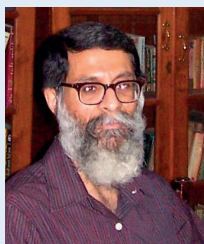


Cost of Treatment as a Placebo Effect in Psychopharmacology: Importance in the Context of Generic Drugs

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Each month in his online column, Dr Andrade considers theoretical and practical ideas in clinical psychopharmacology with a view to update the knowledge and skills of medical practitioners who treat patients with psychiatric conditions.

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ABSTRACT

Nonspecific factors have long been known in both psychotherapy and psychopharmacology. In recent years, 2 studies showed that placebo benefits were lower when the treated subjects were told that the placebo, presented as an active treatment, cost less. One of these studies had assessed motor and other outcomes in Parkinson disease patients; the other had assessed analgesia in paid, healthy volunteers to whom electric shocks were administered. The implication of the finding that lower treatment cost may diminish treatment gains is that patients who receive generic medicines may have lower expectations and may consequently derive less placebo-related benefit. This could be of concern in psychiatric disorders that are characterized by a large placebo response. Although the 2 "placebo cost" studies cannot be easily generalized to clinical and especially psychiatric contexts, clinicians should consider offering reassurance to patients receiving generic drugs that cost, per se, has no bearing on treatment-related benefit.

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Clinical Question

Clinicians have reservations about the use of generic medications because of concerns related to the absolute content of the active drug, the bioavailability of the active drug, and the presence of impurities in the formulation,^{1–3} all of which can reduce efficacy of the treatment, increase adverse effects, or both. Generic drugs, however, continue to be prescribed because they carry the substantial advantage of affordability. Can this very advantage be a limitation, as well? The reason for this unusual question arises from the findings of 2 studies on the influence of treatment cost on clinical outcomes. These studies are briefly discussed.

Introduction

Over a decade ago, de la Fuente-Fernández et al⁴ presented landmark evidence for a biological mechanism of placebo in Parkinson disease. The sample comprised 6 patients with Parkinson disease. These patients were examined under 2 conditions: (1) an apomorphine versus placebo condition, in which patients did not know when they were receiving apomorphine and when they were receiving placebo, and (2) an apomorphine-only unblinded condition.

Subjects were studied using positron emission tomography (PET) and labeled raclopride. Raclopride binds to D₂ and D₃ dopamine receptors; greater raclopride binding, detected by PET, indicates lesser receptor occupation by endogenous dopamine. In an extension of this study, a second group of patients was studied. These patients were matched with the patients in the first group on age and severity of illness. All patients in the second group received apomorphine only, without blinding.

The findings of the study are summarized in Table 1. In brief, the study showed that, in Parkinson disease, placebo treatment under blinded conditions acts through release of dopamine in all parts of the striatum. Furthermore, the placebo effect possibly overlaps with and does not add to the effects of apomorphine.

Placebo in Parkinson Disease: The Effect of Treatment Cost

Very recently, Espay et al⁵ described a randomized crossover study that examined the influence of stated medication cost on the efficacy of a subcutaneously administered dopamine agonist (actually, placebo). These authors recruited 12 patients with Parkinson disease. All patients had levodopa-responsive motor fluctuations. The mean age of the sample was 62 years. The sample was 75% male. The mean duration of illness was 11 years.

These patients were assessed in an "off" state and then in an "on" state following the administration of levodopa. At the next study visit, the patients were randomized to receive 1 of 2 injections. About 4 hours later, when the effect of the first injection had worn off, they were crossed over to receive the other injection.

Patients were told that the injections were different formulations of the same dopamine agonist and that the study sought to prove that

- Two single-dose laboratory studies have shown that placebo is associated with better treatment outcomes when it is stated to cost more. One study assessed motor and other outcomes in Parkinson disease patients; the other study assessed analgesia in paid, healthy volunteers to whom electric shocks were administered.
- There is no certainty that these findings can be generalized to real-world psychiatric patients who require medication for long periods. Nevertheless, the possibility remains that patients may derive less placebo-related benefit from generic medicines because of lower expectations related to lower treatment costs.
- Clinicians should therefore reassure patients that treatment costs do not necessarily have a bearing on treatment outcomes; this is especially important when generic medicines are prescribed.

Table 1. Findings of the Study⁴ on Apomorphine and Placebo Administration to Patients With Parkinson Disease

Main study

1. There was a significant decrease in raclopride binding during placebo administration, relative to baseline. This implies that placebo administration was associated with an enhanced release of endogenous dopamine.
2. This enhanced release of endogenous dopamine was observed in all parts of the striatum and was greatest in the posterolateral part of the putamen.
3. The decrease in raclopride binding was 8%–25% (mean = 17%) in the caudate nucleus and 8%–28% (mean = 19%) in the putamen. Thus, some patients experienced very small placebo effects, while others experienced modest placebo effects.
4. Greater decrease in raclopride binding (ie, greater release of endogenous dopamine) was associated with greater perception of therapeutic benefit.

Extension study

1. The positron emission tomographic (PET) changes with apomorphine in the first group (under blinded conditions) did not differ significantly from the PET changes with apomorphine in the second group (under unblinded conditions). This implies that placebo and apomorphine effects in the first group may have been overlapping rather than additive.
2. The PET changes with placebo in the first group were similar in magnitude to the PET changes with apomorphine in the second group. This suggests that placebo may act as powerfully as an active drug.

both were similar in efficacy although, for reasons related to manufacturing, one injection cost \$100, and the other, \$1,500. The patients did not know that both injections were actually placebo (saline). They also did not know the real objectives of the study. Unlike the patients, the assessment team was blinded to treatment allocation.

