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The placebo effect: illness and interpersonal healing

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Abstract

The placebo effect has been a source of fascination, irritation, and confusion within biomedicine over the past 60 years. Although scientific investigation has accelerated in the past decade, with particular attention to neurobiological mechanisms, there has been a dearth of attention to developing a comprehensive theory of the placebo effect. In this article, we attempt to address this gap by reviewing evidence relating to the reality and clinical significance of the placebo effect. We suggest the hypothesis that the placebo effect operates predominantly by producing symptomatic relief of illness, such as pain, anxiety, and fatigue, rather than by modifying the pathophysiology of disease. The placebo effect as a clinical phenomenon is characterized as representing the interpersonal component of healing, as distinct from spontaneous natural healing and technological healing dependent on physiologically active pharmaceuticals or procedures. Speculations regarding the evolution of the placebo effect are entertained. Finally, we argue that research on the placebo effect has the potential to revitalize the art of medicine and discuss ethical issues relating to the use of placebo interventions in clinical practice and in research on the placebo effect. We hope that this preface to developing a theory of the placebo effect will provoke debate and alternative conceptualizations and theoretical hypotheses in service of promoting a deeper and more fruitful understanding of this elusive phenomenon.

Writing over a decade ago, Ader (1997, p.138) noted that "[t]here has been relatively little systematic exploration of the scope of placebo phenomena, a fact that may reflect the lack of any theoretical position(s) within which to organize existing data and upon which to base the design of new research." Recently, scientific investigation of the placebo effect has flourished, yielding substantial progress in understanding psychological and neurobiological mechanisms. And Benedetti (2009) has recently provided a "systematic exploration of the scope of placebo phenomena," in his book, *Placebo Effects*. Nevertheless, the poverty of theory has continued to characterize placebo research. We suggest that lack of adequate attention to theory has hindered scientific investigation of the placebo effect and translation of scientific research into improved clinical practice. The concept of theory has been applied narrowly within the literature on the placebo effect to refer to various mechanistic theories of how the placebo effect works: e.g., expectation and conditioning. Here we adopt a broad and general conception of

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theory, offering a preface to development of a theory of the placebo effect, with emphasis on conceptual and normative dimensions.

A theory of the placebo effect needs to pose and explore several questions:

- What is the placebo effect?
- Does the placebo effect exist as a clinically significant phenomenon?
- What type of healing is produced by the placebo effect?
- Why does the placebo effect exist?
- What psychological and neurobiological mechanisms account for the placebo effect?
- Why does the placebo effect matter?
- How can placebo effects be optimized and nocebo effects minimized within clinical practice, consistent with respect for patients' rights?

In articulating a preface to a theory of the placebo effect we can do no more than briefly address these questions. We devote the least attention to the mechanisms of the placebo effect, because this is the most extensively addressed aspect of the placebo effect in the scientific literature and has recently been summarized comprehensively by Benedetti (2009).

Investigation of the Placebo Effect

There is no standard definition of "the placebo effect." As a clinical phenomenon, "the placebo effect" is a generic name for beneficial effects that derive from the context of the clinical encounter, including the ritual of treatment and the clinician-patient relationship, as distinct from therapeutic benefits produced by the specific or characteristic pharmacological or physiological effects of medical interventions. Although the "inert" placebo (such as a sugar pill or saline injection) is a tool for scientific understanding of the placebo effect, there is no need for the use of a placebo intervention to elicit it. The placebo effect may accompany and enhance the effectiveness of medical interventions with demonstrated specific treatment efficacy. Moreover, the communicative interaction of practitioners with patients, both verbal and nonverbal, may produce placebo effects even without the use of discrete treatments.

Evidence of placebo effects derives mainly from two types of experimental research: randomized placebo-controlled clinical trials of drugs and procedures and laboratory experiments specifically aimed at evaluating the placebo effect. Patients in the placebo arm of randomized clinical trials often show substantially improved outcomes relating to symptoms of their disorder as compared with their pretrial baseline (Beecher 1955; Kaptchuk 1998; Walsh et al. 2002; Bendsten et al. 2003; Dorn et al 2007). However, at best, this only suggests the possibility of a placebo effect—improvement *caused* by the placebo intervention and its surrounding clinical context; for patients may have improved as a result of the natural history of their condition or regression to the mean (Kienle and Kiene 1997; Hrobjartsson 2002; Miller and Rosenstein 2006). Without comparing a placebo group with a no-treatment control group, which is not typical for randomized trials, a placebo effect cannot be demonstrated.

Even when no-treatment control groups are included, randomized clinical trials have distinctive limitations in demonstrating placebo effects. Because these experiments are typically designed to evaluate treatment efficacy, as measured by the difference between treatment and placebo groups, trialists have an interest in minimizing placebo effects. Most importantly, the double-blind design, in which patients are told that they may get a drug or a placebo masked to appear indistinguishable, likely creates a lower expectation of benefit from the placebo intervention than when placebos are presented deceptively as a known beneficial treatment (Vase et al.

2002). Some experimental evidence aimed at evaluating responses to placebos under different informational contexts supports this point (Pollo et al. 2001; Kirsch and Weixel 1988; Geers et al 2006). Consistent with these methodological limitations, a meta-analysis by Hrobjartsson and Gotzsche (2001) of 114 randomized clinical trials including placebo and no treatment groups, with 8,525 patients across a wide range of medical conditions, found no evidence of placebo effects for objective and binary outcomes and only a small, and doubtfully clinically relevant, effect for continuous subjective outcomes, such as pain.

