The placebo effect

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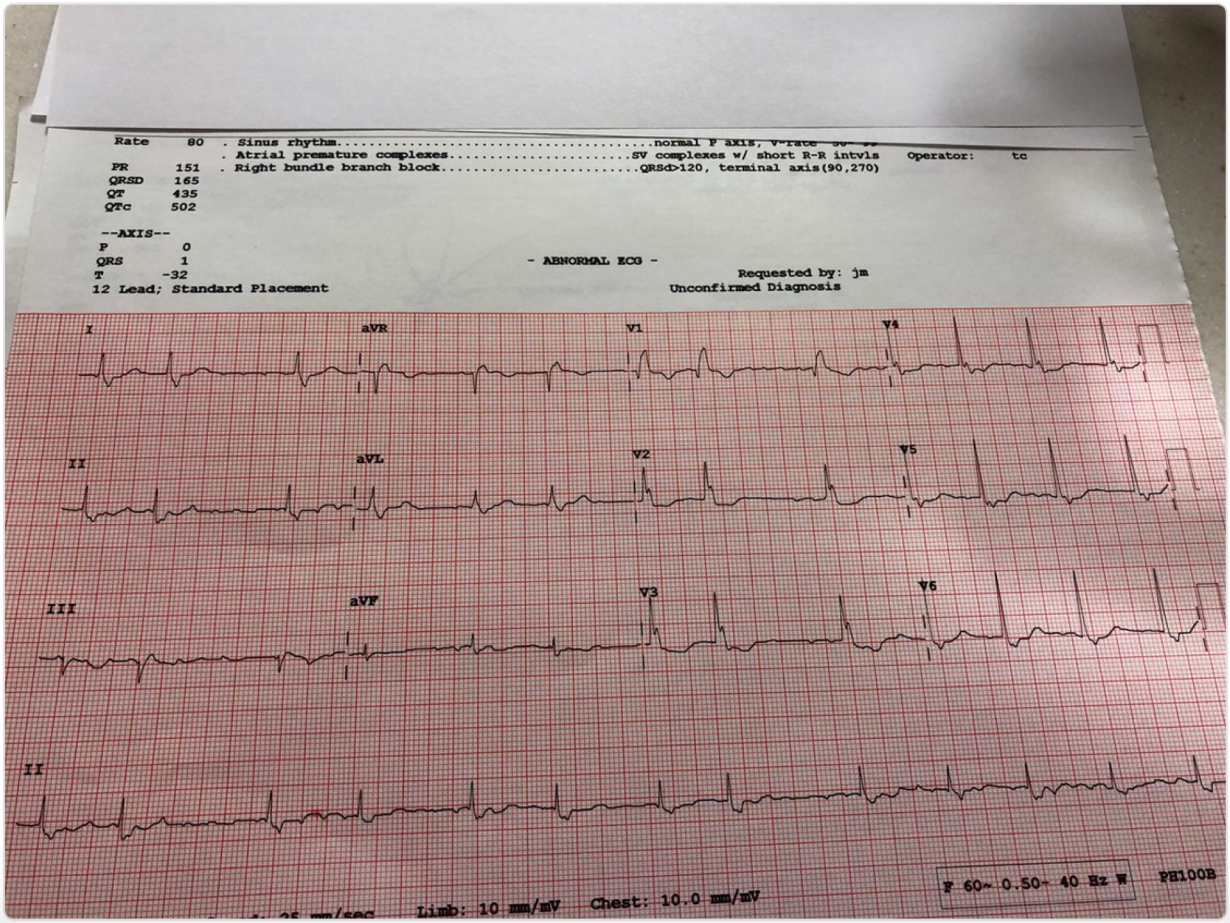
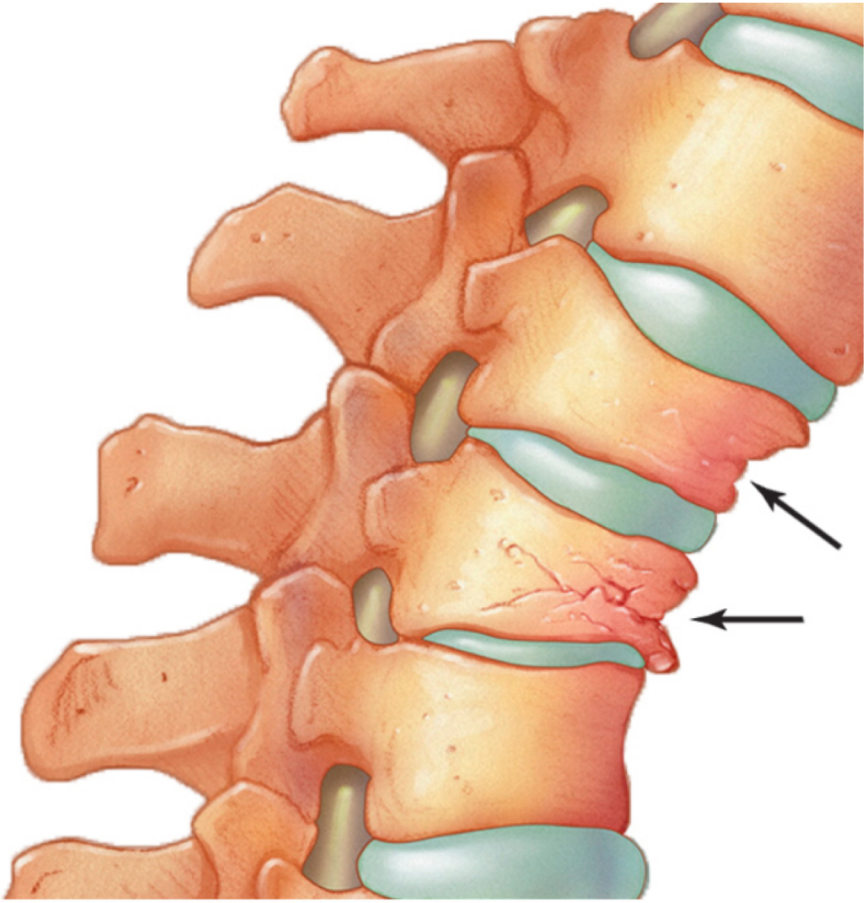
Post AF-ablation ECG below. “Doc, I feel great! I’m swimming and walking and I have my life back.” Tell me we don’t need a #sham trial. cc @ProfDFrancis @DrDave01 —keep working on those ECG computer reads.

