Special Article

Placebos, Placebo Effect, and the Response to the Healing Situation: The Evolution of a Concept

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Summary: In spite of its impressive progress, medicine has been strongly criticized for relying on its modern biomedical tradition to the neglect of the psychosocial aspects of health. This neglect may account for patients’ dissatisfaction and eventual use of alternative health approaches. The concept of placebo has sustained dramatic “protean” metamorphoses through the ages. For centuries, placebos have been regarded as powerful deceptive therapies. From the middle of the twentieth century, however, conventional medicine has used placebos as methodologic tools to distinguish the specific from the nonspecific ingredients in treatments. In modern medical research, the double-blind, placebo-controlled, randomized clinical trial has been established as the gold standard for the assessment of any new treatment. Recently a new trend regarding placebos seems to have emerged. The placebo and other nonspecific effects elicited by the “healing situation” have been independently subjected to scientific study. Progress in this area may promote useful clinical applications, enabling physicians to broaden their perspectives on the healing process. We present the historical changes of the concept of placebo and the ethical issues raised by their use. Key Words: Placebo—Nocebo—Randomized controlled trials—Equivalence trials—Ethics—Response to the healing situation.

STAGE I: PLACEBOS

Basic concepts

In a group of untreated patients with depression, it is expected that a certain percentage will improve after a few weeks. With the administration of an inactive pill, the percentage may be higher, and even higher if an antidepressant is used. This example illustrates at least three hypotheses that may explain patients’ improvement after a certain therapy (12–16). First, a whole spectrum of “nonspecific” factors such as the natural course of the disease, the regression toward the mean, and other overt or covert influences may contribute to this healing through the time course of an untreated illness (17). Second, in the case of the active drug, the patients improved because of the “specific” or “characteristic” effects of the treatment that can be scientifically studied, isolated, and predicted through specifically designed studies, the randomized controlled trials (RCTs) (7,8). Finally, in the case of the “inert” therapy, it is obvious that the inactive pill, because it lacked a specific pharmacologic effect, response to the healing situation, as well as to discuss certain ethical issues raised from their use.

Socrates: “good doctors . . . (it) is not possible for them to attempt to treat the head by itself, apart from the body . . . or the body without the soul . . . . and the treatment of the soul by means of certain charms, and these charms are words of the right sort . . . ” Plato, Charmides (1)

The history of placebo follows the same pattern as other phenomena in science recognized as “artifacts” (2,3). For centuries, healers, including physicians, have used inactive placebos or “dummy pills” worldwide, although the official medical community ignored them (4–6). Next, the nonspecific placebo effect was studied, isolated, and eliminated in the randomized controlled trials as a nuisance factor, in contrast to the “specific” pharmacologic effect (7,8). Finally, the placebo effect or “the response to the healing situation” has recently become a subject of study in its own right, along with the exploration of its clinical usefulness (3,9–11).

The purpose of this article is to present the historical transition from placebos, to the placebo effect, and to the
acted therapeutically through its “symbolic power” and its impact on the patient’s imagination, beliefs, expectations, and emotions (7,12). Patients were under the impression that they were taking an active or specific drug with known efficacy for their condition. This therapy with the inert sugar pill lacking specific activity represents a typical example of what is called *placebo therapy*, and the “dummy” pill is called a *placebo* (from the Latin: “I shall please”) (4). Besides the administration of a drug, this nonspecific “therapy” can take the form of a physical (i.e., manipulation), psychological (i.e., conversation), or any other form of therapy.

The elicited and measurable response after the administration of a placebo, the ingestion of the inert pill, is called a placebo response. It may not necessarily be elicited by the symbolic characteristics of the inert pill but may constitute a “time effect,” such as spontaneous improvement (18). *Placebo effect* is the nonspecific psychophysiologic effect produced by placebos through the symbolic significance of the administered therapy (5). The “true” placebo effect may be estimated as the difference between the magnitude of the placebo response (“perceived placebo effect”) minus the magnitude of the “time effect” on untreated patients (“other nonspecific effect”) (17). In practice, however, distinguishing the “true” placebo effect from the “perceived placebo effect” is not easy (13,19,20). Actually, because these terms are hard to define precisely (13,21), it was suggested that they should be abandoned (19).

Nocebo (from the Latin: I shall harm) and nocebo effects are terms less familiar to physicians, used in cases when patients attach negative meanings and emotions to a treatment perceived as harmful. In contrast, the definition of a treatment as “placebo” depends on the degree of patients’ positive (beneficent) meanings and emotions toward it (22). The most common adverse effects of systemic placebos are headache and drowsiness (23). Placebos used in healthy volunteers usually cause negative effects because healthy persons anticipate no medical benefit (24).

