The placebo effect is a phenomenon in which an inactive substance - such as a sugar pill, saline solution, or another so called ‘fake treatment’ which should have zero therapeutic impact when given to a patient as treatment - has a mysteriously beneficial effect.

The placebo effect was first observed by an American medic named Henry Beecher on an Italian battlefield toward the end of World War II. Beecher and an unnamed nurse were tending to wounded US troops when they ran out of morphine. Not having access to additional medication supplies and unable to find another solution, the nurse gave the soldier a shot of saline (salt water) while reassuring him that he was getting a potent painkiller and should be feeling much better very soon. It worked. The injection of saline solution somehow relieved the intense pain and agony, preventing shock.

In the months ahead Beecher would often duplicate this outcome when they would run out of morphine – as happened frequently near the end of the war. He reports in his writings that nearly 40% of the soldiers who received the “sham” treatment of the saline injection reported a notable lessening of their pain. The experience had a lasting impact on him making him wonder which medications and treatments were truly effective in of themselves, and which were in fact useless and simply had the placebo effect as their most effective component.

After returning home, Beecher would continue his research into the placebo effect, becoming the leading figure in reforming how we vet and test efficacy in new medications. He introduced and advocated for what is now the gold standard in clinical trials: the double-blind, placebo controlled, randomized clinical trial (RCT) and is responsible for helping usher in safer medications that work for a much greater percentage of the population, and keeping ineffective treatments and medications out of the realm of accepted medicine.

Since its discovery, the placebo effect has been something of an embarrassment to pharmacology, and a huge obstacle to pharmaceutical companies. The positive response to placebo in patients in clinical trials has similarly been viewed in a negative light as a trait related to a naïve or gullible nature in the patients. However, there is another perspective to consider as we examine the placebo effect. What can we learn from this phenomenon, and can we use its powers responsibly to improve outcomes and patient wellbeing?
Researchers at Harvard Medical School contributed much to the serious and academic consideration of this question when in 2011 they established the world’s first interdisciplinary center for placebo research - the Harvard-wide Program in Placebo Studies and the Therapeutic Encounter (PiPS,) hosted at one of Harvard’s major teaching hospitals, the Beth Israel Deaconess Medical Center. They are not, by any stretch however, the only researchers investigating the placebo effect and its implications. The newly emerging field of placebo studies is robust, and has already produced evidence of physiological changes in patients reacting to placebos.

So what exactly is at play during a high level placebo response? Research points to a number of psychosocial factors and cues.

The Doctor-Patient Interaction

This rather unquantifiable notion of the age-old ritual of medicine is still carried out in most modern doctor-patient interactions. The confidence inspiring physician in the white coat, their focused attention, comforting touch and sympathetic ear, and the reassurance that a positive interaction with a supportive medical professional can instill - all of these things, when present in the interaction, can work to build trust in the practitioner, ease anxiety, and inspire hope and optimism in the patient, triggering the start of the placebo response.

A 2008 study titled, “Components of placebo effect: randomized controlled trial in patients with irritable bowel syndrome,” sought to investigate three factors suspected to contribute to a placebo response: assessment and observation by medical providers, the placebo treatment alone, and lastly the supportive doctor-patient interaction.

The researchers separated study participants into three groups: the waiting list group - who were simply observed and their symptoms tracked, the placebo treatment group itself (in this instance the placebo treatment being sham acupuncture, where the needles appearing to be inserted into the skin simply retract into the handle and do not penetrate the skin), and lastly the “augmented” placebo treatment group - where the sham acupuncture was accompanied by a warm, supportive, and attentive patient-practitioner relationship.

The study found that the combination of the placebo treatment with the supportive patient-practitioner relationship produced the highest placebo response rate, with 62% of those in the augmented placebo treatment group reporting adequate relief, compared to 44% of the placebo treatment only group (with no supportive interactions), and 28% of the waiting list / observation-only group. The authors concluded that the patient-practitioner relationship was the most significant factor in this study, and that different components contributing to a placebo response can be progressively combined - similar to a graded dose escalation of treatment1.

Patients’ Expectations and Neurochemical Functions

Using functional MRI (fMRI) and other neuroimaging techniques, numerous studies have documented the impressive effects expectations can have on brain activity and neurochemical functions. Most notable of these are studies investigating the placebo response in pain and analgesia, and movement disorders such as Parkinson’s disease.

Pain processing and pain regulation are associated with several regions of the brain, including the thalamus, insula, and the anterior cingulate cortex, among others. A number of studies have demonstrated through fMRI a notable reduction of signals in the brain’s pain-responsive regions when study participants were told they were receiving a pain relieving agent (and thus expected pain relief) even though, just like Beecher’s saline injections on that battlefield, the participants were actually only administered a placebo.

Similarly, researchers have been able to demonstrate the “nocebo” effect (the dark side of the placebo effect, in which adverse effects are brought on by the patient’s own expectations or fears.) In many studies researchers found that when participants expected to
feel an unpleasant sensation - that is when they were misled to believe that a painful event was about to occur - their brain’s pain-responsive regions were activated and signals in those regions increased, even though no painful stimuli was actually administered. All of these studies strongly suggest that many of the brain’s neurochemical functions can be manipulated not only through pharmaceuticals, but through the mind’s own expectations.2,3

Where We Go from Here

So what does all of this mean for patients and physicians outside of clinical trials and experiments, and in actual clinical practice? Can components responsible for the placebo response be utilized in appropriate and ethical ways to enhance treatment outcomes? Many researchers and physicians believe so.

In fact, in a 2008 national survey of US internists and rheumatologists, about half of the 679 physicians participating in the survey reported having recommended a treatment primarily to “enhance the patient’s expectation of getting better.” The majority reported introducing the treatment as something that is not typically used for the patient’s condition, but that they believed may be of help. 62% of the physicians said that recommending such a treatment was ethical and permissible in their opinions. The survey did not report the efficacy rates of the placebo treatments recommended4.

Perhaps more importantly, and as we’ve seen above, attentive and supportive doctor-patient interactions can enhance the efficacy of even placebo treatments, and as other studies suggest, make real medications more effective. The nature of this particular component of the placebo response - the supportive interaction with the physician - is ethically beyond reproach, has no side effects, and improves patient wellbeing in a multitude of ways. It also demonstrates the immeasurable value and clinical significance of a truly supportive bedside manner.

“To really do the best for your patients, you want the best placebo response plus the best drug response,” says William Potter, MD, PhD who has conducted, overseen, and analyzed hundreds of clinical trials5.

As for the burgeoning field of placebo studies, it seems to keep expanding in multiple directions with recent studies examining the role genetics may play in a person’s susceptibility to the placebo response. Though the study of human genetic variants in the placebo response is in its early stages, some interesting initial discoveries have already been made. Of particular interest to researchers studying the genetic influence on placebo are the dopamine, opioid, serotonin, and endocannabinoid systems, as these systems are found to impact both neural and cognitive elements in a placebo effect1. Analyzing the genetic differences within these particular systems and how they correlate with placebo responses has begun, and promises to be a worthwhile endeavor.

References: