There's More to Placebo-Related Improvement Than the Placebo Effect Alone

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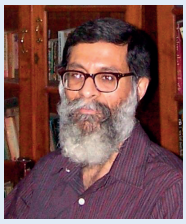

Each month in his online column, Dr Andrade offers practical knowledge, ideas, and tips in psychopharmacology to *JCP* readers in psychiatric and general medical settings.

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Most patients who receive pharmacotherapy improve with treatment. It is generally believed that some of this improvement is due to the specific action of the medication and that the rest is due to the placebo effect. This is not quite the case, because there are many additional reasons why treated patients get better, whether they receive active drug or placebo (Table 1). These reasons are discussed below to help clinicians better understand what drives improvement in clinical trials as well as in clinical practice.

Why Patients Improve With Treatment: The Effects of Medication and Placebo

The medication effect. This is the response that is mediated, hypothetically, by the mechanisms ascribed to the drug that is administered. Examples of such mechanisms include serotonin reuptake inhibition, dopamine D_2 receptor blockade, and neuroplasticity changes.

The medication effect is typically characterized as the extent to which response in the medication group exceeds that in the placebo group. Besides the medication effect, with the possible exception of the halo effect, the remaining mechanisms listed in Table 1 are common to both drug and placebo. In a clinical trial, therefore, if depression ratings improve by 10 points with placebo and by 14 points with the trial drug, the medication effect is represented by the extra 4 points of improvement. Or, in the same trial, if 40% of placebo-treated patients meet response criteria at the end of the study, and if this figure is 55% with the trial drug, then the medication effect is represented by the extra 15% in the response rate.

However, this does not mean that medication accounts for only 4 points of improvement in depression ratings or that medication is responsible for response in only 15% of treated patients. It is quite likely that different patients have different capacities to respond to treatment, based on a variety of genetic, illness, environmental, and other factors; the effects of the different mechanisms listed in Table 1 may overlap to varying and unmeasurable extents in the elicitation of this response. As an example, overlap in the effects of apomorphine and placebo has been demonstrated using positron emission tomography in Parkinson's disease patients.[1]

The placebo effect. The placebo effect is the response mediated by the belief that the patient holds regarding the benefits of the administered treatment. Placebo mechanisms probably vary with the condition being treated. For example, in patients with pain, placebo mechanisms may involve the release of endogenous opioids[2] and endogenous cannabinoids[3]; in patients with Parkinson's disease, placebo mechanisms may involve the release of dopamine.[1] Such mechanisms, in turn, may depend on expectancy and classical conditioning[4]; after all, if the sound of a bell can trigger salivation or if the sight of food can stimulate the secretion of gastric juices, then perhaps the sight of a doctor's office, the swallowing of a colored pill, or the prick of a syringe may trigger the release of the appropriate chemicals for the relief of pain, anxiety, or depression. Nevertheless, what the placebo mechanism is in complex psychiatric disorders is poorly understood. How faith in medication, expectation, and classical

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conditioning cause the release of opioids, cannabinoids, dopamine, or other chemicals (or how they trigger other mechanisms of response) is an even greater mystery.

The placebo effect probably adds to the medication effect; for example, when patients do not know that they are receiving treatment, the benefits of analgesic medications are less pronounced than when these medications are given in full view.[5] The placebo effect may be enhanced when patients are unblinded because of medication-induced adverse effects, and, conversely, the placebo effect may be diminished when patients believe that they are receiving placebo, such as when medications are free of discernible biological effects, whether favorable or adverse.

In clinical trials, the placebo effect may be enhanced by the hype surrounding the trial drug. The placebo effect may also be greater when there is more than 1 active treatment arm because patients realize that they have a higher chance of receiving active medication.[6,7]

In a clinical trial in which depression ratings improve by 10 points with placebo, and in which 40% of placebo-treated patients improve, it is technically incorrect to conclude that placebo mechanisms are entirely responsible for the improvement or the response rate noted. In fact, there are many reasons for improvement beyond those related to the placebo effect; these may overlap with the placebo effect to varying and unmeasurable extents in the elicitation of improvement. These reasons are listed in Table 1 (in no particular order) and are discussed in the next section. Readers who wish to learn more about the subject are referred to the useful reviews of Ernst and Resch,[8] Oken,[9] and Finniss et al.[10]