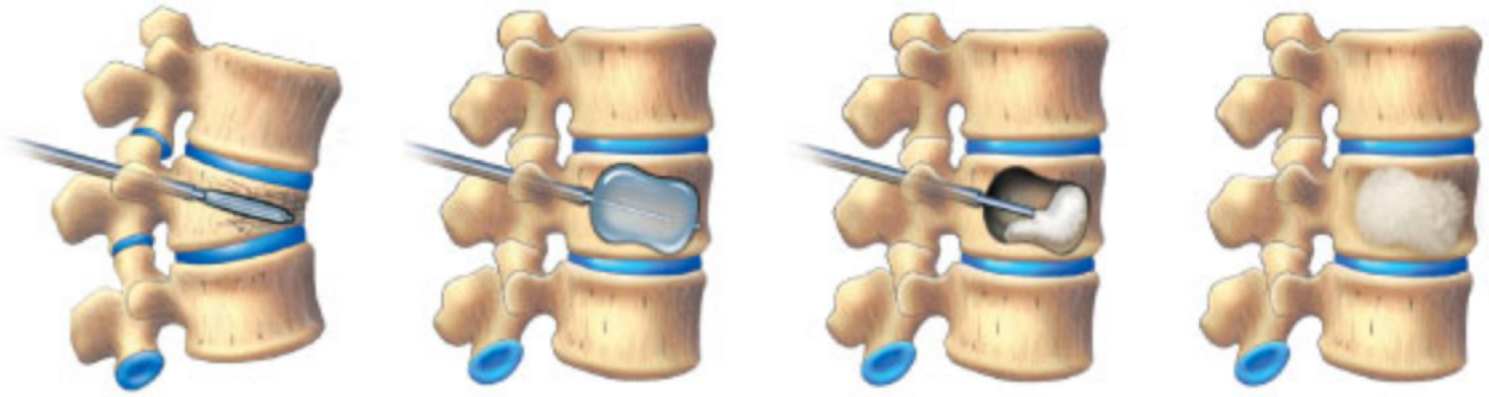


The problem

- 67 year old male witnessed fall from bicycle
- X-rays show new compression fractures in thoracic spine and lumbar spine
- Significant pain and disability



14,000 patients received vertebroplasties in 2015



But does it work?

- David Kallmes noticed:
- Pain relief does not correlate with amount of cement injected, or the location
- In one case, cement injected in the wrong vertebra resulted in substantial relief.

