

PLACEBOS: OUR MOST EFFECTIVE THERAPY?

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ABSTRACT

Placebos remain highly controversial therapies largely because of their widespread use in research as a comparator rather than a focus of analysis. While a recent systematic review of placebo versus no therapy arms in trials found no difference, the placebo effect in some areas of drug trial research is large and increasing. We attempt to explain this paradox and suggest how clinicians may use the placebo effect to advantage.

Any busy clinician will recognize these phrases: "... But Mrs. S, your sleeping pills may do you more harm than good!" "I'm sorry, Mr. P, there is nothing more that we can do for your cancer," or "Ms. A, I'm so glad that your son J is feeling better on Herbal Miracle #1 but I really can't explain why it works." These are but a small sample of the many situations daily where we fail to acknowledge and use one of our most powerful therapeutic interventions: the placebo effect. Why this occurs speaks to gaps in medical education, evidence-based medicine, clinical skills and patient expectations. In this commentary, we propose that one of the great remaining frontiers of clinical pharmacology science and patient care is to understand and apply placebos and the placebo effect more systematically and effectively.

Before we proceed, let's define *placebo* (derived from Latin "I shall please") as an inert substance provided as therapy and the *placebo effect* as the psychophysiologic effect, both positive and negative, associated with placebos. This overall placebo effect is the sum of the *true placebo* effect plus other *non-specific* effects including the natural course of disease, regression to the mean, unidentified co-intervention effects and other time-dependant effects.^{1,2} For brevity, we will ignore the fascinating and likely more potent placebo effect involved in surgery and other invasive procedures to concentrate on placebo as a medication. Few medications are more

topical or controversial in regulatory, research, ethics or clinical circles.

A recent, widely reported systematic review of randomized trials where placebo and no-treatment arms could be compared, concluded that while there was evidence of a mild true placebo effect for subjective outcomes related to pain, there was no evidence of a true placebo effect for more objective outcomes (blood pressure, weight loss, asthma outcomes).³ The report was followed by a remarkable series of correspondence polarized into two main themes, either praising the death of placebos or declaring the review invalid. Two key points in the review escaped attention. One, while a specific pharmacologic effect of an inert substance could not be found (and one might reasonably ask, why would it be expected?), the authors did not in any way discount the potency of an overall placebo effect. Second, although the allocation to placebo versus no treatment would not be blind to either the caregiver or the patient, the "trial effect" which is a positive impact on participants' outcomes may have narrowed the discernable difference between placebo and no treatment groups. The placebo effect may, in fact, be the best example of therapeutic power that is more evident in routine clinical care than in high quality randomized trials. In routine clinical care, the placebo itself (injection, tablet colour, smell, etc.), clinician advocacy for the placebo and support for the patient's improvement,

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presumably can all be tailored to the patient's prior expectations to maximize the desired clinical response.

How large is the placebo effect? This speaks to the provocative title of this paper. The traditional view of a 30% placebo effect or response rate has been discounted in favour of a highly variable (to the extremes of 0% to 100% in pain trials⁴) placebo effect depending on the condition being treated, the treatment options and the setting of treatment. Both clinicians and patients appear to have strong influences over the magnitude of the placebo response - the former through their ability to diagnose (diagnosis as therapy⁵), convey compassion, offer hope and encouragement for the patient's improvement and the latter through their expectation of benefit from the therapy and their ability to cope with symptoms and signs as they are healing. Indeed the systematic review results would suggest that the placebo effect is entirely a product of the provider-patient relationship, regression to the mean of the patient's symptoms, signs or disease severity, etc. For many diseases, for example depression, multiple sclerosis, insomnia, pain, asthma, ulcer, the overall placebo effect can be greater than the specific drug effect.^{6,7} The understanding of the mechanisms of the placebo effect is at a very early stage and currently focuses on exploration of the neuropsychological pharmacology behind theories of expectancy, conditioning and meaning. It is indeed ironic that a therapy so heavily studied as a comparator and therefore involved in evidence-based therapies has so little evidence directed towards its own benefit, harm and cost-effectiveness.

While awaiting better evidence, we suggest that application of the clinician's part of the placebo effect as described above, is an important part of clinical practice. Whether identification and modification, if necessary, of patient expectations regarding therapies or an actual placebo product is useful to further enhance the placebo effect, is not clear. The case vignettes that opened this discussion invite debate on the appropriateness of use of

a placebo (as opposed to attempting to enhance the placebo effect of a proven active therapy) in situations where usual therapies may have failed or do not exist. Here we are more cautious and suggest that issues including informed decision-making by the patient, referral for expert opinion or entry into trials of promising therapies, must be considered. We await with interest the first formulary submission arguing the cost-effectiveness of a placebo.

REFERENCES

1. Papakostas YG, Daras MD. Placebos, placebo effect, and the response to the healing situation: the evolution of a concept. *Epilepsia* 2001;42:1614-25.
2. Ernst E, Resch KL. Concept of true and perceived placebo effects. *BMJ* 1995;311:551-3.
3. Hrobjartsson A, Gotzsche PC. Is the placebo powerless? An analysis of clinical trials comparing placebo with no treatment. *N.Engl.J.Med* 2001;344:1594-602.
4. Wall PD. The placebo effect: an unpopular topic. *Pain* 1992;51:1-3.
5. Brody H, Waters DB. Diagnosis is treatment. *J.Fam.Pract.* 1980;10:445-9.
6. Benson H, Friedman R. Harnessing the power of the placebo effect and renaming it "remembered wellness". *Annu.Rev.Med* 1996;47:193-9.
7. Ernst E. Towards a risk-benefit evaluation of placebos. *Wiener Medizinische Wochenschrift* 1998;148:461-3.