In contrast to the lack of evidence of clinically significant benefit from placebo interventions in this meta-analysis of randomized trials, the results of several recent acupuncture trials conducted in Germany show evidence of clinically significant benefit from interventions that appear to work by virtue of the placebo effect (Linde et al. 2005; Melchart et al. 2005; Witt et al. 2005; Brinkhaus et al. 20006; Haake et al. 2007). This series of 3-arm trials compared traditional Chinese acupuncture, sham acupuncture (superficial needling at non-acupuncture points) and either no-treatment (wait list) groups or those receiving usual clinical care. (It is noteworthy that the sham acupuncture was described to research participants not as a placebo intervention but as a non-traditional form of acupuncture shown to be beneficial in previous clinical trials, thus enhancing expectations of benefit for participants randomized to verum or sham interventions under double-blind conditions.) Conditions studied included migraine, tension headaches, chronic low back pain, and osteoarthritis of the knee. Generally, across the various trials, no difference was detected between verum and sham acupuncture, but patients receiving either of these interventions experienced substantially greater symptom improvement than no-treatment and usual care control groups. For example, in a trial of over 1100 patients with chronic low back pain receiving ten 30-minute acupuncture sessions over 5 weeks (Haake et al. 2007), the response rate after 6 months was 48% for verum acupuncture and 44% for sham acupuncture, as compared with 27% for patients receiving usual care (physiotherapy plus as-needed pain medication).

The results of these trials suggest that traditional acupuncture lacks specific efficacy for the conditions investigated: that is, there is nothing specific to the needling characteristic of traditional acupuncture that contributes to therapeutic benefit. This conclusion is bolstered by a recent systematic review of 13 randomized trials of 3025 patients with pain conditions that included acupuncture, sham acupuncture, and no treatment groups (Madsen et al 2009). A small effect favoring acupuncture was detected, but this was not considered clinically significant and could easily be attributed to bias created by patients in the unblinded no treatment groups. While it may be premature to infer with absolute confidence that acupuncture is no better than a placebo intervention, the accumulated evidence strongly points in this direction.

Does it follow that acupuncture produces clinical benefit by virtue of the placebo effect? It is possible that the repetitive physical stimulus common to real and sham acupuncture is responsible for observed analgesic effects by means of some physiological mechanism (Haake et al. 2007). However, there is evidence that expectation influences the clinical benefit associated with acupuncture in both verum and sham groups. In an analysis of four of the German acupuncture trials, Linde and colleagues (2007) found that the odds ratio for a clinical response to real or sham acupuncture was twice as high among those patients reporting a positive expectation of benefit. In general, sham devices may produce distinct or especially large placebo effects as compared with placebo pills (Kaptchuk et al 2000; Kaptchuk et al 2006). More research will be needed to clarify the placebo response to acupuncture, but these trials at least suggest that this type of invasive but safe intervention, characterized by an elaborate treatment ritual and frequent clinician-patient interaction, may be a potent method of interpersonal healing by means of the placebo effect (Kaptchuk 2002). Interestingly, more recent acupuncture trials using more sophisticated non-invasive sham needles have obtained

similar results to the German trials' sham superficial needling (Goldman et al 2008, Lembo et al 2009).

Hrobjartsson and Gotzsche have recently updated their meta-analysis of randomized trials including placebo and no-treatment groups, with a data set now encompassing 234 trials and 16,570 patients (Hrobjartsson 2009). They found essentially the same pooled results: modest effects of placebo on continuous, subjective outcomes, most notably with respect to relief of pain and nausea. The increased sample size, however, permitted more powerful sub-group analyses. Placebo effects were significantly larger for physical placebos as compared with pill placebos, for patient-reported outcomes as compared with observer-reported outcomes, when patients were not informed about the possibility of receiving a placebo intervention, and when the trials were explicitly designed to study placebo effects.

Independently of randomized clinical trials, the reality of placebo effects has been demonstrated repeatedly in laboratory experiments over the past 60 years, starting with Stuart Wolf's (1950) pioneering experiments involving a janitor with a stomach fistula and two pregnant women. In the last 30 years, as reviewed comprehensively and in depth by Benedetti (2009), laboratory studies have shown that placebo interventions can elicit quantifiable changes in neurotransmitters, hormones, and immune regulators. During the past decade, numerous studies have investigated the neurobiological mechanisms underlying placebo effects by means of brain imaging techniques (Colloca et al. 2008; Faria et al. 2008). As Benedetti (2009, p.75) notes, mechanistic research on the placebo effect, beginning with experiments in the late 1970s indicating that placebo analgesia is mediated by release of endogenous opioids, gave "scientific credibility to the placebo phenomenon by unraveling the underlying biological mechanisms." This scientific credibility is particularly important in light of the dismissive and confusing characterization of the placebo phenomenon within biomedicine.

Nevertheless, despite impressive progress in understanding the fascinating interactions of mind and body in connection with the placebo effect, the clinical significance of findings from placebo mechanism experiments remains open to question. Most of these studies have enrolled healthy volunteers administered experimental manipulations aimed at understanding placebo analgesia. The relevance of these experiments to placebo effects in clinical pain conditions is unclear. Those studies that have enrolled patients with a variety of medical conditions have, with a few exceptions, examined very short term effects of placebo or placebo-like interventions, lasting from several minutes to a few hours to, on occasion, a few days in duration. Especially lacking and needed is translational placebo research involving patient-subjects, aimed at understanding clinical implications of placebo effects over time and at testing hypotheses relating to how placebo effects can be tapped and enhanced in service of patient care.

A recent clinical experiment is noteworthy in attempting to identify components of the placebo effect and their impact on therapeutic outcomes (Kaptchuk et al. 2008). Patients with irritable bowel syndrome were randomized to two placebo acupuncture interventions that varied in the intensity and quality of communicative interaction between practitioner and patient; and both groups were compared with a waiting list group without the sham acupuncture. All patients received sham acupuncture during a run-in phase of a randomized trial comparing verum and sham acupuncture. Different from the German trials, this study used a validated sham acupuncture intervention consisting of a device with a retractable needle that does not penetrate the skin but retracts into the handle, creating the illusion of needling. Patients received sham acupuncture twice a week for three weeks. In the "limited" arm, communication between practitioner and patient was "business-like" and reduced to a minimum. Patients in the "augmented" arm had a 45 minute conversation relating to their condition with the practitioner at the initial visit (as compared with 5 minutes in the limited arm), which was structured to be

supportive and empathic and to promote positive expectations from acupuncture therapy. Patients in the augmented arm had superior outcomes of symptom relief and quality of life to those in the limited arm, which in turn had better outcomes than those in the waiting list control arm. For example, at 3 weeks 62% of the patients in the augmented group reported adequate symptom relief, as compared with 44% in the limited group and 28% in the waiting list, a difference that was sustained for the 3-week follow up.

