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Review

The placebo response: How words and rituals change the patient's brain

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ABSTRACT

Objective: The placebo effect, or response, has evolved from being thought of as a nuisance in clinical and pharmacological research to a biological phenomenon worthy of scientific investigation in its own right. The study of the placebo effect and of its negative counterpart, the nocebo effect, is basically the study of the psychosocial context around the treatment and the patient, and it plays a crucial role in the therapeutic outcome.
Methods: In recent years, different types of placebo responses have been analyzed with sophisticated biological tools that have uncovered specific mechanisms at the anatomical, physiological, biochemical and cellular level.
Results: Most of our knowledge about the neurobiological mechanisms of the placebo response comes from pain and Parkinson's disease, whereby the neuronal circuits involved in placebo responsiveness have been identified. In the first case, opioidergic, dopaminergic and cholecystokinergic networks have been found to be involved. In the second case, dopaminergic activation in the striatum and neuronal changes in basal ganglia have been described.
Conclusion: This recent research has revealed that these placebo-induced biochemical and cellular changes in a patient's brain are very similar to those induced by drugs. This new way of thinking may have profound implications both for clinical trials and for medical practice.

Contents

1. Introduction

Any medical treatment that is performed in routine medical practice has two components, one related to the specific effects of the treatment itself and the other related to the perception that the therapy is being administered [1]. The latter is labeled as placebo

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effect or placebo response. Placebo is the latin word of "I shall please". The study of the placebo effect is basically the analysis of the relationship between the complex psychosocial context surrounding the patient and its effects on the patient's brain [2,3]. Today there is increasing evidence that beliefs and expectations, which are associated to the therapeutic procedure *per se*, can play a salient role in human health, and placebos can mimic, enhance, mask or prevent the beneficial responses to pharmacological agents.

Two terms are commonly encountered in placebo literature: placebo effect and placebo response. Although they are often used as synonymous, technically they refer to different concepts. The placebo effect is that observed in the placebo arm of a clinical trial, and is produced by the placebo biological phenomenon in addition to other potential factors contributing to symptom amelioration, such as natural history (the time course of a symptom or disease in the absence of any external intervention), regression to the mean (a statistical phenomenon whereby the second measurement of a symptom is likely to yield a value nearer to the average, i.e. an improvement), biases, judgement errors. The placebo response, on the other hand, designates the biological phenomenon in isolation, as can best be studied in specifically designed experimental protocols.

The definition of nocebo effect also needs to be stated precisely. The term nocebo (latin "I shall harm") was originally introduced to designate noxious effects produced by a placebo, e.g. side effects of the drug the placebo is substituting for [4]. In that case, however, the negative outcome is produced in spite of an expectation of benefit. True nocebo effects, on the other hand, are always the result of negative expectations, specific or generic (like a pessimistic attitude).

The word placebo (or nocebo) calls attention to the sham drug, but what really matters is not the drug but the changes it elicits in the patient's brain. Moerman has proposed to substitute the term *placebo response* with *meaning response*, to underscore the importance of the patient's beliefs about the treatment and stress what is present (something inducing the expectation of a benefit) rather than what is absent (a chemical or manipulation of proven specific efficacy) [5]. At the limit, a physical substance or treatment needs not be administered at all, that is, a placebo/nocebo effect can also be induced by raising expectations in the complete absence of a treatment, just by inducing expectations. These effect are sometimes called "placebo/nocebo-related" effects [6].

2. The psychological explanation

Different explanatory mechanisms have been proposed for both placebo and nocebo effects, each supported by experimental evidence. They need not be mutually exclusive and can actually be at work simultaneously.

