THREE CLINICAL EXPERIMENTS

Can placebo effects be administered in a way analogous to dose dependence?

What is the relationship between effective pharmaceuticals and placebo effects? Can a single word change the effect of pharmaceuticals?

Can placebo pills be administered honestly without deception or concealment and induce placebo effects?
"I want you to take this placebo two times a day for ten days. If your condition doesn't improve, I'll give you a stronger one."
HYPOTHESIS:

\{\text{INTAKE}\} < \{\text{INTAKE + PLACEBO}\} < \{\text{INTAKE + PLACEBO + ENGAGEMENT}\}
Flow of Participants in Placebo-IBS Study

Randomized (n=262)

- Augmented Placebo (n=87)
  - Completed Augmented Placebo (n=82)
    - Genuine Acupuncture (n=41)
      - Completed Follow-Up Augmented Placebo (n=39)
  - Limited Placebo (n=88)
    - Completed Limited Placebo (n=71)
      - Genuine Acupuncture (n=37)
        - Completed Follow-Up Limited Placebo (n=31)
- Waitlist (n=87)
  - Completed Waitlist (n=77)
    - Completed Follow-Up Waitlist (n=72)
PLACEBO ACUPUNCTURE NEEDLE

a) acupuncture needle  b) placebo needle  c) verum needle

Streitberger. Lancet 1998
OUTCOME MEASURES

IBS Adequate Relief
IBS Global Improvement
IBS Symptom Severity Scale
IBS QoL
Global improvement

- Waiting list (n=87)
- Limited (n=88)
- Augmented (n=87)

Mean (SE)

Test of trend: P<0.001; 95% CI 0.18 to 0.90 for limited v waiting list; 0.32 to 1.11 for augmented v limited

Adequate relief

- Waiting list (n=87)
- Limited (n=88)
- Augmented (n=87)

Percentage (SE)

Test of trend: P<0.001; 95% CI 2.7 to 30.7 for limited v waiting list; 3.2 to 32.3 for augmented v limited

Symptom severity

- Waiting list (n=87)
- Limited (n=88)
- Augmented (n=87)

Mean change (SE)

Test of trend: P<0.001; 95% CI -7.9 to 31.2 for limited v waiting list; 16.2 to 63.2 for augmented v limited

Quality of life

- Waiting list (n=87)
- Limited (n=88)
- Augmented (n=87)

Mean change (SE)

Test of trend: P<0.001; 95% CI -2.1 to 3.2 for limited v waiting list; 1.7 to 8.8 for augmented v limited
Global Improvement

Mean (SE)

- Waiting list (n=77)
- Limited (n=34)
- Augmented (n=41)

Test of trend: P=0.001; 95% CI 0.5 to 1.4 for limited v waiting list; -0.1 to 1.1 for augmented v limited

Adequate relief

Percentage (SE)

- Waiting list (n=77)
- Limited (n=34)
- Augmented (n=41)

Test of trend: P=0.005; 95% CI -2 to 38 for limited v waiting list; -14 to 30 for augmented v limited

Symptom severity

Mean change (SE)

- Waiting list (n=77)
- Limited (n=34)
- Augmented (n=41)

Test of trend: P=0.001; 95% CI -14.6 to 50.5 for limited v waiting list; 15.7 to 95.2 for augmented v limited

Quality of life

Mean change (SE)

- Waiting list (n=77)
- Limited (n=34)
- Augmented (n=41)

Test of trend: P=0.002; 95% CI 4.2 to -4.4 for limited v waiting list; 0.9 to 13.0 for augmented v limited
Altered Placebo and Drug Labeling Changes the Outcome of Episodic Migraine Attacks

Slavenka Kam-Hansen,¹ Moshe Jakubowski,² John M. Kelley,³,⁴,⁵ Irving Kirsch,⁵,⁶ David C. Hoaglin,⁷ Ted J. Kaptchuk,⁵* Rami Burstein²*†
## Migraine Study Design: Label Change

<table>
<thead>
<tr>
<th>Label</th>
<th>Placebo</th>
<th>Maxalt</th>
</tr>
</thead>
<tbody>
<tr>
<td>Label</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>Correct</td>
<td>Incorrect</td>
</tr>
<tr>
<td>Maxalt or Placebo</td>
<td>Correct</td>
<td>Correct</td>
</tr>
<tr>
<td>Maxalt</td>
<td>Incorrect</td>
<td>Correct</td>
</tr>
</tbody>
</table>
MIGRAINE STUDY

DESIGN 2 X 3 + 1

N=66 X 7 ATTACKS = 459 DOCUMENTED BASELINES

OUTCOME: PAIN REDUCTION AT 2.5 HOURS. RESCUE RX
RESULTS

General Outcomes:

N=66 x 7 attacks = 459 documented baselines

Yielded: 435 2.5 hr. outcomes and 18 imputed

453 analyzable attacks using Generalized Linear Mixed Models with a random component and a logarithmic link function

Specific Results:

Treatment (Maxalt vs. placebo):  p<0.001

Labeling of Pill:  p=0.010
Fig. 3. Changes in headache intensity as a percentage of the 30-min pain score. The data are estimates for the seven experimental conditions, with negative values indicating reductions and positive values indicating increases.
"If you tell them they’re in the placebo group, it ruins it!"
OPEN-LABEL PLACEBO IN IBS: PILOT STUDY FLOW

