Review

Harnessing the placebo effect: the need for translational research

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Laboratory research recently has greatly enhanced the understanding of placebo and nocebo effects by identifying specific neuromodulators and brain areas associated with them. However, little progress has been made in translating this knowledge into improved patient care. Here, we discuss the limitations in our knowledge about placebo (and nocebo) effects and the need for translational research with the aim of guiding physicians in maximizing placebo effects and minimizing nocebo effects in their routine clinical practice. We suggest some strategies for how, when and why interventions to promote beneficial placebo responses might be administered in the clinical setting.

Keywords: clinical practice; patient–doctor relationship; placebo theory; ethics; expectation; nocebo

1. INTRODUCTION

Laboratory research on the placebo and nocebo effects has provided extensive evidence about the neurobiological nature of these phenomena, which can produce health-related effects [1,2]. Beyond the scientific interest in exploring the mechanisms underpinning these fashionable mind–body interactions, the ultimate aim of research on the placebo (and nocebo) effects is to develop knowledge that can be translated into improved patient care. To do this, it is necessary to focus on translational placebo research emphasizing the clinical significance of placebo and nocebo effects.

In biomedicine, translational research aims at applying basic in vitro and in vivo science to develop knowledge that can be used to improve the diagnosis, treatment or prevention of human diseases [3]. New treatments and research knowledge should reach patients and clinicians for whom they were intended, by promoting access, reorganization and coordination of systems of care, encouraging clinicians and patients to modify their behaviours, and improving the patient–clinician relationship. In light of the general purposes and objectives of translational research, we analyse salient points of current scientific knowledge on placebo and nocebo research and suggest strategies to promote clinical benefits.

Translational placebo (and nocebo) research involves a number of important issues such as (i) analysing current theories of placebo and nocebo effects and their relevance to clinical practice; (ii) integrating the best evidence of clinically significant placebo and nocebo effects with physician’s expertise and patient’s attitudes; and (iii) bridging the gap between mechanistic research and clinical practice. Together these points suggest the need for coordinating research efforts among different disciplines and experts (basic scientists, clinical researchers, trialists, anthropologists and bioethicists) and for providing tentative indications and recommendations for future patient-oriented placebo (and nocebo) investigation.

In mapping translational placebo (and nocebo) research, it is important to clarify some of the terminology that relates to these phenomena. The word placebo has been often used to refer to inert substances and simulation of interventions. Placebo research indicates the study of the impact of expectations on brain–mind–body interactions. Inert substances and simulation of interventions have been extensively used as tools in placebo research. Substances and interventions are considered placebos when they lack the potential to produce benefit on the basis of pharmacological properties or physical manipulations. Some authors have distinguished between ‘pure’ and ‘impure’ placebos [4,5]. Examples of pure placebos are talc, sugar and bread pills that physicians have historically administered to placate patients and comply with their wishes to receive medications. (Most pharmacological placebos in clinical trials are also pure placebos.) Impure placebos are treatment interventions that typically have a specific active principle that is known to be effective in conditions other than the condition being treated: e.g. use of a vitamin to treat fatigue not related to vitamin deficiency. Clinically speaking, what makes substances or interventions count as placebos is the lack of specific efficacy in treating a specific patient’s condition based on the inherent properties of the treatment. Finally, the placebo effect refers to the multiple changes occurring in the body that are produced by a placebo administration or treatment simulation. However, these effects do not depend necessarily on the

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One contribution of 17 to a Theme Issue ‘Placebo effects in medicine: mechanisms and clinical implications’.
administration of ‘inert’ substances. The effects following the administration of a placebo can be due to the general psychosocial context around the therapy. As a positive psychosocial context may induce a placebo effect, a negative context, including information about side effects, may lead to opposite expectations and outcomes, called the nocebo effect.

2. PLACEBO AND NOCEBO THEORIES

Contemporary placebo and nocebo research has been inspired by prior and current theories. Ideally, the development and refinement of theoretical approaches to understanding placebo and nocebo effects works in tandem with translational research. Theoretical perspectives inform hypotheses and the design of experiments to test them. Patient-centred research provides insights for evaluating and reframing theoretical perspectives. Placebo (and nocebo) phenomena have been mainly attributed to expectation and conditioning.

