

Great Expectations:

The Placebo Effect

CHARLES J. VELLA, PHD

JUNE 30, 2016

The Placebo Effect: The Books

- ▶ Frank JD. *Persuasion & Healing*. 1973.
- ▶ Shapiro and Shapiro. *The Powerful Placebo: From Ancient Priest to Modern Physicians*. 1997
- ▶ Evans D. *Placebo: the Belief Effect*. 2003
- ▶ “Placebo Effects: Biological, Clinical and Ethical Advances” Damien G Finniss, Ted J. Kaptchuk, Franlin Miller and Fabrizio Benedetti, *Lancet*. 2010 February 20
- ▶ “Reframing Placebo in Research and Practice” Wayne B. Jonas, *Philosophical Transactions of the Royal Society* 2011
- ▶ *Placebo Effects (2nd Ed)* - Fabrizio Benedetti, 2014
- ▶ *The Cure: A Journey into the Science of Mind over Body* - Jo Marchant Crown, 2015

Purpose of this lecture

- ▶ In 1954, article in *The Lancet* stated that placebos comfort the ego of “unintelligent or inadequate patients.”
- ▶ Placebos are now being studied as psychobiological phenomenon and the placebo response as a potentially import part of the success of many medical treatments.
- ▶ The context in which treatment is given, and the patient’s and the practitioner’s beliefs, play a major role in the patient’s response to treatment

Lecture

- ▶ Change the question of concern from “are placebos ethical?” to “how can we make our treatments most effective.”
- ▶ We want to be the best clinicians possible
- ▶ We need to use all possible methods of increasing effectiveness of treatments.
- ▶ We need to understand how beliefs can ease our symptoms.

History of Placebos = History of Medicine

- ▶ Medicine kills, nature heals
 - ▶ Paracelsus, 15th century
- ▶ The art of medicine is to amuse the patient while nature cures the illness.
 - ▶ Voltaire, 17th century
- ▶ Until the early 20th century, most treatments were placebo

History of Placebos

Common placebos are sugar pills and saltwater injections.

Until the 20th Century, the placebo was a commonly used medical treatment.

- ▶ Patients wanted treatment,
- ▶ there was no treatment,
- ▶ so doctors gave them “dummy” pills and told them they would help.

Traditional concept of placebo

- ▶ History of medicine is basically the history of placebos, as most medical interventions until the 20th century were nothing but placebos – that is, inert.
- ▶ Over the centuries doctors started using sham treatments to see whether clinical improvement was attributable to the patient's imagination and/or spontaneous remission.
- ▶ Today placebos are widely used in clinical research to validate the efficacy of a therapy.
- ▶ Besides clinical research, doctors and nurses use placebos to please and placate anxious patients.

Traditional concepts

- ▶ The placebo effect is a good example of how a mental activity may affect several physiological functions; thus it is an excellent model for studying mind-body interactions
- ▶ The nocebo effect, which is the opposite of the placebo effect, is another good model for understanding mind-body interactions.
- ▶ Placebo: a meaning or symbolic response to TX; it's not the sugar, but the expectation, the symbolic significance of TX, the meaning of the context and therapeutic ritual

First blind assessment

- ▶ 1918- Bingel: 937 pts for effectiveness of diphtheria antitoxin - double blind (neither pt.. or doctor knew which was antitoxin vs horse serum)
- ▶ To assess influence of suggestion and imagination on outcome, as well as course of a disease
- ▶ Idea that not only patients, but doctors and investigators were subject to suggestion, imagination and biases. Lead to wider spread use of double blind design (neither patient nor doctor knows nature of tested therapy (real or sham))
- ▶ Today active (non-inert) placebos are used: mimics side-effects of a treatment; for when blinding is problematic

The Beginning

- ▶ 1955 – The idea of the placebo in modern times originated with H. K. Beecher. He evaluated 15 clinical trials concerned with different diseases and found that 35% of 1,082 patients were satisfactorily relieved by a placebo alone ("The Powerful Placebo," 1955).
- ▶ Other studies have since calculated the placebo effect as being even greater than Beecher claimed. For example, studies have shown that placebos are effective in 50 or 60 percent of subjects with certain conditions, e.g., "pain, depression, some heart ailments, gastric ulcers and other stomach complaints."

Placebo in Clinical Trial Phases

- ▶ Phase 1: determine safety dosage, how drug is metabolized and excreted, and identify side effects; $n = 20-80$ healthy volunteers
- ▶ Phase 2: further safety data; $n = 200-300$ who have the disease that medication could treat; indicates effectiveness and acceptable risks
- ▶ Phase 3: $n = 1000-3000$. tests effectiveness, monitors side effects, and comparison to a standard treatment
- ▶ Phase 4: long term risks, benefits, optimal use & with special populations (i.e. kids)
- ▶ Placebos used in Phase 2 and 3
- ▶ Without comparing a placebo group with a no-treatment control group, which is not typical for randomized trials, a placebo effect cannot be demonstrated.

Dealing with Placebo and Nocebo Effects in Experiments

Study Designs

(randomly assigned to experimental/placebo arms; passive vs active placebos)

- **Blinded Study**- Participant doesn't know if they are receiving treatment or placebo
- **Double-Blinded Study**- Participant and Experimenter do not know if treatment or placebo is being given
- **Double-Blind, Crossover Study**- Same as double-blinded, except participants get treatment and placebo in random order (controls for Ss **variability**)

RCT

- ▶ Randomized, double-blind, placebo controlled trial
- ▶ The placebo-controlled trial is the gold standard of medical research.
Current tenet of clinical research today for validating a therapy
- ▶ Controls for patient and doctor expectations, suggestion, imagination and biases; as well as to control other confounding factors (spontaneous fluctuations of diseases and sxs)
- ▶ Also crossover design: each patient receives all the treatments (first real, then placebo, or vice versa in same person); can reduce the sample size; reduction of variance here leads to greater statistical power; limitation due to persistence of effect of 1st TX; increased drop-out rates because longer trials

Classic Placebo effect experiment

- ▶ A sugar pill has no physiological action that will cure a headache:
 - ▶ N = 90 with headache
 - ▶ 30% - no TX; 30% - real aspirin; 30% - sugar pill
- ▶ No TX: pain will cease in 20 % after one-half hour (disease process simply reverses itself without any intervention)
- ▶ Real aspirin: get relief
- ▶ Sugar pill: Same relief as aspirin (not spontaneous remission or self delusion)

So what is the Placebo effect

- ▶ Placebo: "a substance or procedure... that is objectively without specific activity for the condition being treated"
- ▶ The placebo effect is the measurable, observable, or felt improvement in health or behavior not attributable to a medication or invasive treatment that has been administered.
- ▶ 'The placebo effect' has become a catchall term for a positive change in health *not attributable to medication or treatment*.

Working definitions

- ▶ Placebo effect: a favorable response to any intervention — a pill, a procedure, a counseling session, you name it — that doesn't have a *direct* physiological effect. But some do...
- ▶ Placebo: “An intervention designed to simulate medical therapy that at the time of use is believed not to be a specific therapy for the condition for which it is offered.
- ▶ Placebo Effect: “A change in a patient’s illness attributable to the symbolic import of a treatment rather than a specific pharmacologic or physiologic property.

▶ Brody H. *Placebos and the Philosophy of Medicine. Clinical, Conceptual, and Ethical Issues*. Chicago: University of Chicago Press, 1980

The Nocebo Effect

‘Placebo’ is Latin for “I will please,” and the placebo effect is when a treatment that doesn’t by itself cause any improvement leads to positive expectations in the patient that cause improvement.

‘Nocebo’ means “I will harm,” and the nocebo effect is when an inactive treatment causes harm, because we believe that it will.

An expectation of a drug’s side effects can cause us to experience them as well.

Placebo's Evil Twin, "Nocebo"

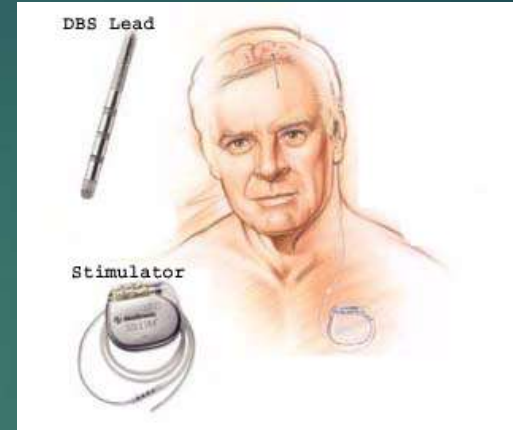
- ▶ Lactose intolerance study: both people with and without lactose intolerance took what they thought was lactose (it wasn't). 44% of those with intolerance and 26% without it developed symptoms of gastrointestinal discomfort.
- ▶ Men taking Finasteride for enlarged prostates: Half told that erectile dysfunction was a possible side effect and the other half were not. Of the group told about the side effect, 44% reported erectile dysfunction compared to only 15% of the group that had not been told.
- ▶ One patient participating in a trial for antidepressant medication swallowed 26 of the placebo pills in a suicide attempt. Even though they were completely harmless, his blood pressure somehow dropped dangerously low.

Nocebo effects

- ▶ Placebos can cause side-effects associated with real treatment.
- ▶ Withdrawal symptoms can also occur after placebo treatment. This was found after the discontinuation of the Women's Health Initiative study of hormone replacement therapy for menopause. Women had been on placebo for an average of 5.7 years.
- ▶ Moderate or severe withdrawal symptoms were reported by 5% of those on placebo compared to 21% of those on hormone replacement.

Classic Examples of Placebos

- ▶ Inert pills, drugs, or injections
- ▶ Sham surgeries
- ▶ Inactive medical devices
- ▶ Effective/non-effective acupuncture



Strange Powers of the Placebo Effect

- ▶ Saying that the same P will reduce pain, reduces pain; saying that the same P will increase pain, increases the pain
- ▶ Believing that a P will make you feel better, makes you feel better; believing that it will make you feel worse, has opposite effect (Nocebo)
- ▶ Placebos are not just pills. They can be creams, injections, surgery, drinks, interactions, buttons (walk button at an intersection; don't do anything, but make you feel in control).

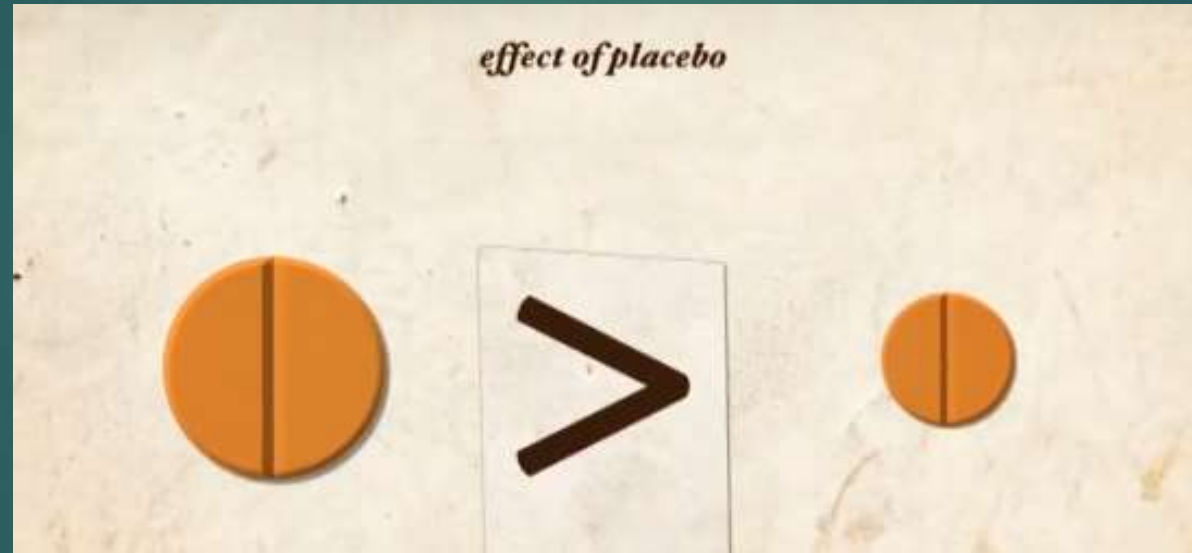
Strange Powers of the Placebo Effect

- ▶ Placebo effect: Something with no known therapeutic value can make people feel better
- ▶ If you believe and expect something to work, it actually does
- ▶ Strange issues related to effectiveness (strength of effect):
 - ▶ Same placebo can treat pain half as well as an aspirin while at same time half as well as morphine; P is half as effective as both

Placebos

- ▶ Not all Placebos are equal
- ▶ There is a Hierarchy of Effectiveness in Placebos
- ▶ Effectiveness of a placebo is bigger...

