Mechanisms of Open-Label Placebos in Pain and Sadness

Tobias Kube, PhD
Agenda

- Study 1: Experimentally induced pain
- Study 2: Experimentally induced sadness
Study 1

Deceptive and non-deceptive placebos to reduce pain - An experimental study in healthy people

Kube, T, Rief, W, Vivell, M-B, Schäfer, NL, Vermillion, T, Körfer, K., & Glombiewski, J. A. (under review)
Is the rationale more important than deception? A randomized controlled trial of open-label placebo analgesia

Cosima Locher, Antje Frey Nascimento, Irving Kirsch, Joe Kossowsky, Andrea Meyer, Jens Gaab
Why hope might matter - Patient statements

- „I don’t expect anything. I hope it will help“
- „Hey, you know, maybe there’s some treatment that can help me. But I have no idea. I’m just hopeful“

- “I’m really interested and want to try it, I mean um, I don’t have any particular expectations, I guess I’m, I’m not, not expecting any miracle outcomes but I’m open to whatever happens”

- “Having already tried a few things on my own and, and not saying that they’ve had like stellar results, I guess the cynic in me would say, I have hopes but I don’t have expectations...(laughs) um, I guess my expectation is that I’m going to learn something new. And that’s as high as I would rate it”
Hope vs. expectancies

1. Positivity
   - Hope almost always refers to desirable events/experiences, whereas expectations also include the anticipation of negative events/experiences (e.g., „This drug will cause serious side effects“).

2. Probability
   - Expectation = driven by a sense of probability
   - Hope = driven by a sense of preference

3. Cognitive vs. emotional components
   - Expectation: primarily a cognitive construct albeit with corresponding emotional reactions (Rief et al., 2015)
   - Hope: closely linked to despair as revealed by the literature on chronic pain (Corbett et al., 2007; Eaves et al., 2014, 2015, 2016)

Leung et al., 2009
Conceptualization of hopes vs. Expectancies in our study

- Cognitive vs. Affective
- High probability vs. Low probability

Expectancy

Hope
Our study

- Healthy people (N = 117)
- Induction of heat pain
Pretreatment pain assessment

Deceptive Placebo (DP)

“Lidocaine will make you react less sensitively to painful stimuli”

Open-Label Placebo with hope (OLP-H)

Induction of hope for the effectivity of a placebo cream

Open-Label Placebo with expectancy (OLP-E)

Evoking expectancies about the effectiveness of a placebo cream by providing a scientific rationale

No treatment (NT) group

Receiving no treatment

Assessment of hope and expectation of pain relief

Applying a placebo cream

Standard basic cream with oil of thyme

Posttreatment pain assessment

Follow-up measures and debriefing
Planned contrasts

1. Contrast: NT vs. all treatment groups (DP, OLP-H, OLP-E)

2. Contrast: DP vs. OLP (OLP-H, OLP-E)

3. Contrast: OLP-H vs. OLP-E

Primary outcome (as for Locher et al., 2017): Pain tolerance and corresponding pain intensity and unpleasantness ratings
Primary results: pain tolerance

NT < DP = OLP-E = OLP-H

* p < .05
Primary results: subjective pain ratings

* $p < .05$, ** $p < .001$

NT = OLP-E = OLP-H < DP
Secondary results: hopes and expectancies

Table 2

Results of the manipulation check regarding the induction of hope and expectancies in the open-label placebo conditions

<table>
<thead>
<tr>
<th>Variable</th>
<th>OLP-H (n = 25)</th>
<th>OLP-E (n = 25)</th>
<th>Group differences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjective likelihood of placebo analgesia, M (SD)</td>
<td>31.08 (21.09)</td>
<td>47.16 (24.69)</td>
<td>$F(1, 48) = 6.132, p = .017$</td>
</tr>
<tr>
<td>Hope scale sum score, $M (SD)$</td>
<td>17.36 (6.39)</td>
<td>21.48 (5.31)</td>
<td>$F(1, 48) = 6.150, p = .017$</td>
</tr>
<tr>
<td>Expectancy scale sum score, $M (SD)$</td>
<td>15.00 (5.80)</td>
<td>18.88 (5.80)</td>
<td>$F(1, 48) = 5.601, p = .022$</td>
</tr>
</tbody>
</table>

