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What Should Clinicians Tell Patients about Placebo and Nocebo Effects? Practical Considerations Based on Expert Consensus

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Keywords
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Abstract
Introduction: Clinical and laboratory studies demonstrate that placebo and nocebo effects influence various symptoms and conditions after the administration of both inert and active treatments. ***Objective:*** There is an increasing

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need for up-to-date recommendations on how to inform patients about placebo and nocebo effects in clinical practice and train clinicians how to disclose this information. ***Methods:*** Based on previous clinical recommendations concerning placebo and nocebo effects, a 3-step, invitation-only Delphi study was conducted among an interdisciplinary group of internationally recognized experts. The study consisted of open- and closed-ended survey questions followed by a final expert meeting. The surveys were subdivided into 3 parts: (1) informing patients about placebo effects, (2) informing patients about nocebo effects, and (3) training clinicians how to communicate this information to the patients. ***Results:*** There was consensus that communicating general information about placebo and nocebo effects to patients (e.g., explaining their role in treatment) could be beneficial, but that such information needs to be adjusted to match the specific clinical context (e.g., condition and treatment). Experts also agreed that training clinicians to communicate about placebo and nocebo effects should be a regular and integrated part of medical education that makes use of multiple formats, including face-to-face and online modalities. ***Conclusions:*** The current 3-step Delphi study provides consensus-based recommendations and practical considerations for disclosures about placebo and nocebo effects in clinical practice. Future research is needed on how to optimally tailor information to specific clinical conditions and patients' needs, and on developing standardized disclosure training modules for clinicians.

Introduction

Placebo and nocebo effects can substantially modulate the efficacy and tolerability of medical and psychological interventions for many symptoms and conditions [1–3]. Placebo and nocebo effects refer to favorable or adverse effects, respectively, that can arise as part of an active or inert intervention due to factors such as what the patient expects, the patient-clinician relationship, and other contextual factors [4–9]. These effects can be clinically meaningful, with effect sizes for some conditions approaching treatment effect sizes [10]. Placebo effects can be shaped by a wide range of factors relating to medical practice, e.g., verbal suggestions made by the clinician, nonverbal cues in the patient-clinician interaction, or situational factors in the health care environment [11–16]. Differing viewpoints as to how these effects should be handled exist, e.g., they are often seen as a nuisance in randomized controlled trials as they complicate the testing of new drugs and therapies [17, 18]. On the other hand, there are potential benefits of utilizing placebo effects to boost treatment effects in clinical practice that have been recognized [16, 19, 20], although there is a variety of proposed approaches. Moreover, some caution in utilizing the mechanisms of placebo effects in clinical practice may be prudent, as unforeseen adverse consequences (e.g., violation of expectation and loss of trust) may occur when effects are inadequately explained or elicited by deception (e.g., [21–23]).

Due to these controversies, only a few ideas have been generated on how knowledge about placebo and nocebo effects should be translated into clinical practice [20]. For example, there are not many national guidelines about the use of placebo effects in medical practice [8], and they typically do not provide concrete clinical recommendations on how to optimize care by maximizing placebo and minimizing nocebo effects in clinical practice [24, 25]. It is also important to clearly distinguish between the deceptive use of inactive placebo treatments in clinical practice, which is not recommended, and the systematic use of the mechanisms underlying placebo and nocebo effects to enhance standard treatments in an open way. When considering the potentially wide application of placebo and nocebo effects across health care, there is a need for recommendations on how to communicate about them (e.g., during patient-clinician interactions) to optimize patient outcomes.

As a preliminary step, we provided consensus on the use of placebo and nocebo effects in clinical practice as part of the first official conference of the Society for Interdisciplinary Placebo Studies (SIPS) (https://www.placebosociety.org) [20]. This paper describes a follow-up to the previous recommendations [20] by collecting expert opinion on what should be communicated to patients about placebo and nocebo effects, and how clinicians should be trained to communicate about these topics in the context of medical patient-clinician interactions.

Materials and Methods

A modified Delphi study was organized for a panel of interdisciplinary experts by invitation (i.e., the speakers invited to participate at the 2019 SIPS conference) [26–28].