When the size of pill is bigger



More effective

When you take 2 pills instead of one



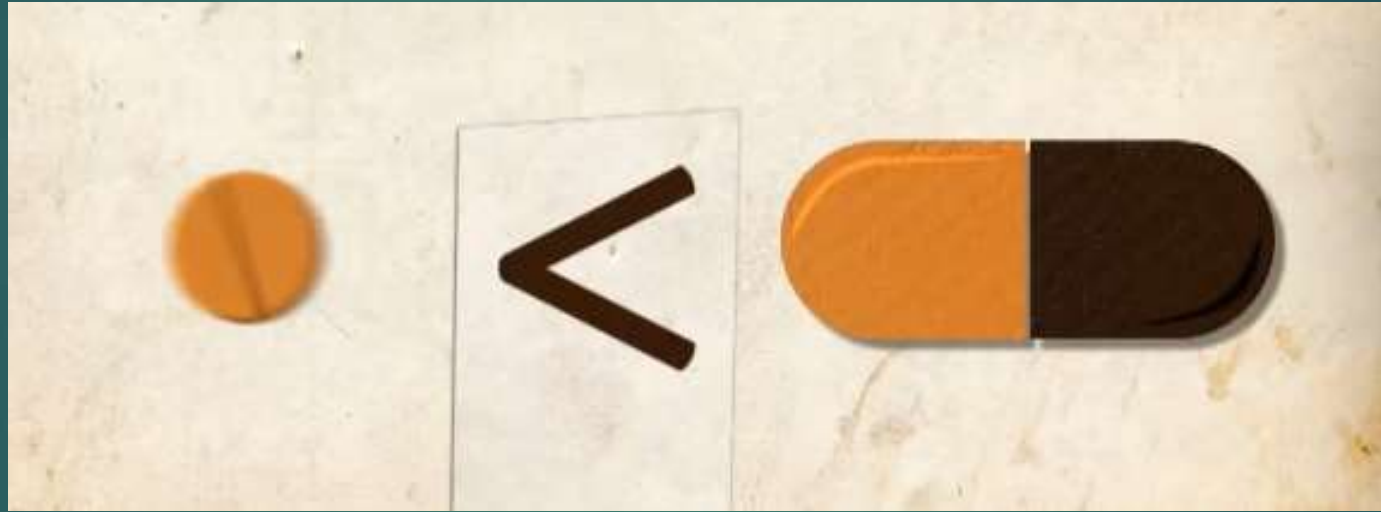
Placebos follow the same dose-response curve as real medicines.

When taking two pills once a day rather than one twice a day



The more placebo pills taken the better: four times a day more effective than 2x daily

A capsule is more effective than a pill



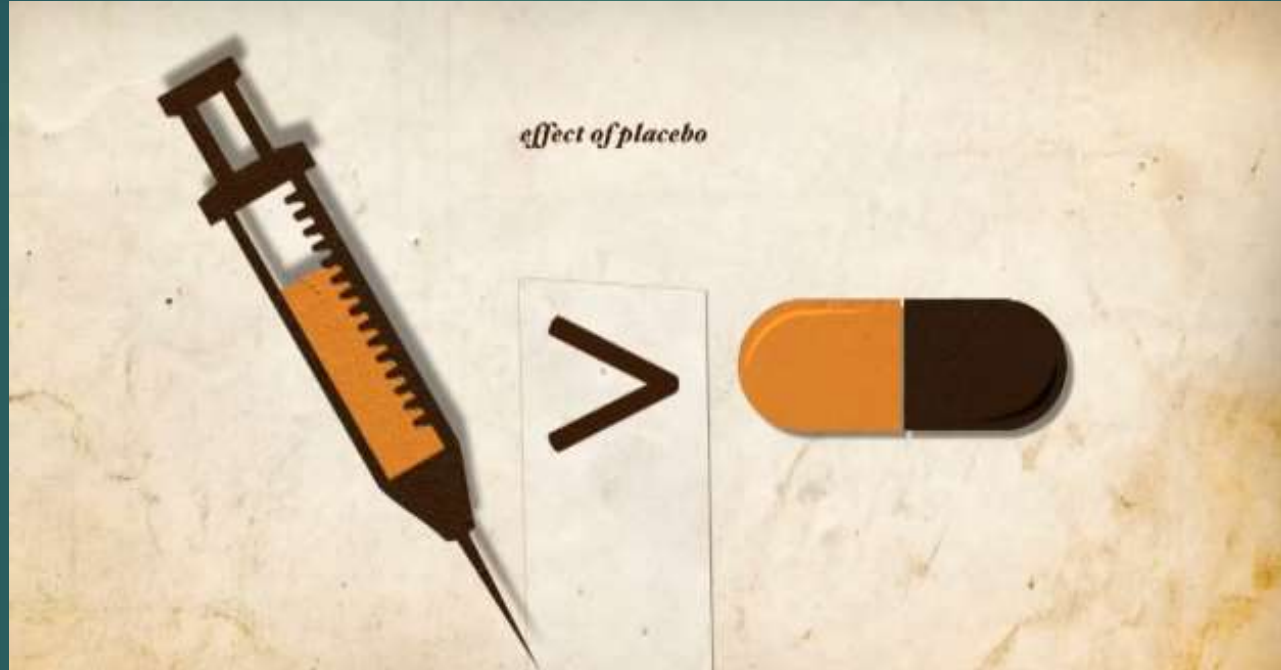
Capsules Better than Pills

One study of a sedative in 1970 of a sedative found that the same dosage of the drug was more effective in capsule form than in pill form.

At the time capsules were new and they seemed more “sciencey” to people.



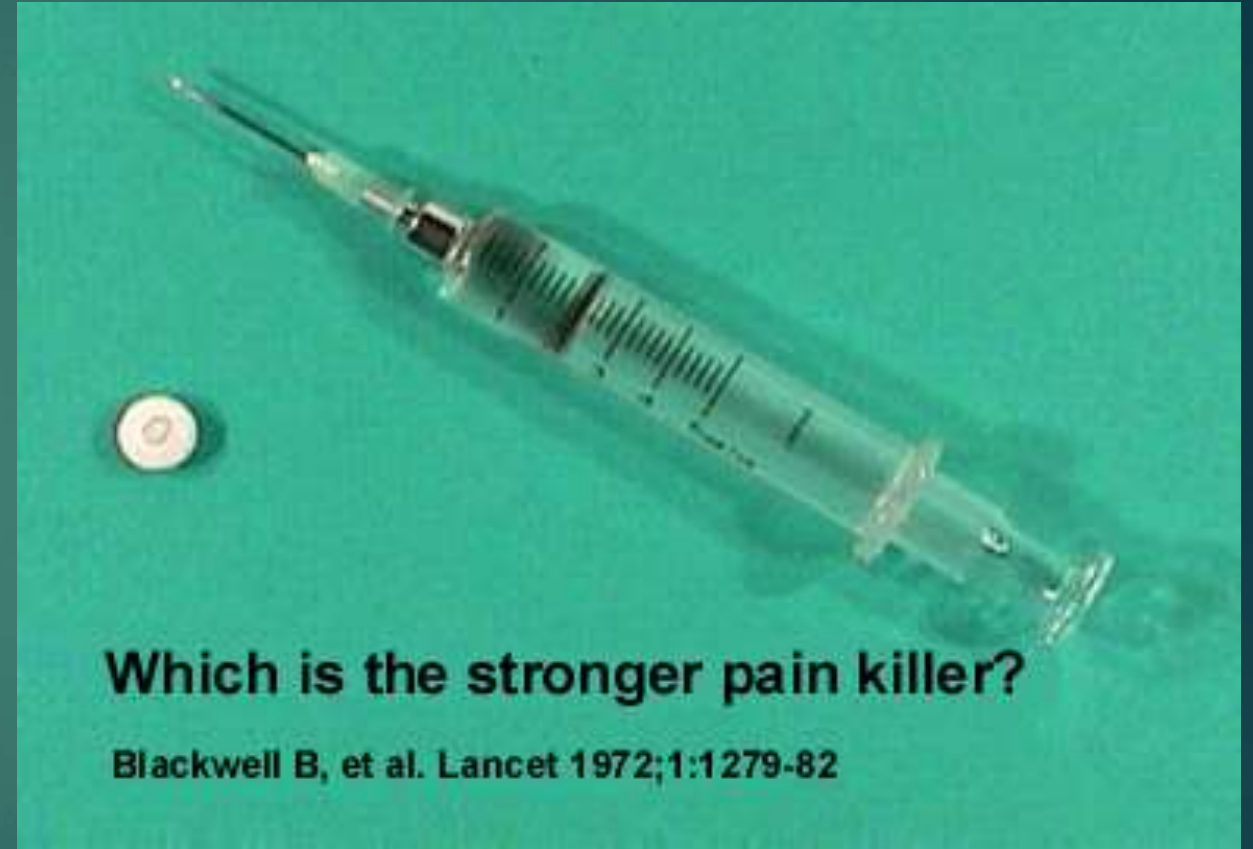
An injection is more powerful than a capsule



Injection Better than Pill

Several other studies have found that saltwater injections are better than sugar pills—

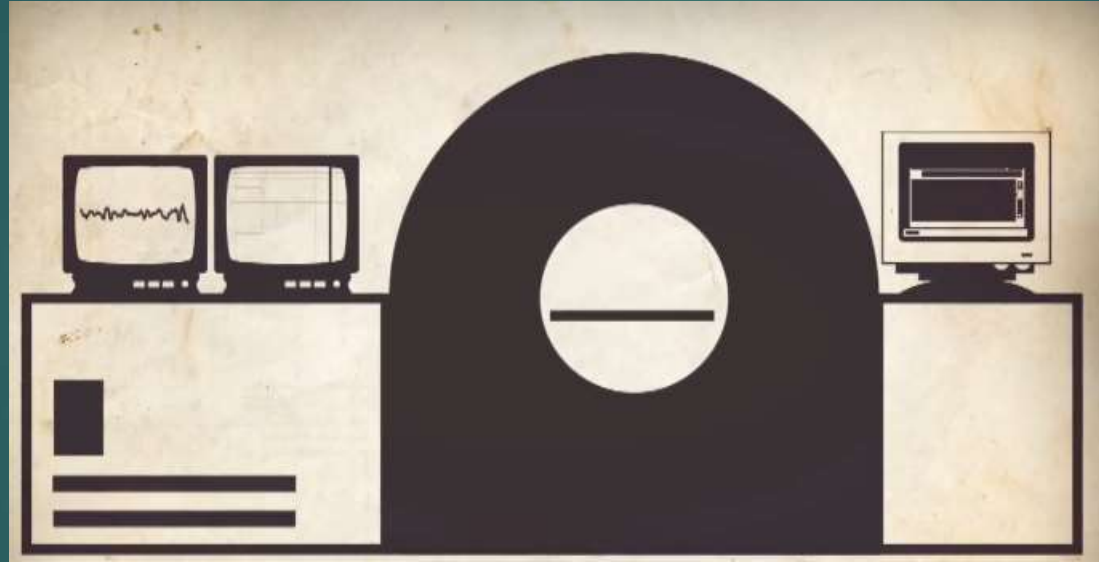
For headaches, blood pressure, and pain after an operation



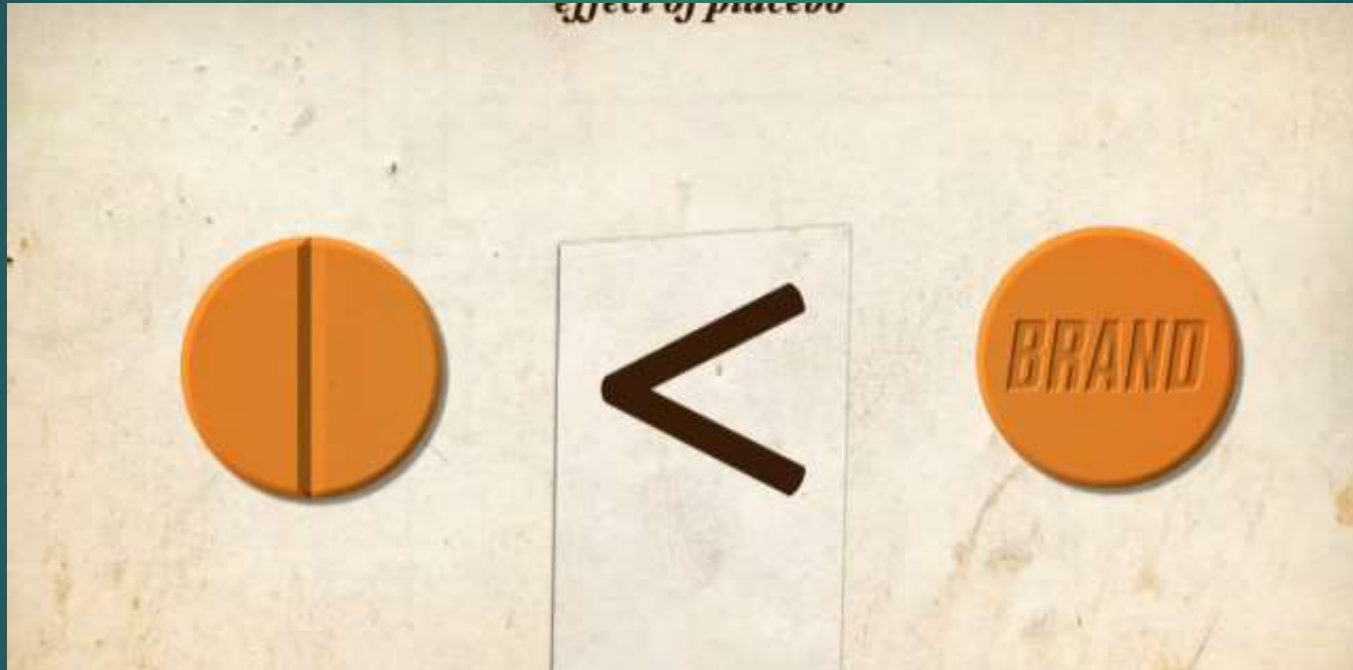
Saline as placebo

- ▶ A 2001 study led by neuroscientist Fabrizio Benedetti of the University of Turin Medical School in Italy similarly observed that:
 - ▶ a saline solution described to patients recovering from surgery as a powerful painkiller produced more pain relief than
 - ▶ an drip labeled accurately as saline solution
 - ▶ a saline drip depicted as a possible painkiller reported levels of pain relief in between those of the other groups.

Science devices are better than all of them



A plain pill works worse than a branded one



Brand name pills are better than generics



A discount priced pill works worse than a costlier one



Expensive Better than Cheap

If you take the same pain medication—the very same pills— and charge people more for it, the medication works better.

People feel less pain when they've paid more.