Note. M = Mean, SD = Standard deviation, N = Number, OLP-H = open-label placebo with hope induction, OLP-E = open-label placebo with expectancy induction
Questions to discuss

- Open-label placebo analgesia on an „objective“ (temperature) level but not on a subjective level?
- Did we actually induce hope?
- Can hope be meaningfully investigated in healthy people?
Study 2

Components Of Placebo Effects in Sadness (COPES)

Friehs, T, Rief, W, Glombiewski, JA, Wittkowski, J, & Kube, T (ongoing)
Sadness induction

“The Champ“
Study design

- Five groups: “2x2 +1“ Design

- Type of placebo:
  - Open-label placebo (OLP)
  - Deceptive Placebo (DP)

- Administration style
  - Personal-emotional style (PES)
  - Scientific matter-of-fact style (SMS)

“These spray contains a fast-working antidepressant, which protects you from sadness“
Study design

- Five groups: “2x2 +1“ Design

- Type of placebo:
  - Open-label placebo (OLP)
  - Deceptive Placebo (DP)

- Administration style
  - Personal-emotional style (PES)
  - Scientific matter-of-fact style (SMS)

„This spray contains a fast-working antidepressant, which protects you from sadness“

Personalised, emotion-focused language: “You may react less emotionally“
Study design

- Five groups: “2x2 +1“ Design

- Type of placebo:
  - Open-label placebo (OLP)
  - Deceptive Placebo (DP)

- Administration style
  - Personal-emotional style (PES)
  - Scientific matter-of-fact style (SMS)

- Control group: no treatment

„This spray contains a fast-working antidepressant, which protects you from sadness“

Neutral, non-personalised language; explanation of the suggested mechanisms of action
Preliminary results

Aim: $N = 150$ (5 groups à 30 persons); currently: $N = 68$
Preliminary results: Main effect “Type of Placebo”
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Main effect “Type of Placebo”
Preliminary results:
Main effect “Administration style”

Randomisation

Sadness (PANAS)

Personal-emotional  Scientific matter-of-fact  Control Group

T1  T2  T3

Randomisation
Preliminary results:
Interaction “Placebo x Administration”
Both studies provided evidence for the “traditional” placebo effect based on deception.

In Study 1, some evidence for the efficacy of Open-Label Placebo in pain was found; in Study 2: no open-label effect at all.

The effects of Open-Label Placebo seem to be weaker in healthy volunteers than in clinical populations.

Understanding the mechanisms of Open-Label Placebo remains an ongoing challenge.
Thank you for your attention!

Study 1

Karoline Körfer

Maj-Britt Vivell,
Leonora Schäfer,
Teresa Vermillion

Study 2

Winfried Rief

Thilo Friehs

Julia Glombiewski

Julia Wittkowski
Induction of hope

“The cream you are going to receive is a placebo cream that the actual lidocaine cream is compared with. This means that this cream does not contain any pharmacological ingredients. Therefore, it is unlikely that the cream alone will affect your pain perception.

However, a few people, especially women/men of your age, reported that the placebo cream had a strong analgesic effect when applying it, even though they knew that they were receiving a placebo cream. For instance, a young woman/man who participated in the study last week told us that the placebo cream helped her/him to bear the unpleasant heat stimulus and to perceive it as less painful. Therefore, you may become less sensitive to painful stimuli after applying the cream.”
Induction of expectancies

- “Several scientific studies have shown that placebos are very effective, even if participants knew that they were going to receive a placebo. In particular, placebo creams lead to substantial pain reduction in approximately 70% of participants.

- Similar to Pavlov’s dogs, a placebo cream that looks like an actual analgesic cream can activate automatic bodily reactions, which in turn may lead to an effective analgesia. Thus, placebos actually affect physical processes, e.g. immune parameters. Therefore, you may become less sensitive to painful stimuli after applying the cream compared to in the first trial.”

- In general: close to the recommendations of Ted