The placebo effect in pain studies

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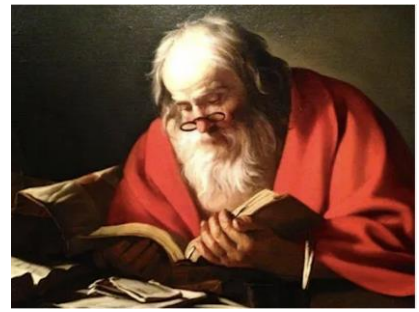
Definition (1)



“Placebo” is the Latin word for “I shall please” and appeared in the opening phrase, “Placebo domino in regione vivorum,” of the Catholic Vesper for the Dead, psalm 116, 9th verse.

The New Medical Dictionary, published in 1785, described placebo as “a commonplace method or medicine”

In 1811, the revised Quincy's Lexicon-Medicum defines placebo as 'an epithet given to any medicine adapted more to please than to benefit the patient'

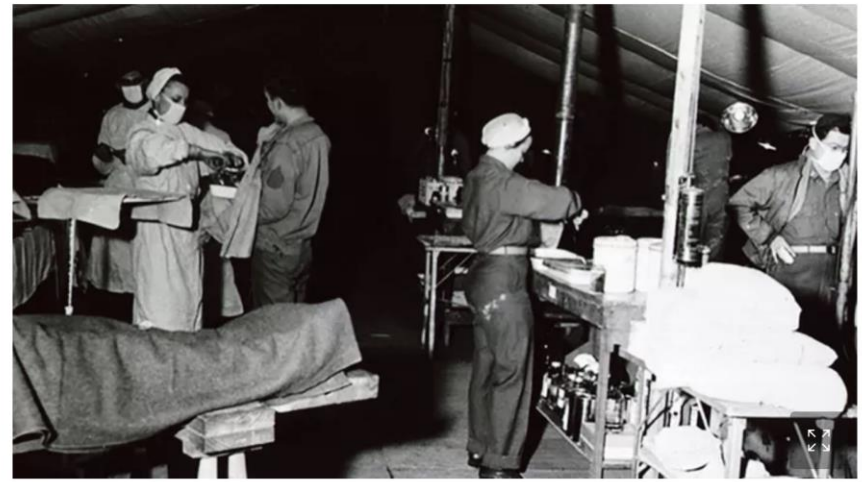
In the context of RCTs

Placebo effect

=

Clinical effects induced by an “inert” agent or sham treatment

Pioneer scientific studies



Une opération sur le front italien, en 1944. *US National Library of Medicine*

Henry Beecher

THE POWERFUL PLACEBO

Henry K. Beecher, M.D., Boston

Placebos have doubtless been used for centuries by wise physicians as well as by quacks, but it is only recently that recognition of an enquiring kind has been given the clinical circumstance where the use of this tool is essential ". . . to distinguish pharmacological effects from the effects of suggestion, and . . . to obtain an unbiased assessment of the result of experiment." It is interesting that Pepper could say as recently as 10 years ago "apparently there has never been a paper published discussing [primarily] the important subject of the placebo." In 1953 Gaddum [1] said:

> Such tablets are sometimes called placebos, but it is better to call them dummies. According to the Shorter Oxford Dictionary the word placebo has been used since 1811 to mean a medicine given more to please than to benefit the patient. Dummy tablets are not particularly noted for the pleasure which they give to their recipients. One meaning of the word dummy is a "counterfeit object." This seems to me the right word to describe a form of treatment which is intended to have no effect and I follow those who use it. A placebo is something which is intended to act through a psychological mechanism. It is an aid to therapeutic suggestion, but the effect which it produces may be either psychological or physical. It may make the patient feel better without any obvious justification, or it may produce actual changes in such things as the gastric secretion. . . . Dummy tablets may, of course, act as placebos, but, if they do, they lose some of their value as dummy tablets. They have two real functions, one of which is to distinguish pharmacological effects from the effects of suggestion, and the other is to obtain an unbiased assessment of the result of experiment.

drugs have an important part of their action on the reaction or processing component of suffering, as opposed to their effect on the original sensation.