Kirsch [6] posited an expectancy theory whereby a placebo produces an effect because the recipient expects it. Because the placebo intervention does not have physical properties with the potential of producing specific effects of interest, it is assumed that these effects are due to the recipient’s expectations. According to this view, Kirsch labelled the beliefs that appear to mediate the placebo effects ‘response expectancies’, defining them as ‘anticipation of the occurrence of non-volitional responses’. Response expectancies may also enhance effects of active treatments that do have specific efficacy based on their pharmacological or physiological properties. Response expectancies can be distinguished from ‘stimulus expectancies’, which ‘are the anticipation of the occurrence of external consequences’, such as conditioned experiences as well as from ‘anticipation of voluntary response which have been labelled intention’ [6].

As noted above, placebo responses can also be produced by conditioning. Although expectancy-induced placebo responses created by verbal suggestions are conceptually distinct from conditioned placebo responses, the two models clearly overlap to some extent [7] and, expectations per se can be actively built up through prior experience via conditioning.

Previous direct experience of benefit via pharmacological or biologically significant cue exposure can powerfully change behaviour and clinical outcomes. Originally demonstrated by Pavlov [8] with animals, associative learning was considered essentially as a pairing of two stimuli. One, initially neutral in that by itself it elicits no response, is called the conditioned stimulus (CS); the other that consistently elicits a response is called the unconditioned stimulus (US). The response elicited by the pairing of the CS and the US is called conditioned response (CR). The formation of the CRs may be due to repeated association of the CSs with active medication, the USs. Pairing placebos with effective medication followed by administering placebos without the medication can produce a CR that is similar to the response to medication [9,10]. Humans classical conditioning probably often involves a cognitive process, which forms and/or changes expectations [11]. In his model of expectation, Reiss stated that ‘…what is learned in Pavlovian conditioning is an expectation regarding the occurrence or non occurrence of a US onset or a change in the US magnitude or duration’ (p. 387). However, while the CR may be modulated by cognition, a fundamental aspect of classical conditioning is the automatic, non-cognitive aspect of the effect, making it a widespread process across different species.

In 1980, Brody [13] drew on an earlier anthropological analysis of doctor–patient relationship by Adler & Hammett [12], arguing that the placebo response can be explained by means of a meaning model. A placebo response would occur when ‘the meaning of the illness experience for the patient is altered in a positive direction,’ and the factors that contribute to that positive change in the mind–body unit are essentially the patient’s awareness of being listened to and attended by the caregiver. Additionally, the empathetic communication between physician and patient (and the support by other individuals) helps to create a sense of mastery and control over the illness. Moerman & Jonas [14] echoed Brody [15] in emphasizing that ‘meaningfulness… can make a huge difference for patients in the objective and subjective dimensions of their illness’ and suggested to reframe the placebo response as ‘meaning response’.

The meaning model highlights the potential therapeutic effects of the psychosocial context of clinical practice and the ritual of treatment. The context is made up of words, attitudes, providers’ behaviour and medical devices, or in other words the whole atmosphere around the patient and the treatment. The placebo response might derive from the processes of tapping the body’s own powers of healing that are not activated automatically but depend on intervention by a healer [16]. This view of placebo effects finds confirmation in a series of studies showing a cognitive and emotional modulation of therapeutic outcome following open versus hidden administration of the same drug (for a review see [17]) and business-like versus augmented clinician–patient interaction [18]. By hiding the specific treatment from the patient’s view and comparing the response to hidden and open administration of medication, it becomes possible to focus on all the factors in the clinical encounter that are not attributed to the pharmacological properties of the treatment but may contribute to clinically relevant patient outcomes. This paradigm also directs attention away from the placebo as an ‘inert’ intervention, because in both the open and hidden treatment conditions, the same dose of medication is provided to patients. Greater pain relief for a given dose of open treatment, when compared with hidden administration, demonstrates the therapeutic effects of the context of the clinical encounter. What is present in open treatment that is absent in hidden treatment? Described globally, it is the presence of the clinician—the way he or she relates to the patient through sight, speech, body language and touch.

The open/hidden paradigm also illustrates the role of clinician–patient interaction and communication in the formation of nocebo effects. Patients openly
informed about the interruption of either anxiolytic or analgesic treatment experienced a sudden increase of anxiety and pain, while a hidden interruption (controlled by a computer) did not induce any worsening. Anxiety seems to play a crucial role in nocebo effects [2,19]. For example, anxiogenic verbal suggestions are also capable of activating cholecystokinin pathways [20] and turning tactile stimuli into pain [21]. Some have suggested that anxiety might take part in placebo responses as well [22–24]. High-anxiety volunteers showed greater placebo and nocebo responses [24] and patients with irritable bowel syndrome experienced a reduction of anxiety when they were given a placebo [25]. However, a causal link between placebo effects and anxiety has not been demonstrated.