Discounted implies poorer quality;

- ▶ Medicare should not say “discounted drugs” to older people;
- ▶ Better to label them as Government’s own brand



**GOVERNMENT
BRAND**

A pill in a plain box works worse than one in a shiny box



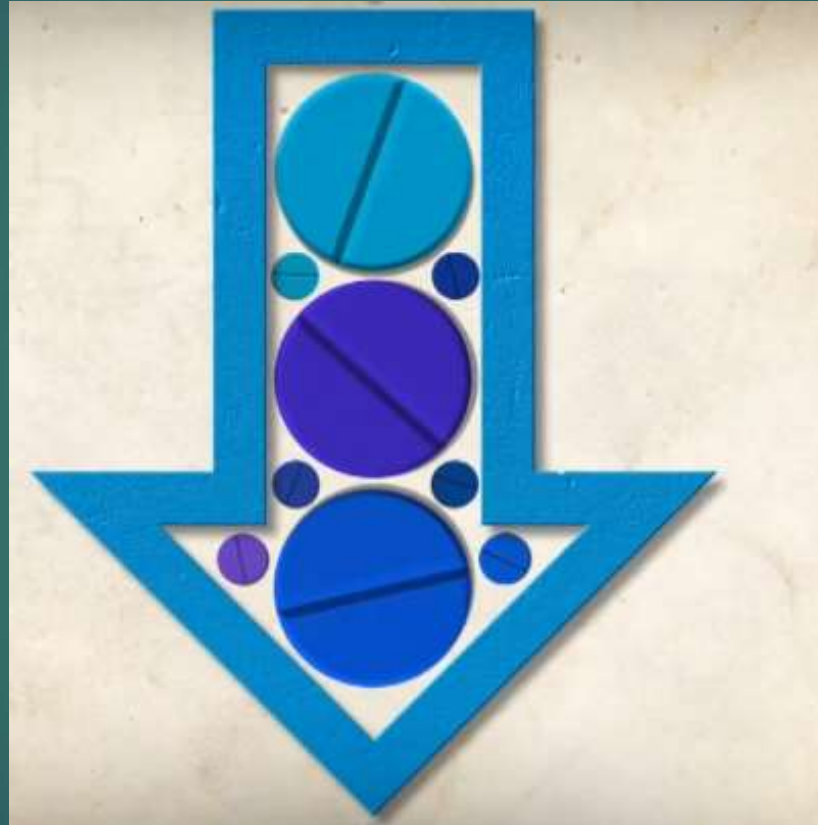
Flashy Packaging Better than Dull

Studies have also found that medicine is more effective if it comes in flashy brand-name packaging, rather than generic packaging.

Placebos work better in flashy packaging too.



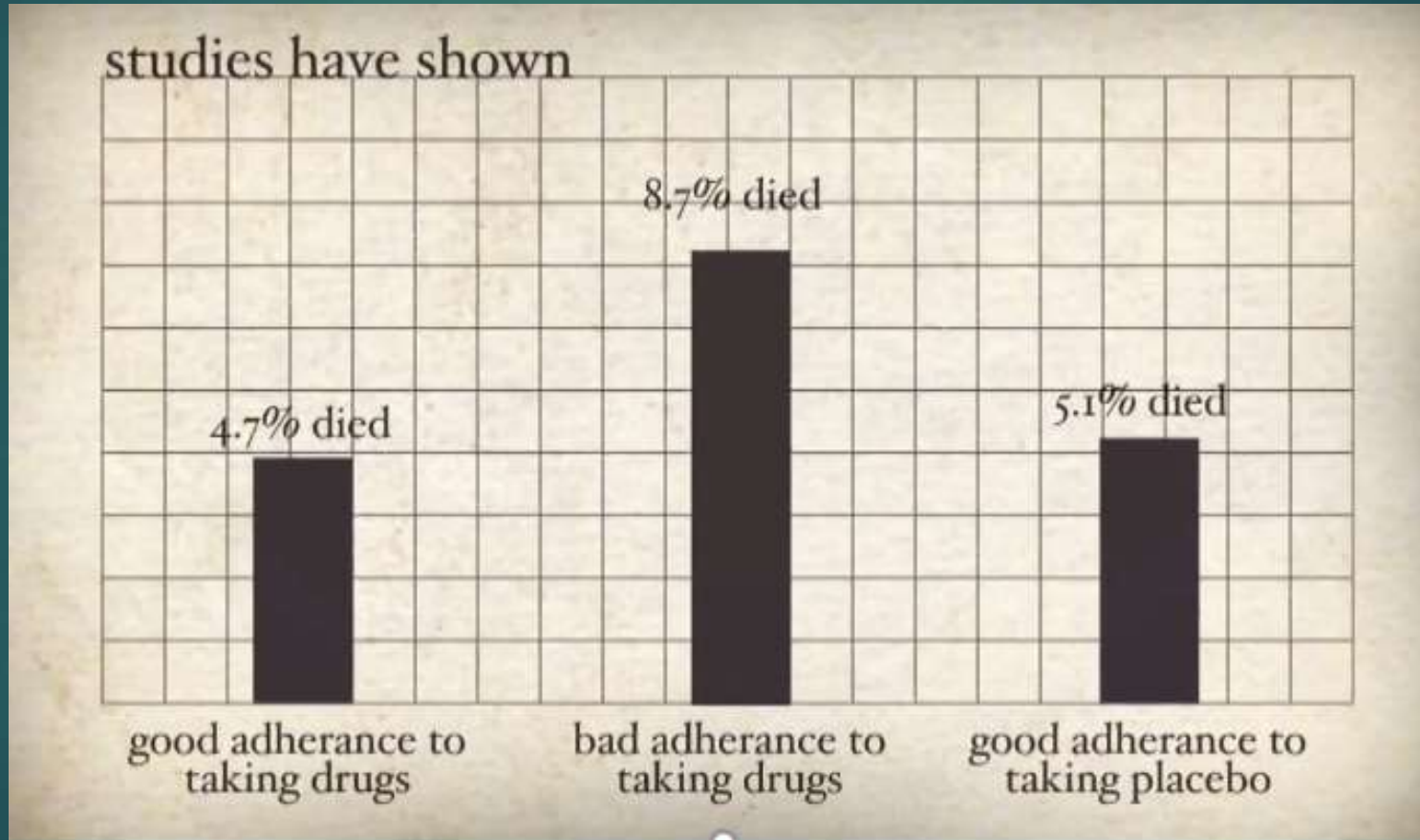
Pills that are blue work better as depressants



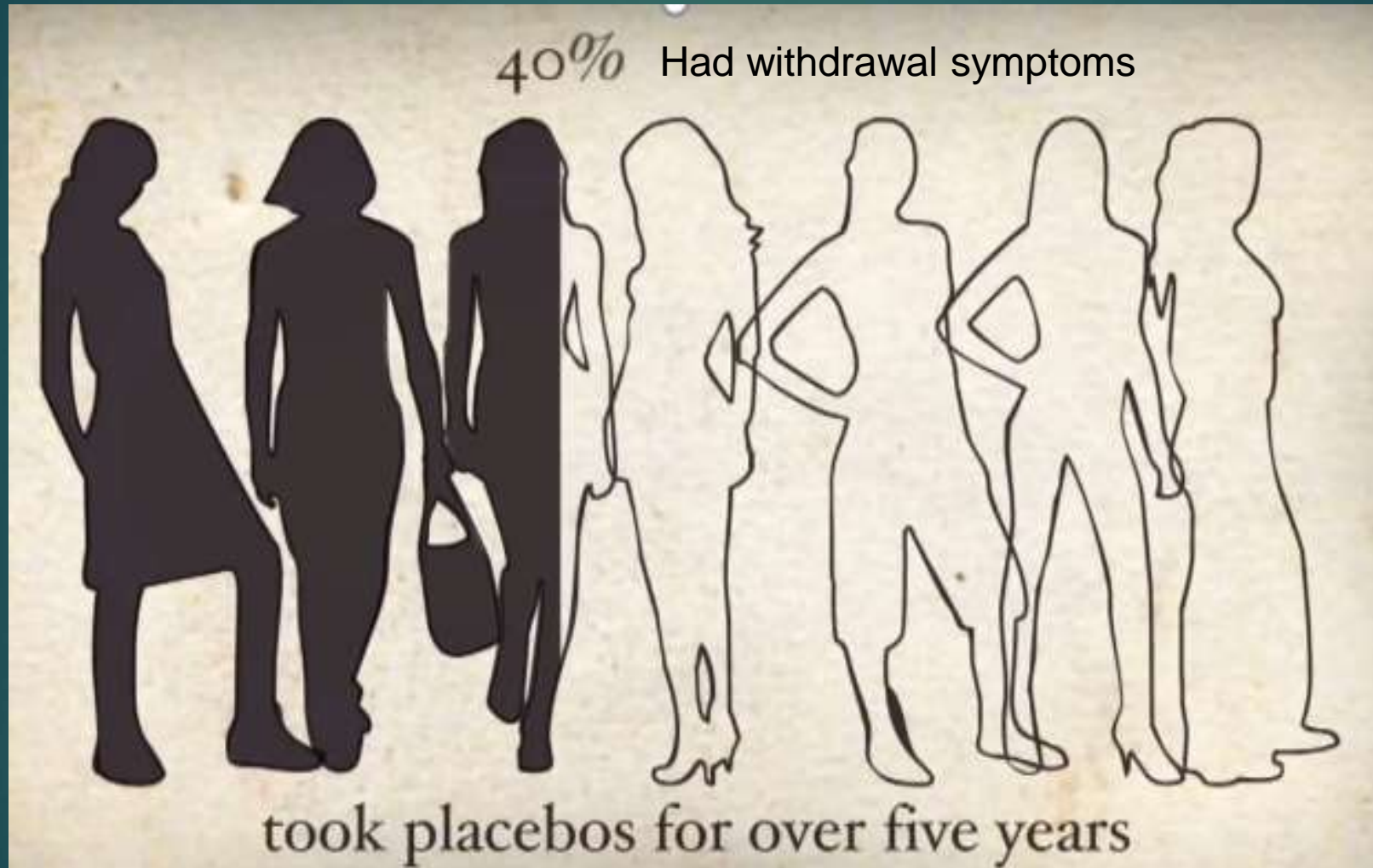
Pills that are red work better as uppers



People who take their meds are less likely to die than those who don't; even if those meds are both placebo



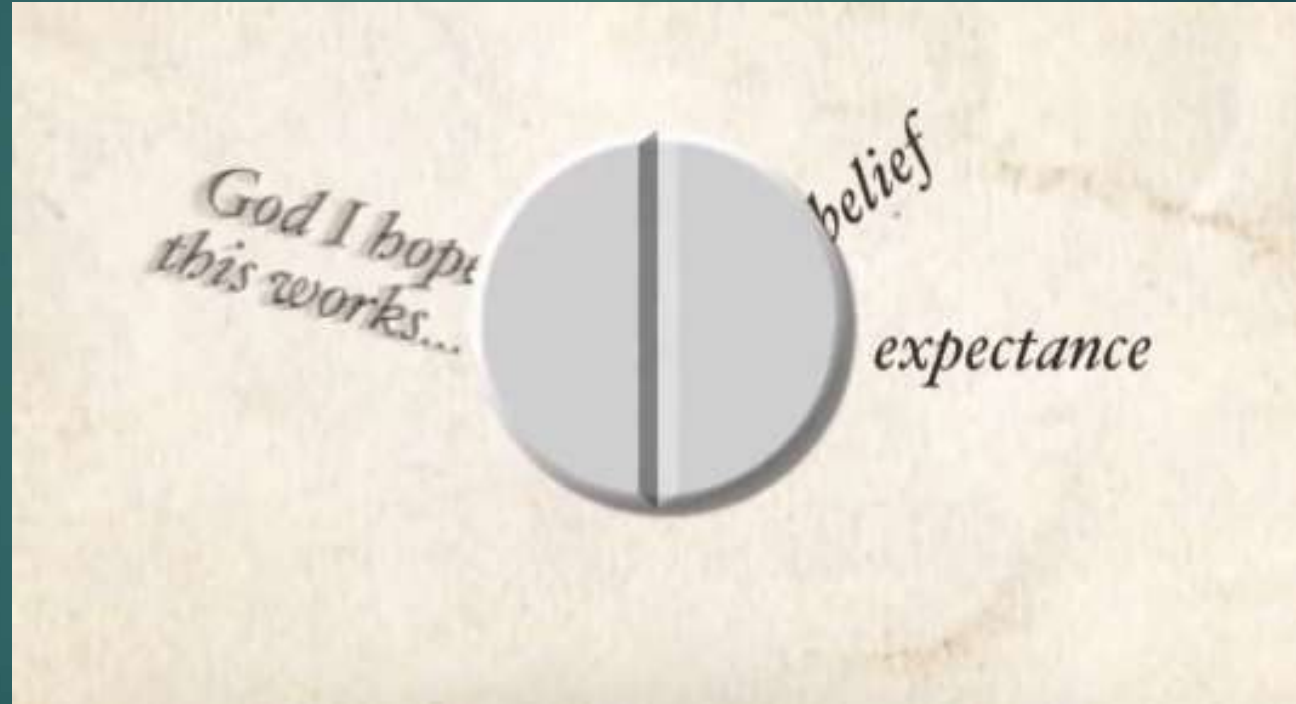
You can get addicted to placebos



Placebos are geographically sensitive



Placebos are inert; depends on belief;
not what's in it but the beliefs we load on to it



Placebo effect

- ▶ This "cure" in the absence of any truly therapeutic agent is the placebo effect
- ▶ The placebo effect is not deception, fluke, experimenter bias, or statistical anomaly. It is, instead, a product of expectation.
- ▶ The human brain anticipates outcomes, and anticipation can produce those outcomes.
- ▶ The placebo effect is the brain's self-fulfilling prophecy

Placebo effect

- ▶ Estimates of the placebo effect rate range from a low of 15 percent to a high of 72 percent.
- ▶ Placebo effect is not restricted to subjective self-reports of pain, mood, or attitude.
- ▶ Physical changes are real. For example, studies on asthma patients show less constriction of the bronchial tubes in patients for whom a placebo drug works

Benedetti: Placebo Effects help illness, not disease

- ▶ The scientific evidence relating to placebo effects in clinical situations suggests the hypothesis that placebo effects are salient predominantly in ameliorating illness, as distinct from curing or controlling disease.
- ▶ The most studied and well-understood area of placebo research concerns placebo effects on pain and related forms of distress, which are primary manifestations of illness
- ▶ Unfortunately, there is a dearth of systematic reviews of placebo outcomes in particular medical conditions restricted to trials with no-treatment controls.