The opportunities opened up by the placebo are unique, for it cannot possibly enter into any process by virtue of its chemical composition. It has, so to speak, neither the reactivity nor the physical dimensions required of an "effective" drug. It does not matter in the least what the placebo is made of or how much is used so long as it is not detected as a placebo by the subject or the observer. Thus the placebo provides an indispensable tool for study of the reaction or processing component of suffering. This will be referred to later on in this paper. I have discussed it extensively elsewhere.[2]

REASONS FOR USE

Reasons for the use of the placebo can be indicated by summarizing, then, its common purposes: as a psychological instrument in the therapy of certain ailments arising out of mental illness, as a resource of the harassed doctor in dealing with the neurotic patient, to determine the true effect of drugs apart from suggestion in experimental work, as a device for eliminating bias not only on the part of the patient but also, when used as an unknown, of the observer, and, finally, as a tool of importance in the study of the mechanisms of drug action. Moreover, as a consequence of the use of placebos, those who react to them in a positive way can be

1784: first reported placebo-controlled medical experiments to debunk the healing practices of mesmerism.

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

A study designed by Benjamin Franklin and Antoine Lavoisier

The placebo controversy

SPECIAL ARTICLE

Is the Placebo Powerless? — An Analysis of Clinical Trials Comparing Placebo with No Treatment

Asbjørn Hróbjartsson, M.D., and Peter C. Gøtzsche, M.D.

ELSEVIER

Journal of Clinical Epidemiology 55 (2002) 430–435

Journal of Clinical Epidemiology

What are the main methodological problems in the estimation of placebo effects?

Asbjørn Hróbjartsson*

Department of Medical Philosophy and Clinical Theory, University of Copenhagen, Panum Institute, Blegdamsvej 3 DK-220,0 Copenhagen N, Denmark

Received 16 April 2001; received in revised form 11 October 2001; accepted 12 October 2001

ELSEVIER

Journal of Clinical Epidemiology 64 (2011) 1223–1229

Journal of Clinical Epidemiology

Placebo effect studies are susceptible to response bias and to other types of biases

Asbjørn Hróbjartsson[a,*], Ted J. Kaptchuk[b], Franklin G. Miller[c]

[a]*The Nordic Cochrane Centre, Rigshospitalet, Copenhagen, Denmark*

[b]*Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA*

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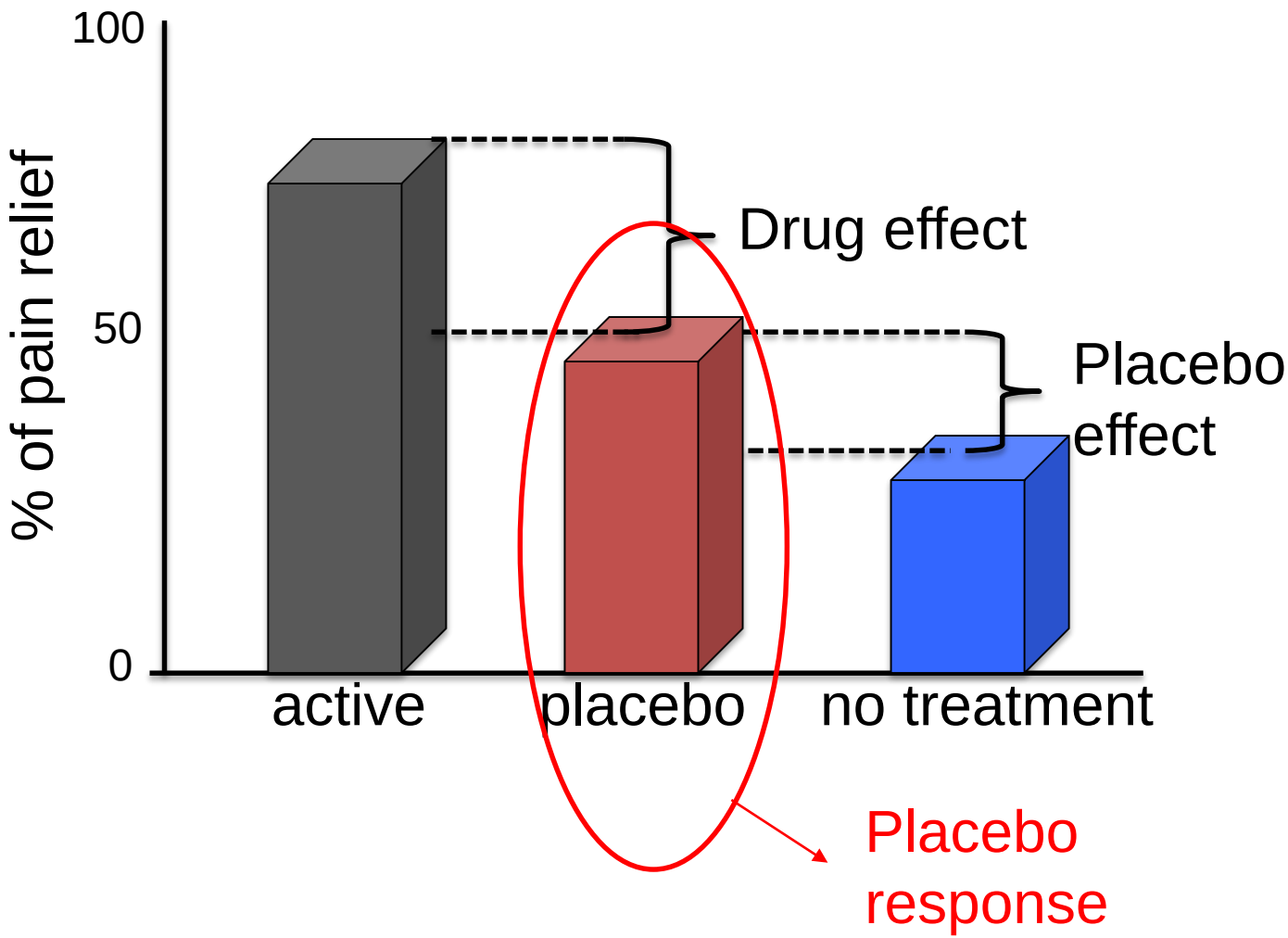
Accepted 28 January 2011; Published online 23 April 2011