The first theory considers the placebo effect as an example of classical conditioning. As described in the studies on conditioned reflexes by the Russian physiologist Ivan Pavlov, the repeated co-occurrence of an unconditioned response to an unconditioned stimulus (e.g. salivation after the sight of food) with a conditioned stimulus (e.g. a bell ringing) induces a conditioned response (i.e., salivation that is induced by bell ringing alone). Likewise, aspects of the clinical setting (e.g. color, taste, shape of a pill, as well as concurrent aspects of the therapeutic environment, such as white coats or the peculiar hospital smell) can also act as conditioned stimuli, eliciting a therapeutic response in the absence of an active principle, just because they have been paired with it in the past [7–9]. Similarly, the conditioned response can also occur for a nocebo effect. For example, nausea can be elicited by the sight of the environment where chemotherapy has been administered in the past. Conditioning was exploited in the development of a protocol widely used in placebo studies to strengthen the ability of a sham treatment to induce a placebo response. Voudouris and colleagues paired a placebo analgesic cream with a painful stimulation, which was surreptitiously reduced with respect to a baseline condition to mislead the subject regarding the analgesic effect. Direct comparison between a conditioned and an unconditioned group showed that pain reduction following conditioning was invariably larger, indicating the effectiveness of conditioning in mediating a placebo response [10]. Classical conditioning seems to work best where unconscious processes are at play, as in placebo/nocebo effects involving endocrine or immune systems, but it has also been documented in clinical and experimental placebo analgesia and nocebo hyperalgesia.

The second explanation centers on expectations, generated as the product of cognitive engagement, when the patient consciously foresees a positive/negative outcome, based on factors such as verbal instructions, environmental clues, emotional arousal, previous experience, the interaction with care-providers. This anticipation of the future outcome in turn triggers internal changes resulting in specific experiences (e.g. analgesia/hyperalgesia). By grading the degree of expectation, graded responses can be obtained: the same placebo cream applied onto three contiguous skin areas induces a progressively stronger analgesia, according to the strength of the accompanying words ("it is a powerful/weak analgesic cream") [11]. This is true also in the clinical setting, where changing the symbolic meaning of a basal physiological infusion in postoperative patients resulted in different additional painkiller request. In spite of all patients receiving a physiological solution, those who believed that they would receive an analgesic drug demanded significantly less pain reliever than those who believed that they would receive no analgesic at all. An intermediate level of certainty in those believing to have a 50% chance to receive the drug resulted in an intermediate request [12]. The expectation of forthcoming pain can further be modulated by a number of emotional and cognitive factors, like desire, self-efficacy and self-reinforcing feedback. Desire is the experiential dimension of wanting something to happen or wanting to avoid something happening [13], while self-efficacy is the belief to be able to manage the disease, performing the right actions to induce positive changes, for example to withstand and lessen pain. Self-reinforcing feedback is a positive loop whereby the subject attends selectively to signs of improvement, taking them as evidence that the placebo treatment has been successful. This has sometimes been termed the somatic focus, i.e. the degree to which individuals focus on their symptoms [13]. A related proposed mechanism posits that anxiety reduction also plays a role in placebo responses, because the subject interpretation of ambiguous sensations is turned from harmful and threatening to benign and unworthy of attention. Accordingly, Vase and collaborators found decreased anxiety levels in patients with irritable bowel syndrome who received a placebo treatment [14]. The importance of anxiety is shown by the role of anticipatory anxiety in the nocebo hyperalgesic response (see below).

A particular type of expectation which has been suggested as a contributor to the genesis of placebo effects is the expectation of reward. Our brain is endowed with a so-called reward system, which through the activation of the mesolimbic and mesocortical pathways and the release of dopamine fulfills its natural task to provide pleasurable feelings in response to life sustaining functions, such as eating, drinking or sex, in order to encourage repetition of those functions. It has been argued that placebos have reward properties, associated with the beneficial outcome they provide. In other words, the expected clinical benefit is a form of reward, which triggers the placebo response [15]. Since reward mechanisms may play a role in placebo responsiveness, it will be interesting to assess whether instrumental, or operant, conditioning is involved.

