



Using the Placebo Effect

-or-

“It’s Going to Work”

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August 2010

It's going to work.



Sucrosa[®]
500 mg tablets placebo

It's a pill.

Laboratory studies have shown Sucrosa (placebo) to be occasionally effective in the treatment of pain and discomfort associated with chronic rhinitis, allergies, hives, sinusitis, arthritis conditions, ankylosing spondylitis, fibromyalgia, gout, lupus, osteoarthritis, psoriatic arthritis, reactive arthritis, rheumatoid arthritis, asthma, acute and chronic pain, low back pain, inflammatory bowel disease (IBD), abdominal pain, ulcerative colitis, constipation, diarrhea, dyspepsia (indigestion), intestinal gas, heartburn, hemorrhoids, irritable bowel syndrome (IBS), lactose intolerance, constipation, motion sickness, ankle pain, tendinitis, bursitis, heel spurs, knee pain, lower back pain, muscle cramps, tinnitus, vertigo, asthma, erectile dysfunction, migraine headaches, attention deficit disorder (ADD), bedwetting, lactose intolerance, rheumatoid arthritis, sleep disturbance, rosacea, scleroderma, shingles, insomnia, jet lag, narcolepsy, sleep apnea, somnolence, urinary incontinence, urinary tract infections, premenstrual syndrome, and yeast infections.

Side effects associated with the use of a placebo include alterations in heartbeat; increased blood pressure and cold extremities; muscle weakness, stiffness, and spasm; muscle and bone pain; nervousness; decreased mental sharpness; tremor; headache; abnormal sensation; vertigo; sleep disturbance; mood and personality changes; alterations in speech and movement; memory impairment; confusion and dream abnormality; stomach upset; diarrhea; dry mouth; constipation; gas; thirst; acid reflux; difficulty swallowing; changes in appetite; burping and inability of the tongue to move; flushing; hot flashes; sweating; itching; rash; acne; skin reaction to sunlight; difficult or rapid breathing; dryness or discomfort of the throat or nose; nose bleed; yawning and sinus disorder; cold-like symptoms; cough; hiccups; visual disturbances; ringing in the ears; ear pain; eye discomfort; swelling or tearing; alterations in hearing and smelling; visual intolerance to light and bad taste; allergic reactions including swelling of face, lips, tongue, and/or throat, which may cause difficulty in breathing and/or swallowing; wheezing; hives; rash; severe sloughing of the skin; chills; heat sensitivity; swelling; bloating; hangover effect; fever; fainting; dizziness on standing up; warm/cold sensations; dehydration; and changes in urination and menstruation.

AstraZeneca 

Take Home Points

- The Placebo effect is real, powerful and difficult to measure
- The Placebo Effect is more likely to be evident for non-binary outcome measures (e.g. pain or depression scales), and for particular diagnoses.
- There are ethical pitfalls in using the placebo effect, but ignoring it perils the loss of a powerful therapeutic tool
- Honest presentation of therapeutic options, including placebo, is best.

The Talk

- Define placebo effect and how we measure it
- Describe examples of placebo effect in medical, surgical and other therapeutic intervention modalities.
- Describe the possible mechanisms of action of the placebo effect
- Outline the ethical pitfalls involved in using the placebo effect
- Suggest ways to use the placebo effect ethically.

Placebo Effect: Definition

- Placebo – Latin for “I shall please”
- “The placebo effect is the measurable, observable, or felt improvement in health not attributable to treatment.” - The Skeptic’s Dictionary
- “The desirable psychological and physiological effects of meaning in the treatment of illness.” – Daniel Moerman, University of Michigan Department of Behavioral Science

Placebo Effect – how do you measure it?

- Very hard to measure placebo effect for a given condition. Usually need a 3-arm trial (intervention group, placebo group, “natural history” group).
- Placebo group better than “natural history” → placebo effect.
- Natural history group very difficult to create – every intervention such as taking a history, stating a diagnosis, measuring blood pressure, keeping a symptom journal - may alter natural history

The Echinacea Study

- 400 volunteers receiving one of 3 preparations of echinacea or placebo in either prophylactic or treatment mode then exposed to rhinovirus (susceptability confirmed). Subjective and objective outcome measures
- No benefit to given echinacea extracts for either prophylaxis or treatment.
- Those patients who thought they were getting the echinacea had statistically significant improvement in their symptom score.