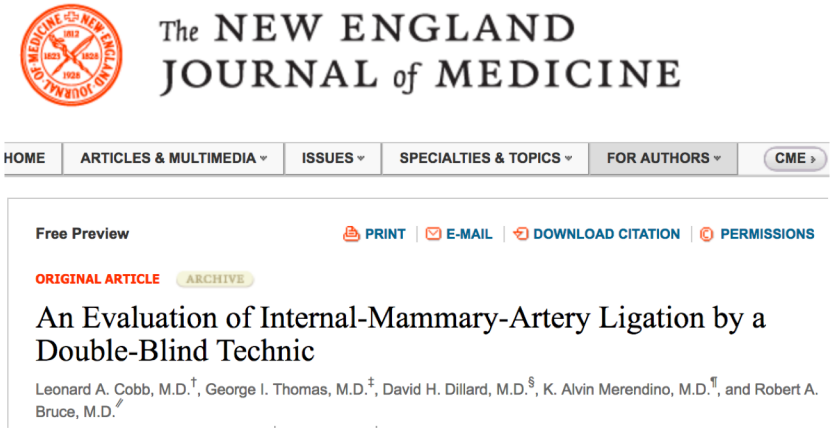
Design a Clinical Trial

- Randomization in human clinical trials
- Mitigates selection bias and insures against the accidental bias.
- It produces the comparable groups and eliminates the source of bias in treatment assignments.
- Experiment: randomize to vertebroplasty versus no vertebroplasty

Sham procedure

- Randomized subjects to vertebroplasty versus no vertebroplasty
- Subjects blinded to the result
- Interventional radiologists would not know until the patient was on the operating room table whether they would perform vertebroplasty or sham surgery
- Is this ethical?

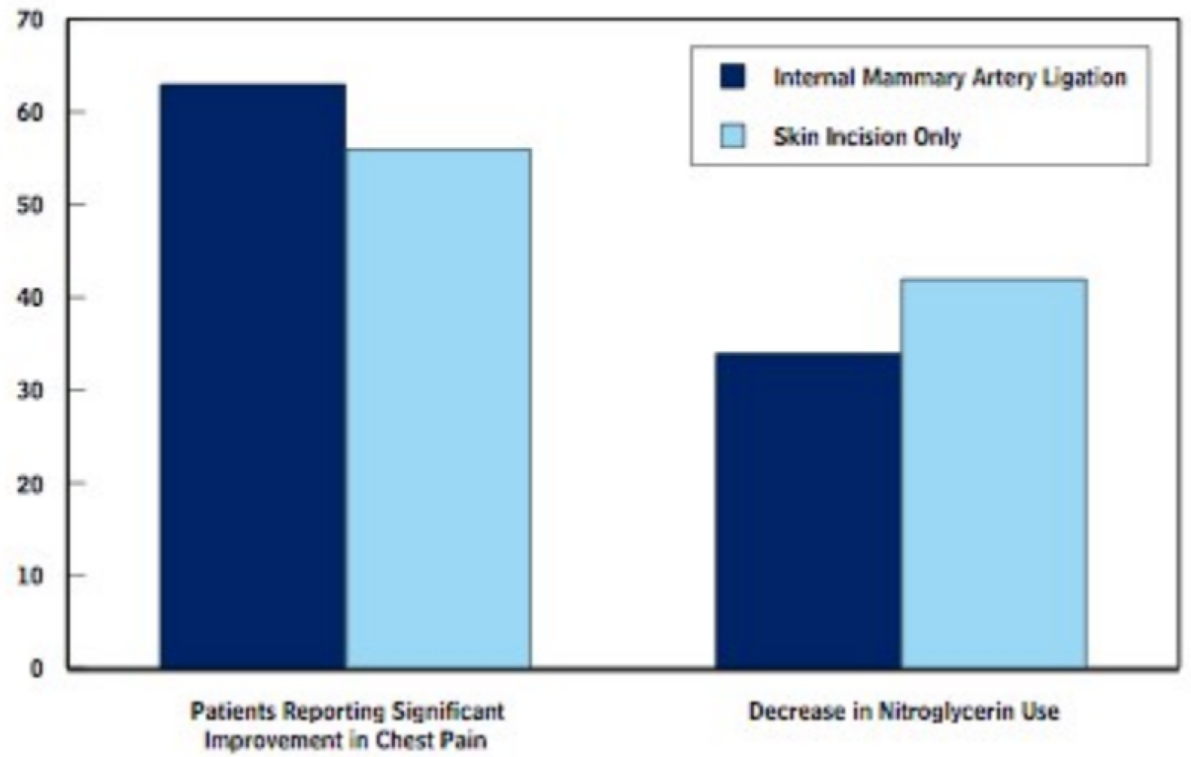
Sham surgery - history



Cobb and colleagues randomized 17 patients "seriously limited by angina" to bilateral internal mammary artery ligation or a blinded sham procedure consisting of skin incisions without ligating the artery

The patients were told only that they were participating in an evaluation of this operation; they were not informed of the double- blind nature of the study

Mammary artery ligation versus sham procedure



At 6 months, patients in both groups had increases in exercise tolerance, and substantial reduction in use of nitroglycerin use (34% ligated and 42% not ligated)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Randomized Trial of Vertebroplasty for Osteoporotic Spinal Fractures

David F. Kallmes, M.D., Bryan A. Comstock, M.S., Patrick J. Heagerty, Ph.D., Judith A. Turner, Ph.D., David J. Wilson, F.R.C.R., Terry H. Diamond, F.R.A.C.P., Richard Edwards, F.R.C.R., Leigh A. Gray, M.S., Lydia Stout, B.S., Sara Owen, M.Sc., William Hollingworth, Ph.D., Basavaraj Ghdoke, M.D., Deborah J. Annesley-Williams, F.R.C.R., Stuart H. Ralston, F.R.C.P., and Jeffrey G. Jarvik, M.D., M.P.H.