In dealing with placebos, at least two important questions arise: first, does a clinically significant “true” placebo effect exist, and second, because their use, either in clinical practice or in research, almost invariably implies some form of deception, what are the ethical issues involved?

**Does a clinically significant “true” placebo effect exist?**

It is generally accepted that placebos are associated with powerful nonspecific effects (3,25–29). According to Oh (27), placebo is “the most effective medication known to science, subjected to more clinical trials than any other medication, yet generally always does better than anticipated. The range of susceptible conditions appears to be limitless.” The response is not limited to subjective (such as pain or anxiety) end points but also includes objective end points (such as blood pressure, EEG, serum hormone concentration), whereas the improvement can be long lasting (10,30,31). Double-blind RCTs have shown that placebos can have healing effects in diverse conditions as angina pectoris (32), epilepsy (33), and cancer (34).

The notion, however, of a powerful placebo has not been unchallenged. By reanalyzing the classic Beecher’s review (25), Kienle and Kiene (35) pointed to ≥19 possible reasons for the changes in the placebo-treated groups. They argued that the significance of the placebo effect has been grossly overestimated and that the reported placebo effect may not be a distinctive one but may be part of a spectrum of care and treatment (35). They further consider these reports as misleading, perpetuating widespread misconceptions about the magnitude of the placebo effect. Indeed, the placebo response rates quoted from clinical trials may indiscriminately include both the spontaneous and natural recovery from disease and the “true” placebo effect (15,17,35). Review of clinical trials with patients randomly assigned to either a placebo or no treatment showed small differences in clinical outcome, leading to the conclusion that there is little evidence to support the assertion that placebos have powerful clinical effects (36). Therefore, far from being resolved, the question of the existence and magnitude of a true placebo effect is valid and should be addressed by the scientific medical community.

**The ethics of giving placebos**

There are at least two distinct uses for placebos: in research as tools for reducing bias in clinical trials and in clinical practice for therapeutic purposes. In both cases, major ethical issues may arise whenever two key considerations or requirements, beneficence and autonomy, are violated. (37). *Beneficence* refers to the physician’s fundamental duty to respond according to the best interests of an individual patient by providing the best available treatment and optimal care to this patient (37,38). This old principle dates back to the Hippocratic code urging physicians to provide benefits to the patient and balancing them against risks: “As to diseases, make a habit of two things, to help, or at least to do no harm” (κοσεῖν περὶ τὰς νοσήματα δό, ὠφέληνέν ὢ μη βλάπτειν) (39). Conflicts may arise whenever the physician has the additional role of a researcher whose primary concern is to produce valid, generalized knowledge that may benefit future patients (40–42). Hence, research differs from optimized individual clinical treatment as it typically contains an element of increased risk. Administration of placebo instead of standard treatment, as it usually occurs in research, may be considered unethical because it places some people at risk for the good of others, future patients, and society (43). According to the Hippocratic code and the Declaration of Helsinki, the
physician’s role as a healer must take precedence over his role as a researcher. The advancement of scientific knowledge, therefore, must always be secondary to the concern for the individual, whose well-being is the physician’s highest priority. Nevertheless, physicians also have an ethical obligation to find better treatments for diseases (44); thus one duty may be at times in discord with the other.

Autonomy refers to the patient’s right to be informed about treatment options, the pros and cons of each, and to decide about health matters without coercion (37,38). For centuries, beneficence, in the form of benevolent paternalism, not truthfulness, was the modus operandi of physicians (7,45). During the second half of the twentieth century, however, autonomy became a major issue, and the new medical ethics replaced “beneficence” with “informed consent” (7). Violation of autonomy (deception) may occur whenever placebos are used without adequate patient information and consent. Because some form of deception is believed to be necessary for placebos to exert their effect, the patient’s autonomy is threatened by a (benevolent) paternalistic attitude that may influence physicians to administer placebos against the patient’s knowledge and consent (45). Deception can be detected by evaluating the patient’s understanding and voluntary participation, the two main components of the modern informed-consent process (46). The issue of autonomy becomes even more pressing in individuals with questionable capacity to consent (47).

Mechanism of the placebo action

As an example of the mind–body relations and compatible with a holistic view (27), the placebo effect offers unique opportunities to study the interplay of environmental, mental, and brain processes (48). Because the placebo effect seems to exist across all medical disciplines, a single universal theory that can explain all placebo effects is unlikely (4). Hence, several psychological and biologic explanations have been proposed (2,50). Currently two psychological theories, the classic conditioning theory and the expectation theory, have been used to account for the placebo effect.

