

Review

Placebo interventions, placebo effects and clinical practice

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This article reviews the role of placebo interventions and placebo effects in clinical practice. We first describe the relevance of different perspectives among scientists, physicians and patients on what is considered a placebo intervention in clinical practice. We then summarize how placebo effects have been investigated in randomized controlled trials under the questionable premise that such effects are produced by placebo interventions. We further discuss why a shift of focus from the placebo intervention to the overall therapeutic context is necessary and what research methods can be used for the clinical investigation of the relevance of context effects. In the last part of the manuscript, we discuss why placebo or context *effects* are seen as positive in clinical practice when they are associated with active treatments, while placebo *interventions* pose major ethical and professional problems and have to be avoided.

Keywords: clinical practice; placebo; placebo effects; randomized controlled trials; ethics

1. INTRODUCTION

There are three major areas in which placebo interventions have an important role: (i) as control interventions in experimental studies to determine specific effects and to reduce bias by enabling blinding; (ii) as experimental interventions in placebo research to study placebo effects; (iii) as a tool in clinical practice. If one searches a major bibliographical database such as Medline for references including the word placebo, the overwhelming majority of articles identified are either placebo-controlled trials or articles referring to such trials. A small minority of articles are review articles on general or specific aspects of the placebo phenomenon, or original reports of experimental placebo research. Only a very small number of articles report empirical investigations or are essays of placebo use or placebo effects in routine practice. In this article, we first describe the relevance of different perspectives among scientists, physicians and patients on what is considered a placebo intervention in clinical practice. We then summarize how placebo effects have been investigated in clinical research under the questionable premise that such effects are produced by placebo interventions. We further discuss why a shift of focus from the placebo intervention to the overall therapeutic is necessary and what research methods can be used for the clinical investigation of the relevance of context effects. In the last part of the manuscript, we discuss why placebo or context *effects* are seen as positive in clinical practice when

they are associated with active treatments, while placebo *interventions* have to be avoided.

2. WHAT IS A PLACEBO INTERVENTION IN CLINICAL PRACTICE?

According to the classical definition by Shapiro & Morris [1, p. 371] ‘a *placebo* is defined as any therapy or component of therapy used for its nonspecific, psychological, or psychophysiological effect, or that is used for its presumed specific effect, but is without specific activity for the condition being treated’. Shapiro & Morris further distinguish pure placebos, which are ‘treatments that are devoid of active, specific components’, and impure placebos, which ‘contain non-placebo components’ (p. 372). While this definition has been severely criticized on a conceptual level [2,3], it is summarizing well the implicit view of placebo interventions in biomedicine. We will not discuss conceptual issues here, but we will demonstrate—by using simple case scenarios of interventions classifying as placebos according to this definition—that, in clinical practice, it is often quite difficult to decide what should actually be considered a placebo (table 1). These difficulties are owing to the fact that the perspective of the definition by Shapiro & Morris is scientific, while physicians providing an intervention and patients receiving it might hold a different view.

In scenario 1, a typical pure placebo (a saline injection) is administered to a pain patient. Both the provider and the scientist ‘know’ that the intervention is a placebo. The patient is informed in a deceptive manner which makes him believe he is receiving a ‘true’ treatment. If he were to be informed correctly he would also consider the treatment a placebo.

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Table 1. Five clinical scenarios and related views of providers, patients and scientists whether the intervention provided is to be considered a placebo.

scenario	provider	patient	scientist
1. saline injection in a pain patient	placebo	specific therapy (deceptive information)	placebo
2. antibiotic in a patient with suspected viral infection	probably not indicated	specific therapy	placebo
3. homoeopathic remedy in a child with a cold (prescribed by a sceptic but uncertain physician)	(probably) placebo	specific therapy	placebo
4. homoeopathic remedy in a child with a cold (prescribed by a homoeopath)	specific therapy	specific therapy	placebo
5. arthroscopic débridement in a patient with osteoarthritis of the knee	specific therapy	specific therapy	placebo

According to surveys, between 17 and 80 per cent of physicians and between 51 and 100 per cent of nurses have used pure placebos intentionally at some point in their professional career [4]. However, the data also indicate that the actual frequency is rare, because pure placebos are usually applied only once or a few times to a small minority of patients.