Expert Group

Twenty-seven internationally recognized and interprofessional placebo researchers took part in the panel, 67% of whom worked clinically (39% physicians, 56% psychologists, and 5% other, e.g., acupuncturists). Their backgrounds included anesthesiology, neurology, cognitive neuroscience, primary care, internal medicine,

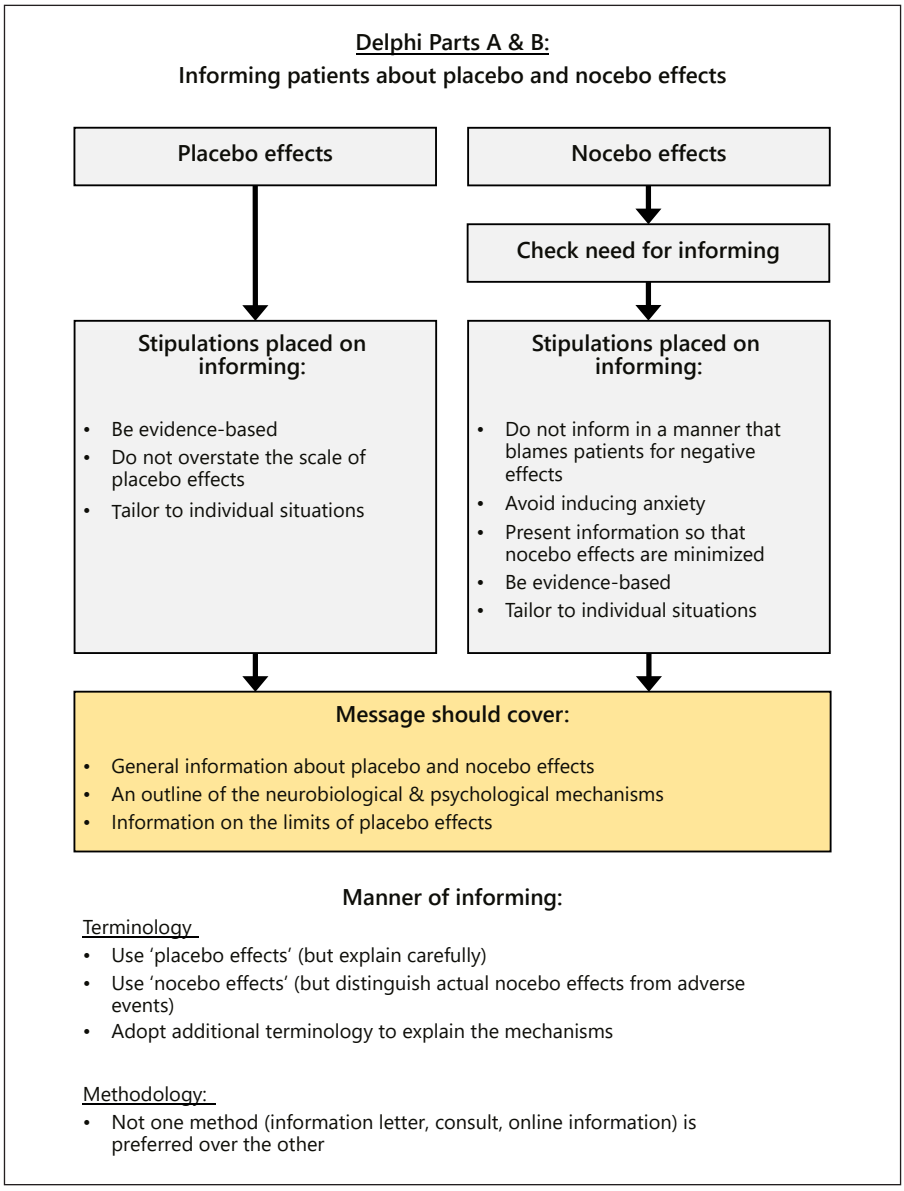

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Fig. 1. Schematic overview of the considerations and the content of information needed for informing patients about placebo and nocebo effects in clinical practice.

health and medical psychology, clinical psychology, psychological medicine, science communication, sports science, sociology, epidemiology, ethics, and philosophy.

Modified Delphi Study

Input for the Delphi study was derived from the existing literature [20]. An open-ended survey was used to generate content for expert consensus on informing patients about placebo and nocebo effects in clinical practice (e.g., what, when, and how should we communicate about these effects?), and how clinicians should be trained to communicate about placebo and nocebo effects. Answers were transcribed verbatim and aggregated into 158 individual items ranked on a scale of 0–10 (0 = totally disagree; 10 = totally agree) in round 2. Means and SD were calculated for each item. During round 3 (a preconference face-to-face clinical expert meeting, added to facilitate a nuanced discussion of possibly differing opinions on survey items), items with high agreement were discussed as input for the recommendations. More details on the methods used can be found in the online supplementary Material (see www.karger.com/doi/10.1159/000510738 for all online suppl. material).

Results

In the sections below and in Figure 1, we briefly describe the results of the Delphi study. The main recommendations are listed in Table 1.

