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Meaningful Placebos — Controlling the Uncontrollable

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In this issue of the *Journal*, Wechsler et al.¹ report data from a study that compared four interventions involving patients with asthma (ClinicalTrials.gov number, NCT01143688). They found that three of the interventions — active albuterol, sham albuterol, and sham acupuncture — were all equally effective in controlling asthma symptoms, as judged by patient-reported improvement. In contrast, lung function was improved only in those given active albuterol, as measured by an increase in the forced expiratory volume in 1 second (FEV₁). The fourth intervention was “no treatment,” in which patients were told to wait for several hours and then return home. Waiting had no effect on either subjective asthma symptoms or lung function. Although albuterol improved FEV₁ by a factor of 3, as compared with the other three interventions, patients reported no differences in improvement of asthma symptoms. They all felt better, so from the patients' perspective all three interventions, save simply waiting, worked.

What do we learn from this study? The authors conclude that the patient reports were “unreliable,” since they reported improvement when there was none — that is, the subjective experiences were simply wrong because they ignored the objective facts as measured by FEV₁. But is this the right interpretation? It is the subjective symptoms that brought these patients to medical care in the first place. They came because they were wheezing and felt suffocated, not because they had a reduced FEV₁. The fact that they felt improved even when their FEV₁ had not increased begs the question, What is the more important outcome in medicine: the objective or the subjective, the doctor's or the patient's perception? This distinction is important, since it should direct us

as to when patient-centered versus doctor-directed care should take place.

In a number of other trials in which both sham and actual treatments were evaluated, results were very similar. In one study of major depressive disorder (NCT00005013), placebo, hypericum (St. John's wort), and sertraline all resulted in about the same level of improvement on the Hamilton Rating Scale for Depression.² Similarly, in studies of low back pain in both the United States (NCT00065585)³ and Germany,⁴ true acupuncture and sham acupuncture had about the same effectiveness yet were substantially better than usual medical care in relieving the pain. A number of surgical procedures — such as arthroscopic knee surgery⁵ and spinal vertebroplasty (NCT00068822)⁶ — have led to similar results with actual and sham treatments. In these studies and many more, inert treatments have had effects similar to their “active” analogues.

For subjective and functional conditions — for example, migraine, schizophrenia, back pain, depression, asthma, post-traumatic stress disorder, neurologic disorders such as Parkinson's disease, inflammatory bowel disease and many other autoimmune disorders, any condition defined by symptoms, and anything idiopathic — a patient-centered approach requires that patient-preferred outcomes trump the judgment of the physician. Under these conditions, inert pills can be as useful as “real” ones; two inert pills can work better than one; colorful inert pills can work better than plain ones; and injections can work better than pills.⁷ Usually the control is designed to convince the doctor yet is irrelevant for the patient and patient-centered care. Often the very assumption that there is a correct control simply

is not the case. One observer has noted that, to most medical people, this way of thinking simply makes no sense at all; rather, it makes as much sense as filling up the gas tank with Earl Grey tea.⁸

All medical procedures (active or inert) are meaningful — that is, they represent something — and meaning has effects. Clinicians often dress up in special uniforms that convey power and authority. They have very expensive machines that can look inside your heart or brain. All this, plus the magnificence of the hospital building (ours has two helipads!), the decor of the office, the lights of the operating room, the computers on every lap, the magical prescription pad, and the caring nurse, piles up meaning with increasing power regardless of what may be in the capsule or syringe.⁷

These meanings create expectations that can dramatically modify the effectiveness of even the most powerful proven treatments. In a recent experiment, the average effects of the opioid remifentanyl were either doubled or extinguished by manipulating subject expectations; functional magnetic resonance imaging scans showed that regulatory brain mechanisms differed as a function of these expectations.⁹ Does this mean that we might double our gas mileage if we wished for it hard enough? Well, no. But people are not machines, and we shouldn't treat them as such.

Do we need to control for all meaning in order to show that a treatment is specifically ef-

fective? Maybe it is sufficient simply to show that a treatment yields significant improvement for the patients, has reasonable cost, and has no negative effects over the short or long term. This is, after all, the first tenet of medicine: "Do no harm."

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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