There are three basic motivational patterns for such intentional use of a pure placebo. First, the physician aims primarily to promote the patient's wellbeing. For example, in a young patient suffering from severe headaches at risk of becoming dependent on morphine, a physician tried to reduce this risk by substituting some applications with placebo injections without informing the patient or his parents [5]. In another example, a woman with newly diagnosed advanced cancer for which a curative treatment was not possible still had great hopes of being cured. In order not to dash the patient's hopes and making her remaining time unbearable, she received a placebo intervention described as a form of cancer treatment [6]. While in both cases the patient was informed in a deceptive manner and the physician placed the relevance of his intent to help over the patient's autonomy and the ideal of shared decision-making, some authors believe that such placebo applications can be ethically justifiable (e.g. [7]). Physicians move in a grey area, and opinions on the acceptability of using pure placebos vary. The first is a real case in which the mother of the patient filed a professional grievance against the physician and a nurse [5]. The second case is fictive from a survey asking both physicians and patients to assess the acceptability of the placebo treatment. Sixty-three per cent of participating patients and 18 per cent of physicians found the procedure acceptable as it was likely to preserve the patient's hope [6].

A second motivational pattern could be summarized as 'convenience' [8]. For example, several surveys have found that pure placebos are given to difficult or complaining patients, or to avoid conflicts with a patient [9–13]. While understandable to some extent in a busy routine practice, such actions seem highly problematic both on a professional and on an ethical level [8]. It is likely that in reality many intentional applications of pure placebos are owing to a mixture of both the aim to promote wellbeing and convenience.

A third pattern, which seems to have become more and more infrequent but still occurs, is the use of placebo for diagnostic purposes. In such cases placebos are given to see whether the complaints are 'real' or 'simulated' or 'only psychological' [4]. Such a use is not only ethically problematic, but also contrary to the evidence which clearly shows that 'real' complaints can react to placebo applications.

Scenario 2 involves a patient with suspected viral upper respiratory tract infection who asks to receive the antibiotic that has helped so greatly in previous infections, and the physician complies. Antibiotics are potent and highly effective drugs when applied adequately but they are not indicated in viral infections. Therefore, this is considered as a classical example of an impure placebo. Obviously, the patient considers the treatment specific. The physician considers the antibiotic non-indicated, but there might be some uncertainty regarding the viral origin or a risk of bacterial super-infection. Based on general pathophysiological reasoning and clinical trial data, the scientist makes a general judgement that antibiotics do not have an effect over placebo in patients with viral infection.

Surveys show that the non-indicated use of active drugs is much more frequent than the use of pure placebos [11,13,14]. Qualitative interview studies addressing the prescribing of antibiotics in uncomplicated upper respiratory tract infections have shown that physicians are aware of the problems of their behaviour in such situations, but the word placebo does not come up [15,16]. However, when asked explicitly about placebo use [14], physicians seem to accept that such prescriptions can be considered placebo therapy.

The main reason for prescribing antibiotics and other unnecessary treatments is the perceived wish of or pressure from the patient [15–18]. There is some data that physicians overestimate the extent to which patients expect a prescription [19], suggesting that other, possibly subconscious, reasons might also play a role. Placebo prescription in such a situation is not a case of deception, but a conflict between the professional integrity of the physician and the patient's wish [8]. Physicians also often raise the issue of remaining uncertainty as a justification [15,16]. For example, a bacterial origin of the infection or a bacterial super-infection cannot be ruled out. However,

one could suggest that convenience is often a more important motivation for using a non-indicated treatment than uncertainty. It has been argued that such a use of antibiotics is unethical, unprofessional and harmful [8,20].

In scenario 3, a mother firmly believing in homoeopathic remedies is seeking a paediatrician for her 2-year-old child suffering from symptoms of a common cold. Homoeopathy is a widely used alternative therapy practised both by physicians and non-medical practitioners. Its most controversial aspect is the use of remedies which are prepared in serial dilution steps with vigorous shaking in between (potentization), commonly to the extent that no molecules of the original substance remain. Homoeopaths believe that during the dilution process information passes from the diluted agent to the solvent, which, in the light of current knowledge, seems implausible. Therefore, many scientists are convinced that highly diluted homoeopathic remedies are placebos. As they often do not contain any 'active substance' in a chemical sense, they might even qualify as pure placebos. From such a perspective, homoeopathy could be considered a pseudo-therapy.