This experiment suggests that the simulation of treatment, as reflected in the sham acupuncture intervention administered in the limited arm, by itself contributes to therapeutic benefit. When enhanced by supportive communication, the ritual of treatment produces a dramatic placebo response over a 3-week period and continued in the 3-week follow-up in a difficult-to-treat patient population.

The Placebo Effect in Relation to Illness and Disease

In light of the emerging evidence suggesting the potential for the placebo effect to produce clinically significant benefit, what is the scope and limits of the placebo effect as a mode of healing? The distinction between illness and disease, described by various commentators over the past 30 years, may be fruitful for locating the placebo effect within the domain of healing (Eisenberg 1977; Kleinman 1988). Disease consists of biological dysfunction of the human organism—the primary focus of diagnosis and treatment within biomedicine. Illness is the experience of detriments to health, including the symptomatic manifestation of disease. Disease adversely affects the organism; illness adversely affects the person. The body is the locus of both disease and illness; however, the impact on the body is understood differently in these two domains. Disease is understood scientifically in terms of pathophysiology; illness is understood phenomenologically, as lived experience (Carel 2008). Diseases can occur without illness when they are asymptomatic. Conversely, people can suffer from illness without any diagnosable disease. Despite these differences between illness and disease, they are not mutually exclusive categories. The pathophysiology of diseases produce characteristic symptoms, which are often experienced as illness. Commonly for a sick person, illness and disease co-habitat in a dynamic and not necessarily stable relationship.

Part of why the placebo phenomenon has been relatively neglected, and often maligned, within biomedicine is that biomedicine conceptually focuses on a biological conception of disease that is treated by technological interventions (including drugs, medical procedures, implanted devices, and surgery), with relatively less attention to illness relieved by the context of the medical encounter, including the doctor-patient relationship. As Frank (1973, p.47) notes, “scientific medicine … while paying copious lip service to the doctor-patient relationship, in actuality largely ignores it.” Yet relief of suffering (from illness) is a major goal of medicine. From a historical and cultural perspective, the response to illness by healers is a universal phenomenon. Although traditional forms of medicine know virtually nothing about disease from a scientific perspective and may have had few treatment interventions with any specific efficacy, much of the success of traditional medicine can be attributed to the placebo effect, operating on illness.

The scientific evidence relating to placebo effects in clinical situations suggests the hypothesis that placebo effects are salient predominantly in ameliorating illness, as distinct from curing or controlling disease. The most studied and well-understood area of placebo research concerns placebo effects on pain and related forms of distress, which are primary manifestations of illness (Benedetti 2009). As reviewed above, the best evidence for placebo effects derives from two situations. First, laboratory experiments have demonstrated short-term symptomatic relief associated with mechanisms such as release of endogenous opioids and dopamine. Second, patients with chronic conditions marked by pain or distress have obtained significant and

lasting symptomatic relief following sham acupuncture, as compared with no-treatment and usual care control groups. There is little reliable evidence that the placebo effect can play a role in curing or controlling disease by modifying pathophysiology. This absence of solid evidence of placebo interventions producing objective benefit in treating disease beyond its distressing symptomatic manifestations is most visible in the meta-analysis mentioned earlier of 114 trials that included placebo and no-treatment controls (Hrobjartsson and Gotzsche 2001). In this study placebo treatment was found superior to no-treatment control groups only for continuous subjective outcomes, such as pain.

Unfortunately, there is a dearth of systematic reviews of placebo outcomes in particular medical conditions restricted to trials with no-treatment controls. Yet an examination of meta-analyses and systematic reviews of the observed responses in the placebo arms of randomized controlled trials is suggestive. For example, the substantial placebo response in gastrointestinal disease for such symptoms as pain, emesis, bloating/fullness, and early satiety does not correlate to pathophysiological changes in motility or gastric hypersensitivity (Mearn et al 1999; Reingard et al 2004). When objective changes occur in the placebo arm of trials with more serious gastrointestinal conditions, such as ulcerative colitis and Crohn's Disease (which alternate between intermittent acute exacerbation and remission), the dominant interpretation seems to be that these are not genuine placebo responses, but likely represent "spontaneous" natural improvement (Meyers and Janowitz 1989; Su et al 2007; Garud et al 2008; Su et al 2004). In the absence of evidence from clinical trials with no-treatment control groups, any claims that placebo interventions cure ulcers or other gastrointestinal conditions are suspect. While urinary symptoms, such as overactive bladder and voiding problems, typically improve in patients randomized to placebo, these outcomes are rarely, if ever, accompanied by detectable changes in pathophysiology (van Leeuwen et al 2006; Moyad 2002; McConnell et al 1998).

While very short-term laboratory experiments have demonstarted objective improvement with placebo treatment in Parkinson's Disease (Benedetti et al 2004, de la Fuente-Fernandez 2001), claims that placebo treatment produces lasting changes in objective measures of Parkinson's Disease (Goetz et al 2000; Goetz et al. 2008) have never been tested with no-treatment groups to control for normal fluctuations. A meta-analysis of randomized trials that included 213 patients with sleep disorders treated with placebo for two weeks found subjective improvement but no changes in objective measures such as polysomnographic sleep latency (McCall et al 2003); however, a subsequent laboratory within-subject experiment with 10 subjects who were deceptively told that they were taking a new hypnotic found both subjective and objective changes from placebo treatment compared to no treatment controls (Fratello et al 2005).