- An Evaluation of *Echinacea angustifolia* in Experimental Rhinovirus Infections

Turner R. B., Bauer R., Woelkart K., Hulsey T. C., Gangemi J. D.
N Engl J Med 2005; 353:341-348, Jul 28, 2005

Post molar extraction ultrasound for swelling reduction

- 79 patients – sham vs. real ultrasound vs. untreated group for postop swelling after 3rd molar extraction.
 - Reduced swelling by both U/S and Sham U/S compared to untreated group. Equal magnitude of effect.

Ho KH, Hashish I, Salmon P, Freeman R, Harvey W.

Reduction of post-operative swelling by a placebo effect. J Psychosom Res. 1988;32(2):197-205.

Exercise Duration and Functional Class in Heart Failure

- Retrospective review of 15 patients that had received placebo in various drug trials at Ohio State University vs. 9 patients from a “natural course” controlled trial
 - Statistically significant 81 second improvement in exercise duration and 27% improvement in functional class for the placebo patients. No improvement in LVEF for either group.

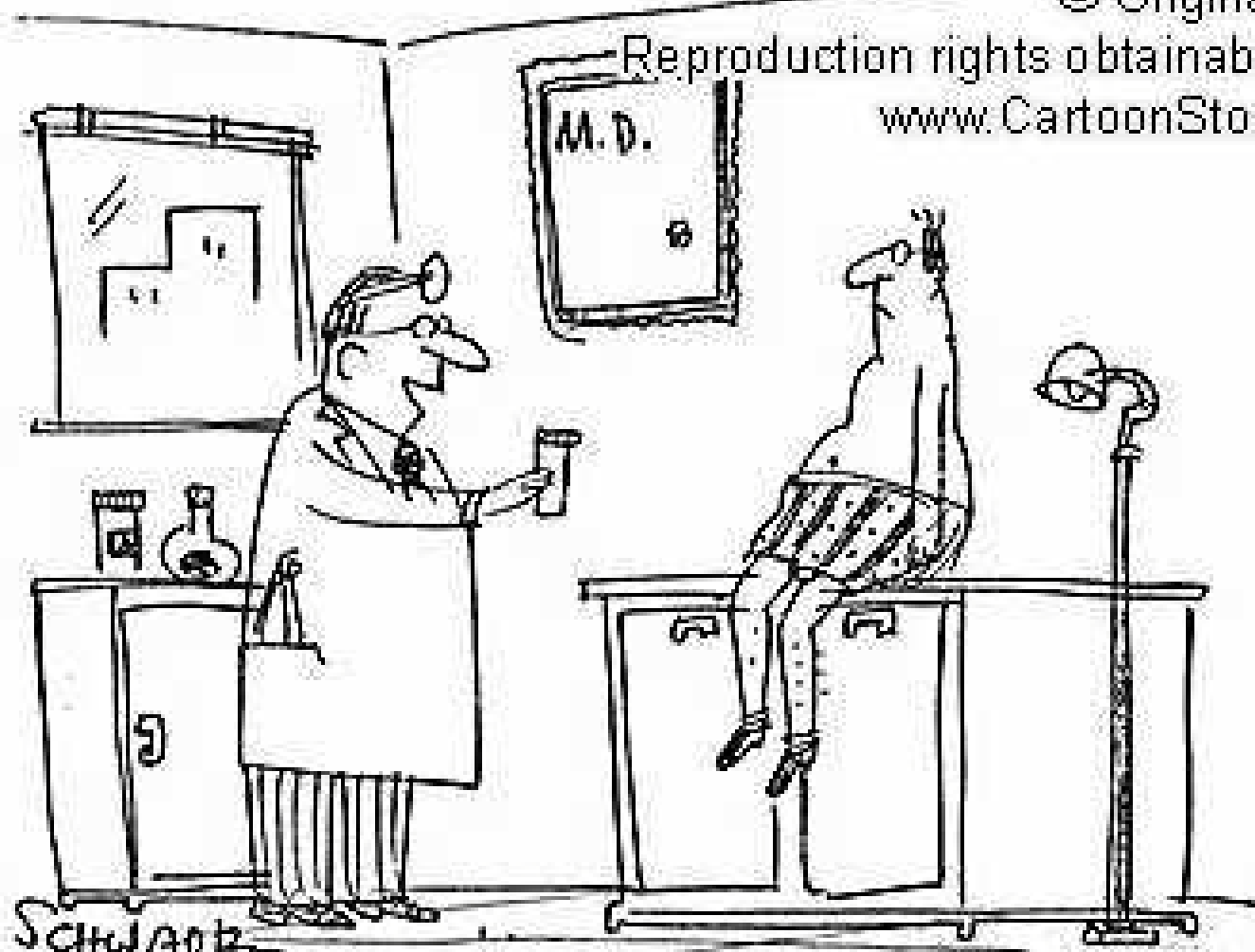
Archer TP, Leier CV. Placebo treatment in congestive heart failure.

