Mechanisms Involved in Placebo and Nocebo Responses and Implications for Drug Trials

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Drug trials often compare active drugs with inert placebos under double-blind conditions. This standard design is increasingly being questioned in light of recent progress in understanding the mechanisms behind the placebo response.[1,2] The growing knowledge of the neurobiology of placebo is forcing us to reconsider the significance of the placebo in clinical practice, with consequent profound implications for the design of clinical trials.

THE NEUROBIOLOGY OF PLACEBO AND NOCEBO RESPONSES: WHAT WE HAVE LEARNED

In this article, we use the terms "placebo group" for groups of subjects receiving nonspecific treatments in clinical trials, "placebo response" for positive effects that are caused by nonspecific treatment ingredients, and "placebo mechanisms" for experimentally investigated mechanisms that contribute to placebo responses, e.g., expectation and conditioning. Correspondingly, the terms "nocebo response"/"nocebo effects" (negative effects that are caused by nonspecific treatment ingredients, e.g., side effects in placebo groups) and "nocebo mechanisms" are used.

The placebo response is mediated primarily through distinct but interrelated mechanisms: cognitive factors such as patient expectations of the benefit of a treatment,[3–5] the quality of the patient–doctor relationship,[6] and associative learning (conditioning).[7,8] Interestingly, intensive research in the past decade has revealed how these psychological mechanisms trigger complex neurobiological phenomena involving the activation of distinct brain areas as well as peripheral physiology, including the release of endogenous substrates.[2] Placebo analgesia, for instance, the most intensively studied placebo effect, is mediated by activation of the opioidergic descending pain modulatory system. This opioid-dependent system originates in the forebrain and ultimately controls nociceptive input at the earliest central stage, i.e., the dorsal horn of the spinal cord.[9] Similarly, the involvement of system-specific brain and peripheral changes has been shown to underlie placebo responses in Parkinson's disease (in which placebos trigger dopamine release),[10] depression/mood conditions, and even the immune system (**Table 1**). Nocebo effects have been less investigated, although first results in this area also highlight neurophysiological pathways and the role of hormones (e.g., cholecystokinin).[1] Taken together, placebo and nocebo responses may be mediated by the same biological systems through which drugs exert their treatment effects.

The role of expectation in active pharmacologic treatments

Placebo experiments, even though they are traditionally performed using biologically inert compounds (i.e., milk-sugar pill, saline), have increased our awareness that the effects of active pharmacologic treatments also have interacting physiological and psychological components. The crucial role of expectation in the therapeutic outcome is best illustrated in the so-called "open/hidden" drug paradigm. In this paradigm, identical concentrations of active drugs are administered either in an open condition, in which the active medication is administered to the patient by the doctor in a visible way, or in a hidden condition, in which the patient is unaware of the timing of the medication administration (e.g., using a computer-controlled infusion). This allows for dissociating the pure pharmacodynamic effect of the (hidden) treatment from the psychological effect that comes from knowing that treatment is being administered. The difference between the respective outcomes after the administration of the expected and unexpected therapy can be seen as the "placebo" or psychological component even though no placebo pill has been used.[11,12] These studies reveal that psychological factors such as awareness of a drug being given can considerably enhance the analgesic effect of a drug.[11] Conversely, hidden administration of the drug reduces the analgesic effect of nonsteroidal anti-inflammatory drugs to nonsignificance and even reduces, to a substantial extent, the effects of opioids.[11] As a result of hidden administration, drug doses had to be doubled to achieve the result achieved by open administration. This phenomenon is not restricted to analgesic use; similar effects

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Table 1 Mechanisms of placebo/nocebo effects in medical conditions and physiological systems

