

## Review

# The Placebo and Nocebo Phenomena: Their Clinical Management and Impact on Treatment Outcomes



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## ABSTRACT

**Purpose:** This overview focuses on placebo and nocebo effects in clinical trials and routine care. Our goal was to propose strategies to improve outcomes in clinical practice, maximizing placebo effects and reducing nocebo effects, as well as managing these phenomena in clinical trials.

**Methods:** A narrative literature search of PubMed was conducted (January 1980–September 2016). Systematic reviews, randomized controlled trials, observational studies, and case series that had an emphasis on placebo or nocebo effects in clinical practice were included in the qualitative synthesis. Search terms included: *placebo*, *nocebo*, *clinical*, *clinical trial*, *clinical setting*, *placebo effect*, *nocebo effect*, *adverse effects*, and *treatment outcomes*. This search was augmented by a manual search of the references of the key articles and the related literature.

**Findings:** Placebo and nocebo effects are psychobiological events imputable to the therapeutic context. Placebo is defined as an inert substance that provokes perceived benefits, whereas the term nocebo is used when an inert substance causes perceived harm. Their major mechanisms are expectancy and classical conditioning. Placebo is used in several fields of medicine, as a diagnostic tool or to reduce drug dosage. Placebo/nocebo effects are difficult to disentangle from the natural course of illness or the actual effects of a new drug in a clinical trial. There are known strategies to enhance clinical results by manipulating expectations and conditioning.

**Implications:** Placebo and nocebo effects occur frequently and are clinically significant but are underrecognized in clinical practice. Physicians should be able to recognize these phenomena and master tactics on how to manage these effects to enhance the quality of clinical

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**Key words:** adverse effects, clinical trial, nocebo, pharmacology, placebo, treatment.

## INTRODUCTION

The placebo effect has been studied extensively throughout history.<sup>1,2</sup> The nocebo effect, also called “the evil brother of the placebo effect,” has been less studied, but in recent years has become a subject of growing interest.<sup>3–5</sup> Both phenomena are composed of several intertwined biological and environmental mechanisms, displaying a complex interaction. Their operative mechanisms not only are affected by the characteristics of the individuals but also on the context in which they operate; thus, the search for a simple equation to predict the effect of placebo and nocebo has been met with limited success.

A precise definition of the placebo and nocebo phenomena is difficult to pinpoint, as different researchers have used different definitions, often depending on the context. A starting definition would be psychobiological events attributable to the overall therapeutic context<sup>6</sup>; herein, placebo effect would be the benefits provoked by an inert substance, and the nocebo effect is the induction of true or perceived harm after treatment with an inactive substance. Thus, a response to treatment, not attributable to the known mechanism of action of the treatment, is the core feature of both phenomena. This means that the definition can also be applied to an active substance treatment, then referring to the (extra) effects it elicits and that are not explained by its pharmacologic action. Many disorders have a natural course of illness in which symptoms fluctuate, making it difficult to differentiate between a placebo or nocebo response and the natural course of illness at an individual patient level. Similarly, many “side effects” occur commonly with or without pharmacotherapies (eg, headache), making it often difficult to disentangle, at an individual patient level, between a treatment-emergent adverse event that is a nocebo response or one that has occurred independently of treatment.

Paradigmatically, the placebo and nocebo phenomena have been most extensively studied in analgesia<sup>7–10</sup> and irritable bowel syndrome (IBS).<sup>11</sup> These phenomena have been studied more recently in the field of dermatology<sup>12–14</sup> and in psychiatry, particularly in depression.<sup>15</sup>

The underpinnings of placebo and nocebo are psychological and neurobiological. Psychological mechanisms

include expectancies, conditioning, learning, memory, motivation, somatic focus, reward, anxiety reduction and meaning, and “placebo-by-proxy” induced by clinicians and family members.<sup>16</sup> Two principal mechanisms are well supported. The first aspect involves expectancy: the administration of placebo creates expectations in future responses by using simple verbal cues as modulators of expectations. Researchers can nudge a subject's expectations and boost the placebo effect. The second aspect involves classical conditioning: repeated associations between a neutral stimulus and an unconditioned stimulus (active drug) can result in the ability of the neutral stimulus by itself to provoke a response characteristic of the unconditioned stimulus.<sup>4,17,18</sup> In a study of placebo/nocebo in thermal pain, neither conditioning nor expectation alone seemed to be able to elicit placebo or nocebo effects; however, the combination of experience (conditioning) and expectation resulted in significant placebo (analgesia) or nocebo (hyperalgesia) effects.<sup>19</sup>

