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Reevaluating the placebo effect in medical practice

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Abstract

Recent findings on placebo research corroborate the evidence that the placebo effect represents a promising model to shed new light on the brain-mind-body interactions. In particular, this research has partially elucidated the role of how patients' expectations and the quality of physician-patient communication can influence the efficacy of interventions and overall clinical outcomes.

Accordingly, the study of the placebo effect should be incorporated in the core clinical practice curriculum of all health practitioners. While the growing knowledge of the placebo effect points to it as an irreducible primary reality of the medical sciences, an ethical analysis aimed at avoiding the misuse of placebos is needed, while maximizing the opportunity for beneficial placebo effects.

Keywords

Expectations; Ethics; Policy; Communication

Introduction

The placebo effect is a well-recognized and clinically-important phenomenon in medicine. Over the past several years there has been considerable research in elucidating the mechanisms underlying the placebo effect (Colloca, Flaten, & Meissner, 2013; Colloca, Klinger, Flor, & Bingel, 2013; Enck, Bingel, Schedlowski, & Rief, 2013; Meissner et al., 2011). In particular this research has elucidated understanding of the role of how patients'

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Contributors and sources:

This work was developed by first convening at National Institutes of Health representatives from academia, not-for-profit organizations, and pharmaceutical industry with expertise in placebo research. A sub-group of members including Luana Colloca, MD, PhD, Wayne B. Jonas, MD, John Killen, Jr., M.D., Franklin G. Miller PhD, David Shurtleff, PhD, subsequently refined the emerging concepts and drafted the manuscript. The opinions expressed by the authors are those of the authors and do not necessarily reflect the position or policy of the National Institutes of Health, the Public Health Service, or the Department of Health and Human Services.

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expectations and the quality of physician-patient communication can influence the efficacy of an intervention (Bingel et al., 2011; Colloca, Lopiano, Lanotte, & Benedetti, 2004). In addition, a more complete understanding of these psychobiological effects may help investigators to better detect intervention-specific effects, and help clinicians to optimize patients' adherence and response to therapeutic regimens, thereby leading to even greater efficacy of treatment (Klinger, Colloca, Bingel, & Flor, 2013).

Here we discuss some implications of current research on physicians' use of placebos as they seek to balance patients' desires and demands, while also maximizing the opportunity for beneficial placebo effects. We also emphasize the need for better evidence on the safety and true relative effectiveness of placebos and placebo effects in clinical practice.

For the purposes of this article, we use the term '*placebo*' to describe simulated medical treatments - i.e. interventions which lack pharmacological or physiological properties that lead to specific efficacy in treating a specific patient's condition. Conversely, when we use the term '*placebo effect*', we are focusing on various measurable psychobiological phenomena resulting from expectations that a treatment will be effective.

Examples of placebo effects in laboratory encounters

Recent research involving clinical investigations and state-of-the-art neuroimaging techniques has unearthed a number of important findings regarding mechanisms of placebo effects that are not necessarily related to the administration of any placebos (Colloca et al., 2004; Enck et al., 2013). The study of the placebo effect is increasingly being framed as the investigation of the psychosocial context and inner factors surrounding the patient and any medical treatments, and the effect of this context on the patient's mind, brain and body when one expects a therapeutic benefit (Colloca, Klinger, et al., 2013; Di Blasi & Reilly, 2005).

Placebo effects are formed through verbal anticipations of benefits, learning mechanisms and patient-clinician interactions (Colloca, Klinger, et al., 2013). After repetitive administrations of an efficacious painkiller paired with a placebo, the placebo alone is capable of inducing conditioned responses similar to those of the active drug. Verbal suggestions of therapeutic benefit by clinicians can also trigger placebo effects. Moreover, expectation of symptomatic relief can be created by the observation of a benefit in another person and by interpersonal interactions. In sum, when triggered by the appropriate environmental signals, placebos can produce clinically meaningful symptomatic relief for a wide variety of medical conditions (Benedetti, 2008; Colloca, Flaten, et al., 2013; Klinger et al., 2013).

For example, Linde et al. reported that patients with higher expectations regarding acupuncture's efficacy, showed higher benefit than those with low expectations, suggesting that patients' beliefs can dramatically shape reported outcomes (Linde, Fassler, & Meissner, 2011). Similarly, in patients with Parkinson's disease, the perceived treatment assignment had more impact on motor function improvement and quality of life than the actual surgical treatment -real or sham human embryonic dopamine neuron implantation (McRae et al., 2004). These (and other recent) studies indicate that patient expectations have an impact on

relief of symptoms and quality of life thus indicating that patients' preferences should be taken into account when equivalent therapeutic strategies are available.

On the other hand it is critical to emphasize that current evidence suggests that expectations and placebo effects influence primarily subjective symptoms, and evidence that they can influence the pathophysiology of serious diseases is scant. An interesting recent study clearly illustrates the lack of evidence about the influences of the placebo effect on serious diseases (Wechsler et al., 2011). Asthmatic patients were randomized to receive an albuterol inhaler, a placebo inhaler, sham acupuncture, or no intervention and subjective measures of asthma and pulmonary functions were evaluated. Patients' reports of improvement were 50% after the albuterol inhaler, 45% after the placebo inhaler, and 46% after the sham acupuncture and the three interventions were significantly greater than the no-intervention control (21%). However, pulmonary functions improved under albuterol active treatment only as compared with the placebo interventions, suggesting a substantial difference between patient's needs and satisfaction and therapeutic effects (Wechsler et al., 2011).

