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# Considerations and Caveats for the Use of Placebo Responses in Clinical Care: Minding the Matter of Mechanisms—and Morality— in Medical Treatment

Response to  
**Harnessing the Placebo Effect:  
A New Model for Mind-Body Healing**, by Gabriel Crane  
(p. 39, this issue)

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Gabriel Crane astutely describes the placebo effect as physiological and psychological responses that can mitigate signs and symptoms of several types of disorders, and more generally, perhaps produce salutary effects (Crane, 2016). Crane rightly notes that placebo effects have been somewhat enigmatic to both research and medical practice(s), in part because of inappropriate and/or insufficient theoretical orientations to the nature of such responses and effects. In many ways, this reflects the mechanistic conundrum common to much of Western science and medicine: we do not accept that something may or can be effective unless we can demonstrate a viable mechanism for such effects (Giordano, 2010). Indubitably, mechanistic understanding is important to define substrates involved, the potential for these to be elicited in particular individuals, and if and how such processes might incur various beneficial/desirable or deleterious effects.

As Crane has shown, ongoing studies by a number of groups have been important to elucidating such mechanisms, and in this way, may have provided a proverbial “check in the block” toward fortifying mechanism-to-effect considerations that could substantiate the viability of use-in-practice (Crane, 2016). Given the substance and findings of this work, Karen Rommelfanger (2013), like Crane, has queried whether we are harming patients by withholding placebo treatment. In attempting to posit an answer I herein offer that it is – and will be increasingly – important to contextualize putative mechanisms and empirically observed effects of placebo to the act of medicine and

clinical encounter. This approach can serve to fortify a deepened understanding of if, why and how placebo responses – and the events that evoke them – may be valid and of value, and how these can and perhaps should be utilized in clinical practice.

## **Putative Mechanisms of Placebo Response(s)**

As Crane has reported, several neural loci and networks are likely engaged in and by placebo responses. Brainstem systems engage sensory input from a variety of stimuli from the external and internal environment to attend to feature orientation and attendance. Differential activation of reticulo-thalamic neuraxes involved in attention, emotion and ‘directed’ consciousness (i.e.- ‘consciousness of’ a circumstance and the attendant emotional ‘valence’) can create a basal emotional state that, when taken together with activation of networks involving the amygdala, insula and regions of the associative, cingulate, temporal and parietal cortices, fosters a sense of ‘intentionality’. Concomitant and/or subsequent engagement of hippocampal, and parahippocampal cortical neuraxes conjoin working and declarative memory to frame experience within past and current circumstance(s). Networks of right and/or left prefrontal and orbitofrontal cortices participate, at least to some extent, in higher order expectational or anticipatory cognitions to afford objectification and intentionality to situational experience, and relate such experience to prior, current or potential circumstances. (Benedetti, Mayberg, Wager, et al, 2005; Kohls, Sauer, Offenbacher, & Giordano, 2011)

These mechanisms appear to function in hierarchical processing. During initial stages of placebo response, frontal and prefrontal cortices (that contribute to network processing of expectation), activate the periaqueductal grey region (PAG) and decrease activity of the anterior insula, thalamus, and anterior cingulate gyrus, to evoke direct sensory, rather than perceptual modulation of physiological input. Late(r) stage placebo responses involve reduced activity of the anterior and medial cingulate gyrus and amygdala, and support that progressive and relatively durable placebo responses reflect the involvement of other brain loci and networks (Benedetti, Mayberg, Wager, et al., 2005).

### **Fitting “Treatment” to the “Disorder”: Research to Indicate “Right Use”**

**A**n understanding of these mechanisms is important when attempting to meet the clinical adage of the “right treatment for the right diagnosis”. In this light, ongoing research will be crucial to determining what works (and what doesn’t), in whom, when, under which conditions, and what mechanisms are involved. Such studies can define how psychophysiological variables incur patient responses and therapeutic outcomes as influential and applicable, albeit with caveat, to the conduct of the clinical encounter. Reflecting the Sydenhamian tradition, the key elements of the clinical encounter are the determination of 1) what is wrong with the patient, 2) what can be done (given knowledge of and about the disorder as expressed in/by the specific patient and the range of potential interventions that target mechanisms and effects of the disorder); and from these variables 3) what should be done. But here it is necessary to recognize the multi-dimensional nature of “good” relevant to not only what is biomedically sound, but if and how the application or engagement of biomedical factors affect an individual patient’s nature and predicament of illness, circumstances, values, and choices (Pellegrino and Thomasma, 1993). So, for those disorders that have been shown to involve neural substrates that have been demonstrated to be affected in and by placebo responses, evoking placebo may aptly align the treatment with the disorder (Giordano 2007).