- Besides a true medication effect and a true placebo effect, there are a large number of overlapping reasons why patients improve.
- Reasons for improvement include nonspecific psychotherapeutic effects, regression toward the mean, spontaneous response or remission, the Rosenthal effect, the Hawthorne effect, the halo effect, favorable changes in the stress-support dimension, and known or unknown use of other treatments.
- Clinicians should be aware that some of these mechanisms result in fleeting improvement or in false impressions of improvement only. They should make efforts to enhance the placebo response and recruit nonspecific psychotherapeutic effects and other mechanisms that result in true improvement.

Why Patients Improve With Treatment: Looking Beyond the Drug and Placebo Effects for Nonspecific Mechanisms Common to Drug and Placebo Treatments

Nonspecific psychotherapeutic effects. The clinical interaction during initial and follow-up visits is usually emotionally supportive to the patient because clinicians and research teams are generally welcoming, display concern, spend time with the patient, and allow the ventilation of illness-related concerns; interactions are often characterized by other nonspecific, supportive psychotherapeutic elements as well, such as those described in the psychotherapy literature.[11,12] Although there is no formal intention to provide psychotherapeutic support, such support is built into clinician-patient interactions and can result in clinical improvement.

Regression toward the mean. Patients who come for consultation are usually ill, not well, and patients who enter clinical trials tend to be more ill than average (those with milder illness are usually screened out, not recruited). Therefore, given that the severity of illness fluctuates across time, there is a greater chance of illness fluctuation occurring in the direction of improvement than in the direction of worsening. This phenomenon is known as *regression toward the mean*.[13]

In clinical trials, regression toward the mean may also be a spurious consequence of recruitment pressure when investigators inflate illness ratings and randomize patients who do not meet the inclusion criteria for illness severity. When such patients are correctly rated at the next visit, their illness scores appear to have "improved."

Spontaneous response or remission. It is well known that, given sufficient time and a favorable environment, episodes of unipolar depression[14] or bipolar illness[15] may spontaneously remit. As the duration of follow-up increases, progressively fewer patients with attention-deficit/hyperactivity disorder continue to meet diagnostic thresholds.[16] Spontaneous fluctuations in the severity of obsessive-compulsive disorder[17,18] may be so large as to meet criteria for response. Remission with the passage of time has also been described in dysthymia[19] and generalized anxiety disorder.[20] Thus, with many psychiatric disorders, the longer the treatment duration (whether with active drug or placebo), the greater the chance that at least some patients will respond or remit as a function of the natural course of illness.

The Rosenthal effect. This is also known as the "Pygmalion effect" or the "expectancy effect."[21] In therapeutic contexts, clinicians and raters may attach less importance to reported symptoms as the weeks pass because they expect patients to get better across time. This results in a false impression of improvement. Expectancy effects can also influence the quality of interactions between clinicians and patients, resulting in a greater placebo effect, or in greater psychotherapeutic effects and hence true improvement.

The Hawthorne effect. The Hawthorne effect is said to occur when the act of measurement influences the value of what is being measured.[22] The hospital environment may be less stressful to the patient than a critical-hostile domestic environment; the process of rating may be laden with implicit supportive-appreciative interactions that make the patient feel transiently better; the patient may consciously or unconsciously provide socially desirable responses that

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indicate more improvement than is real. In all of these situations, the improvement is untrue or transient. Nevertheless, there is some overlap in concepts and mechanisms among the Hawthorne effect,[22] the Rosenthal effect,[21] the Heisenberg effect,[23] and nonspecific psychotherapeutic effects, as described in this article.

The halo effect. The term *halo effect*[24] describes what occurs when improvement in one symptom domain results in expressions of optimism and well-being that decrease the adverse impact of symptoms in other domains even though those symptoms have not improved. For example, if an antidepressant drug is associated with sedation, the resultant improvement in the specific domain of sleep may magnify perceptions of treatment response, making the patient and/or rater attach less importance to the continued presence of other symptoms and thereby giving the false impression of general improvement. If placebo is associated with similar beneficial changes, it is possible that the halo effect may spuriously magnify improvement with placebo, as well.

