



# **B** Placebo and Nocebo Effects in Public Health:

## What Do Placebo and Nocebo Effects Have to Do with Health Equity

**Kathryn T. Hall PhD, MPH**  
Deputy Commissioner  
Population Health and Health Equity  
Boston Public Health Commission

BOSTON  
PUBLIC  
HEALTH  
COMMISSION



*Building a Healthy Boston*

# No Disclosures







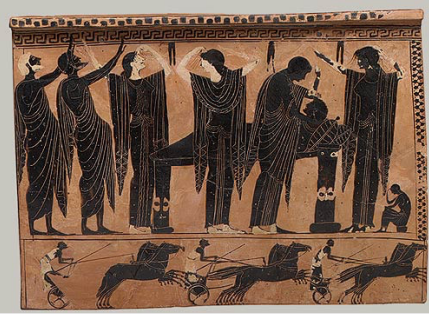
# Summary

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- 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



# got placebo?



## “placebos”

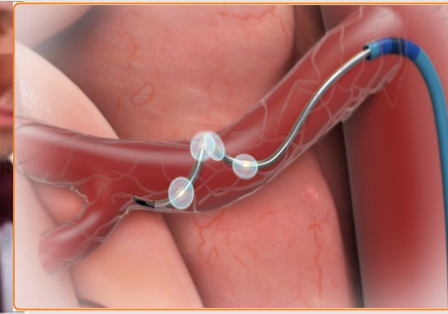
**Placebo** Domino in regione vivorum. *Psalm 116:9*  
“Call for the wailing women to come; send for the most skillful of them.” *Jeremiah 9:17*



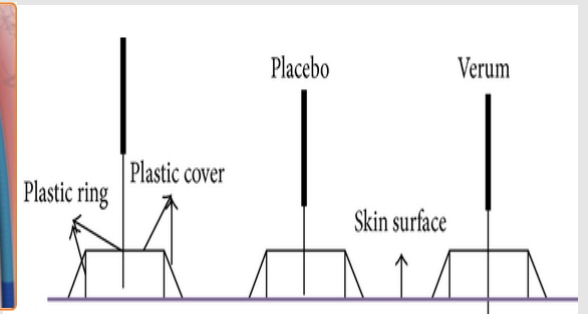
“I prescribed therefore in pure placebo, but I make it a rule even in employing placebos to give what would have a tendency to be of use to the patient” **William Cullen (1710-1790)**



dummy pills



sham surgery



sham acupuncture

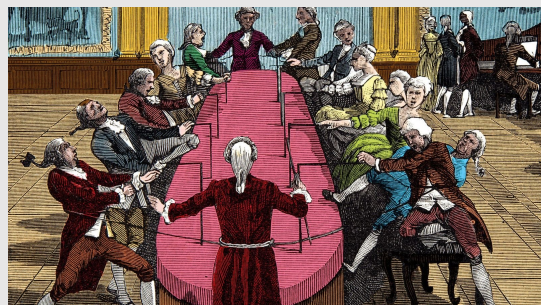


# Debunking Mesmerism - An early clinical trial



## Conclusion:

Not that animal magnetism didn't work,  
but sham magnetism worked equally well



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.



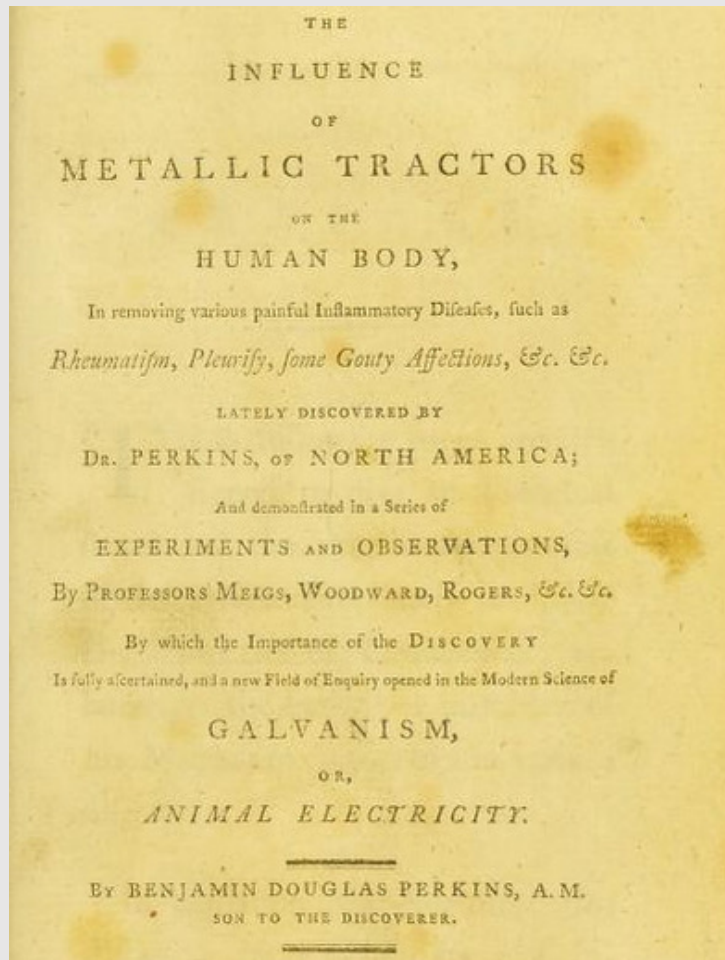
Franklin routs the mesmerists. "Le magnétisme dévoilé."  
BIBLIOTHÈQUE NATIONALE DE FRANCE.



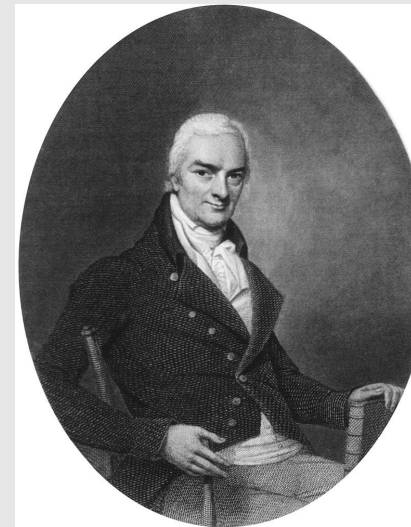
Louis XVI commanded a Royal  
Commission led by Benjamin Franklin to  
investigate Mesmer's Animal Magnetism



# Haygarth and Perkin's Tractors - An early clinical trial

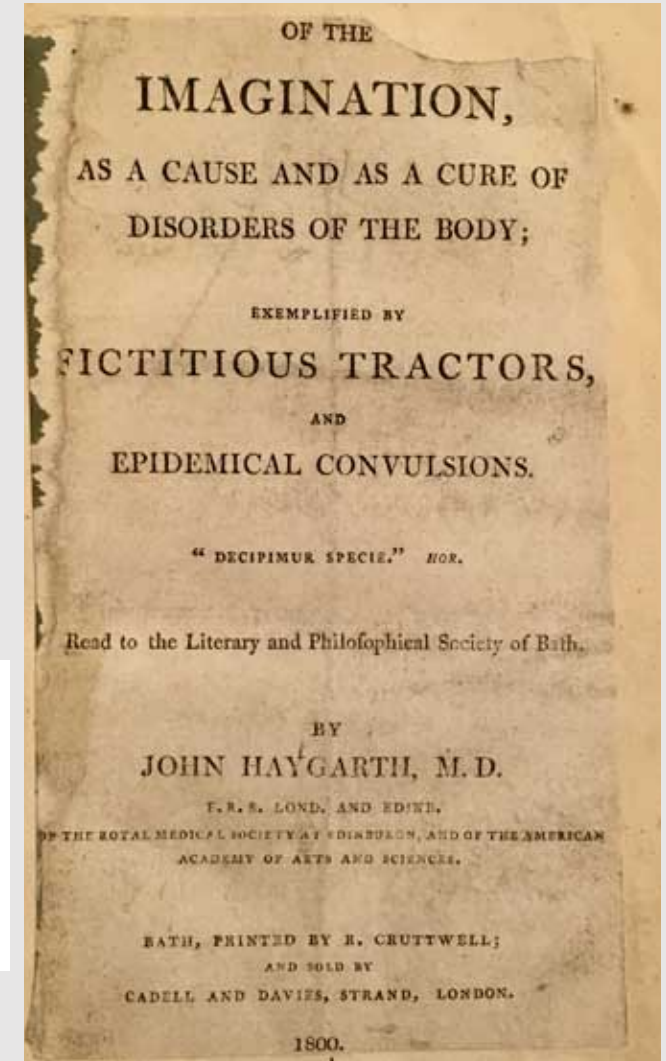


Elisha Perkins (1741-1799)  
*Perkins Tractors*



John Haygarth (1740-1827)

Conclusion:  
not that tractors  
didn't work, but that  
sham tractors  
worked equally well





# A brief history of placebos

**Placebo** Domino in regione vivorum. *Psalm 116:9*  
 "Call for the wailing women to come; send for the most skillful 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**



**Franklin vs. Mesmer**  
**Haygarth vs. Perkins**



**Regular, University trained physicians**  
 Blood letting, purging, sweating



**Randomized Clinical Trials**



**CLINICAL TRIAL OF PATULIN IN THE COMMON COLD**  
 REPORT OF THE PATULIN CLINICAL TRIALS COMMITTEE, MEDICAL RESEARCH COUNCIL  
 In November 1955, a report was published of the effects of a metabolic product of a bacterium, called patulin.<sup>1</sup> It was shown that patients treated with patulin in the common cold had a significant advantage over those treated with placebo. The results were significant. The results

BC

1300

1700

1800

1900

**Deception  
Unethical**

1955

1978

"Flatterers are the Devil's chaplains, always singing **Placebo.**"  
*Chaucer's Canterbury Tale*

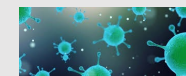
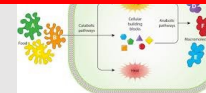


**Quacks, nostrums and patent medicine**



**Three**  
 Receptor pharmacology  
 Homeostasis physiology  
 Metabolism biochemistry

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



**UL PLACEBO**



"It is evident that placebos have a real therapeutic effect being produced in 35% of cases."