The evidence for objective changes in hypertension produced by placebo interventions is equivocal, at best. Although high placebo responses have been reported in hypertension randomized trials (Materson et al 1993), large trials including no treatment controls generally have not shown any difference between placebo and no-treatment groups (e.g., Report of MRC Working Party on Mild to Moderate Hypertension 1977; Gould et al 1981). In contrast, one very small trial comparing placebo and no treatment demonstrated significant effects of placebo on systolic blood pressure, diastolic blood pressure, and mean arterial pressure (Asmar et al. 2001). Several meta-analyses of observed placebo response rates in other cardiovascular conditions have shown changes in both symptoms and pathophysiology, but these trials have not controlled for natural history (Archer and Leier 1992; Olshansky 2007; Bienenfeld et al 1996). For oncological diseases, a systematic review of randomized trials found that placebo treatment is associated with improvement in subjective complaints like pain and appetite (Chvetzoff and Tannock 2003). Slight rates of tumor response in placebo-treated patients were attributable to "spontaneous remission."

Some randomized trials have detected an association between compliance with placebo interventions in randomized trials and outcomes such as mortality (Simpson et al. 2006). Does this suggest that the placebo effect can have an impact on mortality from disease? It is highly doubtful that taking placebo pills faithfully, and expectations associated with taking them, can have any impact on mortality. More plausible is the hypothesis that compliant patients engage in health-promoting behavior, which itself may influence survival.

This cursory examination of meta-analyses of observed placebo responses in randomized trials without solid and consistent evidence of objective improvement in disease outcomes could easily be extended. Nevertheless, we do not dispute the possibility that placebo interventions may produce beneficial (and lasting) modification of disease beyond symptomatic relief, especially in the context of classical conditioning (Ader 1997). There is experimental evidence that classical conditioning, pairing an immunosuppresive drug with a neutral stimulus, can produce a conditioned response that enhances survival in mice with a lupus-like disease (Ader and Cohen 1982). Giang and colleagues (1996) produced decreased peripheral leukocyte counts in patients with multiple sclerosis following a conditioning experiment with cyclophosphamide and a flavored syrup. More recently, investigators have demonstrated conditioned immunosuppression in healthy human volunteers (Goebel et al. 2002). These studies suggest the disease-modifying potential in substituting placebo interventions for drugs in conditioning paradigms, though the efficacy of such paradigms in treating disease with therapeutic outcomes has yet to be demonstrated in humans (Benedetti 2009, pp. 157–9). In any case, if placebo interventions in deliberate conditioning paradigms have the power to modify disease, this therapeutic potential is, so to speak, borrowed from the known-effective drugs with which they are paired. Placebo effects that derive from other psychological mechanisms may inherently lack the potential to produce therapeutic benefit beyond relief of symptoms of illness. Understanding the scope and limits of clinically-relevant placebo effects awaits further investigation.

In evaluating the hypothesis that the placebo effect predominantly relieves illness rather than cures or controls disease, it is important to avoid the presumption that illness is an exclusively mental or subjective phenomenon. Illness concerns the way in which the body presents itself to the suffering person. Heartburn is pain in the chest and fatigue is felt as a lack of energy in the body. Although pain is an inherently subjective phenomenon, the pain behavior it elicits can be detected by others. In addition, areas of the brain related to pain can be imaged in the context of placebo analgesia experiments that administer pain stimuli and placebos described to human subjects as pain-relieving agents (Petrovic et al 2002; Wager et al 2004; Zubieta et al 2005; Kong et al 2006; Craggs et al. 2008). As the symptomatic manifestation of disease, illness has subjective and objectively measurable dimensions, both of which may be modified by placebo effects. For example, reduced arthritic pain from a placebo effect may also be associated with improved mobility. Accordingly, the thesis that the placebo effect predominantly operates on illness does not imply that it is “all in the mind” or that it only involves subjective outcomes, based entirely on patient reports.

Whereas placebo effects can rarely be demonstrated in individual cases, the following historical example is instructive concerning the potential impact of the placebo effect on illness. William James, who suffered from angina, consulted “mind cure” therapists to obtain relief. After a visit with such a healer, he noted in his diary in 1907, “Remarkable improvement in moral and physical ‘tone’—and what was unlooked for in my power to walk without angina” (Myers 1986, p. 388). Assuming that James experienced a placebo response, it both reduced his pain and improved his ability to walk. Yet it is unlikely that this symptomatic relief (in both subjective and objective dimensions) had any impact on the underlying pathophysiology and progression of his heart disease.

The Placebo Effect and Interpersonal Healing

Understanding the placebo effect is hampered by its connection with the confusing concept of the placebo (Grunbaum 1986; Miller and Kaptchuk 2008a). Especially problematic for understanding the placebo effect and its therapeutic potential are a variety of negative and muddled characterizations of the placebo, which at best are half-truths, if not complete distortions. The placebo is thought to be merely "inert," nothing at all. Whatever effects are produced by placebo interventions are "non-specific." In clinical practice, the placebo treatment—typically an "impure" placebo consisting of an active agent without specific efficacy for the patient's condition (Tilburt et al. 2008)—is given just to please or placate; it is a fake treatment that is mediated by deceptive verbal suggestions. Within randomized controlled trials, the "gold standard" of evidence-based medicine, the placebo effect is merely noise or a nuisance variable that needs to be factored out in order to detect the real effects of real treatments.

Moerman (2002) has advocated "the meaning response" as a better characterization of the placebo effect and related phenomena, which avoids the misleading language associated with the placebo concept. This conceptualization has the merit of emphasizing one component that is important to the placebo effect as a mode of healing. This is the communication to the patient of an intelligible account that explains the illness—the diagnosis within medicine—and provides a credible rationale for the potential efficacy of treatment. As Frank (1973, p.65) observes "[n]aming something is the first step toward controlling it." Brody and Walters (1980) argue that diagnosis may itself be a form of therapy. Elaborating on this meaning component within "nonmedical healing," Frank remarks that "[a]nother source of the patient's faith is the ideology of the healer or sect, which offers him a rationale, however, absurd, for making sense of his illness and treatment procedure, and places the healer in the position of transmitter or controller of impressive healing forces" (Frank 1973, p.73). This is no less true of scientific medicine.

