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Dr. Brown discusses how to incorporate the placebo effect into clinical practice

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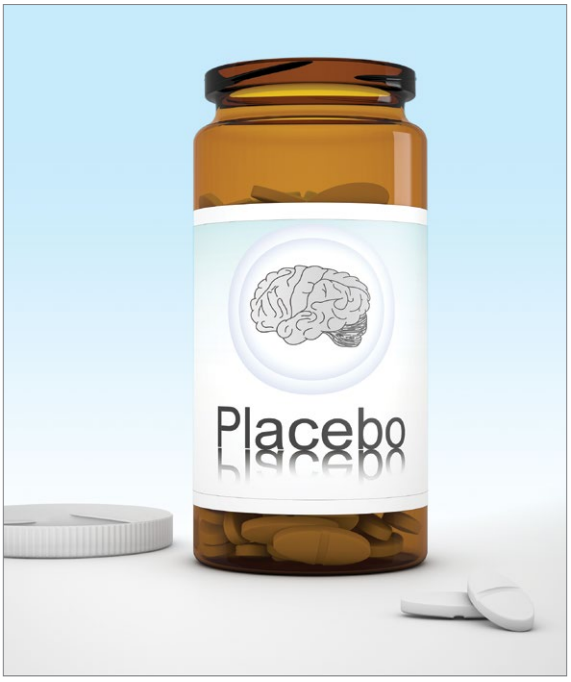
The placebo effect in psychiatric practice

This well-known effect can be harnessed to improve treatment



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"It is a mystery how a ubiquitous treatment used since antiquity was unknown, unnamed, and unidentified until recently. It is even more remarkable because this is the only treatment common to all societies and cultures."[1]

The treatment discussed above is not a specific pill, surgery, plant, or herb. Rather, the authors are referring to *placebo*. Indeed, the history of medical treatment is largely a chronicle of placebos. When subjected to scientific scrutiny, the overwhelming majority of treatments have turned out to be devoid of intrinsic therapeutic value; they derived their benefits from the placebo effect. Despite these benefits, the term "placebo" comes with unfortunate baggage. Latin for "I shall please," it is the first word of the Christian vespers for the dead. In the 12th century these vespers were commonly referred to as placebos. By the 1300s, the term had become secular and pejorative, suggesting a flatterer or sycophant. When the word entered medical terminology in the late 18th century, the negative connotation stuck. A placebo was defined as a medicine given to please patients rather than to benefit them. In the modern era, the lack of pharmacologic activity became part of the definition as well.

The word placebo brings with it connotations of deception, fakery, and ineffectiveness. But one of the things about placebos that contribute mightily to the health care community's aversion toward them is, in fact, their effectiveness. They bring relief across a wide range of medical conditions.[2] In doing so, placebos impugn the value of our most cherished remedies, hamper the development of new

Disclosures
The authors report no financial relationships with any company whose products are mentioned in this article or with manufacturers of competing products.

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Patients with panic disorder or mild to moderate depression get almost as much relief from placebo as from conventional treatment

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therapeutics, and threaten our livelihoods as health professionals.[3]

Placebos often are conceptualized as any treatment that lacks intrinsic therapeutic value, such as sugar pills. But looking at what placebo treatment actually entails, both in placebo-controlled treatment trials and in clinical settings, suggests a more comprehensive definition. Placebos encompass all the elements common to any treatment or healing situation. These include a recognized healer, evaluation, diagnosis, prognosis, plausible treatment, and most importantly, the expectation that one will recover. Along these lines, the placebo response can be thought of as the response to the common elements of the treatment or healing situation.[3]

Research regarding the placebo effect has mushroomed in the past 2 decades. Over this time, we have learned a good deal about both the mechanisms underlying the placebo effect and how the placebo effect can be applied to enhance the benefit of conventional treatment. Brain imaging technology has revealed that when placebo treatment alleviates pain, Parkinson's disease, and depression, brain changes occur that are similar to those observed with active pharmacologic treatment.[4,5] Recent studies also show that deliberate, open (nondeceptive) use of placebo can improve the symptoms of several conditions, including depression, pain, and irritable bowel syndrome.[6] Furthermore, intermittent substitution of placebo pills for pharmacologically active treatment in a conditioning paradigm can be as effective as the "real" treatment.[7] Also, research over the past decade has verified that certain common features of the treatment situation, particularly the quality of the doctor–patient encounter, contribute to the placebo response and have a demonstrable impact on the outcome of treatment.[8] Clearly, the placebo effect has gone from being simply a nuisance that interferes with the evaluation of new treatments to a variable worthy of study and application in its own right. Although, for the most part, clinical practice has not kept up with these advances.

