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Placebo Research: The Evidence Base for Harnessing Self-Healing Capacities

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ABSTRACT

Placebo effects are often considered irrelevant at best and a nuisance at worst for determining what is valuable in medicine. In this paper, we argue that research that involves placebo provides critical information for how the mind, body, and culture heal. Following a newly proposed definition of placebo as a therapeutic meaning response, empirical evidence is reviewed that emphasizes the importance of these effects for developing a science of healing. It is likely that the effects resulting from the individual meaning of an intervention are an important factor of any therapeutic approach. It would be therapeutically desirable to maximize these factors and have good evidence on which to base healing interventions. We show how this could be achieved.

INTRODUCTION

Until recently, many authors dealing with placebo effects were not interested in the placebo effect as such, nor in conceptual clarity. Rather, they combined a number of possible confounding factors such as spontaneous remission, measurement artifacts, and regression to the mean, all under the heading of "placebo."[1–4] This has fueled a debate and obscured the real issue, namely, whether psychologic processes and social contexts that facilitate hope, expectation, positive feelings, relief of anxiety and anticipation of improvement are able to truly affect physiologic processes, and contribute to healing over and above pharmacologically mediated processes.

It is necessary to distinguish between the true placebo effect and artifacts.[5] Placebo-controlled clinical trials normally cannot distinguish between a true therapeutic response and other confounding factors.[6] Hence, it is not helpful to average improvement rates of placebo arms of clinical trials to find out about the magnitude of the placebo effect. However, evidence from the psychologic literature, and from experiments especially targeting the question of mechanisms of placebo effects, are beginning to clarify the message that behind the facade of what we normally call placebo effects are the self-healing capacities of the person, a fact normally neglected. We argue in this review that this body of literature teaches how we could maximize healing by harnessing these factors in any therapeutic context.

HISTORY OF THE NOTION OF PLACEBO AND THE MEANING RESPONSE

The term "placebo" derives from the Latin psalm verse, "*placebo Domino in regione vivorum*" (Psalm 116:6 modern counting): I shall please the Lord in the land of the living.[7,8] This psalm was part of the prayers offered at the deathbed in the Middle Ages. At later times, it was customary to pay others to sing the rites. Hence the connotation of "placebo" emerged as a fraudulent replacement of the real. Placebos were popular in the era of medicine when effective pharmacologic interventions were scarce and often fraught with side effects. The emergence of randomized controlled trials (RCT) tagged the placebo as all those "unreal" effects that were not the result of pharmacologic interventions.[9] Today, "placebos" normally mean inert substances that are given to subjects, mostly in the context of a scientific study, to control for psychologic and social or nonspecific effects of treatment.

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The many attempts at a definition of placebo effects all have one thing in common.[10] They all define placebo effects as something negative. As either the psychologic (side) effect of an intervention, as unintended effects, as nonspecific effects or even as effects caused by a pharmacologically inert substance. A more useful definition has been presented recently by Moerman and Jonas,[11] based on similar and earlier work by Brody[12]: Placebo response is defined as the effect that is due to the meaning of a therapeutic intervention for a particular patient and context. This new definition has two virtues:

1. It is a semiotic definition in that it acknowledges that humans are not deterministic machines reacting to mechanical causes (e.g., pharmacologic agents). Rather, they are responding to signs and the meaning those signs generate in a highly complex, often self-determined and sometimes unpredictable fashion.[13] The meaning is something that is not fully determined by the external stimuli themselves, but arises from the interaction between the external environment and the internal conditions of persons, their history, their social circumstances, their individual predilections and their expectations.
2. The meaning response definition allows the context factors of an intervention to enter the stage. This definition underlines the individual differences in response to otherwise similar conditions, and brings into focus the importance of individuality in therapy. This makes plausible why one and the same situation, for instance surgery, may arouse hope in one patient and induce fright in another with completely different physiologic reactions and clinical outcomes.

