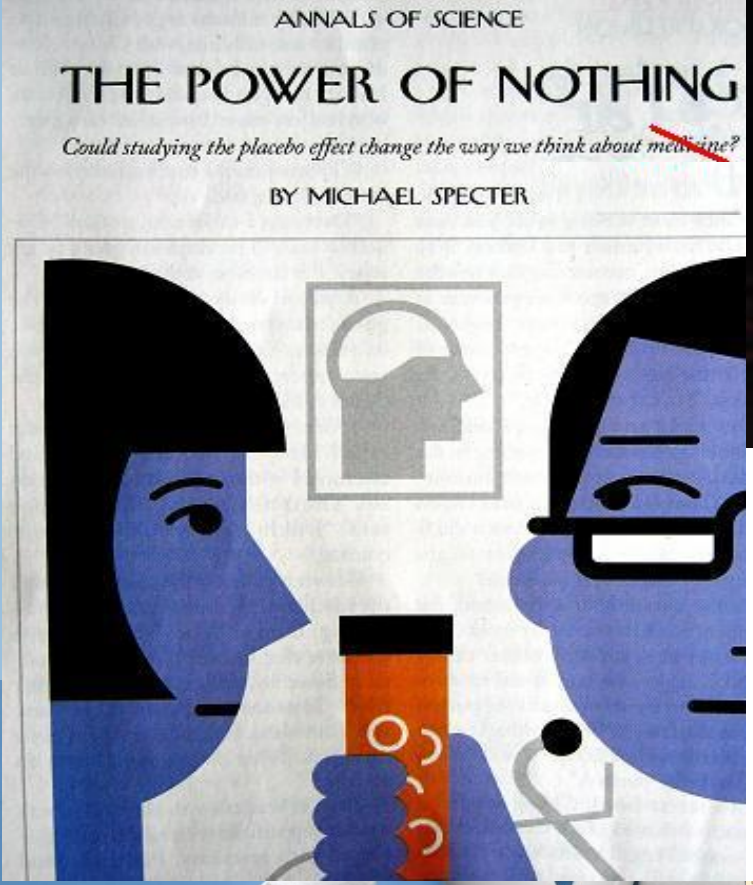
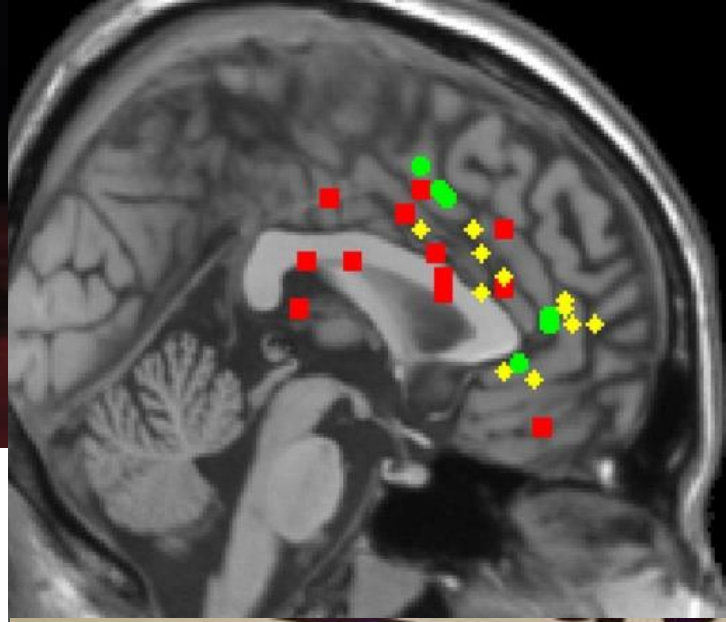


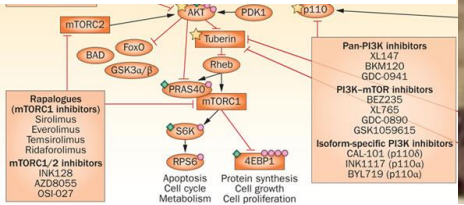


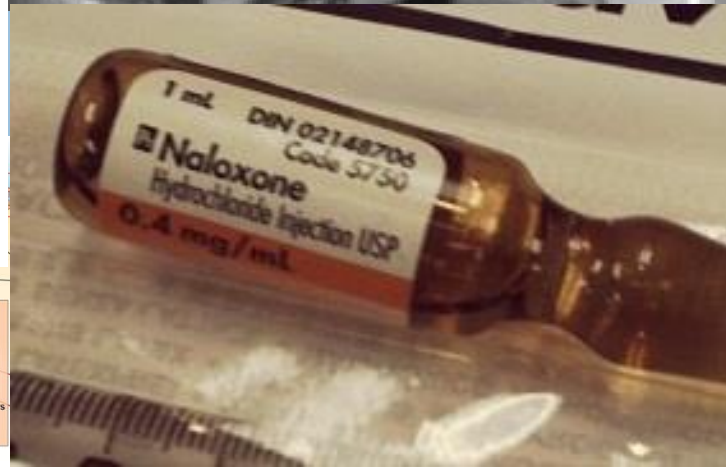
Power of the Placebo

Kathryn T. Hall, PhD, MPH

Senior Vice President, Research

New York Academy of Medicine





No disclosures

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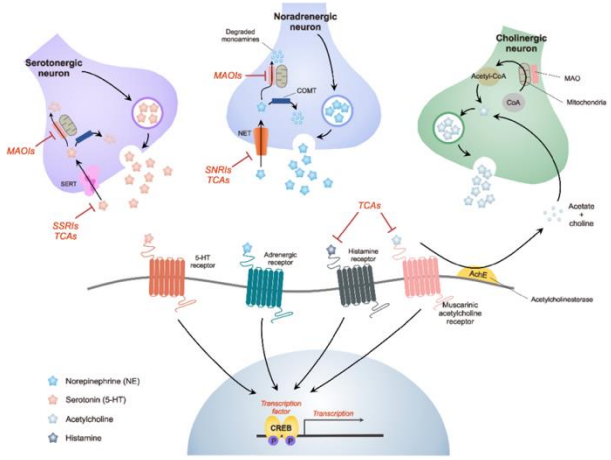
Better Health for Life



FDA Approved	Novel
• SSRIs (Selective Serotonin Reuptake Inhibitors) • SNRIs (Serotonin-Norepinephrine Reuptake Inhibitors) • TCAs (Tricyclic Antidepressants) • MAOIs (Monoamine Oxidase Inhibitors) • Antagonism at Presynaptic Receptors • Antagonism at Postsynaptic Receptors • NMDA Receptor Antagonism • BDNF Induction	• Kappa opioid receptor (KOR) antagonist • Targets synaptic function via mTORC1 pathway • Enhances neural plasticity in the hippocampus • Inhibits 11β-HSD1 enzyme, reducing cortisol levels • NMDA receptor channel blocker • GABA-A receptor positive allosteric modulator • NMDA receptor channel blocker

The "Placebo Problem" is widespread

News | Article | October 23, 2024

Alto Neuroscience's ALTO-100 Fails to Beat Placebo in Improving Depressive Symptoms

Author(s): Chelsie Derman

BIOTECH

STAT+

In stunning outcome, Amylyx's ALS drug fails large clinical trial

By Adam Feuerstein March 8, 2024

Reprints

Johnson & Johnson Discontinues Pivotal Depression Drug Trial Due to Lack of Efficacy

J&J said aticaprant showed insufficient efficacy in a Phase 3 test in major depressive disorder. The disappointing result follows the Phase 3 failure of a Neumora Therapeutics drug that addresses the same central nervous system target.

By Frank Vinluan on March 07, 2025 12:43 pm Share

ALS Therapy Trial Fails to Benefit Patients Over Placebo

By Jordana Jampel - Last Updated: April 8, 2025

BIOTECH

Neumora's dig into phase 3 depression data disappoints analysts

By Nick Paul Taylor · Jan 15, 2025 9:35am

News › Drug Development

Lexicon to Advance Non-Opioid Painkiller Despite Mid-Stage Trial Failure

March 3, 2025 | 2 min read | Dan Samorodnitsky

Vertex Pain Drug Doesn't Beat Placebo. The Company Says It Still Sees Promise.

