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The placebo in practice: how to use it in clinical routine

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Purpose of review

Recent placebo literature provides the scientific basis for the different psychological factors that influence the outcome of a medical treatment. The aim of the present review is to summarize the recent findings of placebo research offering useful tools for everyday medical routine.

Recent findings

Treatment efficacy is influenced by the patient's expectations of therapeutic benefit. Indeed, positive or negative expectations may lead to symptom improvement or worsening, respectively. Therefore, in clinical practice, patients' expectations and beliefs need to be considered and controlled appropriately. In addition, previous experience influences the healing process, as shown by classical conditioning studies. This knowledge can be used to increase the effect of pharmacological or procedural treatments, to reduce drug intake, and to minimize psychological adverse events. Overall, a significant enhancement of the therapeutic outcome can be obtained by potentiating empathic communication and establishing a cooperative patient-provider relationship.

Summary

Placebo research provides solid scientific ground for all those psychological aspects that characterize every medical treatment. It also gives us information on the functioning of the human brain, with the possibility to exploit some of these mechanisms in routine medical practice.

Keywords

Placebo, expectations, learning, healing process

Key points

- Placebo research provides scientific ground for the use of practical tools to improve daily medical routine.
- Patient’s beliefs and expectations about the outcome represent crucial factors in every medical treatment, influencing therapy efficacy.
- The use of cooperative and empathic approaches should be encouraged, to increase patients’ expectations.
- Patients’ previous experiences and learning through classical conditioning mechanisms could be exploited for optimization of drug administration.
- The open/hidden protocol of drug administration allows enhancement of patient’s awareness of the therapy and minimization of adverse effects of therapy interruption.

Introduction

In the course of history, medical practice has considerably changed. The ancient and primitive medicine of shamans and priests was psychological in nature, and centered on words and rituals. The outcome of those psychological treatments was in many cases remarkable and aimed to treat the person. Modern medicine, also called “evidence-based”, consists in the administration of specific drugs and treatments, which first have to be tested in a randomized double blind placebo controlled trial. The healing effect of these chemical treatments is surely important, nonetheless it is aimed at treating the disease rather than the person. In spite of the clear advantage of modern medicine, we are now witnessing increasing interest and awareness of the importance of the psychological factors that surround every medical act. This knowledge comes from different fields. On the one hand palliative medicine is promoting a healing process which aims to take care of the person rather than to cure the disease: it emphasizes the care of the personal, physical and social needs of the patient, the quality of life and the relationship and communication between doctor and patient. On the other hand, research about the placebo effect has demonstrated the crucial role of the psychosocial context, leading to a comprehensive model of medicine that includes both chemical and psychological processes. Indeed, any therapeutic treatment, be it pharmacological or procedural, can be described as the result of two different processes, both contributing to the therapeutic benefit: the specific chemical process, i.e. the action of the pharmacological agent (e.g. morphine), and the ritual process, i.e. the psychosocial context surrounding the treatment, including the act of its administration (e.g. the color of the morphine pill, the words used to describe the features of the drug, and such like). In a placebo treatment the active drug is replaced with an inert substance (placebo) and only the ritual process is present. Accordingly, the placebo effect and its opposite nocebo effect, can be defined as the neurobiological modifications that occur in the patient’s brain after the simulation of a therapy [1**]. Remarkable placebo effects have been shown in several conditions, such as pain [2*-4], itch [5], Parkinson’s disease [6-9], depression [10-11], anxiety [12-13], immune functions [14-17], motor performance [18-20], asthma [21**].

Modern neuroscience have focused on two main aspects related to the placebo effect: first, the identification of the placebo underpinnings, such as the systems and the brain regions responsible for the placebo phenomenon, and second, the implications of placebo research for clinical practice. For example, the opioid system [22-27**] and the anti-opioid cholecystokinin (CCK) system [28-29] have been found to be involved. In addition, recent work has also shown that the endocannabinoid system mediates the non-opioid component of placebo analgesia [30**] and dopaminergic and serotoninergic systems have been documented in Parkinson’s disease and social anxiety, respectively [6-7-9-13]. Neuroimaging studies have also demonstrated that the placebo effect occurs along with the activation of a complex neural network, with prefrontal areas playing a crucial role [25,31-36*,37*].

Rather than focusing on these neurobiological, neuropharmacological and neuroanatomical advances of placebo research, which are described in detail in other reviews [38-41], in the present article we want to discuss some practical implications which have emerged in the course of the past years. We believe that these implications have the potential to positively affect the practice of those health professionals who work in the palliative care setting, who have to use the appropriate words, and who have to adopt the adequate attitudes and behaviors in their everyday medical practice.