N=80

N=43

N=39

No Treatment Control Completers

N=37

N=31

Open Label Placebo Completers
A. Global Improvement (IBS-GIS)

B. Symptom Severity Change (IBS-SSS)

C. Percent with Adequate Relief (IBS-AR)

D. Quality of Life Change (IBS-QOL)

P-values:
- A: p=.002
- B: p=.03
- C: p=.03
- D: p=.08
OPEN LABEL PLACEBO FOR CHRONIC LOW BACK PAIN
CARVALHO ET AL., 2016

Pain (0-10)

Disability (RMDQ)

Baseline   Endpoint   Follow-up

• TAU   • OLP

Baseline   Endpoint   Follow-up

• TAU   • OLP
THANK YOU!
Table 1. Polymorphisms in candidate genes that may be part of the placeboome

<table>
<thead>
<tr>
<th>Placebo pathway</th>
<th>Gene name</th>
<th>Gene symbol</th>
<th>Chromosomal location</th>
<th>Placebo SNPs</th>
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<tbody>
<tr>
<td>Dopamine</td>
<td>Catechol-O-methyltransferase</td>
<td>COMT</td>
<td>22q11.2</td>
<td>rs4680</td>
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<tr>
<td></td>
<td>Monoamine oxidase</td>
<td>MAO-A</td>
<td>Xp11.3</td>
<td>rs6323, rs6609257</td>
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<tr>
<td></td>
<td>Dopamine B hydroxylase</td>
<td>DBH</td>
<td>9q34</td>
<td>rs2873804</td>
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<tr>
<td></td>
<td>Dopamine receptor 3</td>
<td>DRD3</td>
<td>3q13.31</td>
<td>rs6280</td>
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<tr>
<td></td>
<td>Brain-derived neurotropic factor</td>
<td>BDNF</td>
<td>11p14.1</td>
<td>rs6265</td>
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<tr>
<td>Serotonin</td>
<td>Tryptophan hydroxylase-2</td>
<td>TPH2</td>
<td>12q21.1</td>
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<td>5-Hydroxytryptamine transporter</td>
<td>SLC6A4</td>
<td>17q11.2</td>
<td>rs4251417</td>
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<td></td>
<td>5-Hydroxytryptamine receptor 2A</td>
<td>HTR2A</td>
<td>13q14.2</td>
<td>rs2296972, rs622337</td>
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<td>Serotonin transporter gene-linked</td>
<td>5-HTTLPR</td>
<td>17q11.2</td>
<td>Variable tandem nucleotide</td>
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<td></td>
<td>polymorphic region</td>
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<td>repeat</td>
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<td>Opioid</td>
<td>Opioid receptor</td>
<td>OPRM1</td>
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<td>Endocannabinoid</td>
<td>Fatty acid amide hydrolase</td>
<td>FAAH</td>
<td>1p33</td>
<td>rs324420</td>
</tr>
</tbody>
</table>
Catechol-O-Methyltransferase val158met Polymorphism Predicts Placebo Effect in Irritable Bowel Syndrome

Kathryn T. Hall¹,²*, Anthony J. Lembo²,³, Irving Kirsch²,⁴, Dimitrios C. Ziogas⁵, Jeffrey Douaiher⁶, Karin B. Jensen²,⁷, Lisa A. Conboy², John M. Kelley²,⁷,⁸, Efi Kokkotou²,³, Ted J. Kaptchuk¹,²

PLoS 2012
COMT val158met rs4680

valine high-activity

methionine low-activity

val/met

val/val high-activity less dopamine

met/met low-activity more dopamine
Figure 1. Effect of COMT genotype on change in IBS-SSS.
Number of val158met met alleles showed a significant linear effect on IBS-SSS (beta = 0.17; p = .032). IBS-SSS includes abdominal pain severity, abdominal pain frequency, abdominal distention severity, dissatisfaction with bowel habits, and disruption of quality of life. Change in IBS-SSS = (IBS-SSS at baseline - IBS-SSS at 3-weeks). Regression model included COMT genotype (number of met alleles) and baseline IBS-SSS. Error bars indicate the standard error of the mean. N = 104. doi:10.1371/journal.pone.0048135.g001
Catechol-0-Methyltransferase (COMT) genotype is associated with IBS placebo response.

COMT genotype ($\beta = 0.19; p = .02$)
COMT genotype x treatment arm ($\beta = 0.17; p = .035$) 
(N=104)
Incidence of drug side-effect and nocebo effects in 34 participants during 83 attacks

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Number of subjects</th>
<th>Number of attacks</th>
<th>Percent of attacks (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Maxalt treatments</td>
</tr>
<tr>
<td>Chest tightness</td>
<td>11</td>
<td>23</td>
<td>57</td>
</tr>
<tr>
<td>Heart palpitation</td>
<td>10</td>
<td>22</td>
<td>45</td>
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<tr>
<td>Throat tightness</td>
<td>11</td>
<td>20</td>
<td>60</td>
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<tr>
<td>Skin sensitivity</td>
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<td>21</td>
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<tr>
<td>Gastrointestinal</td>
<td>11</td>
<td>17</td>
<td>71</td>
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<tr>
<td>Drowsiness</td>
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<td>14</td>
<td>93</td>
</tr>
<tr>
<td>Other*</td>
<td>7</td>
<td>8</td>
<td>38</td>
</tr>
</tbody>
</table>

* Including: lip tingling, cheek tingling, scalp and toe tingling, dry mouth, throbbing, moodiness, tiredness.