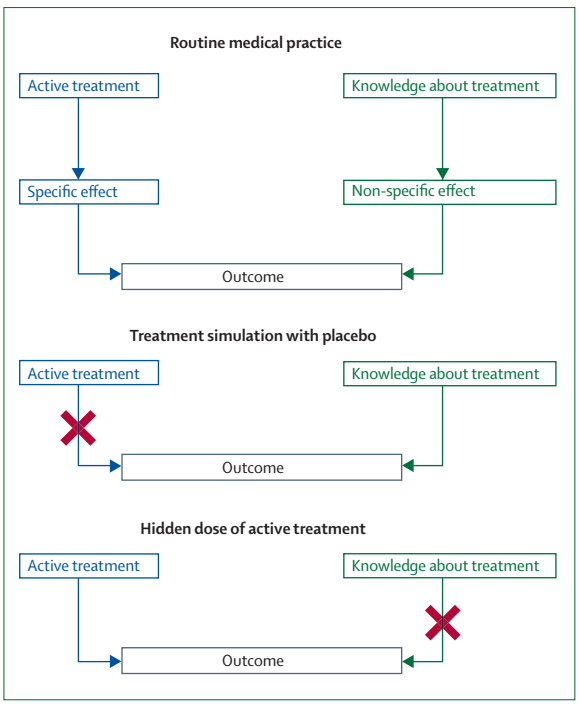

***Figure 3*: Rationale of the open-hidden study design**
In routine clinical practice, any treatment has a specific and a non-specific effect. The non-specific effect might come from the knowledge that a treatment is being given. The effectiveness of the active treatment can be assessed either by eliminating its specific effect (placebo study) or by eliminating the non-specific effects (hidden treatment). Reproduced from reference 94.

the placebo ritual alone group.[80] The investigators also reported significant differences in outcomes between practitioners. Future integration of such study designs in RCTs with mechanistic laboratory work will allow for better understanding of these placebo mechanisms and how they can be augmented in clinical practice.

Several RCTs have examined whether different methods for delivery of placebo produce different effects.[81] The largest such study, in 270 patients with chronic arm pain caused by repetitive use, compared a sham device (placebo acupuncture) with an inert oral pill.[82] At 2 weeks of treatment, patients assigned to placebo pills had greater improvement in ability to function (mainly related to less disturbed sleep because of pain) than did patients assigned to sham acupuncture ($p<0·05$); however, pain did not differ between groups. At the end of the study (6 weeks), patients assigned to sham acupuncture had a significant reduction in pain compared with those in the placebo pill group ($p<0·001$). Depending on the complaint and the length of time that placebo was received, different placebos had different effects. Not all medical rituals are the same: placebo pills are better for sleep and sham needles are better for pain. Nocebo effects also differed between treatment delivery groups. Patients in the placebo pill group were told they might have the adverse effects (eg, drowsiness) of a medication (amitriptyline) and the sham acupuncture group was informed about the side-effects of acupuncture. Although 30% of people in both placebo groups reported adverse effects, the type of effects differed between groups and mimicked the information provided during the informed consent process.

Some commentators have suggested that alternative therapies with elaborate procedures and distinct environmental cues might have pronounced and clinically significant placebo effects.[83,84] Recent RCTs of acupuncture, although not designed to study placebo effects, have provided results that lend support to this hypothesis. A series of large trials in Germany compared acupuncture done according to traditional Chinese medicine (verum acupuncture), sham acupuncture (superficial needling at non-acupuncture points), and either no-treatment or usual clinical care. Conditions studied included migraine,[85] tension headaches,[86] chronic low back pain,[87,88] and osteoarthritis of the knee.[89] Generally across the various trials, outcomes did not differ between verum and sham acupuncture groups; however, participants in both of these groups had substantially greater symptom improvement than did those in the no-treatment and usual clinical care control groups.[90] Linde and colleagues[91] reported that in four of these RCTs (n=864), patient's expectation of pain relief was the most robust predictor of efficacy of acupuncture treatment, irrespective of the group assignment to genuine or sham treatment. The effect of positive expectation on outcome lasted for 1 year. These results therefore accord with the hypothesis that acupuncture works by means of a placebo effect. A more recent study in 640 patients with chronic low back pain showed that participants assigned to 8 weeks of toothpick simulation sham acupuncture plus usual care had clinically meaningful improvements in outcomes compared with those assigned to usual clinical care alone, and such effects also lasted for 1 year.[92] This study however did not find a correlation between measured expectation and outcomes.[93]