Work with expectations

The expectation of an outcome represents a crucial factor in every medical treatment. In fact, a therapeutic procedure produces an effect partly because of the patient's expectations. These can be fostered by an internal locus of control (e.g. "I believe in myself and with the help of the drug I can cope with the disease) or by an external locus of control (e.g. "The doctor told me that the drug is so powerful that I will get better soon) [42]. Indeed, according to the cognitive theory of placebo, cognitive processes such as expectancy, anticipation, motivation, desire, belief, and optimism [43] are at play in the healing process. These are conscious processes activated by several factors, such as verbal instructions, patient-doctor interaction, emotional arousal of the patient. Different studies have investigated the role of these factors in both the laboratory and the clinical contexts. Recently, in the laboratory setting VanLaarthoven et al. [5] have manipulated expectations through verbal suggestions in a new experimental model of itch. Different somatosensory stimuli were delivered along with high (nocebo) or low (control) expectations of itch. As expected, following the suggestions of itch increase the subjects experienced significantly higher levels of itch compared with controls. The power of expectation through verbal suggestions has been documented also in clinical conditions. In a double-blind study, patients with asthma were randomly assigned to receive an active treatment with an albuterol inhaler, a placebo inhaler, sham acupuncture or no intervention [21**]. Even if albuterol administration resulted in a 20% increase in the forced expiratory volume (FEV_1), the patients reported no subjective differences between albuterol and placebo treatments. In terms of subjective outcome therefore, the placebo effect proved equivalent to the drug effect, confirming the importance of the patient's expectation about therapy effectiveness. In another study with Parkinson's disease patients, participants were told that they had a specific probability (25%, 50%, 75% or 100%) of receiving dopamine but they actually always received a placebo [9]. Significant dopamine release in the nigrostriatal and mesoaccumbens pathways occurred when the declared probability of receiving active medication was 75%, suggesting a close relationship between the improvement belief and the resultant clinical benefit. In a different study, it was demonstrated that the open-label administration of a placebo in irritable bowel syndrome (IBS) patients produces an improvement in IBS symptoms when patients know that “the placebo, at least in some circumstances, works as a real drug through the release of endogenous-opioids” [44]. Therefore, the knowledge and the understanding of a treatment boost positive expectations which, in turn, lead to symptom amelioration.

Use empathy and cooperation

Besides the importance of knowing and understanding the effect of a treatment, a second important aspect is represented by the patient’s needs. There are both cognitive and affective needs, the later being aimed at creating an empathic doctor-patient relationship [45]. Kelley et al. [46] investigated the affective needs in an experimental design with placebo acupuncture. IBS patients were divided into three groups. Two groups were treated with placebo acupuncture with either a warm empathic interaction, or a neutral interaction: the only difference between the two conditions was the quality of interpersonal interaction between the practitioner and the patient (warm and empathic or neutral and minimal). A third group (waiting list group) was periodically monitored but no treatment was delivered. A single outcome measure was constructed by combining 4 different IBS symptom scales. The empathic interaction produced an improvement compared with the neutral or waiting list interactions. This study highlights the importance of the clinical interaction during the healing process but does not differentiate between the emotional and the cognitive needs. The difference between these two aspects has been documented in a recent work [47], in which either empathic or cold communication was combined with positive or uncertain expectations about the effect of a painkiller on menstrual pain, in a 2 x 2 randomized control trial. Only warm and empathic communication with positive expectation led to a relevant decrease in anxiety state. Even if no measures of pain rating were reported, the key role of communication style is nonetheless documented, suggesting important implications for medical practice.

In the last decade the relationship between doctor and patient has considerably evolved. From a directive approach, in which the doctor prescribed a specific cure to the patient without discussion, a better refinement of the informed consent has increased the patient involvement in the therapeutic process, leading to a more cooperative relationship, embracing both cognitive and emotional needs. Rose et al. [48*] studied the effect of this cooperative relationship by testing the effect of the treatment choice. Participants underwent the cold pressor test for pain tolerance following the application of a novel painkiller (actually a placebo). They were split in three groups: a "choice" group was permitted to choose the analgesic treatment to be used during the pain task, a "no-choice" group received a random treatment and a control group was administered a treatment without eliciting expectations or giving a choice. Pain ratings were obtained during the test at different times, and after the test by means of a questionnaire. The choice group experienced less pain during and after the test compared with the no-choice and control groups, and the authors suggested a possible involvement of anxiety mechanisms. These results are useful especially in light of the recent emphasis on "patient-oriented" medicine [49]. Indeed the authors suggest that one positive consequence of the enhanced involvement of the patient in a therapy is a greater placebo response. On the whole, the increase of patients'expectations and the use of a cooperative and empathic approach clearly enhances medical treatments.