By Josh Nathan-Kazis Follow

Dec 19, 2024 10:43 am EST

AbbVie's $9B bet collapses as closely watched schizophrenia drug fails studies

Emraclidine, a promising psychiatric medicine AbbVie acquired by buying Cerevel Therapeutics last year, didn't outperform placebo in two Phase 2 trial tests.

Published Nov. 11, 2024

Cassava ends simufilam Alzheimer's programme after second Phase III failure

While investigations into the drug are stopping in Alzheimer's disease, the therapy is now being evaluated in TSC-related epilepsy.

Abigail Beaney | March 26, 2025

Approved Sickle Cell Drug Fails to Beat Placebo in Trial

— Rates of vaso-occlusive crises similar with two doses of crizanlizumab

by Mike Bassett, Staff Writer, MedPage Today

March 14, 2025 · 3 min read

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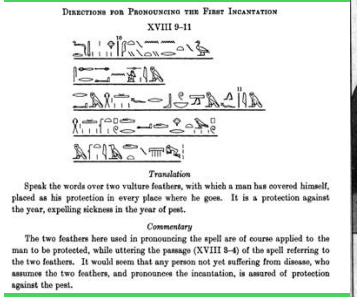
got placebo?

From salve...



DIRECTIONS FOR PRONOUNCING THE FIRST INCANTATION

XVIII 9-11

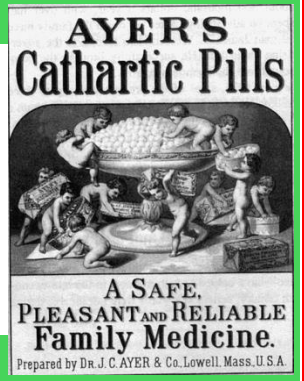
Translation

Speak the words over two vulture feathers, with which a man has covered himself, placed as his protection in every place where he goes. It is a protection against the year, expelling sickness in the year of pest.

Commentary

The two feathers here used in pronouncing the spell are of course applied to the man to be protected, while uttering the passage (XVIII 8-4) of the spell referring to the two feathers. It would seem that any person not yet suffering from disease, who assumes the two feathers, and pronounces the incantation, is assured of protection against the pest.

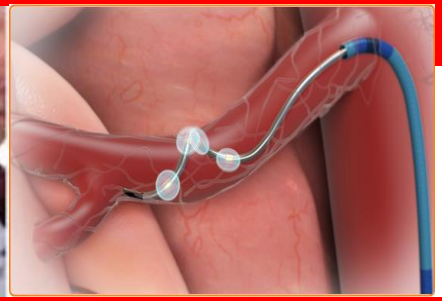
Incantations and Rituals



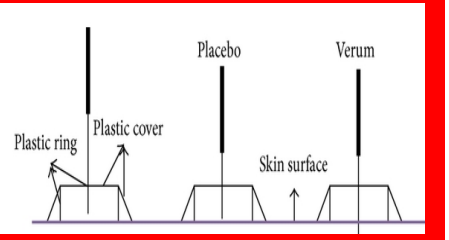
Nostrums and Patent Medicine

...to control

Dummy pills



Sham Surgery



Sham Acupuncture

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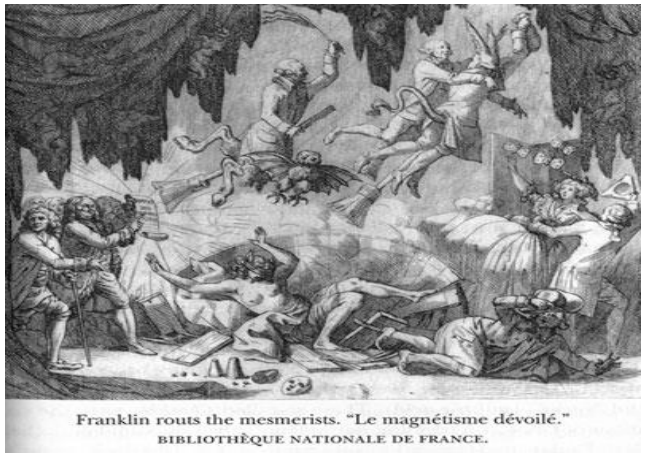
Debunking Mesmerism - An early clinical trial

Not that magnetism didn't work, but that 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

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Haygarth vs. Perkin's Tractors – Franklin's Legacy

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

THE

INFLUENCE

OF

METALLIC TRACTORS

ON THE

HUMAN BODY,

In removing various painful Inflammatory Diseases, such as

Rheumatism, Pleurisy, some Gouty Affections, &c. &c.

LATELY DISCOVERED BY

Dr. PERKINS, of NORTH AMERICA;

And demonstrated in a Series of

EXPERIMENTS AND OBSERVATIONS,

By Professors Meigs, Woodward, Rogers, &c. &c.

By which the Importance of the Discovery

Is fully ascertained, and a new Field of Enquiry opened in the Modern Science of

GALVANISM,

OR,

ANIMAL ELECTRICITY.

By BENJAMIN DOUGLAS PERKINS, A.M.

SON TO THE DISCOVERER.

John Haygarth (1740-1827)

METALLIC-TRACTORS.

OF THE

IMAGINATION,

AS A CAUSE AND AS A CURE OF

DISORDERS OF THE BODY;

EXEMPLIFIED BY

FICTITIOUS TRACTORS,

AND

EPIDEMICAL CONVULSIONS.

"DECIPIMUR SPECIE." HOR.

Read to the Literary and Philosophical Society of Bath.

BY

JOHN HAYGARTH, M.D.

F.R.S. LOND. AND EDINB.

OF THE ROYAL MEDICAL SOCIETY AT EDINBURGH, AND OF THE AMERICAN ACADEMY OF ARTS AND SCIENCES.

BATH, PRINTED BY R. CRUTTWELL;

AND SOLD BY

CADELL AND DAVIES, STRAND, LONDON.

1800.

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Opioid antagonist, naloxone inhibits placebo analgesia

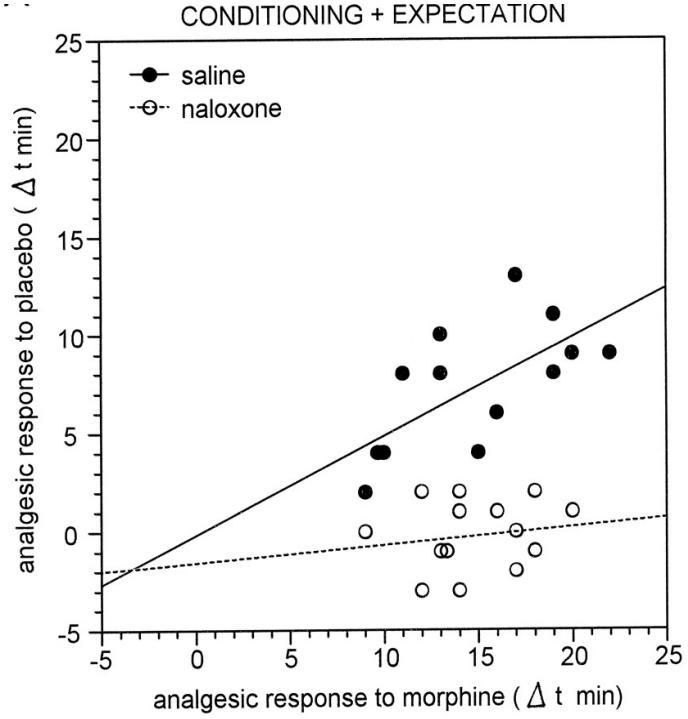
THE LANCET, SEPTEMBER 23, 1978

THE MECHANISM OF PLACEBO ANALGESIA

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

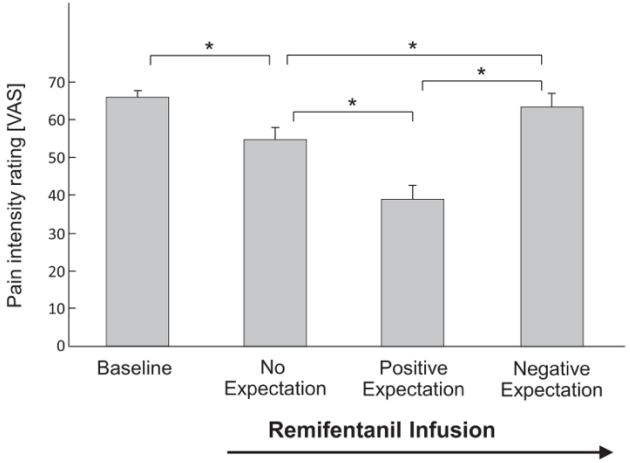
Departments of Neurology, Physiology, and Oral Surgery, University of California, San Francisco, California 24143, U.S.A.