Some of the clearest evidence supporting the involvement of placebo effects in clinical care comes from trials with an open-hidden study design (figure 3). In this experimental approach, a treatment is given in a routine manner (open treatment), in which the psychosocial context surrounding treatment administration is present, and in a hidden manner, in which the treatment is given without the patient's knowledge. In the case of a drug intervention, the open treatment mimics normal clinical care; the clinician injects a drug in full view of the patient with verbal and contextual interactions. For the hidden treatment, the drug is infused by a computer pump in the absence of the clinician and the therapeutic context. Patients receiving hidden treatment 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

treatment. Because the hidden administration removes the psychosocial context of treatment, the placebo component is defined as the difference in outcome between open and hidden treatments, although no placebo is given.[94,95]

The open-hidden study design has been used in several clinical settings. Hidden treatment with widely used painkillers (morphine, buprenorphine, tramadol, ketorolac, metamizol) has been shown to be markedly less effective in reducing pain than has open treatment.[94,96,97] This finding was seen in both healthy volunteers receiving experimentally induced pain (pain ratings were higher in the hidden treatment group than in the open treatment group) and in patients with postoperative pain (the dose needed to reduce pain by 50% was much higher in the hidden treatment group than in the open treatment group).[96] Similar differences between open and hidden treatment groups have been reported after drug treatment in patients with anxiety and after deep brain stimulation in patients with Parkinson's disease.[31,97] Slightly different methods have been used in patients with drug addiction; the absence of an expectation component in patients given stimulant drug treatment resulted in reduced regional brain glucose metabolism and verbal reports of efficacy.[30] Thus, the overall outcome of a treatment combines the specific pharmacological or physiological action of the treatment and the psychosocial context in which it is delivered. The psychosocial context represents the placebo component, which is based on patient expectations.

The open-hidden study design has provided a means of exploring the interaction between placebo effects and responses to active treatments. This analysis has not been possible in standard RCTs designed to assess treatment efficacy, since they only compare the response to placebo with the response to the index intervention without providing an understanding of the interaction between the two. For example, findings from a clinical trial done in 1995 showed that the cholecystokinin antagonist proglumide was more effective in reducing intensity of postoperative pain than was placebo, which in turn was more effective than no treatment.[59] According to methods of analysis used in classic clinical trials, these results would suggest that proglumide is a good analgesic drug that acts on pain pathways, whereas placebo reduces pain by activating placebo analgesic mechanisms (through expectation pathways). However, this conclusion is erroneous, since a hidden injection of proglumide had no analgesic effect. If the drug is an effective modulator of pain pathways, such a difference between open and hidden treatment would not be seen. In this instance, the drug achieves a response by interacting with and enhancing placebo mechanisms (expectation pathways), not by acting on pain pathways, and therefore is only effective when combined with the placebo mechanisms inherent in the clinical encounter. Placebo mechanisms can interact with drug treatments, even if no placebo is given, since every treatment is given in a therapeutic context that has potential to activate and modulate placebo mechanisms, many of which can act on similar biochemical pathways to the actual drug (figure 2).

A short-term experimental trial done in 2001 has advanced our understanding of the clinical implications of modulating placebo effects in routine clinical care. In this trial, which assessed postoperative pain over several days, patients were given intravenous saline (placebo) as a background infusion in addition to routine analgesic treatment (buprenorphine on request).[98] One group of patients was told that the basal infusion was a rehydrating solution (natural history control group) and another group was told that it was a powerful painkiller (maximum placebo context). Overall intake of buprenorphine was monitored throughout the trial. The clear differences in the context (mainly expectation of benefit) of the basal infusion resulted in substantial differences in drug intake. The group who believed the solution was assisting in analgesia took 33% less buprenorphine for the same pain control than did those in the natural history control group, showing an important clinical effect and the potential for use of placebo effects in conjunction with an active treatment to reduce overall drug intake. A third group were told that "the solution may or may not be a powerful painkiller", representing classic double-blind treatment used in placebo-controlled trials. In this group, patients took 20% less buprenorphine than did controls.