ARE PLACEBO EFFECTS REAL? COMPARISON BETWEEN PLACEBO GROUPS AND UNTREATED GROUPS IN CLINICAL TRIALS

Two-armed clinical trials with one placebo group do not tell us much about the placebo effect, because both groups control for many different factors affecting treatment apart from the real intervention. Therefore, reviews of three-armed trials are preferred. A meta-analysis of 130 three-armed trials that included only randomized studies compared the placebo arms of those studies against the untreated controls.[14] It yielded equivocal results: those studies with binary outcomes showed a small effect of a relative risk = 0.95 (95% confidence interval [CI]: 0.88 to 1.02). Studies with continuous outcomes, mostly visual analogue scale (VAS) measures of pain, showed a small, but significant effect of $d = -0.28$ (95% CI: -0.38 to -0.19). These results suggest that in those trials, true placebo effects compared to natural history are therapeutically not very important, because effect sizes are rather small.

The study, while methodologically sound, can be criticized on three grounds: (1) by restricting the analysis only to randomized studies, many intriguing results from earlier studies that were not randomized were discarded. Many of those studies show clear and impressive results.[15] Also, treatments that were not pharmacologic were dismissed, thereby not including the effects of many healing interventions such as psychotherapy. A more narrative and qualitative approach shows that the evidence is in favor of effects of placebo interventions compared to no treatment.[10] (2) A recent review[14] did not consider what type of placebo intervention had been administered. For instance, a study had been included that compared the administration of an analgesic in still unconscious patients after surgery to placebo and no treatment.[16] It is hardly surprising no placebo effect was observed. (3) No attempt was made to differentiate between studies that used measures to maximize the placebo effect and those that tried to minimize it or did not pay attention to it.[17] If the 23 studies that used placebo as a control procedure are analyzed separately and compared with 14 studies that tried to maximize meaning responses through suggestions, there is a clear and significant difference between those two sets of effect sizes. Studies that did not attempt to maximize meaning responses showed an effect size of $d = 0.15$ of placebo against no treatment, and studies that tried to enhance meaning responses had an effect size of $d = 0.95$, which is both significantly different and clinically important.

An indirect attempt at quantifying placebo effects against no treatment controls was made by Kirsch and Sapirstein.[18] In a meta-analysis of 19 antidepressant medication trials, they looked at improvement rates with antidepressants and placebos. Additionally, they compared the improvement rates obtained in the placebo groups of the antidepressant trials with those of the effects of psychotherapy trials that had included waiting list control groups. Thus, their comparison with no-treatment controls was indirect and weaker, although the populations in the two sets of studies were comparable. They found a medium effect of $d = 0.39$ for the comparison between pharmacologic intervention and placebos, and an effect of $d = 1.6$ for the comparison between psychotherapy and no treatment. By indirect comparison, the authors estimate the placebo effect against no treatment to be $d = 0.79$, which is sizeable, but less than the one reported by Vase et al.[17]

These results show that there is a beneficial effect of placebo administration in the context of clinical trials over and above natural history, spontaneous remission, and regression to the mean.

CONTEXT AND EXPECTATION

The meaning model of the placebo effect suggests that the context within which a treatment is offered changes its meaning and hence its effects. This has been supported by

a systematic review[19] that included studies that offered a treatment and the corresponding placebo under different conditions. This review concluded that neither interventions nor placebos are indifferent to meaning and context factors. Treatments can be more effective than their placebos or vice versa depending on those context factors. An example is the study by Bergman et al.[20] in which the same trial was conducted twice. Patients with cancer who regularly received naproxen as a routine analgesic were either given their normal bedside medication or a placebo. Some knew they were part of a trial, and some were informed about the trial and knew that they would be randomized to either naproxen or placebo. Informed patients who received the active medication had the greatest pain relief, followed by their placebo counterparts. Patients who had received placebo in the formal trial had greater pain relief than the patients who had received the normal naproxen medication without knowing that they were part of the trial.

Thus, expectation of potential effects is important. Another example is a study of the effects of analgesics in postpartum pain in two separate trials, one with paracetamol against placebo, and one with paracetamol against naproxen. Patients were informed in one study they would be receiving placebo with a chance of 50%, and in the other study one of two active medications. The difference in effectiveness of paracetamol was 20 mm on a 100-mm VAS between the trials with all other variables including researchers, setting, time, and patient population being the same.[21–23]