Misattribution is the inappropriate attribution of improvement or worsening to a treatment when it was actually caused by the disorder's natural fluctuation of symptoms or other causes.<sup>20</sup> Misattribution may have a more significant role in nocebo effects than in placebo effects, although this theory remains a focus of active debate.<sup>21,22</sup>

The neurobiology of the response to placebo and nocebo has been studied mostly in the paradigmatic field of analgesia and has been shown to be mainly related to the opioid and dopaminergic pathways.<sup>6,23,24</sup> A companion paper published in this issue of *Clinical Therapeutics* reviews the theoretical and biological underpinnings of the nocebo and placebo phenomena.<sup>25</sup>

It is important to note that placebo and nocebo responses are highly variable across individuals. Some individual differences have been associated with genetic polymorphisms or underlying neurologic impairments. For example, patients with frontal lobe impairment, especially prefrontal lobe, have decreased expectancy and learning, and thus they partially or totally lose their placebo response. In a study of Alzheimer's disease and pain, patients with reduced Frontal Assessment Battery scores exhibited a reduced placebo component of the analgesic treatment.<sup>26</sup> In intellectually disabled patients, a higher intelligence quotient was positively related with placebo response.<sup>27</sup>

Catechol-O-methyl transferase is involved in dopamine degradation, affecting the prefrontal lobe. The catechol-O-methyl transferase Val<sup>158</sup>Met polymorphism

is a G to A mutation leading to amino acid substitution at codon 158 in the transmembrane form of the enzyme.<sup>28</sup> It was suggested as a biomarker of placebo response in IBS and a potential biomarker of placebo response in other conditions.<sup>11</sup> Thus, people who carry this polymorphism are more likely to experience the placebo effect.

The tryptophan hydroxylase-2 polymorphism (serotonin-related gene) seems a significant predictor of clinical placebo response in social anxiety disorder. Homozygosity for the G allele was associated with serotonergic modulation of amygdala activity and greater improvement in symptoms of anxiety.<sup>29</sup> People who experience anxiety disorder and carry this polymorphism are more likely to experience the placebo effect. Thus, psychological and neurobiological factors can predict individual differences in placebo and nocebo response.

The present review first focuses on the impact of placebo and nocebo effects in routine clinical settings as well as in clinical trials, and then offers strategies on how to use that knowledge to improve the quality of care and results in research.

## MATERIALS AND METHODS

A literature search of PubMed was conducted for articles published between January 1980 and September 2016. Search terms included: *placebo*, *nocebo*, *clinical*, *clinical trial*, *clinical setting*, *placebo effect*, *nocebo effect*, *adverse effects*, and *treatment outcomes*. This search was augmented by a manual search of the references of the key articles and the related literature. Systematic reviews, randomized controlled trials (RCTs), observational studies, and case series were identified. Articles that had an emphasis on placebo or nocebo effects in clinical practice were selected for the qualitative synthesis.

## CLINICAL APPLICATION

The clinical understanding of the placebo effect is a relevant issue. Placebo responses may be a major driver of clinical change after diverse therapies. Placebos are used in several fields of medicine (eg, neurology, psychiatry, rheumatology, pain management, ophthalmology), although ethical considerations limit their use in some areas. When surveyed, 45% of American physicians admitted to having used a placebo.<sup>30</sup> An English study found that only 12% of general practitioners use pure placebos (totally inert interventions)

but the number was 97% for impure ones (interventions with clear efficacy for certain conditions but are prescribed for conditions in which their efficacy is unknown).<sup>31</sup> The most common reason to use a placebo was to tranquilize the patient (18%) and as a supplemental treatment (18%). Other reasons included “after ‘unjustified’ demand for medication” (15%), “for nonspecific complaints” (13%), “after all clinically indicated treatment possibilities were exhausted” (11%), “to control pain” (6%), “to get the patient to stop complaining” (6%), and “as a diagnostic tool” (4%).<sup>30</sup> It has been argued that the clinical benefits from many poorly evidence based complementary and alternative disciplines derive largely or even solely from cultivation of the factors that drive placebo effects.<sup>32</sup> Local regulations, however, preclude clinical use of placebos in some jurisdictions.