*Henry Beecher*

**J.A.M.A., Dec. 24, 1955**

# Mechanisms of Placebo and Nocebo Effects

Verbal  
suggestions

Context factors

Expectation



Learning and  
Memory

Personality

Genetic  
makeup



# Opioid antagonist, Naloxone inhibits placebo effect

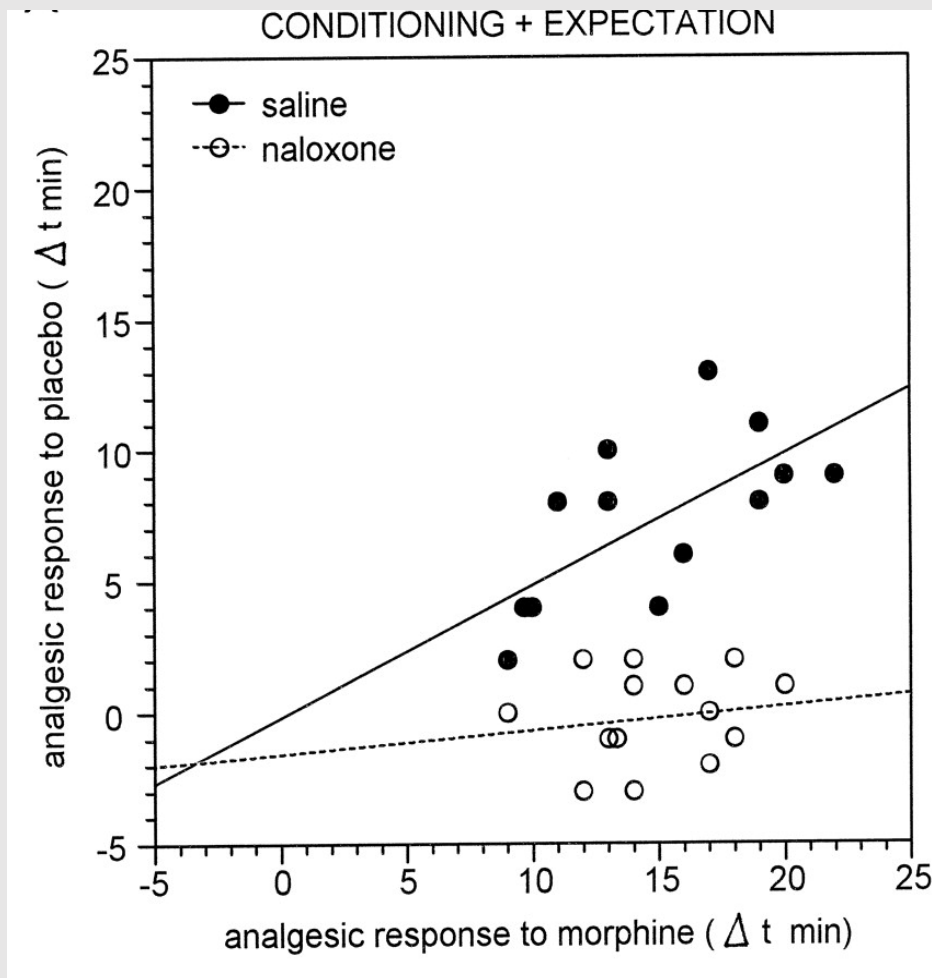
THE LANCET, SEPTEMBER 23, 1978

## THE MECHANISM OF PLACEBO ANALGESIA

JON D. LEVINE      NEWTON C. GORDON  
HOWARD L. FIELDS

*Departments of Neurology, Physiology, and Oral Surgery,  
University of California, San Francisco, California 24143,  
U.S.A.*

**Summary** The effect of naloxone on dental post-operative pain was studied to examine the hypothesis that endorphins mediate placebo analgesia. All patients had extraction of impacted mandibular third molars with diazepam, N<sub>2</sub>O, 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. Pa-

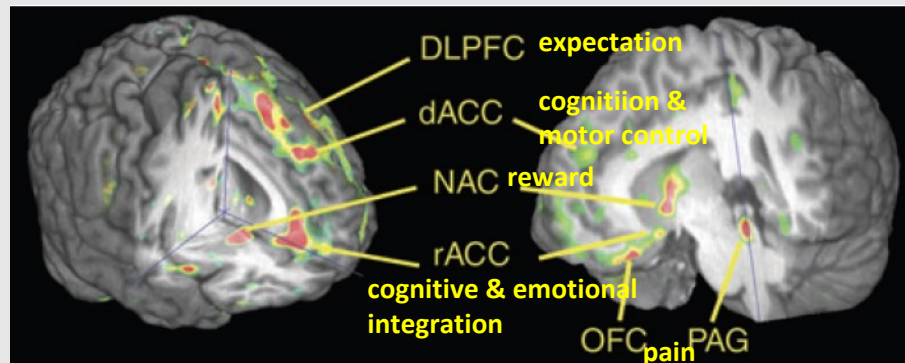


Amanzio and Benedetti, 1999. J. Neurosci.

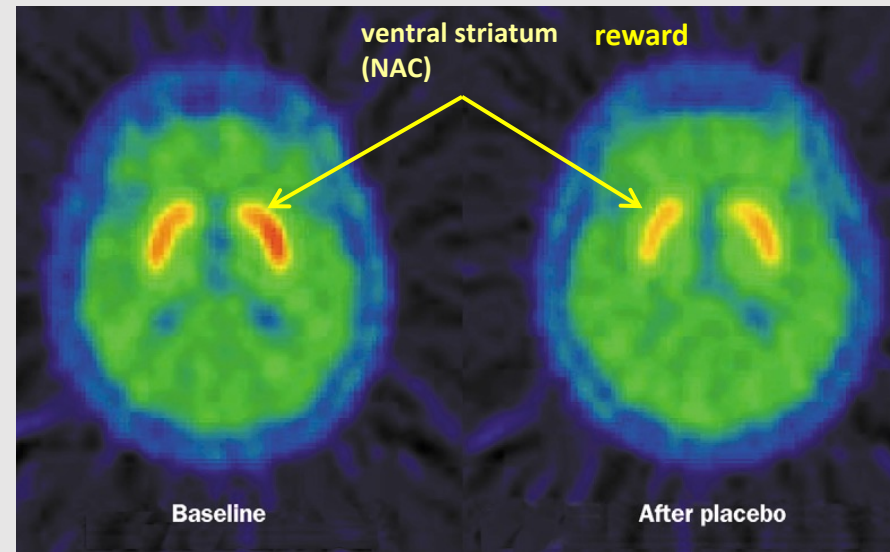
# Placebo responders show activation of Opioid and Dopaminergic signaling



Proportional to anticipated and perceived placebo analgesia



Zubieta & Stohler Ann NY Acad Sci 2009



De la Fuente-Fernandez et al., Behavioral Brain Research 2002

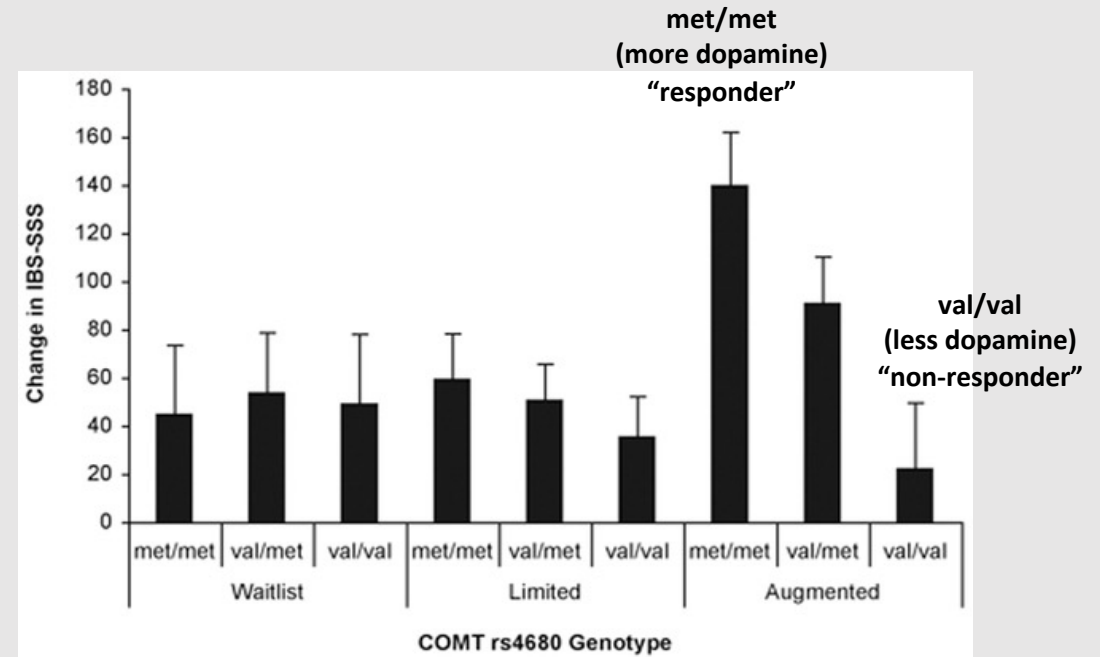
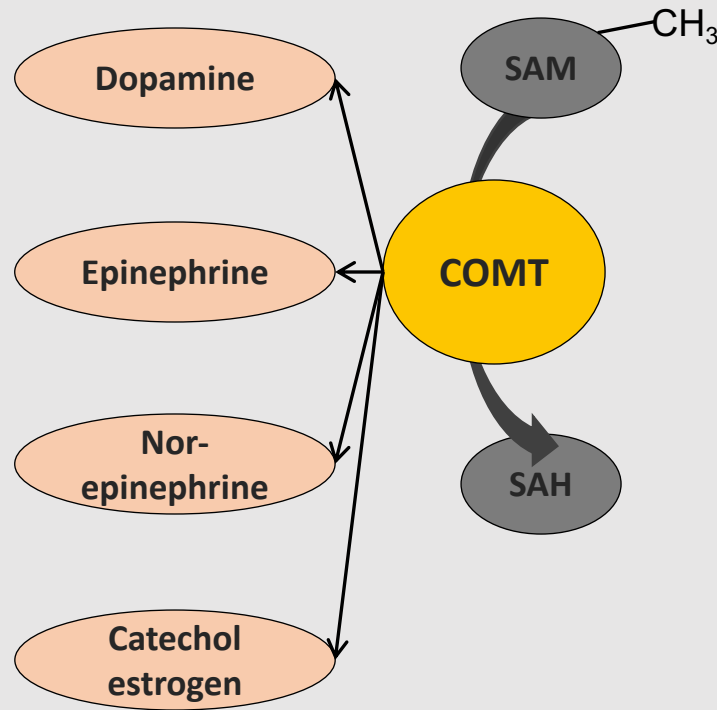