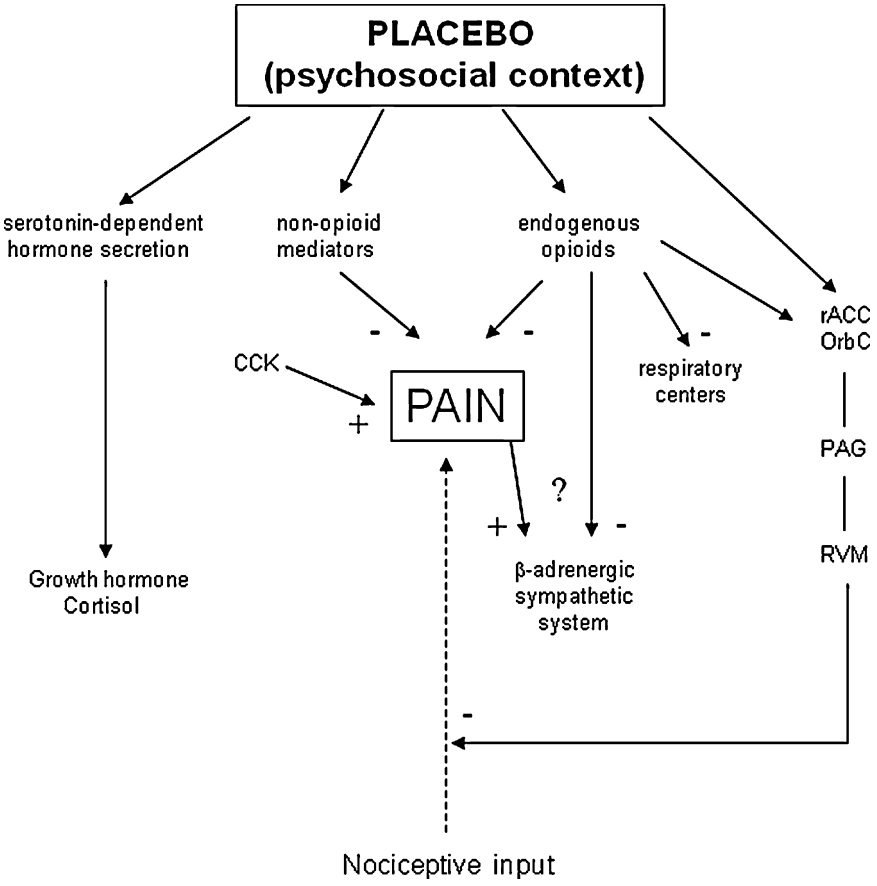

Fig. 1. Cascade of events which may take place during a placebo analgesic response. Pain is inhibited by a descending inhibitory network involving the rostral anterior cingulate cortex (rACC), the orbitofrontal cortex (OrbC), the periacqueductal gray (PAG) and the rostral ventromedial medulla (RVM). Endogenous opioids inhibit pain through this descending network and/or other mechanisms. The respiratory centers may be inhibited by opioid mechanisms as well. The β-adrenergic sympathetic system is also inhibited during placebo analgesia, although the underlying mechanism is not know (reduction of the pain itself and/or direct action of endogenous opioids). Non-opioid mechanisms are also involved. Cholecystokinin (CCK) counteracts the effects of the endogenous opioids, thus antagonizing placebo analgesia. Placebos may also affect serotonin-dependent hormone secretion, like growth hormone and cortisol.

It is also worth noting that personality and situational variables interact to determine placebo responding. For example, the personality variable 'optimism–pessimism' has been found to be related to placebo responding, and this may help identify placebo responders and non-responders [16].

