

Placebo Effects: From the Neurobiological Paradigm to Translational Implications

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Today we are witnessing a new science of placebo, a complex discipline that encompasses several experimental approaches and translational implications. Modern neurobiological tools have been used to answer important questions in placebo research, such as the top-down modulation of sensory and motor systems as well as the influence of cognition, emotions, and learning on symptoms, diseases, and responses to treatments. What we have learned is that there is not one single placebo effect, but many. This review highlights the translational implications of this new knowledge, ranging from clinical trial design to medical practice to social and ethical issues.

Introduction

A placebo is an inert treatment with no specific therapeutic properties, whereas the placebo effect is the response to the inert treatment. Although this is the most common definition, it is not completely correct, for placebos are made of many things, such as words, rituals, symbols, and meanings. Thus, a placebo is not the inert treatment alone, but rather its administration within a set of sensory and social stimuli that tell the patient that a beneficial therapy is being given. Indeed, a placebo is the whole ritual of the therapeutic act.

When a placebo is administered to a patient, observed clinical improvements can be due to several factors. Spontaneous remission can occur, with the improvement misinterpreted as an effect of the placebo itself, even though it would have occurred anyway. Methodological biases can also make the experimenter believe that an amelioration is taking place when the supposed benefit is actually attributable to the patient's biased report and/or the experimenter's biased measurement, a typical situation in the assessment of subjective symptoms. Finally, therapeutic benefit can be due to the patient's positive expectations, which in turn may reduce anxiety and/or activate reward mechanisms. All of these factors may contribute to the amelioration of a symptom. Therefore, in order to assess the efficacy of a therapy, it is necessary to compare the effects of a real treatment with the effects of a placebo, and the observed improvement can be due to spontaneous remission and/or methodological biases and/or the patient's expectations (Benedetti, 2013a, 2014b).

The still persisting confusion and misconception within the scientific community about the word placebo come from the different meaning that this word has for the clinical trialist and the neuroscientist. In fact, the former is mainly interested in comparing a therapy with a placebo and to establish whether the therapy is superior to the placebo. Although today most clinicians know and value the placebo effect, usually they are not interested in understanding whether the placebo-treated patients improve because of a spontaneous remission, a bias, or psychobiological factors. Conversely, the neuroscientist wants to isolate the psychobiological component from the spontaneous fluctuations of the symptom, the patient's biased reports,

and the experimenter's biased measurements. In this sense, the neuroscientist uses the placebo to probe brain functions ranging from endogenous pain modulation to anxiety mechanisms and from Pavlovian conditioning to social learning. Therefore, when the neuroscientist talks about placebos and placebo effects, he means the psychobiological component of the clinical improvement, that is, all those psychological factors that contribute to change the time course of a symptom or ailment.

In the recent history of the placebo effect, and in general of placebo research, one of the main objectives has been its control within the setting of clinical trials. The reduction of the placebo effect in a clinical trial is considered today a priority in clinical research so as to better evidence the specific effect of the treatment. Many new designs have been devised in different medical conditions, such as depression (Fava et al., 2003), and different placebo components have been described within the setting of a clinical trial (Kaptchuk et al., 2008). Therefore, the methodological aspect of placebo research is an important element in the design of clinical trials, both in the past (Kaptchuk, 1998) and in more recent times (Enck et al., 2011, 2013).

Today we are witnessing a resurgence of placebo research that is mainly aimed at using a neurobiological approach (Benedetti, 2013a, 2014b). In fact, in contrast to several decades ago, when placebo research was mainly based on a psychological approach, today we utilize tools ranging from pharmacology to brain imaging and from genetics to animal models to explore what is going on in the patient's brain when he expects a therapeutic benefit. In this sense, we are witnessing the emergence of a new science of placebo that encompasses complex issues in the neurobiological domain as well as translational implications, particularly for the clinical trials setting but also for medical practice and society. In this article, I will review all these aspects, in order to give an idea of the complexity of the topic and provide some recommendations for how clinical trial designs can address the challenges of placebo responses.

Recent Insights into the Neurobiological Mechanisms

Taking a neuroscientific perspective to the study of the placebo response, isolating the psychobiological component from

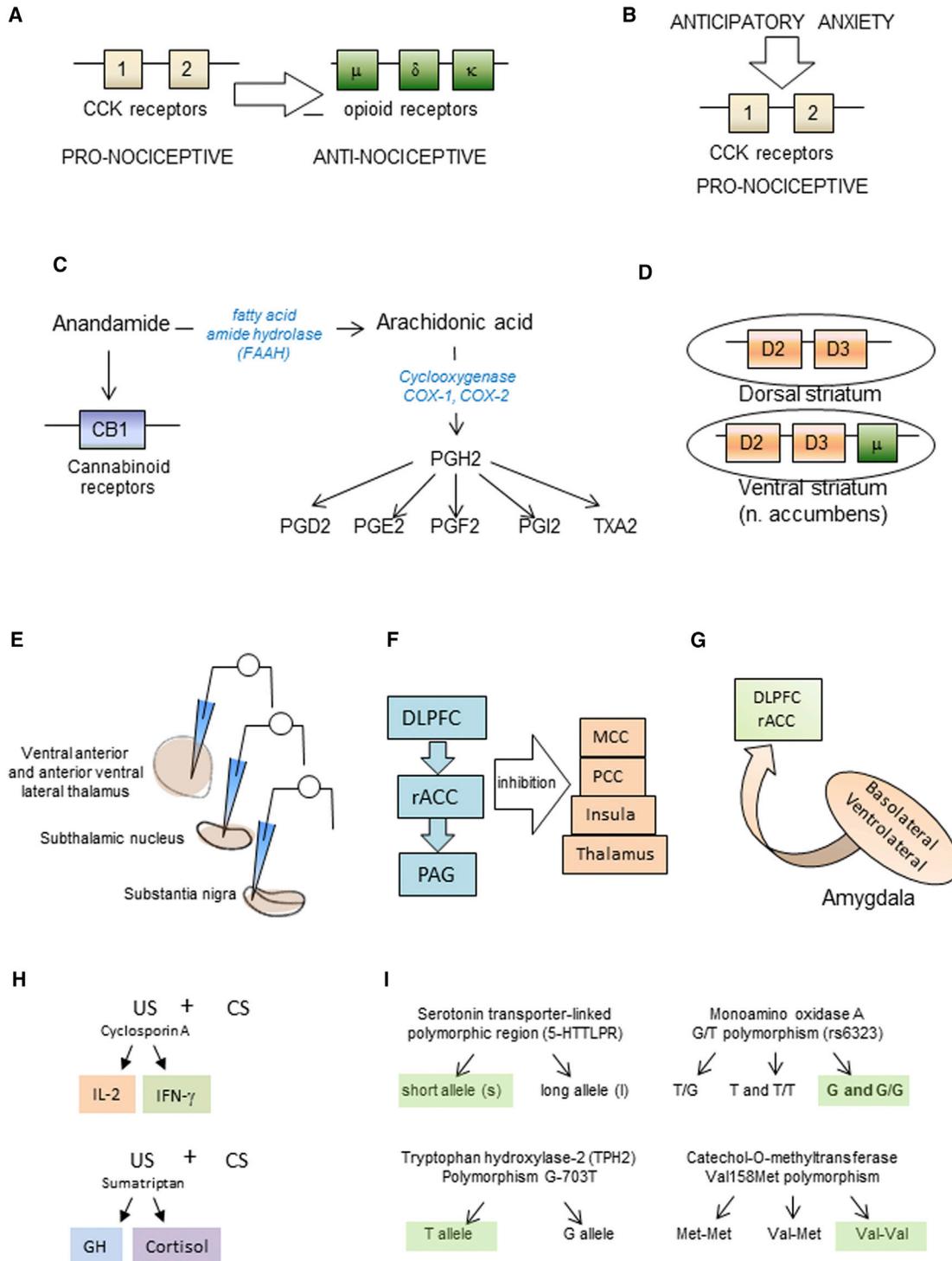


Figure 1. Principal Neurobiological Mechanisms of the Placebo Response that Have Been Identified across a Variety of Conditions
 (A) The antinociceptive opioid system is activated in placebo analgesia in some circumstances, and the μ opioid receptors play a crucial role. The pronociceptive cholecystokinin (CCK) system antagonizes the opioid system, thus blocking placebo analgesia.
 (B) The pronociceptive CCK system is activated by anticipatory anxiety in nocebo hyperalgesia, with some evidence that the CCK-2 receptors are more important.
 (C) Different lipidic mediators have been identified in placebo analgesia and nocebo hyperalgesia. Whereas placebos activate the CB1 cannabinoid receptors and inhibit prostaglandins (PG) synthesis in some circumstances, nocebos increase PG synthesis. In addition, different genetic variants of FAAH affect the magnitude of placebo analgesia.

