Placebo and Nocebo Effects in Public Health: What Do Placebo and Nocebo Effects Have to Do with Health Equity

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No Disclosures
Placebo and nocebo effects are a back door to our health
Long “troubled” history in medicine and clinical trials
Evidence of neurological processes driving their effects
Fake news can drive nocebo effects
Individual nocebo effects can influence public health
We are battling two pandemics – COVID and the infodemic
Fake news via the echo chamber leads right to the back door making us all vulnerable
“placebos”

Placebo Domino in regione vivorum. Psalm 116:9
“Call for the wailing women to come; send for the most skilful of them.” Jeremiah 9:17

“I prescribed therefore in pure placebo, but I make it a rule even in employing placebos to give what would have a tendency to be of use to the patient.” William Cullen (1710-1790)
Debunking Mesmerism - An early clinical trial

Franz Anton Mesmer (1734-1815)
Used metal wands then a baquet, a large oak tub of magnetized water with patients pressing afflicted areas against protruding metal. With music playing patients fell into trances, cathartic and curative “crises” - violent convulsions, fits of laughter, or piercing shrieks.

Conclusion:
Not that animal magnetism didn’t work, but sham magnetism worked equally well

Louis XVI commanded a Royal Commission led by Benjamin Franklin to investigate Mesmer’s Animal Magnetism.
Haygarth and Perkin’s Tractors - An early clinical trial

Elisha Perkins (1741-1799)  
Perkins Tractors

John Haygarth (1740-1827)

Conclusion: not that tractors didn’t work, but that sham tractors worked equally well
Placebo Domino in regione vivorum. *Psalm* 116:9
“Call for the wailing women to come; send for the most skilful of them.” *Jeremiah* 9:17

“Flatterers are the Devil’s chaplains, always singing *Placebo*.”
*Chaucer’s Canterbury Tale*

“I prescribed therefore in pure placebo, but I make it a rule even in employing placebos to give what would have a tendency to be of use to the patient”
*William Cullen*

Regular, University trained physicians
Blood letting, purging, sweating

Randomized Clinical Trials

It is evident that placebos have a real therapeutic effect being produced in 35% of cases.”
*Henry Beecher*
*L.A.M.A., Dec. 24, 1955*

Placebos would enter the modern era with a strong dose of stigma

Three Big Ideas
Receptor concept in pharmacology
Homeostasis in physiology
Metabolism in biochemistry

Deception
Unethical
Mechanisms of Placebo and Nocebo Effects

- Verbal suggestions
- Context factors
- Expectation
- Learning and Memory
- Personality
- Genetic makeup
Opioid antagonist, Naloxone inhibits placebo effect

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.

Placebo responders show activation of Opioid and Dopaminergic signaling

Proportional to anticipated and perceived placebo analgesia

Zubieta & Stohler Ann NY Acad Sci 2009

De la Fuente-Fernandez et al., Behavioral Brain Research 2002
Catechol-O-methyltransferase (COMT) associated with placebo response in IBS

Hall et al., PLoS ONE. 2012
**COMT** also associated with side- or nocebo effects metabolizes dopamine, nor-epinephrine, epinephrine, and catechol estrogen. 

![Diagram of COMT pathways](image)

\[
\begin{align*}
\text{Dopamine} & \rightarrow \text{SAM} \\
\text{Epinephrine} & \rightarrow \text{SAH} \\
\text{Nor-epinephrine} & \\
\text{Catechol estrogen} & \\
\end{align*}
\]

\[\text{CH}_3\]

**Wendt et al., PLoS ONE. 2014**
Altered Placebo and Drug Labeling Changes the Outcome of Episodic Migraine Attacks

N = 66
459 documented attacks

Fig. 3. Changes in headache intensity as a percentage of the 30-min pain score. The data are estimates for the seven experimental conditions.


No difference between placebo labeled as Maxalt and Maxalt labeled placebo
Nocebo Effects in Medicine and Popular Culture

- Verbal suggestions
- Context factors
- Expectation
- Learning and Memory
- Personality
- Genetic makeup
Expectation and Nocebo Effects

Prank gone awry, Hamburg, 2014

Boot and nail, Minerva 1995
Nocebo Effects

Getting the pain you expect: mechanisms of placebo, nocebo and reappraisal effects in humans
Statin denialism

• “It’s mass murder. It always leads to hardening of the liver, it cuts off at least twenty years of your life span.”

• “Your brain is made from cholesterol. Statin is a cholesterol-lowering drug. So, if you want to have a brain that’s the size of a marble, keep on taking them. You do not die of too much cholesterol, you die of not enough. There is no such thing as too much cholesterol. In a burn unit, we use twenty to twenty-eight hard-boiled eggs a day, in a burn victim...”
“In patients who had discontinued statin therapy because of side effects, 90% of the symptom burden elicited by a statin challenge was also elicited by placebo.”

- Patients with history of discontinuing statin treatment due to side-effects
- 60 patients followed for 12 months
- Patients received 1 month of pills (placebo, atorvastatin, or empty bottle) at a time
- Order of months randomized
- 50% restarted statin use after trial

Wood, et al. NEMJ, 2020
Nocebos in clinical trials

- Concern about adverse events can lead to vaccine hesitancy
- AE reports for 45,380 trial participants
- Systemic AEs or nocebo responses were experienced by 35% of placebo recipients after the first dose and 32% after the second
What Do Placebo and Nocebo Effects Have to Do With Health Equity? The Hidden Toll of Nocebo Effects on Racial and Ethnic Minority Patients in Clinical Care

Hailey E. Yetman**, Nevada Cox³, Shelley R. Adler², Kathryn T. Hall¹,* and Valerie E. Stone¹,*
Nocebos and vaccine hesitancy

CDC Director: Covid vaccines can't prevent transmission anymore
CDC Director Rochelle Walensky went on CNN and said that vaccines cannot prevent transmission of Covid-19.