Another trial illustrates how expectancy is a factor mediating a meaning response. In a study comparing the experimental drug to sumatriptane, an established drug and placebo, the ethics committee decreed that the randomization ratio to placebo should be 16:1, because it is known that triptanes are effective and hence as few patients as possible should be exposed to the risk of placebo. This study was unable to show superiority of any of the two active drugs against placebo.[24,25] The active medication showed an effect in 42% of the cases, and the placebo an effect in 38%. Because patients in the placebo group knew the randomization ratio, they had a strong hope and expectation of actually receiving active treatment, and it was this expectation that contributed to the strong effect. A meta-analysis of all triptane studies[26] shows that those studies that had a randomization ratio to placebo different from 1:1, and hence provided a greater likelihood for patients to expect real treatment, yielded higher placebo response rates than studies with symmetrical randomization. The authors conclude that ethical requirements threaten scientific progress if they require unsymmetrical randomization ratios, which in turn drive patients' expectations, which again inflate placebo response rates due to these expectations.

Supportive evidence of the importance of such expectations resulting from the context comes from a meta-analysis that studied the question whether more frequent application of placebos yields larger effects.[27] The authors compared interventions of acid blockers in ulcers. Earlier drugs had to be taken four times per day, while the newer drugs had to be taken only twice a day. They compared the placebo response rates in 51 studies with a regimen of four times per day dosage with 28 studies with a twice daily dose. Although the difference in the response rate of the placebo groups is only 6% to 8%, the effect is significant with a number needed to treat of 14. This suggests that the more frequent application of a drug raises different expectations than an application twice daily to the point of needing to treat 14 more patients with a twice per day regimen to obtain the same effect as a four times per day regiment.

Perhaps one of the most direct proofs for the power of expectation is a recent experimental study on irritable bowel syndrome.[28] Thirteen (13) patients received an experimental rectal distention and heat stimulus as a pain stimulant to test different analgesic interventions. Apart from the natural history of the pain, each patient received in randomized order all of the following interventions: rectal lidocaine, oral lidocaine, rectal placebo (a lubricant) with the suggestion of improvement, and rectal placebo with the suggestion of potential aggravation (i.e., a nocebo intervention). Desire for pain control and expectation of pain reduction were also measured. There was a highly significant effect for the placebo intervention, the oral and the rectal lidocaine compared to natural history. While neither the rectal nor the oral lidocaine were distinguishable from the placebo, the nocebo intervention produced a nonsignificant increase in pain perception. The effect size of placebo-pain reduction versus natural history was $d = 2.0$, and versus nocebo was $d = 2.27$. Desire and expectation of pain control could explain 77% of the variance in pain ratings in a regression model for placebo and 81% for lidocaine. Thus, expectation was the most important factor in this study, even for the effectiveness of the pharmaceutically active agent. The authors underline that it was probably important that the same physician who treated the patients in a normal context was responsible for the experimental interventions, and thus these effects might depend on a good relationship between the patients and the physician.

The same conclusions can be drawn from a recent clinical trial of massage, acupuncture, and self-education in 262 patients with chronic low-back pain. This trial showed massage and self-education were superior to acupuncture after a year.[29] This trial also assessed general and specific expectation of patients and reanalyzed the data according to expectations.[30] Those patients who had the largest expectation of change for a specific treatment had the largest therapeutic benefit. When all other factors were controlled statistically, specific expectation alone showed a significant odds ratio (OR) of 5.3, meaning that patients with high expectation had a fivefold chance of benefiting from the treatment, all other things being equal. The authors underline that this effect of expectation was larger than the treatment effect in comparable low-back pain trials.

Taken together, these data show that expectation is probably the most important meaning factor of a treatment, and can be as powerful as a specific pharmacologic intervention. It is plausible, then, to suppose that the meaning response is nourished to a large extent by the expectation a specific treatment raises in patients.

SUGGESTION AND EXPECTATION

Expectations may be indirectly altered or manipulated directly by suggestion. The power of suggestion historically was brought to the attention of the scientific community by the investigation of Mesmerism in Paris 1784.[9] These studies showed that the claims made by the followers of Mesmer, at least in formal studies, were largely the result of suggestions, as the effects could only be seen when therapist and subject had visible contact, allowing subtle communication.[31,32] The interest in suggestion waned with the rise of behaviorism and later cognitive therapy. Interest in suggestion now is increasing,[33] as the neurosciences are able to measure and better understand the intricate complexities of subconscious and preattentive processes.[34,35]