Table 1. Main recommendations formulated by the expert group for communicating information about placebo and nocebo effects

Informing patients about placebo and nocebo effects	
1	Patients should be informed that placebo effects are beneficial effects, represent a genuine reaction of the body that promotes healing and treatment response, are inherent to any treatment, and that anyone can experience them
2	Patients should be informed about the potential role of nocebo effects in increasing adverse effects
3	Patients should receive information about the underlying psychological and neurobiological mechanisms of placebo and nocebo effects, such as associative learning and expectations
4	Information provided to patients about placebo and nocebo effects should be evidence-based and not overstate the scale of placebo effects. When informing about nocebo effects, care should be taken to avoid inadvertently eliciting iatrogeny
5	How patients are informed about placebo and nocebo effects should be tailored to specific circumstances, patients, and health care context
6	When informing patients, the terms placebo effect and nocebo effect as well as related terms to explain the mechanisms (e.g., expectations, trust, and fear of side effects) should be used
Training clinicians to communicate about placebo and nocebo effects	
7	Training of clinicians to communicate about placebo and nocebo effects should include an outline of the effects and clinical implications of both placebo and nocebo effects for different conditions as well as the underlying neurobiological and psychological mechanisms
8	Training should emphasize the need for tailoring information to the specific needs of individual patients, the type of treatment and the context in which it is offered, incorporating ethical considerations regarding informing patients about placebo and nocebo effects
9	Training should emphasize what clinicians can do to maximize placebo effects and minimize nocebo effects
10	Training should make use of different formats to inform clinicians about placebo and nocebo effects (e.g., face-to-face, online assignments, and written information)

Informing Patients about Placebo and Nocebo Effects

Based on the broad evidence for placebo and nocebo effects in clinical, neurobiological, and laboratory outcomes [5–7, 19, 22, 29–39], the experts agreed that placebo and nocebo effects should be explained, and that patients should receive at least general information about these effects. Providing an outline of the neurobiological and psychological mechanisms could also be helpful, as could informing patients about the limits of placebo effects (e.g., placebo effects are likely to affect symptoms but not the progression of a disease) [40]. The experts recommended placing several stipulations on informing patients about placebo and nocebo effects, e.g., information must be evidence-based and should not overstate the size of placebo effects. For both placebo and nocebo effects, the experts agreed that the information should be tailored to specific patients, conditions, and circumstances. For nocebo effects, this need was particularly emphasized, as a consequence of a delicate balance between following the ethics guidelines of informed consent (according to which patients need to be fully informed about risks and side effects of treatments as well as the possibility of treatment failures) and simultaneously preventing and reducing nocebo effects as much as possible [40–42]. Moreover, for nocebo effects, the need for informing should be considered, and, when deemed necessary, such disclosures should be made carefully in a manner that does not increase anxiety and is not perceived as blaming patients for negative treatment effects (i.e., side effects). Information should, moreover, be presented in a way that minimizes nocebo effects.

Regarding terminology, it was agreed that using the terms "placebo effect" and "nocebo effect" is acceptable, provided they are explained carefully, and that actual nocebo effects be distinguished from adverse events. When explaining the mechanisms involved, or if information is difficult for a patient to understand, clinicians may consider using slightly different terminology (e.g., classical conditioning or response expectancy). Regarding the manner of informing, no one method (information leaflet, consultation, or online information) was preferred over the others.

Training Clinicians in Communicating about Placebo and Nocebo Effects

Next to substantive information about placebo and nocebo effects (e.g., mechanisms, neurobiological and physiological underpinnings, variations in effect sizes and duration of effects, and that placebo effects can also work when people know about the effect), the experts agreed that clinicians should be taught about the relevant ethical issues concerning placebo and nocebo effects.

Training could, moreover, emphasize that different patients might require different information, and that placebo and nocebo effects can operate differently for different conditions. Finally, an emphasis should be placed on what clinicians can do to maximize placebo effects and minimize nocebo effects (i.e., deploying strategies such as optimizing verbal and nonverbal communication [15, 30–33, 43–52]).

As to the content of training, the experts agreed that it may be useful to use both general modules as well as modules relevant to specific medical conditions or specialists. They agreed that medical ethics education regarding placebo and nocebo effects should be a routine part of clinical training. Training should preferably be embedded in a medical school or other standard education. However, the experts concluded during the meeting that more research is needed and that empirical testing of the efficacy of training methods is essential.

More details on the Delphi results can be found in the online supplementary Material.

Discussion

This paper supplies the most up-to-date consensus-based recommendation for communicating information about placebo and nocebo effects in clinical practice (Table 1). The recommendations can support clinicians in their communications with their patients about placebo and nocebo effects.

The results reflect several established and emerging strands of literature in this area. For example, the need to communicate about side effects in ways that do not induce nocebo effects is gaining more widespread recognition [30, 32, 53–58]. Because of ethical considerations [40, 41], tailoring information seems to be particularly imperative for nocebo effects, especially for those patients who may have a high risk of developing these effects [30–32, 43, 53, 59]. The consensus on communicating information about mechanisms is also reflected in studies showing that understanding the mechanisms of placebo effects may help to maximize these effects in clinical practice [2, 20, 42, 60–62].