LOCAL NEWS
Woman suffers ‘life-altering injuries’ after COVID vaccine, teams up with Utah senator to demand answers
By Jillian Smolker
Updated: Jul 13, 2021 / 08:47 AM MDT
The Infodemic echo chamber

Media tries to discount us

Scientists don’t see or believe in God

Telling the truth in today’s cancel culture is not easy

Above all I am committed to hearing what God says

Not just following rules following a person

Jesus, the only one to walk this earth sinless is the ultimate healer

I research things pretty thoroughly

Expectation drives our experience

The echo chamber promotes confirmation bias

Continuum of Vaccine Acceptance

refuse all refuse but unsure delay/refuse some accept all accept but unsure

Building a Healthy Boston
COVID-19 deepened health and educational inequities

• Disproportionately affect groups made vulnerable by historical and contemporary systems of oppression including structural racism
  • redlining, gentrification, exclusionary zoning, disinvestment

• Public school infrastructure shaped by environmental racism
  • poor air quality, absent or outdated ventilation systems and more crowded classrooms

• These factors increase the risk of COVID-19 infection and more severe disease

1936 Federal Housing Administration (FHA) Redlining Map of Boston Area
Background and Study Objectives

- **Feb 25, 2022** CDC removed universal masking requirement in K-12 schools, shifting policy decisions to state & local level
- **Feb 28, 2022** MA Department of Elementary and Secondary Education (DESE) ends statewide mask requirement
- **In the following 3 weeks** most MA Public Schools ended required masking for staff and students
- **Boston** and neighboring **Chelsea** were two of a small minority of school districts that maintained required mask protections
- **Study Objective:** Staggered lifting of masking provided an opportunity to examine impact of masking policies in the school setting
  - Estimate difference in COVID-19 incidence among students and staff attributable to lifting masking protections
  - Compare social demographic and physical characteristics of school buildings in these districts
Lifting Universal Masking in Schools — Covid-19 Incidence among Students and Staff


- Districts that lifted masking in first reporting week after statewide policy rescinded (N=46)
- Districts that lifted masking in second reporting week after statewide policy rescinded (N=17)
- Districts that lifted masking in third reporting week after statewide policy rescinded (N=7)
- Districts that sustained masking (N=2)

A Students and Staff

B Students

C Staff
### Results: Cumulative difference in COVID-19 cases per 1000

Lifting mask requirements was associated with additional 45 COVID-19 cases per 1000 staff & students

![Graph showing cumulative rate difference per 1000](image)

<table>
<thead>
<tr>
<th>Group</th>
<th>Rate Diff. (95% CI)</th>
<th>Attributable cases (95% CI)</th>
<th>Attributable Fraction (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall (Staff &amp; Students)</td>
<td>44.9 (32.6, 57.1)</td>
<td>11,901 (8,651, 15,151)</td>
<td>33.4% (24.3%, 42.5%)</td>
</tr>
<tr>
<td>Students</td>
<td>39.9 (24.3, 55.4)</td>
<td>9,168 (5,594, 12,743)</td>
<td>32.1% (19.6%, 44.7%)</td>
</tr>
<tr>
<td>Staff</td>
<td>81.7 (59.3, 104.1)</td>
<td>2,882 (2,092, 3,673)</td>
<td>40.4% (29.4%, 51.5%)</td>
</tr>
</tbody>
</table>
Placebos and Nocebos in 2023 ...
Open Label placebos

https://www.tiktok.com/@americanbaron/video/7164929336582229294?r=1&t=8XHiE17oE2w&is_from_webapp=v1&item_id=7164929336582229294
1. The placebo effect is powerful. It is well known that placebos are very effective, particularly in the area of pain, Parkinson's disease, depression, migraine, and asthma.

2. The body can automatically respond to placebos like Pavlov's dogs who salivated when they heard a bell.

3. Researchers assume that this culturally anchored ritual activates automatic self-healing processes, which in turn may lead to an effective analgesia.

4. An advantage of placebos is that a positive attitude can be helpful but is not necessary.

5. Adherence, taking the placebos faithfully is critical.
Increasing number of drugs fail to beat placebo in clinical trials: a major threat to new drug development
Increasing placebo response in depression and schizophrenia

Dunlop et al., *Neuropsychopharmacology* (2012) 37, 2830–2836

Summary

• Placebo and nocebo effects are a back door to our health
• They have a long “troubled” history in medicine and clinical trials
• There is strong evidence of neurological processes driving their effects
• Genes like COMT may influence placebo and nocebo effects
• Fake news can drive nocebo effects
• Individual nocebo effects can influence public health
• We are battling two pandemics – COVID and the infodemic
• Fake news via the echo chamber leads right to the back door making us all vulnerable
Safeguarding the back door is the work of us all.
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val/val patients took 2400 fewer steps on clonidine than placebo

\( P_{\text{interaction}} = 0.04 \)
COMT associated with outcomes in the placebo arm

Hall KT. et al., 2014 Atherosclerosis Thrombosis and Vascular Biology
COMT modified outcomes in both placebo and drug treatment arm

**Graphical Representation**

- **Axes:**
  - Y-axis: Cumulative Incidence of Major CVD
  - X-axis: Years

- **Lines:**
  - met/met placebo
  - val/val aspirin
  - met/met aspirin
  - val/val placebo

- **Statistical Information:**
  - $p = 0.0008$
  - Interaction $p = 0.0022$