Definitions (2)

Placebo response vs placebo effect



The placebo effect is only one of the non specific mechanisms

Natural history

Regression to the mean

Co-interventions

Placebo effect

Biases and false positives

Hawthorne effect

Colloca L, Finniss D, Benedetti F. Placebo and Nocebo. Hodder Arnold, 2008:499-513

Colloca L, Benedetti F. In: Price D. D., Bushnell C., eds. Seattle, WA: IASP 2004, 29:187-205

Cochrane Database Syst Rev. 2010 Jan; 2010(1): CD003974.
Published online 2010 Jan 20. doi: 10.1002/14651858.CD003974.pub3
PMCID: PMC7156905
PMID: 20091554

Placebo interventions for all clinical conditions

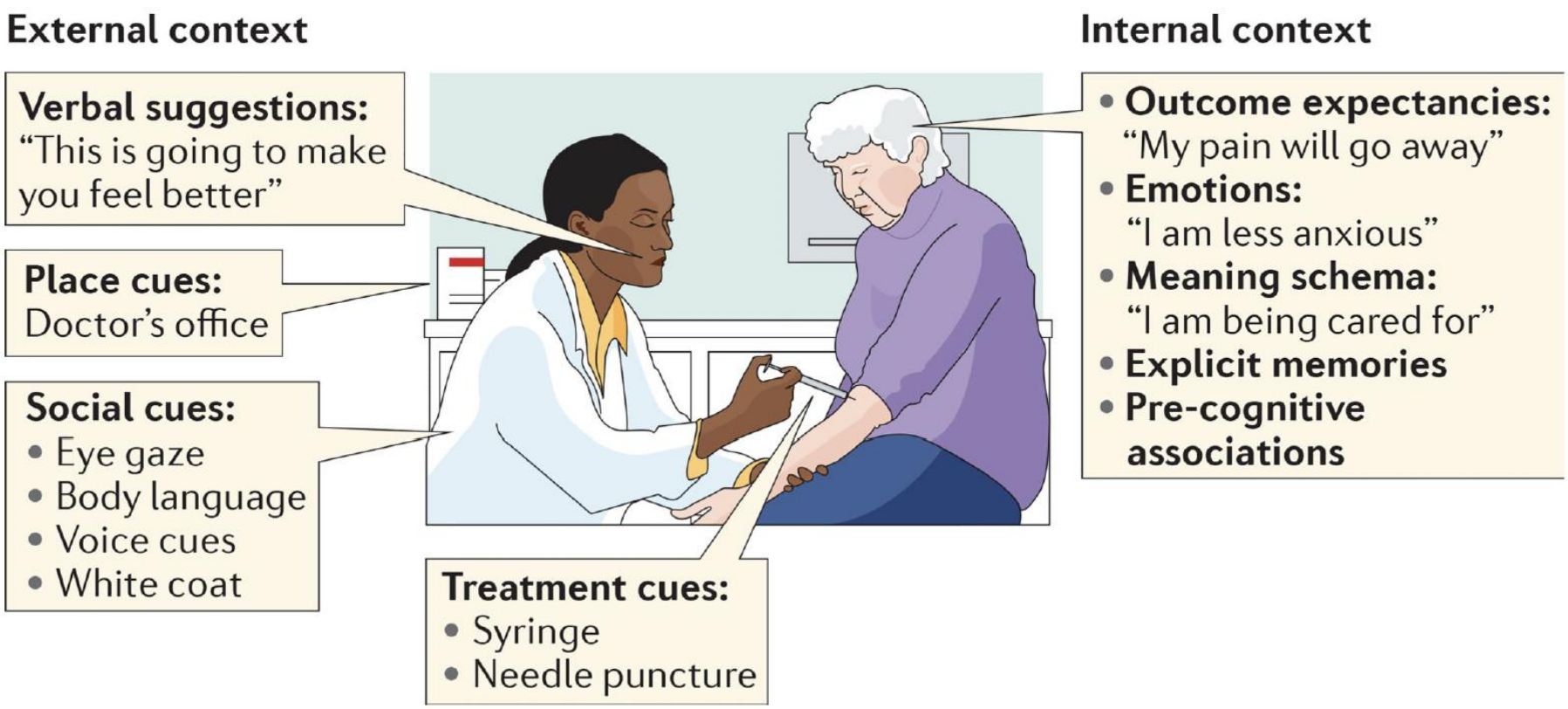
Monitoring Editor: Asbjørn Hróbjartsson,[✉] Peter C Gøtzsche, and Cochrane Consumers and Communication Group
Rigshospitalet, The Nordic Cochrane Centre, Blegdamsvej 9, 3343, CopenhagenDenmark, 2100
Asbjørn Hróbjartsson, Email: ah@cochrane.dk.

Overall moderate placebo effect in studies related to pain, nausea, asthma and phobia (ES about 0.5)