	Mechanisms
Pain	Activation of endogenous opioids and dopamine (placebo); activation of cholecystokinin and deactivation of dopamine (nocebo)
Parkinson's disease	Activation of dopamine in the striatum and changes in activity of neurons in basal ganglia and thalamus
Depression	Changes of electrical and metabolic activity in different brain regions (e.g., ventral striatum)
Anxiety	Changes in activity of the anterior cingulate and orbitofrontal cortices; genetic variants of serotonin transporter and tryptophan hydroxylase 2
Addiction	Changes of metabolic activity in different brain regions
Cardiovascular system	Reduction of β-adrenergic activity of heart
Respiratory system	Conditioning of opioid receptors in the respiratory centers
Immune system	Conditioning of immune mediators (e.g., interleukin 2, interferon γ, lymphocytes); conditioning of antihistamine effects in allergic rhinitis
Endocrine system	Conditioning of some hormones (e.g., growth hormone, cortisol)
Gastrointestinal system	Conditioning of symptoms, prefrontal cortex activation–cingulate cortex deactivation

Adapted from ref. 2. Individual study references are not listed because of space limitations; they can be obtained from the authors.

have also been reported for treatments in other domains, such as in motor function in Parkinson's disease and responses in anxiety-related disorders.[11] Therefore, the elimination of positive expectations by patients for outcomes of drug treatments would result in substantially increased costs.

The power of expectations: latest findings

A recent study illustrates the power of expectations.[3] In this study, the potent opioid analgesic remifentanil was administered to healthy volunteers in three different conditions: without expectation of analgesia (hidden application), with expectation of a positive analgesic effect, and with negative expectation of analgesia, i.e., expectation of hyperalgesia. Importantly, functional magnetic resonance imaging was used to study the efficacy of the opioid (so as to exclude a reporting bias) and to elucidate the underlying neural mechanisms (**Figure 1**). Whereas positive expectation doubled the analgesic effect of remifentanil, analgesia was completely absent when remifentanil was given under conditions of negative expectation. Functional magnetic resonance imaging revealed that these expectation-dependent changes in opioid analgesia were mediated by specific brain areas—in this case, the endogenous pain modulatory system, which complemented and thereby modulated the pharmacologic effect of remifentanil. This study provides objective neurobiological evidence that a patient's expectation of a drug's effect critically influences its therapeutic efficacy and modulates the biological pathways of action. We believe that these results obtained in healthy volunteers have fundamental implications for clinical practice and clinical trials. They open up a new avenue of research dedicated to understanding how drug, therapeutic context, and disease-specific interactions between pharmacologic agents and cognitions influence endogenous neurobiological mechanisms.

PREDICTOR RESEARCH: WHAT IS YET TO BE LEARNED

In experimental and clinical approaches, the presence of placebo responses typically varies tremendously among individuals. There is therefore a great need to detect specific psychological, neuroendocrine, or genetic conditions that render subjects particularly susceptible to placebo effects. This is particularly important for diseases for which drug development has been compromised by rising placebo response rates.

Moreover, deeper knowledge is needed regarding the differences in placebo mechanisms between diseases and physiological and psychological systems. Placebo effects have been shown to be substantial not only for psychological outcome variables (e.g., pain sensations) but also for biological parameters (e.g., dopamine release in Parkinson's disease,[10] forced expiratory volume in asthmatic disease,[13] and antihistamine response in allergic reactions[14]). However, the mechanisms that steer placebo responses can differ between systems (e.g., there may be a greater impact of expectation on subjective outcomes but a greater impact of conditioning on biological parameters).

HOW PLACEBO RESEARCH CAN HAVE AN IMPACT ON THE CURRENT METHODOLOGY OF PHARMACOLOGIC TRIALS

Although novel designs to study the placebo response have been developed in experimental placebo research,[15] such attempts have been missing in clinical trials. In the following section, we describe how traditional double-blinded placebo-controlled randomized trials could be modified to accommodate recent findings about placebo and nocebo mechanisms so as to optimize placebo effects instead of minimizing them. This approach better addresses the researcher's need to have an understanding of the mechanisms of action and the clinician's need to understand how to optimize treatment conditions.

