The power of Placebo in medicine

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PLACEBO EFFECT: OUTLINE

- A lesson from DPN clinical trials.
- Definitions and history.
- Factors that influence placebo effect.
- Mechanisms of placebo effect:
  - Logistic factors
  - Expectation
  - Conditioning
- Neurobiology.
- Benefits, risks and abuse of Placebo effect.
- Ethical implications
Nerve and muscle center of Texas

- Pregabalin
- DS5565-A-U201
- SKL11197C006
- Lacosamide
- Dextromethorphan
- AGN 203818
- ADL5859
- CLO-027
- Oxcarbazepine
- Lamotrigine
- Topiramate
- Memantine
- Memantine
- NGF Ab
- Mexilitine
- Paroxetine
- Fluoxetine
Placebo is used in trials to objectively test the efficacy of new therapies.
Serotonin Noradrenaline Reuptake Inhibitor

Duloxetine in painful diabetic neuropathy

Randomised, double-blind, placebo-controlled, parallel-group study

12-week treatment

Multicentre

Duloxetine 20 mg/day
Duloxetine 60 mg/day
Duloxetine 120 mg/day
Placebo

NNT = 4.1

Goldstein et al

Mean change-24 hour average pain severity score

*p ≤ .01 vs. placebo
**p ≤ .001 vs. placebo
Efficacy and Safety of Dextromethorphan/Quinidine at Two Dosage Levels for Diabetic Neuropathic Pain: A Double-Blind, Placebo-Controlled, Multicenter Study

Shaibani A, Pain Medicine, 13, 2, 243-254, 7 FEB 2012
Placebo: Alternative rock band

- Loud like love
Placebo

- A substance, device or a procedure that is not intended to treat a medical condition but to:
  - Reinforce a patient's expectation of getting well.
  - or used as a control in a clinical research trial to determine the effectiveness of a potential new drug

- The placebo effect is
  - the measurable, observable, or
  - subjective improvement in health in response to a placebo.
“Placebo Domino in regione vivorum.” (I shall please the Lord in the land of the living.). verse 9 of Psalm 116
Placebo appeared for the first time in 1811 in Hooper’s *Medical Dictionary*:

“any medicine adapted more to please than benefit the patient.”
NOCEBO

Negative expectations produce symptoms
Post LP headache is more common when patients are told headache is possible.

IV: 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

He mesmerized his client including Marie Antoinette

King Louis VXI 1784 asked a commission of the French Academy of science to look into this.
A French scandal

MARIE ANTOINETTE

KING LOUIS VXI
The first Clinical trial
First placebo trial

- Under direction of Benjamin Franklin.
- Chemist Antoine Lavoisier
- Joseph Guillotine who proposed the tool that would cut the king’s head.
- They replicated a session and asked a young boy to hug a magnetized tree that presumed to contain healing power. He shook and convulsed. The tree was not magnetic. Mesmer was denounced.
First RDBCT

The first published RCT appeared in the 1948: Br Med J 2 (4582): 769–82 "Streptomycin treatment of pulmonary tuberculosis", which described a Medical Research Council investigation. One of the authors of that paper was Austin Bradford Hill, who is credited as having conceived the modern RCT.
XONOTRANSPLANTATION OF GOAT TESTICLES INTO HUMANS.

JOHN R. BRINKLEY

- Had a radio show
- Ran for Kansas governor
- LA times press
- Transplanted 16,000 testicles, $750 each.
- Claimed cure for dementia.
Examples of Placebos

- Pills, injections
- Sham surgeries
- Medical devices
- Acupuncture
Placebos

- Magnet therapy
- Wrist bands
- Chiropractics.
- Snails for wrinkles
- Hypnosis
- Biofeedback
- Yoga
A Controlled Trial of Arthroscopic Surgery for Osteoarthritis of the knee
Dramatic Example: Knee Surgery

- Doctor **conducted** controlled experiment on three groups of patients with knee pain.
  - first group: shaved off thin **layers** of damaged cartilage
  - second group: flushed out the knee joint and **disposed of** unhealthy tissue

What do you think the doctor did with the third group?
Third Group

• The surgeon simulated surgery by anesthetizing patients and making incisions.
• No knee surgery was performed.
• Patients were informed of staged operations two years later.

Do you think that this experiment was ethical? Why or why not?
Mean Values (and 95 Percent Confidence Intervals) on the Knee-Specific Pain Scale.

Mean Values (and 95 Percent Confidence Intervals) on the Walking–Bending Subscale of the Arthritis Impact Measurement Scales (AIMS2).

From mental power to muscle power—gaining strength by using the mind. Ranganathan VK, et al. Neuropsychologia. 2004;42(7):944-56
In postoperative pain following oral surgery, a hidden injection of 6–8 mg of morphine was found to correspond to an open injection of placebo.