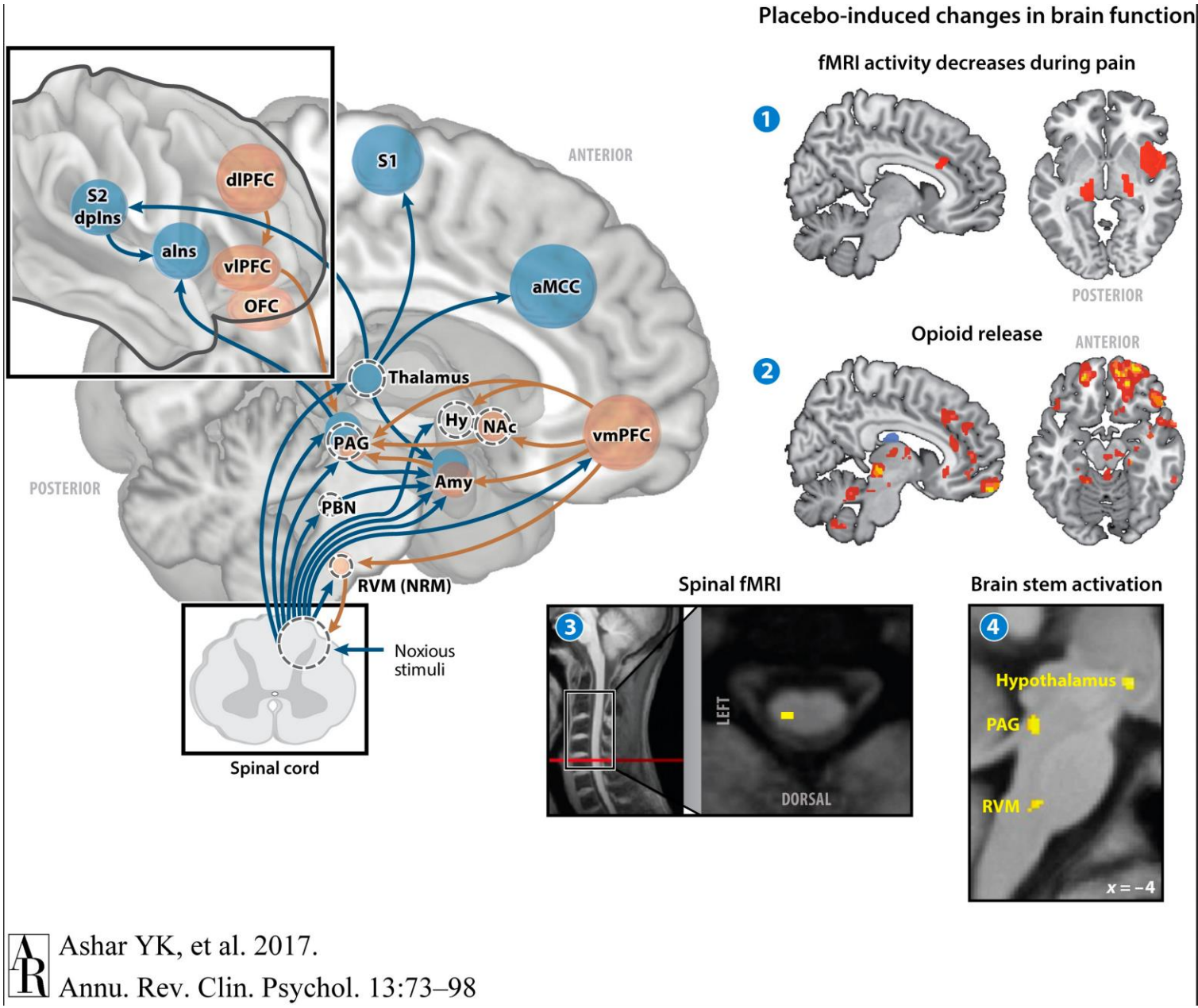
Larger placebo effects in pain studies using devices in comparison with those using pills (ES over 0.8)

Definition (2)

« Placebo effects are improvements in patients' symptoms that are attributable to their participation in the therapeutic encounter, with its rituals, symbols, and interactions » (Kaptchuk, 2015)



The placebo effect is not a response bias, but involves specific neurobiological mechanisms



Ashar YK, et al. 2017.
Annu. Rev. Clin. Psychol. 13:73–98

Decreased activity in The “pain matrix”

Increased activity in areas involved in pain modulation

Placebo effect is present in many conditions

- Pain, depression, anxiety, Parkinson disease, asthma, nausea, etc.

Placebo effect is seen with all kind of treatments

- Drugs, surgery, complementary medicine, psychotherapies, etc.

Placebo does not “cure” (no pathophysiological effects) but can significantly improves symptoms