According to the classic conditioning theory, a variety of inert substances, procedures, persons, or places, if associated with effective treatments (e.g., penicillin, insulin, morphine) come to function as conditioning stimuli eliciting similar responses to the unconditioning stimuli (51–53). Conversely, the expectation theory proposes that a special type of cognition called expectations or expectancies triggers the placebo response (54,55). It has been suggested that specific expectations, which reflect knowledge about the therapeutic agent, the circumstances under which it is administered, and the condition to be treated, are directly linked to the placebo effect (36).

The biologic approach aims at identifying pathways in the brain associated with the perception of a stimulus as “meaningful” in a healing-related sense, thus producing end-organ changes (57). Various “mind–body” healing pathways of the brain such as the endogenous opioid (58), the neuroendocrine (59), and the psychoneuroimmune pathways (60) have been implicated. Mental and emotional stimuli related to the placebo phenomena can reach the immune system through the autonomic nervous system and the neuroendocrine outflow via the pituitary, linking the brain to the immune system (60,61).

Although nothing is expected to be absorbed, distributed, and metabolized by the ingestion of an “inert” substance, placebos nevertheless display certain “pharmacologic,” behavioral, or physiologic characteristics noted in active drugs (62). “Peak effects,” “cumulative effects,” “carryover effects,” “tolerance,” and “dependence” are some of the subjective or behavioral characteristics of placebo administration (63,64). Similarly, placebo-generated perceptions can result in the production or release of active materials, or may influence the enterohepatic circulation or the local blood flow and the rate of the agonist turnover, thus leading to physiologic alterations (62).

STAGE TWO: PLACEBO EFFECT

For centuries, placebos were the most physicians could to offer their patients and through them maintain their reputation (5,26). In that regard, the history of medicine was the history of placebos (5). After World War II, as medicine adopted biologic principles, the “art” of healing was replaced by the “science” of therapeutics (65,66), and the traditional beneficence paternalism yielded to informed consent (67). As a result, the use of placebos for therapeutic purposes started to decline. Treatments with “specific” action replaced “nonspecific therapies,” and the principle of autonomy overrode the principle of benevolence. Therapeutic or even diagnostic use of placebo in noninformed patients, with rare exceptions in well-defined cases, is considered ethically unacceptable and may have detrimental effects on the patient–therapist relationship (20,41,68–70). Nevertheless, even today there are instances in which clinicians prescribe placebos, intentionally or unintentionally, in a covert (deceptive) form and frequently in the least-appropriate cases (71). This practice illustrates ignorance and prejudice (41) and can be considered nothing more than “a face-saving disguise for medical impotence” (72). For example, controlled studies have shown that vitamin C for cold prevention is ineffective, as are small doses of antidepressants, tricyclics in particular, for depression; yet both are common clinical practices (73,74), occasionally leading to serious side effects (75). It should be emphasized, however, that even if placebos were given in a direct, nondeceptive way (i.e., patients were informed about the inertness of the given substance), a placebo effect might still be obtained (76,77). This raises
PLACEBOS AND HEALING

PARIBUS

(ALL OTHER FACTS BEING EQUAL) (88).

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CONTROLLED RCTS, THE EXPERIMENTAL DRUG IS COMPARED WITH THE "NONSPECIFIC

ACTION" AND NOT WITH "NOTHING" (16,42,91). IT IS POSSIBLE THAT THE PLACEBO EFFECT ELICITED UNDER THESE CIRCUM-

STANCES MAY BE EVEN MORE POWERFUL THAN THAT OF EVERYDAY CLINICAL PRACTICE (92).

THE LONG-STANDING TRADITION OF CLINICAL USE OF PLACEBOS TO PROMOTE THE HEALING PROCESS WAS REPLACED BY THE INVESTIGATORS’ ATTEMPT TO DISENTANGLE, ISOLATE, AND REMOVE THE PLACEBO AND OTHER NONSPECIFIC EFFECTS FROM THE "SPECIFIC" ACTION (10,78). BEGINNING WITH THE STREPTOMY-


RANDOMIZED CONTROLLED TRIALS

THE RCT TECHNOLOGY OFFERS TWO DISTINCT WAYS TO SHOW THE EFFECTIVENESS OF A NEW TREATMENT: COMPARING IT WITH EITHER A PLACEBO OR AN ACTIVE THERAPY. EACH APPROACH HAS ITS PROS AND CONS.