# Catechol-O-methyltransferase (*COMT*) associated with placebo response in IBS

OPEN ACCESS Freely available online

PLOS ONE

## Catechol-O-Methyltransferase val158met Polymorphism Predicts Placebo Effect in Irritable Bowel Syndrome

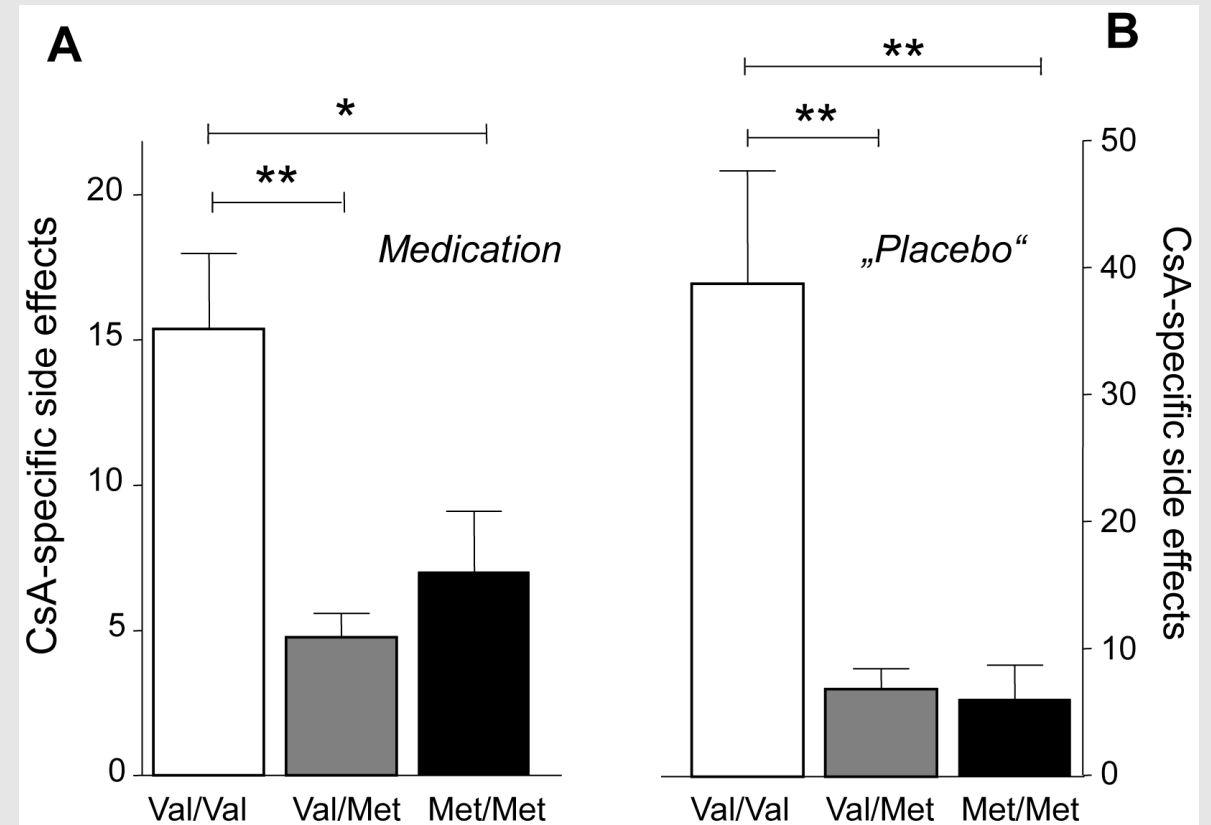
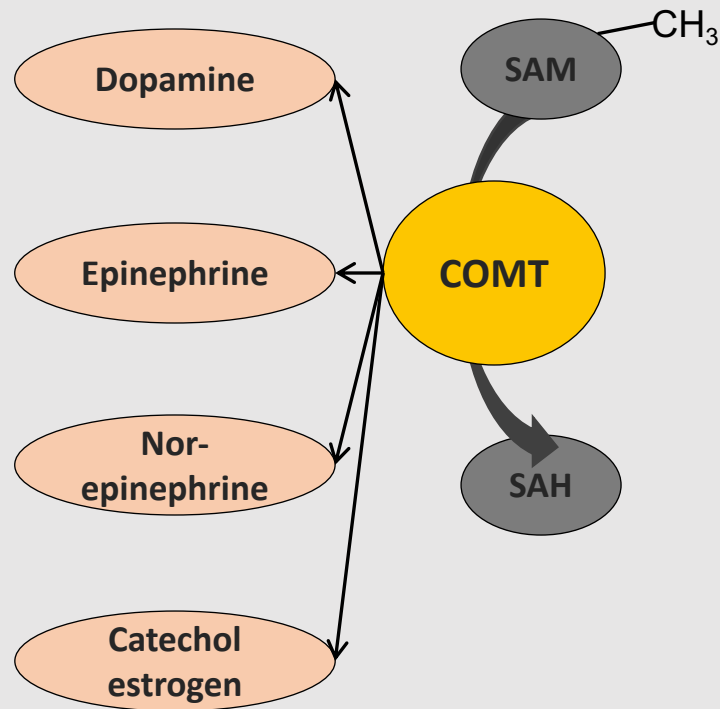


COMT genotype ( $\beta = 0.19$ ;  $p = .02$ )

COMT genotype x treatment arm ( $\beta = 0.17$ ;  $p = .035$ )  
(N=104)