3. The neurobiological explanation

The last decade has witnessed the beginning of clarification of neurochemical and pharmacological details of placebo analgesia, and Fig. 1 gives an example of the main mechanisms involved in placebo analgesia. In 1978, a pioneering study by Levine and co-workers showed that the opiate antagonist naloxone was able to reduce the placebo response in dental postoperative pain [17]. That was the first indication that endogenous opioids were involved in placebo analgesia. Subsequent experiments provided ever more compelling evidence that the secretion of endogenous opioids in the brain was the key event in placebo pain modulation. Placebo responders had levels of β-endorphin in the cerebrospinal fluid which were more than double those of non-responders; opioids released by a placebo procedure displayed the same side effects as exogenous opiates; naloxone-sensitive cardiac effects could be observed during placebo-induced expectation of analgesia. Indirect support also came from the placebo-potentiating role of the colecystokinin (CCK) antagonist proglumide. In fact, the CCK system effects counteract those of opioids, delineating a picture where the placebo effect seems to be under the opposing influence of facilitating opioids and inhibiting CCK. In some situations, however, a placebo effect can still occur after blockade of opioid mechanisms by naloxone, indicating that systems other than opioids are also implicated. For example, with a morphine conditioning and/or expectation-inducing protocol, naloxone was able to completely reverse placebo analgesia induced in experimental ischemic arm pain. Conversely, with the use of ketorolac (a non-opioid analgesic) in the same protocol, only a partial blockade could be observed. Almost nothing is currently known on these non-opioid systems, and further research is needed to clarify them.

The advent of neuroimaging techniques and of their use for experimental purposes added anatomical and temporal details to the neurochemical information. The first positron emission tomography (PET) study to investigate placebo analgesia was conducted in 2002 [18]. It showed overlapping in the brain activation pattern generated by opioid-induced analgesia (by the μ-agonist remifentanil) and by placebo-induced analgesia. Common activated areas included the rostral anterior cingulate cortex (rACC) and the orbitofrontal cortex. In the following years, in spite of some discrepancies likely explained by methodologic and procedural differences, PET, functional magnetic resonance imaging (fMRI), and magnetoelectroencephalography (MEG) studies all suggested placebo activation of the descending pain control system, with modulation of activity in areas such as periaqueductal gray (PAG), the ventromedial medulla, the parabrachial nuclei, the ACC, the orbitofrontal cortex, the hypothalamus and the

central nucleus of the amygdala. Notably, direct demonstration of endogenous opioid release was obtained through [^{11}C]carfentanil displacement by the activation of opioid neurotransmission, with the decrease in binding correlating with placebo reduction of pain intensity reports. Recently, naloxone was observed to block placebo-induced responses in pain modulatory cortical structures and in key structures of the descending pain control system [19]. For a review on neuroimaging studies see [20].

Also of interest is the fact that knowledge of placebo analgesia can be gained by focusing on changes in brain activity that take place with modulation of expectation alone. In fact, expectation of benefit can induce a placebo effect even without the physical administration of a placebo. Since no placebo is actually given, these effects may be more appropriately called "placebo-like" effects. Thus, activity in pain areas following a constant painful stimulus can be modulated just by varying the subject's expectation of the level of stimulation: the higher the *expected* level of the stimulus, the stronger the activity in ACC and other areas implicated in the activation of the descending inhibitory pathway. Taken together, these studies show how the same result, i.e. the activation of the same receptors in the brain, can be obtained by a pharmacological (drug) or a psychological (placebo) means. A more comprehensive description of the studies mentioned here can be found in Zubieta and Stohler [20].

Interestingly, the activation of the above mentioned areas are part of a general circuit underlying the voluntary regulation of affective responses [see 21–23]. In this direction, both placebo analgesia [18,24,25] and emotional regulation [26,27] are associated with increased activation in a modulatory network that includes the rACC and the ventrolateral prefrontal cortex. This suggests a functional–anatomical relationship between placebo analgesia and emotional regulation in which top-down modulation of the pain or emotional network is implemented.

4. Nocebo hyperalgesia

Compared to placebo effect research, the investigation of the nocebo effect raises more ethical difficulties, especially in the clinical setting. However, in recent times a few experimental studies have begun to shed light on this phenomenon, focusing mainly on the model of nocebo hyperalgesia. In the protocols used, an inert treatment is given along with verbal suggestions of pain worsening, resulting in exacerbation of pain. It has been suggested that the anticipatory anxiety about the impending pain, brought about by negative expectations, triggers the activation of CCK, which in turn facilitates pain transmission and results in hyperalgesia. Accordingly, this hyperalgesia can be blocked by proglumide, a non-specific CCK-1 and CCK-2 antagonist, in a dose-dependent manner. The proglumide block is related specifically to nocebo/anxiety-induced hyperalgesia rather than to the more general process of nocebo-induced anxiety, as it is selectively exerted on nocebo hyperalgesia but not on the concurrent stress-induced hypothalamic–pituitary–adrenal axis hyperactivity.

