Are sham operations and placebos justifiable in research?

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Key Issues

• What makes research ethical?
• What is equipoise?
• What is the placebo effect?
• What is placebo surgery?
• Can placebo surgical trials be ethically justified?
Example: Chronic stable angina

• Fluctuating courses with spontaneous remissions
• associated with a placebo-response rate of 30 to 80%
• long history of apparently successful treatments that have been disproved by blinded, placebo-controlled trials
No benefit to IMA ligation vs. sham procedure
## What makes Clinical Research Ethical?

Ezekiel J. Emanuel, MD, PhD; David Wendler, PhD; Christine Grady, PhD. JAMA. 2000;283(20):2701-2711

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Equipoise

Genuine uncertainty in the clinical community
What is the placebo effect?
Placebo Effect

How The Placebo Effect Can Help Your Body Heal
Placebo Effect

• May be very strong
• Hard to quantify
• Strongest in conditions that wax and wane, have spontaneous remissions (e.g. pain, depression, migraine, Parkinson’s, IBS)
• High levels of stress and rituals involved with surgery can lead to a strong placebo effect.
When is a placebo trial required from scientific standpoint?

• Existing therapies only partly effective or have serious side-effects

• Low frequency of condition means that an equivalence trial would have to be so large that it would reasonably prevent adequate enrollment and completion of study.

Placebome

• The study of genomic effects on placebo response
• There are genetic variations in neurotransmitter pathways that mediate placebo effects
• Future of placebo trials?
  – Screen to identify placebo responders
    • Increase RCT efficiency
    • Improve therapeutic care
  – Possibility of interaction between placebo and drug molecular pathways warrants consideration in RCTs.
Placebo surgery

It looks like I've had an operation...

That's the main thing...

Wilcox
Surgery and the Placebo Effect

• Intervention of surgery may have a particularly strong placebo effect

• Although risks seem higher, avoiding a procedure or implant of device that later turns out to be ineffective or in fact dangerous may be of great benefit to patient.
Is placebo surgery different from placebo medication?

- Placebo medication by itself has no risk
- Risks come from omission of treatment for the relevant condition, either to individual participant or a population
- Placebo surgery has risks (no surgery is without risk)
- Risks are greater if “sham” operation more closely resembles the real operation
Results of placebo surgery trials

- Stable angina – Ligation IMA
  - >50% in both groups substantial improvement in angina
- Vertebroplasty
  - Both groups substantial improvement in disability and pain
- Parkinson’s – fetal tissue transplant into brain
  - Neither group improved
- Knee pain – debridement vs. lavage. vs sham
  - All groups some improvement in disability and pain
- Migraine – decompression of cranial nerves
  - 1 randomized sham trial with excellent result
    - Many methodological flaws
Does the researcher have an ethical responsibility to act in the best interests of subjects?

- Placebo Surgery appears to violate the principles of beneficence and nonmaleficence
- This confounds the ethics of clinical care vs. those of clinical research
You never got a placebo. You're only acting as if you got a placebo.

Placebo Affect
Summary

- Placebo surgery is inherently different than placebo medication
- It can be equally justified and ethical if strict guidelines are followed
  - Clinical equipoise exists (honest disagreement)
  - Scientifically valid study design
  - Risks and harms minimized
  - Subjects fully informed
Placebo MAX STRENGTH

As effective as the leading homeopathic treatment

16 capsules
References


2. Emanuel EJ, MD, PhD; David Wendler, PhD; Christine Grady, PhD What Makes Clinical Research Ethical? JAMA. 2000;283(20):2701-2711.


Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.