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spontaneous remissions and methodological biases, allows for an excellent model to investigate several brain functions within the medical context. Two main mechanisms have been the focus of attention: expectation and learning. Expectation is a conscious event whereby the subject expects a therapeutic benefit, although this notion has recently been challenged in a study on nonconscious placebo responses (Jensen et al., 2012). The link between expectation and the clinical improvement is 2-fold. First, positive expectations may reduce anxiety, and anxiety is known to affect different symptoms, such as pain, in opposite directions, i.e., either decrease or increase, depending on the circumstances (Colloca and Benedetti, 2007). Second, expectation of a positive event, i.e., the therapeutic benefit, may activate reward mechanisms. Learning mechanisms, ranging from behavioral conditioning to social learning, are crucial because the previous experience of effective treatments leads to substantial placebo responses. It is important to point out that expectation and learning are not mutually exclusive, since learning can lead to the reinforcement of expectations or can even create de novo expectations. Therefore, although today it is not always clear when and how expectations and learning are involved in different types of placebo responses, they may overlap in a number of conditions (see Büchel et al., 2014 for a recent review). Certainly, what is emerging today is that there is not a single placebo response, but many with different mechanisms across different conditions and different systems. The following is a brief description of the main mechanisms that have been identified by using a neurobiological approach (for a detailed description, see Benedetti, 2014b).

The opioid system activated by placebos is the most understood (Figure 1A). The μ opioid antagonist, naloxone, prevents some types of placebo analgesia, thus indicating that the opioid system plays an important role (Amanzio and Benedetti, 1999; Eippert et al., 2009a; Levine et al., 1978). By contrast, the cholecystokinin (CCK) antagonist, proglumide, enhances placebo analgesia on the basis of the antiopioid action of CCK (Benedetti, 1996; Benedetti et al., 1995), whereas the activation of the CCK type 2 receptors by means of the agonist pentagastrin disrupts placebo analgesia (Benedetti et al., 2011a). Therefore, the activation of the CCK type 2 receptors has the same effect as the μ -opioid receptor blockade, which suggests that the balance between CCKergic and opioidergic systems is crucial in placebo responsiveness in pain (Figure 1A). Some brain regions in the cerebral cortex and the brainstem are affected by both a placebo and the opioid agonist remifentanyl, thus indicating a related

mechanism in placebo-induced and opioid-induced analgesia (Petrovic et al., 2002). In vivo receptor-binding techniques show that a placebo activates μ -opioid neurotransmission in the dorsolateral prefrontal cortex, the anterior cingulate cortex, the insula, and the nucleus accumbens (Wager et al., 2007; Zubieta et al., 2005). Although all of these studies have been performed in humans, more recent studies in rodents confirm these pharmacological findings (Guo et al., 2010; Nolan et al., 2012; Zhang et al., 2013). For example, by using different antagonists of different subtypes of opioid receptors (μ , δ , κ), Zhang et al. (2013) found that placebo analgesia is mediated specifically by the μ opioid receptors only.

The CCK pronociceptive system has also been found to mediate the nocebo hyperalgesic response (Figure 1B). The nocebo response is a phenomenon that is opposite to the placebo response, whereby negative expectations may lead to clinical worsening. For example, expectations of pain increase lead to nocebo hyperalgesia, and this increase can be blocked by the CCK antagonist proglumide (Benedetti et al., 1997, 2006a). Anticipatory anxiety plays a key role here, for nocebo verbal suggestions are anxiogenic and induce negative expectations. Support to this view comes from a social defeat model of anxiety in rats in which CI-988, a selective CCK type 2 receptor antagonist, prevents anxiety-induced hyperalgesia (Andre et al., 2005).

When nonopioid drugs, like ketorolac, are administered for 2 days in a row and then replaced with a placebo on the third day, the placebo analgesic response is not reversed by naloxone, whereas the CB1 cannabinoid receptor antagonist, rimonabant, blocks this placebo analgesia completely (Benedetti et al., 2011b). Therefore, in some circumstances, for example following previous exposure to nonopioid drugs, placebo analgesia is mediated by the CB1 cannabinoid receptors. Interestingly, there is compelling experimental evidence that the whole lipidic pathway, involving arachidonic acid, endogenous cannabinoid ligands (e.g., anandamide), and the synthesis of prostaglandins and thromboxane, is important in the modulation of the placebo response in pain (Figure 1C). For example, the functional missense variant Pro129Thr of the gene coding fatty acid amide hydrolase (FAAH), the major degrading enzyme of endocannabinoids, affects the analgesic responses to placebo as well as placebo-induced μ opioid neurotransmission (Peciña et al., 2014). In addition, cyclooxygenase activity, which is involved in prostaglandins and thromboxane synthesis (Figure 1C), has been found to be modulated by both placebo and nocebo in hypobaric hypoxia headache with a mechanism similar to that of

(D) The activation of D2-D3 dopamine receptors in the striatum is related to the placebo response in Parkinson's disease. Likewise, in placebo analgesia there is an activation of D2-D3 receptors and μ opioid receptors in the nucleus accumbens, whereas in nocebo hyperalgesia there is a deactivation of D2-D3 and μ receptors.

(E) Placebo administration in Parkinson patients produces a decrease of firing rate and bursting activity of the subthalamic nucleus neurons. It also produces a decrease of firing rate in the substantia nigra pars reticulata and an increase in the ventral anterior and anterior ventral lateral thalamus.

(F) The neuroanatomy of placebo analgesia has been described through brain imaging. Different regions are modulated by both placebos and nocebos, but the most studied and understood regions are the dorsolateral prefrontal cortex (DLPFC), the rostral anterior cingulate cortex (rACC), and the periaqueductal gray (PAG), which represent a descending pain-modulating network. This, in turn, inhibits those regions that are involved in pain processing, such as the mid and posterior cingulate cortex (MCC, PCC), insula, and thalamus.

(G) In social anxiety disorder, placebos affect the basolateral and ventrolateral amygdala as well as its projections to DLPFC and rACC.

(H) In the immune and endocrine system, the mechanism of the placebo response is classical conditioning, whereby an unconditioned stimulus (US) is paired with a conditioned stimulus (CS). For example, after pairing a CS with either cyclosporine A or sumatriptan, the CS alone can mimic the responses to cyclosporine and sumatriptan.

(I) Different polymorphisms have been found to be associated to low (colored squares) or high placebo responsiveness.

aspirin (Benedetti et al., 2014). Overall, the involvement of all these lipidic mediators represents a challenge for future research. In particular, what we need to understand is when they are activated.