As noted before, proglumide also exhibited placebo-potentiating effects, raising the question of how the two endogenous systems, CCK and opioids, may interact in producing negative or positive outcomes. It can be speculated that the placebo–nocebo phenomenon is a continuum, with opioid and CCK-ergic systems acting as the mediators of opposing effects.

As for placebo analgesia, neuroimaging techniques have also brought important contributions to the knowledge of nocebo hyperalgesia. Here again, expectations without the physical administration of a nocebo treatment have been exploited ("nocebo-like" effects). Inducing negative expectations resulted in both amplified unpleasantness of innocuous stimuli as assessed by psychophysical pain measures (subject report) and increased fMRI responses in ACC, insula, hypothalamus, secondary somatosensory areas and prefrontal cortex. From these studies it appears that the circuitry underlying nocebo hyperalgesia largely involves, with opposite modulation, the same areas engaged by placebo analgesia [6].

5. Placebo response in Parkinson's disease

Parkinson's disease is particularly interesting for investigating the mechanisms of the placebo response. In fact, different approaches, ranging from PET to micromapping methods (microrecording and microstimulation) have significantly increased the body of knowledge of the placebo effect. Although micromapping methods in humans are highly invasive, as they are carried out in awake patients during neurosurgery, they have provided important insights at the single neuron level.

5.1. PET studies

By using PET imaging, de la Fuente-Fernandez and colleagues [28,29] detected a significant drop in [^{11}C]raclopride binding potential (BP) when Parkinson patients were injected with a saline solution along with the suggestion of motor improvement. A reduction in [^{11}C]raclopride binding is indicative of an increase in extra-cellular dopamine concentration. In the studies by de la Fuente-Fernandez et al. [28,29], it occurred in the dorsal and ventral striatum. As the patients who experienced symptomatic benefit released more dopamine in the dorsal striatum than those who did not, the degree of placebo-induced dopamine release in the dorsal striatum seems to be related to the degree of perceived improvement by the patient [28]. Conversely, the level of placebo-dopamine release in the ventral striatum is independent of perception of clinical benefit [29]. As the ventral striatum (NAc) is involved in the circuitry of reward mechanisms, de la Fuente-Fernandez et al. [28,29] suggested that placebo-induced dopamine release might be related to expectation of reward. In the case of the placebo effect, the reward would be the clinical improvement.

Strafella et al. studied whether the expectation of therapeutic benefit from rTMS induced changes in striatal [^{11}C]raclopride BP [30]. Placebo-rTMS induced a significant bilateral reduction in [^{11}C]raclopride BP in the dorsal and ventral striatum as compared to the baseline condition. With respect to previous studies, i.e. de la Fuente-Fernandez et al. [28,29], they did not observe significant differences in [^{11}C]raclopride BP in the dorsal striatum between the group of patients who perceived the clinical benefit and the group who did not. In fact, placebo-rTMS induced a significant biochemical response in the striatum in all patients, although only four patients perceived a certain degree of clinical benefit. Patient group characteristics, type of given information, previous medication exposure could explain this discrepancy.