A recent explanation of the formation of placebo effects focuses on *signs* and conveying information [26,27]. Placebo interventions and the context in which they are administered consist of signs that are detected and interpreted by patients. Miller & Colloca [26] applied the semiotic theory developed by the philosopher Charles Peirce to account for placebo responses. Iconic, indexical or symbolic signs convey information that is processed by a patient or a research subject. In clinical encounters, these signs can be vehicles of placebo responses. When placebo responses occur, the interpreted sign is the therapeutic agent and the response involves learning, by which the patient processes and responds to the information the signs convey [27]. Emotion and cognition shape the interpretation of the signs, producing positive and negative impacts on health and perception.

Overall, it is important to note that these theories are not necessarily in opposition to each other; rather, they emphasize different aspects of placebo and nocebo phenomena. Further work is needed to integrate conceptual and theoretical insights concerning placebo and nocebo effects, with the aim of facilitating translation of scientific knowledge into improved patient care.

3. BEST EVIDENCE, CLINICIAN BEHAVIOURS AND PATIENT ATTITUDES TOWARDS PLACEBOS

The definition of circumstances and reasons for promoting healing processes based on placebo and (undesirable) nocebo mechanisms in clinical practice represents the core of translational research and the endpoint of patient-centred placebo research. Translating knowledge about placebo and nocebo effects for the benefit of patients requires a rigorous evaluation of potential benefits and harms associated, respectively, with placebo and nocebo effects. Two parallel underlying questions need to be addressed: (i) Can placebo treatments produce clinically significant benefit? (ii) Can nocebo effects produce clinically significant worsening?

(a) Evidence of placebo benefits

A recent series of meta-analyses have shed light on the magnitude and clinical significance of placebo effects in the randomized clinical trial (RCT) and experimental settings. A systematic review of clinical trials was conducted in which patients were randomly assigned to either placebo or no treatment [28–30]. The authors’ goal was to study the clinical significance of placebos by discerning whether patients randomized to placebo under blind conditions have better outcomes than those randomized to no treatment. Hróbjartsson and Gøtzsche considered the effect of three types of placebos: pharmacological (e.g. a pill), physical (e.g. a manipulation) and psychological (e.g. conversation), and binary (e.g. the proportion of alcohol abusers and non-alcohol abusers) and continuous outcomes (e.g. the amount of alcohol consumed). No significant effects of placebo, when compared with no treatment group, were detected on objective outcomes. There was a statistically significant but modest effect of placebo on subjective, continuous outcomes, most notably in relief of pain. The authors suggested that the observed significant effect of placebos on subjective outcomes may have been due to biased reports of subjects: those receiving placebos probably believed that they were receiving an active treatment intervention, while those in the no-treatment groups knew that they were not receiving a treatment intervention.

By assessing the heterogeneity of included trials, Hróbjartsson and Gøtzsche found a statistically significant effect for pain, nausea, asthma and phobia out of 60 medical conditions. The variations in the effect of placebos were partially explained by trial designs and whether patients were informed about the inclusion of inert substances. For example, larger placebo effects were present when patients were not informed that they would receive a placebo intervention. Meta-regression analyses showed a positive association between magnitude of placebo effects and physical placebo interventions (e.g. sham acupuncture) and outcomes (larger effects in patient-reported outcomes than in observer-reported outcomes) [30].

Most of the research supporting a placebo effect powerful enough to influence body perception and clinical symptoms arises from laboratory investigation. Vase et al. [31] conducted a meta-analysis aimed at comparing the placebo analgesic effects observed in laboratory settings versus clinical trials. They included 23 clinical trials from the meta-analysis by Hróbjartsson & Goetzche [28] and 14 studies that investigated placebo analgesic mechanisms. The magnitudes of the placebo analgesic effects were dramatically higher in studies investigating placebo analgesic mechanisms compared with clinical trials in which placebos served as a control. In a follow-up meta-analysis with many more laboratory studies (from 14 to 21 studies including control, placebo treatment, randomization and pain measures), the authors found that the magnitude of placebo analgesia in laboratory settings was fivefold larger than analgesia in placebo control studies [32].

