The Great? Placebo

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“The history of medical treatment can be characterized largely as the history of the placebo effect”


The placebo is the “most effective medication known to science, subjected to more clinical trials than any other medicament yet nearly always does better than anticipated. The range of susceptible conditions appears to be limitless”
Understanding and appreciating the placebo EFFECT AND the placebo RESPONSE is one of the most powerful therapeutic concepts in all of medicine.
8 patients had internal mammary/thoracic artery ligated
9 had skin incisions
5 in each group reported significant improvement

146 patients age 52
partial meniscectomy OR SHAM surgery (arthroscopic lavage - asked for all instruments, manipulated the knee etc)

No difference in symptoms or knee pain 12 months after
Placebo

= an inert substance that provokes perceived benefits

Nocebo

= an inert substance that causes perceived harm

The most common symptoms - nausea, diarrhea, constipation, dry mouth, drowsiness, anxiety, nervousness, headache, dizziness, asthenia, flushing, flatulence, low blood pressure and a feeling of heaviness
Inert placebos are used a lot

77% of the surveyed physicians prescribed placebo at least once a week, with impure placebos accounting for more than 90% (Howick et al. 2013)

Colace
Vitamins
Homeopathy
Antibiotics for viral infections
Understanding HELPS YOU FIGURE OUT

If you should try a medication
When to start with low/very low doses
If a medication is working
How to empower your patients to help you figure out if the medication is working
"It is evident that placebos have a high degree of therapeutic effectiveness in treating subjective responses."

He claimed that the symptoms of 35% of 1082 patients in 15 studies were relieved by placebo.
"For 14 out of the 15 trial publications detailed analysis was possible. The overall result was that for none of these trials was there any reason to assume the existence of the slightest placebo effect."

"In all these trials the reported outcome in the placebo group can be fully, plausibly, and easily explained without presuming any therapeutic placebo effect"

"In some of the original trial publications even the authors themselves had explicitly written that there were no placebo effects"
“Beecher misquoted 10 of the 15 trials listed in [his paper]”

“he cited…a percentage of patients” when in fact it was “the number of pills”
PLACEBO GROUP EFFECT

Outcome in treatment group (natural history, placebo, and treatment effects)
Outcome in ‘placebo’ group (natural history and placebo effects)
Outcome in no treatment group

Treatment effect

Placebo effect

Effect of being in a ‘no treatment’ group (Hawthorne effects, natural history, regression to mean)
Regression to the mean

When they will come to see you

When they won’t come to see you

“If it’s bad it will likely get better and if it’s good it will likely get worse”
“the symptoms of 35% of 1082 patients in 15 studies were relieved by placebo”
Meta-analysis - 202 trials of placebo versus no treatment

60 clinical conditions

44 studies with BINARY OUTCOMES
the effect was 0.93 (0.88-0.99) - BUT no statistical effect in conditions (pain, nausea, smoking, depression) investigated by 3 or more trials BUT still had similar relative differences

158 trials with CONTINUOUS OUTCOMES
found an effect (Standard Mean Difference) on pain (~0.2), nausea (0.25), asthma (0.35) and phobia (0.63) - effects on phobia and asthma uncertain due to high risk of bias
SMD of 0.2 is considered small - for pain this would be ~0.5 on a 10 point scale

Placebo interventions for all clinical conditions (Review)
Hróbjartsson A, Gøtzsche PC
CD003974 - 2010

Placebo effects in low back pain: A systematic review and meta-analysis of the literature  
Eur J Pain 2021;25:1876–97

Effectiveness of placebo interventions for patients with nonspecific low back pain: a systematic review and meta-analysis  
Pain 2021 162;2792–2804

a significant moderate effect size of placebo for pain intensity (SMD = 0.57) and disability (SMD = 0.52)

placebo interventions are more effective than no intervention for pain intensity at short-term follow-up (SMD -0.37) - corresponds to about 8 point on a 0 to 100 scale
FEV1 - Objective Outcomes

no effect

Symptoms - Subjective Outcomes

20% absolute

Figure 3. Percent Change in Maximum Forced Expiratory Volume in 1 Second (FEV₁) with Each of the Four Interventions.
The relative improvement in FEV₁, achieved with albuterol was significantly greater than that achieved with each of the other three interventions (P<0.001). No other differences among the four experimental conditions were significant. T bars indicate standard errors.

