What is the placebo worth?

The doctor-patient relationship is a crucial part of its value

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George Bernard Shaw described a miracle as "an event that creates faith." Belief is a powerful tool, and many factors influence it. A recent study testing pain relief from analgesics showed that merely telling people that a novel form of codeine they were taking (actually a placebo) was worth $2.50 (£1.25; €1.58) rather than 10 cents increased the proportion of people who reported pain relief from 61% to 85.4%.[1] When the "price" of the placebo was reduced, so was the pain relief. A meta-analysis of decades of clinical trials proposed that the placebo effect was more hype than reality.[2] However, the resulting backlash against it has had the implicit effect of clarifying what is best practice with regard to the placebo.[3]

Hovering over much of the research is a practical question for clinicians—what does all this mean for patient care? In the accompanying randomised controlled trial, Kaptchuk and colleagues undertake a dismantling approach to the examination of placebo effects.[4] In 262 adults with irritable bowel syndrome, they examined the effects of placebo acupuncture in circumstances that involved observation only (evaluating a "Hawthorne effect"), sham acupuncture alone, and an enriched relationship with the treating doctor along with the sham procedure. The proportion of patients who reported moderate or substantial improvement on the irritable bowel syndrome global improvement scale was 3% in the observation group, 20% in the procedure alone group, and 37% in the augmented intervention group (P<0.001 for trend).

Clearly the group with the greatest relief of symptoms was the one that received not only sham acupuncture but 45 minutes of quality contact with a clinician. This contact involved questions about the patient's symptoms and beliefs about them, a "warm, friendly manner," empathy, and communication of confidence and positive expectations. In contrast, the doctor-patient relationship in the sham acupuncture only group sounds like a caricature of procedure based medicine practised under strict time limitations: the practitioners explained that this was "a scientific study" and they had been instructed not to talk about it with patients.

Global improvement scores were higher and quality of life and amelioration in symptom severity were almost doubled in people receiving augmented care, which raises some interesting questions. Perhaps the ratcheting down of the time that doctors spend with patients and our modern overemphasis on drugs and procedures is "penny wise and pound foolish." Patients might respond better to real as well as placebo interventions if they were associated with a good doctor-patient relationship. Although the increased time and concern may enhance the effects of the placebo, it also changes the context of associations with the treatment—the doctor may enhance the effect of the sham needle, but the needle also becomes a reminder of the enriched relationship.

That this study chose to evaluate placebo effects associated with an unconventional treatment raises further interesting questions. It is already widely assumed by sceptics that most if not all of the benefit of "alternative" or integrative medicine comes from the placebo effect. It is then assumed that demonstration of a powerful placebo effect, without proving a specific effect, is enough to consign the treatment to the realm of quackery.

But what if we asked a different question? Is it possible that the alternative medical community has tended historically to understand something important about the experience of illness and the ritual of doctor-patient interactions that the rest of medicine might do well to hear? Many people may be drawn to alternative practitioners because of the holistic concern for their wellbeing they are likely to experience, and many may also experience appreciable placebo responses. Why shouldn't we try to understand what alternative practitioners know and do, as this may help explain why so many patients are prepared to pay to be treated by them, even when many of the treatments are unproven?[5]

In seeking such understanding we should think about the conditions for which patients often seek alternative treatment, and what that might teach us. Patients with irritable bowel syndrome have a chronic condition that can deeply affect their quality of life. They usually have a story to tell about their suffering and want it to be heard, and an empathetic ear may be just what they need. Both the emotional and physical needs of a patient needing emergency surgery, however, might be very different. Such patients might well have a strong placebo response to a calm, orderly, high-tech hospital environment and a kind but focused doctor who does not stop long to chat but instead brings his or her full attention to the pressing business at hand.