In our scenario, history and physical examination do not provide any indication for relevant risks but the child clearly suffers from bothersome symptoms. The mother asks for a homoeopathic remedy because the child improved very quickly in a similar situation when another physician prescribed the remedy. The paediatrician is sceptical about homoeopathy but he has seen some astonishing cases, so he is not really certain. Furthermore, he considers the risk minimal. He prescribes the remedy saying that he personally is a bit sceptical about homoeopathy, but it might be worth trying, and if the symptoms deteriorate the mother should return.

Surveys have shown that the use of complementary therapies such as homoeopathy, herbal medicines or vitamins by sceptical physicians is also much more widespread than the use of pure placebos [14,21,22]. The motivational pattern for the physician is a mixture of convenience (he wants to respect the mother's wish, and to avoid a conflict or losing a client) and uncertainty (he cannot rule out with certainty that homoeopathy is an active therapy). Scientists would clearly consider this a placebo prescription, but might have diverging views on whether the pragmatic approach of the physician is acceptable.

In scenario 4, the mother and her 2-year old child visit a convinced homoeopath who prescribes a highly diluted homoeopathic remedy. Obviously, for the scientist, homoeopathy remains a placebo (or pseudo-therapy). Instead, based on his daily experience, the homoeopath is convinced that the prescribed remedy is a 'true' active treatment. The scientific doubts of researchers not using this therapy are regularly discarded. Patients seeking a homoeopath usually believe that this is or at least could be an active therapy, although some are sceptic.

Surveys on placebo use among physicians do not include questions on this type of placebo use. The reason is obvious: those using the treatment in this manner do not consider it a placebo. As they believe

to act in the best interest of their clients, neither do they have any ethical problem. Surveys on the use of often highly controversial complementary and alternative therapies show that they are highly prevalent in many countries [23]. Some scientists see it as their duty to inform society about the 'truth' and consider it as ethically problematic that providers use therapies they consider disproven by science [24, pp. 244–250].

In the last scenario 5, an orthopaedic surgeon performs an arthroscopic débridement in a patient with osteoarthritis of the knee. This is a procedure in which an endoscope is introduced into the arthritic joint. The joint is then lavaged, rough cartilage is shaved and loose debris removed. Surgeons who perform this procedure usually consider it to be an active and effective therapy. Patients are unlikely to undergo this invasive treatment unless they share this view (after probably having been informed in a way supporting this view). However, many scientists consider improvements seen after such a treatment to be a placebo effect, as a rigorous randomized trial did not find any improved outcomes over those of a sham intervention [25].

The case differs considerably from scenario 4: arthroscopic débridement clearly cannot be considered a pure placebo but is an invasive, intense intervention. Compared with homoeopathic treatment, it is associated with much greater direct risks. Contrary to homoeopaths, surgeons usually claim to practice scientific medicine based on the best available current evidence. To justify their behaviour, they therefore have to question the validity of the relevant study results, at least for the selection of patients in whom they actually perform the procedure, and claim that the way they use the intervention is clearly not a placebo.

If physicians discuss the use of placebo interventions in practice, they typically think of the intentional application of pure placebos (scenario 1). In this classical case providers, scientists and informed patients all agree that this is a placebo intervention. In the remaining scenarios, the situation is far less clear. Most readers would probably agree that scenarios 2 and 3 can be considered examples of placebo interventions as the provider at least to some extent uses the intervention for placebo purposes. Scenario 4 is a typical example of a strong conflict between perspectives. Many readers might have problems in considering scenario 5 a good example of a placebo intervention but according to the best available evidence, the procedure meets the definition by Shapiro and Morris. The scientific perspective summarized in this definition postulates an objective knowledge on what has specific effects and what not. This knowledge is often uncertain and incomplete. Those involved directly in the clinical encounter—physicians and patients—sometimes ignore the scientific perspective. In the discussion on placebo use, these differences in perspectives are often not reflected. This leads to misunderstandings. We suggest that apart from the intentional use of pure placebos (scenario 1), the word placebo interventions should be used more carefully.

3. INVESTIGATING WHETHER PLACEBO EFFECTS ARE CLINICALLY RELEVANT. THE CONVENTIONAL APPROACH

According to Shapiro & Morris, 'a placebo effect is defined as the psychological or psychophysiological effect produced by placebos' [1, p. 371]. This questionable view of placebo effects has strongly influenced the approaches for quantifying such effects used in clinical research.