A controversial use of placebos in medical practice

Despite the recent advances in mechanistic and translational research, placebos are used in daily clinical practice often in an inappropriate fashion. A recent systematic review of twenty-two cross-sectional, qualitative and longitudinal studies investigating frequency of placebo use among health care professionals from twelve countries indicated that the prevalence of placebo use in clinical practice ranged from 17 to 80% among physicians and from 51 to 100% among nurses (Fassler, Meissner, Schneider, & Linde, 2010). In particular, 46% of a random sample of 1200 internists and rheumatologists in the United States reported recommending an intervention "primarily to enhance patient expectation," at least 2-3 times per month. Only 5% reported using pure placebos, such as sugar pills and saline injections; others recommended using over-the-counter analgesics, vitamins, sedatives, and antibiotics (Tilburt, Emanuel, Kaptchuk, Curlin, & Miller, 2008).

In Denmark, 503 physicians including general practitioners, hospital-based clinicians and private specialists engaged in the use of antibiotics, physiotherapy, sedatives, or vitamins prescribed as placebos "to follow the wish of the patient and avoid conflict" (Hrobjartsson & Norup, 2003).

In Germany, when asked about the placebo use, 208 general practitioners reported that they used a placebo at least once in their practice; 45% used placebos, such as saline injections and sugar pills, at least once per year and 76% of general practitioners used medical interventions that have pharmacological or physical activity but have no intrinsic effect on the patient's disease or symptoms. The rationale for the use of placebo was to elicit "a psychological effect, followed by the expectation of patients to receive a treatment" (Meissner, Hofner, Fassler, & Linde, 2012).

In the United Kingdom, 782 general practitioners indicated that 12% of general practitioners used placebos while 97% used active treatments given as placebos at least once in their careers; 1% of respondents used placebos, and 77% used active treatments (e.g. antibiotics,

vitamins, probiotics, and sub-clinical doses of otherwise effective therapies) as placebos at least once per week (Howick et al., 2013).

Of particular concern is the prescription of drugs that are not medically indicated, with little likelihood of actual benefit but potentially serious side effects. This practice raises many serious medical and ethical concerns, most notably serious side effects, unjustifiable rationale, and lack of a plausible motivation (Miller & Colloca, 2009). The prescription of such placebo interventions is generally associated with a deceptive or *opaque* disclosure although, the general belief that deception is necessary to induce placebo effects has been challenged. In fact, an open-label study showed that placebos induced improvement of symptoms in patients with Irritable Bowel Syndrome who were explicitly instructed to take placebos, described as pills without medication, with the purpose to evoke a placebo effect (Kaptchuk et al., 2010). This observation suggests that patients can develop placebo effects from a simulated medical intervention even when transparently informed. While additional research is needed to confirm or elaborate on the perspective of open-label placebos, their prescription may put physicians in an uncomfortable position. Physicians should not give placebos deceptively but should understand how placebo mechanisms can be activated when valid therapies are given to patients (Colloca & Miller, 2011; Klinger et al., 2013; Miller & Colloca, 2009).

Beyond placebo pills: the impact of the patient-clinician relationship

While the use of placebo pills in clinical practice remains controversial, placebo effects are central in daily clinical practice and clinician-doctor relationships (H. Brody & Miller, 2011). Formal ritualized encounters, notably including a supportive patient-clinician relationship, can indeed trigger placebo effects (Jonas, 2011). For example, irritable bowel syndrome (IBS) patients in a randomized, sham-controlled acupuncture trial assigned to three groups with different patient-clinician interactions (treatment with minimal interaction, with augmented interaction, and wait-list) showed significant relief, primarily in the augmented interaction group (Kaptchuk et al., 2008). Furthermore, patients with post-operative pain and anxiety required substantially lower dose of morphine and benzodiazepines when treatments were delivered by informing patients about the time and benefit of treatments (Amanzio, Pollo, Maggi, & Benedetti, 2001; Colloca et al., 2004). The same treatments delivered by a computerized-pump of infusion were less or not efficacious. This so-called 'overt' and 'covert' administration of treatment suggests that the placebo effect is part of any treatment and that *enhanced* therapeutic outcomes can be achieved without any placebos (Colloca et al., 2004).

These and other studies suggest that a caring, mutually respectful and engaged relationship with the patient can lead to placebo-mediated benefits (H. Brody, 1980; H. Brody, 1997).

The ostensibly ordinary encounter between patient and clinician constitutes a pervasive medical ritual (Adler & Hammett, 1973). Research on placebo effects provides a substantial body of neurobiological and psychological evidence underscoring the importance of encouragement of positive expectations, hallmarks of caring clinical interaction (Brody & Miller, 2011). Clearly there is no harm in harnessing placebo effects in medicine, as long as deception is avoided. Accordingly, the study of the placebo effect should be incorporated in

the core clinical practice curriculum of all health practitioners. However, whether placebos can or should be otherwise intentionally used is still a subject for ongoing and future research.

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Key messages

- Clinicians should convene to produce guidance on how to address the potential demand for the use of placebos and placebo effects with clear and unequivocal recommendations.
- Clinicians should lay out the rationale and justification to guide decision making as evidence evolves, and a transparent process would be needed for weighing benefits and risks associated with the use of placebos and placebo effects.
- Scientific investigation of placebo effects holds the promise of guiding the art of medicine in service of patient care.