Placebos seem to have their greatest impact on the subjective symptoms of disease—pain, distress, and discouragement. It should come as no surprise, then, that placebos are particularly effective in certain psychiatric conditions. In some forms of anxiety and depressive disorders, for example, distress *is* the illness, and placebos reliably bring relief. Patients with panic disorder, mild to moderate depression, or generalized anxiety disorder get almost as much relief with placebo as they do with conventional treatment (about one-half improve with placebo).[9-11] But <20% of those with obsessive-compulsive disorder improve with placebo, and placebo response rates are also low in patients with schizophrenia or dementia. Mania, attention-deficit/hyperactivity disorder (ADHD), and severe depression fall somewhere in the middle.[3]

Harnessing the placebo response

There may be a few circumstances in psychiatric practice when it makes sense to intentionally prescribe a placebo as treatment, and we discuss those below. But far more frequently, what we know about the elements that contribute to the placebo effect can be applied to enhance the benefits of any treatment. Patients might be best served if deliberate mobilization of the placebo effect was a standard adjunct to conventional clinical care.

Various components of the treatment situation, collectively referred to as placebo, are a powerful antidote for illness, and some of these healing components exert their influence without special activity on the clinician's part:

- Simply seeking psychiatric care can bring relief by providing some sense of control over distressing symptoms. The standard trappings of the office or clinic and customary office procedures—from the presentation of one's insurance card to taking a history—offer reassurance and evoke the expectation that improvement or recovery is around the corner.
- The comfort provided by the psychiatrist's presence is enhanced when patients feel that they are in the hands of a recognized healer. Psychiatrists inspire confidence when they look like a psychiatrist, or more precisely, like the patient's idea of what a psychiatrist should look like. In our culture, that means a white coat or business attire.

A thorough evaluation is one of the common treatment elements that does the most to reduce distress and inspire confidence. The quality of an evaluation bears a strong relationship to patients' satisfaction with the medical encounter, and can influence the amount of disability they suffer.[3,12-15]

Although guidelines for conducting effective psychiatric interviews have been around for almost 100 years, psychiatrists vary considerably in the extent to which they elicit complete and accurate information, build rapport, give patients the sense that they are listened to, and provide a thorough assessment. The degree to which patients feel that the clinician is responsive to their concerns depends as much on the style of the interview as on the amount of time devoted to it. Nonverbal behavior can carry the message that the clinician is paying full attention. Something as simple as not answering the phone during an interview (this seems obvious, but a surprising and troubling number of mental health professionals take phone calls during interviews and treatment sessions) conveys an important message about the importance that the clinician places on the patient's problems.[3]

The idea that the treatment situation itself provides reassurance and reduces distress, and in doing so, powers a good bit of the placebo effect, is enshrined in such concepts as the importance of good bedside manner. Many feel that the doctor's thoughtful attention, positive regard, and optimism—so valued by patients—are justified on humanitarian grounds alone; actual evidence that this caring behavior contributes to healing isn't required. To many, the healing properties of the treatment situation are self-evident. But as the costs of health care snowball and the demands for efficiency and cost-effectiveness rise, the time that psychiatrists can devote to patients has dwindled. Third-party payors demand evidence, beyond intuition and common sense, that diagnostic procedures and treatments have some usefulness, and rightly so.

Is there any evidence that the common components of the treatment situation provide benefit?[3] More specifically, does the quality of the doctor–patient relationship and the patient's feelings about a therapeutic encounter promote healing? Several studies suggest that the doctor–patient relationship has a demonstrable impact on symptom relief.[16] In 1 study, oncologists were randomly assigned to receive a Communication Skills Training (CST) program or not. CST included a 1.5-day face-to-face workshop and 6 hours of monthly videoconferencing that focused on improving communication skills with patients.[17] Lessons included building rapport, engaging in appropriate eye contact, and normalizing difficult experiences. One week after initially consulting with their physician, patients who saw an oncologist in the CST group experienced less anxiety and depression than those who saw an oncologist who did not receive CST. The benefit of CST for patient anxiety mostly persisted at a 3-month follow-up.

A recent meta-analysis pooled the results of 47 studies to examine the relationship between how much trust patients have for their doctors and health outcomes. There was a small to medium association: More trust was associated with greater improvement.[18] It is possible that a good doctor–patient relationship enhances expectancies. However, it is also likely that a positive therapeutic relationship is inherently soothing and reduces distress or dysfunction independent of expectation. Regardless of the precise mechanism, these studies warrant attention. We all understand that it is important on ethical grounds to treat patients with respect and kindness. Research shows that this type of behavior also promotes recovery.