PLACEBO-CONTROLLED TRIALS

THESE TRIALS AIM TO SHOW THAT THE EXPERIMENTAL TREATMENT IS SUPERIOR TO THE "NONSPECIFIC" ELEMENTS SOLIDIFIED AND ASSESSED THROUGH THE USE OF A PLACEBO ARM. THEY INTEND TO PROVE IF THE EXPERIMENTAL DRUG HAS ANY SPECIFIC OR PHARMACOLOGIC EFFECT (89). THE NONSPECIFIC ELEMENTS IN RCTS OFTEN INCLUDE MANY INFLUENCES, SUCH AS SUPPORT, ATTENTION, EDUCATION ABOUT THE TREATMENT OR THE ILLNESS, AND SO ON (49,90). HENCE, IN PLACEBO-CONTROLLED RCTS, THE EXPERIMENTAL DRUG IS COMPARED WITH THE "NONSPECIFIC TREATMENT" AND NOT WITH "NOTHING" (16,42,91). IT IS POSSIBLE THAT THE PLACEBO EFFECT ELICITED UNDER THESE CIRCUMSTANCES MAY BE EVEN MORE POWERFUL THAN THAT OF EVERYDAY CLINICAL PRACTICE (92).

ASSUMING THAT A PLACEBO-ARM STUDY WAS DESIGNED AND PERFORMED IN A SCIENTIFICALLY REASONABLE MANNER, A STATISTICALLY SIGNIFICANT DIFFERENCE FAVORING EITHER THE EXPERIMENTAL DRUG OVER PLACEBO OR VICE VERSA IS INFORMATIVE (93). THE FIRST OUTCOME SUGGESTS A SPECIFIC PHARMACOLOGIC EFFECT EXHIBITED BY THE NEW DRUG, WHEREAS THE OPPOSITE SUGGESTS LACK OF SUCH AN EFFECT AND/OR EVEN ADVERSE EFFECTS. A DEMONSTRATION OF A DIFFERENCE CAN SERVE AS COMPELLING EVIDENCE, DEFINED AS EVIDENCE THAT "ON ITS OWN, WITHOUT THE NEED FOR ANY SUPPLEMENTARY SANGUINE ASSUMPTION BASED ON ASSERTIONS ABOUT CONDITIONS EXTERNAL TO AN EXPERIMENT, LEADS TO ONE AND ONLY LOGICAL CONCLUSION ABOUT THE MEANING OF THE EVIDENCE ADDED IN THE RCT..." (93). THE ABSENCE OF DIFFERENCE IS NOT SO INFORMATIVE, BECAUSE THE NEW DRUG MAY LACK EFFICACY, BUT NOT NECESSARILY SO, FOR VARIOUS REASONS (93).


ACTIVE CONTROL "EQUIVALENCE" TRIALS

THESE TRIALS ARE USED TO SHOW THAT THE NEW THERAPY IS EQUIVALENT TO OR NOT WORSE THAN A KNOWN EFFECTIVE TREATMENT, EITHER AS AN ALTERNATIVE OR AS HAVING ADVANTAGES IN SAFETY, CONVENIENCE, OR COST (97,98). BECAUSE "EQUIVALENCE" OR "NONINFERIORITY" IS THE MOST PROBABLE EXPECTATION (SINGULARITY IS Seldom ASKED), THESE TRIALS HAVE BEEN CALLED "ACTIVE CONTROLLED EQUIVALENCE STUDIES" (99).

UNfortunately, A STUDY THAT SUCCESSFULLY SHOWS "EQUIVALENCE" IS UNINFORMATIVE, AS IT DOES NOT BY ITSELF DEMONSTRATE THAT BOTH TREATMENTS WERE EFFECTIVE. IT ALSO CAN MEAN THAT BOTH WERE INEFFECTIVE IN THE STUDY (93,97,100–103). THE CONCLUSION THAT THE NEW TREATMENT IS EFFECTIVE ON THE BASIS OF ITS SIMILARITY TO THE ACTIVE CONTROL REQUIRES THE CRITICAL ASSUMPTION THAT THE ACTIVE TREATMENT HAD AN EFFECT IN THAT PARTICULAR STUDY. ONLY IN TRIALS IN WHICH "SENSITIVITY" IS PROVEN (THAT IS THE STANDARD TREATMENT IS SUPERIOR TO PLACEBO) CAN CORRECT CONCLUSIONS OF EQUIVALENCE BE MADE. BUT SUCH AN ASSUMPTION CANNOT BE MAINTAINED, HOWEVER, AS IT IS KNOWN THAT ONE THIRD TO
one half of RCTs are negative, even when the standard therapy is known to be clinically effective (104). Clearly, a third group taking placebo is needed. Conversely, even if the experimental therapy is less effective than the active one, the possibility exists that it may still have clinical use for a subpopulation or because of a better side-effect profile. These advantages cannot be known without comparison to a placebo.