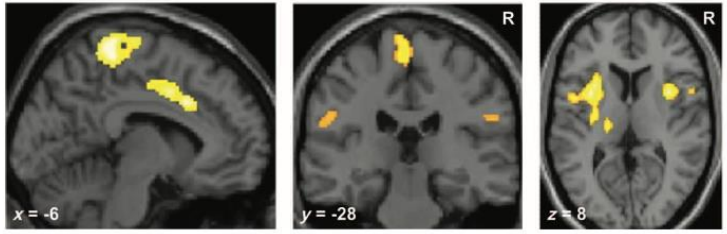
Summary The effect of naloxone on dental post-operative pain was studied to examine the hypothesis that endorphins mediate placebo analgesia. All patients had extraction of impacted mandibular third molars with diazepam, N_2O, and local block with mepivacaine. 3 h and 4 h after surgery naloxone or a placebo was given under randomised, double-blind conditions. Pain was evaluated on a visual analogue scale. Pa-



Amanzio and Benedetti, 1999. J. Neurosci.

The Brain on Placebos
Expectations are a key driver of placebo effects





Placebo 2.0: the impact of expectations on analgesic treatment outcome
Bingel, U. Pain *2020*

- Positive expectations doubled analgesic effect of remifentanil
- Negative expectations nullified its pain-relieving benefits
- Subjective effects linked to significant changes in brain activity in areas related to pain perception
- fMRI findings:
  - Altered processing of nociceptive input due to expectancy
  - Positive expectancy increased activity in cingulo-frontal and subcortical areas
  - Negative expectancy increased activity in the hippocampus and medial prefrontal cortex, linked to anxiety and pain exacerbation

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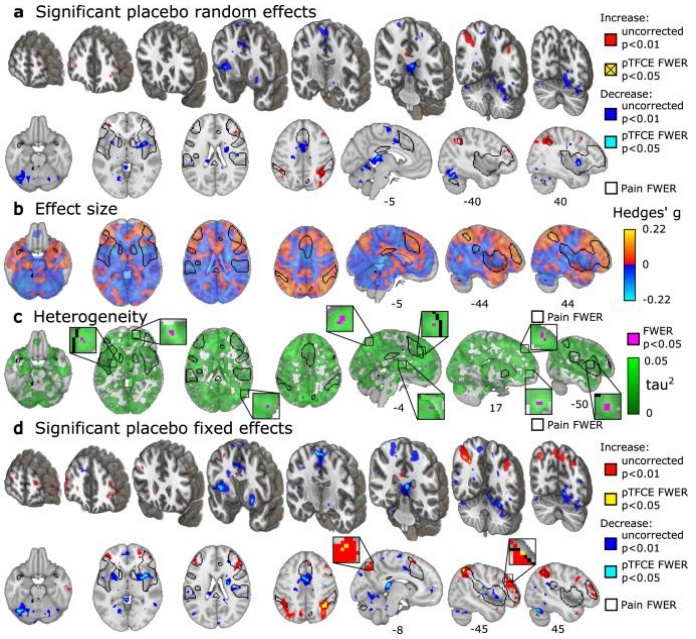
Meta-analysis of neural systems underlying placebo analgesia from individual participant fMRI data

- **Participants**: N=603 from 20 studies
- **Pain-Related Activity Reduction**:
  - Ventral attention network
  - Somatomotor network
- **Reduced pain-related activity**
  - Thalamus
  - Habenula
  - Mid-cingulate
  - Supplementary motor area
- **Placebo-associated increases** mainly in frontoparietal regions

Placebo affected pain-related activity in multiple brain areas, reflecting changes in nociception and other affective and decision-making processes surrounding pain



Zunhammer, M., Spisák, T., Wager, T.D. *et al.* Meta-analysis of neural systems underlying placebo analgesia from individual participant fMRI data. *Nat Commun* **12**, 1391 (2021).

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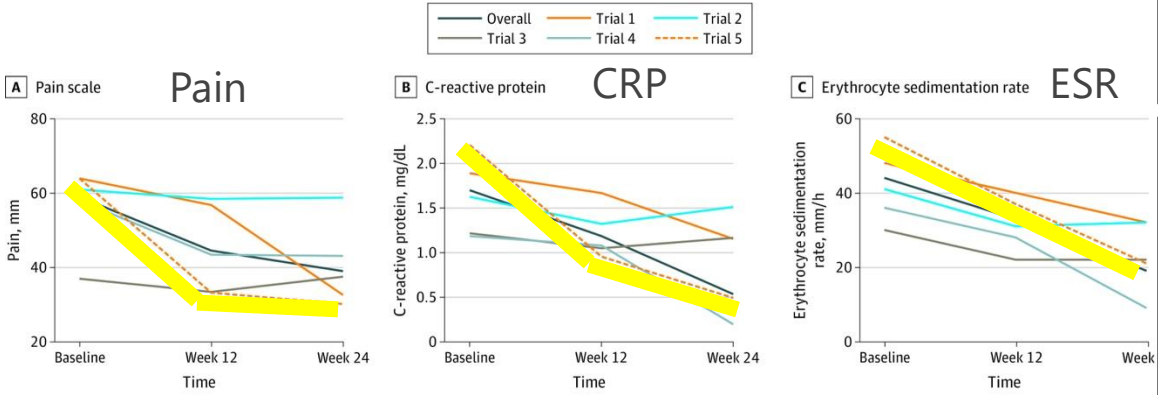
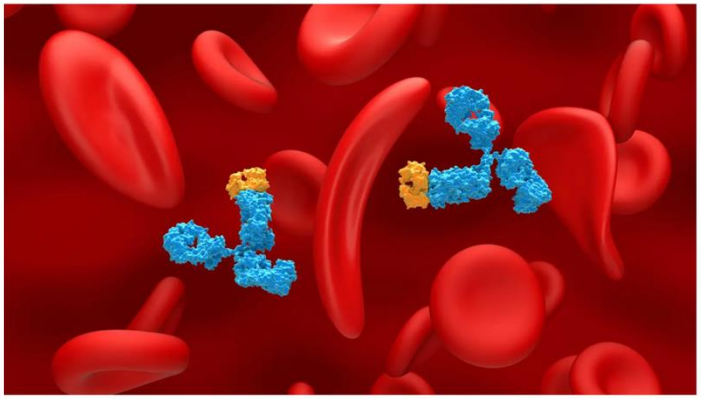
Subjective as well as some Objective outcomes are susceptible to high placebo response in trials



Approved Sickle Cell Drug Fails to Beat Placebo in Trial

— Rates of vaso-occlusive crises similar with two doses of crizanlizumab

by Mike Bassett, Staff Writer, MedPage Today
March 14, 2025 · 3 min read



Vollert J, Cook NR, Kaptchuk TJ, Sehra ST, Tobias DK, Hall KT. JAMA Netw Open. 2020

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Increasing trial size does not necessarily result in greater separation from the placebo response

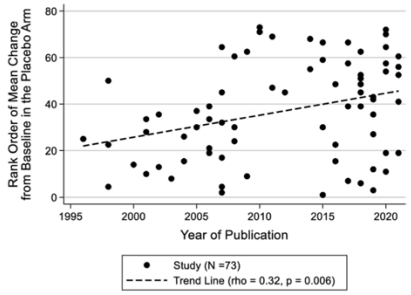
Small effect size
(need greater power)

Larger trials
(global trials)

Greater Heterogeneity
Access to medical care
Inclusion/Exclusion criteria
Cultural norms wrt to care

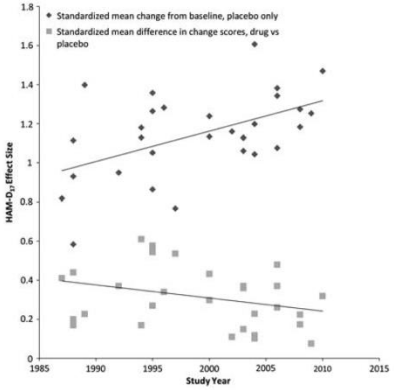
Smaller differences between drug and placebo
Drugs ineffective
Placebo response increasing?

