Unsolved, forgotten, and/or ignored features of the placebo response in medicine

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The "Placebo Box"

Currently (until 2015) contains > 3000 papers on the placebo/nocebo effect or response

≈ 200 papers/year
≈ 4-5/week

The heuristic approach
The empirical approach
The "Placebo Box"
The "Placebo Box" - The empirical approach
The "Placebo Box"
In our study, participants with stronger beliefs in supplements tended to lose a smaller proportion of weight. Participants with 100% expectancy of receiving the active supplement tended to report a decline in self-efficacy over the course of the study and to increase their beliefs in the supplement’s effects. The group with 50% expectancy of active supplement remained somewhat stable in self-efficacy scores and did not change in their level of belief in the supplements, while those taking no capsules increased in self-efficacy and tended to reduce their belief in the value of supplements.
Trials of pharmacological interventions had a moderate placebo effect size significantly greater than the small placebo effect size seen in trials of dietary supplements ($Q = 5.02$, $df = 1$, $P = 0.03$; Figure 3). Trials of adjunctive interventions, which included both pharmacological and dietary supplement treatments, also had a moderate placebo effect size significantly greater than the small placebo effect size in monotherapy trials ($Q = 5.26$, $df = 1$, $P = 0.02$; Figure 3). There was no difference in the placebo effect size for primary outcome measures compared with secondary outcome measures ($Q = 3.20$, $df = 1$, $P = 0.07$).
Clinical: Drug Food Phys Thx

Box Dimension Papers in Box Important Questions

about 2400 500 300

Are the mechanisms operating (conditioning, expectation) the same than with drugs?

Are placebo effects larger or smaller with nutrients & foods than with drugs?

To the best of our knowledge, no direct comparison has yet been made testing the difference experimentally

Using the Placebo Effect to Isolate Control Mechanisms of Athletic Performance: A Research Protocol

Ellen K. Broelz¹, Paul Enck¹, Andreas M. Niess², Patrick Schneeweiss³ and Katja Weimer¹

Food over Drugs: Salience Hypothesis

Drugs over Food: Conditioning Hypothesis
Are there sex differences in placebo analgesia during visceral pain processing? A fMRI study in healthy subjects

N. Teyssohn, * J. Schmid, † A. Icenhour, † C. Mewes, † M. Forsting, * E. R. Gizewski, † M. Schedlowski, † S. Elsenbruch † & S. Benson †
There is very little beyond occasional reports of differences in the placebo response in RCTs between Europe and the US, Canada, Japan ...
**Societal: Ethics**  
**The Law**  
**Economy**

<table>
<thead>
<tr>
<th>Box Dimension</th>
<th>Papers in Box</th>
<th>Important Questions</th>
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<tbody>
<tr>
<td>about 800</td>
<td>450</td>
<td>Do the ethics of placebo use in patients cover the ethics of placebo research in science?</td>
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<tr>
<td></td>
<td>100</td>
<td>How do the different legal systems handle placebo use?</td>
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<td>Does the placebo effect help saving money?</td>
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A: Is utilizing the placebo response ("harnessing") in medicine in conflict with better patient education and "shared decision making"?

B: Is partial reinforcement ("dose extension") a strategy that not only benefits the patient but also the society, for instance by saving drugs and money?
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Self-efficacy and placebo response are inversely related!

High self-efficacy = internal Locus of Control (LoC)

Low self-efficacy = external LoC = Placebo responder

Prediction of placebo responses: a systematic review of the literature

Bjoem Horing1,2*, Katja Weimer1, Eric R. Muth2 and Paul Enck1
... if this holds true for all conditions and not only for nausea and for healthy volunteers....

... then the current approach in health economics, to educate the patients and train them to engage and participate in "shared decision making" may result in higher self-esteem and self-efficacy and in lower placebo responses ...

.... which is the opposite of "harnessing the placebo response".
B: Is partial reinforcement ("dose extension") a strategy that not only benefits the patient but also the society, for instance by saving drugs and money?

Table 2 Systematic use of placebo pills

<table>
<thead>
<tr>
<th>Acquisition period</th>
<th>Maintenance treatment</th>
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<tbody>
<tr>
<td>1 2 3 4 5 6 7 8 9 10 11 12 13 14</td>
<td>15 16 17 18 19 20 21 22 23 24 25 26 27</td>
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This example shows a drug administration regimen with a 2-week acquisition period, followed by drug administrations with interspersed placebo administrations (likelihood of placebo administration in 3rd week: 0.33).

D, drug; P, placebo.


Conditioned Pharmacotherapeutic Effects: A Preliminary Study
Robert Ader, PhD, Mary Gail Mercurio, MD, James Walton, BS, Deborra James, RN, Michael Davis, PhD, Valerie Ojha, RN, Alexa Boer Kimball, MD, MPH, and David Fiorentino, MD, PhD
Psychosomatic Medicine 72;2010:192-7

Conditioned Placebo Dose Reduction: A New Treatment in Attention-Deficit Hyperactivity Disorder?
Adrian D. Sandler, MD,* Corrine E. Glesne, PhD,* James W. Bodfish, PhD†‡
(Inv Dev Behav Pediatr 31:369–375, 2010)
Corticosteroid therapy in psoriasis

Amphetamine therapy in ADHD
Technical: eHealth, mHealth, VR

Papers in Box:
- about 100 (internet)
- 2 (eHealth)

Important Questions:
- The future
- The presence

How contemporary is placebo and nocebo research?

This growth is much faster than the growth of knowledge in placebo research.

A two-sided coin: Health Monitoring and Communication
There are more than 165,000 medical apps .... Here, we introduce the concept of the digital placebo effect, referring to placebo-like effects seen from mobile health interventions, such as smartphone apps. Many people have a high level of affinity for their

Self-monitoring Using Mobile Phones in the Early Stages of Adolescent Depression: Randomized Controlled Trial

Review and Evaluation of Mindfulness-Based iPhone Apps

Results: The “mindfulness” search identified 700 apps. However, 94 were duplicates, 6 were not accessible and 40 were not in English. Of the remaining 560, 23 apps met inclusion criteria and were reviewed. The median MARS score was 3.2 (out of 5.0), which exceeded the minimum acceptable score (3.0). The Headspace app had the highest average score (4.0), followed by Smiling Mind (3.7), iMindfulness (3.5) and Mindfulness Daily (3.5). There was a high level of inter-rater reliability between the two MARS raters.

Conclusions: Though many apps claim to be mindfulness-related, most were guided meditation apps, timers, or reminders. Very few had high ratings on the MARS subscales of visual aesthetics, engagement, functionality or information quality. Little evidence is available on the efficacy of the apps in developing mindfulness.
Can a "virtual doctor" elicit reliable placebo responses?

Thanks for your attention!