Dopamine is involved in placebo responsiveness in at least two conditions: pain and Parkinson's disease. In placebo analgesia, an increase in dopamine binding to D2/D3 receptors and in opioid binding to μ receptors occurs in the nucleus accumbens, whereas a decreased binding to the same receptors is present in nocebo hyperalgesia (Scott et al., 2007, 2008) (Figure 1D). Likewise, dopamine receptors are activated in both ventral (nucleus accumbens) and dorsal striatum when a placebo is administered to patients suffering from Parkinson's disease (de la Fuente-Fernández et al., 2001, 2002; Lidstone et al., 2010) (Figure 1D). The release of dopamine corresponds to a change of 200% or more in extracellular dopamine concentration and is comparable to the response to amphetamine in subjects with an intact dopamine system, although a more recent study by the same authors (Lidstone et al., 2010) found this effect only when expectation of drug was around 75%. Certainly, this requires further analysis, but the fact that dopamine has been found to be involved in both pain and Parkinson's disease makes these two conditions excellent models to understand whether common placebo mechanisms can be involved in different pathologies. For example, dopaminergic activation in the nucleus accumbens in both pain and Parkinson's disease suggests that reward mechanisms could play an important role in many conditions.

Intraoperative single-neuron recording in Parkinsonian patients during the implantation of electrodes for deep brain stimulation (Figure 1E) shows that the firing rate of the neurons in the subthalamic nucleus and substantia nigra pars reticulata decreases, whereas the firing rate of thalamic neurons in the ventral anterior and anterior ventral lateral thalamus increases, along with the disappearance of bursting activity in the subthalamic nucleus (Benedetti et al., 2004, 2009; Frisaldi et al., 2013). Although the dopamine findings and the electrophysiological data were obtained in different studies (de la Fuente-Fernández et al., 2001, 2002 and Benedetti et al., 2004, 2009, respectively), it is tempting to speculate that the changes in firing pattern of the subthalamic and thalamic neurons were triggered by dopamine release.

Modern brain imaging techniques have been fundamental in the understanding of the placebo response, particularly placebo analgesia, and many brain imaging studies have been carried out to describe the functional neuroanatomy of the placebo analgesic effect (e.g., Bingel et al., 2006; Eippert et al., 2009a, 2009b; Hashmi et al., 2012; Kong et al., 2006, 2007; Lui et al., 2010; Meissner et al., 2011; Petrovic et al., 2002; Price et al., 2007, 2009; Scott et al., 2007, 2008; Tracey, 2010; Wager et al., 2004, 2007, 2011; Zubieta et al., 2005). A meta-analysis of brain imaging data using the activation likelihood estimation method identified two phases: the expectation phase of analgesia and the pain inhibition phase (Amanzio et al., 2013). During expectation, areas of activation are found in the anterior cingulate, precentral and lateral prefrontal cortex, and in the periaqueductal gray. During pain inhibition, deactivations are found in the mid- and posterior cingulate cortex, superior temporal and precentral gyri, in the anterior and posterior insula, in the claustrum

and putamen, and in the thalamus and caudate body. Overall, many of the regions that are activated during expectation are likely to belong to a descending pain inhibitory system that inhibits different areas involved in pain processing (Figure 1F).

In social anxiety disorder, positron emission tomography has been used to assess regional cerebral blood flow during an anxiogenic public speaking task, before and after 6–8 weeks of treatment with selective serotonin reuptake inhibitors (SSRI) under double-blind conditions (Faria et al., 2012, 2014). Conjunction analysis reveals a common attenuation of regional cerebral blood flow from pre- to posttreatment in responders to SSRI and placebo in the left basomedial/basolateral and right ventrolateral amygdala, including amygdala-frontal projections to dorsolateral prefrontal cortex and rostral anterior cingulate cortices (Figure 1G). This pattern correlates with behavioral measures of reduced anxiety and differentiates responders from nonresponders, with no differences between SSRI responders and placebo responders. Therefore, this pattern is capable of differentiating responders from nonresponders to both SSRI and placebos, which indicates that drugs and placebos act on common amygdala targets and amygdala-frontal connections (Faria et al., 2012, 2014).

Immune and endocrine responses can be behaviorally conditioned (Pacheco-López et al., 2005). When an unconditioned stimulus (US), e.g., the effect of a drug, is paired with a conditioned stimulus (CS), e.g., a gustatory stimulus, after repeated pairings, the CS alone can mimic the effect of the drug (conditioned response, CR). Since the CS is a neutral stimulus, it can be conceptualized as a placebo in all respects. Indeed, both immune mediators, like interleukin-2 (IL-2) and interferon- γ (IFN- γ), and hormones, like growth hormone (GH) and cortisol, can be conditioned in humans (Figure 1H). After repeated associations of a CS with cyclosporine A or sumatriptan, which produce IL-2/IFN- γ decrease and GH increase/cortisol decrease, respectively, the CS alone can induce the same immune and hormonal responses (Benedetti et al., 2003b; Goebel et al., 2002).

An association of placebo responsiveness with some genotypes has been described in some conditions (Figure 1I). Patients with social anxiety disorder have been genotyped with respect to the serotonin transporter-linked polymorphic region (5-HTTLPR) and the G-703T polymorphism in the tryptophan hydroxylase-2 (TPH2) gene promoter. Only patients homozygous for the long allele of the 5-HTTLPR or the G variant of the TPH2 G-703T polymorphism show robust placebo responses and reduced activity in the amygdala, whereas carriers of short or T alleles do not show these effects (Furmark et al., 2008). In addition, in patients with major depressive disorder, polymorphisms in genes encoding the catabolic enzyme monoamine oxidase A are associated to the magnitude of the placebo response. Patients with monoamine oxidase A G/T polymorphisms (rs6323) coding for the highest activity form of the enzyme (G or G/G) show small placebo responses (Leuchter et al., 2009). Functional Val158Met polymorphism of the catabolic enzyme catechol-O-methyltransferase (COMT) has been found to be associated with the placebo response in irritable bowel syndrome. The lowest placebo responses occur in Val/Val homozygotes (Hall et al., 2012). As already described above, the functional missense variant Pro129Thr of the gene coding

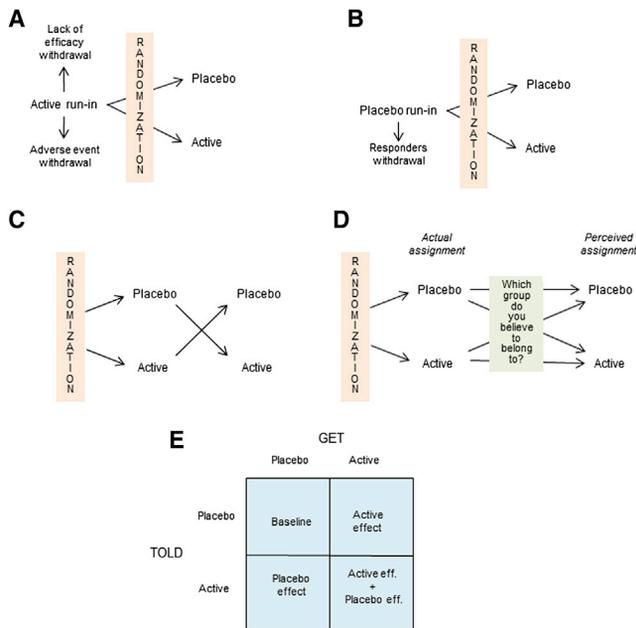


Figure 2. Examples of Clinical Trial Designs

- (A) In the enriched enrollment with randomized withdrawal, after a first active treatment run-in period, subjects are discarded if they either do not respond to the active treatment or show severe adverse events. Only good responders are randomized to either placebo or active treatment.
- (B) In the placebo run-in design, after a first phase in which placebo is administered, only nonresponders are randomized to either placebo or active treatment.
- (C) In crossover designs, subjects first receive placebo and then are switched to active treatment. Another group first receives active treatment and then is switched to placebo.
- (D) In some clinical trials, both actual assignment and perceived assignment can be tested, thus assessing the role of expectations.
- (E) In the balanced placebo design, the interaction between expectations and the action of active treatment can be assessed.

FAAH has also been found to affect the analgesic responses to placebo (Peciña et al., 2014). It should be emphasized, however, that these genetic data must be considered with some caution because all of these studies have investigated rather small samples, particularly when compared to modern genetic standards.