Figure 4. Percent Change in Subjective Improvement with Each of the Four Interventions.
The relative improvement in subjective outcomes, assessed with the use of a visual-analogue scale (with 0 indicating no improvement and 10 indicating complete improvement), was significantly greater with the albuterol inhaler, placebo inhaler, and sham acupuncture interventions than with the no-intervention control (P<0.001). No other differences among the four experimental conditions were significant. T bars indicate standard errors.
Effects of open-label placebos in clinical trials: a systematic review and meta-analysis

“gives healthcare-providers the possibility to administer placebos without deception and thus, with fewer ethical concerns”

The Power of Drug Color

A pill’s hue can affect how it’s judged by patients, how it’s marketed, and even how well it works.

By Tessa Fiorini Cohen
Effect of colour of drugs: systematic review of perceived effect of drugs and of their effectiveness

BMJ1996;313:1624-6

CITED 400+ times

TYPICAL COMMENT

“The typical finding that has emerged from much of the previous research is that changing the colour of a medicine can indeed influence perceived efficacy”

Author’s conclusion “the available evidence suggests that green and blue may have more sedative effects and red and orange may have more stimulant effects”

6 publications - NONE SINCE 1978

Nagao - 1968 - [ARTICLE IN JAPANESE] - “large trial” analgesic after dental surgery - “79% of patients experienced adequate pain relief with RED tablets, whereas 73% of patients reported adequate pain relief with WHITE tablets”

Schapira 1970 - 48 patients with anxiety - oxazepam - different colors “though the difference between RED, YELLOW and GREEN tablets DID NOT REACH STATISTICAL SIGNIFICANCE certain trends were observed”

Cattaneo 1970 - 120 patients awaiting surgery - placebo - ORANGE vs BLUE capsules - NO DIFFERENCE IN SLEEP

Blackwell 1972 - 100 medical students - placebo - told they would either get a stimulant or sedative “66% of subjects on blue capsules felt less alert compared with 26% on PINK; 72% on BLUE capsules felt more drowsy compared to 37% on pink” - no other info given

Huskisson - 1974 - 22 patients - analgesics for arthritis - 3 different meds (narcotic/aspirin) and placebo - all RED, BLUE, GREEN or YELLOW - NO EFFECT OF COLOR IF A DRUG but if placebo at 2-6 hours (but not 1) RED was better

Lucchelli 1978 - 96 hospitalized insomniacs - hepabarbital and placebo - ORANGE or BLUE - NO DIFFERENCE IN NUMBERS OF PEOPLE WITH A “GOOD SLEEP” NOR “UNSATISFACTORY” SLEEP - they were also asked when they woke up the next day - how long it took them to fall asleep and how long they slept - BLUE fell asleep 32 minutes faster (took them ~1.5-2 hours to fall asleep) and slept 33 minutes longer
“In a series of experiments in Italy..., blue sleeping tablets, or blue placebos worked better than did tablets of other colours, for Italian women; blue tablets tended to have a stimulating effect on men!”

“Checking with an Italian-American anthropologist colleague, we came up with this speculation.”

“Many Italian women have a special relationship with the Virgin who is, in Roman Catholic tradition, the protector of women; in religious art, the Virgin Mary is almost always shown in blue.”

“What about men. “Azzuri” is the name (and the colour) of the Italian national football team. Blue, for many Italian men, is not a colour of solace but of excitement and stimulation, of joy and madness, of exhilaration and, too often, of catastrophe. But it’s hardly the colour of sleep.”
Colours of Psychotropics

Question - does industry use colours designed to enhance their intended medicinal action?

1. **Stimulants/antidepressants** - primarily bright in colour - **ORANGE, YELLOW, RED**
2. **Anxiolytics/sedatives/hypnotics/anti-panic/anti-mania/anti-psychotics** - primarily darker in colour - **GREEN, BLUE, PURPLE**
3. **Neutral** - **WHITE, GREY**

<table>
<thead>
<tr>
<th>176 medications/doses</th>
<th>COLOUR corresponded to “desired effect” (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antianxiety</td>
<td>50</td>
</tr>
<tr>
<td>Antidepressant</td>
<td>46</td>
</tr>
<tr>
<td>Antimania</td>
<td>23</td>
</tr>
<tr>
<td>Antipanic</td>
<td>29</td>
</tr>
<tr>
<td>Antipsychotic</td>
<td>16</td>
</tr>
<tr>
<td>Sedative</td>
<td>33</td>
</tr>
<tr>
<td>Stimulant</td>
<td>46</td>
</tr>
</tbody>
</table>

Only ~1/3 of the time did the colour correspond to the “best” colour.
Placebos in clinical care: a suggestion beyond the evidence

The recent enthusiasm for the clinical use of placebos seems driven by myths and misunderstandings

“the notion that placebo pill appearance is important is based on a very small and weak evidence base”