Participants – 131 Patients who had one to three painful osteoporotic vertebral compression fractures

N Engl J Med 2009

Hypothesis

- Hypothesized that patients who had undergone vertebroplasty would report less pain and back pain–related disability at 1 month (the primary outcomes) than those in the control group
-

N Engl J Med 2009

Outcome

- How long follow up? One month
- (Allowed to cross over into the other treatment group if they wanted to)

Primary outcomes at 1 month – not significantly different

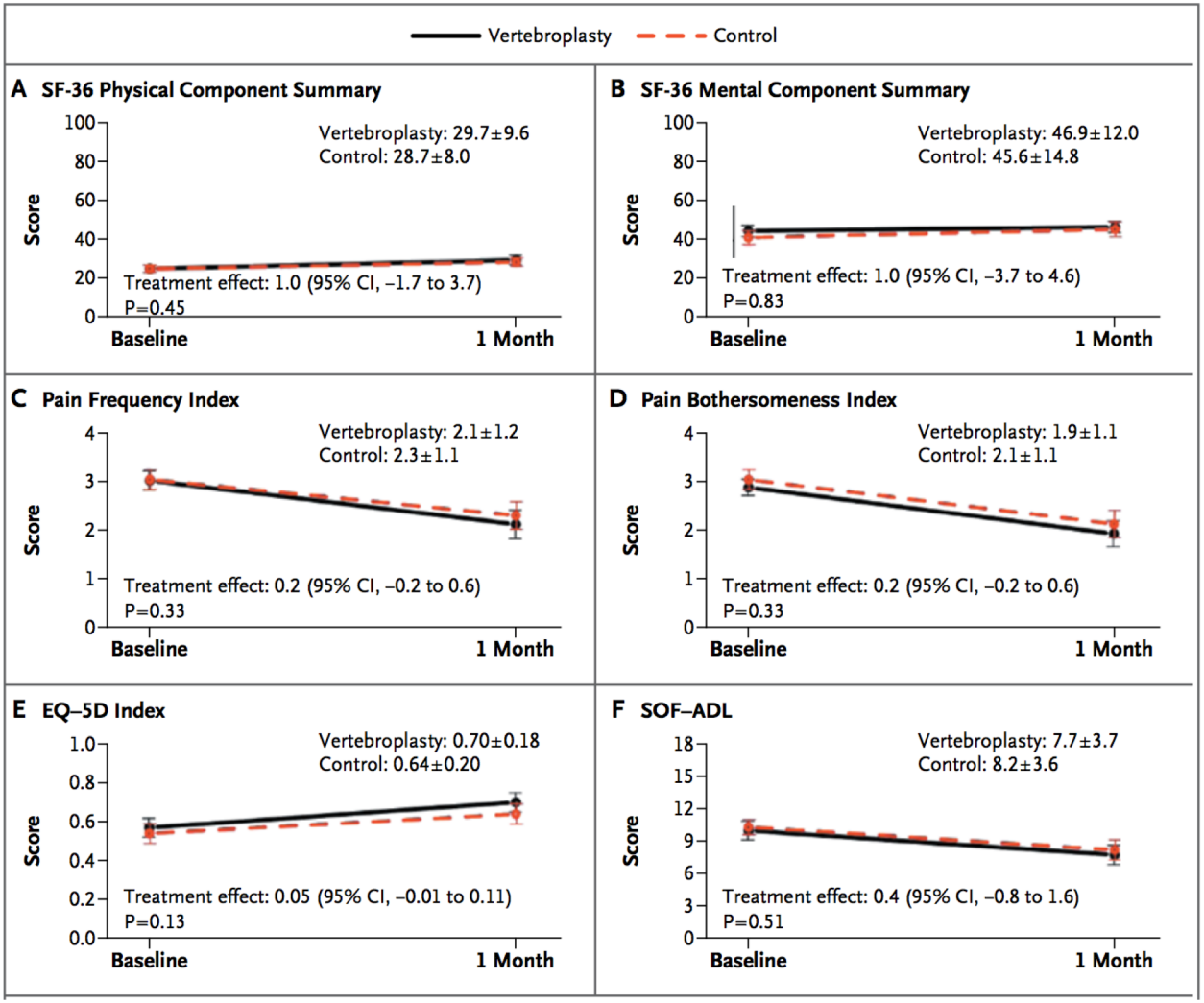
Table 2. Primary Outcomes (Intention-to-Treat Analyses).*