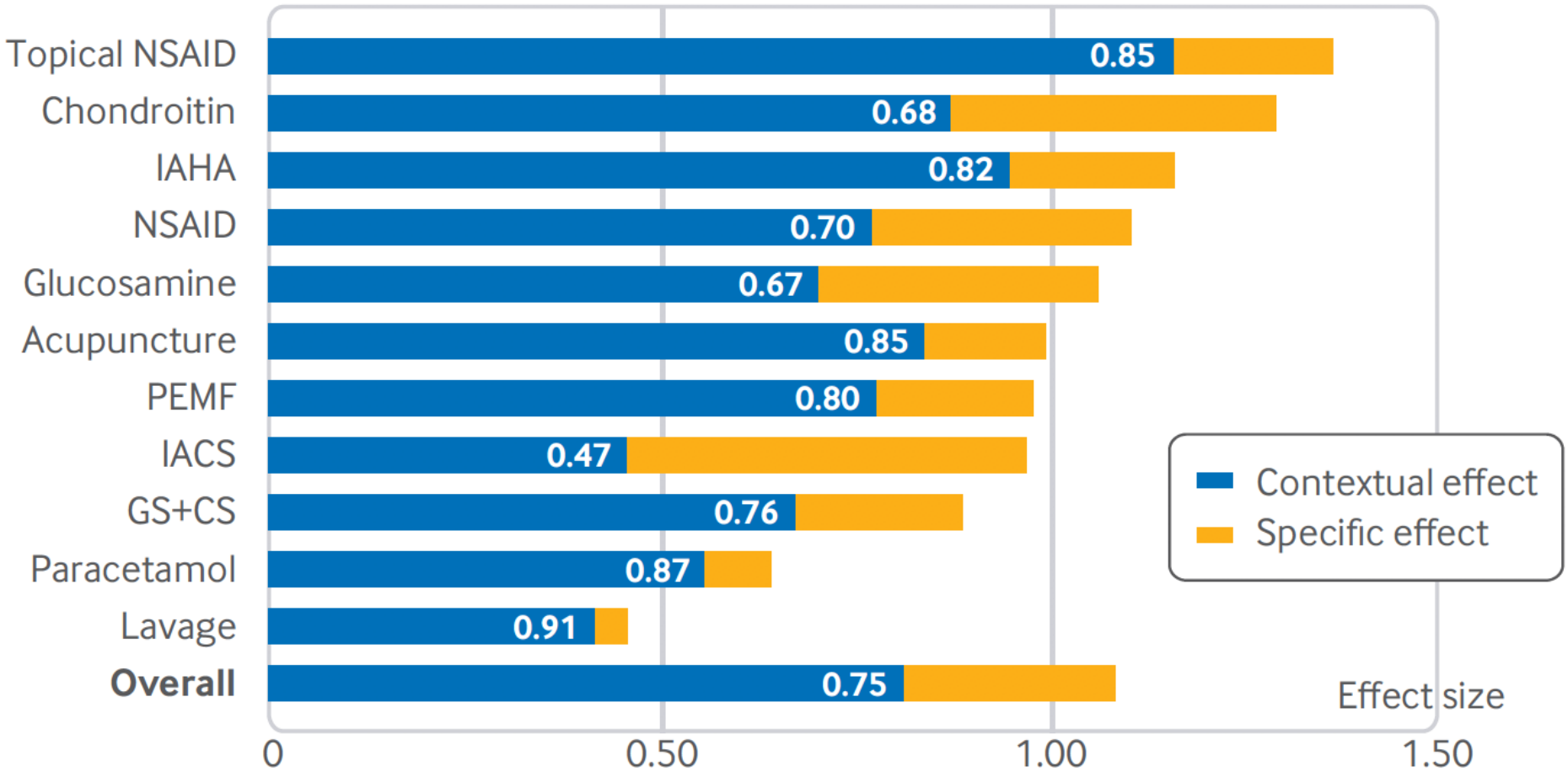
Magnitude of the placebo response

10 % to 50 % across various pain conditions
(50% decrease in pain intensity)

- 15-30% in neuropathic pain studies (Arakawa et al., 2015)
- 16% in dental pain (Averbuch and Katzper, 2015)
- 20-50 % in migraine (Macedo et al. 2006)
- 15-40% in fibromyalgia (Hauser et al., 2011)
- 20% pancreatic pain (Capurso et al., 2012)

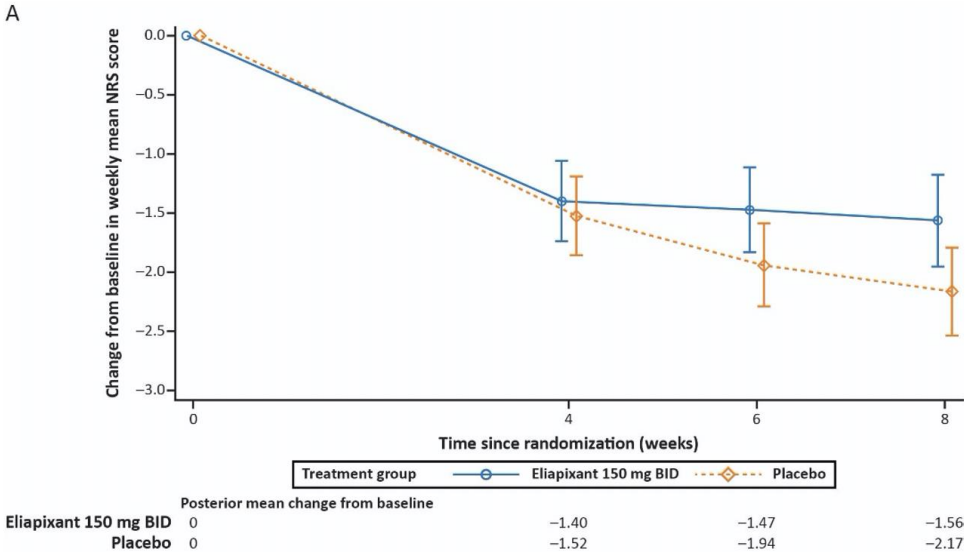
Up to 75-85% of the active treatment effects could be due to unspecific effects