10.5694/mja2.51230 - 2021
Placebo effect - the bottom line

there likely is some sort of a placebo effect for some people for a few conditions
it is nowhere close to 30-35%
the placebo group effect is >>> than the placebo effect
understand how to “harness” the placebo group effect (of which a little bit could be the placebo effect - but it doesn’t really matter)
there are no ethical issues around the placebo group effect
Ethics of using actual placebos

Clinical Care
undermine trust
compromise the patient-clinician relationship

Clinical Research
Use of placebos when you have a proven treatment - debate
All hinges on appropriate consent
If we can do “first-in-human” trials then we can certainly do placebo controlled trials in conditions for which we already have effective treatments - subjects just need to be informed
The Placebo Group Effect
these are ballpark numbers and depend somewhat on the outcome measured

~0% - general anesthesia
~5% - psychosis, ankylosing spondylitis (remission)
~10% - sildenafil, OCD, rheumatoid arthritis (remission), Crohn’s (remission)
~20% - Alzheimer’s meds, acetaminophen for headaches, Crohn’s disease, side effects (nocebo)
~25% - menopausal symptoms, migraine (frequency/severity), ulcerative colitis
~30% - blood pressure goal, depression, anxiety, PTSD, PPIs/H2RA, sore throat, NSAIDs for OA, inhalers for COPD (symptoms)
~40% - panic disorders
You need to know what goes on in the placebo group

![Graph showing placebo response percentages](image)

- Placebo group
- 10% absolute NNT 10
- 20% absolute NNT 5

**X% = the chance it was the medication**

100% response in the placebo group

Antidepressants: 33% response
<table>
<thead>
<tr>
<th>CONDITION</th>
<th>Erectile dysfunction</th>
<th>UTI</th>
<th>Strep throat</th>
<th>Acute bronchitis</th>
<th>Acute sinusitis</th>
<th>Depression</th>
<th>Overactive bladder</th>
<th>Dementia</th>
<th>Neuropathic pain</th>
<th>Knee osteoarthritis</th>
<th>Acute MSK</th>
<th>Gout</th>
<th>Asthma</th>
<th>COPD</th>
<th>Smoking cessation</th>
<th>Heart burn</th>
</tr>
</thead>
<tbody>
<tr>
<td>TREATMENT</td>
<td>Sildenafil</td>
<td>Antibiotic</td>
<td>Antibiotic</td>
<td>Steroid</td>
<td>Antibiotic</td>
<td>SSRI</td>
<td>Anticholinergic</td>
<td>Donepezil</td>
<td>Antidepressant</td>
<td>Steroid Injection</td>
<td>Topical NSAIDs</td>
<td>Low dose colchicine</td>
<td>Inhaled steroids</td>
<td>LABA vs LABA/LAMA/ICS</td>
<td>LABA vs LABA/LAMA/ICS</td>
<td>Nicotine/bupropion</td>
</tr>
<tr>
<td>OUTCOME</td>
<td>Successful intercourse</td>
<td>Asymptomatic day 3</td>
<td>No pain at 3 days</td>
<td>Complete pain relief 24 hours</td>
<td>No cough at follow-up</td>
<td>Cure/improvement</td>
<td>ADAS-COG change of 4</td>
<td>30% reduction in pain score</td>
<td>Pain reduction target or global improvement</td>
<td>&gt;50% reduction in pain at 24-48h</td>
<td>&gt;50% reduction in pain at 24h</td>
<td>No exacerbation</td>
<td>No exacerbation</td>
<td>Not smoking at 1 year</td>
<td>No symptoms</td>
<td></td>
</tr>
</tbody>
</table>

**BLUE = the ADDITIONAL benefit over placebo**
1) Erectile dysfunction

2) UTI
https://www.journalofinfection.com/article/S0163-4453(09)00002-4/fulltext

3) Strep throat antibiotic
Cochrane Library CD000023

4) Strep throat steroids

5) Bronchitis
https://doi.org/10.1002/14651858.CD000245.pub4

6) Sinusitis
Cochrane Library CD000243

7) Depression
https://www.bmj.com/content/360/bmj.k1073

8) Overactive bladder

9) Dementia

10) Neuropathic pain

11) Knee osteo
https://www.cfp.ca/content/cfp/66/3/191.full.pdf

12) Acute MSK

13) Gout Low dose colchicine
Arth Rheum 2010;62:1060-8

14) Asthma exacerbations on inhaled steroids – depends what numbers/evidence you use – the bottom line is the absolute benefit is ~10-15%

Lancet 2003; 361: 1071–76
Mild persistent asthma budesonide vs placebo (adults and children)
45% of patients on placebo (vs 31% on budesonide) received inhaled, oral, or systemic steroids during
Severe exacerbation 6% vs 3% over 2 years