Similar modulations in short-term placebo effects have been reported in more recent studies in patients with irritable bowel syndrome.[42,99] In these studies, patients were exposed to a painful stimulus (rectal distention balloon) under two conditions: local anaesthetic and placebo. In one study, patients were told that they "may receive an active or a placebo agent",[99] whereas in the second, they were told that "the agent you have been given is known to significantly reduce pain in some patients".[42] The subtle changes in expectations affected the magnitude of placebo responses, with larger placebo responses reported in the second trial, which had more definite instructions.

Clinicians' expectations also seem to affect placebo responses. In a small, double-blind trial done in 1985, patients with postoperative dental pain were divided into two groups and told that they could receive a drug which would increase their pain (naloxone), decrease their pain (fentanyl), or have no effect (placebo).[100] By contrast, the clinicians were told that in one of the groups, there was no chance of receiving an active analgesic drug, and to this extent it was the clinicians who were manipulated and not the patients. The placebo response was substantially lower in the group that clinicians believed would receive no analgesic treatment. The double-blind nature of the study

suggests that alterations in clinicians' beliefs might alter the therapeutic context (and placebo effect) in subtle ways, since patients were not aware of the information given to the clinicians.

Loss of placebo mechanisms can have important clinical ramifications. For example, an open-hidden study in patients with Alzheimer's disease showed that the placebo component (difference between open and hidden treatments) was correlated with cognitive status and functional connectivity between brain regions.[101] Reductions in both cognitive status and functional connectivity correlated with reduced placebo mechanisms and reduced overall analgesic effect, so much so that an increase in dose was needed for the same level of analgesia. This finding shows the importance of not only attempting to increase placebo components of treatments, but also of assessing situations in which loss of placebo mechanisms might necessitate an increased therapeutic dose.

Ethical principles of enhancing placebo effects in clinical care

Any ethical assessment of efforts to promote placebo effects in clinical practice first requires knowledge as to the clinical relevance and importance of placebo effects. The evidence reviewed here outlines 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 needed before use of treatments with the primary aim of promoting 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 placebo effects are inherent in routine clinical care, and the psychosocial context surrounding the patient (including the patient–clinician interaction and the therapeutic procedure) can be enhanced to improve these placebo effects, it is ethically acceptable, 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 treatment. Therefore, 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 improve 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 used 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,[102] the problem of deception in clinical practice raises even stronger concerns. To recommend or give a placebo intervention deceptively as a treatment with specific efficacy for a patient's condition violates informed consent and threatens the trust that is central to clinical practice.[103] Recent data suggest that prescriptions of sugar pills and saline injections are rare,[104,105] but that clinicians often prescribe various active treatments with the main 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 a 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 acupuncture treatment 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, this clinician thinks that acupuncture might 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 fake acupuncture treatment, but that both of these produce substantially greater symptom improvement in patients with chronic low back pain compared with those patients who receive no treatment or conventional medical therapy. Although the specific type of needling does not seem to make any difference, it is possible that acupuncture works by a psychological mechanism that promotes self-healing, known as the placebo effect". At face value, this disclosure seems 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 or her clinician.

Can it be ethical for clinicians to prescribe inert placebos with a disclosure that the treatment being given "has been shown to be effective by altering pain transmission in similar ways to other treatments"? As is the case with most studies of the placebo effect,[102] an element of deception is involved. In this case, 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—ie, not only to modulate pain transmission but to do so through a placebo effect. Therefore, as with acupuncture, completely eliminating deception would require additional disclosure that the placebo had no active drug in it and would be working through psychological mechanisms that promote self-healing. How such disclosure might affect placebo responses is unknown, and apart from two small trials in patients with various mild psychiatric symptoms (and without a no-treatment control group),[106,107] no research

has addressed this important question. It is therefore important that clinicians who are recommending treatments for the primary aim of enhancing placebo effects are 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 prescribing treatments aimed at promoting placebo effects.

Conclusions

Laboratory evidence supports the existence of several placebo mechanisms and placebo effects in both healthy volunteers and patients with a variety of medical conditions. Furthermore, clinically relevant evidence shows that placebo effects can have meaningful therapeutic effects, because of their long magnitude and duration, in different patient populations. Although substantial progress has been made in understanding placebo effects, much laboratory and translational clinical trial research remains to be done, with the ultimate aim of harnessing placebo effects to improve patient care.

Contributors

All authors participated in the search of the published work and the writing of the report. All authors have seen and approved the final version.

Conflicts of interest

We declare that we have no conflicts of interest.

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