Meta-analysis

- ▶ There is little reliable evidence that the placebo effect can play a role in curing or controlling disease by modifying pathophysiology.
- ▶ This absence of solid evidence of placebo interventions producing objective benefit in treating disease beyond its distressing symptomatic manifestations is most visible in the meta-analysis mentioned earlier of 114 trials that included placebo and no-treatment controls (Hrobjartsson and Gotzsche 2001).
- ▶ In this study placebo treatment was found superior to no-treatment control groups only for continuous subjective outcomes, such as pain.
- ▶ Nevertheless, there is no dispute that placebo interventions may produce beneficial (and lasting) modification of disease beyond symptomatic relief, especially in the context of classical conditioning.

9 Facts About the Placebo Effect

- ▶ Placebos affect animals
- ▶ Antidepressants are mostly placebo
- ▶ Placebo Drunkenness
- ▶ Placebos work even when you know it's a placebo
- ▶ Placebo Through Infections
- ▶ Pill colors
- ▶ Placebo Surgeries
- ▶ Placebo Effect Has Become More Powerful Over The Years.

Can Animals Respond to Placebos?

- Pharmaceutical companies employ the same double blind procedures on dogs when testing K9 medication as they do for human medications.
-
- They can develop a learned response to a drug and then respond similarly to a placebo.
- Humans can experience placebo effect for their pets by perceiving effect where there is none.
-

You Can Placebo Yourself Into Inebriation

- ▶ We can simply trick ourselves into thinking we are drunk.
- ▶ Researchers have found that those who believe they have been drinking vodka (which was actually simply tonic water and lime) had impaired judgement.
- ▶ They did worse on simple tests and their IQ tested lower

Where You Live Affects Placebo

- ▶ Location Variations effect placebo
- ▶ Europeans react more positively to placebo pills than injections. Americans the reverse
- ▶ The placebo effect in treating gastric ulcers:
 - ▶ low in Brazil,
 - ▶ higher in northern Europe (Denmark, Netherlands),
 - ▶ and extremely high in Germany.
- ▶ However, the placebo effect in treating hypertension is lower in Germany than elsewhere

Does ethnicity have a placebo effect?

- ▶ Participants were told that the pain reliever was either from a Chinese drug company, or from a U.S. drug company.
- ▶ No significant overall difference between the “American” and “Chinese” drugs.
- ▶ However, Asian-American subjects had greater pain reduction from the “Chinese” drug.



Waber, R. (MIT), 2006, The role of branding and pricing on health outcomes via the placebo response, Master of Science Thesis – Massachusetts Institute of Technology, p. 26.

Placebo Still Works even Though You Know its A Placebo

- ▶ Even when patients find out or are previously told, they are receiving a placebo drug, it still functions effectively

Fake infections

- ▶ You can derive positive placebo through fake Infections of unrelated diseases: Sufferers of asthma infected with hookworm
- ▶ Asthma sufferers into two groups: infected one with hookworm while making the second group think they had also been infected with hookworm.
- ▶ Placebo effect: The group that had actually been infected with hookworm saw improvement. But so did the group that had been infected with fake hookworm
- ▶ Stranger yet, much of the group that had been infected chose to keep the infections after the study finished because of the perceived benefits.

The Color of Placebo Pill You Take Affects How Well It Works.

- ▶ The perceived effectiveness of a medication is based in large part on the size, shape and color of the pill.
- ▶ Colored pills are more likely to relieve pain than white pills
- ▶ Green capsules work best for anxiety medication
- ▶ White pills soothe stomach issues such as ulcers.
- ▶ Blue pills help people sleep better than red pills

Color Matters: Red = more alert and awake

Blackwell (1972) did a study where students were given one of two pills: a pink one and a blue one.

They were told that one pill was a stimulant, which made you more alert, and the other was a sedative, that made you more sleepy.

Both pills were actually placebos— just sugar pills.

When Blackwell measured alertness at the end of class, he found that pink pills made you more alert than blue pills.



Why is Prozac Blue?

Drug companies know about the effects of color on how you feel.

So if you buy a stimulant, it will be red, orange, or yellow, and an anti-depressant will be blue, green, or purple.



Surgery and Acupuncture as Placebos

- Placebo surgery works better than injections.
- Sham acupuncture works better than a placebo pill.
- Sham acupuncture works no worse than actual acupuncture.

Fake Surgery

The placebo effect isn't just restricted to pills and injections.

Sham surgery, where the doctor pretends to operate on you but does not, has been shown to reduce knee pain.



More Fake Surgery

- ▶ Forty years ago, a young Seattle cardiologist named Leonard Cobb conducted a unique trial of a procedure (mammary ligation) then commonly used for relief from angina, in which doctors made small incisions in the chest and tied knots in two arteries to try to increase blood flow to the heart.
- ▶ It was a popular technique and 90 percent of patients reported that it helped, but when Cobb compared it with placebo surgery in which he made incisions but did not tie off the arteries, the sham operations proved just as successful.
- ▶ The procedure, known as internal mammary ligation, was soon abandoned

Examples of Abandoned Surgeries Based on Sham Surgery Controls

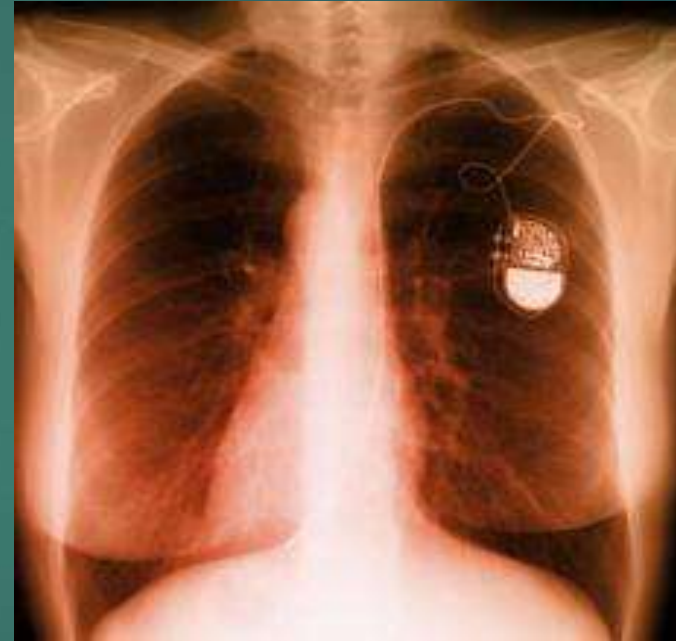
- ▶ Internal mammary artery ligation for angina (1959)
- ▶ Shunt surgery for Meniere's disease (1983)
- ▶ Arthroscopic knee surgery for osteoarthritis pain (2002)
- ▶ Fetal cell transplant for Parkinson's disease
- ▶ Placebos are effective in disproving medical effectiveness of some procedures

Surgery issues

- ▶ Placebo surgery may induce improvement in surgical clinical trials but raises many ethical questions; unclear whether due to P, mean regression, or disease natural hx.
- ▶ Parkinsonism stem cell transplants had P effects

Pacemakers

A Swedish study found that patients who had pacemakers installed to maintain a regular heart rate improved even if the pacemaker was not turned on.



Placebo Effect Has Become More Powerful Over The Years.

- ▶ Placebo effect was first noted in the late 1700s, but the true physiological implications weren't really understood until the 1970s.
- ▶ Still, it seems that the more testing medical experts conduct, the more powerful the placebo effect has become over time.
- ▶ This is largely thought to be a result of our social conditioning; we place a lot of faith in medical professionals.
- ▶ As medical technology improves, mortality decreases and our faith in medicine becomes stronger.

Other Placebo facts

- ▶ The longer the period of treatment and the larger the number of physician visits, the greater the placebo effect.
- ▶ When doctors are warm and encouraging and are engaged with patients, outcomes improve.
- ▶ Directions given to patients are extremely important: Patients told IV contained a powerful pain relief needed 34% less medication than patients told nothing (16%).
- ▶ Patients expecting results, with strong beliefs, and high motivation, do better.

Other facts

- ▶ Patients who are gullible, have less education, or are less skeptical, do better.
- ▶ Warts painted with different colors. Patients were told when color wore off warts would be gone. It usually worked.
- ▶ Fake ultrasound treatment for wisdom tooth pain worked.

Placebos

- ▶ The greater the pain, the greater the placebo effect. It's as if the more relief we desire, the more we attain.
- ▶ You don't have to be sick for a placebo to work. Placebo stimulants, placebo tranquilizers, even placebo alcohol, produce predictable effects in healthy subjects.

Placebo facts

- Telling patient “This will help.” works better than saying “This might work.”
- White coat on caregiver makes effect more potent.
- Confidence of care giver increases effectiveness.
- Children seem to have greater response than adults to placebos
- But Placebo doesn't work on unconscious patients

Placebos Can...

- ▶ Constrict the pupils, alter blood pressure, change heart rate and respiration, influence gastrointestinal secretions and peristalsis, change body temperature, produce white blood cell increase, enhance corticosteroid reactions, and change blood levels of creatine and lipoproteins
- ▶ Negatives: Cause dry mouth, nausea, heaviness, headache, difficulty concentrating, drowsiness, sleep disturbance

(Perry 1981)

Placebo = “I shall please”

- ▶ Placebos in traditional clinical practice are used to please or placate anxious or complaining patients
- ▶ More to please than to cure; use of inert pill or saline shot or sham procedure; often use vitamins, antibiotics, sedatives, or some other active ingredient.
- ▶ In clinical practice, placebo administration entails deception; in research, patient knows about the placebo
- ▶ Use in clinic, has been considered ethically questionable

Psychological study of placebos regarding interaction of mind and body

- ▶ Imagination can play a major role in therapeutic outcome
- ▶ Shapiro and Shapiro, 1997: seminal work
- ▶ Study of impact of therapeutic relationship, patient expectations of outcome, severity of symptoms, type of verbal instructions, environmental milieu
- ▶ In Psychology, focus on expectations, beliefs, and mind-body relationship
- ▶ Neuroscientific investigation of placebo effect as psychobiological phenomena

Nocebos

- ▶ Opposite to placebo: pathogenic effects of imagination and negative expectations and beliefs, originally in tribal societies
- ▶ As opposed to placebos resulting in reduction of discomfort and healing, nocebos are beliefs and expectations that can sicken or kill
- ▶ In Australia, pointing a bone at some
- ▶ In Latin America and Africa, bewitchment, voodoo curses/death, evil eye, black magic
- ▶ Effects due to stress-induced activation of sympathetic nervous system
- ▶ Current phenomena: health warnings may induce negative expectations, anticipatory nausea & vomiting in cancer TX, emotional impact of negative dx, distrust of doctors and therapies, vaccination avoidance

Modern view of Placebos

- ▶ Placebo effect is the effect that follows the administration of an inert TX (the placebo), whereas in a placebo-related effect no placebo is given
- ▶ Placebo effect is a psychobiological phenomena, that is not something else (spontaneous remission, statistical regression, etc.)
- ▶ Nocebo is a negative placebo effect, which goes in opposite direction of placebo effect
- ▶ There are many placebo effects with different biological mechanisms and in different systems and apparatuses, triggered by psychosocial context around patient and therapy.

Modern View

- ▶ Psychosocial context is the ritual of the therapeutic act.
- ▶ Expectation of a future outcome plays a central role, and may act through different mechanisms (i.e. reduction of anxiety, activation of reward circuits)
- ▶ Learning plays a crucial role and powerful placebo effects may be induced through a conditioning procedure. Through conditioning, possible to elicit placebo response in animals.
- ▶ Mediation by complex cognitive factors, personality traits, genetic variation related to good or poor responses

Factors causing false impression of placebo effect

- ▶ Natural course of disease (spontaneous improvement, fluctuation of sxs, regression to the mean, habituation)
- ▶ Additional treatment
- ▶ Observer bias (biased reports of clinical condition)
- ▶ Subsiding toxic effects of previous treatment
- ▶ Patient bias
- ▶ No placebo given (psychotherapy, psychosomatic phenomena, voodoo)
- ▶ Uncritical reporting of anecdotes

Placebo response is a “meaning response”

- ▶ Both aspirin and placebo work better when they have brand name
- ▶ MD's klg of context in which P is given can effect outcome; MD can transmit his expectations to pt..
- ▶ Analgesia following a placebo is blocked by naloxone
- ▶ Chinese and Japanese Americans more likely to die on 4th day of month (4 is unlucky number (4 is similar to word “death”))

Placebo response is a “meaning response”

- ▶ Placebos are deeply meaningful and can help even if one knows it's inert
- ▶ Placebos have been found to determine 80% of clinical improvement of depression; real effect of drug is only 20% (Kirsch et al., 2002)
- ▶ Hidden therapies are less effective than open ones. Klg of TX and its meaning affect therapeutic outcome

Rituals in treatment: the psychosocial context

- ▶ Placebo effect is a context effect (+ or -):
 - ▶ Confession in church, praying
 - ▶ Shamanic drumming or dancing
 - ▶ Taking a pill
 - ▶ Injection
 - ▶ Surgery
 - ▶ Being touched by a medical device (or a faith healer)
 - ▶ Acupuncture
- ▶ Marketing: Branded aspirin most effective (then unbranded aspirin, branded placebo, unbranded placebo)
- ▶ Price: more expensive works better than less