Suggestion and the subconscious processes it triggers may be the link between the meaning of an external situation and physiologic responses. In many ways placebo effects are akin to therapeutic hypnosis,[15,36] with the difference being that in hypnosis a patient actively and willingly agrees to the procedure. The clarifying psychological literature is vast and has been reviewed elsewhere.[15] However, there are relevant aspects that highlight the mechanisms of healing. In a convincing piece of evidence for the physiologic effectiveness of suggestions, Butler and Steptoe[37] gave a water aerosol as an inhalant to 12 subjects with asthma using a balanced, crossover experimental study. While initially subjects were told the aerosol was a bronchodilator, in later sessions it was described as a powerful bronchoconstrictor. The placebo, given with the suggestion of bronchodilation, was able to reverse the suggested bronchoconstrictive effect, both compared to the control situation and the baseline reference measurement.

Psychologic research has studied several pharmacologically active substances, such as caffeine, alcohol, or cannabis, comparing their pharmacologic to psychological properties in balanced placebo design.[38] This design balances substance and expectation in a 2-by-2 factorial design, with one factor being the substance versus placebo. The other factor manipulates meaning by giving either correct or misleading information. This design allows for a separation of pharmacological and psychological effects of substances,[39] and the demonstration of the effects of suggestion. The first review[38] showed that strong effects of expectancy can be observed and vary by the setting. For instance, in studies on sexual arousal, subjects either receive alcohol or an appropriate placebo (normally tonic with a few drops of vodka sprinkled on top) and expectancy manipulations, and then view stimulating visual material. Here, expectancy of receiving alcohol produces strong effects, independent of the substance actually ingested. Measures in these studies were objective measures of sexual arousal, such as penile erection or vaginal blood flow, that address social desirability.[2]

A quantitative meta-analysis of 34 studies on alcohol and alcohol expectancy has found small but significant effects of expectancy.[40] Across all studies, the effect of alcohol is significantly different from zero, $g = 0.18$ (effect size measure Hedge's g, similar to the normally used Cohen's d). The effect of expectation is smaller, but also significantly different from zero, $g = 0.08$. What is more important is the fact that expectancy effects can be quite sizeable and even larger than those of alcohol in situations, whereas the social setting, but not necessarily the pharmacology of alcohol, suggests alcohol should have an effect such as settings of antisocial behavior ($g = 0.4$), sexual arousal ($g = 0.3$), or craving ($g = 0.5$). When interpreting these data, it is important to recognize that the amount of alcohol used in these studies was small, normally equivalent to one drink (a can of beer, a glass of wine). In addition, experimental models are only proxies for clinical situations in which patients are differently motivated by their desire to get healthy again. Recent studies have been published supporting the results of earlier studies.[41–46]

MECHANISMS: ENDORPHINS, CONDITIONING, AND CENTRAL PROCESSES

Endorphins

When Levine et al.[47–52] published findings on the reversal of placebo analgesia by the administration of naloxone, they thought they had solved the placebo puzzle. In these studies, patients suffering from either postoperative or experimental pain, received either a placebo infusion without their knowledge through a covered indwelling line, or naloxone, an opiate antagonist. With their knowledge, they then received another placebo injection that was claimed to be either a potent analgesic or a control substance. Levine and colleagues observed that the opiate antagonist reversed or attenuated a placebo analgesia produced by the suggestion of administering an alleged painkiller. They concluded that the substances responsible for this effect must be endogenous opiates, which mediate centrally modulated pain and analgesia.[53,54] Later studies,[55,56] with added new controls or more sophisticated procedures,[57,58] basically replicated the initial findings of Levine and colleagues. A paper reviewing this evidence concludes that the effects are real and mediated by endogenous opiates.[59]

The same conclusion was reached indirectly by Lichtigfeld and Gillman,[60] with the addition of the central role of

nitric oxide to the placebo response. These researchers conducted studies on the effects of nitric oxide in postwithdrawal depression of alcoholics. When titrated and administered in low doses such that patients remain conscious, nitric oxide, normally a potent narcotic, relieves withdrawal depression quickly and effectively.[61–64] This psychotropic analgesic nitric oxide (PAN) is superior to placebo (air)[61] even though the response rate to this placebo can be as high as 50% of cases. Because PAN is effective in alleviating 95% of the cases of postwithdrawal depression, the authors conclude that the endogeneous opiate system must be involved. Because medical air and oxygen have the same effect in many cases, this effect must be the result of activation of the endogenous opiate system. This is also suggested by Stefano et al.[65] who imply that endogenous nitric oxide is the hub around which both the immunologic and the affective effects of placebo revolve.