Active control equivalence trials can be informative in many areas such as treatment of cancer, infectious, and cardiovascular diseases, provided that assay sensitivity is not in doubt (97). Temple and Ellenberg (97) claimed that “the larger the effect size, the less study-to-study variability in outcomes, and the fewer the instances of unexplained failure of the control agent to show superiority to placebo in well-controlled studies, the more persuasive is the case for using this design.” The active control “equivalence” studies differ from “superiority” studies (i.e., studies designed to detect differences such as the placebo RCTs), in several important ways. The design and analysis of the former, as compared with the latter, are more complex and less precise scientifically (98,105). Among their disadvantages, the approval of drugs that are ineffective or have serious adverse effects remains the main concern (75,93,106). In addition, more patients are exposed to a possibly ineffective and dangerous drug as compared with placebo-controlled RCTs. They also may incur significant cost increase and delay in the process of drug development (44). These drawbacks raise ethical concerns, as it is obviously unethical to engage human subjects in research lacking scientific validity and unable to suggest interpretable conclusions. The most obvious advantage of the active control RCTs is that they pose no ethical dilemmas, if there is a “genuine uncertainty” about which of the two, or more, treatments tested is preferable [a condition known as “equipoise” (107)].

Placebo-controlled trials disputed
Researchers and U.S. Food and Drug Administration regulators (106) prefer and/or require placebo-controlled RCTs at least during the initial phase of establishing the efficacy and safety of a new drug and its superiority against placebo. The use of randomized placebo-controlled, double-blind clinical trial is considered the gold standard in research designs, as it is believed to provide the most definite test of efficacy (93,98). This doctrine, however, has recently been disputed (108,109), and the RCT trials using placebo arms have come under increasing attack on ethical and, perhaps less convincingly, methodologic grounds (110–116). Critics of the placebo-controlled RCTs consider it unethical to give patients placebos when an approved therapy exists, even if the required informed consent has been obtained, because patients are asked to participate in a medical trial with the intent to make sacrifices for the good of others (violation of the beneficence principle). These volunteer patients are exposed to the risks of harm from lack of treatment during their participation in the clinical trial. To support their arguments, these critics usually cite the following sentence from the Declaration of Helsinki in 1997: “In any medical study, every patient including those of a control group should by assured of the best proven diagnostic and therapeutic method” (117). Furthermore, the recent fifth revision of the Declaration of Helsinki in 2000 (118), that medical researchers and ethicists have agreed on, emphasizes in much clearer terms than ever before the already restricted conditions allowing the use of placebo in RCT. Researchers, drug companies, and journal editors may be profoundly affected, as the new principles are expected to tighten the rules for clinical research and use of placebos, putting new limitations on the risks to which patients may be exposed (119–122). Ethicists also raise objections to the use of placebo-controlled RCTs on methodologic grounds. Several researchers (89,90,93,94,97,100–102,123,124), however, have firmly disputed their assertion that placebo-controlled studies are not scientifically sound.

The future of placebos in research
The World Medical Association (WMA) decision is at odds, and clashes with the opinion of those who consider these recommendations impractical, interconflicted, and unattainable (90,94,97,124–127). A literal interpretation of the Declaration means that if an effective treatment exists for any condition, however benign it may be, the use of placebo control is unethical. Several problems arise with such a strict interpretation: first, the use of placebo control will be permissible in only a few cases (116,128). The main bulk of research will be instead conducted through active control equivalence trials with all the aforementioned problems, including the approval of ineffective therapies. As Khan and Brown (90) stated, “The elimination of placebo controls in favor of non-inferiority trials is not only bad science, it is bad for the public’s health.” Second, a strict interpretation of the declaration would exclude not only the use of placebo, but also active-control trials, because patients taking the investigational drug instead of the established therapy would not receive the “best” proven, current treatment (94,97). Any nontherapeutic or nonmedically indicated investigational procedure, such as magnetic resonance imaging (MRI) or positron emission tomography (PET), might also be restricted in clinical research if the same standard of individualized beneficence applied as in clinical medicine (42). Finally, a strict interpretation seems to preclude the free will of patients who, for their own reasons, choose to participate, such as self-interest, altruism, or the desire to “be treated as special patients” (129–131). This may appear as another form of revived
beneficent “paternalism” conflicting with and overpowering the “autonomy” principle (100).

The confusion over the use of placebo forced the WMA recently to establish a task force to investigate the issue and refine changes to the Declaration of Helsinki (132). Meanwhile, the International Conference for Harmonization (ICH) released a statement that considers ethical the use of placebo-arm RCT, even if an effective treatment is available for the condition under study, provided that no serious harm is expected from withholding available treatment, and patients are fully informed about existing therapies and consequences of delayed treatment (133). This report is in agreement with the appraisal of Temple and Ellenberg (97) from the FDA on the ethical and scientific issues of placebo-controlled trials.

It seems that a universal agreement exists that placebos can certainly be used, when no effective treatment exists, and should not to be used in life-threatening situations, when standard treatment exists (37, 97, 116, 128).

