The pharmacodynamics of placebo

Expectation effects of price as a proxy for efficacy

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Neurology® 2015;84:766–767

For shoppers of luxury goods, satisfaction with a purchase might be proportionate to its expense. Suppose, however, that a patient's perception of medication benefit is similarly governed by its cost: does that make sense? Espay et al.,[1] reporting in the current issue of *Neurology*®, would have us think so. Their research takes the study of placebo effect to a new dimension of inquiry by investigating treatment cost as a determinant of antiparkinsonian control. In this small but well-designed study, the authors conclude that price does matter as to how patients with Parkinson disease (PD) perceive benefit. This may be bad news for health care providers committed to cost control, especially if such a mindset assumes better results should arise from more expensive drugs.

This blinded, randomized crossover study of placebo effect tested changes in objective ratings of parkinsonian motor function. The authors compared outcomes from levodopa with 2 sequential placebo (saline) injections. The latter were described to study participants as containing the same dopaminergic agonist but differing in manufacturing cost ($100 per dose vs $1,500). Participants received no further comment as to why treatment expense was mentioned. Secondary study endpoints included 2 quantified motor tasks, a self-rating for global impression of change, and an fMRI brain activation analysis involving a feedback-based visual-motor associative learning task. The authors reported that, when the "expensive" treatment was administered first, the mean improvement on the Unified Parkinson's Disease Rating Scale motor score for the "expensive drug" was 10% greater than with the "cheap" placebo. Both placebo treatments showed improvement over baseline scores, although not as much as enacted by levodopa. The results in this randomized crossover study were confounded with "treatment-by-period" effect, in that results from the same treatment given in the second period differed from first-period results.

The fMRI-monitored associative learning task also provided intriguing findings that differentiated outcomes from the "$100" vs "$1,500" injections. Task performance after levodopa treatment led to deactivation for several left-sided brain regions. In contrast, activation occurring in different brain regions followed the placebo treatments. Given as initial treatment, the cheap but not the expensive placebo resulted in more regional brain activation. As with the motor ratings, the treatment order confounded the interpretation of the second-given treatment results.

Taken together, the results indicate that symptomatic actions of placebo on several measurements were modified by price perception, with "expensive therapy" leading to greater improvement. The implications of fMRI results are more difficult to interpret, especially in a small number of persons undergoing limited testing; however, the placebo "price" also differentiated treatment results. The authors acknowledge several study limitations, and the differential effects conferred by treatment order also challenge their interpretations. A responder analysis might have helped to elucidate whether results were driven by subgroups. Characterizing opinions of subjects regarding drug price would also have been informative. It would also be of interest to learn whether participants receiving a "drug" priced at $100/dose would actually regard this as a "cheap" medication.

Placebo can be the physician's friend when it enhances therapeutic efficacy. The effects of placebo also can confound clinical trial outcomes or lead to endorsement of worthless treatments. For patients with PD, placebo effect is often robust and enduring. A meta-analysis of symptomatic actions from placebo and sham interventions in a number of clinical trials[2] suggested mean improvements averaging 16% (a greater magnitude of effect than reported by Espay et al.[1]). The findings of the current study build on other insights into placebo effect and PD, including evidence that regional release of dopamine in the striatum may be increased in response to expectation of reward or clinical improvement.[3]

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The views expressed are those of the authors and do not represent the views or policies of the NIH, Department of Health and Human Services, or the United States Government.

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The study's design was problematic in that it required deception. The authors complied with Federal research regulations that permitted waiver or alteration of informed consent.[4] Although the description of how participants were debriefed is informative, the authors do not mention whether there was any possible effect (reduction) on trust in doctors or on willingness to engage in future clinical research. Unlike most deception studies (generally, brief psychological experiments with healthy undergraduates), this investigation in a clinic setting involved patients with symptomatic PD who were misled about experimental treatments (albeit as a research activity). The ethical stakes in this study directly impinge on trust that is vital for the physician-patient relationship.

Given the intriguing (but modest) influence of drug price on placebo effect, similar studies are likely in the future. Investigators and institutional review boards would be advised to consider additional protections for research participants. First, authorized deception can be permissible if participants are aware that they might be misinformed without learning the specific details.[5] For this option, expectancy effects still can be detected.[6] Second, debriefing should anticipate the implicit reluctance of patients to express dissatisfaction or criticize their doctors. Consideration should be given to collection of information by an independent party, with guarantees of anonymity and a questionnaire that specifically explores issues of trust, feelings of distress, and willingness to participate in future studies.

The outcome of this study, despite its limitations, opens our eyes to another nuance of placebo effect with implications for clinical practice, the research enterprise, and health policy. Like all deception-related research, future studies should consider enhanced ethical oversight to ensure adequate protection for the rights and welfare of patients as research participants.

STUDY FUNDING

No targeted funding reported.

DISCLOSURE

The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

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