Patient expectations. The idea that expectation of improvement has a major impact on treatment outcome is firmly grounded in research on the placebo effect. Studies have shown that what people expect to experience as an outcome of treatment has a substantial impact on what they actually experience. In a classic study, a doctor told some patients with symptoms of minor illness that they would feel better soon and another group with the same symptoms that he didn't know what ailed them.[19] Two weeks later, 64% of patients in the "positive expectation" group were improved, compared with only 39% of patients in the "negative" group. In another study, adults were exposed to an

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allergen that caused a skin reaction.[20] Hand lotion (ie, a therapeutically inert substance) was then spread on the skin. Patients were led to believe that the cream would either alleviate or exacerbate the itching. The experimentally-induced wheal-and-flare was measured in both groups a few minutes after the allergen and cream were applied. The wheal-and-flare were worse for participants in the group that expected exacerbation.

Not uncommonly, expectation can have more impact on clinical outcome than a drug's pharmacologic activity. In a double-blind placebo-controlled study, patients with depression were treated with St. John's wort, sertraline, or placebo.[21] They improved to the same extent with all 3 treatments. But when patients were asked to guess the treatment to which they had been assigned, those who thought they had received placebo showed little improvement, irrespective of which intervention they actually received, and those who guessed they had been given St. John's wort or sertraline showed uniformly large improvement, irrespective of which intervention they actually received (including placebo). The researchers concluded that "Patient beliefs regarding treatment may have a stronger association with clinical outcome than the actual medication received."

Psychiatrists who wish to use all the therapeutic tools at their disposal must attend to and manage patient expectations. One part of channeling a patient's expectation is to thoroughly assess the patient's beliefs regarding the efficacy of various treatments. If a patient's uncle said that a certain drug is a miracle cure for anxiety, and the patient believes it to be true, then that expectation must be taken into consideration. Many patients prefer alternative treatments to conventional therapies. As long as there is no reason to think an alternative treatment will cause harm, a compromise might be reasonable. For example, if a patient with schizophrenia wants to treat her symptoms with herbal tea, the psychiatrist could say, "In addition to the tea, I recommend that you also take clozapine. The combination is likely to improve your symptoms."[3] More than anything else, the words a psychiatrist uses when recommending treatment shape the patient's expectations. "You should be feeling a lot less anxious soon after you start taking this" has a different effect than "Try this. It may help."

Prescribing 'open-label' placebo

There may be some limited circumstances where an actual placebo (eg, a sugar pill) might be suitable as a treatment. These include when placebo and conventional treatment provide similar results and a patient is reluctant to take conventional medicine, or when there is no effective conventional treatment. The deceptive prescription of placebo (providing placebo and calling it a drug) has a long history and was considered ethical—and recommended by medical authorities—until the latter half of the 20th century. This practice was deemed unethical in the 1980s, because it was dishonest and violated patient autonomy. Because it was widely believed that placebos given openly would be ineffective, the end of placebo treatment seemed at hand. An intriguing body of evidence, however, suggests that placebos can be effective *even when patients know they are taking a placebo*. Patients given an "open-label" placebo are told something along the lines of "the pill being prescribed contains no medicine, but some people improve with it, perhaps because the pill stimulates the body's self-healing." Open-label placebo has been evaluated for depression,[22] low back pain,[23] irritable bowel syndrome,[24] neurosis,[25] allergic rhinitis,[26] and anxiety.[27] Most of these studies are small, and some were uncontrolled. Yet they consistently have shown that symptoms improve with a nondeceptive placebo, and improve to a greater extent than with no treatment.

The most recent trial is a promising example of the potential of open-label placebos. In this study, 96 patients with chronic low back pain were randomly assigned to 3 weeks of treatment as usual (TAU) or 3 weeks of TAU plus open-label placebo.[23] Patients who received open-label placebo were educated about the placebo effect and shown a film clip describing promising results of a prior open-label placebo study. They were then given placebo pills to be take once daily, and clearly told the pills contained no active

medication. After 3 weeks, patients in the TAU plus placebo group reported less pain and less disability than patients who received TAU without a placebo. Some patients even requested a placebo prescription at the end of the study.

The placebo response provides a rational basis for prescribing innocuous alternative therapies with no intrinsic therapeutic value. Patients who prefer and believe in the effectiveness of alternative remedies—herbal compounds, massage, magnets, homeopathic solutions, etc.—can be recommended these treatments to mobilize a placebo response.