For decades, improvements in placebo groups of randomized clinical trials have been interpreted as evidence for placebo effects. An analysis of the proportion of patients reporting satisfactory relief after receiving placebo in 15 controlled trials published by Beecher in 1955 in *JAMA (The Journal of the American Medical Association)* [26] is probably the most cited article in the field of placebo research. This article is the basis of a widely quoted myth that the average size of placebo effects is about 35 per cent. Beecher further claimed that the small standard error in his analysis (2.2%) indicates the constancy of the placebo effect. In 1994, a major review published in *JAMA* claimed even larger placebo effects based on the improvement in placebo groups [27]. A careful re-analysis of the original studies included in Beecher's review concluded that spontaneous improvement, fluctuation of symptoms, regression to the mean, additional treatment, response biases and misquotation were plausible alternative explanations for the presumed placebo effects [28]. These reasons also explain why it is almost impossible to reliably judge in routine clinical practice whether a placebo effect has occurred. A recent analysis of trials including both a placebo and no-treatment control group also found relevant improvement in many no-treatment groups [29]. In conclusion, changes observed in patients receiving placebo over time are not a reliable way to estimate the size of placebo effects.

From a methodological point of view, it seems obvious that for assessing the size of placebo effects, a no-treatment control group is crucial [30]. However, trials including both a placebo and a no-treatment group are comparably rare and widely dispersed in the medical literature. When, in 2001, the leading medical journal, *the New England Journal of Medicine*, published a meta-analysis of 114 such trials by Hróbjartsson & Gøtzsche [31] titled 'Is the Placebo Powerless?' this provoked a major debate. In the trials included in this review, placebo, on average, did not have a significant effect over no-treatment when outcomes were binary, regardless of whether these outcomes were subjective or objective. For continuous outcomes, there was a significant effect over no-treatment when the outcome was patient-reported, but not when it was an objective measure. The authors concluded that they had 'found little evidence in general that placebo had powerful clinical effects'. This meta-analysis has been heavily criticized (e.g. [32–36]) for mixing highly heterogeneous studies with control interventions, which might not always be considered placebo, for including studies in which all study groups including the no-treatment group received basic treatment with potential impact on the outcomes measured, as well as for a variety of other reasons. Furthermore, subsequent analyses have

provided evidence that a subset of studies with outcomes regulated by the autonomic nervous system is susceptible to placebo treatments ([37]; see also [38]). However, the overall conclusion that available trials including both a placebo and a no-treatment group do not provide convincing evidence for *powerful* placebo effects in general remains adequate.

Hróbjartsson & Gøtzsche published updated and expanded versions of their review in 2004 [39] and 2010 [40]. The current analysis now includes 202 trials. While effect sizes remained similar to those in the first analysis, effects of placebo interventions over no treatment are now statistically significant for both patient- and observer-reported continuous outcomes and for binary outcomes owing to the larger number of included trials. While the evidence that there *are* placebo effects is stronger now, the authors still conclude that they 'did not find that placebo interventions have important clinical effects in general', as the overall effect size is small and the influence of bias unclear [40].

4. PROBLEMS OF THE CONVENTIONAL APPROACH TO ASSESS THE CLINICAL RELEVANCE OF PLACEBO EFFECTS

Randomized trials including both a placebo and a no-treatment control group are clearly more appropriate for investigating the size of placebo effects than trials without a no-treatment group. But are they really providing valid evidence on the size of placebo effects in clinical practice? An important methodological problem regarding the reliability of effect estimates is that patients cannot be blinded for comparisons between placebo and no-treatment. This could result in reporting biases (at least in the case of patient-reported subjective outcomes for which the meta-analyses by Hróbjartsson & Gøtzsche provide the most consistent results), differential use of co-interventions and a variety of other biases. This implies that the effect estimates are quite uncertain.