The Influence of Learning and Expectation in Clinical Trials

As mentioned earlier, learning and expectations play a key role across all of these mechanisms. In most of the experimental protocols described above, in order to obtain robust placebo responses, a placebo is given following a preconditioning procedure, for example opioid or nonopioid preconditioning (in pain), apomorphine preconditioning (in Parkinson's disease), cyclosporine preconditioning (in the immune system), or sumatriptan preconditioning (in the endocrine system). As a consequence, all clinical trial designs in which either a placebo or a treatment is given sequentially are at risk of learning effects. For example, many clinical trials that use an enriched design, whereby responders to the active treatment are randomized to either active treatment or placebo (Figure 2A), may produce very good placebo responders. Likewise, placebo run-in designs, in which

placebo nonresponders are selected from a first phase of placebo-treated subjects (Figure 2B), may decrease the overall response to the active treatment due to prior negative experience with treatment. In the classical crossover designs, in which placebo-treated subjects are switched to active treatment and vice versa (Figure 2C), similar sequential learning effects may confound the interpretation of the therapeutic outcome. The problem of sequential learning effects is not easy to work out, for most of the modern trial designs rely on these sequential interventions. In the future it would be advisable to rely more on between-groups designs rather than on within-group designs so as to avoid the sequential administration of different treatments (e.g., first active treatment and then placebo, and vice versa) to the same individual. Certainly, there are boons and banes in both approaches. For example, statistical significance is usually better achieved by using a within-group (repeated-measures) design rather than a between-group (independent-measures) approach. Nonetheless, in light of the robust learning effects observed in the many examples described above, avoiding sequential effects may represent the priority in many circumstances. It should also be emphasized that today we do not know exactly which pharmacological agents produce substantial learning effects. Whereas we know a good amount about narcotics and anti-Parkinson agents, future research should be aimed at evaluating whether this holds true for other drugs as well.

The interpretation of the therapeutic outcome can be confounded by expectation. Evidence from several studies stresses the effects of expectations (Figure 2D). In a clinical trial study, real acupuncture was compared to sham acupuncture. Patients were asked which group they believed they belonged to (either placebo or real treatment). Patients who believed they belonged to the real treatment group experienced larger clinical improvement than those who believed they belonged to the placebo group (Bausell et al., 2005). In another clinical trial, patients were asked whether they considered acupuncture to be an effective therapy in general and what they personally expected from the treatment. Patients with higher expectations about acupuncture experienced larger clinical benefits than those with lower expectations, regardless of their allocation to real or sham groups (Linde et al., 2007). It did not really matter whether the patients actually received the real or the sham procedure—what mattered was whether they believed in acupuncture and expected a benefit from it.

Finally, in a clinical trial of human fetal mesencephalic transplantation (a possible treatment for Parkinson's disease currently under assessment), investigators studied the effect of this treatment compared with placebo treatment for 12 months. They also assessed the patient's perceived assignment to either the active (fetal tissue implant) or placebo treatment (sham surgery). There were no differences between the transplant and sham surgery groups on several outcome measures, such as physical and quality of life scores. However, the perceived assignment of treatment group had a beneficial impact on the overall outcome, and this difference was still present 12 months after surgery. Patients who believed they received transplanted tissue had significant improvements in both their quality of life and motor outcomes, regardless of whether they received sham surgery or fetal tissue implantations (McRae et al., 2004).

Another approach to assess the role of expectations and their interaction with treatment-specific effects is the balanced-placebo design. This design, formulated by [Ross et al. \(1962\)](#), refers to a methodology for studying many aspects of human behavior and drug effects, orthogonally manipulating instructions (told drug versus told placebo) and drug administered (received drug versus received placebo) ([Figure 2E](#)). It has been used in many conditions, such as alcohol research ([Epps et al., 1998](#); [Marlatt et al., 1973](#); [Rohsenow and Bachorowski, 1984](#); [Wilson et al., 1985](#)), smoking ([Sutton, 1991](#)), and amphetamine effects ([Mitchell et al., 1996](#)). This design is particularly interesting for the investigation of placebo effects because it indicates that verbally induced expectations can modulate the therapeutic outcome, in both the placebo group and the active treatment group. For example, cocaine abusers who expect to receive methylphenidate, and indeed receive the drug, show an increase in brain metabolism about 50% larger, particularly in the cerebellum and the thalamus, compared to cocaine abusers who expect to receive a placebo but actually receive methylphenidate. In other words, the increase in brain metabolism is larger when methylphenidate is expected than when it is not. In addition, the self reports of high are also 50% larger when methylphenidate is expected compared to when it is not ([Volkow et al., 2003](#)).

By taking all of these considerations into account, it is clear that the correct interpretation of clinical trials very much depends on all of these elements ([Enck et al., 2011, 2013](#); [Rief et al., 2011](#)). Therefore, all clinical trial designs should incorporate both learning and expectation effects in their methodology and conceptualization. For example, it is interesting to note that expectation has been found to interact with treatment at the level of both pain ratings and neuronal responses in placebo-related brain regions ([Schenk et al., 2014](#)). This might be highly relevant within the clinical trials setting in that expectation and treatment seem to be not necessarily additive as assumed in placebo-controlled clinical trials.

All modern clinical trials should assess both learning and expectation in their designs. For example, an analysis of both actual and perceived assignment ([Figure 2D](#)) could uncover the important role of expectations for a given treatment, as done in studies on acupuncture ([Bausell et al., 2005](#)) and Parkinson's disease ([McRae et al., 2004](#)). Therefore, here I suggest that this analysis always be included in future clinical trials; this can be done by subdividing patients on the basis of the question "which group do you believe to belong to?" Similarly, I suggest that the possible increase in placebo responses in enrichment designs ([Figure 2](#)) always be assessed by comparing the placebo response after previous exposure to active treatment with the placebo response without previous exposure.

At least two further points need to be discussed, for they may represent interesting approaches to clinical trials in the near future, although further research is necessary. First, it is worth noting that negative previous experiences with ineffective treatments may lead to low placebo responses or no responses at all ([Colloca and Benedetti, 2006](#)). Therefore, it is possible today to conceive of a design whereby a mismatch between what subjects expect and what they get is induced so as to generate negative learning. In this way, poor placebo responders or no responders can be created, and these can then undergo random-

ization in a clinical trial ([Benedetti and Frisaldi, 2014](#)). Albeit an interesting approach, the methodological and ethical problems of this design will be further discussed in the section on the ethical implications. Second, a possible genetic screening of placebo responders and nonresponders is worthy of further inquiry ([Servick, 2014](#)), as indicated by some genetics-related placebo responses ([Figures 1C and 1I](#)).

The Effects of Social Propagation of Expectations and the Hawthorne Effect

Today there are some social aspects that are emerging as important factors within the context of both the clinical trial setting and medical practice. The study of social networks over the past years has shown the importance of social interaction and communication in both human behavior ([Chartrand and Lakin, 2013](#); [Fowler and Christakis, 2010](#)) and health ([Luke and Harris, 2007](#); [Smith and Christakis, 2008](#)). Interindividual propagation of behaviors and attitudes is common in a variety of situations, such as the social propagation of emotions ([Cacioppo et al., 2009](#); [Fowler and Christakis, 2008](#)), smoking cessation ([Christakis and Fowler, 2008](#)), obesity ([Christakis and Fowler, 2007](#)), and suicide ([Bearman and Moody, 2004](#)). Overall, these studies suggest that the social environment can be an important contributor to health and emphasize how expectations, both positive and negative, can propagate across a large number of individuals, thus contributing to the dissemination of symptoms and illness across the general population.