No administration of treatment needed for Placebo effect

- ▶ When no TX given, PE due to influence of the context surrounding TX on pt.'s brain
- ▶ Verbal suggestions of either improvement or worsening can be given alone, without administration of inert TX, so as to induce expectancies of outcome
- ▶ What a pt. expects in a clinical trial influences outcome (whether placebo or active TX); pts who believed they belonged to active TX experience greater improvement

There is **not a single placebo effect, but many**

- ▶ Not a single mechanism of placebo effect and not a single placebo effect, but many.
- ▶ Expectations and anticipation of clinical benefit play a crucial role when conscious physiological functions are involved, whereas classical conditioning is main element in unconscious physiological functions.
- ▶ Expectations have no effect on hormone secretion, whereas conditioning procedures do.
- ▶ Expectation of a future outcome is one of the principal mechanisms

Placebo is a **learning phenomenon**

- ▶ After repeated associations, a sugar pill that looks like an aspirin can decrease pain.
- ▶ Shape, Color, taste of pills, as well as syringes, stethoscopes, white coats, hospitals, doctors, nurses, etc., are associated with clinical improvement
- ▶ Via classical conditioning: placebo is conditioned stimulus
- ▶ Placebos given after drugs are more effective than when give first time.
- ▶ But conscious expectation is necessary for placebo analgesic

Doctor-patient relationship

- ▶ The communicative interaction of practitioners with patients, both verbal and nonverbal, may produce placebo effects even without the use of discrete treatments.
- ▶ Placebo responses tightly linked to doctor-patient relationship
- ▶ Four steps: feeling sick, seeking relief, meeting the therapist, receiving therapy
- ▶ Trust, admiration and hope; nonverbal communication

Most studied conditions related to placebo

- ▶ Pain
- ▶ Parkinson's disease
- ▶ Deep brain stimulation
- ▶ Migraine
- ▶ Sleep
- ▶ Depression
- ▶ Anxiety
- ▶ Addiction
- ▶ Psychotherapy
- ▶ Immune and endocrine systems

Moerman on Placebos

- ▶ Placebos do not cause anything because they're inert
- ▶ It is the psychological/emotional meaning that causes the effect
- ▶ This response is elicited by far more than just inert pills
- ▶ The meaning response goes well beyond psychological effects and results in physiological changes as well

Active Placebos

Sometimes placebos are pharmacologically active— they just don't do anything anyone would want.

So, for example, atropine blocks certain nerve receptors and causes dry mouth and other symptoms.

Active Placebos: more side effects, more effect

What's the point of an active placebo? Well, they work better than regular placebos.

The active placebo group will experience less pain, on average than the regular placebo group.

When people take the active placebos, they experience the side effects.

This makes them believe that the drugs are powerful and really work, and the power of their belief then influences what they experience.

Antidepressants are often placebos

- ▶ Irving Kirsch, a psychologist, conducted a meta-analysis of all the drug-company sponsored antidepressant trials sent to the US Food and Drug Administration in 2008
- ▶ Kirsch found that placebos are 82% as good as antidepressants. That means that if you take a placebo, you'll feel about 82% better than someone who takes the real thing.
- ▶ However, there are criticisms about the used methods and the interpretation of the results, especially the use of 0.5 as cut-off point for the effect-size.
- ▶ A complete reanalysis and recalculation based on the same FDA data raised issues. The authors concluded that although a large percentage of the placebo response was due to expectancy, this was not true for the active drug.

Antidepressants

- ▶ Another meta-analysis found that 79% of depressed patients receiving placebo remained well (for 12 weeks after an initial 6–8 weeks of successful therapy) compared to 93% of those receiving antidepressants. In the continuation phase however, patients on placebo relapsed significantly more often than patients on antidepressants.
- ▶ Placebo effect increasing over time: A 2009 meta-analysis reported that, in 2005, 68% of the effects of antidepressants was due to the placebo effect, which was more than double the placebo response rate in 1980.

Research showing that active treatments are effective, but that placebo effects exist as well.

- ▶ Anxiety disorders
- ▶ Asthma
- ▶ Autism: language and behavior problems
- ▶ Benign prostatic enlargement
- ▶ Binge eating disorder
- ▶ Bipolar mania
- ▶ Burning mouth syndrome
- ▶ Cough
- ▶ Crohn's disease
- Depression
- Dyspepsia and Stomach motility
- Epilepsy
- Erectile dysfunction
- Food allergy
- Gastric and duodenal ulcers
- Headache
- Heart failure, congestive
- Intellectual disability
- Itch

More conditions with placebo effects

- ▶ Irritable bowel syndrome
- ▶ Lower urinary tract symptoms
- ▶ Migraine prophylaxis
- ▶ Multiple sclerosis
- ▶ Nausea: gastric activity
- ▶ Nausea: chemotherapy
- ▶ Nausea and vomiting: postoperative (sham acupuncture)
- ▶ Osteoarthritis
- ▶ Overactive bladder
- Pain
- Panic disorders
- Parkinson's disease
- Psoriatic arthritis
- Reflux esophagitis
- Restless leg syndrome
- Rheumatic diseases
- Sexual dysfunction
- Social phobia
- Ulcerative colitis

Placebo effect

- ▶ The placebo effect has a tainted history, as it is associated with the paternalistic and deceptive practice of physicians prescribing inert agents or “impure” placebos. These concerns remain relevant to contemporary clinical practice.
- ▶ Recent surveys have shown that physicians continue to prescribe or recommend “placebo treatments,” which are believed to lack specific pharmacological efficacy for the patient’s condition.

([Brody 1982](#)); ([Tilburt et al 2008](#))..

Do Doctors Prescribe Placebos?

- ▶ NY Times: “Half of doctors routinely prescribe placebos”
 - ▶ 679 internists and rheumatologists from national list
 - ▶ Everything from vitamins and headache pills to vitamins, antibiotics and sedatives
- ▶ Time Magazine: “Is your Doctor Prescribing Placebos?”
 - ▶ 466 faculty surveyed in Chicago medical schools
 - ▶ 45% have prescribed placebos in regular practice
 - ▶ 96% believe placebos can have “therapeutic effects”
 - ▶ 1/5 lied outright, claiming it was medication

Placebos in Academic Practice

- ▶ 45% reported they had used a placebo in clinical practice
- ▶ Reasons for use:
 - ▶ to calm the patient (18%)
 - ▶ as supplemental treatment (18%)
 - ▶ “after ‘unjustified’ demand for medication” (15%)
 - ▶ “for nonspecific complaints” (13%)
 - ▶ “after all clinically indicated treatment possibilities were exhausted” (11%)
 - ▶ “to control pain” (6%)
 - ▶ “to get the patient to stop complaining” (6%)
 - ▶ “as a diagnostic tool” (4%)

Expectations are powerful

- ▶ Confirmation bias: seek out and assign more weight to evidence that confirms your belief, and ignore or underweigh evidence that could disconfirm your belief.
- ▶ Self fulfilling prophecy: an expectation about a subject, such as a person or event, can affect our behavior towards that subject, which causes the expectation to be realized; a belief that comes true because we are acting as if it is already true.
- ▶ Fake it till you make it



Pygmalion Effect

- ▶ Pygmalion effect: higher expectations lead to an increase in performance
 - ▶ positive correlation between leader expectation and follower performance
 - ▶ IQs of students of elementary school teachers who are told they are “bloomers” increase by end of year; and opposite: Teachers reflect what is projected into them by their students.
 - ▶ In most analgesia studies; patients who believe they belong to real treatment group experience greater improvement than those who believe they are in placebo group
- ▶ Golem effect: in which low expectations lead to a decrease in performance;
- ▶ Both effects are forms of self-fulfilling prophecy

Pain analgesia

- ▶ Placebo effect is believed to reduce pain in two different ways.
 - ▶ placebo initiating the release of endorphins, which are natural pain killers produced by the brain.
 - ▶ placebo changing the patient's perception of pain. "A person might reinterpret a sharp pain as uncomfortable tingling."

Snow World

- ▶ Snow World is a virtual reality landscape developed to help burn victims
- ▶ You fly around inside an ice canyon and fire snowballs at characters inside the game, such as penguins and snowmen.
- ▶ It's meant to work as a painkiller: the idea is that the brain has a limited capacity for attention, so if the ice canyon commands that attention, there is less capacity left over for experiencing pain.
- ▶ Trials show that undergoing wound treatment and physiotherapy while immersed in Snow World reduces their pain by an extra 15-40% on top of the relief from maximum level of painkiller medication.

4 Myths about Placebo

- ▶ 1. *The placebo effect is all in the mind.*
- ▶ A significant proportion of patients feel better after taking placebos,
 - ▶ some scientists claim that this improvement is totally mental — that patients only think they feel better.
- ▶ In reality, placebo treatments can cause measurable, biological changes similar to those triggered by drugs.
- ▶ Studies show that depressed patients on placebos experience increased prefrontal activation, which eases their symptoms.
- ▶ In patients with Parkinson's disease, placebos trigger a flood of the dopamine, just as their drugs do.
- ▶ Placebo analgesic dampens pain-related activity in the brain and spinal cord and causes the release of pain-relieving endorphins.

2. *Placebos work only if patients think they're real.*

- ▶ Dr. Ted Kaptchuk, director of the Harvard placebo program, has conducted "open-label" placebo studies, in which patients were told they were taking a placebo and that the placebo effect is powerful.
- ▶ IBS patient study: open-label placebo still produced a placebo effect and was about 20% more effective than no treatment. So Doctors could be more up-front with patients, informing them that a prescription is mainly for placebo purposes, and their patients would still benefit.
- ▶ Expecting to feel better is a key ingredient in placebo responses,.
- ▶ Found the same effect for depression, migraines and ADHD.
- ▶ Evidence that simply being cared for in a trial — even if patients know that a treatment is fake — eases anxiety and helps them feel that their conditions will improve.

Knowing

- ▶ Placebo analgesics are considerably more effective when the patient knows they are receiving them.
- ▶ Pain-killing and anxiety-reducing drugs that are infused secretly without an individual's knowledge are less effective than when a patient knows they are receiving them.
- ▶ Likewise, the effects of stimulation from implanted electrodes in the brains of those with advanced Parkinson's disease are greater when they are aware they are receiving this stimulation

3. *Neurotic people are more likely to respond to placebos.*

- ▶ Recent studies, however, suggest that anyone can respond to a placebo.
- ▶ Crucial factors:
 - ▶ patients' attitudes toward a particular treatment,
 - ▶ their previous experiences (whether, for example, they've responded well to a particular drug),
 - ▶ the information they're given about a treatment,
 - ▶ and personality.

Personality traits may be associated with placebo responsiveness

- ▶ About a quarter of the variation does seem to depend on personality:
- ▶ Certain personality traits can predict placebo responsiveness.
- ▶ Those who are optimistic, altruistic, resilient and straightforward have larger effects. These personality types tend to be more engaged with their treatment and have more positive expectations for it. Neurotic and hostile people are least likely to respond.
- ▶ Differences in suggestibility contributes significantly to magnitude of placebo analgesia. More highly suggestible, more analgesic effect.

4. *You have to take a placebo to get a placebo effect.*

- ▶ The placebo effect is commonly defined as what happens when a patient takes a placebo, or as the benefit experienced by someone in the placebo arm of a clinical trial.
- ▶ But many “real” medical treatments — particularly those that modify symptoms like pain, fatigue, nausea or depression — rely on the placebo effect.
- ▶ Common opioid painkillers such as Tramadol are about a third less effective if you don’t know you are taking them.
- ▶ Study: 459 migraine attacks - the placebo effect accounted for 60 percent of the benefit of the painkiller Maxalt.

How does the placebo effect occur?

- ▶ While there is some evidence that placebo interventions can alter levels of hormones, endocannabinoids or endogenous opioids, and induces brain activations; other prominent components include expectancy effects, regression to the mean and flawed research methodologies.
- ▶ Psychological mechanisms which contribute:
 - ▶ Expectations
 - ▶ Conditioning
 - ▶ Therapeutic and Social Relationships
 - ▶ Motivation
- ▶ Neuro-biological mechanisms
 - ▶ Endorphin release
 - ▶ Brain activation changes

Expectations

- ▶ The placebo effect is related to the perceptions and expectations of the patient;
- ▶ If the substance is viewed as helpful, it can heal, but, if it is viewed as harmful, it can cause negative effects.



