The Future of Healthcare, Placebo and the Doctor Patient Relationship

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Modern Medicine

Tremendous changes are upon us

- Advancement in technology
- Practice guidelines
- Electronic medical records
- Financial drivers – cost-effectiveness
- Benchmarks, guidelines
- Pay-for-performance
- Evidence-based medicine
- -> Depersonalization
- -> Disempowerment

Really a surprise?
Is It All About the Science?
Astonishing Medical Fact:

**Placebos Work!**

So why not use them as medicine? By Margaret Talbot
Placebo and Nocebo

They still play a big role

- Placebo – “I will please” – simulated intervention that may provide benefit
- Nocebo – “I will harm” – simulated intervention that may cause harm
- Until recently, these responses were the crux of medicine

Beecher HK. The powerful placebo. JAMA1955;159:1602-1606
First Principle

*In curing any patient*

The physician should do nothing before improving [the patient’s] state of mind

Maimonides 1135-1204

The nature of mind is the nature of everything

Dudjom Rinpoche 1904-1987
Early Placebo Comments

Trouseau (1801–67): “One should use a new drug as often as possible, while it still has the power to work.”

Hippocrates (ca. 460 BC–ca. 370 BC): “It's far more important to know what person the disease has than what disease the person has”.
The Placebo Test
“to see if a drug will make you feel better”

• Of 6000 psychiatric patients, 51% better, 12% worse, 37% no response to placebo
  – Side effects: 57%
  – Placebo predicted medication response

• None of 78 characteristics defined a placebo responder

• Similar placebo response in pain

Placebo Response

*Placebo and Pain*

- 50% of patients will have pain reduced with a placebo vs. 70% with morphine—even with gunshot wounds, as seen in World War II
- Up to 35% of the effect of a pain medication, even for severe pain, is due to placebo response
Nocebo Effect

*In Healthy Volunteers*

- 109 double-blind, placebo-controlled studies of 1228 volunteers
  - 28% had adverse effect to placebo
  - Queried, up to 71% had adverse effect
- Nocebo -> clinical trial dropouts
- Disability, death are possible
- Nocebo common in practice

Rosenzweig P. Clin Pharmacol Ther 1993;54:579-583
Nocebo - Examples

- Framingham: Women are 4X more likely to die if believe they are prone to heart disease
- Asthmatics, breathing saline, had attack only if told it was an irritant
- Drug side-effects
- Voodoo deaths
- Cardiomyopathy $2^0$ to emotions

Voelker R. JAMA 1996;275:345-47
Barsky A. JAMA 2002;287:622-7
Tako-Tsubo Cardiomyopathy

A Diastole
B Systole
C
D

**β-Blocker Side Effects**

*Partially Nocebo? 15 Trials, >35,000 patients*

- No risk of depression (6/1000; 95% CI -7 -19)
- Small risk of fatigue (18/1000; 95% CI, 5-30)
- Small risk of sexual dysfunction (5/1000; 95% CI, 2-8)
- Conventional wisdom - β-blockers common cause of adverse effects - not supported

*Ko DT. JAMA 2002;288:351-7*
Are Placebos Still Used?

**US Internists and Rheumatologists**

- 679 (57%) responded; 46-58% reported placebo use; most believed it ethical
- OTC analgesics (267, 41%), vitamins (243, 38%), antibiotics (86, 13%), sedatives (86, 13%)
- Rarely described as placebo (18, 5%)

Tilburt JC. BMJ 2008;337:a1938
Apply Directly to the Forehead

*Placebos are used all the time*
If It Isn’t About the Science. . .

What is it about?

“Not controlled for placebo effects”

“I think it is currently inappropriate to consider chiropractic as a broad-based alternative to traditional medical care.” – accompanying editorial PG Shekelle

Mortality - Digoxin vs. Placebo

Placebos are Rampant

*Use of Prescription Drugs*

- 3 billion scripts/year, up 50% from 1992, often for ambiguous, self-limited, nonspecific (or no) complaints
- Side effects can be severe and include death (>100,000/year)
- Prescription is a form of placebo
  - e.g., erythromycin for viral syndrome
Placebo

Size, Color, Shape, Name Matters

- Blue (vs. pink) -> sedative
- Yellow (vs. green) -> stimulant
- Red (vs. beige) -> cardiac
- "Branded" better than generic
- Surgery better than a pill

Larger capsules are stronger. Injections give larger effects. The stronger the placebo, the better the response.