Cardiology. 1992;81(2-3):125-33.

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SCHWAPP.

"YOU'RE IN LUCK! THERE'S AN EXPENSIVE NEW PLACEBO
ON THE MARKET TO TREAT HYPOCHONDRIA."

Positive Versus Neutral Consultation

- 200 British patients with symptoms but no signs of illness treated in a “positive” vs. neutral way:
 - Positive: Firm diagnosis and “you will be better in a few days.”
 - Neutral: “I cannot be certain what is the matter with you”
 - 64% of positive consultation patients got better in 2 weeks compared to 39% in Neutral.

Thomas KB. General practice consultations: is there any point in being positive? Br Med J (Clin Res Ed). 1987 May 9;294(6581):1200-2.

HB/11A

COULD BE
ANYTHING.



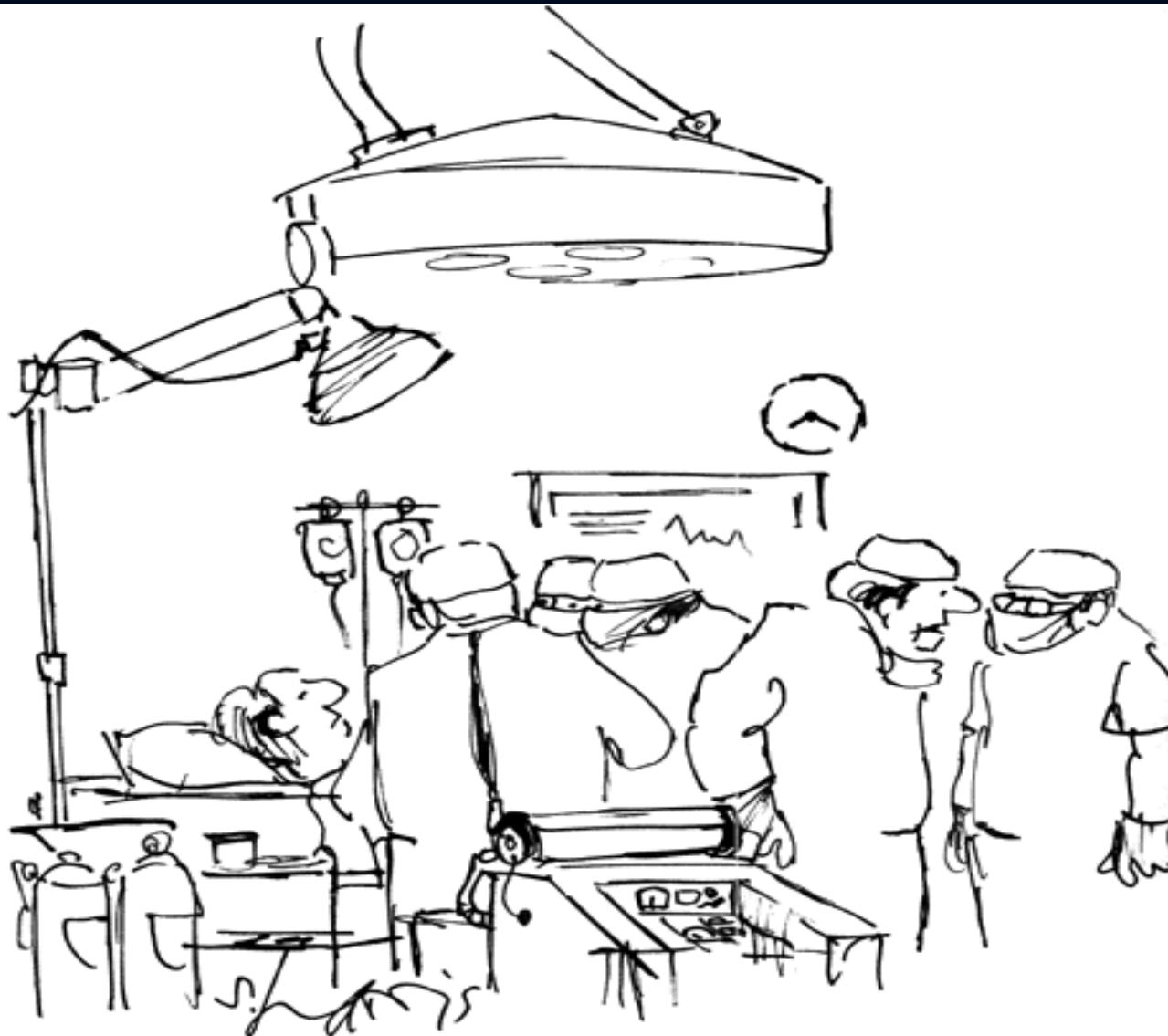
WAY TOO GENERAL PRACTITIONER

Adherence as Placebo

- 2175 Post-MI patients taking propranolol vs. placebo (Beta blocker heart attack trial) with 1 year follow-up:
 - Poor adherers (take <75% of doses) had statistically significant elevated OR of death whether on propranolol (3.1) or placebo (2.5)
 - Difference not accounted for by severity of MI, race, marital status, education, smoking, high life-stress or social isolation.
- Horwitz RI, Viscoli CM, Berkman L, Donaldson RM, Horwitz SM, Murray CJ, Ransohoff DF, Sindelar J. Treatment adherence and risk of death after a myocardial infarction. Lancet. 1990 Sep 1;336(8714):542-5.

Pacemaker as Placebo

- Multicenter, randomized, double-blind study to evaluate “active” vs. “inactive” pacing for hypertrophic cardiomyopathy