Decreased stress and increased support. Entry into treatment, whether in routine clinical practice or in a clinical trial, is often associated with secondary life changes that may or may not have been suggested by the clinical team. Such changes include avoiding stressful situations, decreasing current commitments, receiving greater support from the family, and so on. Given the well-known role of the stress-support dimension in mental illness, there is every reason to expect that less stress and greater social and family support could assist in recovery.

Use of other treatments. Patients may use medications other than those advised by their clinicians. Such medications could include over-the-counter drugs, prescription drugs left over from earlier consultations, and treatments belonging to alternative medicinal systems. These treatments may be knowingly used by the patients or surreptitiously administered by family members. Any or all of these may contribute to improvement.

Clinical trial protocols often permit the emergency use of additional medications to reduce insomnia, agitation, or other troublesome symptoms. These also contribute to lower symptom ratings.

What Does All This Mean for Nondrug Interventions?

Nondrug interventions in psychiatry include psychotherapy, yoga, meditation, aerobic exercise, acupuncture, brain stimulation therapies, and others. All of the points listed in Table 1 are also applicable to nondrug interventions, with the name of the intervention substituted in place of medication (eg, "true cognitive behavior therapy effect" in place of "true medication effect"). Importantly, however, in clinical trials of many nondrug interventions, it is virtually impossible to create appropriate controls; for example, subjects cannot be blinded to the fact that they are or are not exercising, meditating, or receiving psychotherapy. In such circumstances, readers should be aware that the treatment group is biased toward favorable outcomes for far more reasons than just the true treatment effect; this is because waitlist or untreated controls do not have the opportunity to benefit from most of the mechanisms listed in Table 1. A further consequence is that number needed to treat statistics will be more favorable for unblindable interventions than, for example, for drugs, making it potentially fallacious to compare these statistics between, say, psychotherapy and medication clinical trials.

Table 1. Reasons Why Patients Improve With Medications[a]

True medication effect
True placebo effect
Nonspecific psychotherapeutic effects
Regression toward the mean
Spontaneous response or remission
Rosenthal effect
Hawthorne effect
Halo effect
Decreased stress and/or increased family and social support
Use of other treatments

[a]With the exception of the true medication effect and the possible exception of the halo effect, all of these mechanisms are common to active drug and placebo groups in randomized, double-blind, placebo-controlled clinical trials. Some of these mechanisms may work both ways; that is, they may also worsen treatment outcomes.

Other issues germane to the impact of placebo and related mechanisms (Table 1) on clinical trial research are beyond the scope of this article and are not discussed.

What Does All This Mean for Clinical Practice?

Some of the mechanisms listed in Table 1 may not result in improvement; they may result in adverse effects, such as with nocebo action.[25,26] Some of the listed mechanisms may result in inhibition of improvement or in worsening in illness severity, such as with antidepressant-induced suicidality.[27] Worsening may also occur if the clinical trial procedures are stressful, or if the halo effect surrounds an adverse effect of medication, or if alternative medicinal system treatments diminish the effects of the administered drug (as when St John's wort induces the metabolism of medications metabolized by cytochrome P450 3A4[28]).

Clinicians need to be aware that there are many reasons why patients improve with treatment, and that not all apparent improvement is true improvement. Clinicians should make efforts to enhance the placebo response and to recruit nonspecific psychotherapeutic effects and other mechanisms (Table 1) that purvey true improvement; some ideas in this regard have been provided by Brody.[29] For example, all of the following could enhance clinical effectiveness: the exhibition of genuineness, warmth, empathy, enthusiasm, and confidence; building of trust; presentation of a professional appearance and working in a professionally impressive environment; use of clinical rituals; working within a framework of patient preferences; permission of ventilation; and provision of emotional support and reassurance. It is noteworthy that the importance of nonspecific factors in psychopharmacology was recognized nearly half a century ago.[30]

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Concluding Note

It is commonly stated that there is a considerable placebo response in most psychiatric disorders. Readers will now be aware that there is much more to placebo group improvement than placebo mechanisms alone.

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