Cochrane Library CD011032
Interruption ICS, with treatment initiated at the time of early symptoms,
Exacerbations requiring oral corticosteroids
School age children 48% vs 35% over 44 weeks
Adults – 6 months 3.5% vs 0.3%

Cochrane Library CD003135
Fluticasone versus placebo for chronic asthma in adults and children
Withdrawal due to clinical asthma exacerbation 11% vs 2% in adults

Cochrane Library CD002738
Withdrawal due to asthma exacerbation – children and adults
15% vs 3%
Mild to Moderate asthma
15% vs 6%
Overall exacerbations of asthma
6% vs 6%

15) COPD exacerbations
Cochrane Library CD012620

16) Nicotine/bupropion smoking cessation
Cochrane Library CD000146, Cochrane Library CD000031

17) Heartburn
Cochrane Library CD003244
All of this only applies if you are treating a symptom

None of this applies to preventative treatments.

You can NEVER know if a preventative treatment worked - other than the surrogate marker and even then the measurement variation is >> than the effect.
<table>
<thead>
<tr>
<th>BLOOD PRESSURE 10 YEARS</th>
<th>LIPIDS 10 YEARS</th>
<th>DIABETES 10 YEARS</th>
<th>DIABETES 2-3 YEARS</th>
<th>ATRIAL FIB 1 YEAR</th>
<th>POST MI 3 YEARS</th>
<th>HEART FAILURE 2-3 YEARS</th>
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<tbody>
<tr>
<td>CVD BP meds</td>
<td>CVD Statin</td>
<td>CVD Metformin</td>
<td>CVD DP4, Gli</td>
<td>STROKE CVD</td>
<td>CVD ASA War/NOAC</td>
<td>Statin ACE, ARB, BB</td>
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<td></td>
<td>Mortality</td>
<td>Statin</td>
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<thead>
<tr>
<th>% RISK</th>
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<td>19</td>
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<td>0</td>
<td>18</td>
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YELLOW = the REDUCTION over placebo

- Newly diagnosed, Age 55
- Post- MI Age 60
- Low dose
- Class 2-3
- 8%
- 5%
- 4%
- 2%
- 2%
- 3%
- 1%

Diabetes ~10 years
Hx CVD, Age 65
2 risk factors

Aldosterone antagonists
“Everything in Life is Vibration.”

Albert Einstein
The Natural Fluctuation of Pain Scores
Morning pain scores for 25 people with osteoarthritis - 3 months

Average pain is ~5/10
20+ of the 25 people had fluctuations of ≥ 2.5/10 = ~50% of their baseline pain

NSAIDS
Outcome = 30-50% reduction in pain
~60% on drug
~45% on placebo

4 (15% of 25) of these people would likely benefit from an NSAID but what 4?

The red dots are the respective Knee Injury and Osteoarthritis Outcome Score (KOOS) for each month.

The Fluctuation of Depression Scores

96 patients - interpersonal psychotherapy (IPT) vs cognitive behavioral therapy (CBT)

Results - 21 item MCID ~30% reduction - ~50% in both groups had at least an 8 change

Journal for Person-Oriented Research 2019;5:65-79
OTHER FLUCTUATIONS

COPD SYMPTOMS
Daily and/or weekly symptom variability: 63%
  45% during the day
  54% during the week
Seasonal symptom variability: 60%  

Eur Respir J 2011;37:264–272

SYSTOLIC BLOOD PRESSURE
the within-individual coefficient of variation between clinic visits is 10% (~13-15 mmHg) for systolic blood pressure

Am J Hyper 2008;21:3–4
The doses in these books are wrong for most people.

May be the MOST important concept to understand when it comes to prescribing.

% of patients responding
OR
% of the response

No treatment/placebo

LOG DOSE

The doses in these books are wrong for most people.
But sometimes it is like this

% of patients responding

No treatment/placebo

Antidepressants

LOG DOSE

0 10 20 30 40 50 60 70 80 90 100
”Unless the condition is severe or life-threatening, drug treatment can be started at a very low dose (half or one-quarter the recommended starting dose)"

Most of the effect of a medication comes from the “low” starting doses AND doubling a dose never doubles the effect - in fact it sometimes has no additional effect
Getting all the POWER of a placebo WITHOUT the deception

Use **VERY-LOW** doses - you will get **ALL** the placebo effect - and likely **FEWER** side effects

Patients are engaged in the process of finding the **best dose** for them

**Cost savings** can be considerable and most **adverse events** can be minimized

Most clinically relevant **drug interactions can be avoided**