- At 3 month follow-up
 - Quality of life measures – no difference
 - LV outflow gradient – reduction in both groups but more in “active pacing” group.
- Similar results for cardiac resynchronization devices and pacemakers placed for other indications
 - Linde C, Gadler F, Kappenberger L, Ryden L. Placebo effect of pacemaker implantation in obstructive hypertrophic cardiomyopathy. PIC Study Group. Pacing In Cardiomyopathy. Am J Cardiol. 1999 Mar 15;83(6):903-7.



"We'll just mill around till he's asleep, and and then send him back up. This operation is actually for a placebo effect."

Surgery As Placebo

- Probably a greater effect than medical treatment
 - Sham arthroscopy relieved knee arthritis pain as well as real arthroscopy
 - Moseley JB Jr, Wray NP, Kuykendall D, Willis K, Landon G. Related Articles, Arthroscopic treatment of osteoarthritis of the knee: a prospective, randomized, placebo-controlled trial. Results of a pilot study. Am J Sports Med. 1996 Jan-Feb;24(1):28-34.
 - Sham CABG (internal mammary ligation) relieves angina (Cobb, NEJM 1959)

Maybe There is no Placebo Effect

- 2001 meta-analysis of trials with 3-arm designs: 114 trials (32 binary outcomes, 82 continuous outcomes), total of ~8000 patients.
 - Placebo had no statistically significant effect on binary outcomes, yes on continuous outcomes (especially pain).

Is the Placebo Powerless? An Analysis of Clinical Trials Comparing Placebo with No Treatment, *The New England Journal of Medicine*, May 24, 2001 (Vol. 344, No. 21).