5.2. Single-units recordings

The subthalamic nucleus (STN) is now the major target in the surgical therapy of Parkinson's disease and its identification can require the recording of intranuclear electrical activity. The possibility to study Parkinsonian patients who are implanted with electrodes for deep brain stimulation has been exploited to record from single neurons after the administration of a placebo. Benedetti et al. [31] investigated for the first time the placebo effect at the level of single neurons. These authors recorded the activity from single neurons in the STN before and after placebo administration to test whether neuronal changes were linked to the clinical placebo response. A placebo (saline solution) was administered in the operating room after several pre-operative administrations of apomorphine, according to a conditioning

procedure. Those patients who showed a clear-cut clinical placebo response – as assessed by means of both the decrease of arm rigidity and the subjective report of well-being – also showed a significant decrease of neuronal discharge compared to the pre-placebo condition. None of the placebo non-responders showed these differences. Benedetti et al. also found that the STN neurons of all the placebo responders shifted significantly from a pattern of bursting activity to a pattern of non-bursting discharge [31]. None of the placebo non-responders showed any difference in the number of bursting neurons before and after placebo injection.

The above-mentioned study is the first showing that a placebo procedure affects specific neuronal populations. These findings – decrease of frequency discharge and shift from bursting to no-bursting activity – were interpreted as a demonstration of drug-like effects following the pre-operative exposure to the treatment with apomorphine. Indeed, several studies have reported apomorphine-induced changes in the STN firing pattern of patients with PD [32–34]. Although Levy et al. found a certain variability on the firing rates of single neurons under the effect of apomorphine [33], Stefani et al. reported that the administration of apomorphine is invariably followed by reduction of firing activity from 40.4 to 27.2 Hz [34]. Similarly, in the study by Benedetti et al., a reduction of firing rate was induced by a placebo [31].

6. Placebo response in psychiatric disorders and drug addition

The neural mechanisms of placebo treatments have also been studied in psychiatric disorders, such as depression and drug addiction, although only a few pieces of information are available in this case. There is a clear explanation for this. Unlike single-dose trials of an intervention, such as oral or intravenous analgesia or anti-Parkinson acute therapy studies, antidepressants do not work acutely, requiring on average a minimum of two–three weeks to see clinical effects. Therefore, investigating placebo effects in depression is more problematic from both an ethical and methodological point of view. In fact, if one wants to see what happens in the patient's brain by means of neuroimaging techniques, it is necessary to follow the patient for a long period of time or, otherwise, to devise pre- and post-treatment assessment with adequate control groups. Of course, if one wants to compare a placebo group with a no-treatment group to rule out spontaneous remission, this requires that some patients need not to be treated for a long period of time, with the inherent ethical problems and limitations. This is one of the main reasons why depression, albeit an interesting and exciting model to study placebo effects, has not been investigated in detail so far.

6.1. EEG and PET studies in depression

Depressed patients who undergo a placebo treatment have been found to show both electrical and metabolic changes in the brain. Placebos induced EEG changes in the prefrontal cortex of patients with major depression, particularly in the right hemisphere. In fact, Leuchter et al. found distinct neurophysiological patterns in the placebo responders behind the prefrontal region by using an off-line elaboration of EEG recordings, labeled *cordance*, which is a method developed in their laboratory [35,36]. Placebo responders also tended to have slightly enhanced cognitive processing speeds on a variety of neuropsychological tests and they differed in the nature of their sleep complaints in comparison to non-responders.

By using PET, changes in brain glucose metabolism have also been documented in subjects with unipolar depression [37]. Compared to baseline patterns, patients treated with drug (fluoxetine), regardless of response, showed changes in subcortical areas, including the brainstem, and hippocampus, and cortical regions, including the posterior cingulate, the DLPFC, the premotor cortex, the dorsal ACC, and the inferior parietal posterior cortex. It was possible to note a suppression of activity in the subgenual cingulated (area 25). The placebo responders showed similar activity patterns in the cortex as compared to the drug responders, but the magnitude of change was smaller in patients who received placebo. Although these studies on depression need confirmation, as they did not include appropriate control groups, they are a good example of the placebo effect in another pathological condition, and in particular they show the similarity in the activation pattern of the brain by antidepressants and placebos.