The "meaning response," however, has distinctive limitations as a descriptive label for the placebo effect. First, meaning is a pervasive feature of human life, as all forms of human communication involve the perception and expression of meaning. Hence "the meaning response" is too broad a label to specifically characterize healing connected with the contexts of the clinical encounter. Second, and most significantly, this term is question-begging. As Ader (1997, p.139) observes, "[s]ome definitions of the placebo effect … include a phrase that presumes the means by which the effect occurs." The "meaning response" implies an explanatory psychosocial hypothesis relating the placebo effect to perception of symbolic meaning. While attention to meaning—especially the hope and expectation for relief based on contextual features of the clinical encounter—plays a prominent role in eliciting placebo effects, there is abundant evidence that this phenomenon may be evoked by classical conditioning (Siegel 2002). Although expectation and conditioning are not mutually exclusive, at least in some cases conditioned placebo responses are likely independent of perceived meaning (Amanzio et al 1999; Stewart-Williams and Podd 2004). Also, nonhuman animals can manifest placebo effects, which cannot be explained in reference to grasping symbolic meaning (McMillan 1999). In connection with a conditioning experiment in rats, Hernstein (1962, p.678) noted that "Viewed as conditioning, the placebo effect is merely a particular instance of a phylogenetically widespread behavioral phenomenon, and not a manifestation of man's special symbolic capacities." Third, responses to meaning in clinical contexts can be positive or negative. However, the placebo effect has been understood primarily as referring to beneficial effects, in contrast to the nocebo effect, which involves adverse consequences of clinical communication.

Although the placebo concept is fraught with confusion, the terminology of "the placebo effect" and "the placebo response" is entrenched in the language of biomedicine and unlikely to be abandoned in the near future. We suggest that progress in conceptualizing the placebo effect and probing its clinical significance can be promoted by seeing it as a set of related causal processes within "interpersonal healing," by means of which the context of the clinical encounter and the relationship between a healer and a patient produce therapeutic benefit. Compared with "the meaning response," "interpersonal healing" as an orienting concept is more specific (though still very broad), neutral between explanatory hypotheses for how the clinician-patient encounter promotes healing, and focused on positive therapeutic outcomes.

To explicate interpersonal healing, and to locate the role of the placebo effect within interpersonal healing, it is important to distinguish this from two other forms of healing: natural healing and what we call "technological healing." Natural healing is the spontaneous or automatic response of the body to disease or injury, exemplified by internal mechanisms of fighting infections and wound healing. Technological healing consists of the full array of medical and surgical treatments that have pharmacological or physiological properties capable of promoting cure, disease control, or symptomatic relief. It encompasses everything from an herbal remedy in traditional medicine that has specific efficacy for treating a particular condition to heart transplantation accompanied by immunosuppressive drugs. To a large extent, the contrast between technological healing and interpersonal healing tracks two important and related distinctions that are central to understanding the latter and its role within medicine: the distinction between the science and the art of medicine and between disease and illness (discussed above). Technological healing is a major focus of the science of medicine—the development and testing of technological interventions to successfully treat disease and symptoms of illness. Interpersonal healing concerns the art of medicine, oriented therapeutically towards relief of suffering—the illness component of disease and injury. A theory of interpersonal healing will need to illuminate why and how the clinical encounter independently contributes to healing, separate from (though often associated with) natural healing and technological healing.

One obvious, but significant, way in which interpersonal healing differs from both natural and technological healing is that the former, but not the latter, requires a conscious patient, aware of stimuli that may contribute to promoting healing. In contrast, both natural healing and technological healing can occur with unconscious patients. Indeed, at the extreme, wound healing occurs in "brain dead" patients maintained on mechanical ventilation—patients who have permanently lost the capacity for higher brain function (Truog 1997). Not only does interpersonal healing require an alert patient, but some measure of the patient's attention to the context of the clinical encounter is typically necessary in order to produce interpersonal healing, by means of the placebo effect. This is demonstrated by illuminating experiments comparing open and hidden administration of drugs, showing a substantially greater effect of open administration, presented to an alert patient in a ritual of treatment accompanied by a communicated expectation of benefit (Colloca et al. 2004). For example, the substantial difference between patient responses to pain in the open and hidden administrations of analgesic drugs represents the placebo effect component of treatment outcome, without the use of a placebo intervention. Moreover, some of the psychological mechanisms of various types of interpersonal healing via the placebo effect may involve alterations in patient attention: e.g., distraction from a pain or reduction in anxiety, leading to a diminished tendency of morbid attention to bodily dysfunction (Wilson 1999; Allan and Siegal 2002; Geers et al 2006). Nevertheless, the fact that elements of alertness and attention must be involved to generate the placebo effect does not exclude aspects of placebo responses that might happen through direct sensory or affective perception outside of conscious awareness, as hypothesized by anthropological theories of "embodied experience" or "performative efficacy" (Thompson et al. 2009; Kaptchuk et al. 2009).

Another major difference between interpersonal and technological healing relates to the role of the patient. In technological healing, the patient is essentially a passive recipient of treatment interventions administered or prescribed by clinicians. Healing happens *to* the patient. In interpersonal healing, the relationship between clinician and patient promotes healing; it happens *between* them.

The distinction between these three modes of healing by no means implies that they are mutually exclusive. Interpersonal healing may often work by activating, facilitating, or enhancing natural healing. Technological healing primarily occurs within the context of the clinician-patient relationship, and thus will often be assisted by interpersonal healing. However, the scientific and medical focus on technological interventions concerns the specific efficacy of the technology in promoting health and its mechanisms of action.

It is worth noting that the three types of healing each have their opposing, negative dimensions. Autoimmune disorders are pathological developments of natural healing. Technological healing produces iatrogenic illnesses and side effects from treatment interventions. The clinician-patient relationship can give rise to nocebo effects.