Migraine



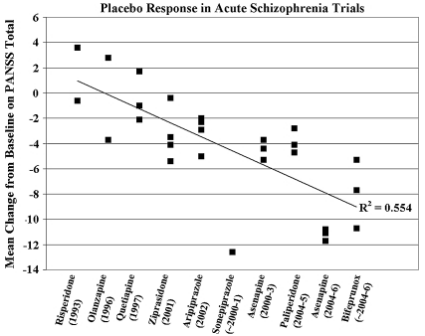
Tepper et al. The Journal of Headache and Pain (2023) 24:54

Depression



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

Schizophrenia



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

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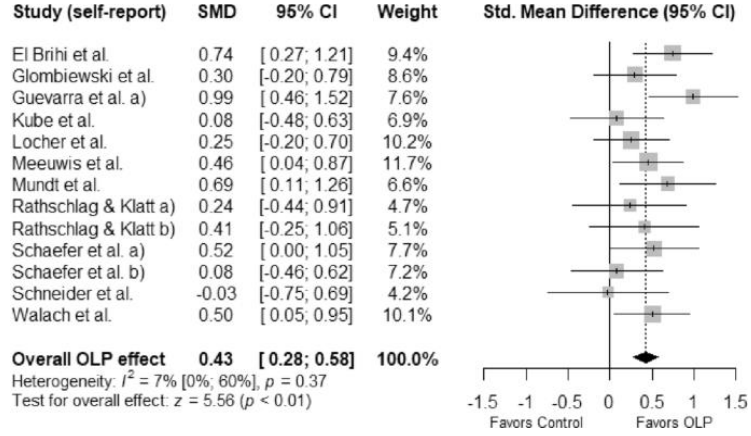
Open-Label Placebos

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.

Condition	N	Arms	Time	Results	Location	Reference
Sleep	117	1 vs. 4 OLP vs. no-treatment	5 days	OLP influenced sleep quality. No diff in pill number		El Brihi et al., Ann Behav Med. 2019
Cancer-related fatigue (CRF)	40	OLP vs. no-treatment	3 wks	OLP reported significantly improved CRF	Dana Farber	Zhou et al., Support Care Cancer. 2018
Wound healing	70	OLP vs. no-treatment	10 days	OLP did not improve healing rate of wounds	New Zealand	Mathur et al., Ann Behav Med. 2018
Allergic rhinitis	46	OLP vs. no-treatment	2 wks	OLP improved allergic symptoms more than control	Germany	Schaefer et al., PLoS One. 2018
Experimental heat pain	160	OLP+rational vs. no-treatment	NA	placebos with a plausible rationale are more effective than without a rationale	Switzerland	Locher et al., Pain. 2017
Chronic low back pain	97	OLP vs. treatment as usual	3 wks	OLP elicited greater pain reduction	Italy	Carvalho et al., Pain. 2017
Migraine	40	placebo or Maxalt told placebo, Maxalt or placebo, Maxalt	6 events	'Placebo' label < 'Maxalt or placebo' label ≤ 'Maxalt' label	BIDMC	Kam-Hansen et al. Sci Transl Med., 2014
Depression	20	OLP vs. waitlist	2 weeks	No statistically significant differences between open-label placebo and waitlist	MGH	Kelley et al., Psychother Psychosom., 2012
IBS	80	OLP vs. no-treatment	3 weeks	OLP significantly better than no-treatment	BIDMC	Kaptchuk et al., Plos One 2010



Spille, L., Fendel, J.C., Seuling, P.D. *et al.* Open-label placebos—a systematic review and meta-analysis of experimental studies with non-clinical samples. *Sci Rep* **13**, 3640 (2023).

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"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

The NEW ENGLAND JOURNAL of MEDICINE

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

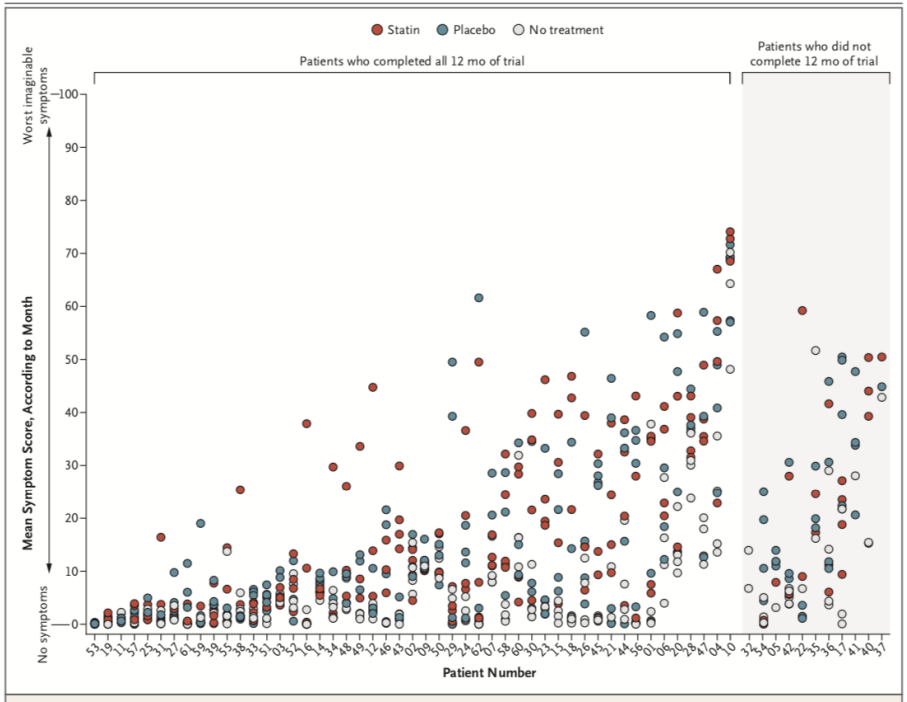

Figure 1. Symptom Scores for All the Trial Patients.
Shown are mean symptom scores for the 49 patients who completed all 12 months of the trial (left) and those for the 11 patients who did not complete all 12 months (right). Each circle represents a single month for each patient. Symptoms were reported 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

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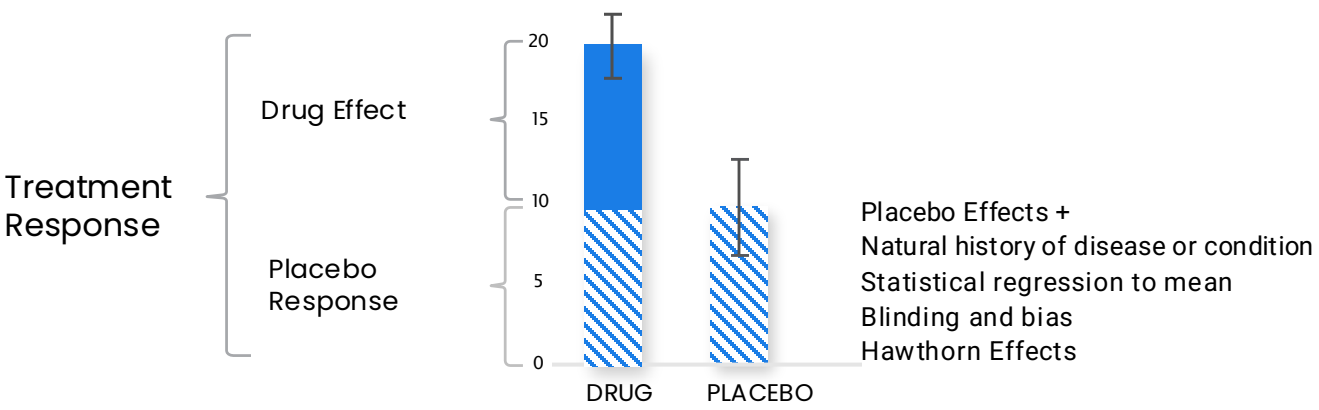
Placebo Response In Clinical Trials