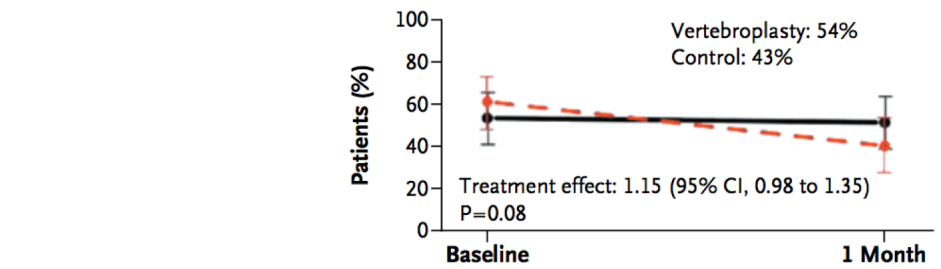
Measure	Vertebroplasty Group	Control Group	Treatment Effect (95% CI)†	P Value†
RDQ‡				
At baseline	16.6±3.8	17.5±4.1		
At 3 days	13.0±5.2	12.5±5.5	−0.9 (−2.7 to 0.8)	0.30
At 14 days	12.4±5.8	12.3±5.9	−0.6 (−2.4 to 1.2)	0.35
At 1 mo	12.0±6.3	13.0±6.4	0.7 (−1.3 to 2.8)	0.49
Pain intensity§				
At baseline	6.9±2.0	7.2±1.8		
At 3 days	4.2±2.8	3.9±2.9	−0.4 (−1.5 to 0.5)	0.37
At 14 days	4.3±2.9	4.5±2.8	0.1 (−0.8 to 1.1)	0.77
At 1 mo	3.9±2.9	4.6±3.0	0.7 (−0.3 to 1.7)	0.19

Intention to treat (ITT) all patients are analyzed in the groups to which they were randomized. i.e. “once randomized, always analyzed”

Pain

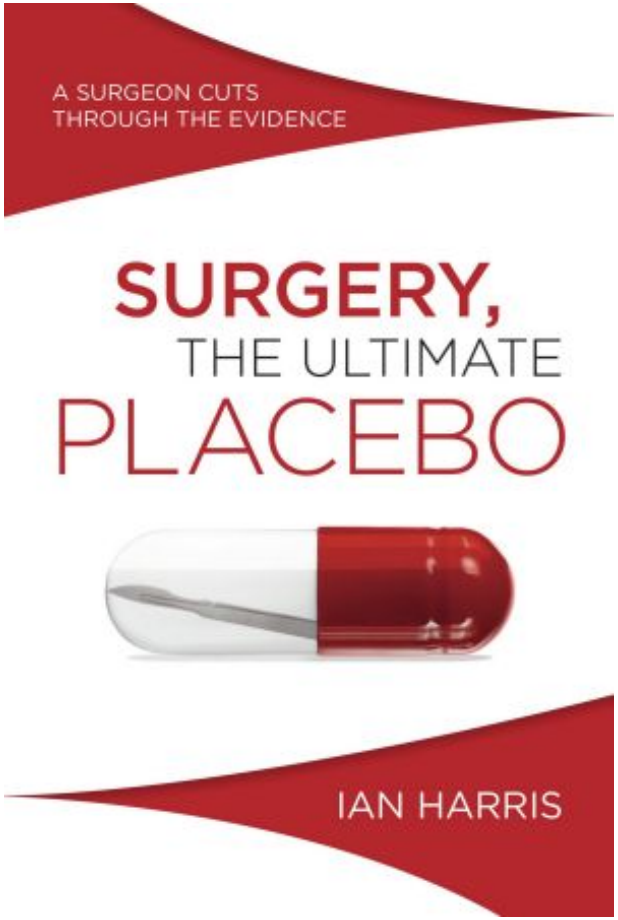
- “Patients in the two study groups showed immediate improvement in pain and disability after the procedure, and this improvement was sustained at 1 month”