Expectancy versus conditioning

Is this system activated by expectancy or by conditioning, or both? That autonomous processes can be subject to conditioning has been uncontested since Ader's groundbreaking studies on conditioning immune responses in rats.[66,67] These studies make plausible that autonomous processes, such as the activation of the immune system or a neurotransmitter system, could be reinforced by operant conditioning or by a keying stimulus as in classic conditioning. Thus, placebo effects could be conceived of as conditioned reactions.[68] On the other hand, social cognitive theorists suggest that the placebo effect is controlled by response expectancies[69]: if a response is expected by an organism, it is more likely to happen. There are studies supporting a conditioning model,[70–72] as well as studies supporting expectancy models. Current evidence suggests that the conditioning effect is mediated by expectancies.[73,74]

Benedetti and colleagues[58,75–84] have presented evidence both for the reality and clinical relevance of placebo effects and their mechanisms through different neurotransmitter systems. There are some pertinent points relevant to healing effects in these complex experiments. First, natural history control groups were run, showing that the effects in the placebo groups are clearly different from the effects in notreatment control groups. Thus, the effects of placebo are not merely artifacts. Second, these studies show both that not only are endogenous opiate systems involved in placebo analgesia, but specific information and meaning given to a patient can modulate specific receptor families involved in producing analgesia and direct those effects to certain areas of the body. For instance, cholecystokinine (CCK) antagonizes morphine effects that operate via opiate receptors. Proglumide is an antidote to CCK, and therefore acts synergistically with opiates. It was shown that proglumide not only potentiates placebo-mediated analgesia,[84] but also operates via different receptor systems independently from those that are affected by naloxone.[58] These opiate dependent effects can be targeted toward specific body parts,[80] a finding that supports the expectancy hypothesis. There are also objective effects (i.e., depression of lung function). Such objective opiate-dependent effects cannot be explained by expectancy, and likely are conditioned.[81] There seem to be two systems active, both of which are mediated by endogenous opiates. One operates via expectancies, and the other operates via conditioning. Additionally, there seem to be conditioned effects which are not dependent on opiates.[79]

Response expectancies are also effective in clinically relevant settings such as postoperative pain.[78] The effect of expectancy was determined by open (unblinded) or hidden (blinded) administration of analgesics to patients, postoperatively or experimentally, without administering placebo. Open administration involved an arousal of expectancies and produced significantly stronger effects.[77] Similar findings were found with patients suffering from Parkinson's disease,[76] who had had subthalamic electrodes implanted to stimulate dopaminergic neurons. In one condition, they were told about the actual stimulation levels and their reduction. In another condition, they expected the stimulation to be active but it was in fact reduced. After 30 minutes, significantly different effects in motor tasks were seen, indicating that endogenic processes were activated by the expectation. The most recent study[75] has shown a clear effect of expectation in a pain model while heart rate variability measures were also taken. Given as an alleged analgesic, placebo reduced pain and the low-frequency power spectrum component of heart rate variability caused by sympathetic activation. This effect was antagonized by naloxone, again supporting evidence that endogenous opioids are responsible for the mediation of this expectancy effect. It remains to be seen which class of opioids influencing the parasympathetic system is responsible for these effects.

There seem to be several processes that mediate meaning responses, depending on the paradigm and the context. It is reasonable to assume that neurotransmitters such as the endogenous opioids have a role. It is also likely other systems like dopaminergic pathways[85] mediate these effects. If central neurotransmitter systems are active in mobilizing expectation effects, it is also plausible that many other effects in addition to pain alleviation or antidepressant responses[85,86] are mediated by those systems. It is well-known, for example, that practically every neurotransmitter,[87] including endogenous opioids[88,89] and serotonin,[90–92] have immunomodulatory effects.