Patients need a greater dose of analgesic to achieve an equivalent outcome if their placebo response is impaired. When patients with postoperative pain were given intravenous saline (placebo), and buprenorphine was made available on request, the group told that the intravenous saline was a powerful painkiller took 33% less analgesia for the same pain compared with a control group (who were told they were receiving a rehydrating solution).<sup>33</sup>

## CHALLENGES IN CLINICAL TRIALS

The placebo or nocebo response is related to common biochemical pathways that are activated both by social stimuli and therapeutic rituals on one hand and by drugs on the other. It has been shown that when an opioid agent is administered, it binds to  $\mu$ -opioid receptors, but the very same  $\mu$ -opioid receptors are activated by the patient's expectations about the drug.<sup>34</sup> This outcome is concordant with the finding that drugs without therapeutic rituals are less effective.<sup>35</sup> A suitable therapeutic setting can thus enhance the placebo response.<sup>36</sup>

The placebo effect has been well established in RCTs. In depression, its magnitude has been shown to vary depending on the investigators. Some propose that up to 75% of the drug effect is mediated by the placebo effect.<sup>37,38</sup> Others question these results, arguing that an unrepresentative subset of clinical trials (including many cases of mild to moderate depression) were analyzed, and therefore the data are not accurate.<sup>39,40</sup> This theory suggests that patients with less severe depression have a lower biological substrate and are more vulnerable to the

placebo effect. In 2002,<sup>41</sup> a meta-analysis was conducted with US Food and Drug Administration data containing RCTs that had not been published. This study revealed a small significant difference between antidepressant drug and placebo but not a clinical difference; the mean difference between drug and placebo was  $\sim 2$  points on the Hamilton Depression Rating Scale. An alternative hypothesis to explain this difference in antidepressant trials is “breached blind.” Because of the side effects of the drugs, the RCT patients may know if they are in the placebo or the active group.<sup>42</sup> Furthermore, when another active antidepressant is used as the comparator, instead of placebo, there is a significant increase in the effectiveness of the drug.<sup>43</sup>

It remains controversial whether the placebo effect is increasing across time in RCTs of depression. It has been proposed that the placebo effect has progressively increased over time<sup>44</sup> within the general population as a result of inflation of baseline severity to meet threshold inclusion criteria; that is, trials with less ill people, in which regression to the mean is more likely, and more comprehensive and frequent assessment procedures. Others have argued that pharmaceutical companies try to select only severely depressed patients because pharmacotherapy RCTs for mild and moderate depression often do not show statistically significant separation between the treatment and placebo trial arms,<sup>45</sup> thus downplaying the role of decreased baseline depression severity as an explanation. In contrast, a recent meta-analysis using published and unpublished data found stable placebo responses in the last 25 years,<sup>46</sup> implying the increase across time effect may be an artifact.

## PLACEBO/NOCEBO AND SEPARATION FROM THE NATURAL COURSE OF ILLNESS

Understanding the natural course of illness is essential before commencing a clinical trial design or trying to separate drug from placebo effects. Given the fact that symptom severity does not stay frozen in time when no intervention is applied, the spontaneous progress or improvement of a pathological process can obviously confound or pose as a placebo or nocebo effect. These types of studies present numerous challenges, especially as modern medicine shifts its attention from infectious disorders to chronic or mental disorders (which wax and wane, where the natural history of

illness extends greatly in time or has poor or no biomarkers available).<sup>47</sup>

Prospective nonintervention studies are increasingly ethically challenging as fewer diseases are lacking effective treatment. Therefore, in many cases, it is impossible to include a nontreatment arm in a clinical trial to guide our interpretation of results and discount the influence of natural progression. A loophole to this problem was found in studies of psychotherapy efficacy on major depressive disorder that use a wait-list as a control group. A meta-analysis<sup>48</sup> found that “wait-listers” experience  $\sim 33\%$  of the symptomatic improvement of treated patients and 40% of the ones receiving placebo. An important caveat is that a wait-list is thus a very poor control group for clinical trials, despite being used often. Some studies even found that wait-list results in nocebo effects.<sup>49</sup>

## STRATEGIES (USING PLACEBO TO IMPROVE RESULTS)

### Maximizing Placebo

Patient expectations contribute toward the outcome of several disorders. This has been demonstrated for analgesia, treatment of myocardial infarction and Parkinson’s disease, deep brain stimulation, orthopedic surgery, and antidepressant treatment.<sup>22</sup> Positively influencing patients’ beliefs about therapeutic success is one way to maximize the placebo effect.<sup>50</sup> However, being too optimistic is also ethically problematic and can be construed as disingenuous if one is not cautious. Manipulating a patient’s expectations may not necessarily require lying or deceiving. In a study of IBS, patients were informed they were being treated with placebo and still developed a positive clinical response.<sup>51</sup>

A partial reinforcement paradigm, placebo-controlled drug reduction (PCDR) (use of a full dose of medication for a set period of time [acquisition period] followed by a maintenance or evocation period with interposed placebo) has been shown to lower the dose needed to elicit a therapeutic response. This finding opens the door for a panoply of chronic disorders treated with medications with substantial side effects (Table I). PCDR allowed children with attention-deficit/hyperactivity disorder to be effectively treated with 50% of their optimal stimulant dose<sup>52</sup> and reduced the corticosteroid dose needed in psoriasis.<sup>53</sup>

Table I. Strategies to maximize the placebo effect.