Percentage of the observed response attributable to placebo responses in studies related to osteoarthritis pain

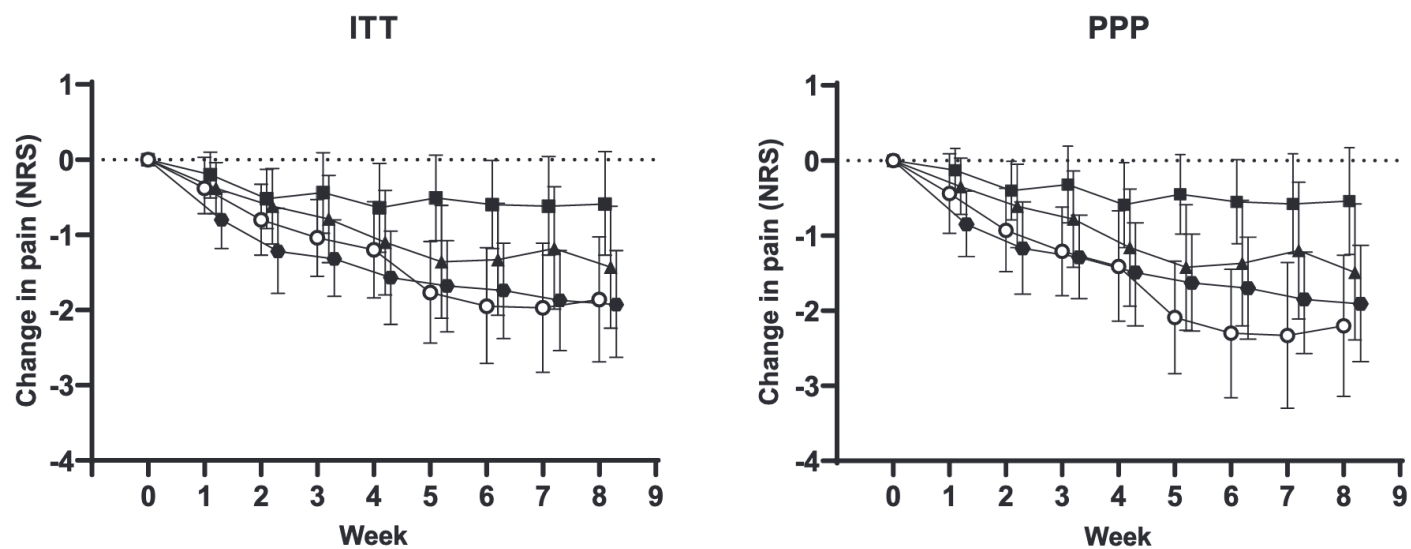


Zou et al., Ann Rheum Dis 2016

The placebo response can be larger than the active drug



Bouhassira et al., Pain 2023



Zubcevic et al., Eur J Pain 2023

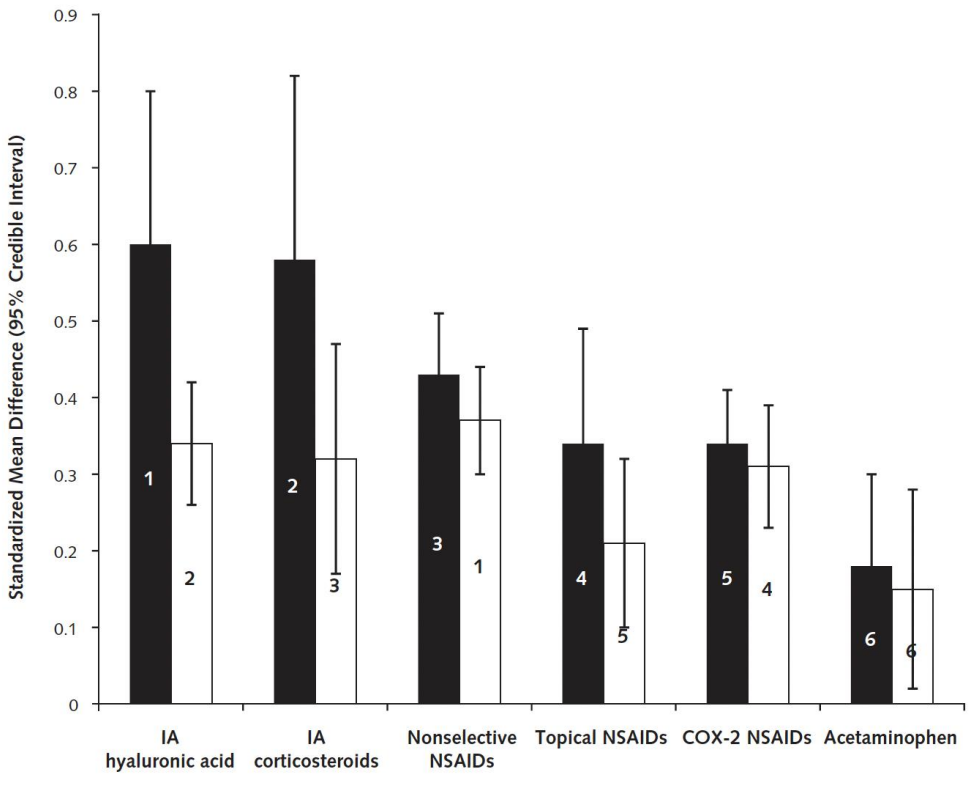
Placebo effect is higher with invasive treatments

Annals of Internal Medicine REVIEW

Effectiveness and Implications of Alternative Placebo Treatments

A Systematic Review and Network Meta-analysis of Osteoarthritis Trials

Raveendhara R. Bannuru, MD, PhD; Timothy E. McAlindon, MD; Matthew C. Sullivan, BA; John B. Wong, MD; David M. Kent, MD; and Christopher H. Schmid, PhD



Intra-articular > topic>oral for OA pain