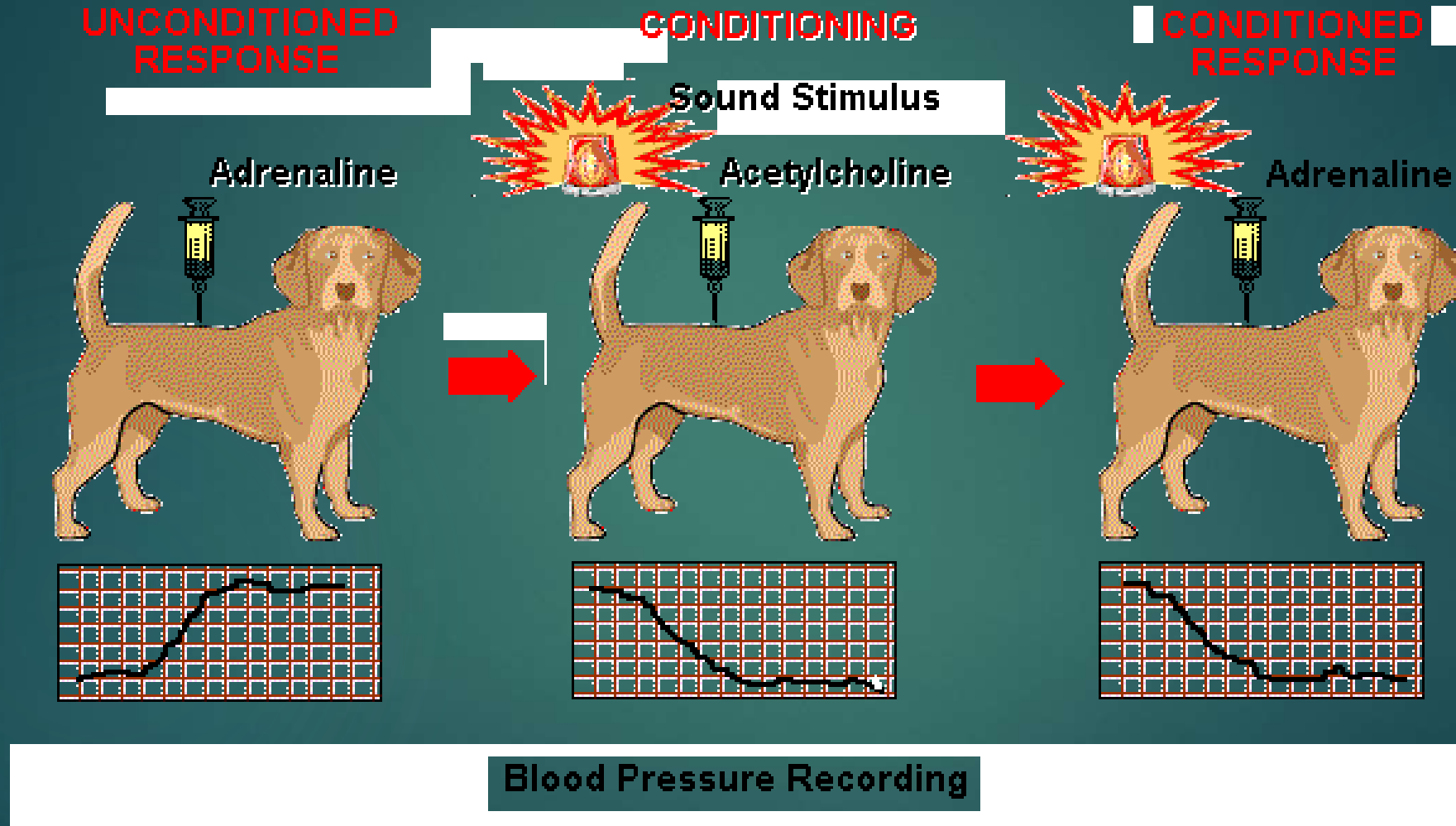
Verbal cues

- ▶ Can manipulate expectations and mediate placebo effects and produce :
 - ▶ Analgesic effects (both experimentally and clinically)
 - ▶ Changes in motor performance in Parkinson's disease patients
 - ▶ Changes in emotions and brain responses

“Expectancy” research:

- ▶ Research on post-operative pain divided patients into three sections
 - 1) Received morphine secretly
 - 2) Received morphine and were told they were getting it
 - 3) Received placebo but told it was a powerful pain reliever
- ▶ Patients who were told they received a pain reliever, whether they actually received it or not, had the same experience as those who secretly received morphine.
- ▶ The covert dose had to be increased to 12 milligrams to surpass the effect of the placebo

Learning Source of Placebo: Pavlovian Conditioning



Classical Conditioning

- ▶ Pavlovian conditioning: repeated associations between a neutral stimulus and an active drug can result in the ability of the neutral stimulus by itself to elicit a response characteristic of the drug
 - ▶ Conditioning responses can produce changes in hormone secretions and immune response
- ▶ Psychological conditioning: once someone benefits from an intervention, the person starts to associate that intervention with a benefit. The association, and the the benefit, may get stronger with additional exposures to the intervention.
- ▶ Patients learn to associate taking a pill with a particular physiological response, so when they subsequently take a placebo, their bodies automatically mimic that response.

Lupus case: **Conditioned learning influences immune responses**

- ▶ Ader study: animals received both saccharin and Cytoxan (an immunosuppressant); associated both the sweet taste with feeling sick and the immunosuppression. They later respond to the sweetened water just as if it were the drug.
- ▶ In human conditioning, a neutral stimulus saccharin is paired in a drink with an agent that produces an unconditioned response. For example, Cytoxan, which causes immunosuppression.

Conditioning

- ▶ After learning this pairing, the taste of saccharin by itself is able to cause immunosuppression.
- ▶ Such conditioning has been found to affect a diverse variety of not just basic physiological processes in the immune system but ones such as serum iron levels, oxidative DNA damage levels, and insulin secretion
- ▶ Teaches your body how to respond to a particular medicine, so that in future it can trigger the same change on its own.

Lupus: placebo-controlled dose reduction via conditioning

- ▶ Rose perfume and cod liver oil paired with medication infusion once a month for the next three months
- ▶ Exposed to cod liver oil and perfume every month, but received Cytosan only every third month.
- ▶ By the end of the year, she had received just six doses of the drug instead of the usual twelve. After 15 months she stopped the cod liver oil and rose perfume but continued to imagine a rose
- ▶ Now other cases: strawberry milk mixed with green food coloring and essential oil, has bright color and overwhelming lavender flavor; after being associated with CsA, the drink reliably induces immunosuppression in healthy volunteers, creating on average 60–80 per cent of the effect of the drug

Conditioning:

- ▶ Has been used in:
 - ▶ saccharin-vanilla-flavored solution that had previously been paired with the immunosuppressant Cytoxan resulted in a reduction of the inflammatory processes in rats
 - ▶ studies on heart transplant demonstrated that behavioral conditioning prolonged transplant survival
 - ▶ in grafting experiments, expressed by a delayed tissue rejection after allogeneic skin transplantation
 - ▶ Possibility that tumor growth could be delayed and lifespan prolonged through conditioned immune responses

Conditioning

- ▶ Aim to reduce the dose of medication required, thereby possibly limiting adverse drug effects and saving costs.
- ▶ Patients suffering from psoriasis were treated with a corticosteroid ointment.
- ▶ However, the experimental group received the real drug only at 25–50% of the treatment settings, and was otherwise treated with a placebo cream.
- ▶ After eight weeks,
 - ▶ patients who received the drug at the reduced dosage (25–50%), and the rest of the time the placebo, showed symptom scores comparable with the group that received the standard therapy (100%)
 - ▶ patients treated with a reduced dose throughout the study showed worsening of symptoms.

Placebo associated with objective brain changes

- ▶ Objective changes in brain chemistry:
- ▶ Brain releases natural pain-relieving substances, called endorphins, when people enrolled in pain studies are given placebos. Activation of endogenous opiates - Creates chemicals produced in the brain that mimic morphine like drugs.
- ▶ Pain relief with placebo is associated with increased activity in the rostral anterior cingulate cortex, an area of the brain that is also affected by opioid medication.
- ▶ Subsequent studies using functional magnetic resonance imaging have also shown that pain relief with placebo involves changes in pain-sensitive areas of the brain
- ▶ Studies show that when people are given placebos but believe that they are getting an analgesic, an anti-Parkinson drug or an antidepressant, they undergo changes in brain activity that mimic in whole or in part those that occur with the active drug.

Neurobiological mechanisms

- ▶ Placebo analgesia: A suggestion that a substance will reduce pain increases the release of endorphins, which make patients feel less pain
- ▶ The placebo effect is the product of chemical changes. Numerous studies have supported the conclusion that endorphins in the brain produce the placebo effect.
- ▶ In patients with chronic pain, placebo responders were found to have higher concentrations of endorphins in their spinal fluid than placebo nonresponders.
- ▶ Subjects who experience elevated pain due to a nocebo response have *reduced* opioid transmission in their reward system
- ▶ When given Naloxone, which lock up key opioid receptors, the pain comes back
- ▶ Fields HL, Levine JD. Placebo analgesia- a role for endorphins. Trends in Neuroscience 1984; 7:271-73

Brain changes

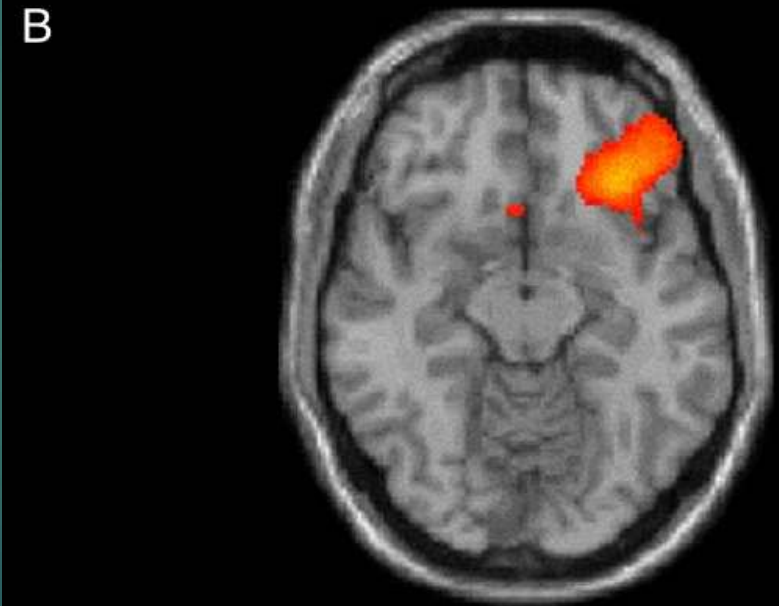
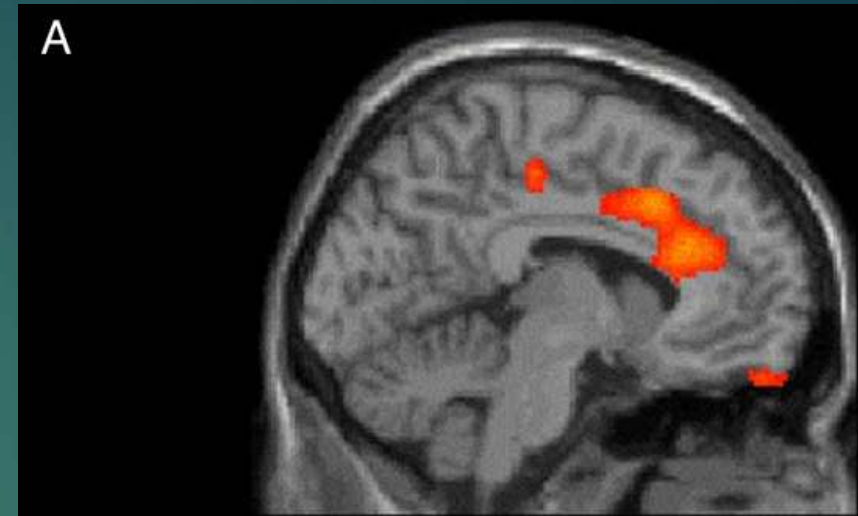
- ▶ Parkinson's disease is associated with a shortage of a brain chemical called dopamine, and in studies of the disease, placebos have increased the production of dopamine.
- ▶ Study of patients with Parkinson's disease using PET technology showed that when patients expected to receive a drug that would relieve their parkinsonian symptoms (apomorphine) but actually received placebo, they showed substantial release (3x) of dopamine in the striatum.
- ▶ The degree of clinical improvement with placebo correlated with the amount of dopamine released.

A) Dorsal anterior cingulate region that correlated negatively &

(B) right ventrolateral prefrontal region that correlated positively with symptom improvement.

A strong positive correlation between pre- to post-placebo increases in RVL-PFC and subjective reports of symptom improvement.

Any activation of RVL-PFC is expected to inhibit dACC activity, which in turn should diminish pain unpleasantness.



Frontal suppression of negative affect

- ▶ Control of pain is a function of regulation of negative affect, a function of the frontal cortex.
- ▶ Data from 15 recent studies of placebo, regulation of emotions, and activation by actual opiate drugs: increased activation in each of these conditions reveals a set of frontal regions that appear to be consistently increased during diverse tasks in which negative affect must be suppressed.
- ▶ On the lateral surface, these regions include the DLPFC, VLPFC, and possibly a third cluster of activations around the rostral PFC.
- ▶ On the medial surface, two clusters appear around the midrostral dorsal anterior cingulate and neighboring superior medial PFC.
- ▶ On the orbital surface, many peaks are grouped around the medial orbital sulcus bilaterally.

Placebo effect for pain in a population of IBS patients

- ▶ IBS patients reported significant symptom improvements over the course of a 3-week placebo regimen (inert pill).
- ▶ The dACC reactivity to physical discomfort was reduced from pre- to post-placebo.
- ▶ Conversely, the RVL- PFC response to physical discomfort increased from pre- to post-placebo to the extent that participants reported symptom improvement.
- ▶ The changes in activity in these two brain regions were negatively correlated
- ▶ dACC activity may be most directly associated with symptom improvement in response to the placebo administration, but RVL PFC may produce the dACC changes and serve a more central role in placebo effects.

Brain changes: **Placebo & Prozac activate similar areas**

- ▶ Measurable changes in brain chemistry may explain the large placebo effect seen in depression treatment.
- ▶ Mayberg et al used PET to measure changes in brain glucose metabolism in 17 men with depression.
- ▶ Some of the men received placebo and some the antidepressant fluoxetine. Those who improved with placebo showed metabolic changes in a number of brain areas including the prefrontal cortex, anterior cingulate, posterior cingulate, and thalamus. These areas of metabolic change overlapped with those that were observed in patients who responded to fluoxetine.
- ▶ The depressed patients who did not respond to fluoxetine or placebo did not show these metabolic changes.

Functional Imaging of analgesic placebo effect

- ▶ Functional imaging upon placebo analgesia shows that it links to the activation, and increased functional correlation between this activation, in the:
 - ▶ anterior cingulate,
 - ▶ prefrontal,
 - ▶ orbitofrontal
 - ▶ insular cortices,
 - ▶ nucleus accumbens,
 - ▶ amygdala,
 - ▶ the brainstem periaqueductal gray matter
 - ▶ and the spinal cord.