But there is a much more fundamental question: are randomized trials including both a placebo and a no-treatment group truly a valid way to estimate the size of placebo effects in practice? The classical definition by Shapiro & Morris states that placebo effects are *produced* by placebos. In line with that thinking, one assumes that the difference between the placebo and the no-treatment group in randomized controlled trials (RCTs) is owing to the placebo intervention. But how should an intervention (e.g. a saline injection) produce an effect if it is objectively without a specific effect? [3] There now seems to exist a consensus among placebo researchers that what we call placebo effects is a heterogeneous class of psychobiological events attributable to the overall therapeutic context [41]. The placebo intervention by itself should not produce any effect (otherwise it would not be a true placebo); it completes a complex therapeutical situation and thus conveys meaning, influences expectations and possibly triggers conditioned responses or behaviour changes. If this hypothesis is correct, the same placebo intervention should be associated with different placebo effects depending on the context. Furthermore, very different

placebos associated with very different contexts (e.g. pharmacological placebo and sham surgery) should regularly produce different placebo effects. The context in an RCT does not reflect any of the scenarios described in the previous section of this paper. Participants in RCTs must be informed in detail about the aims and procedures in a trial (although some studies deviate from this). The motivations of physicians for delivering a placebo differ strongly from normal practice.

In conclusion, the focus on the placebo intervention as the *cause* of placebo effects is misleading and should be replaced by a focus on the context (including the placebo intervention). However, even if this shift of focus will occur, it seems likely that owing to their specific context situation, RCTs can provide only crude estimators of the size of placebo effects (better, context effects) in routine clinical practice.

5. MOVING FROM RESEARCH ON PLACEBO EFFECTS TO RESEARCH ON CONTEXT EFFECTS

Apart from the strong evidence from experimental research supporting the contextual interpretation of placebo effects [41,42], there is also increasing evidence from clinical research. The most recent version of Hróbjartsson & Gøtzsche's [40] review itself found that placebo effects were larger for physical placebos (compared with pharmacological or psychological placebos), in trials not informing patients that a placebo intervention was administered, and in trials with the explicit purpose of studying placebo effects [40]. Meta-analyses of changes over time in placebo groups in trials without a no-treatment control have identified a variety of context factors associated with effects size, too. For example, trials in which placebo was injected subcutaneously reported higher improvement rates than trials using oral placebos [43]. An elegant randomized trial found that a placebo acupuncture intervention was associated with significantly greater clinical effects when provided in an empathic compared with a neutral manner [44].

In principle, studies using the open–hidden paradigm could provide important information as to whether perceiving the act of treatment (be it a placebo or an active intervention) makes a difference. In such studies, an active substance and/or a placebo intervention are administered both in an overt and in a covert fashion [45]. For example, in a study by Benedetti *et al.* [46], patients with post-operative pain with an intravenous drip received either no treatment, an open or a hidden injection of saline (placebo) or of the cholecystokinin antagonist proglumide, which is known to potentiate analgesia induced by morphine and endorphins. Pain intensity was similar in patients receiving no treatment or a hidden injection of saline or proglumide, while it decreased after open injection of saline and even more after proglumide. These results indicate that both saline and proglumide do not have any direct (specific) analgesic effect, but that an overt injection is associated with reduced pain. The results further suggest that proglumide potentiates a placebo-activated endogenous opioid system if applied in an open manner. While the open–hidden paradigm is a fascinating approach, it

is, however, not feasible for most treatments as a hidden administration is not possible.

There are a variety of further approaches to investigate the influence of context factors. If we assume that context factors can modify the clinical response to both placebo and active treatment, this can be investigated directly in randomized trials. For example, trials using a balanced placebo design investigate simultaneously the influence of a specific (e.g. drug versus placebo) and a non-specific or context factor (e.g. positive or neutral information). Such trials are infrequent; however, the available studies suggest that context factors not only have direct effects but also interact with specific effects by either increasing or decreasing the differences between active treatment and placebo [47,48].

If we assume that all healthcare interventions can be associated with context effects and that (as we hope) the majority of interventions have specific activity, the majority of context effects in clinical practice should be associated with active treatments. Obviously, context factors can be and have been investigated directly in randomized trials without manipulating the active treatment. Again a systematic review suggests that context factor matters [49], but owing to the relatively small number of studies and lack of replications the evidence base is relatively weak. There is considerable research on 'specific' context factors such as expectations [50,51] or empathy [52]. However, in our view this should not be called placebo research. What is often described as harnessing placebo effects might be better summarized as harnessing context effects or as attempts to create optimal healing environments [53,54].