Placebo analgesia can be blocked with naloxone.
Body piercing
Factors affect PL effect:

- Patient characteristics
- Practitioner characteristics
- Nature of the illness: functional
- Nature of PL: not all Pl are equal
What is bad about getting better from placebo?

- Larger pills and capsules
- Four sugar pills healed gastric ulcer faster than two (proven endoscopically).
- Injections
- Brand name
- Colored better for pain than white and blue better for sleep than red
It is the faith itself

Christianity
(including Catholic, Protestant, Eastern Orthodox, Pentecostal, Anglican, Monophysite, AICs, Latter-day Saints, Evangelical, SDAs, Jehovah’s Witnesses, Quakers, AOG, nominal, etc.)

Islam (Shite, Sunni, etc.)

“Nonreligious” (incl. agnostic, atheist, secular humanist, + people answering ‘none’ or no relig. preference. Half of this group is “theistic” but nonrelig.

Hinduism

Chinese traditional

6%

Buddhism

6%

other

6%

Judaism (0.22%)

Sikhism (0.36%)

primal-indigenous (incl. African Traditional/Diasporic)

16%

14%

NOTE: Total adds up to more than 100% due to rounding and because upper bound estimates were used for each group.
Why do people get better?

- Natural course.
- Fluctuation of symptoms
- Regression to the mean
- Response bias
- “Inert” placebo
- Biological effect
Placebo contents

- Not regulated.
- May have unintended effect:
  - Olive oil or corn oil as a placebo against lipid lowering agents.
- 90% not reported

CONTROVERSY
Cochrane Review 2010
Placebo interventions for all clinical conditions
Hróbjartsson A, Gøtzsche PC

- 202 trials comparing placebo with no treatment.
- 60 health care problems were covered.
- Placebo provided no major advantage.
Figure 2. Outcomes at the 21-Day Endpoint by Treatment Group.

http://www.plosone.org/article/info:doi/10.1371/journal.pone.0015591
Brain mechanism of placebo

The brain is an endlessly fascinating topic for those who have one

- Expectations: lessons from pain and Parkinson disease studies.
- Conditioning of the immune system.
IBS patients were provoked and then treated with a placebo.

Clinical improvement correlated with activity in the RPFC and ACC.
Effects of pain and placebo on the activation of μ-opioid receptor-mediated neurotransmission.

Parkinson’s disease: dopamine deficiency is a factor
- Patients release dopamine upon ingesting a placebo.

Why do patients need placebos to instigate the placebo effect if it is their own brains that do all the work?
Placebo effects in Parkinson disease

- Clinical improvement correlated with dopamine activation

Radioactive raclopride that competes with dopamine on the receptors.

*Trends in Neuroscience* 25(6): 302-306
Classical conditioning

[Diagram of the brain showing a and b with labeled structures (UCS, UCR, CS).]

[Diagram of a dog's response to meat (unconditioned stimulus) leading to salivation (unconditioned response).]

[Diagram showing conditioning process: meat + sound → salivation.]

[Diagram indicating conditioned response: sound → salivation.]
Meditation reduces arterial plagues
Social bonds improve cancer survival
Stress increases risk of cold
Placebos works not only on mind but immune system
Stress worsens illness or even trigger it.
Stop worrying or you will make yourself sick
Ader and Cohen suspect that immunosupression can be behaviorally induced.
- Investigate in rat paradigm
- CS: saccharin
- US: immunosuppressant

Discovered suppression of immune system by nothing more than taste.

Fig. 2. Hemagglutination titers (means ± SE) obtained 6 days after ip injection of antigen (SRBC). NC = nonconditioned animals provided with saccharin on Day 3 or Day 6; CS0 = conditioned animals that did not receive saccharin following antigen treatment; CS1 = conditioned animals given one exposure to saccharin on Day 3 or Day 6; CS2 = conditioned animals exposed to saccharin on Days 3 and 6; US = conditioned animals injected with cyclophosphamide following treatment with antigen.
Conditioning of the immune system

- Healthy subjects
- Cyclosporine A
- Flavored drink

Bad applications of Placebo
Psychic surgery
God will heal you
Good applications

- Placebo use to treat diseases.
- Minimized placebo effect in trials.
Ethical considerations

- Is it right (or even productive in the long run) to deceive patients? Are placebos deceptive?
- Are the therapeutic results more important than the method?
- Is it right to withhold effective treatment in clinical trials?
- In clinical trials, should new drugs be compared with placebo or with the best current therapy, or with both?
Placebo run out

[Diagram showing the timeline and placebo run in and run out process]
In Brief

- Placebo effect is real.
- Belief impact our health
- Hope, faith, and love work wonders.
- Healing environment improves outcome.
- None should come at the expense of science.
- More studies are needed to characterize and exclude placebo responders.
Who changed the world?
Who served humanity?