The rubric of interpersonal healing might be disputed as a theoretical focus for the placebo effect, as not all placebo effects are related to healing (or contrary to healing, as in the nocebo effect): e.g., placebo effects that mimic the rewarding effects of drugs of abuse (Mitchell et al. 1996;Volkow et al 2003), that produce enhanced performance in sports (Benedetti et al. 2007), that stimulate alertness and arousal, as in placebo caffeine (Fillmore 1994), etc. Nevertheless, the major impetus to studying placebo effects is to understand the mind-body connection in health and illness, making it reasonable to focus on the placebo phenomenon as it relates to health and to conceptualize the area of interest as interpersonal healing. The nocebo effect is also relevant in this context, as it interferes with interpersonal healing. Another potential objection to locating the placebo effect within interpersonal healing is the possibility that individuals can obtain a beneficial placebo response to a drug or herbal remedy obtained over-the-counter without access to a clinician. However, the extent to which individuals acting alone can access therapeutic placebo effects is unknown. Moreover, this is probably a marginal source of placebo effects and probably derivative from past interpersonal forms of taking medicine provided by parents to children and prescribed by physicians. Both of these points indicate that the placebo effect should not be seen as exclusively a phenomenon of interpersonal healing, but they do not challenge the salience or utility of invoking interpersonal healing as an orienting focus for inquiry into the placebo effect.

Pulling these threads together, we submit that “the placebo effect” within health care should be understood as a generic name for the various direct causal pathways from clinician-patient interaction to therapeutic outcomes relating predominantly to symptomatic relief and coping with illness. It works by diverse mechanisms, which may include response expectancies, classical conditioning, learning, or reward on the psychological level; and release of various endogenous mediators, such as opioids, dopamine, or serotonin, and antagonism of cholecystokinins on the neurobiological level (Benedetti 2009). As a form of interpersonal healing, the placebo effect also differs from natural healing that does not require contact with a healer and technological healing by means of interventions with specific treatment efficacy administered or prescribed by physicians. Yet it is related to these other forms of healing insofar as the placebo effect potentiates natural healing and accompanies and enhances technological healing. In sum, the distinctive features of seeing the placebo effect as a mode of interpersonal healing are that it locates this phenomenon within the context of the clinician-patient relationship; it denotes a causal connection between this context and therapeutic outcomes; and this theory hypothesizes that the predominant, if not exclusive, impact of the placebo effect is to relieve illness, rather than to modify disease beyond symptomatic relief.

Consistent with locating the placebo effect within interpersonal healing, Kleinman (1988, p. 245) advocates an informal process of medical psychotherapy as a basic component of care focusing on the illness experience of chronically ill patients: "It is of the utmost importance that physicians achieve the highest possible placebo effect rates. To do this, doctors must establish relationships that resonate empathy and genuine concern for the well-being of their patients." He adds that "The chief sources of therapeutic efficacy are the development of a successful therapeutic relationship and the rhetorical use of the practitioner's personality and communicative skills to empower the patient and persuade him toward more successful coping" (Kleinman 1988, p.247).

The Evolution of the Placebo Effect

Why does the placebo effect exist? Any answer is necessarily speculative, especially as there has been scant attention to the placebo effect from an evolutionary perspective. We begin by entertaining the hypothesis that the placebo effect activates self-healing functions of the organism—what Brody (2000) has called "the inner pharmacy." Various important self-healing functions work automatically, without needing to be elicited by our psychological dispositions or our interactions with others: e.g., homeostatic mechanisms such as fighting infection and wound healing. We know that human beings have internal pain-relieving mechanisms via release of endogenous opioids (and other non-opioid mediators), and that to some extent placebo analgesia works by means of these mechanisms (Benedetti 2009). Why doesn't this happen automatically in response to pain?

One reason is that pain serves an important biological function, signaling a threat to the physical integrity of the organism. As Humphrey (2002, p.265) explains, "The main function of your feeling pain is to deter you from incurring further injury, and to encourage you to hole up and rest." Moreover, the exception to this defense function of pain proves the rule that pain serves survival. In some circumstances of acute and extreme stress, such as in battle, injured people may not feel pain (Beecher 1956), likely because of endogenous opioid release (Willer and Albe-Fessard 1980); and this serves survival in the face of immediate threats to life. In this case, the signaling function of pain is overridden, owing to the stronger survival-oriented need to be free of pain. But the question remains why the "inner pharmacy" doesn't kick in to relieve pain when the organism is at rest and is doing what is needed to avoid further damage to the organism? Why does it so often take the intervention of a healer (or a parent in the case of young children) to relieve the pain?

In contrast, there is some internal mental capacity to relieve anxiety—also a biological defense mechanism—without the therapeutic/placebogenic interventions of others. Anxiety serves to signal threat of impending danger to the organism; and cognitive appraisal of the alarming stimulus (e.g., a startling sound) as not in fact threatening can make the anxiety go away. To be sure, to some extent, it may be possible for the individual to divert attention from a mild acute painful stimulus, and thus to relieve the pain; but as pain become more severe or chronic this does not work. Also, anxiety relating to illness may be difficult to relieve without attention from a healer.

Humphrey (2002, p. 259) poses the right question about the social dimension of the placebo effect: "If placebos *can* make such a contribution to human health, then *what are we waiting for?* Why should it be that we often need what amounts to *outside permission* [the intervention of others] before taking charge of healing our own bodies?" He suggests that we need the emotional trigger of hope for relief in order to activate internal healing mechanisms to counteract the otherwise biologically useful defense mechanisms of pain and anxiety. For example, he states, "that when it's known that the threat posed by the cause of the pain is soon to be lifted, there's much less need to feel the pain as a precautionary defence" (Humphrey

2002, p.274). But why does hope for relief *require* the intervention of others, rather than self-generated cognitive/emotional responses?