Hall et al., *PLoS ONE*. 2012

# COMT also associated with side- or nocebo effects metabolizes

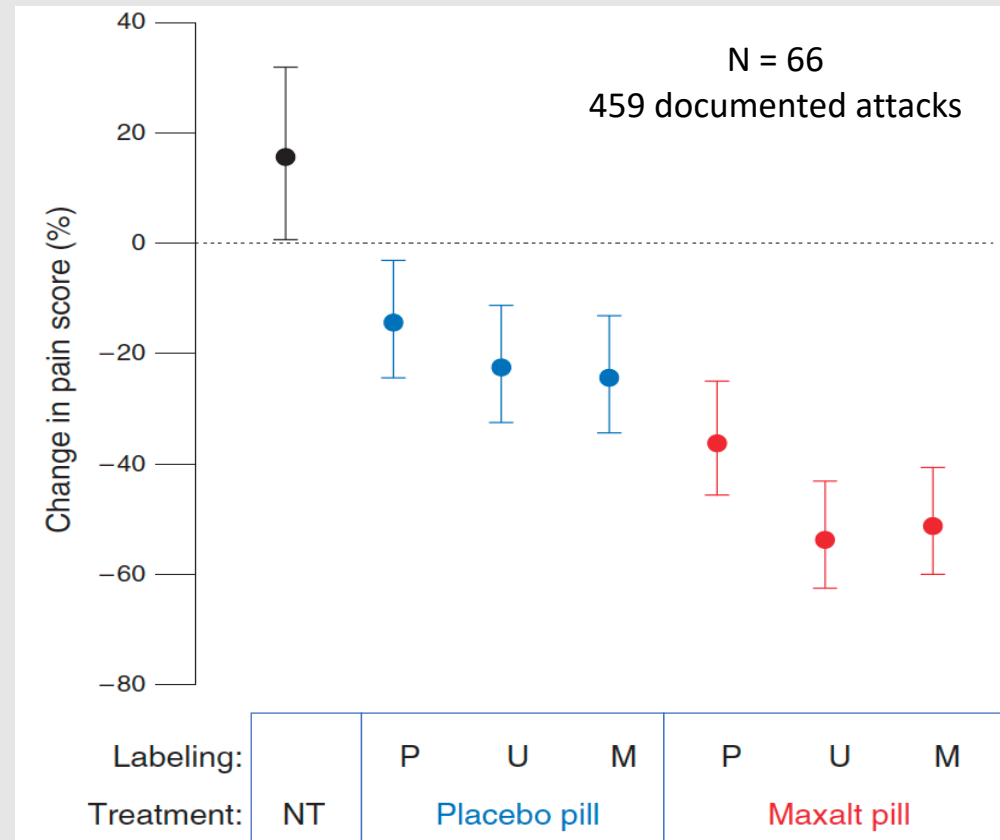


Wendt et al., *PLoS ONE*. 2014



## MIGRAINE

# Altered Placebo and Drug Labeling Changes the Outcome of Episodic Migraine Attacks



No difference between placebo labeled as Maxalt and Maxalt labeled placebo

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

Kam-Hansen et al., *Science Transl. Med.* 2014

# Nocebo Effects in Medicine and Popular Culture

Verbal  
suggestions

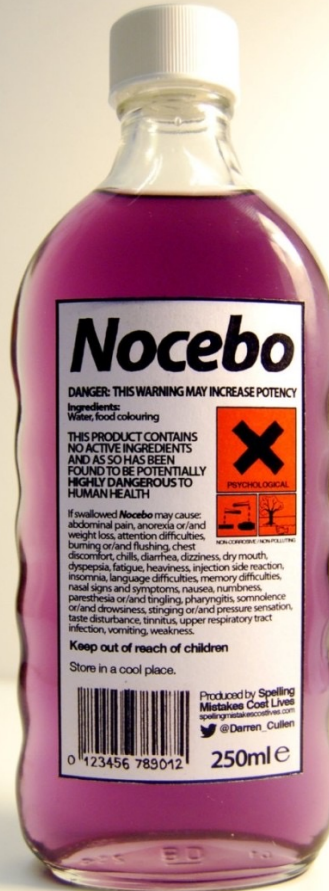
Context factors

Expectation

Learning and  
Memory

Personality

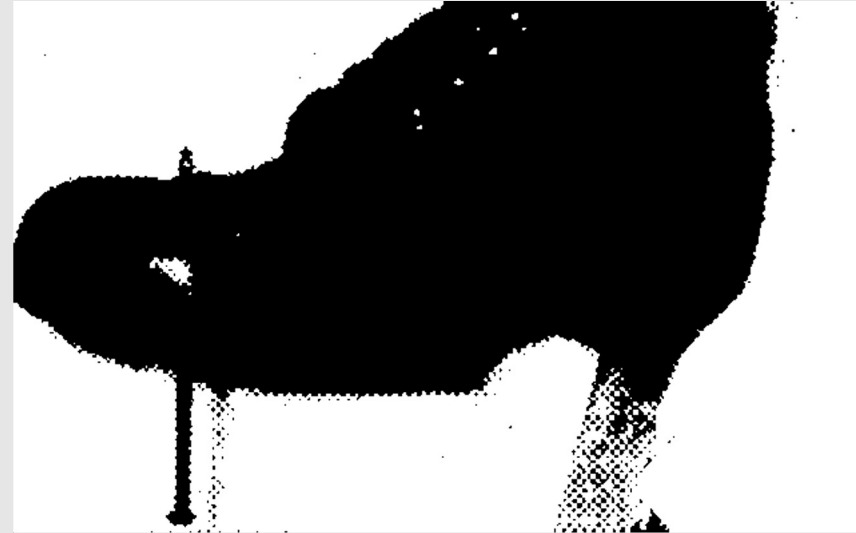
Genetic  
makeup





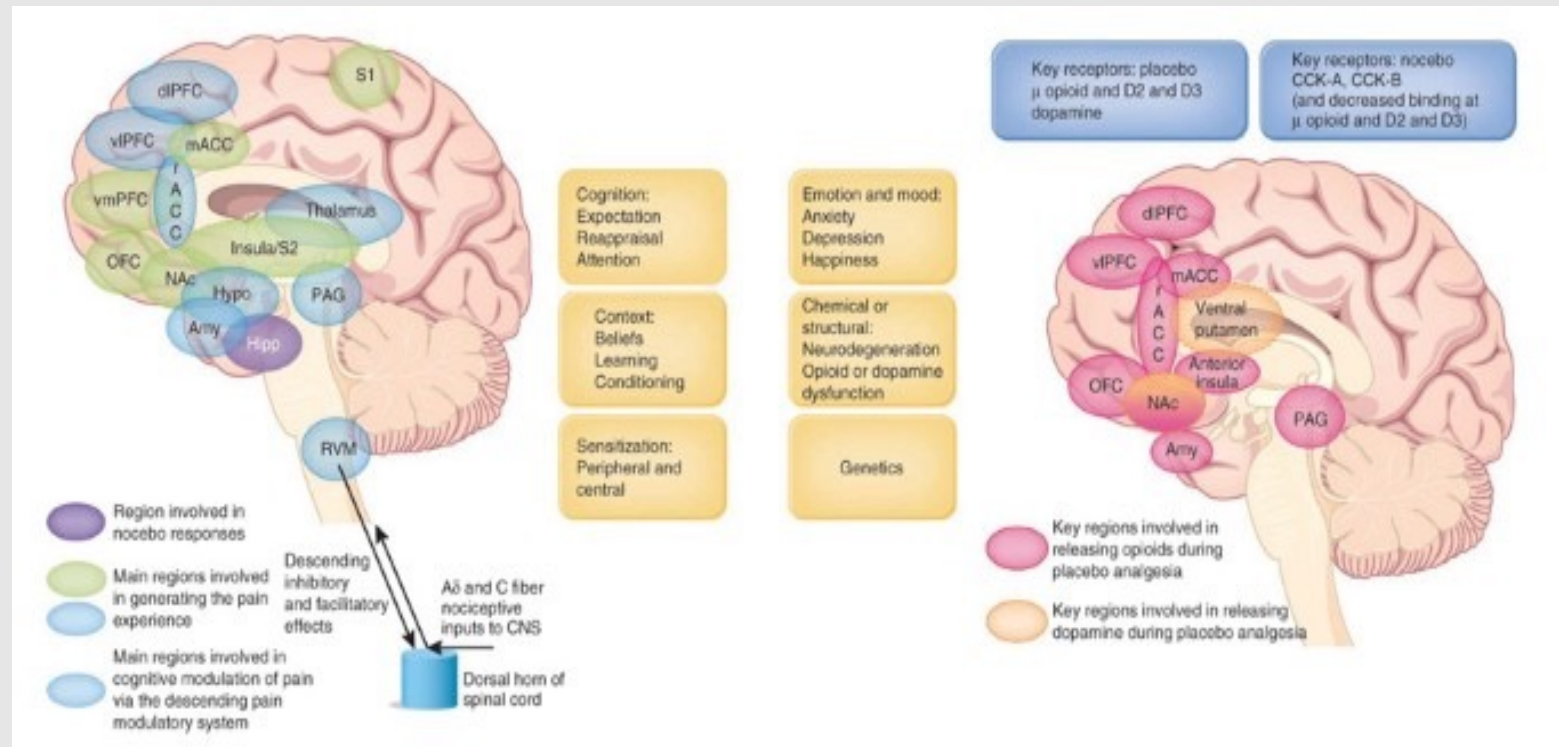
# Expectation and Nocebo Effects

Prank gone awry, Hamburg, 2014



Boot and nail, *Minerva* 1995

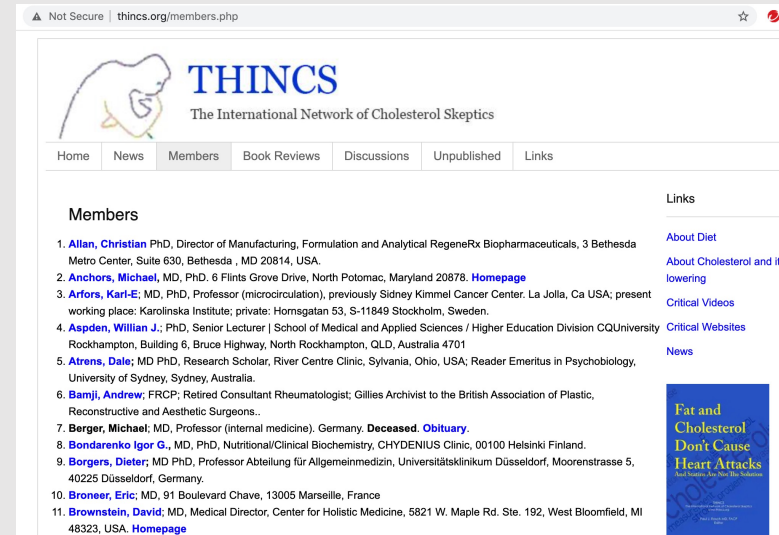
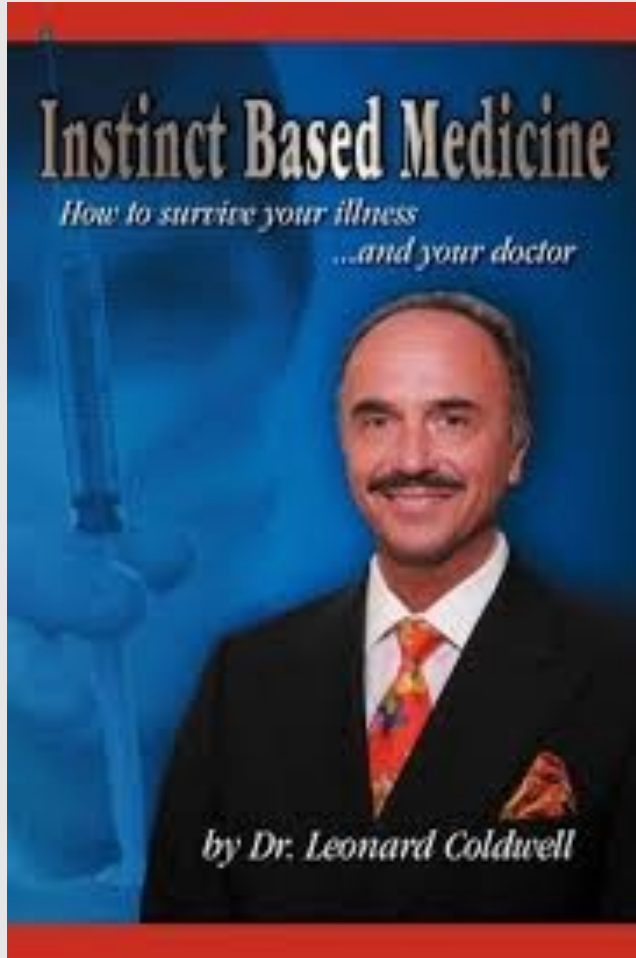
# Nocebo Effects



Getting the pain you expect: mechanisms of placebo, nocebo and reappraisal effects in humans  
[Irene Tracey](#) *Nature Medicine* volume 16, pages1277–1283 (2010)