TABLE 1. EFFECT OF PLACEBO IN TRIALS WITH BINARY OR CONTINUOUS OUTCOMES.*

OUTCOME	NO. OF PARTICIPANTS	NO. OF TRIALS	POOLED RELATIVE RISK (95% CI)†
Binary			
Overall	3795	32	0.95 (0.88 to 1.02)
Subjective	1928	23	0.95 (0.86 to 1.05)
Objective	1867	9	0.91 (0.80 to 1.04)
			POOLED STANDARDIZED MEAN DIFFERENCE (95% CI)‡
Continuous			
Overall	4730	82	-0.28 (-0.38 to -0.19)
Subjective	3081	53	-0.36 (-0.47 to -0.25)
Objective	1649	29	-0.12 (-0.27 to 0.03)

*CI denotes confidence interval.

†The relative risk was defined as the ratio of the number of patients with an unwanted outcome to the total number of patients in the placebo group, divided by the same ratio in the untreated group. A value below 1.0 indicates a beneficial effect of placebo.

‡The standardized mean difference was defined as the difference between the mean values for unwanted outcomes in the placebo and untreated groups divided by the pooled standard deviation. A negative value indicates a beneficial effect of placebo.



Placebo Effect - Modulators

- Brand name Aspirin shown to be better than generic aspirin
- Brand name placebo worked better than generic placebo
- Type of illness
- Patient's expectations



Why the Placebo Effect Works?



“Mind over molecules”

- Belief affects neurochemistry, hormonal and immune systems.

“Mind over behavior” –

- behavior of sick or injured people is socially expected or sanctioned, and the placebo effect may at times be a measure of changed behavior.
 - Alcohol placebo leading to drunken state
 - Emetic placebo leading to vomiting



Natural History Effect

Things often get better on their own – disease is often cyclical in nature

Regression to the Mean

- People join studies often at more symptomatic phases of disease

Process of Treatment

- A process of treatment that involves showing attention, care, affection, etc., to the patient/subject, a process that is encouraging and hopeful, may itself trigger physical reactions in the body which promote healing.



"ONE OF US IS A PLACEBO, MR JONES..."

How many of you have
wished you had a
placebo to give a
patient during a
clinical encounter?

Why?

How many of you have felt guilty for
wishing that?

Why do you use the placebo effect?

- It works
- Prevents taking other, potentially harmful treatments or interventions
- Cheap
- Patient Satisfaction
- Avoids “difficult conversations”

Risks of Using the Placebo Effect

- Deceitful
 - Unethical
 - May impair doctor-patient relationship which itself has a placebo effect
- Reduce diagnostic vigilance
- Not evidence based – no protocols or way to reliably measure the effect (although this is true for “real” medicines too)
- Promotes “pill for every ailment” myth
 - Can also be seen as self-serving for the physician
- Patients may become resistant to definitive treatment (e.g. psychotherapy)

How do you use the placebo effect?

- “this is really going to work”
- “I’m sure you have ____”
- Ordering labs to lessen patient’s anxiety
- Specific medicines (Robitussin, meclizine)
- “This works by stimulating the body’s own healing mechanisms.”
- “Impure placebos” – e.g. Abx for viral URI’s, B12 for fatigue, sham surgery etc.
 - Impure placebos can cause physiologic harm
 - Impure placebos can end up deceiving the doctor – she believes agent has potency when in fact it has none.

The Challenge

- Find a way to use placebo effect without being deceitful
 - Don't use it in patients that you have negative feelings about
 - Don't try to find a “personality type” of people who might respond to placebo (different people respond differently during various times in their life)
 - “What do you think would make you better?” and “What were you hoping to get from your visit today?”
 - Try to get a sense of the implied expectation of the patient
 - “the physician should give me full information about the treatment”
 - “the physician will choose on my behalf any treatment most likely to help”

An Honest Attempt

- “Mrs. Jones, the type of depression you have has been treated in the past with either antidepressant medicine or psychotherapy, one of the talking therapies. These two treatments are still widely used and are options for you. There is a third kind of treatment, less expensive for you and less likely to cause side effects, which also helps many people with your condition. This treatment involves taking one of these pills twice a day and coming to our office every two weeks to let us know how you're doing. These pills do not contain any drug. We don't know exactly how they work; they may trigger or stimulate the body's own healing processes. We do know that your chances of improving with this treatment are quite good. If after six weeks of this treatment you're not feeling better we can try one of the other treatments.”