Both placebos improved treatment outcomes. Importantly, the more expensive placebo was associated with superior outcomes, but only when it preceded the less expensive placebo. Furthermore, brain activation during a functional magnetic resonance imaging task was greater with the less expensive placebo, implying the need for greater brain effort

Table 2. Findings of the Study⁵ on Less and More Expensive Placebos in Patients With Parkinson Disease^a

1. At baseline, levodopa was associated with significant improvements on all measures: UPDRS-III, Purdue, tapping, Hoehn and Yahr staging scale, and Schwab and England Activities of Daily Living scale.
2. Overall, significant improvements were observed with placebo on the UPDRS-III, Purdue, and tapping outcome measures.
3. On the UPDRS-III, benefit with placebo was significantly greater when the more expensive placebo was administered first; the magnitude of benefit was two-thirds of that recorded with levodopa.
4. An advantage for the more expensive placebo, but (again) only when it was administered first, was also observed on the tapping test.
5. There were no significant order of administration effects for less and more expensive placebo on the Purdue and CGI outcome measures.
6. In functional magnetic resonance imaging assessments, during visual-motor association learning task performance, levodopa was associated with reduced activation in the left putamen, left sensorimotor cortices, and left premotor cortex. Less expensive but not more expensive placebo increased bilateral activation in the anterior and posterior cingulate cortices, left lateral sensorimotor cortex, right parietal cortex, and other areas. Brain activation was greater when less expensive placebo was given before more expensive placebo.

^aPatients were assessed using the UPDRS-III, the Purdue Pegboard Test, the Hoehn and Yahr staging scale, a tapping test, the Schwab and England Activities of Daily Living scale, and the patient CGI scale of change.

Abbreviations: CGI = Clinical Global Impressions, UPDRS-III = Unified Parkinson's Disease Rating Scale, Part III (motor subscale).

under the placebo condition of lower treatment expectations. The results are summarized in greater detail in Table 2.

Placebo and Analgesia: The Effect of Treatment Cost

Waber et al⁶ recruited 82 healthy volunteers through an online advertisement. The mean age of the sample was about 30 years. The sample was 62% female. All subjects received electrical shocks to the wrist, calibrated to individual pain tolerance. All subjects also received a placebo pill with the information that the contained drug was similar to codeine but had a faster onset of action.

One half of the sample was told that the cost of treatment was \$2.50 per pill. The other half was told that the cost was discounted to \$0.10 per pill. Allocation to treatment group was random, and no reason was provided for the discounted cost. The subjects did not know the purpose of the study, and the study raters did not know the group to which the subjects had been randomized.

Subjects used a visual analog scale to rate pain at different intensities of electrical shock (mean = 18 shocks per subject). Important findings of the study are summarized in Table 3. In brief, analgesia was significantly greater with the regular-price pill than with the discounted pill.

Critical Appraisal and Clinical Importance

Both of the "placebo cost" studies^{5,6} found that placebo was more effective when its stated cost was higher. Perhaps greater expectations, generated by higher costs, mediate a greater placebo response. If this conclusion can be generalized, patients may equate lower costs with lesser treatment efficacy and thereby benefit less with generic drugs because these are cheaper than the branded originals. This

Table 3. Findings of the Study⁶ on Discounted and Regular-Price Placebos as Analgesic Medication^a

1. Mean pain reduction was observed in 85% vs 61% of subjects receiving the costlier vs cheaper pill, respectively; the advantage for the costlier pill was statistically significant.
2. The advantage for the costlier vs cheaper pill (81% vs 56%, respectively) remained significant even when only the 50% most painful shocks for each participant were examined.
3. Averaged across all stimulus intensities, the costlier pill was associated with greater pain reduction; the advantage was more apparent at higher stimulus intensities.
4. The costlier pill was associated with numerically greater pain reduction for 26 of the 29 stimulus intensities tested; the remaining 3 stimulus intensities were at the bottom of the scale, and the difference between the 2 pills (at these 3 stimulus intensities) was not statistically significant.

^aSubjects were assessed using a visual analog scale.

concern is especially important in psychiatry because there is a strong placebo effect in many psychiatric disorders.⁷

Some points, however, merit consideration. The most important point is that both of the “placebo cost” studies reviewed^{5,6} were single-dose studies. There is no evidence to suggest that treatment cost will continue to influence treatment outcomes across weeks, months, or years of treatment, as is necessary in most psychiatric conditions. Next, both studies were conducted in the artificial setting of a laboratory rather than in the clinic, and the analgesia study⁶ was conducted in healthy volunteers who were paid for participation rather than in patients who had pain of clinical origin. Finally, no study has demonstrated the effect of treatment cost on clinical outcomes in psychiatric disorders, and no study has examined the effect of treatment cost using the same active drug instead of the same placebo.

Just as there are nonspecific factors in psychotherapy, there are nonspecific factors in psychopharmacology. Therefore, limitations notwithstanding, both studies^{5,6} remind clinicians that patient expectations are important and that treatment cost can, perhaps, influence treatment expectations and thereby treatment outcomes. Clinicians who prescribe generic drugs should therefore reassure patients that lower cost does not imply lower potency. Other concerns in the generics versus originals debate are out of the scope of this article and are not discussed here.

Parting Notes

For those who are interested, ethical issues related to the Parkinson disease “placebo cost” study⁵ were discussed by the authors of the study⁵ as well as in an accompanying editorial.⁸

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