Managing Expectations	Conditioning
Screen for patients with negative beliefs	Placebo-controlled drug reduction (PCDR)
Hidden applications when discontinuing a drug expected to cause withdrawal symptoms	Use salient stimuli and constant context when administering treatment including sensorial cues, same room and time of day when giving treatment
Promote social contact with other successful patients	Use effective pretreatments
Reduce anxiety	Avoid extinction in long-term treatments Motivation strategies, changes in situational cues Enhance physician-patient relationship Empathic style, more time of contact Describe the procedure before executing to improve attention

Adapted from Enck et al.<sup>22</sup>

It is usually assumed that more complex, time-consuming, and invasive interventions are more likely to be associated with placebo effects than other interventions. For instance, different colors and sizes of a pill seem to influence the clinical outcome.<sup>54</sup> However, to our knowledge, only 1 systematic review<sup>55</sup> has found mixed evidence of more invasive placebos having larger effects (7 of 12 studies with >1 placebo found no difference, 4 found single-outcome differences, and 1 found a large effect; 2 of 4 studies designed to differentiate placebo intensity were positive). The extant data may not be sufficient to discount its influence. To design studies directly comparing very different placebo interventions (ie, pill vs injection) while ensuring blinding for both patients and researchers ranges from very difficult to impossible. Also, to try to design studies controlling for context or for patient or clinician bias in expectancies might be a Sisyphean-like task, as the differences in context and expectancies themselves may be the cause of the placebo effect.

Although the placebo could be more powerful, deliberately administering a more invasive or intense placebo may be both ethically challenging (especially one with potential to cause harm) and lacking in

evidence. Conversely, a meta-analysis of 41 RCTs assessing the effects of antidepressant agents on major depressive disorder showed that the more follow-up observations that occur, the more intense are the placebo effects elicited.<sup>56</sup> The number of medical visits in clinical trials contrasts with the shorter contact in community settings. This strategy is well established and can be useful because it is nonharmful. Profiling or choosing the right person to try a placebo might be more problematic. There was limited evidence for the role of age or sex, at least in psychiatric disorders.<sup>57</sup> A stronger correlation was found for low symptom severity and short duration of illness. There were 2 studies in children reporting a higher placebo effect in those of non-white ethnic origin.<sup>58,59</sup>

### Managing Placebo in Clinical Trials

When comparing a drug versus a placebo, the first thing to bear in mind is that the effect of an active drug includes in itself a placebo component. Furthermore, issues are further complicated because the relation of the effects between the placebo and drug groups may not always be additive; that is, the measured effect in the active drug arm may be more (or less) than expected just by adding the placebo



**Table II. Strategies to optimize drug-placebo differences in clinical trials.**

Avoid enrichment/multidosing studies
Aim for a 50/50 probability of receiving placebo
Use treatment-naïve patients
Randomized run-in and withdrawal periods
Use active placebos
Incorporate “no-treatment” groups
Avoid comparative effectiveness trials
Prioritize outcome evaluation in the following order:
1. Death
2. Biomarkers
3. Physician assessment
4. Patient-reported outcomes

effect to the actual active drug effect.<sup>22,60</sup> Therefore, perhaps “optimizing the drug-placebo difference” (vs minimizing placebo) is a preferable denomination.

Designing clinical trials is a specialized field in its own right. Separating a drug effect from a placebo effect always at the core of a clinical trial design, so that general quality guidelines for a clinical trial usually will work to optimize the drug-placebo difference: standardizing for symptom severity; avoiding physician’s selection bias; controlling for center effects and patient adherence; and ensuring effective blinding.

However, sometimes these strategies are accompanied by other undesirable effects. For example, if we identify drug responders during a run-in phase or preselect patients who were previously exposed to a similar drug, we may increase the drug-placebo difference, but we also risk limiting a drug indication and overestimating benefits. If the population of previous responders comprised a specific group (eg, women), the trial will never generate approval for men. Some strategies involve deceit and thus have ethical concerns. Cost and feasibility are concerns as well (eg, when considering augmenting sample size). Therefore, it is up to the researcher to weigh the risks and benefits of each strategy.