Optimizing placebo effects

Rather than attempting to minimize the psychological aspects of the placebo effect, trial designs should be developed to capture the real-world therapeutic effects by capitalizing on the effects of expectation and active treatment. As noted above, the overall therapeutic effect is not merely the sum of a specific effect and an independent nonspecific effect; contextual factors can interact with drug-specific effects in modifying biological and psychological pathways of action. Therefore, overall effects cannot be estimated from traditional randomized controlled trials; the maximum benefit that is achievable with a medical intervention must itself be the subject of investigation. There is a need to create and investigate disease- and drug-specific therapeutic contexts that enhance the pharmacologic effects of drug treatments (e.g., optimizing expectation, using preconditioning trials to improve outcome). Corresponding factorial study

designs would include not only standard blinded drug groups vs. placebo groups but also context-optimized drug groups and context-optimized placebo groups.

The need for improved assessment of placebo mechanisms to understand specific drug action

Given that improvements in clinical trials result from a complex interaction of pharmacologic and contextual factors, the isolation of a drug-specific effect becomes more challenging. The expectations of participants can vary over the course of treatment. Prior knowledge and experience with comparable treatments, together with the information conveyed in the informed-consent process, determine the contextual factors at the beginning of the trial. Subsequent perceptions of improvement and/or side effects then modulate the process. It is therefore not surprising to find that *a priori* treatment expectation and initial treatment responses frequently predict outcome.[16,17] Drug-specific effects can be analyzed only if this varying contextual information is carefully controlled or monitored and is taken into consideration in the statistical analysis (e.g., using covariance analyses for multiple expectation assessments). Considering the complex nature of drug–context interactions, crossover designs could impede the disentangling of these effects. Patient expectations are more difficult to estimate in multiarm designs that compare different drugs with one placebo than in two-arm designs that compare one drug with one placebo.

The need for studies using variations of placebo conditions

In double-blind randomized controlled trials, side effects are major determinants of open vs. hidden treatment arms and between placebo and active-drug arms. If patients experience side effects, they assume that they are in the drug arm, and this assumption induces the powerful contextual effects of open administration. By contrast, the absence of side effects mimics the less powerful hidden application effects. If side effects are experienced only in the active-drug arm, a systematic difference in expectations emerges between the placebo and drug arms, and the placebo arm fails to control for the nonspecific factors that play a role in the drug arm. In this context, the traditional, but rarely used, approach of administering active placebo pills (that mimic the side effects of the active drug without actually containing the active ingredients) should be reconsidered. Not surprisingly, some benefits attributed to a group of drugs vanish if they are compared with active placebos (e.g., tricyclic antidepressants).[18] This type of study provides further insight into therapeutic mechanisms and facilitates the differentiation between specific and nonspecific treatment effects.

Depending on the context and formulation of the application, the extent of placebo effects may vary substantially, even within the same disease. Therefore, under optimal context conditions, a placebo application may be more effective than an active, well-evaluated treatment that is applied in other contexts. For example, migraine drug treatment is more effective than placebo pills but seems to be less effective than placebo acupuncture.[19] A placebo involving a more salient intervention (e.g., saline injection) may be more effective than an active-drug treatment, even when the latter has proved to be more successful than a placebo in the form of a pill. These options should be tested in direct comparison to arrive at optimal treatment recommendations.

