

# The Prudent Prescriber

Phil Mohler, M.D. • pmohler69@gmail.com

2775 Crossroads Blvd • P.O. Box 10600 • Grand Junction, CO 81502-5600

## August 2018

Pharm Reps  $\neq$  Rational Prescribing

(PR)



(RP)

## The Power of "Nothing" The Placebo Effect Re-examined

### Background

In a Christmas Eve, 1955 JAMA article Henry K. Beecher M.D., the father of modern placebo science, proclaimed his studies showed that placebos had an effectiveness rate of 35.2% in a myriad of conditions including pain, nausea, mood changes, headaches and seasickness. Beecher's studies were small and loaded with biases, but were harbingers for physicians that placebos and the placebo effect might be clinically useful.

Six decades later, physicians continue to consider this powerful tool with suspicion. This month, we'll update two aspects of the placebo effect: "placebos without deception," and "how to use your powerful placebo effect in practice."

### Definition

Family physician Howard Brody's definition: "The placebo response is a change in the patient's health or bodily state that is attributable to the symbolic impact of medical treatment or the treatment setting." Appropriately, Brody's definition does not get bogged down in mechanisms of action, pills, injections or acupuncture needles.

Antibiotics do  
**NOT**

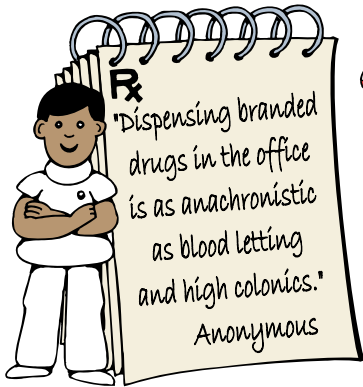


help  
acute bronchitis

**$\beta$ -blockers in  
post-MI  
save  
lives**



Pill splitters save  
BIG



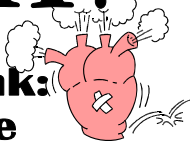
**R**  
"Dispensing branded drugs in the office is as anachronistic as blood letting and high colonics."  
Anonymous



## CHE?

Think:

**Ace**  
**Aldactone**  
**B-blocker**  
**Dig**  
**Diuretic**

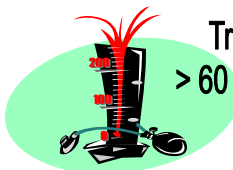


Avoid these expensive  
"me-too" drugs:

 Intermezzo  
Vimovo  
Livalo  
Gralise  
Viibryd  
Edarbi  
Daliresp



Treat patients  
> 60 years to 150/90



**NOW AVAILABLE**  
ON THE  
**GENERIC MARQUEE**

Viagra→sildenafil  
Effient→prasugel  
Strattera→atomoxetine  
Asacol HD→mesalamine DR  
Pristiq→desvenlafaxine

## **Placebos without deception**

It is widely believed that response to placebo requires concealment or deception. This belief creates an ethical conundrum: to be beneficial in clinical practice, placebos require deception, but this violates the ethical principle of respect for patient autonomy and informed consent.

In the last 10 years, a handful of studies have shown that long-term placebo effects can be elicited under open label conditions, in which patients are explicitly informed they will receive a placebo. In spite of the lack of intuitive appeal, numerous studies have demonstrated that deception may not be needed to elicit placebo effects.

In the Journal of Evidence Based Medicine (2017; 10:97–107), Charlesworth *et al.* performed a systematic review and meta-analysis of studies with an open label placebo versus “no treatment” groups. They identified five trials involving 260 participants. The clinical conditions were irritable bowel syndrome, depression, allergic rhinitis, back pain and attention deficit hyperactivity disorder. The risk of bias was moderate. In all five studies, the reviewers found a “modest” positive effect of the placebo (not enough data to calculate NNT). The authors claim, “The effect size estimate for the open label placebos was larger than previous assessment estimates for deceptively delivered placebos suggesting the possibility that open label placebos may have effects that are equal to or perhaps even larger than deceptive placebos.” This could be because 4 of 5 of the open label placebos included positive messages together with the placebos, or it could be that effects of “standard” placebos are underestimated as they are delivered under conditions of doubt.