6.2. PET studies in drug addiction

Another example of the powerful role of expectation in drug responses is the work by Volkow et al. [38,39], who investigated the effect of placebos in both cocaine abusers and non-drug abusing subjects. In particular, they described the effects of methylphenidate on brain glucose metabolism, as measured by [^{18}F]deoxyglucose-PET, when subjects expected (1) to receive the drug and indeed received the drug; (2) to receive the drug but they received the placebo; (3) to receive placebo but they received the drug; (4) to receive placebo and indeed received placebo. The researchers found that when the subjects expected to receive drug, the effects were about 50% greater than when the subjects did not expect the drug. In other words, unexpected methylphenidate induced smaller changes in the thalamic and cerebellar metabolism, thus indicating that expectation potentiates the pharmacological action of methylphenidate [38]. In non-drug abusing subjects, the changes of brain glucose metabolism occurred in regions involved in emotional reactivity and reward, such as the ventral gyrus (BA 25) and NAc [39]. The different findings in cocaine abusers and non-cocaine abusers suggest that in the first case, the enhanced thalamic and cerebellar responses reflect conditioned responses, whereas the changes in the striatum observed in the non-drug abusing subjects may indicate the prevalence of expectations in the absence of prior experience.

7. Implications for clinical practice

The most obvious way of clinically exploiting the potential for therapeutic benefit of a placebo procedure is of course the administration of placebos. However, this is also a most controversial issue on ethical grounds, conflicting with the patient right of being thoroughly informed. Although medicine has been based for centuries on remedies acting mainly by suggestion, modern accessibility to chemicals provided with biological activity warrants that the best available treatment be used. Nevertheless, even today placebo practice is widespread, as demonstrated by the high percentage of physicians surveyed who reported the use of placebo, usually to calm patients, avert requests for unnecessary medication, or as a supplemental treatment [40,41]. It can be argued that deception is not necessarily involved in the use of a placebo, or that it can represent an effective treatment which it would be unethical to withdraw [42,43]. While it might be too soon to draw conclusions on ethical justifiability, there is ample space for placebo use in less direct ways.

The therapeutic environment is a complex context, in which the active principle contained in a drug is not the sole agent acting on the patient body. In fact, any treatment administered in routine health care can be regarded as having two components: one pharmacodynamic, the other psychosocial. As described throughout this chapter, expectations have a central role in determining this second component (placebo or nocebo), and as they can be elicited by any aspect of the therapeutic context, it is in its optimization that the knowledge on placebo/nocebo mechanisms

can both fruitfully and ethically be applied. To the extreme, total elimination of the context-induced expectations can be achieved with hidden drug administration carried out by a machine unbeknownst to the patient. In this case, dose requirement for the achievement of a given level of analgesia are invariably higher than in the open condition [44].

The first and foremost aspect of the psychosocial context is the patient–provider interaction. Indeed, the placebo effect has recently been defined as a form of interpersonal healing [45]. A list of eight specific clinical actions has been proposed, including the following: speak positively about treatments, provide encouragement, develop trust, provide reassurance, support relationships, respect uniqueness, explore values, and create ceremony [46]. Also non-verbal clues intentionally or unintentionally conveyed by the therapist are important. Deceiving clinicians as to the substance (placebo or drug) being administered to two groups of patients, when in fact both groups received a placebo, resulted in a bigger effect in the group believed by the clinicians to receive a drug [47]. Equal attention should be paid to avoid nocebo suggestions. Even a seemingly innocuous act like communicating to the patient that a therapy is going to be interrupted can have a negative impact, as showed by the faster and of larger intensity relapse of pain after open, rather than hidden, interruption of morphine analgesic therapy [48]. By using a nocebo procedure, whereby verbal suggestions of painful stimulation were given to healthy volunteers before administration of either tactile or low-intensity painful electrical stimuli, Colloca et al. showed that these anxiogenic verbal suggestions are capable of turning tactile stimuli into pain, as well as low-intensity painful stimuli into high-intensity pain [49]. Therefore, by defining hyperalgesia as an increase in pain sensitivity and allodynia as the perception of pain in response to innocuous stimulation, nocebo suggestions of a negative outcome can produce both hyperalgesic and allodynic effects. Language incorporating negative suggestions should be changed to offer positive hints (e.g. from "here's your pain medicine" to "Here's some medicine to help you get better"), in order to minimize anxiety [50,51].