# Statin denialism

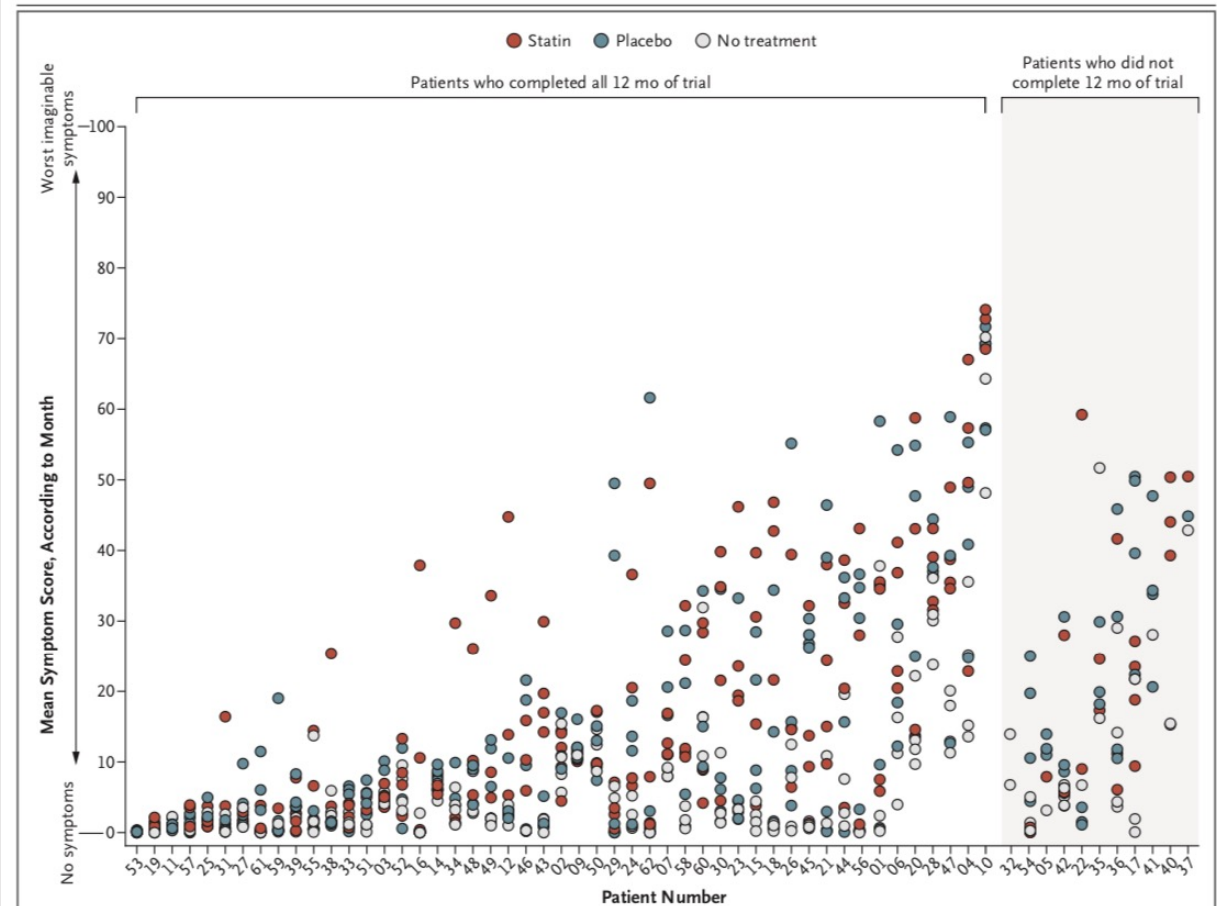


- “It’s mass murder. It always leads to hardening of the liver, it cuts off at least twenty years of your life span.”
- “Your brain is made from cholesterol. Statin is a cholesterol-lowering drug. So, if you want to have a brain that’s the size of a marble, keep on taking them. You do not die of too 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

### N-of-1 Trial of a Statin, Placebo, or No Treatment to Assess Side Effects



**Figure 1. Symptom Scores for All the Trial Patients.**

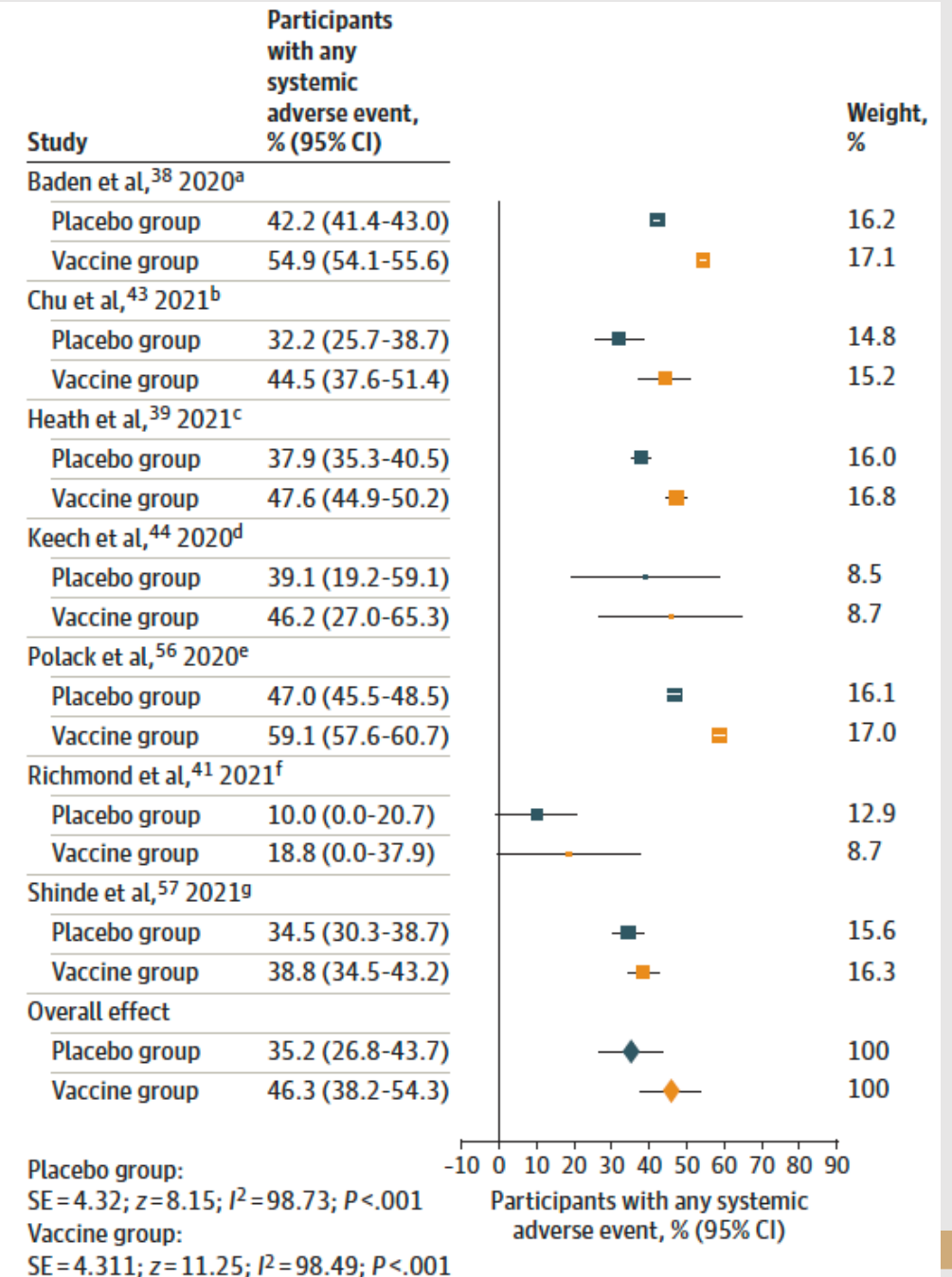
Shown are mean symptom scores for the 49 patients who completed all 12 months of the trial (left) and those for the 11 patients who did not complete all 12 months (right). Each circle represents a single month for each patient. Symptoms were reported daily, and the mean symptom score was calculated for the month regardless of whether the patient discontinued the assigned bottle at any time during that month.

Wood, et al. *NEMJ*, 2020



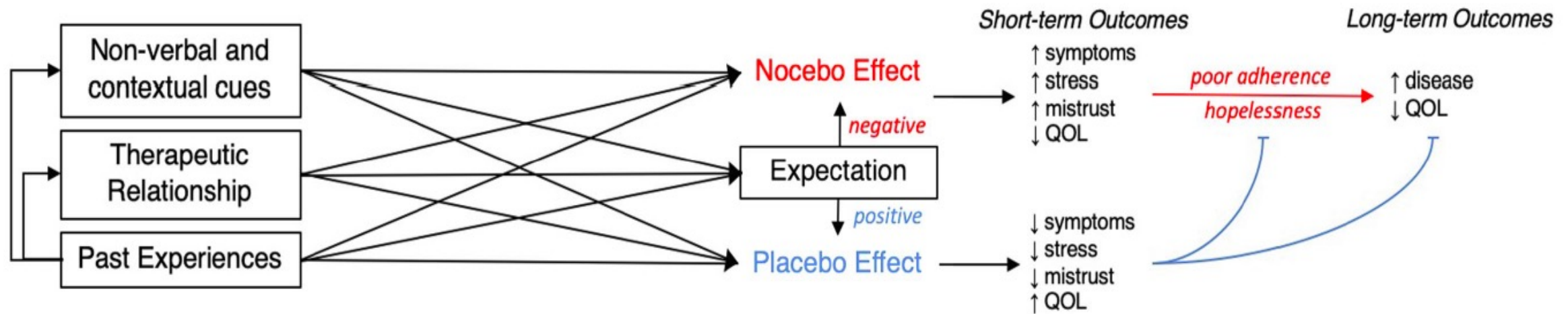
# Nocebos in clinical trials

- Concern about adverse events can lead to vaccine hesitancy
- AE reports for 45,380 trial participants
- Systemic AEs or placebo 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<sup>1\*</sup>, Nevada Cox<sup>2</sup>, Shelley R. Adler<sup>3</sup>, Kathryn T. Hall<sup>1,4</sup> and Valerie E. Stone<sup>1,4\*</sup>