Zulus and Strong Medicine
The Role of the Doctor

“The doctor himself is a powerful therapeutic agent. The doctor is a placebo.”

- 200 with symptoms, no definite diagnosis
- “Positive” consult with/without treatment vs. "non-positive," consult with/without treatment
- 64% with positive consult improved vs. 39% with negative consult (p = 0.001)
- 53% treated improved vs. 50% not treated (p = 0.5)
Tests: Another Placebo Effect

Benign, Atypical Chest Pain

Percent Disability

Tests

No tests

Do something . . . even if not needed

Vasodepressor Syncope

Do Pacemakers Work?

The VPS I Study

What?

No Placebo?

Connolly S. J Am Coll Cardiol 1999;33:16-20
A Big Placebo Effect

The VPS II Trial

Sham vs. Active Device
Prevention of Syncope Trial

- Metoprolol vs. placebo - patients with recurrent neurocardiogenic syncope
- Metoprolol – same as placebo

Sheldon R. Circulation 2006;113:1164-1170
Placebo Beats Placebo!
The SYDIT Trial – Neurocardiogenic Syncope

Ammirati F. Circulation 2001;104:52-57
Irritable Bowel Syndrome – Placebo vs. Placebo vs. Placebo

1. waiting list, 2. placebo acupuncture ("limited"), 3. placebo acupuncture patient-practitioner relationship augmented by warmth, attention and confidence ("augmented")

Kaptchuk TJ. BMJ 2008;336:999-1003
Is CRT Good Therapy?

The MIRACLE Trial
Cardiac Resynchronization on or off

Control (N = 117)

Baseline 6-Months

93% 64%

93% 64%

CRT (N = 124)

Baseline 6-Months

90% 52%

90% 52%

Chi-square test

Atrial Fibrillation Ablation

Ablation is for symptoms, after all

- Post-ablation monitoring
  - Asymptomatic “silent” AF ~30%
  - Symptomatic and AF ~40%
- Improvement even if AF persists
- Improvement is it in part placebo?
- Of 3,000 reports, no placebo controlled AF trial
Would SCD-HeFT have similar impact without a placebo?

Is a placebo pill a fair comparison to ICD?

Would placebo ICD give the same results?

SCD-HeFT Trial

Would placebo ICD give the same results?

<table>
<thead>
<tr>
<th>Treatment</th>
<th>HR</th>
<th>97.5% CI</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodarone vs. Placebo</td>
<td>1.06</td>
<td>0.86, 1.30</td>
<td>0.529</td>
</tr>
<tr>
<td>ICD Therapy vs. Placebo</td>
<td>0.77</td>
<td>0.62, 0.96</td>
<td>0.007</td>
</tr>
</tbody>
</table>

Revascularization Studies

Using a Sham Operation Control

- IMA ligation – small studies
  - 70% improvement both groups
- Sham/CABG study - Unethical?

Dimond E. Am J Cardiol 1960;5:483–6
Embryonic Fetal Cells

A New Treatment of Parkinsonism?

• 40 pts active vs. sham surgery
  – sham - holes drilled in skull
• $1^0$ outcome, disease severity, same in both groups

70% disappointed/outraged having sham surgery, yet, still wanted ineffective surgery

We need stronger placebos!