In one of the studies reviewed above, Kaptchuk *et al.* (PLoS ONE, December 2010) randomized 80 primarily female patients (70%), mean age 47 with IBS diagnosed by Rome III criteria to a three week trial of either open-label placebo pills or no-treatment controls with the same quality of interaction with providers. The primary outcome was IBS Global Improvement Scale (IBS-GIS) change. The 1.2 unit improvement of the open placebo group over the no-treatment group on the 7point IBS-GIS scale suggests a modest effect size. The critical element of this study was how the open label placebo was presented:

*The provider clearly explained that the placebo pill was an inactive (inert) substance like a sugar pill that contained no medicine and then explained in an approximately 15 minute script the following four discussion points:*

- 1. the placebo effect is powerful*
- 2. the body can automatically respond to taking the placebo pills like Pavlov's dogs who salivated when they heard a bell*
- 3. a positive attitude helps but is not necessary*
- 4. taking the pills faithfully is critical*

## **Revitalizing physicians' powerful personal placebo effect**

I cringe at times, recalling my own words to patients for whom I was prescribing a new drug, “Give this new drug a try and come back in six weeks and we’ll see if it worked.” I cringe because I was, in the distant past, an active participant in a Balint group that met for two years and that weekly preached, “**Remember, you, the physician are the most potent drug available.**” I am the same guy who loves George Bernard Shaw’s Doctors Dilemma, where Sir Ralph Bloomfield Bonnington is described, “**Cheering, reassuring, healing by the mere incompatibility of disease or anxiety with his welcome presence. Even broken bones, it is said, have been known to unite at the sound of his voice.**”

Lucassen and Olesen (Scandinavian Journal of Primary Health Care vol. 34, NO. 4, 428-433) tell a story that may help explain why I (you?) sometimes forgot the potent placebo effect that we clinicians have.

*There are these two young fish swimming along, they happen to meet an older fish swimming the other way, who nods and says, “Morning boys. How’s the water?” And the two young fish swim on for a bit, and then eventually one of them looks over at the other and goes, “What the hell is water?”*

In primary care, our work is to diagnose and treat patients. We use focused questions and provide targeted treatment; we prescribe drugs, we give injections, we propose referrals. This is the core of what we learned in our training. However, we tend to forget that each treatment is conducted in a specific context.

As the fish may forget the importance of water, we may forget the role of context in which our activities take place. Here, context is the doctor-patient relation, the different rituals around treatment and the total environment surrounding the doctor-patient encounter.

When I go see my family physician, it's Pat or Deb greeting me warmly at the front desk; Dallas, Dr. Mike's MA regaling me with a story as she leads me to an exam room; it's the wall rack with a brochure that teaches me "50 ways to avoid becoming a father"; a sign that reminds me that with test results, "no news is no news"; it's Dr. Mike's smile and greeting, looking me in the eye; it's the time that I know I will get from Dr. Mike to lay out my concerns.

What's context have to do with the placebo effect? Everything! There is emerging evidence that the effect of context often exceeds the effect of a specific treatment.

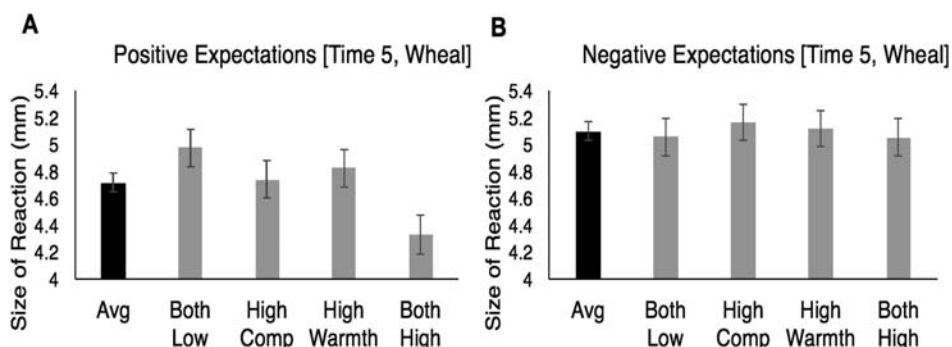
In another study engineered by Kaptchuk *et al.* ([BMJ.2008; 336:999-1003](#)), 262 adult patients with irritable bowel syndrome were randomized to a waiting list or two other groups. Both of the active intervention groups received sham acupuncture. In the first group (limited interaction), the therapist carried out the procedure with limited interaction with patients; the therapist introduced himself shortly and stated "I know what to do." He placed the sham needles (blinded for the patient who was unaware that it was not real acupuncture). In the other group (augmented interaction), the therapist discussed symptoms and consequences of IBS with the patient and did so in a warm friendly and empathetic manner providing positive expectations about the results of the procedure and then provided the sham acupuncture.