Although one can only speculate regarding an answer, it appears that in the face of illness-related distress, it is difficult to generate hope for relief by personal strategies. The illness itself impedes hoped-for relief. Typically, in the throes of suffering from illness we can't think, wish, or will the expectation that relief is in store. It takes the intervention of an authoritative figure to promote hope and expectation for relief, leading to the placebo effect. Moreover, as social animals, we are attuned from infancy to look to authoritative or protective figures—initially, our parents—to intervene to relieve distress. Adler and Hammett (1973, np.596) describe the healer as "a culturally sanctioned parental figure." From a psychodynamic perspective, the healer's authority and ability to comfort may be a projection of parental care, operating by a process of transference (Brody 1980, p.20). Both conditioning from prior exposures to healers and expectations, as well as anxiety reduction, generated by the healer are likely to activate the placebo effect.

If we are correct that the placebo effect operates predominantly on illness rather than disease, then it may not be favored directly by natural selection. Instead, it may be a byproduct of the prolonged nurturance of human infants and the social solidarity of early human communities, both of which have survival value. Viewed as interpersonal healing, the placebo effect may be explainable in terms of ontogenesis, in which neocortical structures are crucial in processing language, social attitudes, and elements of interpersonal context. Additionally, the propensity to be conditioned and the potential for placebo interventions to modify disease by means of classical conditioning are part of our biological heritage. In the future, genetic research may improve our knowledge of evolutionary meanings and advantages of placebo effects by clarifying if and how specific polymorphisms are transmitted from one generation to the next.

In any case, the placebo effect probably contributes to the emergence of the healer role and the profession of medicine, by underlying the efficacy of interpersonal healing. In addition, the healer role is supported by natural human bias and fallacious reasoning—in particular, the fallacy of *post hoc ergo propter hoc*. We are inclined to attribute recovery from disease to the ministrations of healers when, in point of fact, it is often due to self-limiting diseases and the automatic natural healing of the organism.

Why Placebo Research Matters: Revitalizing the Art of Medicine

The goal of translating placebo research into improved patient care, via "harnessing the placebo effect," has been repeatedly articulated (Benson and Friedman 1996). Nevertheless, this remains, so to speak, an attractive business plan that has failed to yield substantial profit. We suggest that it is fruitful from a theoretical perspective to conceive the placebo effect, in the context of interpersonal healing, as a central tool of "the art of medicine." To make optimal use of this tool in service of patient care, however, requires breaking down the traditional dichotomy between the art and the science and medicine. Placebo research has the potential to bridge the chasm between the science and the art of medicine. To realize this potential, it should be oriented to providing scientific insight and experimental guidance towards enhancing the art of medicine.

Traditionally, clinical medicine was, at best, an art of healing, with minimal scientific foundation. Whatever genuine therapeutic success physicians achieved was likely due to placebo effects or natural healing, rather than benefit produced by the active ingredients of treatment agents (Shapiro and Shapiro 1997). As science transformed clinical practice, first with respect to diagnostic technology and later with powerful drug treatment, commentators remarked on a disjunction between the "art" and the science of medicine (Armstrong 1977; Reiser 1978). Concerns were raised that the art of healing, based on intuitive clinical judgment

and the physician-patient relationship, was being eclipsed by the science and technology of medicine.

The advent and ascendancy of the randomized controlled trial has further eroded the status of the art of medicine. The randomized trial focuses on outcomes in groups of patients administered treatment interventions in accordance with specified protocols. Therapeutic benefit deriving from the clinical encounter is a confound that needs to be eliminated or minimized in order to detect "specific" treatment efficacy. Under evidence-based medicine, the randomized trial is the arbiter of medical value—the "gold standard" for evaluating medical interventions. Commenting on the implications of the methodology of randomized controlled trials for the practice of medicine, Sullivan (1993, p.227) remarks that "Medical scientists set themselves apart from the doctor-patient relationship in order to obtain a knowledge that is stripped of personal elements. This allows the development of a context-independent expertise and therapeutic technology that can be delivered by a profession to its patients." This biomedical orientation puts a premium on the clinical value of discrete medical therapies, demonstrated to be effective in randomized trials, leaving the art of medicine outside the purview of evidence-based medicine, and thus in danger of becoming merely a cultural relic.

Indeed, the very distinction between the science and the art of medicine, when hardened into a rigid dichotomy, contributes to the marginalized status of the art of medicine and to interpersonal healing as a basic component. It suggests that the art of medicine is impervious to scientific inquiry. Accordingly, it discourages devoting scientific investigation to the therapeutic potential of the clinical encounter, with the aim of promoting improved, evidence-based, outcomes for patients. In contrast, placebo research offers promise in breaking down this dichotomy by directing scientific investigation to techniques of ameliorating illness, thus enhancing the art of medicine and patient care.

We do not suggest, however, that the art of medicine can be reduced to a set of evidence-based rules for the clinical encounter. Physicians necessarily rely on individualized judgments about how to relate to particular patients. The art of medicine can never be rule-governed in a mechanical way. Nevertheless, it is reasonable to suppose that discrete patterns of interaction between clinicians and patients are more or less likely to promote optimal therapeutic outcomes; and these patterns can be evaluated by rigorous, hypothesis-based experimental inquiry. Many important questions remain to be answered in pursuit of the goal of providing evidence-based support and guidance for the art of medicine via therapeutically-oriented research on the placebo effect. The following questions seem especially pertinent for experimental inquiry:

- What components of the clinical encounter contribute to or detract from interpersonal healing?
  - What communicative techniques can clinicians adopt to optimize relief of suffering from illness and enhance patient care?
- Is the ritual of treatment necessary to make optimal use of the placebo effect?
- What types of treatment interventions that lack specific efficacy are effective in promoting clinically significant placebo effects?
  - Does this include openly administered placebo pills without pharmacologically active agents, provided with non-deceptive communication of positive expectation?
  - Do complementary and alternative medical interventions that are not better than placebo controls produce clinically relevant placebo effects (as compared with no treatment or usual care groups)?