The task, therefore, of the research community is to evaluate specific cases that fall in between, balancing ethical and scientific considerations. Examples of the types of data that the research community may need, come from the work of Al-Khatib et al. (134) and Khan et al. (135). They evaluated through meta-analysis the risks of using placebo controls as opposed to the active drug condition in short–term treatment of mild to moderate hypertension and acute treatment of depression, correspondingly. They both found no additional risks from the use of the placebo as compared with those of the standard medication arm.

Furthermore, researchers should consider reducing the number of patients exposed to placebos. For example, because measurement errors are compensated by increasing the number of studied subjects (136), improvement of raters’ reliability through systematic training or use of multiple raters will reduce placebo requirements. Next, adaptive allocation designs aiming at reducing the number of patients receiving either ineffective and/or potentially dangerous treatments may be considered (137). In the “play the winner” design, the probability of ending up in one arm of the trial or the other depends on how well previous subjects responded to the treatment (138).

In such a paradigm, the better the experimental treatment, the greater the odds that the subsequent patient will be assigned to this study arm, and, therefore, the smaller the number of patients taking placebos. These types of adaptive allocation designs, however, are at their very beginning, are logistically complex, and lack supportive evidence (137).

Other strategies, common in cancer, heart failure, and epilepsy trials that seem to pose no ethical dilemmas, are the “add-on” designs in which the patient’s baseline medication is maintained and then either a placebo or the new investigational drug is added (97). Finally, clinically significant evidence may come from sources other than the RCT, when randomization is inappropriate, impossible, or unacceptable. Thus in spite of their limitations, well-designed observational studies can provide valuable information, because their results may not overestimate the magnitude of the therapeutic effect, as previously thought (139, 140).

It seems but erroneous that the use of placebos in RCT, the principal research tool or the gold standard, through which medicine in the twentieth century had made all its great therapeutic discoveries, is seriously challenged (7). Some expect that the use of placebos in research will progressively change or decrease as medical knowledge accumulates (105, 114), whereas others believed that the continued use of a placebo control group is vital (89, 141).

STAGE III: RESPONSE TO THE HEALING SITUATION

In spite of its impressive progress, medicine has been strongly criticized that by relying on its modern biomedical tradition has neglected the psychosocial aspects of health (142). The price is significant, leading among others to patients’ dissatisfaction and use of alternative health approaches associated with allegedly powerful nonspecific effects (67, 143, 144). The last approaches are often described with such desirable characteristics as Hippocratic, integrative, preventive, and holistic, whereas conventional medicine suffers by being considered galenic, analytic, curative, and specific (145).

The accumulated knowledge on placebo and the other nonspecific effects of medical care may offer medicine a unique opportunity scientifically to explore and expand the therapeutic processes within a broader biopsychosocial framework and, therefore, a more integrative, yet scientific, approach. Physicians may learn how to use these effects in a nondeceptive and ethically acceptable manner. This can be possible because the administration of a placebo is neither a necessary nor a sufficient condition for the initiation of a placebo effect (3, 146). Not only placebos but also any feature of the nonspecific elements (concomitants) of the physician–patient encounter may recruit the healing response. Hence, it is probably more appropriate to speak of the “response to the healing situation” than of the “placebo response” (3). Instead of, therefore, being conceptualized as the product of placebo administration (5), the placebo effect can be redefined as any effect attributable to the symbolic importance of a treatment, treatment setting, or treatment process (11). This reconceptualization bypasses the controversial issue of the existence or the magnitude of the placebo effect as it encompasses all the nonspecific influences. In addition, because the elicited effect is not solely dependent on placebo administration, it has the potential of being ethically immune.
It seems that a new era in the life of an artifact has come of age, and the growing debate on ethics (87,108) as well as the changing face of medical curricula (147) may be instrumental in this transition. The phenomena of placebo and the other nonspecific effects have become objects of scientific scrutiny on their own right.

Harnessing the placebo effect

By recognizing the importance of the response to the healing environment, the clinician should be interested in developing strategies to optimize this effect in clinical practice (3,9–11,148). The new “healing art,” however, is in its infancy, lacking a conceptually elaborated and empirically tested body of knowledge. As opposed to a placebo-elicited effect that has been systematically studied, there are only few studies of the “response to the healing situation” (3). It is still unknown which of the nonspecific factors and to what extent each of them contributes to the healing effect. Future research should address these questions in studies comparing two situations differing in only one nonspecific factor (14,49). The need for a multidisciplinary approach to formulate the most important questions pertinent to the nonspecific factors in the healing process is mandatory (2,50,92,148).