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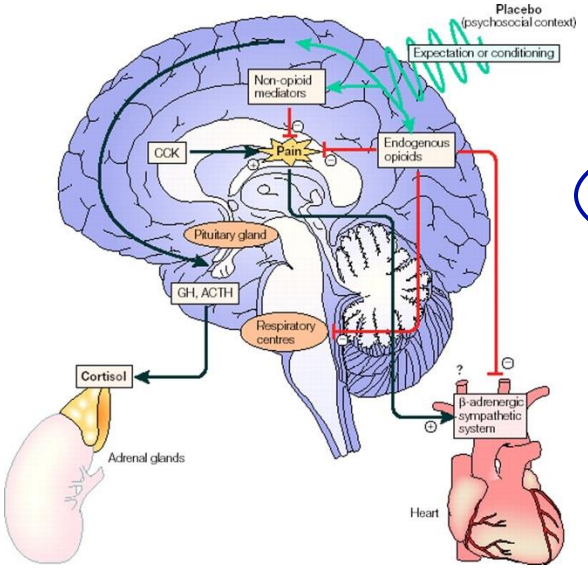
Candidate genes

Dopamine signaling
DRD2, DRD3, COMT
DAT, BDNF, MAO-A,B

Endocannabinoid signaling
FAAH

Cholecystokinin signaling
CCK



Opioid signaling
OPRM1, OPRK1,
OPRL1

Serotonin signaling
TPH2, SLC6A4,
HTR2A, HTTLPR

Adrenergic signaling
COMT, MAO-A,B

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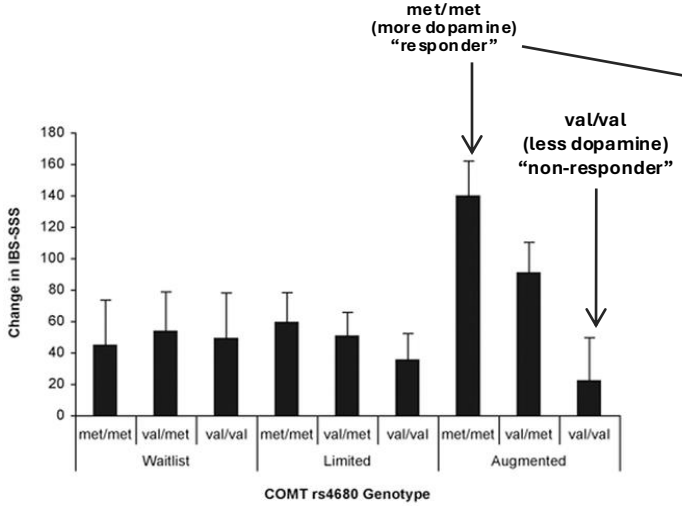
COMT metabolizes dopamine

COMT rs4680 genetic variant associated with placebo response in IBS

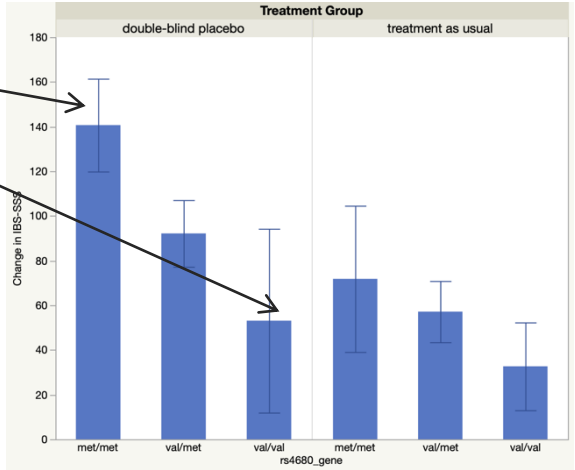
OPEN ACCESS Freely available online

PLOS ONE

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



Hall et al., *PLoS ONE*. 2012



Wang et al., *Frontiers in Pain*. 2022

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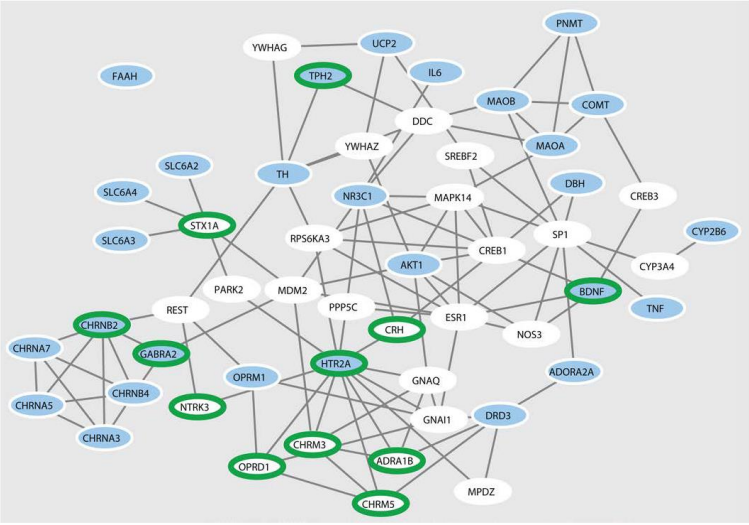
Network analysis suggests placebome overlaps with disease and drug-related genes

Network analysis of the genomic basis of the placebo effect



48 studies
Seed genes = 28
Seed connectors = 26
Placebome module = 54

Drug-related genes

Drug categories	Size of the targets	Placebome module Proximity	*P*
Analgesics, non-narcotic	142	0.96	3.5×10^{-10}
Appetite depressants	88	1.04	1.78×10^{-12}
Antidepressive agents	262	1.04	8.6×10^{-5}
Sympathomimetics	165	1.07	2.6×10^{-6}
Antiparkinson agents	179	1.07	6.0×10^{-6}
Cardiotonic agents	72	1.09	1.2×10^{-11}
Serotonin uptake inhibitors	140	1.11	6.5×10^{-7}
Central nervous system depressants	78	1.13	6.1×10^{-9}
Antioxidants	116	1.19	1.4×10^{-5}
Dopamine agents	78	1.22	6.5×10^{-7}
Excitatory amino acid antagonists	99	1.22	1.5×10^{-5}
Dopamine uptake inhibitors	74	1.30	1.7×10^{-5}
Adrenergic α-agonists	126	1.30	9.1×10^{-3}
Neuroprotective agents	43	1.31	2.5×10^{-7}
Adrenergic β-agonists	28	1.50	3.1×10^{-4}