- What are the best scientific and ethical methods of evaluating placebogenic treatments?
  - How should clinical trials be optimally designed to evaluate clinically significant placebo effects?
  - What types of well-controlled laboratory experiments have the most promise for guiding translational placebo research?
- How do interpersonal and contextual effects interact with natural and technological healing?
- Can placebo interventions be used (by means of conditioning, expectation, or anxiety reduction) to reduce the doses of medically indicated treatments, such that adverse side effects are reduced without decreasing treatment efficacy?

Ethics and the Placebo Effect

From the perspective of bioethics, the placebo effect has a tainted history, as it is associated with the paternalistic and deceptive practice of physicians prescribing inert agents or "impure" placebos (Brody 1982). These concerns remain relevant to contemporary clinical practice. Recent surveys have shown that physicians continue to prescribe or recommend "placebo treatments," which are believed to lack specific pharmacological efficacy for the patient's condition (Tilburt et al 2008). There is reason to be on guard against invoking the placebo effect, building on public fascination and enthusiasm for mind-body interactions in the domain of health, as a rationalization for paternalistic and unprofessional practices. Promoting the placebo response is not the same as merely trying to please the patient. To be sure, there may be situations in which it is appropriate to satisfy patient expectations of receiving a medicinal treatment and thus to support the physician-patient relationship (e.g., recommending vitamins to treat fatigue for conditions without a medical diagnosis); however, these do not include, for example, the prescription of antibiotics for viral infections. The latter practice is objectionable owing to the side effects of antibiotics and the public health risk of promoting drug-resistant bacteria. On the other hand, it is possible that prescribing benign treatments to "please" or placate the patient may also promote a genuine placebo response.

Two questions are particularly salient to the ethics of prescribing treatments genuinely aimed at promoting a placebo response: (1) can this be done without deception, and thus compatible with informed consent? and (2) is there adequate evidence of clinically significant benefit? Empirical research is needed to address both these questions.

These ethical concerns do not arise in the case of efforts to tap the placebo effect solely by means of clinician-patient interaction, without a placebo treatment (Brody 1982). A therapeutic alliance, based on listening, empathy, reassurance, and therapeutic optimism, constitutes good clinical practice. Scientific investigation of the placebo effect derived from the clinician-patient relationship holds promise for improving patient care in service of the fundamental goal of relief of suffering.

However, concerns about paternalism and informed consent are relevant to the nocebo effect —especially, adverse effects on patients of clinical communication (Barsky et al. 2002). The fact that informing patients of side effects of drugs may itself, by means of expectation or anticipatory anxiety, produce these adverse effects does not license withholding material information from patients. Likewise, concern that communicating grim prognostic information may, by means of "the self-fulfilling prophecy," demoralize patients with life-threatening conditions and adversely affect clinical outcomes does not justify withholding information relevant to patients' choices of goals of care and treatment regimens (Christakis 1999). The "therapeutic privilege," which traditionally has permitted physicians to withhold potentially

harmful clinical information from patients, has been rejected by the law and bioethics in the United States (Berg et al. 2001, pp.79–85). Although pertinent to patient care, research on the nocebo effect does not warrant rehabilitating this paternalistic doctrine. Whereas information material to patient decision-making should not be withheld from patients, the way in which this is communicated is very important. In this regard, research on the placebo and the nocebo effects has the potential to guide methods of communication that are respectful and minimize adverse outcomes.

Research methods for investigating the placebo effect also pose ethical issues. Deception in study design is often necessary in order to create a credible placebo intervention. For example, in placebo analgesia research inert placebos are typically described to subjects as a powerful pain-relieving medication (Miller et al. 2005). In addition, subjects typically are not informed that the purpose of the research is to investigate the placebo effect, in order to avoid biasing subject responses to experimental manipulations. Although necessary or desirable to promote scientific validity, such use of deception violates informed consent and respect for the autonomy of research subjects (Miller et al. 2005). Debriefing is typically employed in deceptive research: at the end of study participation subjects are informed of the true purpose of the research and the nature of research procedures. This, however, does not cancel the ethical problem with research that deviates from informed consent (Miller et al. 2008).

The use of "authorized deception," alerting subjects before study enrollment to the use of deception without disclosing how they will be deceived, has been recommended as a way to eliminate or minimize the ethical concern with use of deception (Wendler and Miller 2004; Miller et al. 2005). Subjects are thus given a fair opportunity to decide whether they are willing to volunteer for research that involves deception. Some experimental evidence indicates that authorized deception does not bias research results (Weiner and Erker 1986), but this has not been examined systematically. Moreover, the potential for authorized deception to compromise scientific validity has not been evaluated in the context of placebo research. From an ethical perspective, it is an urgent priority to conduct experiments comparing undisclosed deception with authorized deception in research on the placebo effect.

Finally, published reports of research on the placebo effect have not been sufficiently transparent about the way in which deception deviates from informed consent (Miller et al. 2005; Miller and Kaptchuk 2008b). Typically, research reports of studies involving initially undisclosed deception assert that informed consent was obtained from research participants. Signing consent documents, however, does not mean that subjects have given informed consent when the disclosure about the study fails to provide an accurate description of its purpose or the nature of research procedures. Published scientific articles should forthrightly report deviations from informed consent and the use of remedial procedures, such as debriefing and the offer to subjects to withdraw their data during the debriefing process.

Conclusion

We suggest that, using the language of Kuhn (1970), scientific research on the placebo effect has taken the shape of "normal science" without guidance by any systematic theoretical paradigm. To begin to address this gap in theory development, we have sketched the contours of a theory of the placebo effect. Our aim has been to suggest a series of interconnected themes by locating the placebo effect within the concept of interpersonal healing and in connection with the key distinction between disease and illness. In addition to promoting conceptual clarity regarding the placebo effect, we have noted the limited rigorous evidence relating to its clinical significance and recommended experimental inquiry aimed at translating the scientific understanding of the placebo effect into improved patient care. This is the ultimate test of a theoretical paradigm for the placebo effect—its fruitfulness in guiding future patient-centered

research. Finally, we have highlighted ethical issues that need to be addressed in optimizing placebo effects and minimizing nocebo effects within clinical practice and in conducting justifiable research on placebo effects.

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