Such a difference might be due to the context features of clinical trials versus experimental settings. Participants’ expectations may vary based on receiving different information about treatments and differing perceptions of the interest of investigators. Trialists typically avoid giving verbal suggestions of analgesia in favour of neutral instructions, whereas investigators looking at the placebo mechanisms tend to emphasize
the analgesic properties of placebo treatments and procedures. Most of the experimental placebo analgesia studies involved healthy volunteers with outcomes monitored for a short time, thus raising doubts about their clinical significance. However, acute pain has major clinical implications in medicine, not only for the acute episode, but also for memory effects potentially influencing future pain management. To elucidate the clinical significance of placebo responses, more clinically oriented research with patient subjects is needed.

(b) Evidence of clinical nocebo harms

Translational placebo research, aimed at improving patient care, should consider the nocebo effects that can negatively influence clinical outcome in addition to placebo effects. Indeed, nocebo responses are common in clinical trials and practice and can produce discontinuation of trial participation, alteration of treatment schedules and lack of adherence.

Communicating about potential side effects of drugs may produce nocebo effects. For example, nocebo effects (or placebo adverse effects) have been observed in systematic reviews of randomized, double-blind, placebo-controlled studies for migraine treatments [33,34]. A systematic review of randomized placebo-controlled clinical trials including 56 trials for triptans, nine trials for anticonvulsants and eight trials for non-steroidal anti-inflammatory drugs (NSAIDs) revealed a high rate of adverse events in the placebo arms of trials matching those described for real drugs. For example, anticonvulsant placebos produced anorexia, memory difficulties, paresthesia and upper respiratory tract infection—all adverse events reported in the side-effect profile of this class of anti-migraine drugs [33].

Nocebo effects are high in sexual dysfunctions [35,36]. Silvestri et al. [35] assessed the effect of the beta-blocker atenolol on erectile dysfunction in patients diagnosed with cardiovascular disease (40% hypertension, 60% angina) and not suffering from sexual dysfunctions. Patients were randomly assigned to one of three groups. Group A was blind to the drug administered; group B was informed about the drug but not the side effects; group C was informed about the drug and the side effects on erectile function. After three months of treatment, the incidence of erectile dysfunction according to the International Index of Erectile Dysfunction was 3.1 per cent in group A, 15.6 per cent in group B and 31.2 per cent in group C. Similar results came from a study by Mondaini et al. [36] who randomized patients active sexually to receive 1 year finasteride (5 mg) for benign prostatic hyperplasia (BPH) along with two different disclosures (informed or not about probable occurrence of erectile dysfunction, decreased libido, problems of ejaculation). The six- and 12-month follow-up showed that finasteride treatment produced a substantially higher rate of sexual dysfunction in those patients who were informed about sexual adverse effects.

These and other nocebo studies demonstrate that merely knowing about potential adverse effects may lead to nocebo responses. In general, the clinical implications of nocebo effects illuminate the importance of cognitive appraisal in symptom worsening and the power of words in the context of clinicians—patient interaction. The findings from these studies raise the clinically and ethically important issue of how physicians should frame information so that the truth relating to risks of treatments is preserved and the probability of producing harms is minimized. (A detailed analysis of this point has been developed by the authors elsewhere.)

(c) Clinician behaviours and patient attitudes towards placebos

A recent systematic review of empirical studies from 12 different countries investigating the frequency of placebos in clinical practice and motivations of healthcare professionals, students and patients for their use indicated that their prevalence varies between 17 and 80 per cent among physicians and 51 and 100 per cent among nurses, and that patients’ attitudes towards placebos differ considerably among individuals [37].

Some recent surveys of clinicians report more details about the widespread use of placebo therapy, physician behaviours and motivations in prescribing placebos [38–40]. For example, in Denmark, 503 physicians were asked about the use of placebo described as ‘an intervention not considered to have any ‘specific effect’ on the condition treated, but with a possible ‘unspecific’ effect’. Eighty-six per cent of general practitioners, 54 per cent of hospital-based clinicians and 41 per cent of the private specialists had prescribed placebos at least once in the last year with a trend to reach 10 times for half of general practitioners. Commonly they prescribed antibiotics (70% of general practitioners, 33% of hospital-based physicians and 18% of private specialists), physiotherapy (59% of the general practitioners, 24% of hospital-based physicians and 13% of private specialists), sedatives (45% of the general practitioners, 24% of hospital-based physicians and 10% of private specialists) and vitamins (48% of the general practitioners, 10% of hospital-based physicians and 9% of private specialists). ‘Inert’ placebo treatments (talc and sugar pills, saline solution and so on) were prescribed rarely. The primary motivation for prescribing placebos was ‘to follow the wish of the patient and avoid conflict’ [38,39].