Use previous experiences and learning

The placebo literature has taught us that, in some circumstances, the healing process can be due to classical conditioning. For example, a painkiller is a significant event (unconditioned stimulus, US) that induces *per se* a natural response such as analgesia (unconditioned response, UR), whereas the physical features of the painkiller (e.g. shape, color, taste) or contextual cues that accompany its administration (e.g. hospital environment, white coats, or syringes) are neutral stimuli (conditioned stimuli, CS) that are not related to a specific innate behaviour. However, after repeated associations between the CS and the US (acquisition phase), the CS alone (evocation phase) can evoke the therapeutic benefit (conditioned response, CR). Following this schema, the placebo effect can be considered a learned CR that takes place after the repeated pairing between the CS and the US [50]. As recently shown, the higher the number of US-CS pairings, the stronger the placebo response [3]. The authors delivered tactile and painful stimuli on the dorsum of the foot, and exposed the volunteers to 1 or 4 conditioning sessions in which decreased (placebo) or increased (nocebo) perceived intensities (US) were induced and paired with green or red lights (CS), respectively. After 4 conditioning trials the subjects experienced more robust placebo and nocebo responses that lasted for the entire experiment. This study suggests that prior exposure to effective treatments may be clinically important, inducing long-lasting placebo responses. At the same time, avoiding negative experiences is crucial, in order to prevent the occurrence of nocebo effects.

In a clinical setting, Ader et al. [51] used a conditioning procedure to reduce the drug regimen while at the same time maintaining the symptoms improvement. Following an acquisition phase during which a corticosteroid therapy was given, patients with psoriasis were treated for eight weeks in different ways: a first group was administered a full medication for the entire experiment (standard therapy group without conditioning), a second received the full medication for 25-50% of the time and a placebo medication for the remaining time (conditioning group with partial reinforcement), a third group was treated with 25-50% of the full dose for the entire experiment (dose control group). A similar improvement was observed in the standard therapy and conditioning groups by using the Psoriasis Severity Scale index, whereas the dose control group showed severe worsening. This study demonstrates that the intermittent reinforcement, consisting in the combined administration of real drugs and placebos, is capable of producing beneficial effects, with the further advantage of reducing possible side effects often associated with a long lasting pharmacological treatment [52].

Enhance the knowledge about the therapy and avoid symptom worsening

In current medical practice, the doctor usually notifies the patient about the timing and effects of a treatment: this modality can be defined “open” or “expected”, because the patient is aware of the treatment administration and expects the therapeutic benefit. Conversely, when the patient receives the treatment without information about its administration (e.g. when the therapy is delivered by a computer-controlled infusion pump) the condition can be defined “hidden” or “unexpected”, because no expectations about the therapeutic outcome are elicited. Of course, in both the open and hidden conditions the same analgesic is administered, so that the only difference between the two conditions is represented by the patient’s expectations of clinical improvement [53**]. In a recent fMRI study [54**], it was shown that a hidden administration of a painkiller induced pain decrease, associated with decreased activity in several pain matrix regions, such as the primary somatosensory cortex, the insula, the anterior cingulate cortex and the thalamus. However, the effect doubled after an open administration, with increased activity in the pregenual anterior cingulate cortex and the dorsolateral prefrontal cortex. Therefore, in this study the psychological component, represented by the expectations of being treated, enhanced the pharmacological effect of the painkiller.

In another study, Bjorkedal et al. [55] used caffeine as an active placebo, i.e. a drug without effects on the symptom under investigation but mimicking the side effect of the active treatment. Zero or 4 mg/kg of caffeine were administered along with suggestions of analgesia (placebo and active placebo groups, respectively) or with no information (control or caffeine group, respectively) about the administration of a painkiller. The results showed that 4 mg/kg of caffeine reduced pain, and that the expectation of painkiller administration produced longer analgesia compared with the no-information group. As suggested by the authors, the drug might have provided an interoceptive cue interacting with the verbal information. Overall, the open-hidden design highlights the key role of medical rituals and expectations.

Whereas the open administration of a treatment boosts the pharmacological effect of the drug, the open interruption of a therapy may lead to opposite effects, for the ritual of interruption may induce negative expectations of worsening. Interestingly, the relapse of symptoms in both pain and anxiety is faster with an open compared with a hidden interruption [53**]. Psychological adverse reactions (nocebo effects) can also be produced in clinical practice by the informed consent, in which the possible occurrence of side effects is usually described in some detail [56]. It is therefore necessary to find a compromise between the opposing needs of information disclosure and nocebo effects minimization.

Conclusions

The placebo effect is an interesting topic for neuroscience because it represents a good example of the top-down influence of cognitive factors on behavior. Health professionals often know that emphatic communication and cooperation, attention to the context, patients’ expectation and previous experiences, are important factors to be considered for a positive outcome. This common knowledge is now given scientifically sound ground by the findings of placebo research, which can be incorporated into a sort of “vade mecum” for better clinical practice.

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