



Great expectations

New research is leading to an understanding of how placebos work — findings that may lead to more effective treatments and better drug research.

By Stacy Lu • *Monitor* staff



To watch Dr. Bret Rutherford discuss “Deconstructing the Placebo Response in Antidepressant Trials” as part of Columbia University’s Psychiatry Grand Rounds, go to www.veomed.com/va07-2899020-3

Last year, 40 people participated in a study that tested, essentially, the power of their beliefs. University of Colorado at Boulder psychology student and neuroscience researcher Scott Schafer and colleagues asked participants to apply a “powerful analgesic” on their hands and arms. The researchers then administered small bursts of heat where the cream had been applied. The cream was really petroleum jelly, but as expected, participants reported that the so-called powerful

cream protected them from feeling as much of a burn as a control cream. Even when the researchers showed participants that the active cream was just petroleum jelly, it made little difference. The participants still reported less pain from the heat when they were re-tested with it versus the control cream (The Journal of Pain, 2015).

Welcome to the world of open-label placebo research, where it’s not a question of whether placebos work, but how.

For decades, placebo response was generally seen as “an uninteresting source of noise that interfered with pharmacological research,” says Bret Rutherford, MD, assistant professor of clinical psychiatry at Columbia University.

But these days, scientists are studying placebos as a psychobiological phenomenon and the placebo response as a potentially important part of the success of many medical treatments. Researchers are using psychological assessments, brain scans and genotyping to better understand how placebo responses work and to identify who may be most likely to respond to them.

The research could lead to changes in how psychologists and others conduct research and in how health-care professionals treat patients.

“Understanding the mechanisms underlying placebo effects can shift our understanding of when and how treatments work and how to use them — not in terms of giving people fake drugs, but in terms of changing the principles by which we learn to care for each other,” says Tor Wager, PhD, an associate professor of psychology and neuroscience at the University of Colorado at Boulder, who worked with Schafer on the open-label cream study.

Like cognitive therapies, Wager says, placebos tap into people’s beliefs that there’s hope and that they can get better.

How the mind makes medicine

Researchers have been examining placebos for centuries. In 1784, Benjamin Franklin tested whether magnetic force

fields could cure illnesses, a notion that Austrian physician Franz Anton Mesmer had profitably introduced and used in his practice. In Franklin’s experiments, participants responded dramatically to plain water they were told had been “mesmerized.” These days, researchers use neuroimaging to see how our brains respond to placebos and have found that placebos mimic symptom relief for a number of ills.

For example, a meta-analysis of 25 neuroimaging studies of pain and placebos conducted by Wager and Lauren Atlas, PhD, of the National Center for Complementary and Integrative Health (NCCIH), found that people who took placebos and expected to have reduced pain had less activity in brain regions often associated with pain processing, including the dorsal anterior cingulate, thalamus and insula (Handbook of Experimental Pharmacology, 2014).

Though placebos may work through various mechanisms, research suggests that they have the greatest effect in neural systems involved with processing reward seeking, motivation and emotion. Placebos seem to be particularly effective in patients with depression, Parkinson’s disease and pain. All three conditions, Atlas says, involve the neurotransmitter dopamine.

“They’re also all areas where people can consciously monitor their own treatment results: ‘I know how much pain I’m feeling’ or ‘I know how slow my movements are.’ That’s why neuroimaging markers of placebo response are so important when paired with subjective reports. We can now show that when people say they’re getting better, they really are.”

In one study of patients with Parkinson’s disease, Wager and colleagues found that simply expecting medication altered brain activity in the striatum and ventromedial prefrontal cortices — brain areas associated with reward learning — in ways similar to actual dopaminergic medication (Nature Neuroscience, 2014). And in a recent study of patients with depression, Andrew Leuchter, MD, and colleagues at the University of California, Los Angeles, found that participants who received placebo pills and supportive care did better than those who had only

supportive care. These results were closely tied to the patients' expectations of how well the pills would work (British Journal of Psychiatry, 2014).

Wager says this, too, makes sense according to the neuroscience of placebo effects, noting that depression is a motivational disorder as much as a mood disorder. "Patients can't get out of bed — they can't muster up the energy. The disorders that show the most reliable placebo effects are those in which the brain's motivational circuitry, including the prefrontal cortex and striatum, plays an important role."

Beliefs and expectations are a potent mix, Wager says, and future neuroimaging research must try to tease out how much of a placebo response is due to conscious expectations versus an unconscious learning from prior experiences. Expectations can be influenced by verbal instructions, nonverbal cues about care, and other elements of the treatment context, whereas unconscious learning requires prior experiences of success (or failure) with a treatment, such as experiencing pain relief after taking a pill. In one study of people with migraines, placebos elicited a response without any verbal cue to effectiveness. Slavenka Kam-Hansen, MD, and colleagues openly labeled placebo pills for some patients, who reported as much pain relief as those who also got a placebo but had been told they'd received a real medication (Science Translational Medicine, 2014).

Identifying responders

Scientists are also exploring who might respond best to placebos. Research suggests that children appear to be particularly receptive to the placebo effect. Peter Krummenacher, PhD, of the University of Basel in Switzerland, tested 6- to 9-year-olds with a placebo or control treatment. The placebo was a "topical analgesic" that the children were told might affect how they sensed applied heat. Their placebo response was 5.6 times greater than adults in a similar study (The Journal of Pain, 2014).