Motivational circuitry effected: PFC, striatum, Nacc

- ▶ Disorders that show the most reliable placebo effects are those in which the brain's motivational circuitry (prefrontal and striatum) play an important role.
- ▶ High placebo responses link with enhanced dopamine and mu-opioid activity in the circuitry for reward responses and motivated behavior of the nucleus accumbens, and, on the converse,
- ▶ Anti-analgesic nocebos responses were associated with deactivation the dopamine and opioid release areas

Other brain activation for **non-analgesic placebo effects**:

- ▶ Parkinson's disease: Placebo relief is associated with the release of dopamine in the brain.
- ▶ Depression: Placebos reducing depression affect many of the same areas that are activated by antidepressants with the addition of the prefrontal cortex
- ▶ Caffeine: Placebo-caffeinated coffee causes an increase in bilateral dopamine release in the thalamus.
- ▶ Glucose: The expectation of an intravenous injection of glucose increases the release of dopamine in the basal ganglia of men (but not women).
- ▶ Methylphenidate: The expectation of intravenous injection of this drug in inexperienced drug users increased the release of dopamine in the ventral cingulate gyrus and nucleus accumbens, with this effect being largest in those with no prior experience of the drug.

Therapeutic and Social Relationships

- ▶ Results of two randomized control trials with asthma patients and with rheumatoid arthritis patients
- ▶ Active group: patients revealed a significantly difficult conflict or secret about past traumas to the clinician
- ▶ At the 4 month follow-up, asthma patients who were in the active group showed significant improvements in forced expiratory volume, and those with arthritis showed significant improvements in pain, when compared with their control groups.
- ▶ Control group, patients talked about superficial things Smyth, J., Stone, A., Hurewitz, A & Kaell, A. 1999 Effects of writing about stressful experience on symptom reduction...JAMA 281 1304-1309

More relationship research

- ▶ There is a favorable reaction to care and attention from people who patients believe can help ease their suffering and distress.
 - ▶ The placebo effect of the sham acupuncture needles in IBS TX was impressive: 44% of those treated with just the sham needles reported relief from their IBS problems. When sham acupuncture was combined with attentive, empathetic interaction with the acupuncturist, the placebo effect got even larger, with 62% reporting relief from their IBS woes.
- ▶ Large RCT showed that a positive consultation by a physician produced 20-25% greater improvements in functional conditions compared with a negative consultation. Amount of time spent in consultation was equal.
- ▶ **Extensive summaries of this research:** Chez, R.A & Jonas, W. 2005 Developing healing relationships: J. Altern. Complementary Med. 11, S1-S2 and Safran, D., Miller, W. & Beckman H. 2006 Organizational dimensions of relationship-centered care: ...J. Gen. Intern Med. 21, S9-S15.

Placebo effects are not limited to analgesia

- ▶ Increase in respiratory functioning
- ▶ Decreased heart rate
- ▶ Dopamine release and changes in basal ganglia and thalamic neuron firing in Parkinson patients
- ▶ Can see changes in metabolic activity in the brain in depression and expectation manipulation with addiction

Loss of prefrontal functioning reduce placebo's therapeutic efficacy

- ▶ Disruption of prefrontal functions in AD affects placebo responsiveness.
- ▶ In an open-hidden design in Alzheimer's disease, the placebo component was correlated with cognitive status and functional connectivity between brain regions.
- ▶ The lower the cognition and connectivity the less the analgesic effect, to the point where an increase in dose was required for same level of analgesia.
 - ▶ Benedetti F, Arduino C, Costa S, Vighetti S, Tarenzi L, Rainero I, et al. *Loss of expectation-related mechanisms in Alzheimer's disease makes analgesic therapies less effective.* Pain 2006 Mar
- ▶ Pts with prefrontal impairment need larger doses of analgesics.

Alternative therapies with elaborate rituals have clinically significant analgesic placebo effects

- ▶ Large acupuncture trials in Germany compared acu, sham acu, usual care, and no treatment for migraine, tension HA, chronic lower back pain, and osteoarthritis of the knee
- ▶ Real and sham acu resulted in substantially greater symptom improvement than no treatment and usual care.
- ▶ Positive expectations influenced analgesic responses, doubling the likelihood of positive outcomes. Results lasted one year.

Knowing you are getting a placebo is important

- ▶ Hidden administration of 5 commonly used painkillers were markedly less effective than open administration
- ▶ Similar results have been reproduced for drug admin for anxiety and deep brain stimulation for Parkinson's Disease

Colloca L, Lopiano L, Lnotte M, Benedetti F. *Overt versus covert treatment for pain, anxiety, and Parkinson's disease.* La cet Neurology 2004; 3; Amanzio M, Pollo A, Maggi G, Benedetti F. *Response variability to analgesics: a role for non-specific activation of endogenous opiods.* Pain 2001;

Placebos in **physical performance**: Placebo as doping

- ▶ Athlete's expectations are important elements of physical performance
- ▶ Compelling evidence that physical performance in sport activities is boosted by placebos
- ▶ Perceived ergogenic aids (performance enhancing drugs) can increase endurance, speed and weight-lifting ability, leading to the question of whether placebos should be allowed in sport competition; pose doping ethical issues (placebo induced endorphin response by means of preconditioning with illegal drugs)
- ▶ Nocebo effects have been found to counteract good physical performance and can interfere with training programs

Placebo in cognitive performance

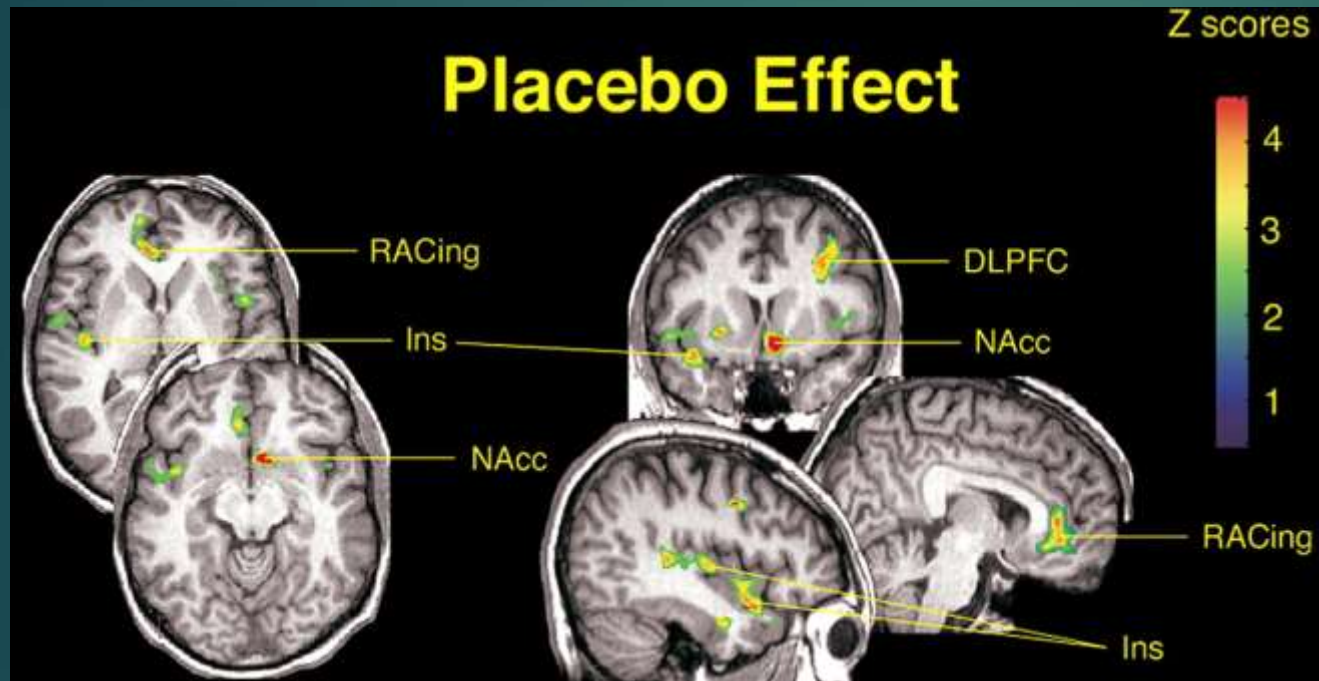
- ▶ Expectations enhance cognitive performance and reaction times
 - ▶ Being told drink was glucose, improved performance on recognition memory and vigilance task
 - ▶ Students told 2 weeks of placebo was cognitive enhancer; improved delayed memory and Stroop
- ▶ Stereotype threat reduces actual WM ability responses in NP testing
 - ▶ Comments about race, gender, etc. prior to assessment will produce lower test results that do not represent actual ability
- ▶ Be aware of any such comments

Most studied condition: Pain

- ▶ Most of klg about neurobiological mechanisms of placebo effect comes from field of pain and analgesia.
- ▶ Expectation of pain reduction plays a crucial role in placebo analgesia. Shown by reduced effectiveness of painkillers when administered covertly (unexpectedly)
- ▶ Placebo analgesic effect is mediated by endogenous opioid systems, as well as by endocannabinoid system.
- ▶ Dorsolateral prefrontal cortex and regions involved in dopaminergic reward mechanisms involved

Why the high responsiveness to expectation of pain relief?

- Evidence that expectation of pain relief activates mu-opioid neurotransmitter system (“endorphins”)



Red & orange indicate regions of heightened mu-opioid activity when P reports positive effect of placebo

Pain 2

- ▶ Prefrontal lobes are fundamental for a placebo response to occur. If no prefrontal control, no placebo response.
- ▶ Nocebo hyperalgesic (more pain) effect mediated by anxiety, which activates a cholecystokinin system, that facilitates pain transmission
- ▶ Endogenous pain modulatory descending circuits represent the biological substrate for action of placebos on pain.

Parkinson's Disease

- ▶ PD pts who receive placebo show high rates of motor improvement in clinical trials of meds and surgery
- ▶ PE in PD is mediated by dopamine release in the striatum and is associated with changes in activity of neurons in the subthalamic nucleus, substantia nigra, pars reticulata, and motor thalamus
- ▶ Therapeutic effects of deep-brain stimulation are powerfully modulated by placebos

Migraines respond to great expectations

- ▶ Although clinical trials on migraine show very high rates of improvement in patients who received placebo, mechanism is unknown; subcutaneous P better than oral P
- ▶ Meds and placebos both fight pain better when patients anticipate getting active drug: Migraine meds labeled as placebos dull headache pain less effectively than the same pills identified either as the real deal or as possibly a genuine drug,
- ▶ Placebo pills mislabeled as the migraine drug Maxalt provided close to as much pain relief as Maxalt mislabeled as a placebo. Overall, though, Maxalt eased migraine pain better than placebos did.
- ▶ These findings suggest that the physiological effects of the drug and the psychological effects of a placebo contributed almost equally to the therapeutic efficacy of the migraine treatment

Other conditions

- ▶ Sleep: Placebos induce behavioral and physiological changes
- ▶ Restless Legs syndrome: shows improvements in placebo groups
- ▶ Seizures: improvement in placebo groups is substantial
- ▶ Chronic fatigue syndrome: large placebo effects
- ▶ Multiple sclerosis: large nocebo effects

Mental and behavioral disorders

- ▶ In depression, SSRI TX and placebo TX affect similar brain areas
 - ▶ 80% of response to active drug is placebo effect; virtually all variation in drug effect size due to placebo effect
 - ▶ Proportion of pts with depression responding to placebos increased from 20% to 35% from 1981 to 2000; same increase for antidepressants (40 to 55%); thus responses to placebos change, as meaning of drug effectiveness changes over time
- ▶ In double blind studies of anti-depressants, patients often figure out if they are getting the “real drug” by side effects. The worse the side effects, the more effective the drug.

Effect of knowing

- ▶ Covert administration of antianxiety drugs is less effective than overt administration, which indicates key role of expectation in antianxiety therapy.
- ▶ Valium has no discernible effect on anxiety unless a person knows he is taking it.
 - ▶ Luana Colloca, Leonardo Lopiano, Michele Lanotte, Fabrizio Benedetti *Overt versus covert treatment for pain, anxiety, and Parkinson's disease* The Lancet Neurology, Volume 3, Issue 11, November 2004, Pages 679-684

