Pharmacogenomics and placebo response in randomized clinical trials

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No disclosures
Overview

• Placebos in clinical trials
• What neuroimaging and pharmacology tell us about placebos
• \textit{COMT} and placebo response in IBS
• \textit{COMT} pharmacogenomic effects in other diseases and conditions
  - CVD, cancer, chronic fatigue, memory
• Additivity and the placebo response in clinical trials
  - Other genes - \textit{FHIT}
  - Other diseases - Asthma and \textit{BBS9}
Placebos in clinical trials

- Regression to the mean
- Natural history of disease
- Placebo effects
- Drug – Placebo = Drug efficacy
Placebo response pathways involve dopamine and opioid signaling

- Brain regions associated with pain, cognition, movement

- Response to placebo can be modified by drugs like naloxone

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**THE MECHANISM OF PLACEBO ANALGESIA**

**Summary**

The effect of naloxone on dental postoperative pain was studied to examine the hypothesis that endorphins mediate placebo analgesia. All patients had extraction of impacted mandibular third molars with diazepam, N₂O, and local block with mepivacaine. 3 h and 4 h after surgery naloxone or a placebo was given under randomised, double-blind conditions. Pain was evaluated on a visual analogue scale. Patients given naloxone reported significantly greater pain than those given placebo. Patients given placebo as their

THE LANCET, SEPTEMBER 23, 1978

Catechol-O-methyltransferase (COMT) metabolizes catechol-containing molecules.
COMT val158met
rs4680

G = valine
high-activity

A = methionine
low-activity

val/val
high-activity
less dopamine
epinephrine and
norepinephrine
catechol estrogen

val/met
intermediate

met/met
low-activity
more dopamine
epinephrine and
norepinephrine
catechol estrogen
COMT associated with placebo effects in IBS

Hall et al., PLoS ONE. 2012

Catechol-O-Methyltransferase val158met Polymorphism Predicts Placebo Effect in Irritable Bowel Syndrome
A Randomized Trial of Low-Dose Aspirin in the Primary Prevention of Cardiovascular Disease in Women


Major CVD events
Placebo group – 522
Aspirin group – 477

Aspirin effect non-significant
RR 0.91, CI [0.80-1.03], P=0.13
COMT associated with major CVD in the placebo arm

Hall et al., *Atherosclerosis Thrombosis and Vascular Biology*. 2014
Catechol-O-methyltransferase (COMT) metabolizes catechol-containing molecules.
COMT has differential effects with randomized placebo and aspirin

Placebo
n=5,814

Aspirin
n=5,815

Vitamin E
n=5,863

Aspirin + Vitamin E
n=5,802

Hall et al., ATVB. 2014
Is this a placebo effect or natural history?

- Regression to the mean
- Natural history of disease
- Placebo effects
COMT in MESA
The Multi-Ethnic Study of Atherosclerosis

- rs4818: P = 0.02
- rs4680: P = 0.46

Testosterone

Sulfatase → CYP19a1

Estrogen-Sulfate → Estrogens → TPH1, 5-HT1B, SERT

Serotonin, Estrogen, Hypoxia, SUGEN + Hypoxia, Shear Stress

CYPs/CYP1B1

16α-hydroxyestrogens → 2-, 4-hydroxyestrogens

ECs, PASMCs, PAFs

COMT

2-, 4-methoxyestrogens

+/− Proliferation of Pulmonary Arterial Cells

Austin et al. Pulmonary circulation. 2013
| rs4680 | Hormone replacement therapy (HRT) use ever |  |  |  |  |  |
|--------|------------------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|        | Race/ethnicity       | Total (%) | met/met | val/met | val/met | No HRT | Ever HRT | P_{interaction} |
|        | Overall             | 1701 (55.4) | 296 (57.7) | 723 (51.8) | 521 (47.1) | 1.14 [0.66-1.95] | 0.75 [0.56-1.02] | 0.07 0.26 |
|        | White               | 772 (64.1) | 205 (66.8) | 381 (63.0) | 186 (62.5) | 2.39 [1.42-4.01] | 0.72 [0.49-1.04] | 0.08 2.00E-04 |
|        | Black               | 419 (50.9) | 45 (50.6) | 158 (47.9) | 181 (46.2) | 0.93 [0.57-1.53] | 0.96 [0.47-1.95] | 0.91 0.43 |
|        | Hispanic            | 302 (45.1) | 39 (41.5) | 138 (40.8) | 91 (39.9) | 0.83 [0.54-1.28] | 0.59 [0.22-1.61] | 0.31 0.26 |
|        | Asian               | 137 (39.6) | 7 (30.4) | 46 (37.4) | 63 (32.6) | 0.81 [0.30-2.19] | 0.88 [0.30-2.61] | 0.82 0.24 |