Using a conditioning model. Prescribing a placebo to obtain a conditioned drug response has enormous but untapped clinical potential. Both animal and human research indicates that a wide range of drug responses, from immune suppression to motor stimulation, can be conditioned (a neutral stimulus, such as a pill or injection, associated with drug administration can in itself evoke the drug effect). In many conditioning or dose-extending models, a particular response to real medication (such as pain relief after analgesics) first becomes conditioned due to repeated exposure to the drug given in a particular vehicle. Then, the treatment shifts to some doses comprising of real medicine and some doses comprising of placebo. Because the drug response has been conditioned, it is thought that the response to an identically appearing placebo will mirror the drug response. The active drug often is only replaced by placebo for certain doses under a schedule of partial reinforcement, given the ubiquity of extinction (the conditioned response lessens when the conditioned stimulus is presented alone on repeated trials).

In 1 version of a conditioning study, children with ADHD were randomized to 1 of 3 groups.[28] One group (full dose) took the standard dose of medication for 2 months, a second group (reduced dose) took a standard dose during 1 month followed by a half dose during the second month, and children in the third group (reduced dose with placebo) took the standard dose plus a visually distinctive placebo during the first month, followed by a half dose plus the visually distinctive placebo during the second month. Not surprisingly, ADHD symptoms were worse among children in the reduced-dose group. However, there was no difference between those in the reduced-dose with placebo group and those in the full-dose group. It appears as though the symptom reduction associated with a 100% dose was an unconditioned response that could be mimicked with the addition of a placebo pill.

In another study, patients with psoriasis were randomly assigned to receive a full dose of active medication (0.1% triamcinolone cream) twice a day, or a full dose of active medication for 25% to 50% of the doses, with a placebo (moisturizing cream) given for the other 50% to 75% of the doses.[29] Relapse rates were not statistically different between groups.

These types of conditioning models hold great promise for psychiatry, particularly for substance use disorder (***Box***).[30,31] They suggest that medication regimens that provide less overall medicine may sometimes perform as well as a standard regimen. This could become a promising strategy

Box

Using placebo to treat substance use disorder

Substance use disorder (SUD) might be particularly well-suited to treat using a conditioning model, which involves prescribing a placebo to obtain a conditioned drug response. Alcohol-dependent patients respond well to placebo,[30] and buprenorphine is not substantially better than placebo at low or medium doses for treating opioid use disorder.[31] Furthermore, because opioids such as buprenorphine are frequently used to treat SUDs, the drugs designed to help with addiction can themselves be addictive. Alternative approaches to treating SUDs are needed, and the conditioning model and other methods outlined in this article should be explored. For example, if a conditioning model was as effective as a typical treatment regimen in preventing heroin relapse, the former approach would be strongly encouraged because patients would receive fewer doses of a potentially addicting drug. A conditioning design could also be explored as a way of minimizing prescription opioids among patients being treated for acute or chronic pain.

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Evidence suggests that placebo can be effective even when patients know they are taking a placebo

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Related Resource

- Wager TD, Atlas LY. The neuroscience of placebo effects: connecting context, learning and health. Nat Rev Neurosci. 2015;16(7):403-418.

Drug Brand Names

Buprenorphine • Buprenex, Suboxone
Clozapine • Clozaril
Sertraline • Zoloft
Triamcinolone • Aristocort A

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Clinical Point

Conditioning models suggest that regimens that provide less overall medication may perform as well as standard regimens

for minimizing the amount of medication a patient receives, thereby reducing toxicity and expense.