Another random sample of 1200 US internists and rheumatologists was also surveyed. Physicians were asked to indicate which of several placebo treatments they had used in the past year, defined as ‘a treatment whose benefits derive from positive patient expectations and not from the physiologic mechanism of the treatment itself’. Fifty-five per cent of the physicians reported having recommended at least one of a list of interventions as a placebo treatment during the past year: 41 per cent recommended use of over-the-counter analgesics, 38 per cent vitamins, 13 per cent sedatives and 13 per cent antibiotics. Only 5 per cent reported using pure placebos, such as sugar pills and saline injections. When asked about their frequency of recommending a therapy ‘primarily to enhance patient expectation’, 46 per cent reported doing so at least two to three times per month. Of those physicians who reported recommending one or
Figure 1. Translational placebo research. The scheme shows the way to move efficiently from animal and molecular findings to clinical research with healthy and patient subjects. The scope is to apply scientific results into clinical research aimed at improving patient care. An evaluation of legal and ethical requirements is necessary to harness placebos in clinical routine practice. In the field of the immune system, molecular and animal findings have been successfully transferred into clinical trials.

more placebo treatments in the past year, 68 per cent described this recommendation to their patients as ‘a medicine not typically used for your condition but may benefit you’ [39].

In contrast, very little research has been conducted on patient attitudes to placebo treatments in clinical practice. A small survey of Swedish patients asking for an evaluation of several case histories and general statements about placebo treatments showed that 78 per cent of 83 patients believed that physicians should follow the wishes of the patient to receive treatment ‘even if the treatment is tantamount to placebos in the opinion of the physician’. Seventy six per cent of them believed that a placebo would be acceptable in terminally ill patients because ‘it preserves the patient’s hope without making her final time unbearable’ [41].

4. BRIDGING THE GAP BETWEEN MECHANISTIC RESEARCH AND CLINICAL PRACTICE

The core of translational science in medicine is to identify the circumstance and requirements for the transfer of knowledge from molecular and animal models to clinical practice. However, two-thirds of highly cited animal experiments fail to translate into human research [42], while 44 per cent of human subject research translates successfully at the level of randomized trials [43]. Interestingly, in the field of placebo and nocebo effects, most research has been conducted in humans, thus facilitating dramatically the potential for translation of scientific knowledge.

(a) Placebo-conditioned pharmacotherapeutic model

An emblematic model of translatability of molecular and animal findings into preclinical and clinical areas is represented by the recent advances in applying classical conditioning involving placebo interventions to the immune system. By using a conditioned strategy of pharmacotherapeutic effects, it is possible to achieve the goal of harnessing placebo effects in improving patients’ care under conditions of chronic diseases.

Animal and human results in the immune system represent an elegant and a critical example of translational placebo research, in which the evidence of immunosuppression via conditioning has been transferred from laboratory to clinical practice (figure 1).

After the early observation by MacKenzie [49] that some people who are allergic to flowers show an allergic reaction when presented with something that superficially looks like a flower, but contains no pollen (an artificial flower), scientific studies have probed for immunological placebo effects in animals and humans. Ader & Cohen [44] provided experimental evidence that immunological placebo responses can be obtained in mice by a sodium saccharin solution administered after repetitively pairing the solution (CS) with the immunosuppressive drug cyclophosphamide (US). At a molecular level, this model of associative learning was able to induce a conditioned enhancement of antibody production (immunization). These results in animals have paved the way to human experiments, which suggest promise for therapeutic conditioning. Interestingly, repeated associations between cyclosporin A and a flavoured drink induced a suppression of the immune functions in healthy volunteers, as assessed by means of interleukin-2 (IL-2) and interferon-gamma (IFN-gamma) mRNA expression, in vitro release of IL-2 and IFN-gamma, as well as lymphocyte proliferation [45]. Similar findings have been observed in patients. A child with lupus erythematosus showed a successful clinical outcome when half of 12 monthly chemotherapy sessions were replaced with taste and smell stimuli alone following cyclophosphamide paired repetitively with the same taste and smell stimuli [46]. In another study, multiple sclerosis patients received four intravenous treatments with cyclophosphamide paired with anise-flavoured syrup. Eight out of 10 patients displayed decreased peripheral leucocyte counts following the syrup alone, an effect that mimics that of cyclophosphamide [47].