Compliance and Placebo Effect

Percent Mortality by Study Group and Level of Compliance in the Coronary Drug Project

<table>
<thead>
<tr>
<th>Drug Compliance</th>
<th>Overall</th>
<th>≥ 80%</th>
<th>&lt; 80%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clofibrate</td>
<td>18.2</td>
<td>15.0*</td>
<td>24.6*</td>
</tr>
<tr>
<td>Placebo</td>
<td>19.4</td>
<td>15.1**</td>
<td>28.2**</td>
</tr>
</tbody>
</table>

* p = 0.00011;

"data . . . demonstrated the great difficulty, if not impossibility, of drawing any valid conclusions from findings about mortality or morbidity"
Beta-blockade after MI

The BHAT Trial

Adherence to Therapy

1-year mortality (%)

Placebo=1094
Propranolol=1082

Similar Results in the CHF Stat Trial

Lancet 1990;336:542
Placebos Prove So Powerful Even Experts Are Surprised

New Studies Explore the Brain’s Triumph Over Reality

The Body Heals Itself

New studies show the placebo effect at work from head to toe in different cultures around the world.
The Wizard of Oz Effect

*Is the Placebo Powerful?*

- Perhaps it is because we think so
- How powerful is nocebo? More than placebo?
Is Placebo Powerless?

No demonstrable effect – 130 trials, 3795 pts

<table>
<thead>
<tr>
<th>By outcome</th>
<th># of participants</th>
<th># of trials</th>
<th>Pooled RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Binary</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>182</td>
<td>3</td>
<td>0.94 (0.77 to 1.16)</td>
</tr>
<tr>
<td>Smoking</td>
<td>887</td>
<td>6</td>
<td>0.88 (0.71 to 1.09)</td>
</tr>
<tr>
<td>Depression</td>
<td>152</td>
<td>3</td>
<td>1.03 (0.78 to 1.34)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type of Placebo</th>
<th># of participants</th>
<th># of trials</th>
<th>Pooled RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Binary</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharmacologic</td>
<td>3099</td>
<td>21</td>
<td>0.97 (0.88 to 1.07)</td>
</tr>
<tr>
<td>Physical</td>
<td>479</td>
<td>4</td>
<td>0.94 (0.83 to 1.08)</td>
</tr>
<tr>
<td>Psychological</td>
<td>217</td>
<td>7</td>
<td>0.88 (0.72 to 1.08)</td>
</tr>
</tbody>
</table>

“No justification to use placebo”

Placebo-controlled Trial in Irritable Bowel Syndrome

Ted J. Kaplan
Joyce P. Singletary

Abstract

Background

Response to treatment for irritable bowel syndrome (IBS) is commonly assessed using self-report measures that measure global improvement (IBS-GIS), symptom severity change (IBS-SSS), percent with adequate relief (IBS-AR), and quality of life change (IBS-QOL).

Methods

Patients were randomized to receive either no treatment or an open placebo pill for 21 days. The open placebo pill was designed to look identical to the active treatment pill.

Findings

Significant improvement was observed in IBS-GIS, IBS-SSS, IBS-AR, and IBS-QOL in the open placebo group compared to the no treatment group. p values for these comparisons were .02, .03, .03, and .08, respectively.

Conclusions

Given the demonstrated differences in both 11- and 21-day midpoints, these results were statistically significant and inform future randomized controlled trials in IBS.

Trial Registration

ClinicalTrials.gov identifier: NCT01234567

References


Placebo Effect in Cardiology

When does it appear to work?

• Pain
• Functionality
• Quality-of-life
• Syncope
• Heart failure
• ? atrial fibrillation
• Survival
Possible Mechanisms

Placebo/Nocebo Response(s)

- Regression to the mean
- Conditioning response
- Expectations
- Endorphin release
- Neurocognitive pathways
- The meaning response

Cultural, ethnic, gender, genetically (?) related
Conditioning Effect

An Animal Model

• Rats given saccharin-flavored water with cyclophosphamide were immunosuppressed

• 10 days later, half exposed to saccharin, half not

• Saccharin lowered antibody titers vs control post antigenic stimulation

Ader R. Comp Physiol Psychol. 1982;96:517-21
Ader R. Science 1966;138:677
Neural Substrate – Conditioned Immunosuppression in Rats

CS, conditioned stimulus, saccharin taste; UCS, unconditioned stimulus; CsA, cyclosporine A; BBB, blood-brain barrier; CVOs, circumventricular organs; VMH, ventromedial hypothalamic nucleus

From Pacheco-Lopez, 2005
Enck P. Neuron 2008;59:195
Behavioral/Systems/Cognitive

A Link between Serotonin-Related Gene Polymorphisms, Amygdala Activity, and Placebo-Induced Relief from Social Anxiety