Because the chance of being in a treatment group increases the magnitude of placebo responses,<sup>61</sup> a study design of equal likelihood of receiving placebo or treatment (ie, avoid enrichment or multidosing studies) should be preferred. Contrary to common belief, trying

to exclude placebo responders using run-in phases early in the study was not able to prevent later placebo response.<sup>62</sup> Randomized run-in (ie, in a double-blind manner, patients first start receiving placebo and are then switched to the active drug after a few days) and withdrawal periods seem to hold more promise.<sup>63</sup> Crossover designs may promote conditioning<sup>64</sup> and may lead to unblinding of the study due to perceived side effects. Using active placebos (drugs that mimic the active treatment side effects) is a possible perfect placebo that rarely exists, mimicking all the side effects without any of the active mechanisms of the drug being tested. Controlling for the natural progression of the disease should also be a concern, even if in many situations it is ethically challenging and may motivate subjects to drop out. A way around this is using Zelen’s design,<sup>65</sup> in which patients are randomly divided into an observational group and an interventional group comprising the active drug and placebo branches, allowing to control for the natural course of illness.

Comparative effectiveness trials are usually used when an efficacious treatment already exists for ethical standards. The new drug must then prove superiority, equivalence, or noninferiority. However, it has been shown that a drug tested against an active comparator performs better.<sup>61,66</sup> The placebo effect is also reportedly stronger when patients report the outcome than when the physician performs the assessment,<sup>67</sup> which is itself stronger than a biomarker-based evaluation.<sup>68</sup> The most objective outcome possible is death or survival rate, but this approach obviously cannot be used for many disorder endpoints (Table II).

### Minimizing Nocebo

In the case of nocebo, no overt ethical dilemma is present. The intention of the physician is always to minimize its risk and effects. Also, we can expect the factors and strategies used to minimize the nocebo effect to be a mirror of the ones in placebo.

Of major importance would be to identify individuals more prone to develop nocebo effects. Several studies have been conducted to identify “risk factors” of the nocebo effect. A systematic review<sup>4</sup> found “learning/social observation,” “perceived dose,” “verbal suggestions of arousal and symptoms,” and “baseline symptom expectations” to be the strongest predictors of nocebo effects. Interestingly, the type of administration again did not appear to be relevant, nor did self-awareness during exposure. Symptom severity at

Table III. Strategies to minimize nocebo.

Managing Expectations	Conditioning
Avoid informed consent overly focused on side effects	Low-dose initial regimen (when possible)
Framing of information	Hidden tapering
Focus on the positive effects of treatment	in when feasible
Conjoint plan	
Sense of control and ownership of the decision-making process (by the patient)	
Empathic attitude	

Adapted from Data-Franco and Berk.<sup>73</sup>

baseline (one of the strongest associations with placebo) also produced mixed results. Demographic factors such as sex, age, and literacy did not change the risk of a nocebo response. One study found that female investigator subjects report nocebo effects twice as frequently as male subjects after a social suggestion paradigm, but these data could have been confounded by the study design (the social cue was presented by a female ).<sup>69</sup> In modern health systems in which access is good, participants who volunteer for trials may have presented with poor response or have not tolerated standard therapy. This earlier adverse experience increases the likelihood of these subjects being primed for nocebo responses.<sup>70</sup>

Managing patients' beliefs and experiences are at the core of possible strategies. Framing of information is an effective way to put the benefits and risks of treatment in perspective, focusing on the positive possibilities.<sup>71</sup> A caring and empathic relationship is beneficial.<sup>72</sup> When the medical problem allows for a small delay in the start of therapy, a lower initial dose might be helpful. Similarly, in RCTs, if a patient does not know when exactly he or she is getting exposed, nocebo effects are reduced (Table III). Nevertheless, this approach may be rarely feasible in outpatient settings or even time- and resource-consuming in a hospital setting.

## CONCLUSIONS

Clinically, placebo and nocebo effects are of major importance, being present in daily medical practice. The overall effect of a drug stems from its pharmacodynamic actions plus the psychological effect derived from the act of its administration. Although both placebo and nocebo have been widely studied, the full complexity of their mechanisms needs further definition. Thus, when correctly applied, there are a number of strategies that can improve responses and patients' quality of life, maximizing placebo and reducing nocebo in clinical practice, and enhancing results in clinical trials. It underlines the impact of creating a good physician–patient relationship, increasing empathic attitudes, exposing information suitably, decreasing expectations of adverse effects, and promoting social contact between successfully treated patients.

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## CONFLICTS OF INTEREST

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