Overall, these findings have important implications for clinically oriented research. According to conditioning and associative learning, placebo responses can be strategically elicited on the basis of a planned sequence of drug
of deception and consistent with requirements of informed consent [51,52].

This line of research suggests that conditioned placebo substitution may be understood as a specific technology for promoting placebo responses, as distinct from more informal expectation-related interventions in the context of the doctor–patient relationship. More research will be needed to evaluate the therapeutic potential and clinical feasibility of placebo conditioning in a range of acute and chronic pathological conditions, including investigation aimed to analyse the optimal number of conditioning trials, the best conditioned stimuli, and the role of conditioning with respect to drug-related adverse events.

(b) Beneficial effects of the physician–patient relationship

We have learned that nocebo adverse effects occur frequently in clinical trials and practice owing to the impact of words and information. Verbal communication can also produce beneficial effects. For example, suppose that a patient experiences chest pain and become worried about heart disease. He visits the doctor for a routine physical examination, which indicates normal heart functioning. He complains about chest pain and the physician suggests that this might be heart burn, which it would be useful to treat with an antacid. As a result of this interaction he is no longer worried about heart disease and feels much less distress when experiencing chest pain relating to heart burn. Consistent with the meaning model, this cognitive reappraisal produces symptomatic relief. Elements of instructional learning are obviously involved. He learned that he was mistaken about having heart disease and he learned that the chest pain is no more serious than heart burn that can be relieved by over-the-counter medication. Verbal instructions can be a potent mechanism for anxiety reduction, with general significance insofar as anxiety exacerbates a wide range of distressing symptoms.

Physicians can also teach patients to gain relief without any placebos. An early study by Egbert et al. [33] demonstrated that encouragement and instructions reduced pain in patients following intrabdominal operation. The ‘active placebo action’ consisted of explaining to patients what to expect during the post-operative period and teaching them how to relax, breathe and move. Compared with a control group, patients who were encouraged and informed by a physician required half the dosage of narcotics to manage the post-operative pain.

Recently, Varelmann et al. [54] shed light on the crucial role of information during a painful procedure. Women at term gestation requesting labour epidural analgesia or non-labouring patients presenting for elective caesarean delivery under spinal anaesthesia were randomized to either gentle and relief-oriented information ('We are going to give you a local anaesthetic injection, a blinded observer came into the room to

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Figure 2. A model of conditioned pharmacotherapeutic effects. The diagram shows an example of a conditioned pharmacotherapeutic trial in patients with severe psoriasis. The three-arm trial included a full-dose treatment group (C\100); a partial reinforced dose group (100\P25–50) and a control-reduced dose group (C\25–50). The cumulative amount of active drug in groups 100\P25–50 and C\25–50 was identical. However, partial reinforcement patients received a full dose of corticosteroid medication 25–50% of the time and placebo medication other times; patients in the control group received 25–50% of the dose continuously. Similar outcomes (frequency of relapse) were observed in the full-dose treatment and partial reinforcement group, suggesting that a regime of reinforcement can gain significant clinical benefits. Data from Ader et al. [48].
assess the patient’s pain (primary outcome). Women in labour informed to expect pain comparable to a bee sting during the local anaesthetic injection (nocebo group) scored pain higher than those receiving the procedure along with gentle positive words.

These (and other comparable) studies indicate the need for educating the medical profession in techniques of communication, ability to interact with patients, as well as self-consciousness that the physician plays an important role in promoting placebo effects and minimizing nocebo responses.

Consider a patient who comes to a physician complaining of chronic low back pain (CLBP), the second most common complaint reported in primary care, and who has tried different therapeutic strategies but is not getting adequate relief. Because standard treatments are often not accompanied by adequate improvement, physicians might propose a series of interventions oriented around promoting placebo responses, reducing symptoms of illness, and improving the ability to cope. After the diagnostic interview, exploring what is troubling the patient by inquiring about the illness experience, the physician would explain the patient that efforts to take advantage of the placebo response may provide beneficial symptomatic improvement.