"Conditioning and learning play a crucial role, especially in infants, before we can use the power of language," says Luana Colloca, MD, PhD, an associate professor at the University of Maryland, Baltimore. "Suggestibility may be higher in children, and they also have less negative experience and experience of disease. And learning mechanisms are powerful at that stage of life."

Studies also suggest that people who respond more to rewarding stimuli show larger placebo effects, Atlas says. One of the most thorough studies on placebo and personality markers, conducted by John Kelley, PhD, and colleagues at Harvard Medical School, found that patients with irritable bowel syndrome (IBS) who responded best to placebo acupuncture tended to be female, agreeable and extroverts who were open to new experiences, but only in a subgroup of participants who had augmented encounters with a health practitioner — warm, communicative and empathic — when receiving the placebo (Psychosomatic Medicine, 2009).

Since then, a meta-analysis by Kelley and colleagues of 13 studies showed that the quality of clinician-patient relationships

in terms of measures like empathy, communication and better attention to nonverbal signals, played a small but significant role in health outcomes for various conditions (PLOS ONE, 2014).

The findings suggest that a focus on human relationships should always be at the forefront of treatment, Kelley says, adding, "I'm very interested in the degree to which [physicians] who have good outcomes are practicing an intuitive form of psychotherapy. They're listening to the patients, helping the patients believe a treatment works. Although this is often referred to as a placebo effect, it's really a relationship effect."

Other research suggests that social influences determine who responds to placebos. Colloca and colleagues found that study participants who watched others benefit from a pain medicine that was actually a placebo had about the same response to it as participants who were exposed to the pain relief. Participants who responded most were also rated as more likely to empathize with other people overall (European Journal of Pain, 2014).

A better knowledge among clinicians of how to create placebo responses using verbal prompts and how to maximize interactions with patients can boost treatment effectiveness, Colloca says. "If you are aware of placebo mechanisms, you are more careful about your communication style, the time you spend with your patient, the words you choose."

Columbia's Rutherford says setting expectations may be particularly helpful when it comes to antidepressant medications. While there is debate about how much of their effect for mild depression is due to the placebo response, he advises psychologists to maximize all potential effects by helping patients already on or interested in medication to believe the pills will work.

"Providing supportive care and eliciting a positive expectancy of improvement — obviously within the bounds of truthfulness — seem to be a very powerful treatment for mild depression," he says. "Whether you use a benign pill or

Further reading

- Atlas, L. Y., & Wager, T. D. (2014). A meta-analysis of brain mechanisms of placebo analgesia: Consistent findings and unanswered questions. *Handbook of Experimental Pharmacology*, 225, 37–69.
- Benedetti, F., Carlino, E., & Pollo, A. (2011). How placebos change the patient's brain. *Neuropsychopharmacology*, 36(1), 339–354.
- Colloca, L., Klinger, R., Flor, H., & Bingel, U. (2013). Placebo analgesia: Psychological and neurobiological mechanisms. *Pain*, 154(4), 511–514.
- Rutherford, B. R., Wall, M. M., Glass, A., & Stewart, J. W. (2014). The role of patient expectancy in placebo and nocebo effects in antidepressant trials. *Journal of Clinical Psychiatry*, 75(10), 1040–1046.

psychotherapy is for researchers to study.”

Genetics may count, too. Kathryn Hall, PhD, and colleagues at Harvard Medical School revisited the patients with IBS in Kelley’s study and found that participants with a specific genotype related to having more dopamine in the prefrontal cortex reported a larger effect from a placebo treatment for their symptoms as compared with participants with a genotype that produces less dopamine in the prefrontal cortex (*PLOS ONE*, 2012). In addition, those who had the more positive and supportive “augmented” treatment encounter with a health professional had a six-fold greater improvement in symptoms than patients who had a “neutral” encounter.

The psychology of medicine

Most experts agree drug research will benefit from a better understanding of placebos.

“The combined R&D budget for the top pharmaceutical companies is over \$90 billion per year, yet probably few or no studies really consider joint behavioral interventions, expectations and the state of a patient’s psychology when they are evaluating drug treatment,” says Wager. “They’re not looking at psychological interactions between patients’ psychological and brain states and drug effects.”

Ongoing placebo research may also help scientists fine-tune studies. In the future, drug researchers might use a multidisciplinary approach to identify who responds to placebo and by how much, based on psychological profiles, DNA studies that identify genetic variants, and brain scans that test for reward response potential, Colloca says. Such tests might even influence how psychologists work, she says.

“Psychologists may take advantage of this phenomenon to develop their strategies and therapeutic plans, perhaps to determine if a person may require longer treatment or multiple approaches, as compared to another patient who may benefit from a specific intervention and placebo responses,” she says.

That said, funding for research in the area is a challenge, says Kelley, adding, “There’s no company with a specific interest in persuading doctors to be more patient-centered.” He is currently doing research on ways placebos might help

cancer patients cope with the side effects of oncology medications, an area he says is promising because many patients are eager for approaches that minimize the number of additional drugs they need to take to manage side effects.

In the end, patients’ interests may help drive placebo research. Rather than fearing they’ve been had, patients are often pleased to discover that they can contribute to their own healing, experts say.

“Patients are interested and enthusiastic about it,” says Colloca, who conducted a phone survey of 853 people about their attitudes on placebos in medical care (*British Medical Journal*, 2013). “They realize that beliefs and expectations and the ritual around a clinical visit are more than just a sugar pill.” n



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