<table>
<thead>
<tr>
<th>Aspirin</th>
<th>No HRT HR [95% CI], P</th>
<th>Ever HRT HR [95% CI], P</th>
<th>P_{interaction}</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 3 days/week</td>
<td>3.02 [1.38-6.58], 0.006</td>
<td>0.46 [0.25-0.85], 0.01</td>
<td>0.61</td>
</tr>
<tr>
<td>≥ 3 days/week</td>
<td>2.25 [0.97-5.24], 0.06</td>
<td>1.27 [0.69-2.35], 0.45</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Hall et al., JAHA. 2019
## COMT and cardiometabolic disease

<table>
<thead>
<tr>
<th>Risk Factor/Condition</th>
<th>PMID</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1C</td>
<td>27282867, 29225702</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>25035343</td>
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<tr>
<td>Hypertension</td>
<td>25035343, 21633377, 21776034</td>
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<tr>
<td>Fibrinogen</td>
<td>31838976</td>
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<tr>
<td>Apolipoprotein B</td>
<td>25035343</td>
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<tr>
<td>ICAM1</td>
<td>25035343</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>27282867</td>
</tr>
<tr>
<td>Pre-eclampsia</td>
<td>21355050</td>
</tr>
</tbody>
</table>
Vitamin E in the Primary Prevention of Cardiovascular Disease and Cancer
The Women’s Health Study: A Randomized Controlled Trial

Lee et al. NEJM 2005
COMT has differential effects with randomized placebo and vitamin E in CVD prevention

Hall et al., ATVB. 2014
COMT differential effects in 2 randomized trials of placebo and vitamin E for cancer prevention (ATBC and WHS)

Hall et al., JNCI 2019
placebo > clonidine in Chronic Fatigue Syndrome

- CFS:
  - higher catecholamine levels
  - overactive sympathetic nervous system

- Clonidine:
  - $\alpha_2$-adrenergic receptor agonist
  - lowers blood pressure
  - lower norepinephrine levels

- The primary outcome:
  - Steps per day after 8-weeks of treatment

Sulheim et al., JAMA Pediatrics 2014
val/val patients took 2400 fewer steps on clonidine than placebo

(\(P_{\text{interaction}} = 0.04\))

Additivity?
Is this one reason why trials fail to show benefit?

Tolcapone a COMT inhibitor appears to modify placebo response?

N=67

Farrell et al., *Biological Psychiatry* 2012
STABILITY and SOLID-TIMI52
Darapladib, a Lp-PLA₂ inhibitor, failed to demonstrate efficacy beyond placebo for the primary endpoint MACE

Yeo et al. PloS ONE. 2017
Other diseases - asthma

Childhood Asthma Management Program (CAMP) adolescents randomized and followed for 4 years
1. **Placebo** – matched budesonide or nedocromil placebo inhalers
2. **Budesonide** – anti-inflammatory corticosteroid with potent glucocorticoid activity
3. **Nedocromil** – mast cell stabilizer, inhibiting degranulation of mast cells

GWAS of Subjective outcome (coughing/wheezing) in the Placebo arm

*BBS9 implicated in lung development and ciliogenesis*

P_{interaction} = 1.48E-07

Wang et al. *CPT* 2019
Summary: drug, placebo arms outcomes not always additive

Hall and Loscalzo, CPT, 2019
Pharmacogenomics and placebo response

• Genes appear to influence response to placebo, the placeboome
• Differential association with randomized drug and placebo response is common and can be attributed to:
  ➢ Natural history of the disease
  ➢ Placebo effects
  ➢ Placebo-pharmacogenomic effects
• These differential effects can result in a null trial
• Pharmacogenomics can identify populations for benefit/harm
• Translation = Precision Medicine