References

1. Shapiro AK, Shapiro E. The powerful placebo: from ancient priest to modern physician. Baltimore, MD: Johns Hopkins University Press; 1997.
2. Beecher HK. The powerful placebo. J Am Med Assoc. 1955;159(17):1602-1606.
3. Brown WA. The placebo effect in clinical practice. New York, NY: Oxford University Press; 2013.
4. Mayberg HS, Silva JA, Brannan SK, et al. The functional neuroanatomy of the placebo effect. Am J Psychiatry. 2002;159(5):728-737.
5. de la Fuente-Fernández R, Ruth TJ, Sossi V, et al. Expectation and dopamine release: mechanism of the placebo effect in Parkinson's disease. Science. 2001; 293(5532):1164-1166.
6. Charlesworth JEG, Petkovic G, Kelley JM, et al. Effects of placebos without deception compared with no treatment: a systematic review and meta-analysis. J Evid Based Med. 2017;10(2):97-107.
7. Colloca L, Enck P, DeGrazia D. Relieving pain using dose-extending placebos: a scoping review. Pain. 2016;157(8): 1590-1598.
8. Kaptchuk TJ, Kelley JM, Conboy LA, et al. Components of placebo effect: randomised controlled trial in patients with irritable bowel syndrome. BMJ. 2008;336(7651): 999-1003.
9. Khan A, Kolts RL, Rapaport MH, et al. Magnitude of placebo response and drug-placebo differences across psychiatric disorders. Psychol Med. 2005;35(5):743-749.
10. Walsh BT, Seidman SN, Sysko R, Gould M. Placebo response in studies of major depression: variable, substantial, and growing. JAMA. 2002;287(14):1840-1847.
11. Kirsch I, Deacon BJ, Huedo-Medina TB, et al. Initial severity and antidepressant benefits: a meta-analysis of data submitted to the Food and Drug Administration. PLoS Med. 2008;5(2):e45.
12. Kaptchuk TJ. Acupuncture: theory, efficacy, and practice. Ann Intern Med. 2002;136(5):374-383.
13. Kelley JM, Kraft-Todd G, Schapira L, et al. The influence of the patient-clinician relationship on healthcare outcomes: a systematic review and meta-analysis of randomized controlled trials. PLoS One. 2014;9(4):e94207.
14. Olsson B, Olsson B, Tibblin G. Effect of patients' expectations on recovery from acute tonsillitis. Fam Pract. 1989;6(3): 188-192.
15. Sox HC, Margulies I, Sox CH. Psychologically mediated effects of diagnostic tests. Ann Intern Med. 1981;95(6): 680-685.
16. Stewart MA. Effective physician-patient communication and health outcomes: a review. CMAJ. 1995;152(9): 1423-1433.
17. Girgis A, Cockburn J, Butow P, et al. Improving patient emotional functioning and psychological morbidity: evaluation of a consultation skills training program for oncologists. Patient Educ Couns. 2009;77(3):456-462.
18. Birkhäuer J, Gaab J, Kossowsky J, et al. Trust in the health care professional and health outcome: a meta-analysis. PLoS One. 2017;12(2):e0170988.
19. Thomas KB. General practice consultations: is there any point in being positive? Br Med J (Clin Res Ed). 1987;294(6581):1200-1202.
20. Howe LC, Goyer JP, Crum AJ. Harnessing the placebo effect: exploring the influence of physician characteristics on placebo response [published online May 9, 2017]. Health Psychol. doi: 10.1037/hea0000499.
21. Chen JA, Papakostas GI, Youn SJ, et al. Association between patient beliefs regarding assigned treatment and clinical response: reanalysis of data from the Hypericum Depression Trial Study Group. J Clin Psychiatry. 2011;72(12):1669-1676.
22. Kelley JM, Kaptchuk TJ, Cusin C, et al. Open-label placebo for major depressive disorder: a pilot randomized controlled trial. Psychother Psychosom. 2012;81(5):312-314.
23. Carvalho C, Caetano JM, Cunha L, et al. Open-label placebo treatment in chronic low back pain: a randomized controlled trial. Pain. 2016;157(12):2766-2772.
24. Kaptchuk TJ, Friedlander E, Kelley JM, et al. Placebos without deception: a randomized controlled trial in irritable bowel syndrome. PLoS One. 2010;5(12):e15591.
25. Park LC, Covi L. Nonblind placebo trial: an exploration of neurotic patients' responses to placebo when its inert content is disclosed. Arch Gen Psychiatry. 1965;12(4): 336-345.
26. Schaefer M, Harke R, Denke C. Open-label placebos improve symptoms in allergic rhinitis: a randomized controlled trial. Psychother Psychosom. 2016;85(6):373-374.
27. Aulas JJ, Rosner I. Efficacy of a non blind placebo prescription [in French]. Encephale. 2003;29(1):68-71.
28. Sandler AD, Glesne CE, Bodfish JW. Conditioned placebo dose reduction: a new treatment in attention deficit hyperactivity disorder? J Dev Behav Pediatr. 2010;31(5): 369-375.
29. Ader R, Mercurio MG, Walton J, et al. Conditioned pharmacotherapeutic effects: a preliminary study. Psychosom Med. 2010;72(2):192-197.
30. Weiss RD, O'Malley SS, Hosking JD, et al; COMBINE Study Research Group. Do patients with alcohol dependence respond to placebo? Results from the COMBINE Study. J Stud Alcohol Drugs. 2008;69(6):878-884.
31. Mattick RP, Breen C, Kimber J, et al. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. Cochrane Database Syst Rev. 2014;(2):CD002207.

Bottom Line

Elements that contribute to the placebo effect, such as the quality of the doctor–patient relationship and patient expectations, can be applied to enhance the benefits of any treatment. Deliberate, open (nondeceptive) use of placebo can improve the symptoms of several conditions, including some depressive and anxiety disorders.