6. BAD PLACEBO INTERVENTIONS AND GOOD CONTEXT EFFECTS

While we do not have sound evidence regarding how relevant they are in clinical practice, there is a common belief that good physicians should harness placebo and/or context *effects* to maximize the benefits to their patients [55–57]—however, the use of placebo *interventions* should be avoided unless absolutely necessary [58]. A qualitative study by Comaroff published in 1976 [17] provided interesting insights into why this is the case. For this study, the views of 51 general practitioners on placebo therapy were elicited indirectly, in the context of a more general discussion about prescribing behaviour. Practitioners were first asked to estimate the proportion of their consultations which culminated in prescribing a treatment. All participants set the proportion at 70 per cent or above. In their elaborate answers, most practitioners spontaneously stated that they did not consider all prescriptions as truly necessary and felt necessitated to provide justifications. Implicitly, the answers clearly indicated that the physicians had internalized a professional ideal, which requires that any treatment should be specific in effect and administered or prescribed only when necessary. However, this ideal conflicted with the realities of general practitioners in the real world. Seeing only unselected patients, general practitioners faced considerable uncertainty but still

needed to make decisions. Making a firm diagnosis in general practice was often impossible or unnecessary, implying that the basis for choosing a specific treatment was weak. On the other hand, physicians usually believed that patients expected a clear diagnosis and a treatment. Therefore, the general practitioners often prescribed treatment which could be considered a placebo.

If the professional imperative of specific and necessary treatment is taken seriously, giving a placebo is nothing else than a therapeutic defeat. The physician fails. Harnessing context or placebo effects is only legitimate if associated with a specific treatment. Therefore, intentional use of pure placebo is usually restricted to exceptional situations. When applying (what scientists call) impure placebos, physicians more or less use conscious rationalization strategies to cope with their dilemma. Apart from perceived demand or expectations of patients, important rationalizations are beliefs in the specific activity of the treatment provided, in spite of conflicting evidence, and arguing for avoidance of potential complications [18].

The available evidence suggests that the use of impure placebos is more frequent in primary care than in specialized care [4]. This seems plausible as diagnostic uncertainty is higher in unselected patient populations where the number of potential diagnoses is high and the prevalence of each single disease is low. However, uncertainty also occurs frequently in specialized settings.

7. SUMMARY AND CONCLUSIONS

In summary, it is often unclear in the clinical setting as to what is a placebo intervention. This does not apply to the intentional use of pure placebos, but such interventions are infrequently used (although the total number of such uses on a population level still might be a cause for concern). Pseudo-treatments, disproven or non-indicated treatments are used much more frequently, but whether they are considered placebos is often a matter of perspective. What are summarized under the term placebo effects are highly heterogeneous phenomena related to the overall context of healthcare interventions. Calling context effects associated with the application of active interventions placebo effects leads to confusion and should be, in our opinion, avoided. We do not know how large placebo effects actually are in clinical practice, but the available evidence suggests that, on average, they are often small. Because of the professional ideal that all treatments used should be specific in action and used when only necessary, the use of placebo interventions is problematic, while harnessing context effects is clearly legitimate when the treatment is active.

There is a clear need for more research on the role of placebo interventions and the relevance of context effects in clinical practice. This research must take the perspectives of providers and patients into account. Qualitative research can provide important insights into why and how physicians use pure and impure placebos. Investigating the relevance of placebo and context effects for clinical practice will remain a challenge. Studies using the open-hidden approach or a

balanced placebo design seem particularly desirable. However, the first approach is rarely possible in clinical practice and the second is expensive. As in a clinical environment many factors cannot be controlled and as effects are likely to be small to modest, such studies need large sample sizes. A promising strategy could be to integrate minor manipulations of context factors (for example, using different communication styles) into randomized trials, which are performed for other purposes. If this is done in a larger number of trials, effects could be investigated with sufficient power in meta-analyses (see also [59]). However, as the context in studies and routine practice differs, uncertainty will remain regarding the size of context effects in clinical practice.

We think that the professional imperative of specific and necessary treatment is adequate. It is an important basis for the quality and authority of medicine and other acknowledged healthcare professions. However, we also think that the amount of uncertainty in medical practice and its consequences on treatment decisions should be discussed more openly. Downplaying the degree of uncertainty and not accepting that the ideal of specific and necessary treatment often cannot be realized pushes healthcare professionals to use questionable rationalization strategies. It should also be accepted that humans very often behave irrationally and that rituals, myths, seemingly plausible explanations, etc., can strongly affect humans, sometimes even on a somatic level. If uncertainty and irrationality are accepted, we believe that there can be ethically, professionally and scientifically acceptable ways for a limited use of impure placebos (provided that they are associated with very low risks) and exceptional use of pure placebos.

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