Disease-related genes

Diseases	Placebo response (S: strong, W: weak)	Proximity	*P*	Proximity	*P*
Schizophrenia	S	0.11	3.4×10^{-22}	0.35	2.4×10^{-22}
Anxiety disorders	S	0.25	8.5×10^{-29}	0.54	4.2×10^{-27}
Alcoholism	S	0.29	3.5×10^{-26}	0.46	1.4×10^{-28}
Depression	S	0.39	1.3×10^{-21}	0.57	3.9×10^{-22}
Parkinson disease	S	0.50	7.5×10^{-18}	0.67	1.3×10^{-16}
Eating disorders	S	0.54	3.8×10^{-20}	0.65	5.7×10^{-26}
Migraine disorders	S	0.79	6.8×10^{-18}	0.87	1.1×10^{-18}
Asthma	S	0.96	7.3×10^{-7}	0.89	1.8×10^{-5}
Epilepsy	S	0.96	1.6×10^{-9}	1.04	1.2×10^{-8}
Fibromyalgia	S	1.14	2.6×10^{-11}	1.11	1.9×10^{-12}
Irritable bowel syndrome	S	1.11	5.3×10^{-9}	1.07	4.6×10^{-12}
Restless leg syndrome	S	1.32	1.6×10^{-7}	1.24	1.4×10^{-9}
Diabetic neuropathies	S	1.50	2.1×10^{-3}	1.41	5.1×10^{-4}
Crohn's disease	S	1.50	0.68	1.39	0.52
Ulcerative colitis	S	1.68	1.00	1.48	1.00
Duodenal ulcer	S	1.71	0.25	1.63	0.48
Osteoarthritis	S	1.75	1.00	1.61	1.00
Pancreatitis, chronic	S	1.79	0.67	1.78	1.00
Infertility	W	1.25	2.6×10^{-3}	1.09	1.2×10^{-5}
Bacterial infections	W	1.32	0.22	1.17	0.022
Carcinoma, hepatocellular	W	1.50	0.52	1.28	0.019
Carcinoma, renal cell	W	1.68	0.46	1.44	4.8×10^{-3}
Viremia	W	1.75	1.00	1.57	0.64
Uremia	W	2.04	1.00	2.00	1.00
Pneumothorax	W	2.32	1.00	2.04	0.21

P values were adjusted using the Bonferroni procedure.

COMT associated with outcomes in the placebo arm

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 31, 2005 VOL. 352 NO. 13

A Randomized Trial of Low-Dose Aspirin in the Primary Prevention of Cardiovascular Disease in Women

Paul M Ridker, M.D., Nancy R. Cook, Sc.D., I-Min Lee, M.B., B.S., David Gordon, M.A., J. Michael Gaziano, M.D., JoAnn E. Manson, M.D., Charles H. Hennekens, M.D., and Julie E. Buring, Sc.D.

Major CVD events

Placebo group – 522

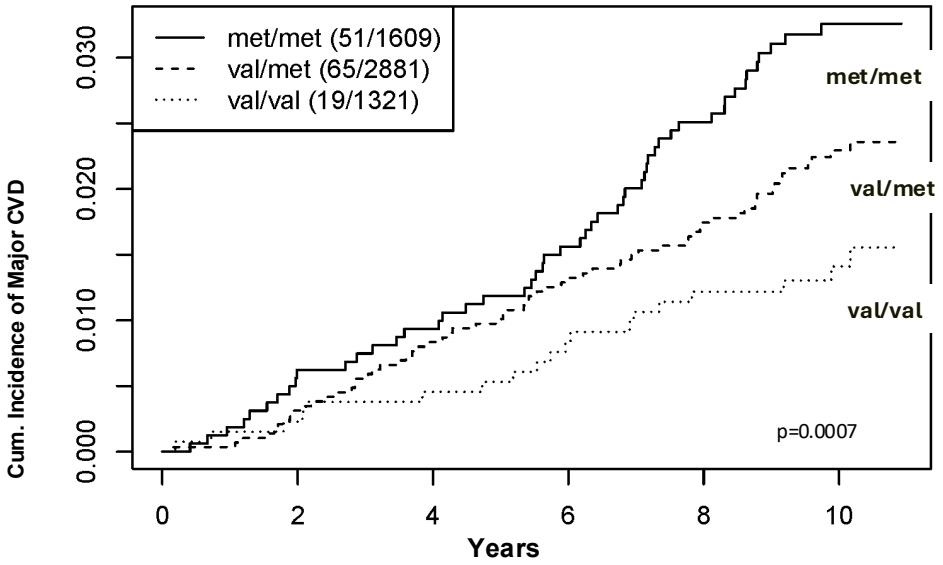
Aspirin group – 477

Aspirin effect non-significant

9% reduction in of major CVD risk

RR 0.91, CI [0.80-1.03], P=0.13

Ridker et al., *NEJM*. 2005



Hall KT. et al., 2014 *Atherosclerosis Thrombosis and Vascular Biology*

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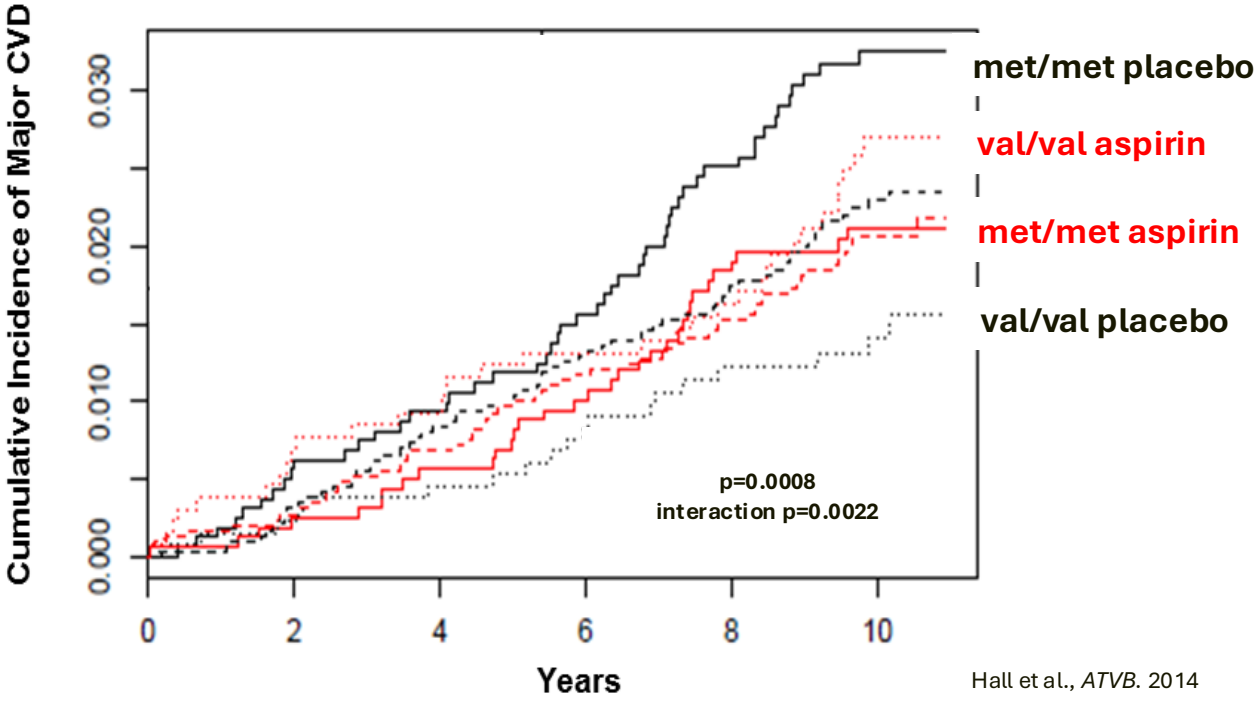
COMT associated with differential CVD prevention in aspirin vs. placebo

Placebo n=5,814	Aspirin n=5,815
Vitamin E n=5,863	Aspirin + Vitamin E n=5,802



Hall et al., *ATVB.* 2014

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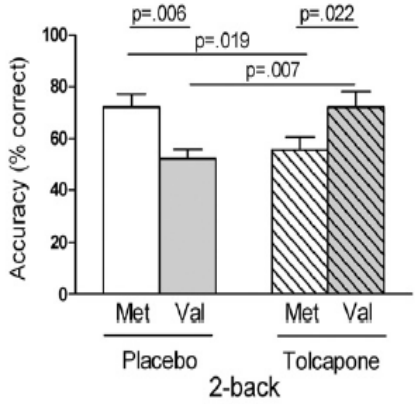
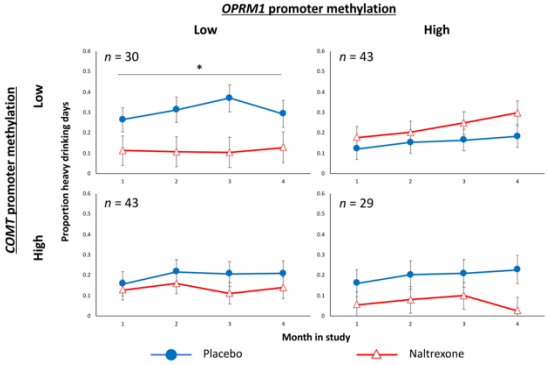
Other conditions