**Results:** the patients in the augmented interaction group scored better on all outcomes. For example, 62% experienced adequate relief compared to 44% in the limited interaction group and 24% in the waiting list group. [NNT to obtain pain relief for one additional patient, comparing wait list vs augmented group =3]

This is in line with what experienced primary care physicians know. A warm, friendly and empathetic attitude is crucial, particularly in the first contact with the patient. This initial encounter may well be the determinant for the success or failure of the ensuing relationship.

But what about placebo effects on objective physiologic outcomes? Howe, Goyer and Crum from Stanford ([Health Psychology 36\(11\): 1074 – 1082, November 2017](#)) induced allergic reactions in 164 healthy participants through a histamine skin prick test. A healthcare provider administered a cream with no active ingredients and set either positive expectations (cream will reduce reaction) or negative expectations (cream will increase reaction). The provider demonstrated either high or low warmth or either high or low competence.

**Results:** The impact of expectations on the allergic response was enhanced when the provider acted both warmer and more competent and negated when the provider acted colder and less competent.



Graphs adapted from Howe *et al.* [Health Psychology 36\(11\):1074 – 1082, November 2017](#).

In graph A, all patients had positive expectations about the value of the placebo cream in shrinking the allergic wheal. For patients of physicians who rated low on both warmth and competence, the average wheal actually increased in size over baseline. For patients of physicians who rated high on both warmth and competence, the average wheal significantly decreased in size compared with baseline.

In graph B, all patients had negative expectations about the value of the placebo cream in shrinking the allergic wheal and the presence or absence of warmth and competence had no effect on the wheal size.

This study suggests that the placebo effect can be boosted or diminished by the social context, in this case marked by the warmth and competence of the clinician. Positive expectations, when delivered by a warm and competent clinician, diminish participants' allergic responses. However when delivered by a clinician that was less warm and less competent, neither positive nor negative expectations had any influence.

### My Take

- ✪ The concept of the placebo response has shifted in emphasis from the placebo effect being associated with deceptively administered sham treatments, to one in which the placebo effect is recognized as the manifestation of powerful social and psychological forces.
- ✪ In selected difficult clinical scenarios, is it time to consider prescribing “placebos without deception”— open-label vitamins or homeopathic products? They work!
- ✪ Although there is never one correct way to communicate with the patient or even an ideal model of the doctor-patient relationship, certain characteristics appear to be universally important: warmth and competence. When the patient meets a physician, he or she rapidly assesses the benevolence of the physician's intentions (warmth) and their ability to carry out these intentions (competence). (Fisk *et al.* Trends in Cognitive Science, 11 (2), 77 – 83.)
- ✪ When clinically appropriate, enthusiastically delivering positive expectations about a proposed intervention is crucial in promoting the intervention's placebo effects.
- ✪ The doctor who fails to have a placebo effect on his patient should become a pathologist. JN Blau

### Pharmaceutical outrage of the month

I thought I had vented my entire spleen last month on ridiculously priced drugs. Then my colleague, Steve Nolan, Pharm. D., reminded me about the avariciously priced mebendazole, trade name Emverm. For decades, I prescribed Vermox (mebendazole) for pinworms. Then Vermox disappeared and Emverm (Impax Laboratories) became the only available mebendazole product. Per GoodRx (July 10, 2018), **Emverm is selling for \$321-\$382 per 100mg tablet in Grand Junction. That's a staggering \$642-\$764 for the standard two dose regimen for pinworms!**

There are a couple reasonable alternatives:

1. Reese's Pinworm Medicine (pyrantel pamoate) is available OTC; two ounces sells for \$16.88 at Amazon.com. That's enough to treat a whole family. Some pediatricians have concerns about pyrantel's potential for G.I. and neurotoxicity in younger children.
2. Or turn to our Canadian friends (yes they are!) to the north via Pharmacy Checker.com. Mebendazole is available as 100 mg sized generic tablets for as little as \$0.50 a tablet. You must buy at least 30 tablets, but it's still a bargain at \$15. The pharmacy pays the freight charges.

I took a parasitology course as a freshman in college. I loved how “enterobius vermicularis” rolled off my tongue. The real worm in this Emverm fiasco is Impax Laboratories.

You may access previous issues at <https://www.rmhp.org/i-am-a-provider/provider-resources/publications-for-providers>.

**DISCLAIMER:** The information and statements contained in “The Prudent Prescriber” constitute the opinions of its author, unless otherwise noted. Nothing contained in “The Prudent Prescriber” is intended to demonstrate, indicate or suggest that any person or company is incompetent or unfit. Likewise, nothing contained in “The Prudent Prescriber” is intended to damage the business, business relationships, business dealings or reputation of any person or company.