Placebo may yield beneficial effects that are indistinguishable from those of active medication, but the factors underlying proneness to respond to placebo are widely unknown. Here, we used functional neuroimaging to examine neural correlates of anxiety reduction resulting from sustained placebo treatment under randomized double-blind conditions, in patients with social anxiety disorder. Brain activity was assessed during a stressful public speaking task by means of positron emission tomography before and after an 8 week treatment period. Patients were genotyped with respect to the serotonin transporter-linked polymorphic region (5-HTTLPR) and the G-703T polymorphism in the tryptophan hydroxylase-2 (TPH2) gene promoter. Results showed that placebo response was accompanied by reduced stress-related activity in the amygdala, a brain region crucial for emotional processing. However, attenuated amygdala activity was demonstrable only in subjects who were homozygous for the long allele of the 5-HTTLPR or the G variant of the TPH2 G-703T polymorphism, and not in carriers of short or T alleles. Moreover, the TPH2 polymorphism was a significant predictor of clinical placebo response, homozygosity for the G allele being associated with greater improvement in anxiety symptoms. Path analysis supported that the genetic effect on symptomatic improvement with placebo is mediated by its effect on amygdala activity. Hence, our study shows, for the first time, evidence of a link between genetically controlled serotonergic modulation of amygdala activity and placebo-induced anxiety relief.
Nocebo - Mechanisms

Based on Benedetti, 2006

Enck P. Neuron 2008;59:195
Reward Mechanism - Simplified

Placebo activates opioid peptides and dopamine systems

Enck P. Neuron 2008;59:195
Molecular PET Scanning

- μ opioid receptor activates with anticipation and saline injection
- Anterior cingulate, insular cortex, prefrontal cortex activates then, less pain

Mapping the Placebo Effect

Quantitative EEG recordings

Leuchter AF. Am J Psychiatry 2002;159:122-9
Expectation Effects
Jastrow Effect

• An explicit expectation about outcome may change outcome

Jastrow (1900) Fact and fable in psychology
Hawthorne Effect

- The influence of being observed


http://www.library.hbs.edu/hc/hawthorne/01.html#one
Pygmalian Effect

*If evaluators expect a benefit, they will see it*

- An enthusiastic doctor has a 70% success rate regardless of effectiveness of a treatment
- An unenthusiastic doctor has only a 17-33% success rate with an ineffective treatment

Integrative Medicine: Principles for Practice, B Kligler and RA Lee

The Halo Effect

• “Treatment" novelty changes expectations or affects attention.
• Unfounded assumptions influence outcomes (e.g. new technology is better)
Experimenter Effects

• Expectations sensed consciously (or not) affect outcomes
• “Stooges”, as subjects, noting an outcome can create a potent expectation (and an effect)

Rosenthal R. Experimenter effects in behavioral research (NY: Appleton, 1966)
Expectation Influences Outcomes

- Past experience
- Medication changes and procedures
- Input of healthcare providers
Is Exercise Placebo?

Crum AJ. Psychological Science 2007;18:165-171
The Meaning Response

• Plausible, understandable explanation of illness and/or treatment
• Do symptoms have a meaning?
• Does therapy have a meaning?
  – e.g. transmyocardial revascularization may provide placebo response due to treatment implications
The Value Effect

• Patients paying for medical care, “buy in” to it, will be affected by it
Does Cost Matter?

Pain Rating by Voltage Intensity

Waber RL. JAMA 2008;299:1016
SPECIAL HEALTH ISSUE

WHO NEEDS DOCTORS?

Your future physician might not be an M.D.—and you may be better off

Lara Bartley, R.N., Oncology Nurse, Hillman Cancer Center, University of Pittsburgh Medical Center
Implications

• Placebo and nocebo effects are common in medical practice and involve our relationship to the patient
• The doctor, the nurse, the healthcare provider are the most valuable resources for healing patients
Challenges for the Future

We Must Remember Our Core Values

- Medicine is about people – the patient, the entire health care team
- The reward is in the care we give
- Our relationship to the patient is key