Placebo and nocebo responses can also be learned through social learning. The observation of the beneficial effects in other people induces substantial placebo analgesic responses that are positively correlated with empathy scores ([Colloca and Benedetti, 2009](#)). Interestingly, observational social learning produces placebo responses that are similar to those induced by directly experiencing the benefit through a conditioning procedure, thus indicating that learning from others can be quite powerful. The same holds true for nocebo effects ([Swider and Båbel, 2013](#); [Vögtle et al., 2013](#)). After the observation phase, the experimental subjects show robust nocebo responses, i.e., hyperalgesic responses, and this can be correlated to either empathy scores ([Swider and Båbel, 2013](#)) or pain catastrophizing ([Vögtle et al., 2013](#)). Therefore, observation and social interaction are important elements in the overall placebo/nocebo phenomenon. These findings may have implications in the clinical trial setting. In fact, observation of others must be taken into consideration whenever a clinical trial is performed. Patients participating in a clinical trial may be influenced by observing other patients belonging to the same trial. For example, communication among patients enrolled in the same clinical trial is common, and this may either positively or negatively influence the therapeutic outcome ([Benedetti, 2013b](#)).

Indeed, negative expectations and nocebo effects can spread across individuals very quickly through the propagation of negative information and communication, and this may produce biochemical changes that impact negatively on health and may modify the baseline of many physiological parameters. Within this context, high-altitude headache has been studied as a model for the investigation of the products of cyclooxygenase, i.e., prostaglandins and thromboxane ([Benedetti et al., 2014](#)). In this experimental model, a subject (the trigger) receives negative

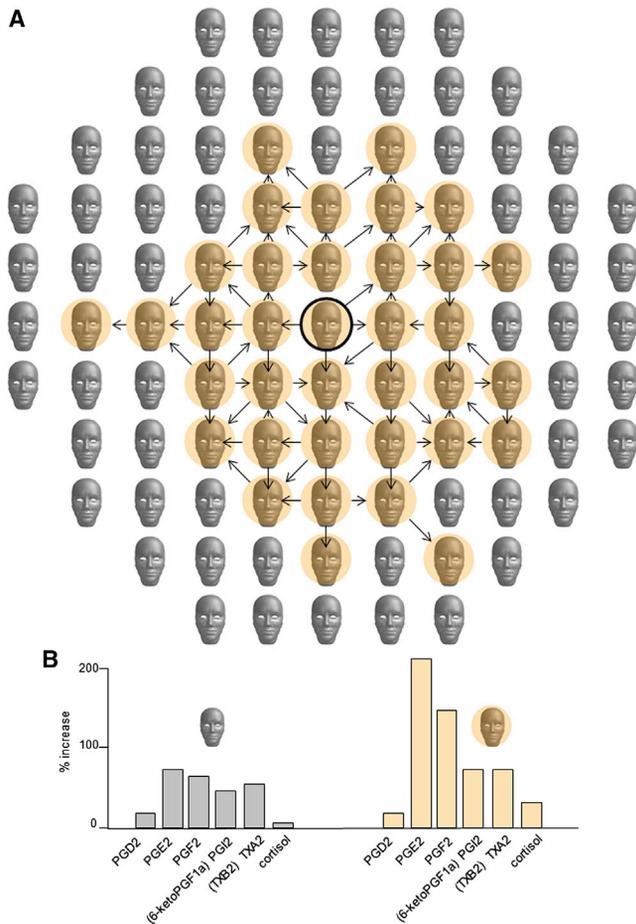


Figure 3. Social Propagation of Negative Expectations
(A) Pattern of interindividual propagation of negative expectations starting from a single person (encircled head). In 1 week, negative communication about the occurrence of headache at high altitude spread across 36 subjects (orange heads).
(B) When on the following days the socially infected subjects reached an altitude of 3500 m, they showed a higher frequency of headache, along with a larger increase in salivary prostaglandins (PG), thromboxane (TX), and cortisol compared to the subjects who were not reached by the negative information (gray heads).

information about the risk of headache at high altitude and disseminates this negative information across a number of other subjects. In 1 week, this negative information propagated across 36 subjects (Figure 3A). This nocebo group showed a significant increase in headache and salivary prostaglandins and thromboxane when at high altitude compared to the control group (Figure 3B). In this novel experimental model, negative information propagated across 36 subjects in 1 week (Benedetti et al., 2014). Over longer periods of time, hundreds or even thousands of subjects might get “socially infected,” thus emphasizing the possible important role of negative social communication in the dissemination of symptoms and illness across the population.

It is worth noting that this interindividual communication may have a crucial role in the outcome of a clinical trial. In fact, the same authors (Benedetti et al., 2014) ran two aspirin versus placebo clinical trials at high altitude for the control of high-altitude

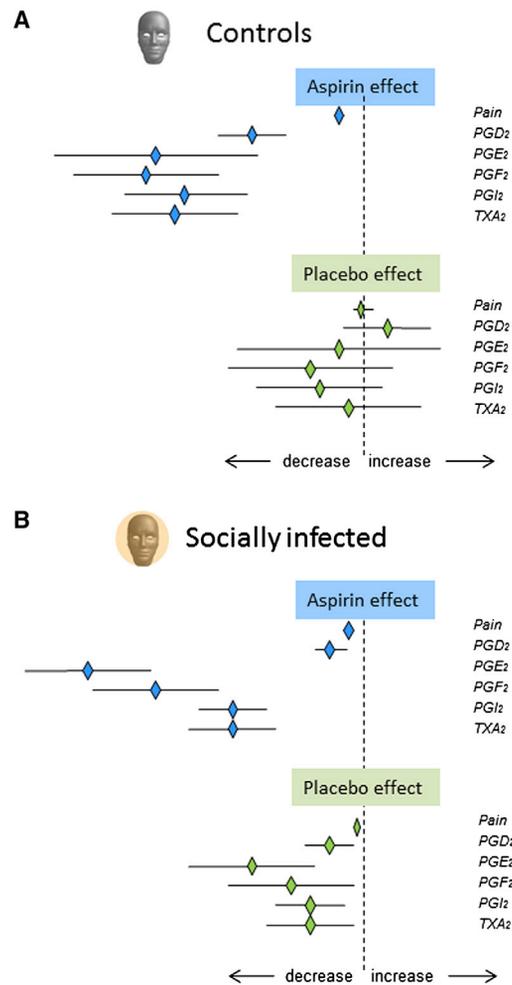


Figure 4. Aspirin versus Placebo Clinical Trial at High Altitude for the Control of High-Altitude Headache in the Controls and the Socially Infected Individuals of Figure 3

(A and B) Aspirin vs placebo clinical trial at high altitude for the control of high-altitude headache in the controls (A) and the socially infected individuals of Figure 3 (B). Means (diamonds) and 95% confidence intervals (horizontal lines) crossing the vertical broken line are statistically nonsignificant. Whereas in controls there was no placebo effect (thus only aspirin was effective), in the socially infected subjects both aspirin and placebo reduced pain, prostaglandins (PG) D₂, E₂, F₂, and I₂, and thromboxane (TX) A₂.

headache (Figure 4). The first trial was performed in the control subjects, whereas the second trial was performed in the socially infected individuals. Aspirin was effective in reducing both pain and prostaglandin synthesis in the control subjects, whereas placebo was totally ineffective (Figure 4A). Conversely, both aspirin and placebo reduced pain and prostaglandin synthesis in the socially infected individuals (Figure 4B). In other words, whereas no placebo effect was present in the controls, a placebo effect occurred in the socially infected subjects, a difference that is attributable to the different baseline levels of prostaglandins induced by the spread of negative information. The placebo effect occurred only in the socially infected individuals because the placebo acted only on the nocebo component of the prostaglandins and pain increase.