Imaging placebo effects

There are two primary opiate networks in the brain, one in the brainstem, and one in the cortex, involving the rostral anterior cingulate cortex, (rACC) and the ventromedial prefrontal cortex, respectively. In an experimental, counterbalanced, within-subject design, nine subjects received heat or warmth, followed by opiate or placebo, while their re-

gional cerebral blood flow was monitored.[93] It could be demonstrated that in placebo responders, the same areas are active during placebo analgesia as with opiates, namely the nuclei in the rACC. Nuclei in the pons covaried with the activities of the rACC. Notably, the activation of the rACC was only seen in placebo responders.

Another part of the puzzle has been illuminated by a positron emission tomography (PET) imaging study of the effects of apomorphin and placebo on dopamine release in patients with Parkinson's disease.[94] The study utilized the competition of radioactively marked raclopride (RAC) and endogenous dopamine. The authors observed a 17% and 19% diminuation of RAC by placebo administration in the nucleus caudatus and the putamen, respectively. Both areas contain many dopamine producing neurons. This finding suggests that patients expecting dopaminergic pharmacological effects will produce dopamine. Dopamine is an important neurotransmitter which activates the reward system,[95] and is important in learning.[86,96,97] Thus, this finding illustrates how placebo may produce effects beyond pain relief and influence areas such as affect, learning and motivation.

An imaging study of placebo effects in an antidepression study using the selective serotonin reuptake inhibitor (SSRI) fluoxetine showed a clear overlap of areas activated in placebo responders and drug treatment responders.[98] While activation of the thalamus was reduced in both groups and activation of prefrontal areas enhanced, fluoxetine showed enhanced activity in the pons and reduced activity in the hippocampus and striatum. These findings were not seen with placebo. Fluoxetine effects were generally more pronounced overall, but activation of the right prefrontal cortex was more pronounced in placebo responders.

This finding is qualified by another recent antidepressant imaging study[99] that used high-resolution quantitative electrocardiogram (EEG) to locate areas of higher or lower electrical activity. In this study, it was found that placebo responders, drug responders, and nonresponders had distinctive activation patterns. While placebo responders showed increased activity in the prefrontal cortex, drug responders showed decreased activity, and nonresponders showed no change. This seems to show that meaning produced specific areas of altered brain metabolism and activity.

These findings are the first of their kind and replications are called for to help confirm and clarify our understanding of the mechanisms of meaning effects. They have already dispersed doubt about the reality of meaning response effects in healing and medicine.

CONCLUDING REMARKS: HARNESSING MEANING EFFECTS

Although this review is not exhaustive, and has highlighted a selective list of findings, it has illustrated a number of issues about healing and its mechanisms:

1. Meaning and healing effects are real and can be quite strong.
2. If conceived as an individual response to the meaning of an intervention, many paradoxes inherent in traditional usages of the concept of placebo disappear.
3. This latter usage of the concept can also contribute to a broader understanding of healing responses, which seem to be triggered by central processes, either through expectation, or through conditioning, or both, and can involve multiple central mechanisms and neurotransmitter pathways.
4. Placebo analgesia is mediated by endogenous opiate systems which are similar to those activated by exogenous opiates.
5. Other systems besides the endogenous opiate system are involved, such as the dopaminergic system.

It is time to change our perspective on placebo and meaning effects in research and medicine. Rather than viewing the placebo effect as an enemy that hampers clinical trials, it should be seen as a ubiquitous healing response mediated by expectations and conditioning. Thus, it can be utilized to enhance or interfere with healing in many clinical settings. By understanding the meaning response, we might understand how optimal healing can be fostered.

Complementary and alternative medical (CAM) therapies may be elegant, efficient and comparatively harmless ways to harness healing processes.[100] We should view that possibility as a virtue rather than a vice. But CAM is not the proprietor of all meaning responses. These responses are ubiquitous and occur in every healing context. Table 1 lists ways to enhance healing with any therapy derived from the research literature on placebo effects.