At the moment, various attempts and suggestions are based on physicians’ clinical experience and some principles drawn from psychological, conditioning, or expectation theories (3,9,11). It is possible that in the future, this healing potential may be deliberately mobilized on an evidence-based manner or invoked in other ways, such as biochemical. Psychosocially or biochemically enhanced, the response to the healing situation can be incorporated into standard pharmacologic and surgical treatments to act synergistically with them, thus providing the medical healing art with a strong integrative and holistic trend. At least theoretically, the placebo effect depends on the patient, the dispensing physician, and prominent between them, the quality of their relationship (10).

Physician–patient relationship

The value of a sound patient–physician relationship has been historically recognized and is considered the cornerstone for achieving, maintaining, and improving health (149). We do not know the key elements of such an ideal relationship and whether they influence the placebo effect.

During the past three decades, the patient–physician relationship has changed more than during the preceding 25 centuries. It cannot any longer be seen as a kind of parent–child relationship, but rather as one between two morally autonomous adults (150). And although the desirable characteristics change over time, the respect for the patient’s autonomy is the core of such an ideal relationship (149). Empathic “listening” that requires appropriate emotional involvement appears to be a basic, nonspecific, healing-promoting component, yet neglected during the modern era. Instead, “seeing” became the primary tool in knowing and understanding during the healing endeavors (151). It has been estimated that the mean length of time that elapses before doctors interrupt the patient’s first response is 18 s (152). As Sir Theodore Fox wrote, “Lack of time made us all bad doctors” (153).

The recent rise of medical interest in the lost tradition of narrative may force physicians to listen more constructively to their patients (154–157). Both patients’ verbal and nonverbal communication should be taken into account, with encouragement to voice their agenda concerning covert fears and hopes (158).

Because doctors and patients talk to each other with different “voices,” it is the doctors’ duty to smooth communication by explaining in clear and comprehensible language the diagnostic, prognostic, and therapeutic aspects of the illness. Additionally, physicians must be sensitive to cultural differences and understand how patients’ models of health and disease affect their beliefs and behaviors (159–161). Patients vary in their desire for involvement in decision making, so the degree of their participation cannot be predetermined, being in need of constant revision throughout the therapeutic endeavor and monitored according to individual needs (158,162–164).

The patient and his or her illness

Placebo history

At one time it was thought that only a specific type of individual responded to placebo, a consistent placebo reactor (165,166), but such an individual has not been identified, and no type of personality is prone to a consistent placebo-elicited effect (167). Hence, physicians must try to elicit the “placebogenic” and/or “nocebo-genic” aspects of each individual patient with a particular disease, positive and negative nonspecific effects in the patient’s previous beliefs and experiences with treatments (background placebo variables), as well as attitudes toward the present illness, and faith in or distrust of a particular physician or form of treatment (situational placebo variables) (9,168). This type of history will provide the physician with valuable information to determine the conditions favoring a placebo effect.

The illness

Although the establishment of predictable placebo response patterns to particular disorders has been proven difficult, the physician should be aware of the limits and potentials of placebo use in each illness. The most thoroughly studied placebo-responsive disorders are chronic pain and psychiatric illnesses (23). Generally, the presence of anxiety and pain, the involvement of the autonomic nervous system, and the immunobiochemical
processes are believed to respond favorably to placebo, whereas hyperacute illnesses (i.e., heart attack), chronic degenerative diseases, or hereditary diseases are expected to resist (27). Conversely, different diseases invoke different meanings for each individual. An encounter with a physician is most likely to produce a placebo effect when it changes the meaning of the illness experience for that individual in a positive direction. This is most likely to occur when the patient is listened to and receives an explanation for the illness that makes sense; the patient feels care and concern by the physician and others in the environment, and experiences an enhanced sense of mastery or control over the illness or its symptoms (11). The physician, however, must be cautious not to raise false hopes that may produce further disappointment.

**The physician and the treatment setting**

The presence of a physician is the most common factor able to induce a placebo effect, the most frequently used “drug” in general practice (57). Furthermore, a well-informed physician, without misconceptions, (31,169) may intentionally use placebo knowledge to optimize the placebo effect in various ways (3,9–11,51).

**Predictive accuracy as a placebo-elicited tool**

According to learning theory, there are at least two reasons for the physician’s strong “placebogenic power” (51). First, the physician possesses treatments with “specific” effects tested by RCTs therapeutic ingredients. The more effective a treatment, the bigger the placebo effect and the placebogenic power of the physician. Second, the physician has exceptional diagnostic and prognostic abilities that represent another source of placebogenesis for the patient, who may confuse them with the physician’s healing potential. Accurate diagnosis and prognosis are, therefore, important tools at the physician’s disposition, because, if properly handled, they bear significant possibilities for eliciting a placebo effect (3,9).