Vertebroplasty
Control
A SF-36 Physical Component Summary
Score
Vertebroplasty: 29.7±9.6
Control: 28.7±8.0
Treatment effect: 1.0 (95% CI, −1.7 to 3.7)
P=0.45
Baseline
1 Month
B SF-36 Mental Component Summary
Score
Vertebroplasty: 46.9±12.0
Control: 45.6±14.8
Treatment effect: 1.0 (95% CI, −3.7 to 4.6)
P=0.83
Baseline
1 Month
C Pain Frequency Index
Score
Vertebroplasty: 2.1±1.2
Control: 2.3±1.1
Treatment effect: 0.2 (95% CI, −0.2 to 0.6)
P=0.33
Baseline
1 Month
D Pain Bothersomeness Index
Score
Vertebroplasty: 1.9±1.1
Control: 2.1±1.1
Treatment effect: 0.2 (95% CI, −0.2 to 0.6)
P=0.33
Baseline
1 Month
E EQ–5D Index
Score
Vertebroplasty: 0.70±0.18
Control: 0.64±0.20
Treatment effect: 0.05 (95% CI, −0.01 to 0.11)
P=0.13
Baseline
1 Month
F SOF–ADL
Score
Vertebroplasty: 7.7±3.7
Control: 8.2±3.6
Treatment effect: 0.4 (95% CI, −0.8 to 1.6)
P=0.51
Baseline
1 Month


G Opioid Use
Patients (%)
Vertebroplasty: 54%
Control: 43%
Treatment effect: 1.15 (95% CI, 0.98 to 1.35)
P=0.08
Baseline
1 Month

- In conclusion…clinical improvement in patients with painful osteoporotic vertebral fractures was similar among those treated with vertebroplasty and those treated with a simulated procedure.
    - - but Kallmes still advocates for the procedure….

Placebo effect



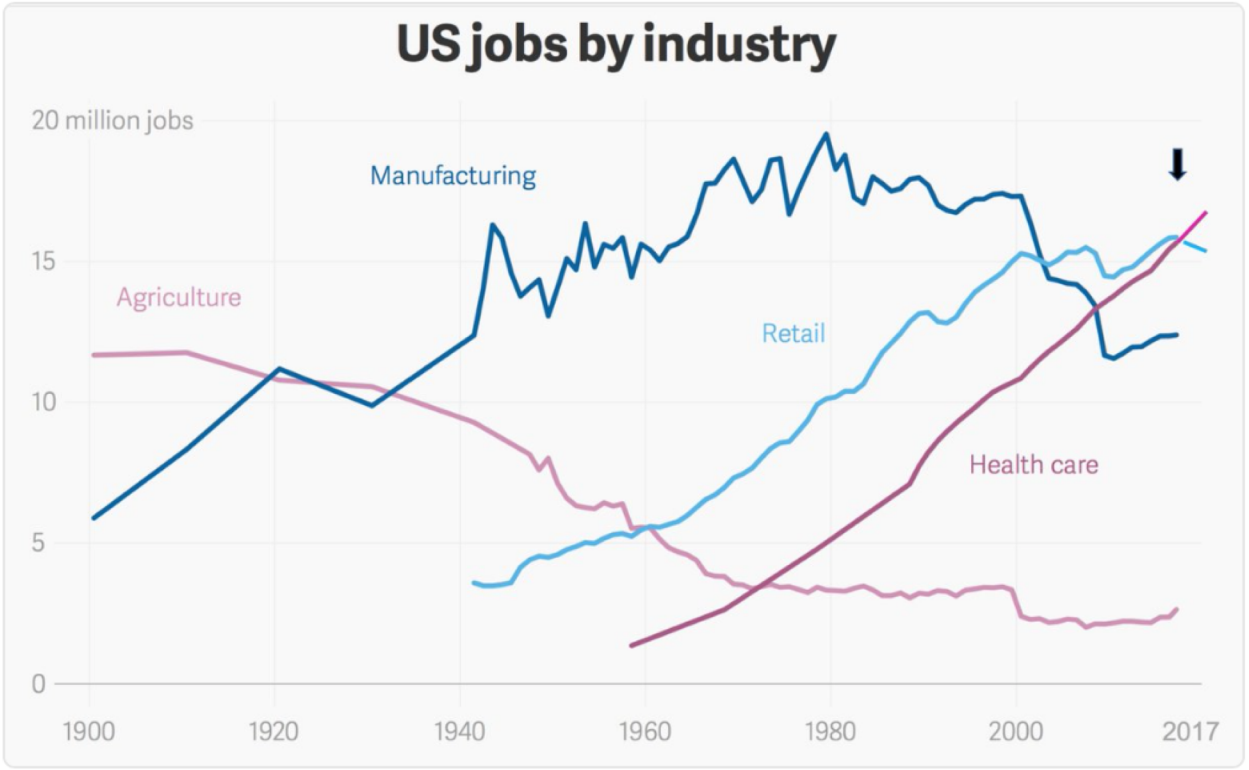
Surgery as placebo

- Massively inefficient
- Massively UNETHICAL – accounting for adverse effects and unintended complications

- Surgeons like it because it works, because they can employ a unique and valued skillset that confers great social status. And $$

- Patients like it because it legitimizes their sickness behavior with the highest level of social imprimatur.