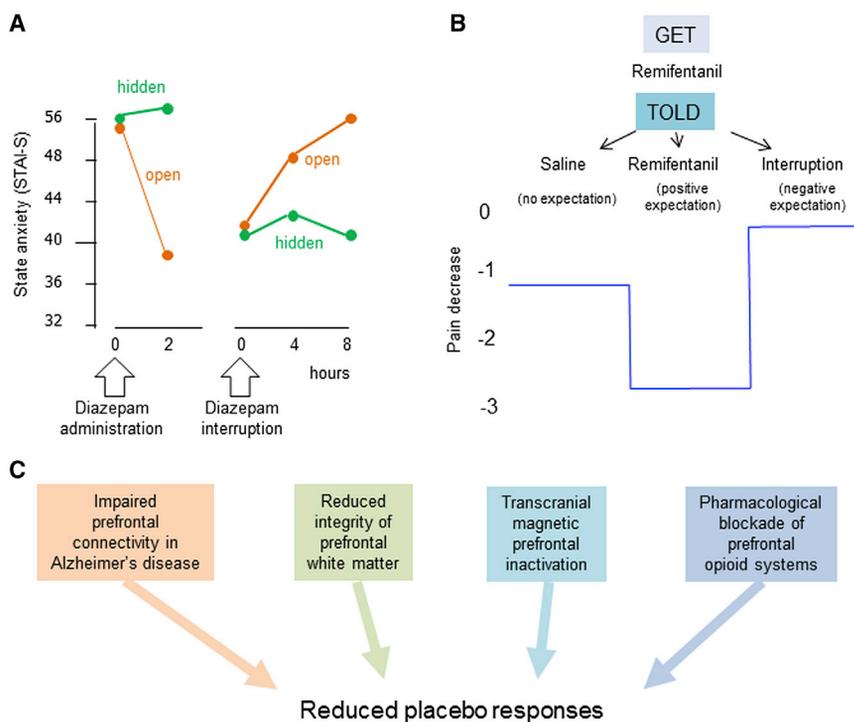


Figure 5. Principal Implications for Medical Practice

(A) Informing the patients (open) about diazepam administration produces different effects compared to no information at all (hidden). The total lack of effect in the hidden condition shows that anxiety reduction in the open condition is due to a psychological effect and not to the pharmacodynamic effect of diazepam. Identical but opposite effects are present with diazepam interruption, indicating that informing the patients about drug discontinuation may have negative effects.

(B) Verbal information, leading to no expectations, positive expectations, and negative expectations, may change the effectiveness of the analgesic remifentanyl.

(C) A reduction of the placebo response is present in all the conditions in which the prefrontal functions are impaired, either naturally (e.g., dementia and reduced white matter integrity) or artificially (magnetic inactivation and pharmacological blockade).

practice as well. Doctors and psychologists must consider the possible negative impact that the observation of unsuccessful treatments may have on their patients. This is true in everyday life as well, whenever others' suffering and negative

That the baseline of a variety of physiological parameters can change by merely being enrolled in a study is another important confound that might affect the outcome and interpretation of a clinical trial. A recent study on obesity (Cizza et al., 2014) showed that improvements in biochemical (fasting glucose, insulin, lipids) and behavioral (sleep duration/quality) parameters occurred between screening and randomization of the patients. These findings are consistent with the Hawthorne effect, which implies that behavior measured in the setting of an experimental study changes in response to the attention received from study investigators (Last, 1983).

As becomes clear from these findings, both the social propagation of expectations (Benedetti et al., 2014) and the Hawthorne effect (Cizza et al., 2014) may influence the baseline of biochemical and behavioral parameters before patients are randomized to either placebo or active treatment, thereby potentially affecting the outcome of a study. In addition to the control and assessment of learning and expectation discussed earlier, future clinical trials should therefore also consider these elements. Whereas it is not easy to control for the Hawthorne effect, because this would imply that participants do not know they are under study, it is relatively easier to control for social interactions and communication across the participants of a clinical trial. Thus, an important caveat is that social interaction while under study should be avoided as much as possible in order to prevent a social contagion effect that could change the baseline biochemical and behavioral parameters (see Figures 3 and 4 and Benedetti et al., 2014).

Implications for Routine Medical Practice

The findings on social propagation of negative expectations, as shown in Figure 3, may have profound implications in medical

outcomes are observed, e.g., through the media. Social observational learning can lead to a negative emotional contagion across different individuals, with the consequent activation of nocebo mechanisms (Benedetti, 2013b).

Hidden administration of therapies has provided compelling evidence that expectation is a key element in therapeutic outcome (Benedetti et al., 2011c; Colloca et al., 2004). If the patient is unaware that a treatment is being performed and has no expectations about any clinical improvement, the therapy is not as efficacious. This has profound implications in terms of medical practice because the information delivered by health professionals can impact therapeutic outcome.

For example, the effectiveness of diazepam, one of the most frequently used benzodiazepines for treating anxiety, is reduced or completely abolished when diazepam is administered unbeknownst to the patient (Benedetti et al., 2003a, 2011c; Colloca et al., 2004). In postoperative anxiety (Figure 5A), there is a clear-cut decrease of anxiety in those patients who receive an overt administration of diazepam, as routinely done in clinical practice, whereas diazepam is totally ineffective if given covertly, which indicates that anxiety reduction after the open diazepam is a psychological effect (or placebo response). Likewise, anxiety increases significantly after 4–8 hr when diazepam is interrupted overtly, whereas its hidden interruption does not change anxiety scores (Figure 5A). Therefore, the anxiety relapse after the expected (open) interruption of diazepam is attributable to the negative expectation of anxiety relapse (nocebo effect) (Benedetti et al., 2003a). These larger effects following open administrations/interruptions are likely to be due to the additive and potentiating effect of expectation and drug. By contrast, the hidden administration does not allow such potentiation because there are no expectations.

The same effects are present in other conditions, such as pain and Parkinson's disease (Benedetti et al., 2003a, 2011c; Colloca et al., 2004). For example, in postoperative pain following the extraction of the third molar (Levine et al., 1981; Levine and Gordon, 1984), a hidden intravenous injection of 6–8 mg morphine corresponds to an open intravenous injection of saline solution in full view of the patient (placebo). In other words, telling the patient that a painkiller is being injected (with what is actually a saline solution) is as potent as 6–8 mg of morphine. This holds true for a variety of painkillers, such as morphine, buprenorphine, tramadol, ketorolac, and metamizole (Amanzio et al., 2001; Benedetti et al., 2003a; Colloca et al., 2004).

Open and hidden administrations have been studied in combination with functional magnetic resonance imaging (Bingel et al., 2011). Expectation of remifentanyl (told remifentanyl, gets remifentanyl) produces more pronounced analgesic effects compared to no-expectation (told saline, gets remifentanyl) (Figure 5B). Moreover, expectation of interruption (told interruption, gets remifentanyl) abolishes the overall analgesic effect. Functional magnetic resonance responses show that the enhancement of analgesia in the positive expectation condition is associated with activity in the dorsolateral prefrontal cortex and pregenual anterior cingulate cortex, whereas negative expectation of interruption is associated with activity in the hippocampus.

The global effect of a drug derives from its specific pharmacodynamic action plus the psychological (placebo) effect coming from the very act of its administration. There is some evidence that these two components operate independently from each other. Both remifentanyl and expectations reduced pain, but drug effects on pain reports and brain activity, as assessed by functional magnetic resonance imaging, do not interact with expectations. Regions associated with pain processing show no differences in drug effects as a function of expectation in the open and hidden conditions. Instead, expectations modulate activity in frontal cortex, with a separable time course from drug effects (Atlas et al., 2012). Therefore, drugs and expectations both influence clinically relevant outcomes, yet they seem to operate without mutual interference. This is an interesting observation because it could be speculated that drugs and expectations would produce additive effects by affecting different brain regions. However, the additive model requires further research, particularly in light of some contrasting findings, whereby expectation has been found to interact with treatment at the level of both pain ratings and neuronal responses in placebo-related brain regions (Schenk et al., 2014).