**Appropriate referrals for testing–reassurance**

While certain referrals and diagnostic tests are necessary and self-reassuring, oftentimes ordering laboratory tests, primarily for reassurance purposes, may not be the best strategy and definitely is not without problems (170). The diagnostic tests may leave a patient more anxious than before unless the true fears are addressed (171). Thus a false-positive test result will not allow reassurance; an inconclusive result may leave doubt and anxiety, and reassurance may not be entirely successful despite a normal test result (170). Obtaining a test should be avoided if an expert clinical opinion suffices because of the risk of residual anxiety and the epidemiologic hazard of a false-positive or inconclusive test result (170). The current skepticism about the benefit/risk ratio of procedures like mammography for breast cancer (172), or cholesterol for ischemic heart disease (173), seems to be relevant to the issue of referral.

**The art of prescribing**

Practitioners tend to prescribe more medications than patients expect, possibly because they fail to consider the patients’ reason for coming (174). From a placebo perspective, a prescription, if needed, should preferably combine the specific ingredients with nonspecific, placebo-promoting concomitants revealed during the placebo history-taking procedure (9). The prescription should be offered with realistic optimism because the placebo effect depends on the confidence of the therapist (175). Based on the placebo-promoting effect of predictive accuracy, the physician should inform the patient about the time course of the effect and possible adverse effects of the treatment (9). A patient who responded well to a particular treatment in the past should be considered to receive the same in case of a recurrence, especially if the disorder is relatively minor, definite treatment does not exist, the prior treatment was not dangerous, or the patient is convinced that the treatment works (9).

**Perceptual characteristics of the treatment**

The potentially important effect of these characteristics is recognized in RCTs, in which various measures are taken to isolate them. From the plethora of these factors and guided by information obtained during the placebo history, physicians may choose treatments whose perceptive characteristics are possibly associated with strong placebo effects. For example, a new treatment, irrespective of the specific effect, appears more effective than an old one (5), or capsules more potent than tablets in anxiety states (176); generally, the more invasive a treatment or the more actively it involves the patient, the larger the placebo effect (177). The color of the pill seems to influence its effectiveness (178), but consistent trends are not universally apparent (148).

The name of the drug is generally considered to possess tremendous symbolic and practical significance. Creating a generic name is a scientific task, but finding a brand name seems to be more an art (179). The FDA forbids use of words that make promises and raise expectations and hopes about cure or safety, but drugs with allusive names implying actions far beyond the known pharmacologic actions of a given product are not uncommon (180).

**Conceptual characteristics of the treatment**

Besides its perceptual aspects, a treatment also has particular meanings for each patient. Physicians, however, who focus their efforts primarily on properties of drugs and their effects often ignore the psychological and behavioral aspects of taking a medication (181). Thus on a personal level, the patient might hold a beneficent or
harmful view on the treatment offered. On an interper-
sonal level, the physician may be perceived by the pa-
tient as caring, and the treatment offered becomes a
token of the physician’s care; the pill also may symbolize
the physician’s substitution of a personal relationship
with the patient with something inanimate and inferior.
Finally, on a social level, the sick role assigned to a
patient might be interpreted either in a constructive or
nonconstructive (i.e., a stigma) way. The physician’s
task is to explore these nonpharmacologic meanings, and
if negative (“nocebogenic”), to try to reconstruct them.
Such interventions may have a profound effect on the
outcome by influencing, for example, compliance.

Compliance (Adherence)

Large-scale trials of drugs for heart disease have
shown that patients who adhere to treatment, even when
that treatment is a placebo, have better outcomes than do
poorly complying patients (182). In view of the impor-
tance of compliance, several attempts to increase it have
been undertaken with rather modest success (183). Modifi-
cation of patient’s “nocebogenic” meanings regarding
the treatment might enhance compliance and the healing
effect (184).

Conclusions

Whereas the use of placebos as methodologic research
tools and the decline of their clinical use characterized
the last half of the twentieth century, a recent trend has
emerged. In the third millennium, placebo phenomena
seem to enter their third phase, a phase of maturity in
which the use of placebos for research has become more
parsimonious, whereas their clinical usefulness is in de-
cline. Instead, physicians have started to learn more
about the therapeutic environment and its healing poten-
tial, so in addition to their scientific approach, they will
be able deliberately to use placebo-related knowledge
synergistically to be more effective and in an ethically
acceptable way. It is the physician’s duty to respect the
benefit of “the response to the healing situation” and
bring its full advantage into everyday practice. Such a
task requires knowledge of the placebo phenomena. Cur-
rently, physicians receive little or no formal training in
placebo knowledge and manipulation. This lack of edu-
cation can be inferred from the many medical myths
surrounding the placebo phenomenon (31). A curriculum
for medical students and residents covering the concepts
and clinical implications of placebo phenomena would
fill in the gaps in conventional training and allow phys-
sicians to broaden their perspective on the healing pro-
cess (23,185).

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