Another important aspect is what the context can teach us about other patients experiences. Just by watching others, it is possible to obtain useful information (so-called social observational learning). Just like other forms of learning (prior experience, conditioning, expectation induced by verbal communication), also social observational learning can induce placebo/nocebo responses. For example, healthy volunteers observing the beneficial effect of a placebo in a demonstrator showing analgesic effects, displayed placebo responses which were comparable to those induced by directly experiencing the benefit through a conditioning procedure, while verbal suggestions alone produced significantly smaller effects [52].

8. Implications for clinical trials

In clinical trials, the desired goal is just the opposite as in clinical practice, namely, to limit and reduce placebo effects as much as possible, in order to isolate the specific effect of the active principle under scrutiny. Research on placebo mechanisms has at least two important implications for clinical trials: (1) the design of protocols that circumvent the need of a placebo arm. An example is the "open/hidden" protocol, where the placebo component stands out as the difference between overt or covert drug administration, with no patients receiving sham treatment; (2) the reevaluation of clinical trial methodology. In fact, patient expectations are not usually among the controlled variables but they have the potential to differentially influence improvement in both control (placebo) and drug arms, thus invalidating the attempt at separating the pharmacodynamic effect. For example, a study on acupuncture has showed that results could be drastically reversed by redistributing the subjects according to what they believed was their group of assignment. In other words, no differences were found with the standard grouping, but the subjects expecting real acupuncture reported significant less pain than those believing to be in the sham group, regardless of the real assignment [53]. Similar results were obtained in another study [54].

Of great theoretical and practical importance is the notion that any drug has the potential of interacting with patient expectation mechanisms, thus the ascription of its effect to the pharmacodynamic or the psychosocial component can be difficult, if not impossible. In other words, a secondary effect of any drug can be to interfere with one or more expectation-activated biochemical mechanisms (e.g. through the opioid, CCK, or dopamine systems), with no possibility for the experimenter to know if the observed effect derives from the activation of non-specific placebo pathways or from the specific action of the drug (uncertainty principle) [1].

The large number of randomized controlled clinical trials has drawn the attention of some authors to the need to improve the design of such trials [55–57]. In particular, adequate methodology is a critical issue in their planning and execution, as different methodological approaches can translate into different results. The side-effects observed in both the active medication arm and the placebo arm are often influenced by non-specific factors. This issue can be quantified by using a systematic review approach to study the rates of adverse events reported in the placebo arms of clinical trials [58,59]. The subjects recruited to take part in a typical randomized double blind clinical trial know they will receive either an active medication or a placebo and they are informed about the possible adverse events (AEs) they may experience. This information is provided in the informed consent form and in the instructions given by the investigator. Informing subjects about the possible AEs they may experience has a significant impact on their expectations. In particular, an expectation of negative symptoms, in terms of adverse effects, may be considered an important element in eliciting negative outcomes. By using the systematic review approach, such as the methodology used in our recent study, it has been shown that symptoms can be provoked by inducing specific expectations in patients. In particular, if the trial is conducted to study the efficacy of an anticonvulsant drug versus placebo, the patients may be influenced by the examiner and/or by the information in the informed consent form and experience the AEs specific to this pharmacological class. On the other hand, the suggestion given to patients taking part in a study to test NSAIDs versus placebo, may lead to different AEs [58]. We hypothesized that the effect observed may specifically depend on the patient's and/or investigator's expectations regarding the occurrence of negative symptoms, in terms of a nocebo effect. These nocebo phenomena may help us better understand the occurrence of psychologically driven adverse symptoms, as well as to improve clinical trial designs and patient–provider communication [60].

Therefore, communication plays a pivotal role in placebo effects both in the clinical trial setting and in medical practice, and a research agenda is certainly needed for testing the role and the mechanisms of communication in both placebo and nocebo responsiveness [61].

Conflicts of interest

The authors declare that they have no conflicts of interest.

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