Psychiatric conditions

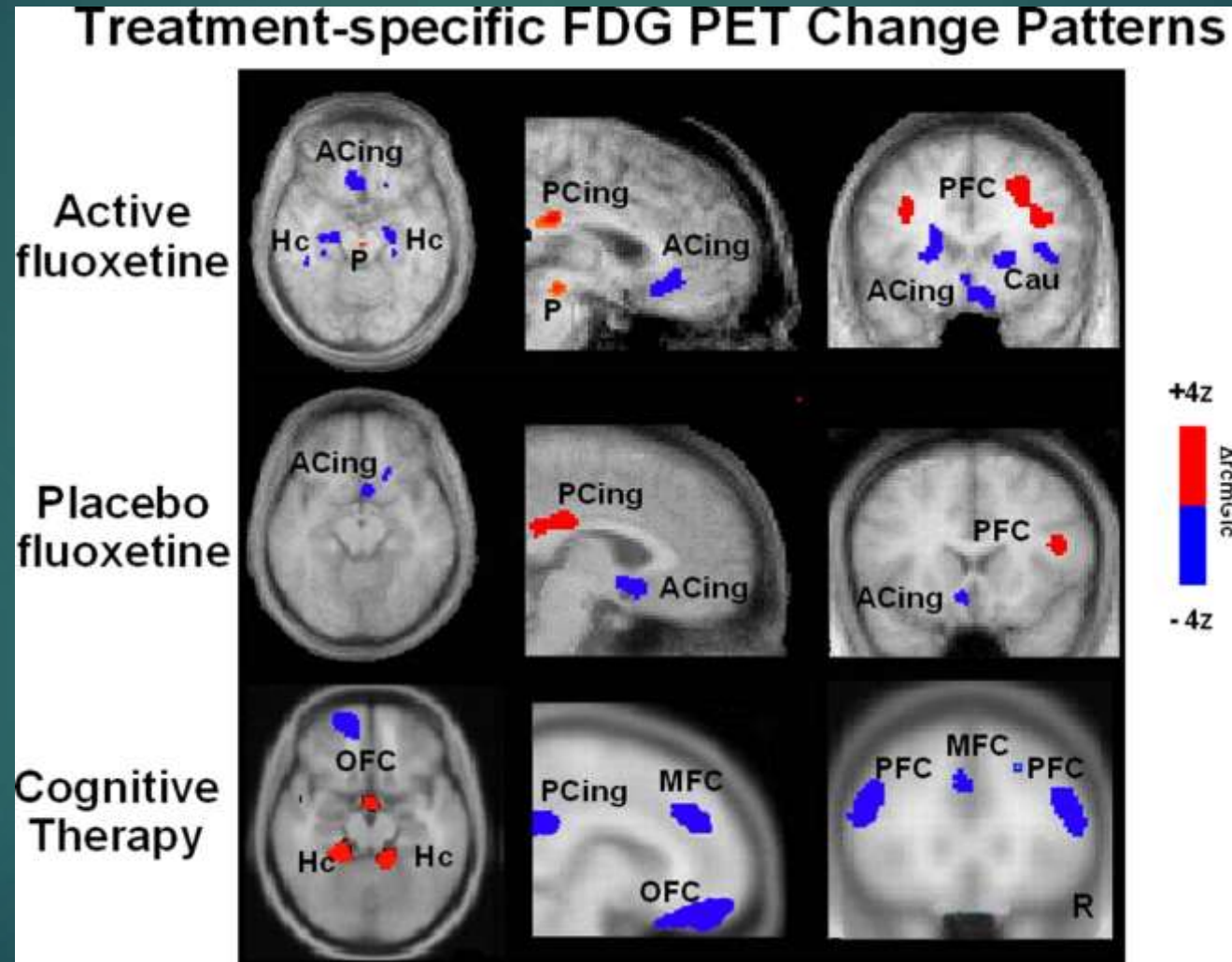
- ▶ Panic disorder is highly responsive to placebo, with a nearly 50% improvement in symptoms among patients assigned to that treatment strategy.
- ▶ In patients with posttraumatic stress disorder or depression, the placebo response is greater than 30%,
- ▶ In generalized anxiety disorder, a response in the 30% range is also seen

Psychiatric conditions

- ▶ Expectations appear to be particularly important when associated with effects of drugs of abuse
- ▶ No definitive role of placebo effects in alcohol abuse (issue of credibility of verbal instructions)
- ▶ Large effects in tobacco smoking and nicotine intake
- ▶ Patients with other conditions, including obsessive-compulsive disorder (OCD) and psychosis, are less likely to exhibit a placebo response.
- ▶ Clearly, the placebo response is not uniformly strong in all psychiatric conditions.

Changes in regional glucose metabolism (FDG PET) in fluoxetine (top), placebo (middle), and cognitive (bottom) therapy responders measured before and after a standard course of each respective treatment.

Common pattern of cortical increases and limbic-paralimbic decreases is seen in both Prozac & placebo



CBT response is associated: DL & ML frontal decreases and hippocampal increases.

The placebo changes attributable to the effects of expectation and conditioning facilitated by the psychosocial context of the trial

Other Disorders

- ▶ Premenstrual dysphoric disorder: placebo effect
- ▶ ADHD: placebo conditioning procedure has been found to reduce drug intake 50% (conditioned placebo = daily pairing of stimulant with visually distinctive placebo capsule administered in open label, with full disclosure to pts and parents)

Immune and endocrine systems

- ▶ Placebo effect in immune and endocrine system is basically a conditioned response
- ▶ Conditioned immunosuppression affects a number of immune mediators (interleukin-2; interferon-gamma)
- ▶ Some negative allergic reactions may be induced by nocebos

Immune and endocrine systems

- ▶ Response of some hormones, like insulin, growth hormone and cortisol, have been successfully conditioned. Insulin secretion can be placebo conditioned.
- ▶ HPA axis may represent an important system in placebo and nocebo responsiveness. HPA can be conditioned.
- ▶ Need normal insula and amygdala for placebo conditioning.

Less studied conditions

- ▶ Gastrointestinal and genitourinary disorders
 - ▶ Irritable bowel syndrome (IBS) sxs are reduced by placebo; Several brain pain related regions are inhibited by placebo TX in IBS pts
- ▶ More placebo txs, more clinical improvement in ulcerative colitis and Crohn's
- ▶ GI sxs and salivary secretion can be P conditioned
- ▶ Gastric functions can be affected by either placebo or nocebo induced expectations

Other conditions

Genitourinary disorders: Subjective sxs are more affected than objective sxs

▶ Expectations are crucial in sexual functions; sexual functions may improve after P, or worsen after N

▶ Cardiovascular and respiratory systems:

▶ Placebo induced activation of endogenous opioids may affect heart activity

▶ Asthma and cough are powerfully affected by placebos by unknown mechanisms.

▶ placebos reduce bronchial hyper-reactivity in asthma

▶ cough is powerfully reduced by placebo

Cancer

▶ Oncology

- ▶ Cancer progression is unaffected by P, but sxs (pain, appetite, anxiety) can be reduced by P
- ▶ CA chemotherapy induces conditioned N responses
- ▶ Nocebo effects are crucially involved in anticipatory nausea and vomiting before a cancer chemotherapy session, via classical conditioning
- ▶ Terminal cancer patients who talked with palliative care specialists focused on quality of remaining life, rather than medical care, had less depression and better experiences than patients who didn't get such care. These patients also lived nearly three months longer.

Alternative therapies

- ▶ Role of expectation is important in Acupuncture: TX for pain induce analgesia expectations
- ▶ Acupuncture is no better than a placebo intervention; accumulated evidence strongly points in this direction.
- ▶ In general, sham devices often produce larger placebo effects than placebo pills

Alternative therapies

- ▶ Invasive but safe intervention, characterized by an elaborate treatment ritual and frequent clinician-patient interaction, may be a potent method of interpersonal healing by means of the placebo effect
- ▶ Acupuncture has both:
 - ▶ a specific effect (real needle activates insula)
 - ▶ a placebo effect (sham needle - dorsolateral prefrontal, cingulate);
 - ▶ Both areas related to placebo analgesia

Therapeutic relationships

- ▶ Interpersonal healing concerns the art of medicine, oriented therapeutically towards relief of suffering—the illness component of disease and injury.
- ▶ This is demonstrated by illuminating experiments comparing open and hidden administration of drugs, showing a substantially greater effect of open administration, presented to an alert patient in a ritual of treatment accompanied by a communicated expectation of benefit
- ▶ Above represents the placebo effect component of treatment outcome, without the use of a placebo intervention.
- ▶ Moreover, some of the psychological mechanisms of various types of interpersonal healing via the placebo effect may involve alterations in patient attention: e.g., distraction from a pain or reduction in anxiety, leading to a diminished tendency of morbid attention to bodily dysfunction

(Colloca et al. 2004).

Relationships entail placebo effects

▶ Doctor-patient relationship:

- ▶ Doctor, nurse, caregiver represents essential but powerful context for a therapy; patient-provider interaction includes many placebo effects
- ▶ Word and attitude interactions can produce placebo therapeutic effects (expectations of improvement), i.e. comforting talk for women undergoing breast biopsies
- ▶ Doctor-patient interaction plays huge role in illness outcome, as do diagnostic tests, as do medication & treatment adherence
 - ▶ Tests: Short-term disability in 20% in those receiving medical test vs no tests (46%); Having Diagnostic tests were an independent predictor of recovery. More than half (57%) of the patients in the test group felt that the care they received was "better than usual."
- ▶ More visits with doctors produce greater P effects

Doctor-patient

- ▶ Placebo effects appear to be powerful in psychotherapy, and the brain areas involved in psychotherapeutic outcome are different from those involved in placebo effect.
- ▶ Also Nocebo effects: negative expectations leads to clinical worsening
(Note that primary reason for law suits in US is not for medical injury per se, but for failure in communication between Dr and pt.)
- ▶ Different verbal instructions lead to different outcomes: firm diagnosis and assurance lead to better outcome

Doctor's Pad

- ▶ A group of 456 sedentary patients were given verbal recommendations to increase their physical activity levels.
- ▶ 2 groups: written exercise prescription or to a verbal advice group.
- ▶ The number of people in both groups who engaged in physical activity increased markedly after 6 weeks
- ▶ But more participants in the written prescription than the verbal advice group were active.
- ▶ In our culture, the written prescription has a large symbolic impact.

Placebo, anti-depressant vs psychotherapy equivalency

- ▶ 3 Conditions: placebo, therapy (CBT or interpersonal psychotherapy), or imipramine. When the results were analyzed, no differences in outcome were evident according to the various treatments. None showed any advantage over the others.
- ▶ In the less severely ill patients, no statistically significant difference was present among the treatments.
- ▶ In the more severely ill patients, imipramine had an advantage over the 2 psychotherapies and placebo. In the severely ill patients, imipramine worked better than any other treatment modality, but placebo was about as good as the psychotherapeutic strategies.
- ▶ Overwhelming majority of studies that have compared CBT with a pill placebo in the treatment of moderately severe depression show no difference in efficacy.
- ▶ Less severely ill patients may benefit from any one of several different types of treatment, including psychotherapy, alternative therapies, and placebo.

Placebo response in Depressed People is a biomarker for TX response

- ▶ Brain's natural "painkiller" system – called the mu-opioid system -- responds to pain when patients get a placebo.
- ▶ How well a person responds to a placebo may determine how well they'll respond to a real one in TX of depression
- ▶ Participants who reported improvement of depression symptoms after getting the placebo also had the strongest mu-opioid response in brain regions involved in emotion and depression & were also more likely to experience even fewer symptoms once they got a real drug.
- ▶ Response to placebo predicted nearly half of the variation between individuals in total response to the entire study, including actual drug treatment.
- ▶ This finding gives us **a biomarker for treatment response in depression**

Placebo by proxy: the effect of parents' beliefs on therapy for children's temper tantrums

- ▶ A placebo by proxy effect occurs when a patient's response to therapy, assessed either objectively or subjectively, is affected by the behavior of other people who know that the patient is undergoing therapy.
- ▶ N= 58 children aged 2–5 years who reported frequent tantrums and examined the effect of a pharmacologically inert substance (flower essence) that is purported by the manufacturers to reduce temper tantrums.
- ▶ Tantrum frequency, tantrum severity, and parental mood were measured on 5 occasions over 8 days before treatment and on a further 5 occasions over 10 days after the start of treatment.
- ▶ Compared to the period before treatment, there was a continuing reduction in tantrum frequency and severity over the 8 days of placebo treatment.
- ▶ There were significant day-to-day correlations between parents' mood and tantrum frequency and severity.
- ▶ Children's response to treatment for tantrums is associated with the beliefs and mood of the adult carer.
- ▶ We cannot say whether tantrum reduction was due to objective changes in child behavior, changes in parental perception, or both, but both are clinically important changes.

The placebo effect is not always present

- ▶ Placebos are not magic
- ▶ They have not been proven to be effective in reducing tumors, changing the course of fatal diseases, reducing extremely high levels of pain...

In what other unconscious ways is our behavior influenced?

Other ways our behavior is unconsciously influenced:

- ▶ Marketing (wine labeled from CA tastes better than wine labeled from IN, even though it is the same wine)
- ▶ Embodied cognition: our rationality is influenced by our bodies (women who wore bikinis did worse on math tests)
- ▶ Enclothed cognition: (the clothes we wear influence how we experience the world)

No placebo controls in brain training program research

- ▶ Active shooter video vs Tetris as control group
- ▶ Merely having an “active control group,” one that does something for the same amount of time as the treatment group, does not protect against the placebo effect; holds true for almost all intervention studies.
- ▶ Are participant’s expectations for improvement equivalent in the 2 conditions.

Reminder:

Placebo is an intervention designed to simulate medical therapy that at the time of use is believed not to be a specific therapy for the condition for which it is offered.

Future may prove it to be actually therapeutic

How can we maximize the therapeutic effects of our treatments?

The definition of treatment needs to be broadened

- ▶ Drugs
- ▶ Surgery
- ▶ What we say
- ▶ How we conduct ourselves
- ▶ The environment in which we work and see patients
- ▶ Therapeutic relationships

Limitations in current research

- ▶ Most have involved lab experiments over short durations with healthy subjects
- ▶ Longer term placebo response has been studied in RCTs; but these rarely include no treatment groups to control for natural history and regression to the mean
- ▶ More research is needed from a basic science, clinical trial and ethical perspectives

Summary

- ▶ A patient's expectations, beliefs, conditioning and anxiety can strongly effect treatment efficacy
- ▶ As practitioners, we can strongly affect those expectations through our words, and behavior.
- ▶ A therapeutic alliance, based on listening, empathy, reassurance, and therapeutic optimism, constitutes good clinical practice
- ▶ We can use the evidence from placebo research in a way that is ethically acceptable and effective.
- ▶ Replace the term Placebo Effect with concepts such as “meaning and context’ response components in research

How to use placebo effect

- ▶ ***Make sure you're getting the support you need from your doctor.*** Placebo effect research has shown how important a supportive doctor-patient relationship can be. If you're not getting the support and attention you need, consider switching doctors.
- ▶ ***Recognize that it might be "in your head" — but there's nothing wrong with that.*** Behind the subjective experience of feeling better (and worse) are objective changes in brain chemistry that we've only started to understand.
- ▶ ***Find treatments you can believe in...*** Expectations that an intervention will have some benefit increase the chances that it will.
- ▶ ***...but keep your healthy skepticism.*** Quacks and charlatans can exploit the placebo effect to peddle treatments that are useless, and even harmful, if for no other reason than they keep people from getting treatment that is directly effective.