### **Practical and Ethical Issues: Toward “Good Use”**

**I**t is from this perspective that I concur with Crane and urge re-examination of the concept – and use - of placebo. While used in the research literature to refer

to a sham treatment, I offer a more accurate definition of placebo responses to be those processes that induce neuropsychological effects that are facilitative to healing, and which I believe, like Crane, can – and should - be more validly considered for therapeutic value in light of current neuroscientific information and understanding. But any such consideration should not be cavalier; adherence to clinical equipoise dictates that like any potential treatment approach, the use of placebo responses must be weighed against other possible and viable interventions in light of available evidence, particulars of the case, and the relative balancing of benefits, burdens, risks and harms (Giordano, 2008). Simply put, knowing that a particular treatment can evoke mechanisms to produce positive outcomes does not explicitly compel or sustain that it should be used.

Additionally, while placebo responses and effect(s) may be viewed as valid means to mitigate the signs and symptoms of certain types of disorders, I believe, pro philosopher Sissela Bok, that achieving these means by blatantly lying incurs ethical harms through: 1) intentional deception, 2) undermining the veracity that establishes and maintains trust within the physician-patient relationship, 3) denying patients information necessary for valid informed consent, and 4) impugning patients’ autonomy, in this sense, the negative right to refuse particular treatments (Bok, 1974; see also: Gillon, 1985; and Bloche, 2000). This impels consideration of if and how placebo responses might be ethically achieved and used in clinical practice.

Disclosing that a certain intervention may induce placebo responses does not necessarily reduce the potential for effects, particularly if and when circumstances in which this information is provided afford sufficiently positive reinforcement for patients’ expectations of the clinical encounter (Colloca and Benedetti, 2005; Geers et al. 2005). A physician could assert that a particular intervention may engage mechanisms that, in some ways, can reduce feelings of illness and perhaps evoke physiological recuperative processes, and that the actual mechanisms of this effect are not fully known. To be sure, despite myriad advances in bioscience and technology, in many ways medicine still remains a relatively uncertain practice. Communicating this uncertainty to patients with a sense of optimism allows for veracity and intellectual honesty, while still fostering trust and hope (Giordano and Boswell, 2005; Geers et al., 2005; Spiro, 1986).

### **Caveats of Placebo Response**

Ethico-legal questions also center upon the cost of interventions that are used to evoke placebo responses (Bok, 1974). Namely, should these be billable? One line of rationalization might be that if a technique is revealed to produce positive outcomes (even in the absence of demonstrated specific, underlying mechanisms for effect), then it is billable (i.e. - what I call the “valued ends justification”). Another is that if (even a putative) mechanism is shown (as is the case, at least in part, for placebo) then this supports or “confirms” the “reality” of the technique as scientifically valid, and thus, a billable intervention (i.e.- the “mechanistic justification”). Lastly, the mere fact that a clinician must devote x amount of time to rendering said intervention may be used to justify incurring costs (i.e., the “professional services” justification). Each may be sustainable on some level, and as history has shown, there have been ample instances of techniques being rendered and patients billed, without (partial, complete and/or correct) understanding of underlying mechanism (e.g.- aspirin, electroshock therapy, lithium, etc.), or even definitive therapeutic benefit gained. Thus, if it is determined that placebo may be employed as a (formal) treatment modality, it will then become necessary to establish not only particular indications for placebo-inducing methods, but also billing requirements and treatment codification for use in practice.

#### **Tools-to-Theory-to-Practice**

**I**ncentives of the federal *Brain Research through Advancing Innovative Neurotechnologies* (BRAIN) initiative, to develop and employ new approaches in neuroimaging, neurogenomics and biomarker identification and analysis that are specifically oriented toward and employable in translation of research to practice will enable more accurate evaluation of if, how, and in whom certain interventions are effective, which can fortify a useful corpus of “medicine-based evidence” (www.whitehouse.gov/BRAIN; Boswell and Giordano, 2009). Such evidence will be important to guide both clinical practice and the economics of patient care, particularly given recent calls for, and developments in personalized and precision medicine (see: www.whitehouse.gov/precision-medicine). But caution is warranted when discerning what types and levels of evidence have meaning and value, and what social and economic implications, effects and practices are derived from these findings (Giordano, 2014; 2010).

In support of Crane I agree that mechanism and outcomes’ studies may strengthen consideration of using placebo as and in clinical practice. As consistent with Bok (1974), I also claim that using placebo in the clinical setting may be acceptable if 1) there is an established clinician-patient relationship; 2) a diagnosis supports the viability of such intervention and does not mandate other treatment(s); 3) the patient requires and requests some form of intervention; 4) it does not interfere with (other) diagnostic and therapeutic interventions, 5) it does not incur costs beyond the minimal fees required for the attendance of the treating clinician, and 6) other treatments have not been effective. By definition, placebo responses are those that evoke a positive effect in the patient. By definition, medicine is a humanistic endeavor of curing, healing, and caring. In conclusion, I argue that the former may prove to be important to—and useful in—the latter. But as with any clinical intervention, ongoing research, education, ethico-legal insight and responsibility, and practical wisdom will be essential to guiding its viability, value, and use in practice.

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