# 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.



### LATEST IN NEWS

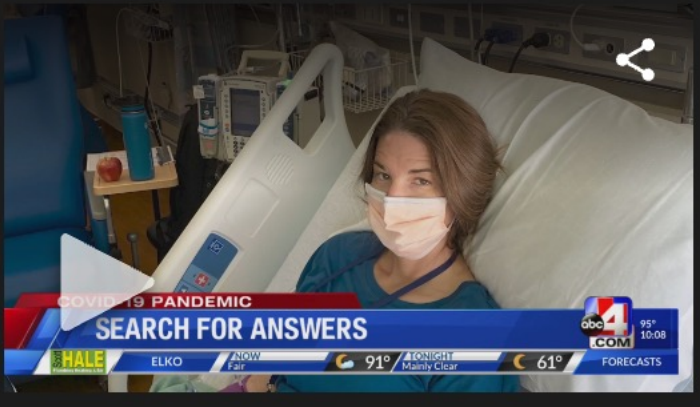
- Virginia General Assembly abandons Commanders stadium bill
- US Military: 5 Marines killed in aircraft crash in desert
- Capitol riot hearings opening, focused on extremists, Trump



### LOCAL NEWS

## Woman suffers 'life-altering injuries' after COVID vaccine, teams up with Utah senator to demand answers

by: Jillian Smukler  
Posted: Jul 9, 2021 / 10:22 PM MDT  
Updated: Jul 13, 2021 / 08:47 AM MDT





# The Infodemic echo chamber

Expectation drives our experience

The echo chamber promotes confirmation bias

Scientists don't see or believe in God

Above all I am committed to hearing what God says

Not just following rules following a person

I research things pretty thoroughly

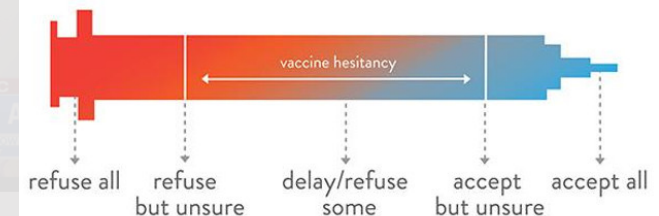
Media tries to discount us

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

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



Continuum of Vaccine Acceptance



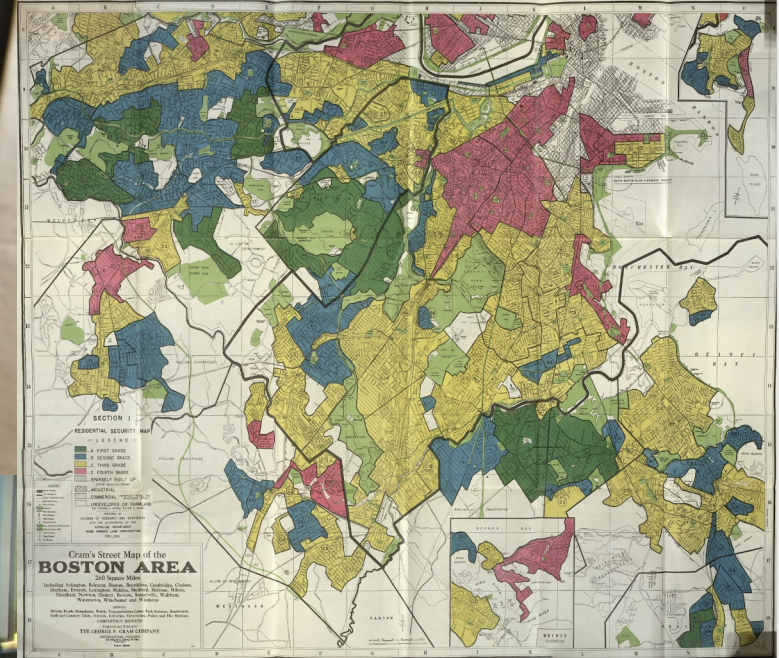






# COVID-19 deepened health and educational inequities

- 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

## New CDC Mask Guidance Marks Major Shift for Schools

New CDC guidance issued Friday is recommending that schools use the same criteria to govern mask requirements as the general community – likely leading to the lifting of mandates.

By [Lauren Camera](#) | Feb. 25, 2022

## The New York Times

### *Why Liberal Suburbs Face a New Round of School Mask Battles*

With the end of many statewide mask mandates, it's up to local districts whether they will keep the requirement. Communities anticipate political and emotional fights ahead.

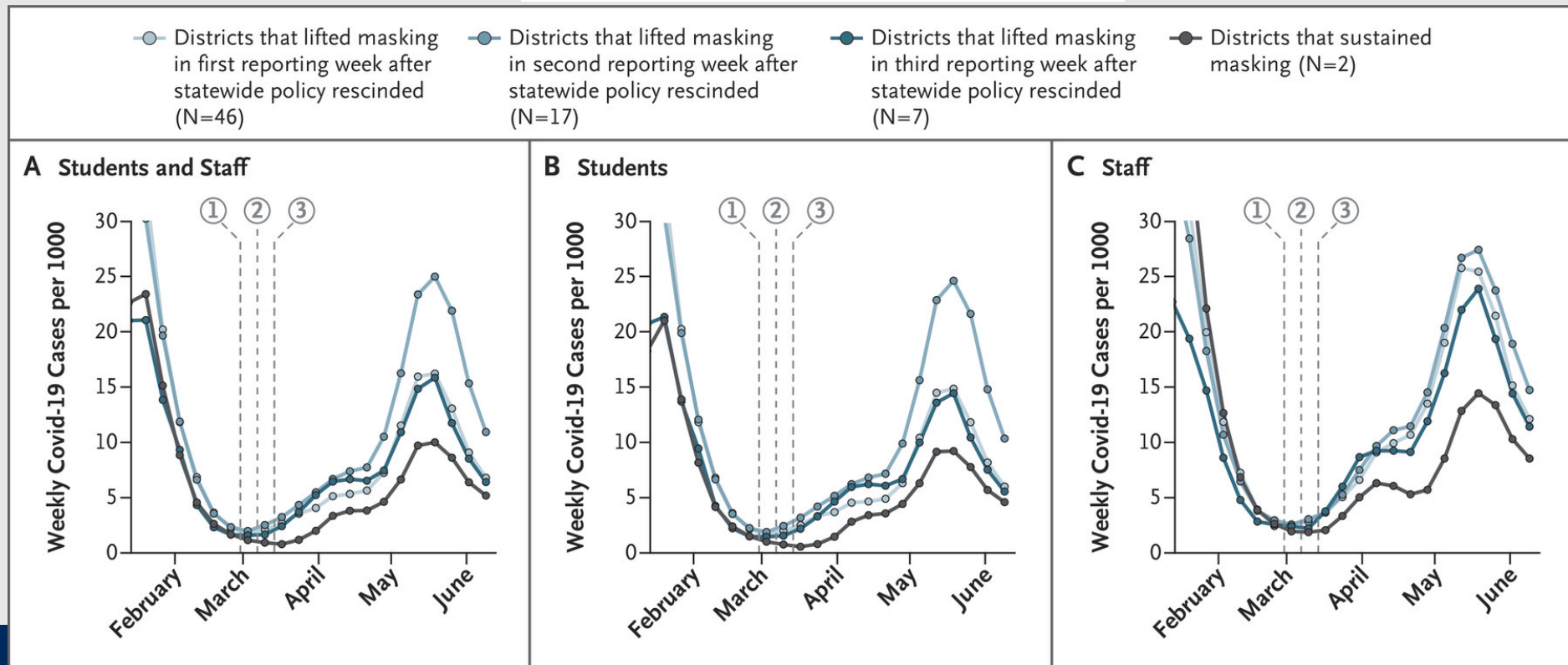


Suzanne Szwarczewicz, an English language learning teacher in Newton, Mass., said masks had presented challenges for young native speakers of other languages. Tony Luong for The New York Times

ORIGINAL ARTICLE

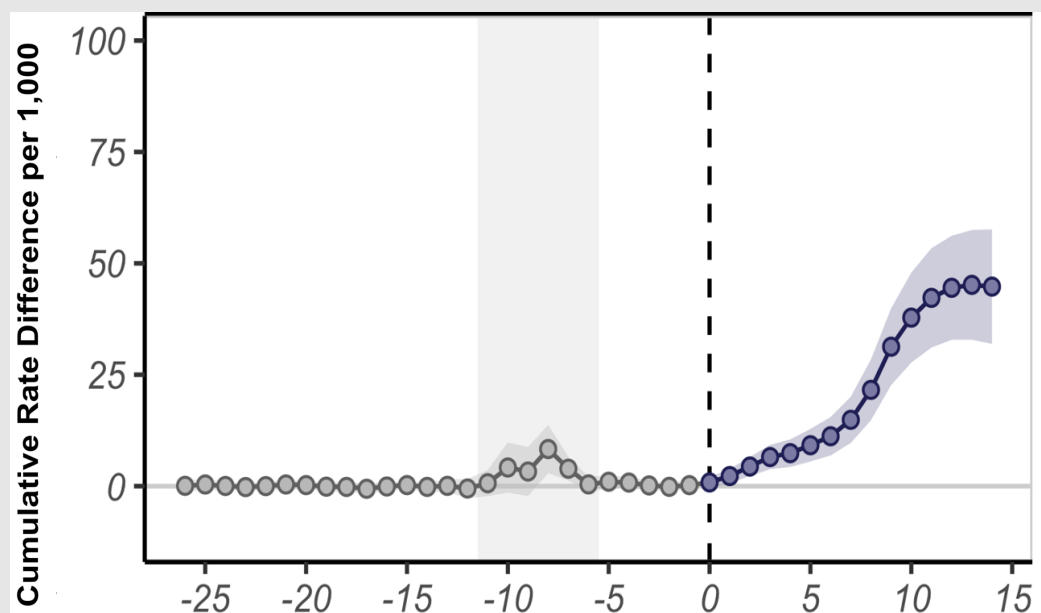
# Lifting Universal Masking in Schools — Covid-19 Incidence among Students and Staff

Tori L. Cowger, Ph.D., M.P.H., Eleanor J. Murray, Sc.D., M.P.H.,  
Jaylen Clarke, M.Sc., Mary T. Bassett, M.D., M.P.H.,  
Bisola O. Ojikutu, M.D., M.P.H., Sarimer M. Sánchez, M.D., M.P.H.,  
Natalia Linos, Sc.D., and Kathryn T. Hall, Ph.D., M.P.H.