Whatever the specifics, the take home message is clear. We treat patients in a social and psychophysiological context that can either improve or, alas, worsen outcome. The meanings and expectations created by the interactions of doctors and patients matter physically, not

just subjectively. Recent brain imaging research on pain and the placebo effect has shown functional connectivity between specific brain regions that process attention (the anterior cingulate gyrus) and pain (periaqueductal grey), involving endogenous opiate receptors.[6] Techniques such as hypnosis improve a range of objective symptoms of irritable bowel syndrome and produce subjective reductions in distress.[7 8] The word "placebo" is Latin for "I will please." On the basis of these and related studies, it seems fair to conclude that a good doctor-patient relationship can tangibly improve patients' responses to treatment, placebo or otherwise.

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Assessment of proteinuria in pregnancy

Urinary spot protein:creatinine ratio can reliably rule out proteinuria in pregnancy

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Pre-eclampsia is a global problem—it affects 2-8% of pregnancies, and an estimated 8.3 million women develop the disease each year. For developing countries, the priority is preventing maternal deaths from multiorgan complications of the disease. The difference in case fatality rates from eclampsia between developing countries and developed countries (5.2% *v* 0.72%) suggests that mortality is easily avoidable.[1] In developed countries where death is rarer, research is directed towards improving prediction and prevention of pre-eclampsia and minimising morbidity. Accurate diagnosis is needed to accomplish this. In the accompanying systematic review, Côté and colleagues assess urinary spot protein:creatinine and albumin:creatinine ratios as diagnostic tests for significant proteinuria in women with hypertension in pregnancy.[2]

Pre-eclampsia is a multiorgan syndrome, the clinical characteristics of which may include kidney, liver, and cerebral damage, an altered coagulant state, and fetal growth restriction.[3] It is defined by two imperfect measures of end organ involvement—hypertension and proteinuria.[4] Early blood markers of the disease can now be identified many weeks before these clinical manifestations,[5] but antenatal diagnosis still relies on measuring blood pressure and urine dipstick inspection. In the United Kingdom alone, 660 000 women each year will have at least 7-10 such antenatal checks during each pregnancy, according to the schedule recommended by the National Institute for Health and Clinical Excellence.[6] In other developed countries, women are seen even more often.

The classic clinical presentation of pre-eclampsia is initial hypertension and subsequent proteinuria, which is a cue to seek other manifestations of the disease. The likelihood of adverse pregnancy outcomes escalates in women with pre-eclampsia rather than gestational hypertension alone, so proteinuria often dictates the need to admit women to hospital or deliver the baby.[7] Screening for proteinuria has traditionally been by urine dipstick, but this method is prone to considerable error.

A previous systematic review reported the pooled negative likelihood ratio for 1+ protein or greater on urine dipstick for predicting 300 mg/24 h proteinuria as 0.6 (95% confidence interval 0.45 to 0.8), with a pooled positive likelihood ratio of 3.48 (1.66 to 7.27).[8] This implies that the test often misleads the healthcare professional but, as no easy alternative is available at point of care, it continues to be used widely in clinical practice.

Comparison of urine dipstick with 24 hour collection is complicated by 24 hour collection not being a precise gold standard. Healthcare professionals and the women rarely follow the correct procedure at the start and end of collection, and because women micturate so often during pregnancy they may forget to add all the samples to the collection. Different laboratory assays for measuring protein give varying results,[9] and the threshold of 300 mg/24 h is not based on reaching a distinct clinicopathological state, but on the 95th centile for normal pregnant women. Proteinuria is key to management, but current clinical assessment is far from perfect. Can we improve on this situation?

In their systematic review, Côté and colleagues report a pooled negative likelihood ratio for a cut-off of 30 mg/mmol of 0.21 (0.13 to 0.31).[2] They conclude that the test is useful for ruling out significant proteinuria but do not advocate its use for quantification as the positive likelihood ratio was only poor to fair (3.53, 2.83 to 4.49). However, assessment of the value of the test must include comparison with its alternatives and the implications of both a positive and missed diagnosis, which are considerable.

Quantification is not crucial to obstetricians, because once a threshold is breached the diagnosis is made. Unlike blood pressure (which is related to risk of a cerebrovascular event), serial assessment of proteinuria after the diagnosis of pre-eclampsia rarely influences management because the rate of increase is not an important