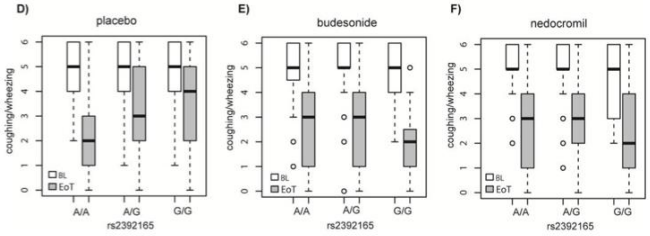


Farrell et al. (2012) *Biol. Psychiatry*

Epigenetic Effects

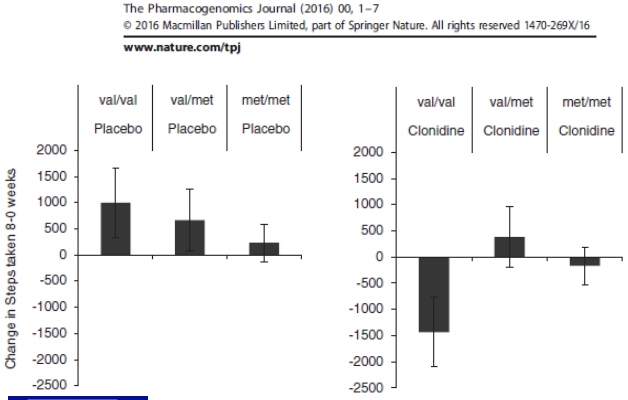


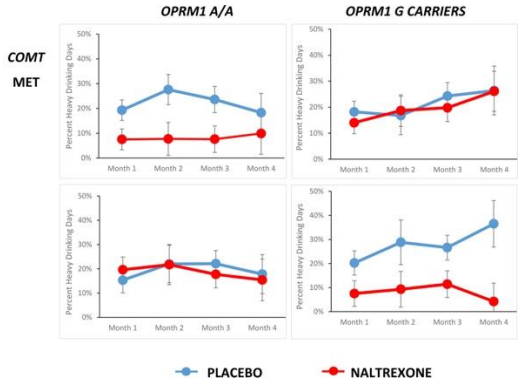
Other Genes



Wang et al. Clin Pharmacol Ther . 2019 December ; 106(6): 1261–1267

Gene*Gene Interactions





Anton et al. (2020) *Alcohol Clin Exp Res*

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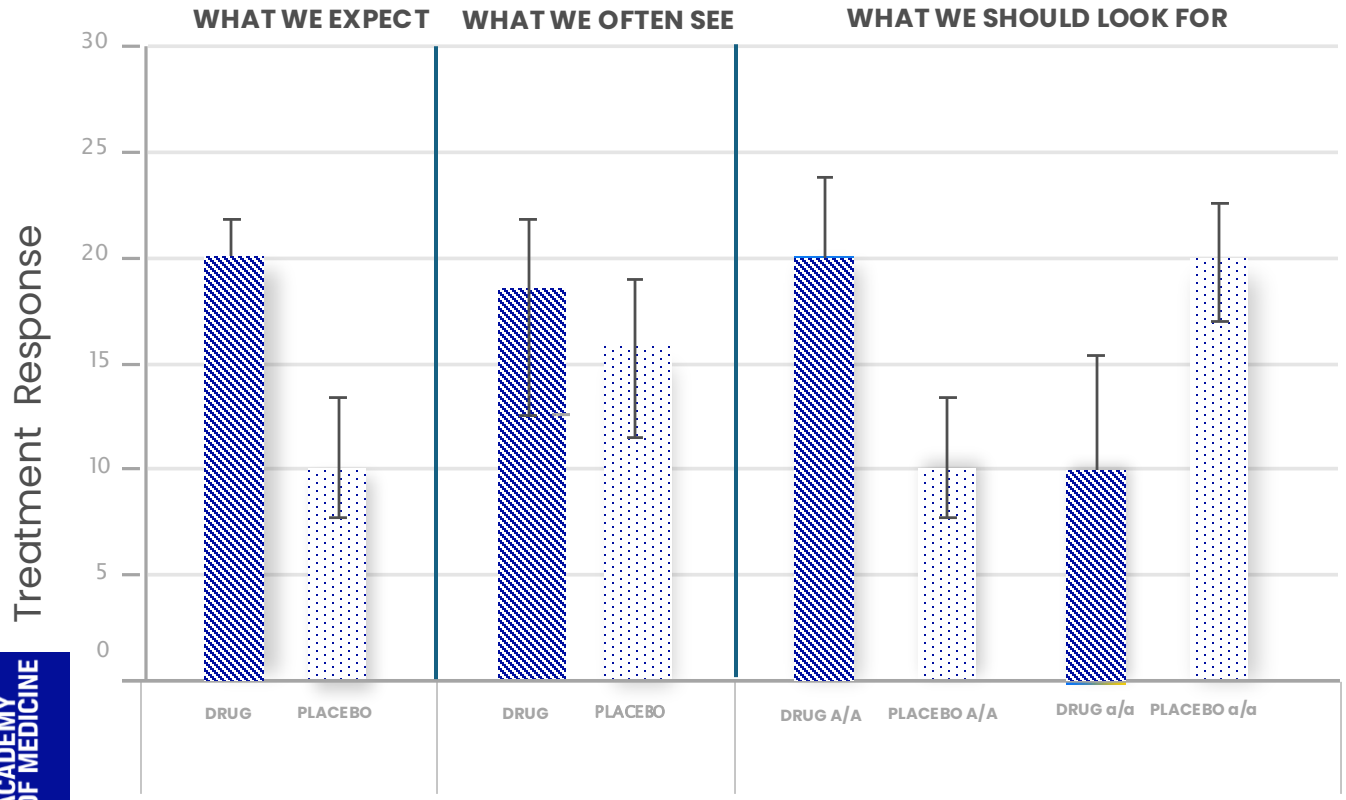
How might genes that modify placebo response influence clinical trials?



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Unmasking the Myths

7 Common “Misconceptions” About Placebos

1. Placebo effects are not just in the mind, they derive from demonstrated neurological responses
2. Objective outcomes: Both objective and subjective outcomes can be influenced by placebos.
3. Larger studies: Increasing study size alone doesn't eliminate placebo effects.
4. Knowing blunts effect: Open-label placebos can still be effective.
5. No side-effects: Placebos can cause side-effects, known as nocebos.
6. Additive responses: Drug and placebo responses are not simply additive.
   Gene*Drug interaction: Genetic factors can influence placebo effects.
7. Placebo arms: Placebo arms provide valuable insights yet are often overlooked.

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Some considerations

- Examine *our* **expectations**
- Investigate **gene*drug and placebo interactions** and how they impact subpopulations
  - Who benefits or is harmed by therapies
- Can we salvage drugs with proven safety and compelling mechanisms of action that failed to beat placebos?
- Can we use drugs to boost or block placebo responses? **Perhaps some drugs already do**
- **Safe, marginally effective, conditional approval?**
- **Placebo first?**
- **Accentuate the positive**