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


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




Estimates of average effect of lifting mask requirements			
Group	Rate Diff. (95% CI) <sup>b</sup>	Attributable cases (95% CI) <sup>c</sup>	Attributable Fraction (95% CI) <sup>d</sup>
Overall (Staff & Students)	44.9 (32.6, 57.1)	11,901 (8,651, 15,151)	33.4% (24.3%, 42.5%)
Students	39.9 (24.3, 55.4)	9,168 (5,594, 12,743)	32.1% (19.6%, 44.7%)
Staff	81.7 (59.3, 104.1)	2,882 (2,092, 3,673)	40.4% (29.4%, 51.5%)



All Verified Mentions

Jaguar  liked a Tweet you were mentioned in

 **Alexis K** @AlexisKat6 · 3d  
Replying to [@JeromeAdamsMD](#)  
This “study” 1) included “control” districts that didn’t have identical mask policies up to 2/28

**doc. who** and 4 others Retweeted  
Tweet you were mentioned in  
Evidence for benefit of masking in

nejm.org/doi/full/10.10...  
pic.twitter.com/OUnyZKafvY

**BMDKCC** @mr94587 · 4d  
Replying to @asosin @KTHallPhDMPH

**Michael L. Barnett**  followed you

Followed by Dr. Michelle E. Morse,  
Camille E. Powe MD, Julia Loewent  
MD, and 38 others



# Placebos and Nocebos in 2023 ...



# Open Label placebos

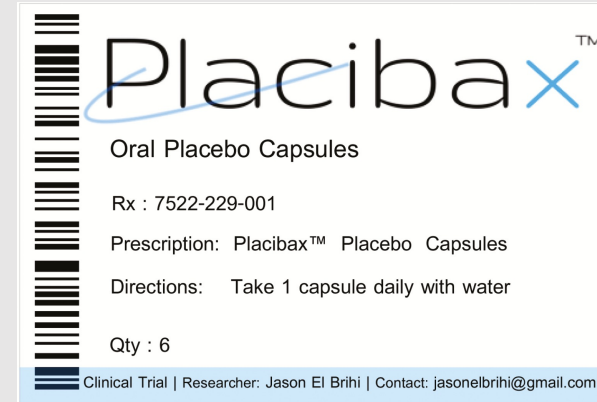


[https://www.tiktok.com/@americanbaron/video/7164929336582229294? r=1& t=8XHiE17oE2w&is from webapp=v1&item\\_id=7164929336582229294](https://www.tiktok.com/@americanbaron/video/7164929336582229294?r=1&t=8XHiE17oE2w&is_from_webapp=v1&item_id=7164929336582229294)



# Open-Label Placebos

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

Axovant Neuro Drug Stumbles and Falls  
in Phase 2, Shares Drop 50%



Business

**Circassia shares tank as cat allergy drug  
fails to beat placebo effect**

Strong placebo response thwarts painkiller trials

Potential pain treatments are struggling to prove their worth over a rising placebo effect  
seen in US trials.

**Vectura takes £40 million  
hit as asthma drug fails  
trial**



**Galapagos falls after rheumatoid  
arthritis candidate failed to show  
benefit in mid-stage trial**

Jul. 15, 2021 8:40 AM ET | Galapagos NV (GLPG) | GLPG | By: Dulan Lokuwithana, SA News  
Editor | 10 Comments



Marinus Pharma's trial of treatment for drug-  
resistant epilepsy failed to meet goals



**Eleven Biotherapeutics (EBIO) Stock Plunges on Yet  
Another Failed Clinical Trial**

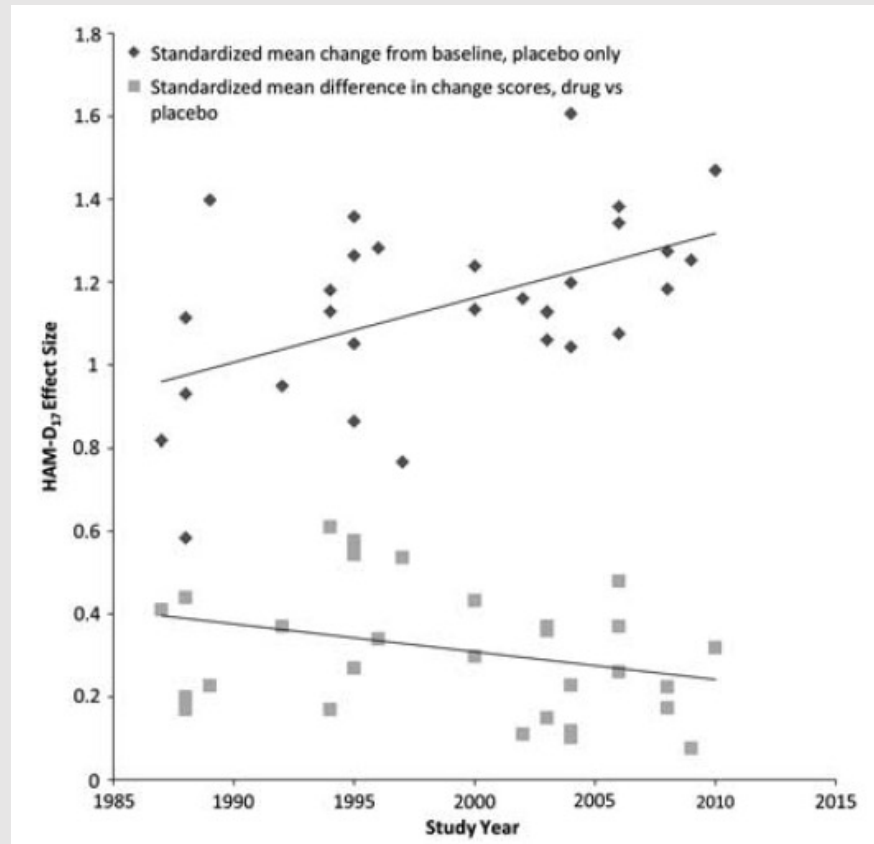


Biotech

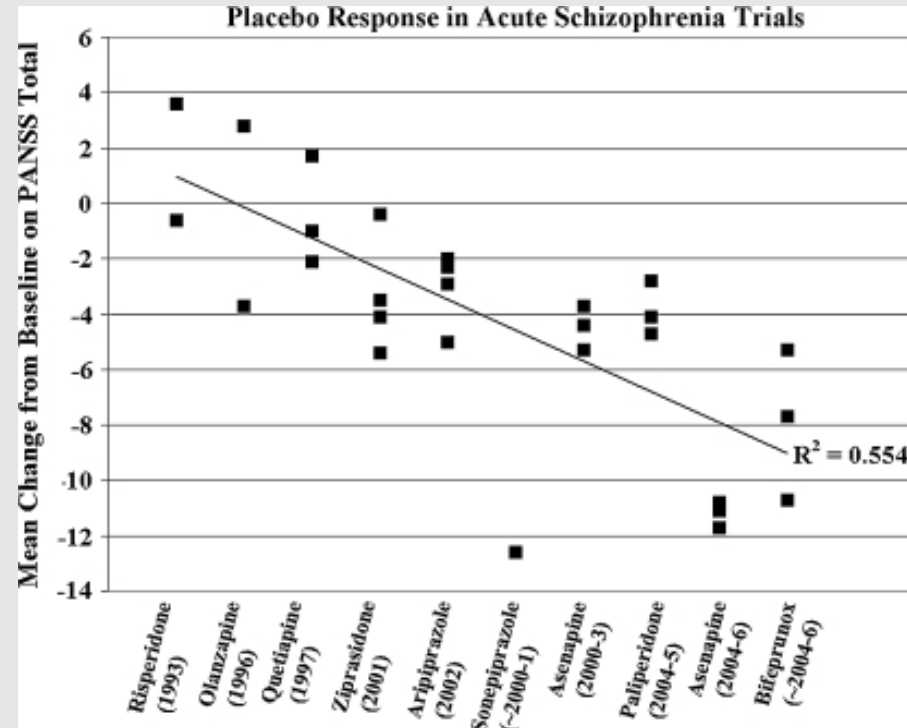
**Midphase failure of Novartis' NASH drug  
crushes Conatus**



# Increasing placebo response in depression and schizophrenia



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



Kemp et al., *Schizophr. Bull* (2010) 36, 504-509



# Digiceuticals and Virtual Reality – what will be the placebo?

therapy placebo-controlled  
meta-analysis smartphone-based  
treatment efficacy first  
apps randomized recommended  
setting standard symptoms  
head to head control clinical  
effect active reliable develop Kaia  
interventions example represent trial studies Akili groups  
usual care course video depressive  
Digital placebo  
group platform CBT app two reduce App-based wait-list  
credible patients consider digital trials  
Sleepio game smartphone Video-game health  
placebo back pain virtual online examples therapeutic  
design mental participants experimental  
behavioural combined development  
solution digital therapeutics  
controlled DTx



# 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.**





# Acknowledgements

## Program in Placebo Studies

Ted Kaptchuk  
Anthony Lembo  
Roger Davis  
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## Boston Children's