For example, the physician might recommend acupuncture treatments [55], described as a treatment that may work either by the physical stimulus of the needling or by promoting a placebo response. Patients would be explained that although clinical trials have demonstrated that traditional acupuncture is not clearly better than a fake acupuncture treatment, both have been shown to be considerably better than either no treatment or usual care. Finally, physicians would recommend a series of follow-up visits to discuss the illness experience and success of the placebo response treatment plan.

Such a plan for promoting placebo-based healing processes represents a general and multiple approach strategy consistent with ethical norms. However, it should be tested for various conditions in ‘pragmatic’ randomized trials compared with ‘usual care’ and active surveillance along with optimal clinical attention. An open question is whether discrete interventions (e.g. action of taking pills and treatment rituals) are necessary to optimally evoke clinical benefit by virtue of placebo effects. Large-scale, randomized trials are needed to obtain evidence about what therapeutic strategies work best.

There is controversy over whether it is ethical to recommend and prescribe placebo treatments in clinical practice [56,57]. Miller & Colloca [57] argued that if the placebo effect is a real phenomenon and there is consistent evidence from randomized, controlled trials that placebo treatments produce significantly improved outcomes, then there may be a legitimate place within contemporary medicine for using strategies and interventions to promote the placebo effect.

According to evidence-based medicine, superiority to placebos is considered the minimal requirement for validating active pharmacological and non-pharmacological procedure therapies. Similarly, treatments that are likely to be effective solely or primarily by means of the placebo response should be evaluated rigorously in randomized trials comparing them with no-treatment or usual care groups. The above-described dose-extender trials [48,50] represent a good example of trials aimed to test and quantify the effectiveness and the magnitude of placebo-induced outcomes. Similarly, 3-arm trials comparing complementary and alternative treatment with usual care and waiting list groups (e.g. traditional Chinese acupuncture, sham acupuncture versus either no-treatment groups or usual care group [58]) would be encouraged to understand if it is feasible and ethically justifiable to prescribe treatments that work primarily, by virtue of placebo effect [59].

Use of placebo treatments in clinical practice must be consistent with the professional integrity of clinicians [4,60]. They must offer a favourable risk-benefit ratio and their use must be compatible with informed consent. The surveys of physician use of placebo treatments suggest that physicians are not only less than transparent with patients about this practice, but that they may not be clear themselves about what they are trying to accomplish. It appears that physicians with some frequency engage in behaviours conflicting with professional norms relating to medically indicated treatment by rationalizing the use of placebos as a way to comply with the pressure of patient demand. In particular, the prescription of antibiotics for probable viral infections is especially problematic [38]. In addition to concerns about side effects, there is an individual and societal risk of promoting bacterial pharmacological resistance, making this type of intervention a poor candidate for placebogenic treatment.

Second, the benevolent use of deception to invoke a placebo response is contrary to the principle of respect for patient autonomy. Very little research has been conducted to understand whether placebo interventions can be prescribed overtly without deception [61–63]. Kaptchuk et al. [63] found that patients with irritable bowel syndrome showed significant improvement of symptom severity after receiving open-label placebo when compared with a no-treatment control group with matched patient-provided interactions. Some may argue that such a practice to promote placebo effects might encourage medicalization and drug dependence; however, this concern needs to be balanced against the potential for promoting clinically meaningful placebo responses without adverse treatment effects.

**Ethical–legal requirements of interventions to promote placebo responses**

Any attempts to harness placebo benefits and reduce nocebo harms in clinical practice should be done consistently with professional norms and the ethical–legal requirements of informed consent (figure 1). Although the present paper does not discuss systematically the complex issue of professional, legal and ethical requirements in using placebos in clinical trials and practices, we briefly list some key points because of their importance for translating findings on placebo (nocebo) research from laboratory to clinical trials, and from trials to clinical practice.
5. CONCLUSIONS
Translational placebo research is still in its infancy, and needs careful development both as a scientific discipline and in its applications in clinical trials. Recent progress in laboratory investigation of the placebo and nocebo effects has paved the way for fruitful investment in clinically oriented placebo research that can guide the promotion of therapeutically valuable results.

The opinions expressed are the views of the authors and do not necessarily reflect the policy of the National Institutes of Health, the Public Health Service, or the U.S. Department of Health and Human Services. This research was supported by the Intramural Research Program of the Clinical Center, NIH, the National Center for Complementary and Alternative Medicine, International Association for Study of Pain (Early Research Grant), and EFIC-EGG Grant.

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