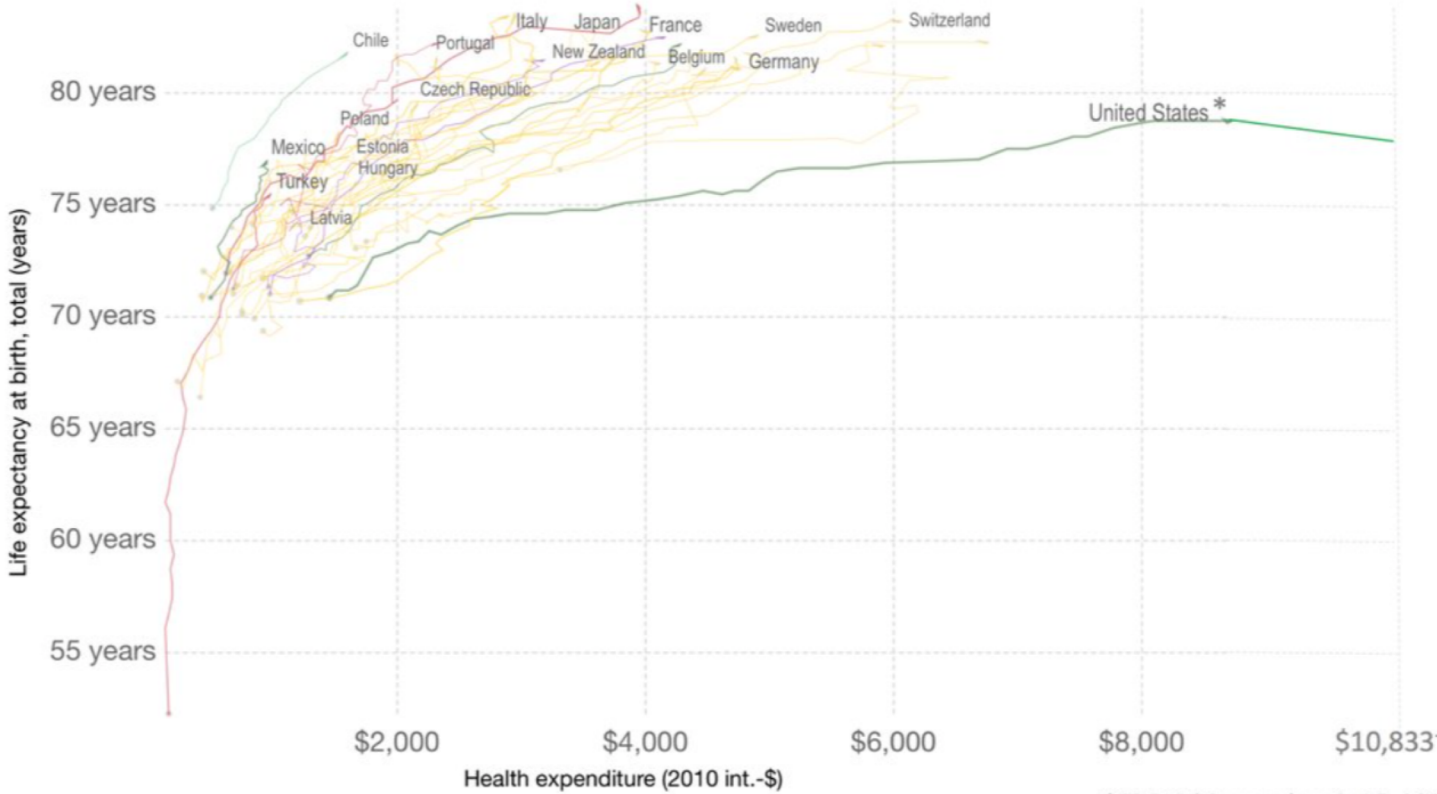
- Does the medical system hack this cognitive/emotional vulnerability in the human OS?



Our World in Data

Life expectancy vs. health expenditure, 1970 to 2017

Health financing is reported as the annual per capita health expenditure and is adjusted for inflation and price level differences between countries (measured in 2010 international dollars).



*CDC: 1st 2-year drop in LE: 2016, 2107 since 1962 +From Statista

Source: World Bank – WDI, Health Expenditure and Financing - OECDstat (2017)
OurWorldInData.org/the-link-between-life-expectancy-and-health-spending-us-focus • CC BY-SA

A world with no suffering

- No pain, no anxiety, no aversive symptoms
- No disease?
- Scientist makes a major discovery – lifespan can be doubled, even tripled
  - with the side effect of pain, distress, anxiety
- Take that bargain?
- Evolutionary medicine: that's ***exactly*** why those things evolved

- Why is the placebo effect so powerful when it comes to aversive symptoms like pain