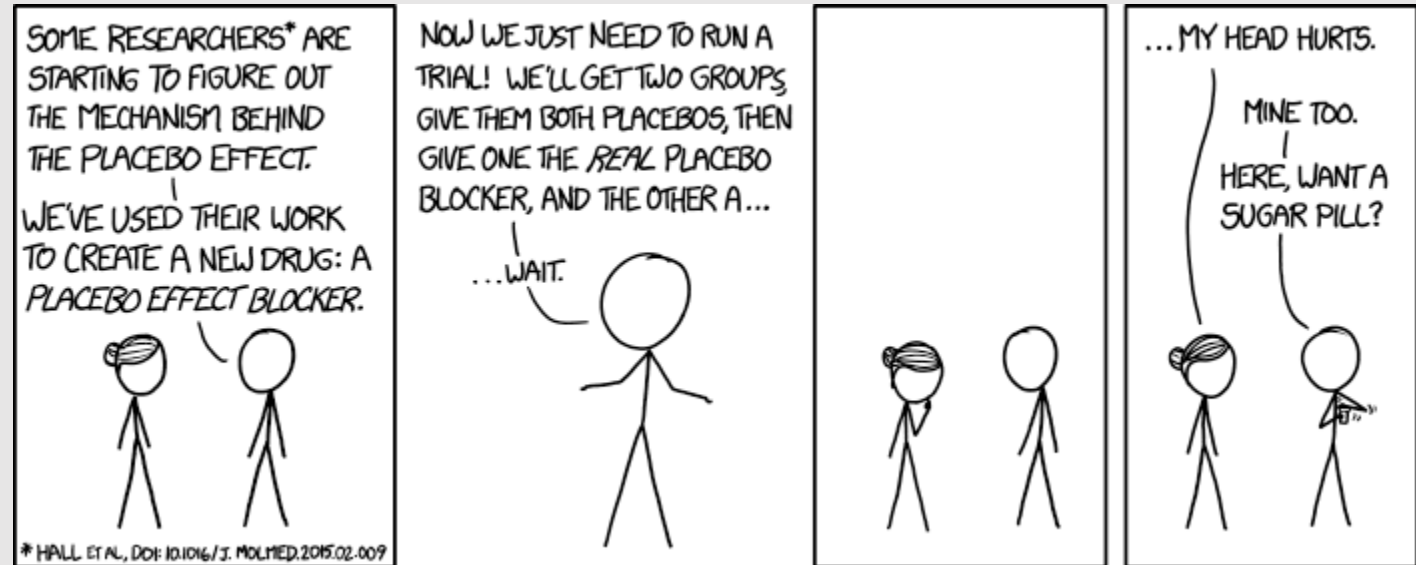
Jocelyn Silvester  
Meena Rao

## Placebome

Rui-sheng Wang  
Joseph Loscalzo

## Women's Health Study/Brigham and Women's Hospital

Daniel Chasman  
Paul Ridker  
Julie Buring  
JoAnn Manson  
Howard D. Sesso  
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**Roy Wada** BPHC

**Eleanor Murray** BU School of Public Health and BPHC

**Puneet Sharma** BPHC

**Melissa Hector** Health Services and BPHC

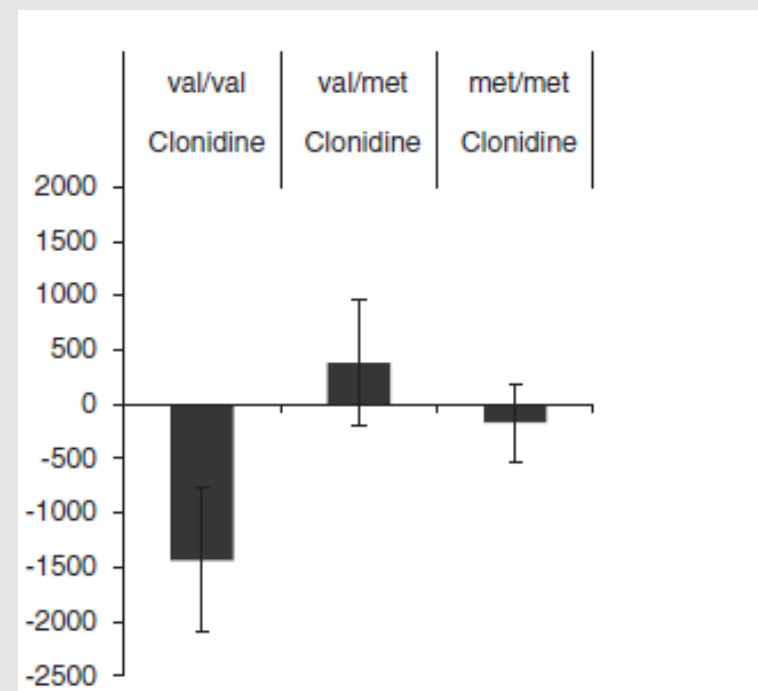
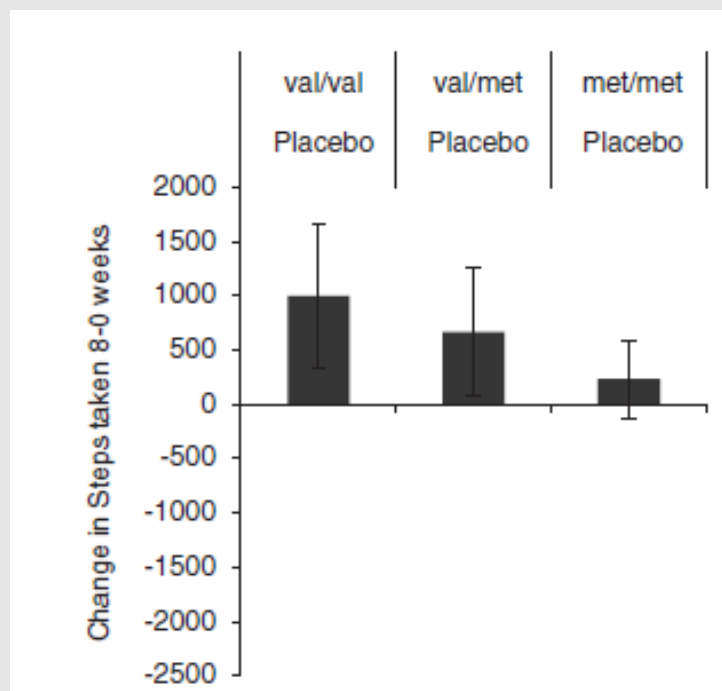
## ORIGINAL ARTICLE

# Genetic variation in catechol-*O*-methyltransferase modifies effects of clonidine treatment in chronic fatigue syndrome

KT Hall<sup>1,2,14</sup>, J Kossowsky<sup>2,3,4,14</sup>, TF Oberlander<sup>5</sup>, TJ Kaptchuk<sup>2,6,7</sup>, JP Saul<sup>8</sup>, VB Wyller<sup>9</sup>, E Fagermoen<sup>10</sup>, D Sulheim<sup>11</sup>, J Gjerstad<sup>12</sup>, A Winger<sup>13</sup> and KJ Mukamal<sup>2,6</sup>

val/val patients took 2400 fewer steps on clonidine than placebo

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



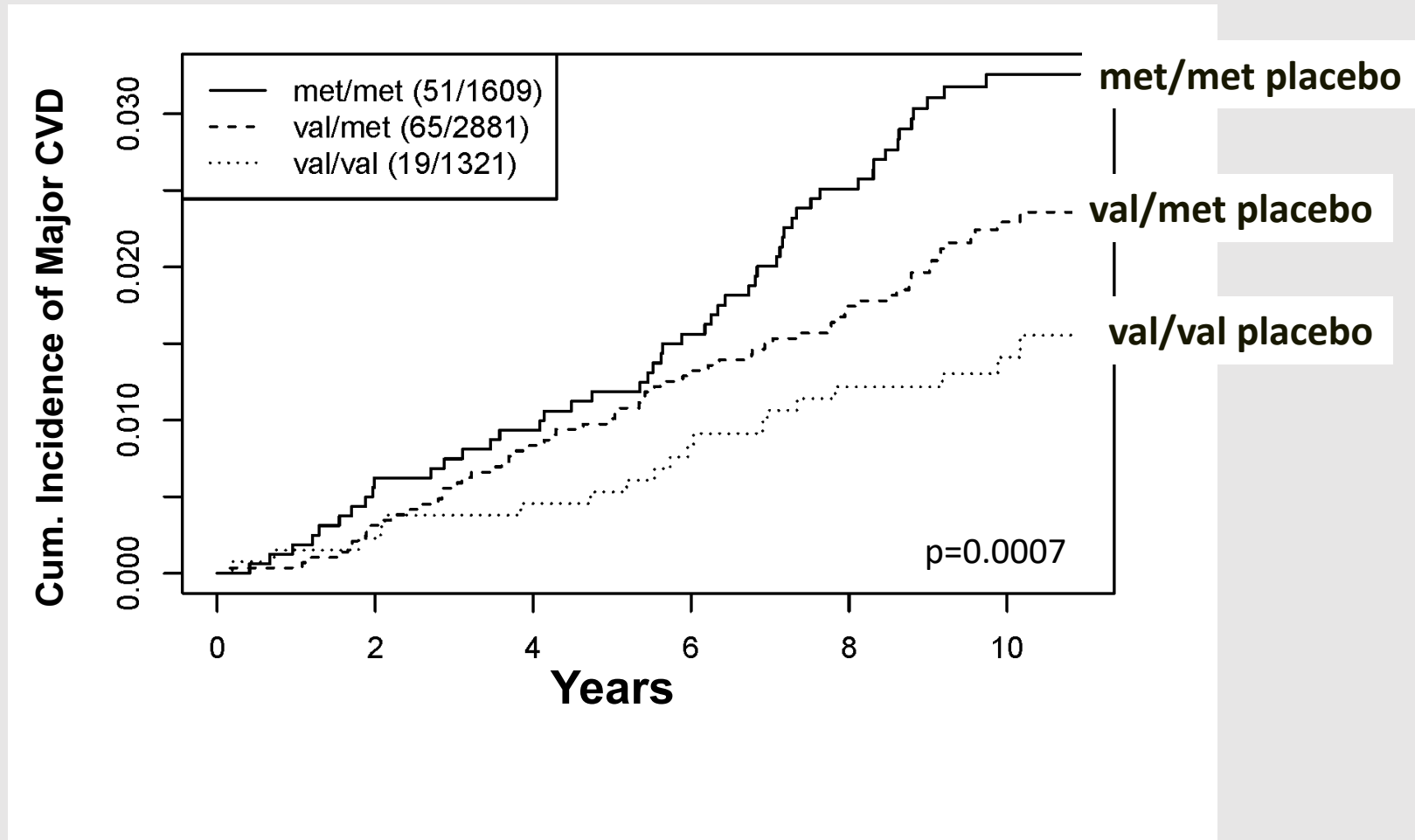
The Pharmacogenomics Journal (2016) 00, 1–7

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# COMT associated with outcomes in the placebo arm



# COMT modified outcomes in both placebo and drug treatment arm