A natural situation in which hidden therapies are delivered is represented by impaired cognition. Indeed, cognitively impaired patients do not have expectations about therapeutic benefits, so the psychological (placebo) component of a treatment is likely to be absent. On the basis of these considerations, Benedetti et al. (2006b) studied Alzheimer patients at the initial stage of the disease and after 1 year in order to see whether the placebo component of the therapy is affected by the disease. The placebo component of an analgesic therapy was found to be correlated with both cognitive status and functional connectivity among different brain regions, according to the rule “the more impaired the prefrontal connectivity, the smaller the placebo response”

(Benedetti et al., 2006b). To support this view, there are a number of studies that indicate that placebo responses are reduced when prefrontal functioning is impaired (Figure 5C). First, the individual placebo analgesic effect is correlated with white matter integrity indexed by fractional anisotropy, as assessed through diffusion tensor magnetic resonance imaging; stronger placebo analgesic responses are associated with increased mean fractional anisotropy values within white matter tracts connecting the periaqueductal gray with the rostral anterior cingulate cortex and the dorsolateral prefrontal cortex (Stein et al., 2012). Second, inactivation of the frontal cortex with repetitive transcranial magnetic stimulation completely blocks the analgesic placebo response (Krummenacher et al., 2010). Third, the opioid antagonist naloxone blocks placebo analgesia, along with a reduction in the activation of the dorsolateral prefrontal cortex, suggesting that a prefrontal opioidergic mechanism is crucial in the placebo analgesic response (Eippert et al., 2009a). Therefore, both magnetic and pharmacological inactivation of the prefrontal lobes have the same effects as those observed in prefrontal degeneration in Alzheimer's disease and reduced integrity of prefrontal white matter (Figure 5C).

At least two clinical implications emerge from these findings. First, in order to compensate for the disruption of placebo/expectation-related mechanisms, we need to consider a possible revision of some therapies in Alzheimer patients, who probably need larger doses of analgesics to compensate for the lack of the placebo response. Second, we should consider the potential disruption of placebo mechanisms in all those conditions where the prefrontal regions are involved, as occurs in vascular and frontotemporal dementia as well as in any lesion of the prefrontal cortex in which the prefrontal executive functions are impaired. Nothing is known about the potential impact on clinical trial design, but these observations warrant further research to better understand the role of placebo responses in those studies involving patients with prefrontal impairment.

Another possible important implication for medical practice is represented by the exploitation of learning mechanisms in order to reduce drug intake (Doering and Rief, 2012). Indeed, the administration of an active treatment for several days in a row, and then its substitution with a placebo, can lead in the long run to a reduction of the treatment dose with no or little changes in the therapeutic effect. This has been found in a number of conditions, such as pain (Amanzio and Benedetti, 1999; Benedetti et al., 2011b), Parkinson's disease (Benedetti et al., 2004; de la Fuente-Fernández et al., 2001), and the immune system (Goebel et al., 2002).

Placebos Boost Physical and Cognitive Performance; Nocebos Reduce It

As for drug development, placebos (and nocebos) can also exert their influence on physical performance. In general, all available data indicate athlete's expectations as important elements of physical performance, in spite of the fact that very different experimental conditions have been investigated (Beedie and Foad, 2009; Pollo et al., 2011).

In a simulation of sport competition in which subjects had to compete with each other in a competition of pain endurance, placebo administration on the day of competition was found to

induce longer pain tolerance compared to an untreated group. However, if pharmacological preconditioning is performed with morphine in the precompetition phase, the replacement of morphine with a placebo on the day of the competition induces an increase in pain endurance and physical performance that is significantly larger than placebo without prior morphine preconditioning. The placebo effect after morphine preconditioning can be prevented by administration of the opioid antagonist, naloxone, which suggests that this placebo response is opioid mediated (Benedetti et al., 2007). Similar findings can be obtained with a nonpharmacological conditioning procedure (Pollo et al., 2008).

The increase in performance following placebo administration may have practical applications, but it also raises important questions as to how these effects should be exploited in sport competitions. The ethical issue is particularly significant when one wants to induce opioid-mediated placebo responses by means of pharmacological preconditioning with illegal drugs, as done by Benedetti et al. (2007).

Nocebo effects are also important in physical performance. For example, in a 30 m repeat-sprint protocol, placebo capsules coupled with different positive or negative instructions lead to increased and decreased speed, respectively (Beedie et al., 2007). Likewise, it is possible to negatively modulate the performance of subjects carrying out a muscle exercise to volitional maximum effort by employing discouraging suggestions and negative conditioning (Pollo et al., 2012). These findings may have profound implications for training strategies because negative expectations may counteract the positive effects of training programs.

A number of studies suggest that placebos and expectations enhance, at least in part and in some circumstances, cognitive performance (Green et al., 2001; Oken et al., 2008; Parker et al., 2011; Weger and Loughnan, 2013) and other cognition-related tasks, such as reaction times (Anderson and Horne, 2008; Colagiuri et al., 2011). For example, Green et al. (2001) used a balanced placebo design (Figure 2E) to investigate the extent of expectancy in the ability of glucose to affect cognitive performance. Glucose administration was found to improve recognition memory times and performance on a vigilance task, but only in sessions where subjects were informed that they would receive glucose and not when they were told that they would receive aspartame. Therefore, expectation contributes to the positive effects of glucose on cognition. Oken et al. (2008) compared healthy seniors who took a 2-week supply of placebo pills, which they were told was an experimental cognitive enhancer, with seniors not taking any pills. The authors found a significant effect of pill taking on a word-list delayed recall task and on a Stroop color word task. Virtually nothing is known about the biological underpinnings of these cognition-enhancing effects by placebos. However, it is interesting to note that Stern et al. (2011) found an opioid-mediated placebo effect in memory tasks in healthy volunteers. This is an interesting area that could provide new information not only for placebo effects, but also for memory mechanisms.

Ethical Implications

In spite of these recent advances in placebo research and the efforts to understand both the biological underpinnings and the

possible applications, paradoxes and ethical dilemmas exist. These can be very simply summarized with the following two questions: is it ethically and methodologically correct to minimize placebo effects in clinical trials, and are any means to maximize placebo effects acceptable in medical practice?

As to the first question, today we are in a good position to modulate the magnitude of the placebo response in both directions, e.g., by minimizing it in the clinical trial setting. For example, by using a negative conditioning procedure, whereby there is a mismatch between what the patient expects and what he gets, it is possible to decrease the magnitude of the placebo effect (Benedetti and Frisaldi, 2014). Likewise, a placebo run-in phase is often used to identify placebo responders and to discard them from further randomization (Figure 2B). The main problem with this kind of placebo manipulation is represented by the fact that the inclusion of poor placebo responders in a clinical trial is arguably correct from both an ethical and methodological point view. In fact, a clinical trial of this sort is not representative of the general population; thus, the interpretation would be biased. In addition, a randomization of placebo nonresponders to placebo and active treatment would lead to low placebo responses in both groups, with no real advantage.

The second question is even more complex and ethically intriguing. Since therapeutic rituals can affect the patient's brain positively, anybody who performs a ritual can change the physiology of the patient's brain positively. Today there is a growing tendency to refer to the effects of placebos as real biological phenomena that need to be triggered and enhanced by a variety of odd, weird, and bizarre procedures. Many claim that there is no difference between sugar pills and talismans if one wants to obtain positive responses, and it makes no difference if deception comes from a doctor or a charlatan or a shaman. According to this worrisome view, any healer would be justified to stimulate the release of endogenous chemicals by enhancing the patient's expectations. In this sense, science risks being exploited in the wrong way, and paradoxically, the neurobiological advances of placebo research can turn into a regression of medicine to past times, when the eccentricity and oddity of the therapies were the rule. It is crucial that we find a better way to communicate placebo research, though this is not an easy task, for scientific advances will inevitably go against ethical concerns as we will learn more and more about the biology of a vulnerable aspect of mankind. We need to better identify and understand the ethical limits to increase expectations because we are dealing with the vulnerability of the patient (Benedetti, 2012).