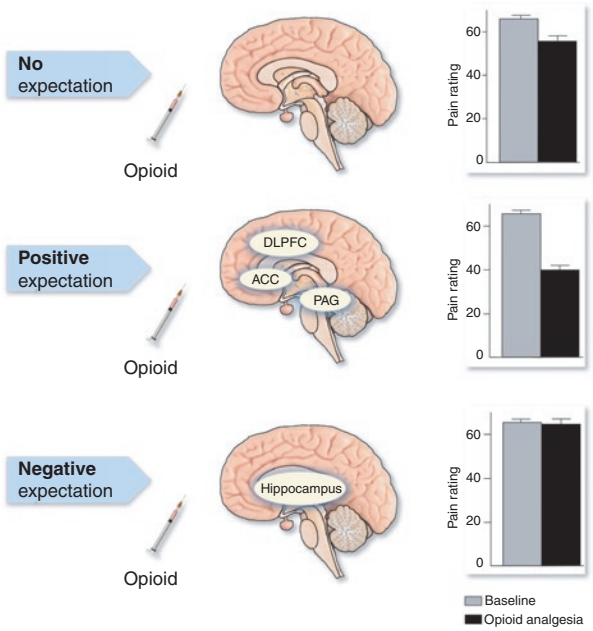

Figure 1 The effect of treatment expectation on drug efficacy. The power of expectations on the therapeutic outcome of pharmacologic treatments is illustrated in a recent study on remifentanil analgesia. In this study, the analgesic effect of the potent opioid remifentanil on experimentally induced thermal pain was studied in healthy volunteers under three different conditions: without expectation of analgesia (no expectation; upper panel), with expectation of a positive analgesic effect (positive expectation; middle panel), and with negative expectation of analgesia, i.e., expectation of hyperalgesia (negative expectation; lower panel), using a within-subject design. Functional magnetic resonance imaging was used to record brain activity to corroborate the effects of expectation on the analgesic efficacy of the opioid and to elucidate the underlying neural mechanisms. Pain ratings (mean values ± SEM) obtained on a visual analog scale (where 0 corresponds to "no pain" and 100 to "unbearable pain") during baseline (saline infusion) and during a constant dose of remifentanil (effect site concentration of 0.8 ng/ml) for the three expectation conditions are shown in the bar graphs on the right side. Positive treatment expectation substantially enhanced (doubled) the analgesic benefit of remifentanil. In contrast, negative treatment expectation completely abolished remifentanil analgesia. These subjective effects were substantiated by significant activation changes in brain regions involved in the coding of intensity of pain (not illustrated in this figure). The positive expectation effects were mediated by the endogenous pain modulatory system, which includes the dorsolateral prefrontal cortex (DLPFC), the rostral anterior cingulate cortex (ACC), and the periaqueductal gray (PAG). By contrast, the effects of negative treatment expectation were associated with hippocampus activity. Data from ref. 3 with permission.

Systematic applications of conditioning mechanisms using placebos

If expectation and conditioning are powerful ingredients of the placebo response, the question arises as to how one can make therapeutic use of them. Under certain circumstances, placebo pills can elicit treatment effects that are comparable to those of an active medication. One helpful precondition is to follow learning and conditioning principles rigorously. Placebo effects

Table 2 Systematic use of placebo pills

Acquisition period														Maintenance treatment											
Day of treatment																									
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27
D	D	D	D	D	D	D	D	D	D	D	D	D	D	D	P	D	D	P	D	P	D	D	P	P	D	D

This example shows a drug administration regimen with a 2-week acquisition period, followed by drug administrations with interspersed placebo administrations (likelihood of placebo administration in 3rd week: 0.33).

D, drug; P, placebo.

can be enhanced if an acquisition period of sufficient duration precedes its administration. In some cases, as few as four conditioning trials may elicit long-term effects.[20] New patterns of drug administration could include 2–3 weeks of regular drug intake followed by intermittent periods of placebo administration during the course of treatment. Such a regimen (see an example in **Table 2**) might reduce the overall dose of drug intake while maintaining the beneficial effects. According to the principles of intermittent reinforcement, interspersing placebos with active drug could actually be even more beneficial than continuous treatment with the active drug. Pilot studies confirm this type of placebo effect in patients with psoriasis receiving corticosteroid treatment[21] and in patients with attention-deficit hyperactivity disorder receiving amphetamines.[22]

Learning processes also suggest other variations in study design. If run-in phases are employed, differential efficacy could result, depending on whether the run-in uses active drug (acquisition of positive drug response) or placebo (with an increased risk of reducing nonspecific effects/extinction learning). Again, these mechanisms require further experimental investigation to enable the development of improved treatment regimens.