The results showed a relatively high agreement among the experts that patients should receive general information about placebo and nocebo effects. This includes consensus that the inherent role of these effects in any treatment should be explained, as should related mechanisms like the patient-clinician relationship, but also that this information needs to be adjusted to the specific context (e.g., the characteristics of the patients, the condition in question, and the treatment). For the latter recommendation, the need for careful consideration by the clinician on when and how to communicate information about placebo and nocebo effects should be recognized. This need is partly reflected in the consensus that, for instance, information should be evidence-based and presented without overstating the scale of placebo effects. Overselling placebo effects may cause a violation of expectations when these are too high, thereby eroding trust in health care professionals, which, in turn, may lead to other negative consequences such as disengagement/nonadherence with care (e.g., [21–23]). It is important to emphasize that placebo effects can help optimize treatment outcomes but that they cannot cure disease.

Moreover, clinicians may want to appraise what information is appropriate for each individual patient, and exercise restraint when the benefit of supplying information to a patient is questionable. Care should be taken to not inadvertently elicit iatrogeny, i.e., unintended negative outcomes due to treatment [63–65]. This is a complex issue, where a difficult balance exists between having to inform a patient of the potential side effects of treatment and not causing too much alarm [65]. When done appropriately, informing patients about placebo and nocebo effects may help enhance naturally occurring placebo effects in clinical practice and can even boost the efficacy of a treatment while simultaneously reducing nocebo effects.

The Delphi method has several advantages: it offers rapid consensus and a wide range of expertise can be included, while a socially desirable response due to group pressure is minimized. However, the methodology is not without limitations [26–28]. For example, the biases of the group (who all focus on studying placebos) may have influenced item selection. Also, some panel members may have been more outspoken than others during group discussions. It was nevertheless possible to reach consensus regarding the main recommendations for informing patients and training health professionals.

The recommendations may not encompass all nuances that are typically found in placebo research. For example, it is recommended that general mechanisms are explained, but no recommendations are provided about interactions of these mechanisms with other treatment factors. Another limitation is that some topics may have been overlooked. Additionally, these guidelines may not be generalizable to nonmedical contexts, such as physical therapy, psychotherapy, or treatments for which the role of placebo and nocebo effects has not yet been illustrated.

It should also be noted that the recommendations do not legitimize any form of nonevidence-based treatment, nor are we suggesting that proven therapies should be replaced with placebo treatments [66, 67]. Our method also did not allow us to draw conclusions about specific strategies that can maximize placebo effects and minimize nocebo effects for a range of different conditions and contexts. Although we acknowledge their likely importance, we also did not focus on sociodemographic, cultural, personality, or genetic differences between patients in view of the limited existing evidence for subgroups of placebo and nocebo responders [68–70]. For example, there is emerging evidence that specific genotypes (e.g., [5, 71–73]) may be associated with variation in the scale of placebo and nocebo effects, but there is not yet enough evidence to include these findings in clinical recommendations.

Methodologically well-conducted replication studies that support the external validity of our findings are needed for all these areas. Finally, the consensus described here should only be seen as hypothesis-generating. As a consequence, the experts emphasized the need for research focusing on tailoring information to different patients and contexts, and developing evidence-based methods for training clinicians to communicate about placebo and nocebo effects.

This study, based on a 3-stage Delphi approach, is an important step forward towards consensus-based recommendations for communicating about placebo and nocebo effects in medical practice. The experts agreed that patients should receive general information about the mechanisms and neurobiology of placebo and nocebo effects, but that care should be taken to adjust this information to the specific needs of patients and the treatment context. Multimodal training in communication about placebo and nocebo effects should be a regular and integrated part of medical training for clinicians. The experts acknowledged the need for future research to expand knowledge about how best to provide information to patients, and about how clinicians can communicate about placebo and nocebo effects in the course of a treatment. Finally, implementation strategies should be developed to integrate these recommendations into clinical practice and the routine training and education of clinicians.

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Statement of Ethics

Ethics approval was not required.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

A workgroup of the SIPS local organizers and international board members (A.W.M.E., L.C., J.G., K.B.J., J.K., L.V., C.J.B., I.K., and S.H.M.) prepared the initiative for the Delphi survey. A.W.M.E. and S.H.M., together with the other work group members, prepared and analyzed the results of the first and second Delphi surveys, prepared the expert meeting, and wrote the paper. All authors contributed to the Delphi survey and/or expert meeting and provided feedback on drafts of the manuscript.

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