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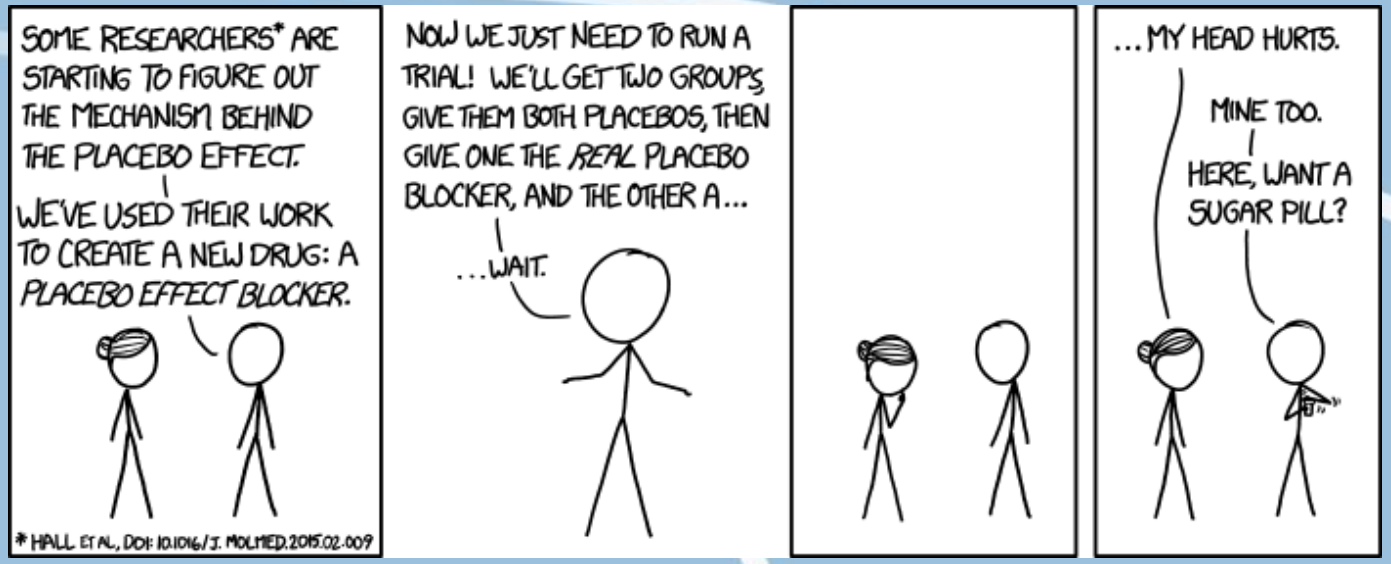
Better Health for Life

Acknowledgements



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Jan Vollert – Imperial College

Rui-sheng Wang - Brigham & Women's
Joseph Loscalzo - Brigham & Women's
Ted Kaptchuk – Harvard Medical School
John Kelley - Endicott College
Daniel Chasman - Brigham & Women's
Joe Kossowsky – Boston Children's

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Better Health for Life

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, 1943, a report was published of the chemical properties and clinical effects of a metabolic product of *Penicillium patulum* Bainier, called patulin.[1] In this report it was shown that the common cold in naval personnel that when 16 patients treated with patulin were compared with 83 controls, the advantage to the treated patients was such that it would usually be regarded as statistically significant. The results

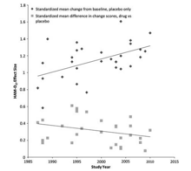
Opioid Signaling Implicated in Placebo Analgesia

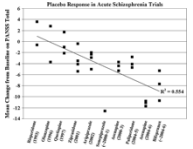
THE MECHANISM OF PLACEBO ANALGESIA

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_2O, 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-





Depression drug trials are failing—and placebos are to blame

BC | 1300 | 1700 | 1800 | 1900 | 1940 | 1960 | 1980 | 2000 | 2020 | ...

The Edwin Papyrus Dynasty 16–17, ca. 1600 B.C. Thebes

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

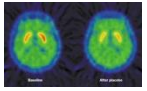
Quacks, nostrums and patent medicine

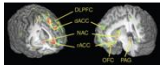
Three Big Ideas
Receptor concept in pharmacology
Homeostasis in physiology
Metabolism in biochemistry

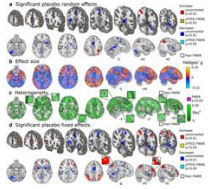
THE POWERFUL PLACEBO

"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

Neural systems underlying placebo analgesia







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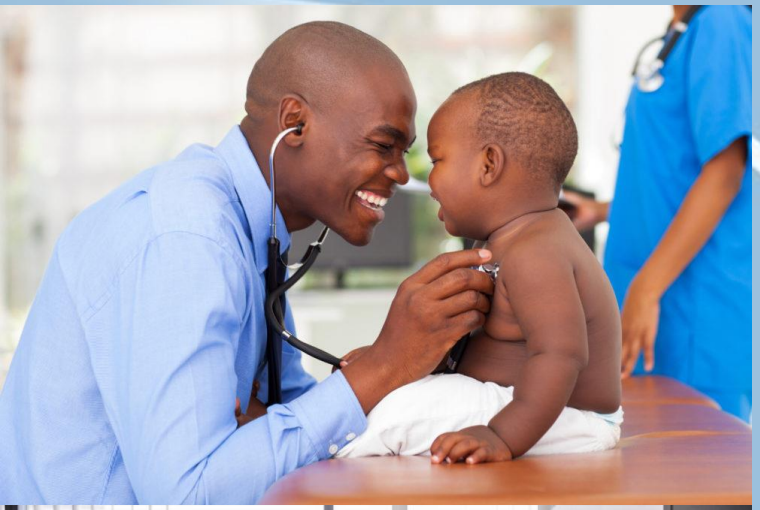
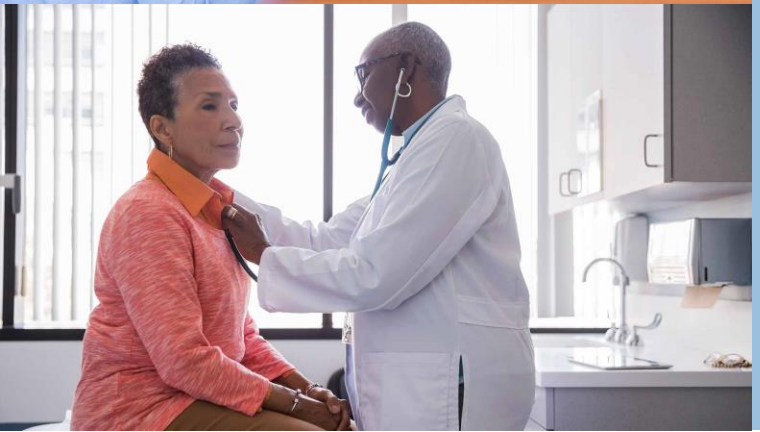
Expectations are a key driver of placebo effects

Prank gone awry, Hamburg, 2014

Practical Ways to Reduce Nocebo and Enhance Placebo Effects





- To maximize placebo effects and minimize detrimental effects of nocebo, experts encourage clinicians to become familiar with placebo and nocebo effects and educate patients about potential mechanisms of effects.
- Encourage conversation with patients about their needs and expectations about their treatment
- Frame information in a reasonably positive context and avoid negative contextual experiences (Barsky et al., 2002; Colloca and Barsky, 2020).

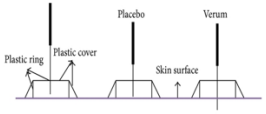
Dissecting components of the placebo effect

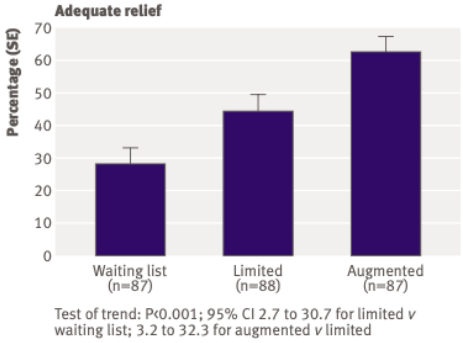
Randomized
(n=262)

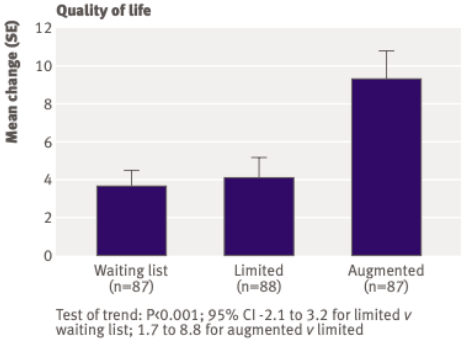
Waiting list (n=87)

Limited placebo
(n=88)

Augmented (n=87)







Kaptchuk et al., BMJ 2008

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Catechol-O-methyltransferase (COMT) metabolizes catecholamines