  Can cause them

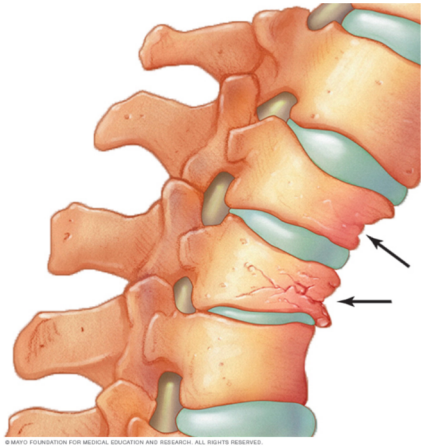
  Can obliterate them

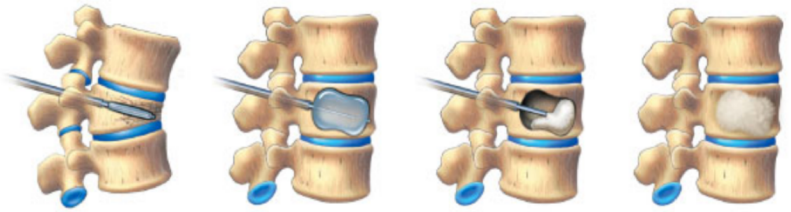
Psychosomatic

- Why does the brain have powerful and impactful mechanisms to invent symptoms?

Homeopathy bashing doctors should not be too self-satisfied

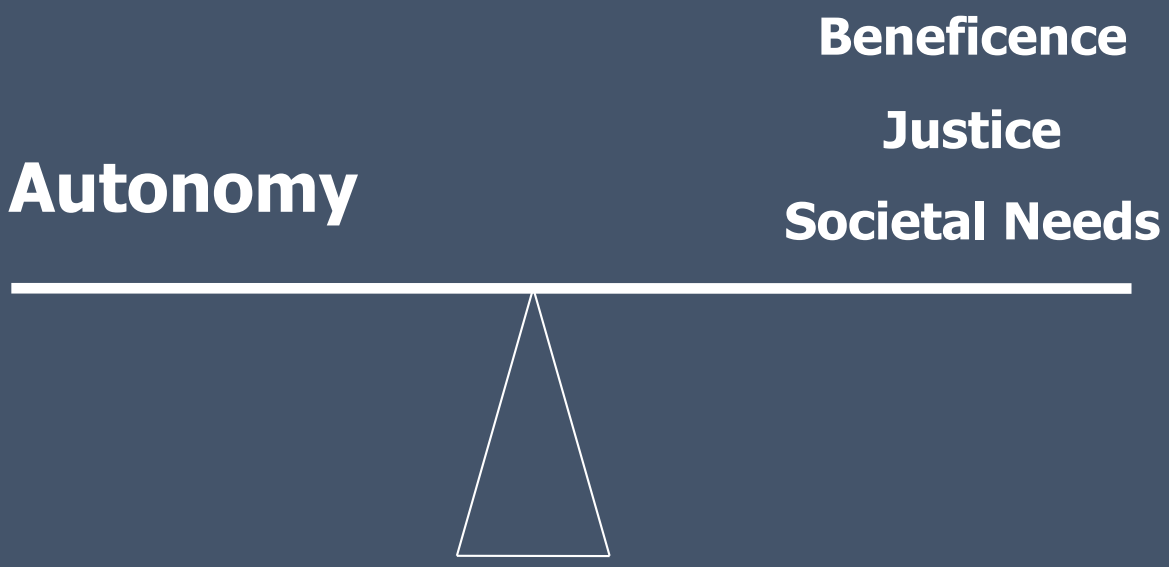
- What is the responsibility of doctors in causing disease, causing suffering with our invented constructs?





- Unethical to not take advantage of the placebo effect?
- to misunderstand it?

Ethical Conflict



- What is the role of sickness behavior, sickness role in a social species like ourselves?

- Shouldn’t this get more attention?

A Matabele ant treats the wounds of a mate whose limbs were bitten off during a fight with termite soldiers.

Erik T. Frank/Julius Maximilian University of Würzburg

Wound treatment and selective help in a termite-hunting ant

Erik T. Frank, Marten Wehrhahn, K. Eduard Linsenmair

Published 14 February 2018. DOI: 10.1098/rspb.2017.2457

- Need to understand why these mechanisms **evolved** to harness the placebo effect in an efficient way

Speculation

- Can we adaptively reduce aversive symptoms by targeting the microbiome?

- Nausea, pain, anxiety are all plugged in to the microbiome. Why has this system evolved? Missing microbes? Hijacking? Adaptive for the host?
- Social benefits from sick role in setting of disadvantageous microbiome?

- Is this why probiotics work? Gut brain axis closes the loop.

Open access, freely available online

Essay

Why Most Published Research Findings Are False

John P. A. Ioannidis

It can be proven that most claimed research findings are false.

http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.0020124