In addition, evidence points to the following suggestions on how to harness these optimal healing processes:

1. Always work with and not against patients' expectations. If patients expect an intervention to be harmful, dangerous, fraught with side-effects, and not curative, they are likely to experience just that. Thus, it should be mandatory for every physician and therapist to find out about those expectations and move them in a positive direction. If multiple treatment choices are available, use the one which is most conforming to patients' expectations for improvement. For instance, if a patient expects to get better from a "natural product" rather than from a chemical one, it is likely that this preference has clinically important influences.
2. If patients' expectations are unhealthy or harmful, work to change them first before jumping from intervention to intervention. Although modern day patients are sometimes surprisingly educated, they also sometimes cling to either outdated or faddish beliefs. It is likely that interventions are unsuccessful or less effective if patients' expectations are not fulfilled. In addition, it is likely that

TABLE 1. WAYS TO ENHANCE HEALING RESPONSES FOUND IN THE PLACEBO LITERATURE

1. Use more frequent dosing rather than less frequent dosing—up to a limit.[27]
2. Apply therapies in "therapeutic" settings such as hospitals and clinics.[a]
3. Match the appearance, such as size and color, to the desired effect.[27,b]
4. Attend to the route of administration.[a]
5. Deliver therapies in a warm and caring way.[c]
6. Deliver therapies with confidence and in a credible way.[d]
7. Determine what treatment your patient believes in or not.[69,104,e]
8. Be sure you as a therapist believe in the treatment and find it credible.[55,e]
9. Align all beliefs congruently: patient, doctor, family, culture.[13,e–g]
10. Deliver a benign but frequent conditioned stimulus along with the effective therapy.[66–73]
11. Use the newest and most prominent treatment available.[h,i]
12. Use a well known name brand identified with success.[j]
13. Cut or stick the skin or poke into an orifice whenever it is believed important.[i]
14. Inform the patient what they can expect.[20,21]
15. Use a light, laser, or electronic device to deliver and track the treatment when possible.[h]
16. Incorporate reassurance, relaxation, suggestion, and anxiety reduction methods into the delivery.[28,33,65]
17. Listen and provide empathy and understanding.[12,c]
18. Touch the patient.[11,29]

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going against expectations will reduce compliance, a factor central to any therapeutic success.[101,102]

3. Talking can induce a response toward cure. Rapport between doctor and patient is an important vehicle for suggesting therapeutic effects and enhancing expectations. Frank,[103,104] in his seminal work on meaning in medicine, made the effects produced by the general ambience of treatment the most important of therapeutic factors.[103,104]
4. One of the greatest skills of a doctor, and a topic often left out of the debate around evidence-based medicine, is individualization. It is in the subtle changes to therapy and how they are delivered by a skilled healer that the meaning response is harnessed to its fullest. It is expected that any therapist who individualizes his treatment will have better results, because he can harness the meaning response.
5. Raising hope and alleviating anxiety in a credible way is one of the most therapeutic acts in general. It has been shown empirically that a simple act, such as giving a clear diagnosis and prognosis, improves outcome.[105] If patients receive clear and positive communications conveyed with trust, credibility, and confidence, healing is more likely. This must be mastered in a world in which knowledge is transitory, and changes quickly and frequently contradicts previous knowledge. Truth and integrity are integral components of a trusting relationship; however, the patient should not be made the primary target for transferring our insecurity.
6. A frequent assumption is that only specific causal effects count, like those produced by drugs or surgery. This review makes it plausible that other effects also count. Believing that one has a potent therapeutic agent at one's command may be the single most important ingredient for producing a broad spectrum of meaning responses. For it is only when a physician believes in what he uses that he can fully convey competence and positive expectations. Thus, applying interventions which patients demand without real conviction is not an evidence-based healing strategy.
7. "Giving placebos" is not identical to using the meaning response therapeutically. One need not give sugar pills. However, in some cases the use of nonactive or minimally active drugs might be a better option than continuous medication of toxic but effective therapies. Should the patient respond favorably, it would be a mistake to attribute the problems to "psychologic problems." The meaning response teaches us that there is not a clear divide between the mental and physical.
8. Therapeutic rituals[103] might be helpful in eliciting the meaning response. A significant portion of the effects from modern devices used in both conventional and complementary medicine may be caused by such effects. It may be useful to develop one's own rituals with patients, like taking a drug after a morning bath, in a special room, before or with prayer, or having it administered by a friend.

Taken together, we have shown that placebo effects, reframed as meaning responses, can evoke powerful healing and should be cherished rather than chided. The meaning

response is ubiquitous, exists and can be used or abused in any therapeutic context. To ignore it is to risk having it produce random and possibly harmful effects. To understand it and use it intelligently is to increase therapeutic benefit. Placebo research can and should be directed toward providing the evidence base for developing optimal healing environments.

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