At least a couple of recommendations should be considered. First, we should strive to better communicate placebo research to the media in order to avoid too much emphasis on the therapeutic properties of placebos and to make people understand that placebos do not work everywhere. Second, it would be advisable and useful to come up with a general consensus on the use of placebos in routine medical practice. For example, only doctors and psychologists should be allowed to exploit the placebo effect, thus making the placebo effect illegal outside the medical and psychological setting. Therefore, the study of the biology of foibles and vulnerable aspects of mankind may unravel new mechanisms of how our brain works, but it may have a profound negative impact on our society if badly exploited.

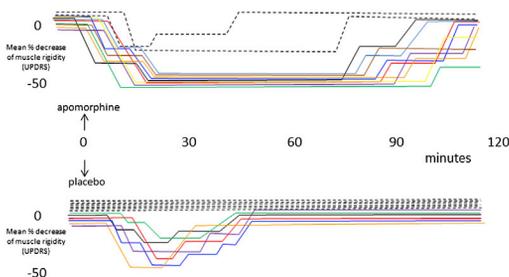


Figure 6. Comparison between the Effects of the Anti-Parkinson Agent, Apomorphine, and Placebo on Muscle Rigidity, as Assessed at the Wrist by Means of the Unified Parkinson's Disease Rating Scale

The responses of 11 Parkinson patients to apomorphine and the responses of 12 Parkinson patients to placebo are shown. Two patients show small responses to apomorphine, and six patients show no response at all to placebo (broken lines). Note that the duration of the effect of apomorphine is longer than that of placebo, and the mean magnitude of the effect of apomorphine is larger than that of placebo, although some placebo responders show responses as large as those to apomorphine. Also, note that the variability of placebo is larger than that of apomorphine.

What Is the Difference between Placebos and Drugs?

After the description of the neurobiological mechanisms and the translational and ethical implications of placebo effects, an important question arises: what is the difference between placebos and drugs, and how does this affect the design and interpretation of clinical trials? One of the most interesting concepts emerging today is that placebos and drugs may share common biochemical pathways, such as the endogenous opioid system, the endocannabinoid system, the cyclooxygenase pathway, and the dopaminergic system. For example, the analgesic morphine and the anti-Parkinson apomorphine act on opioid and dopamine receptors, respectively, but expectation of receiving morphine or apomorphine activates the same opioid and dopamine receptors, respectively. In spite of this similarity in the mechanism of action, placebos and drugs show many differences (Benedetti, 2014a).

- (1) Duration of action: in general, the duration of the effect of a drug is longer than that of a placebo. As far as we know today, this holds true for painkillers and anti-Parkinson agents, whereas much less is known about other therapeutic interventions. For example, the effect of the powerful anti-Parkinson drug apomorphine lasts, on average, much longer than a placebo. The mean duration of apomorphine in a group of 11 Parkinson patients is around 90 min, whereas the mean duration of the placebo effect in another 12 patients is about 30 min (Benedetti et al., 2004, 2009; Frisaldi et al., 2013) (Figure 6).
- (2) Variability of effect: in the 11 patients who received apomorphine, there is a small response only in 2 patients, whereas in the 12 patients who received a placebo, there is no response at all in 6 patients (Figure 6). This larger variability in the response to placebos is also present in other conditions, such as pain. Thus, the response to a pharmacological agent is usually more constant and less variable (Benedetti, 2014a).
- (3) Magnitude of effect: the effect following placebo administration can be as large as the effect following drug

administration (Figure 6). For example, some good placebo responders may show a reduction of the UPDRS (Unified Parkinson's Disease Rating Scale) up to 50%, as occurs for drugs (Benedetti et al., 2004, 2009; Frisaldi et al., 2013). The placebo effect can be even larger in pain, where pain reduction can be of 5–6 points on a scale ranging from 0 (no pain) to 10 (unbearable pain), and usually drug companies strive to produce drugs that reduce pain by 2–3 points. In irritable bowel syndrome, the analgesic response to a placebo can be even larger than that to lidocaine (Vase et al., 2003). However, it is important to point out that only a small percentage of placebo responders may show such huge effects. If we consider the response variability, the average magnitude is larger for drugs compared to placebos (Figure 6).

The differences between placebos and drugs can be exploited in the design of clinical trials. For example, the duration of action, as well as the latency of action, can represent a good way to compare placebos with drugs, although few data are available across different therapeutic interventions (Benedetti, 2014a). A priority of future research should therefore be to better understand placebo mechanisms and the differences between the action of placebos and drugs across a number of pharmacological interventions. In addition, duration and magnitude of drug effects depend on the dose, and dose responses can be used to distinguish between drug and placebo effects. In fact, there would not be a dose component in placebo responses, provided that no information about a possible dose increase is given, as this information would lead to increased expectations. A possible approach could be a covert dose increase of the drug and its comparison with a placebo. The advantage of this approach is that, whereas the psychological expectation effect would not change, the pharmacodynamic effect of the drug under test would increase. If the drug is really effective at a given dose, one should expect no drug-placebo difference below the effective dose, but an increasing difference as the drug dose increases.

Similar differences are present in nocebo effects, whereby duration, variability, and magnitude of the effects are comparable to those observed following the administration of placebos. Interestingly, in analgesic clinical trials for migraine, patients who receive the placebo often report a high frequency of adverse events, and these negative effects correspond to those of the antimigraine medication against which the placebo is compared (Amanzio et al., 2009). This is attributable to the important role of expectation in the placebo/nocebo phenomenon, such that sometimes the patients get what they expect, for example by reading the possible side effects described in the informed consent. The dropouts in clinical trials due to nocebo effects is a crucial aspect that may confound the interpretation of many clinical trials (Amanzio et al., 2009), but unfortunately not all studies compare the adverse events in the active treatment and placebo groups. Future trials should always incorporate this comparative analysis in order to identify all those adverse events that are psychological in nature and not attributable to the specific effect of the therapeutic intervention.

Conclusions

Here I have described the complexity of the science of placebo effects, which ranges from basic research to the clinic and society. Recent insights into both the neuroscience of placebos and the translational implications are already changing the way we look at clinical trials, medical practice, and several aspects of ethics and society, including sport. Our increasing understanding of the placebo effect gives rise to a number of recommendations and caveats. Any previous exposure to drugs can produce huge placebo responses through learning; thus, any clinical trial using an enrichment design is at risk of producing high placebo responses. Placebo nonresponders can be created in the lab, although their inclusion in a clinical trial is arguably methodologically and ethically correct. Expectation is a critical consideration; actual and perceived assignment to a given group (active treatment or placebo) should be evaluated in clinical trials in order to assess whether expectation impacted outcome. Social interaction and communication among the participants in a clinical trial should be avoided, as this could produce changes in baseline physiological/biochemical parameters due to social contagion effects. Adverse events should always be assessed in placebo groups of clinical trials in order to see whether they are attributable to the specific effect of the treatment or rather to nocebo effects. In medical practice, doctors should strive to provide information about efficacy, duration, utility, and risks of the therapy to ensure optimal efficacy of the treatment. It is important to consider how impaired cognitive function may reduce the global efficacy of a pharmacological treatment due to loss of the placebo component of the treatment. In this case, a dose increase of the treatment should be considered in order to compensate for the loss of placebo responses. It is also important to consider how learning mechanisms can be harnessed to the patient's advantage in order to reduce drug intake. Finally, in spite of similarities in mechanisms of action, placebo and drugs show important differences in duration of action and in variability/magnitude of effect, which depend on dose of a drug, which can be exploited in the design of clinical trials.

Until a couple of decades ago, very little was known about the mechanisms and the possible implications of both placebos and nocebos. Today, thanks to a more rigorous scientific and biological approach, we are witnessing an explosion of placebo research both within the domain of neuroscience and within the context of clinical trial methodology and routine clinical practice. A further in-depth analysis of this phenomenon will certainly provide important information in the near future for a better understanding of human biology, medicine, and society.

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