Reduce negative side-effect expectations and increase positive coping expectations

It has been shown that patient expectations are a major predictor of side effects in various clinical disorders, including rheumatoid arthritis, cancer, and depression.[23–25] Unfortunately, this effect is unwittingly perpetuated by informed-consent procedures incorporating long lists of every possible side effect. For the sake of the patient, it would be beneficial to reduce negative side-effect expectations before the onset of treatment. Realistic, positive expectations are more helpful than overemphasis on potential problems. Moreover, with respect to side effects that are likely to occur but are not clinically dangerous or harmful, emphasizing patients' abilities to cope with these symptoms could be beneficial. Finally, hidden-administration procedures for treatments with short-term unpleasant consequences could be a way to reduce negative expectation effects if they are used in an ethically acceptable way.

Improve ascertainment strategies for side effects

With the use of current assessment methods, the reported side effects in treatment groups frequently reflect the presumptions of the assessor rather than being unbiased observations; therefore, investigator-expected side-effect patterns are evident in the corresponding placebo groups as well.[25,26] In many clinical trials, strategies for ascertainment of side effects have been unsatisfactory. Up to 80% of randomized controlled trials either did not use adequate side-effect assessments or did not report them adequately (e.g., refs. 27,28). Strategies such as using a single rating (e.g., "Does the patient report any side effects that can be attributed to the drug intake?") are subject to investigator bias/expectation effects in ascertaining and reporting side effects. Observer ratings are more prone to expectation biases than self-reports of patients.[29] Therefore, a combination of systematic observer assessments and systematic patient self-reports would improve the accuracy of detection of adverse events.[30]

Consider context information in meta-analyses and Cochrane overviews

The recent dramatic increases in the volume of clinical trials have made it necessary to aggregate multiple studies using methods such as meta-analysis. These meta-analyses assume that contextual factors are constant across placebo and active-drug arms, thereby also assuming that differences in effect sizes between arms reflect the specific drug effect. However, as we have seen, contextual effects are not constant, and they also interact with specific drug effects. Clinical trials could vary systematically in terms of nonspecific mechanisms and contextual information, and a small number of studies with specific contextual conditions could serve to tilt the overall results of a meta-analysis. Therefore, a systematic analysis of contextual information of the clinical trials included in a meta-analysis is warranted.

Ethical considerations

The principles underlying the grant of ethical approval vary between countries and frequently hinder or preclude systematic investigations of placebo mechanisms, although placebo mechanisms can increase the ultimate treatment benefit. In placebo research, there are two mutually conflicting ethical principles: autonomy (which requires fully informing the patient) and beneficence (which requires optimizing treatment effects and minimizing the likelihood of negative effects). Many institutional review boards prioritize autonomy/fully informed consent over beneficence; however, this priority should be continuously reevaluated, and new options (such as "patient-authorized concealments") should be discussed.

SUMMARY

Placebo mechanisms such as expectation and behavioral conditioning induce neurobiological alterations that interact with the biochemical pathways of pharmacologic treatments. They have

the potential to increase benefits, to induce side effects, and to modulate both treatment benefits and risks. These findings have implications for the design of clinical trials. Current intervention research is oriented too heavily toward demonstrating the advantage of a specific medication as compared with a placebo, rather than toward seeking to establish optimal treatment contexts. Treatment recommendations should include mention of the contextual circumstances under which optimal drug efficiency can be achieved.

The effects found in drug arms of trials represent not only the sum of specific and nonspecific effects but also the interaction between the underlying mechanisms. Moreover, nonspecific effects are not constant over the course of treatment and can vary systematically. Finally, placebos may have the same biological mechanisms of action as active drugs, thus further obscuring the boundary between specific and nonspecific mechanisms of action.

We are aware that several (but not all) suggestions presented in this paper are more applicable to the second stage of evaluation, which focuses on the applicability and feasibility of pharmacologic treatments in daily clinical practice and comparator studies with conventional treatment strategies, whereas the first stage of evaluation usually targets the introduction of a new drug ("efficiency") and receiving regulatory approval.

Although our understanding of the mechanisms involved in placebo and nocebo phenomena has increased, we are only at the beginning with respect to determining the implications for clinical research and clinical practice. More information about predictors of placebo and nocebo responses is needed, and ethically acceptable applications of the relevant mechanisms should be developed for the benefit of patients.

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CONFLICT OF INTEREST

The authors declared no conflict of interest.

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