Placebo and surgery

Comparison of Internal Mammary Artery Ligation and Sham Operation for Angina Pectoris*

E. Grey Dimond, M.D., F.A.C.C., C. Frederick Kittle, M.D. *and* James E. Crockett, M.D.
Kansas City, Kansas

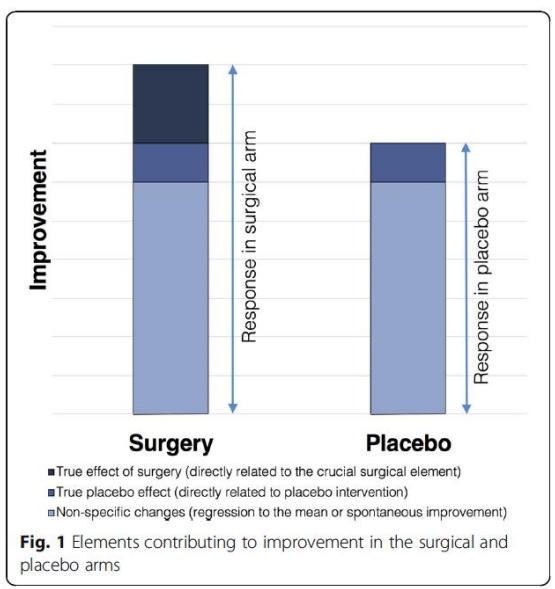


Fig. 1 Elements contributing to improvement in the surgical and placebo arms

Clinical Science

Surgery as Placebo

A Quantitative Study of Bias

Henry K. Beecher, M.D., Boston

BMJ Open

To what extent are surgery and invasive procedures effective beyond a placebo response? A systematic review with meta-analysis of randomised, sham controlled trials

Wayne B Jonas,[1] Cindy Crawford,[1] Luana Colloca,[2,3] Ted J Kaptchuk,[4] Bruce Moseley,[5] Franklin G Miller,[6] Levente Kriston,[7] Klaus Linde,[8] Karin Meissner[9]

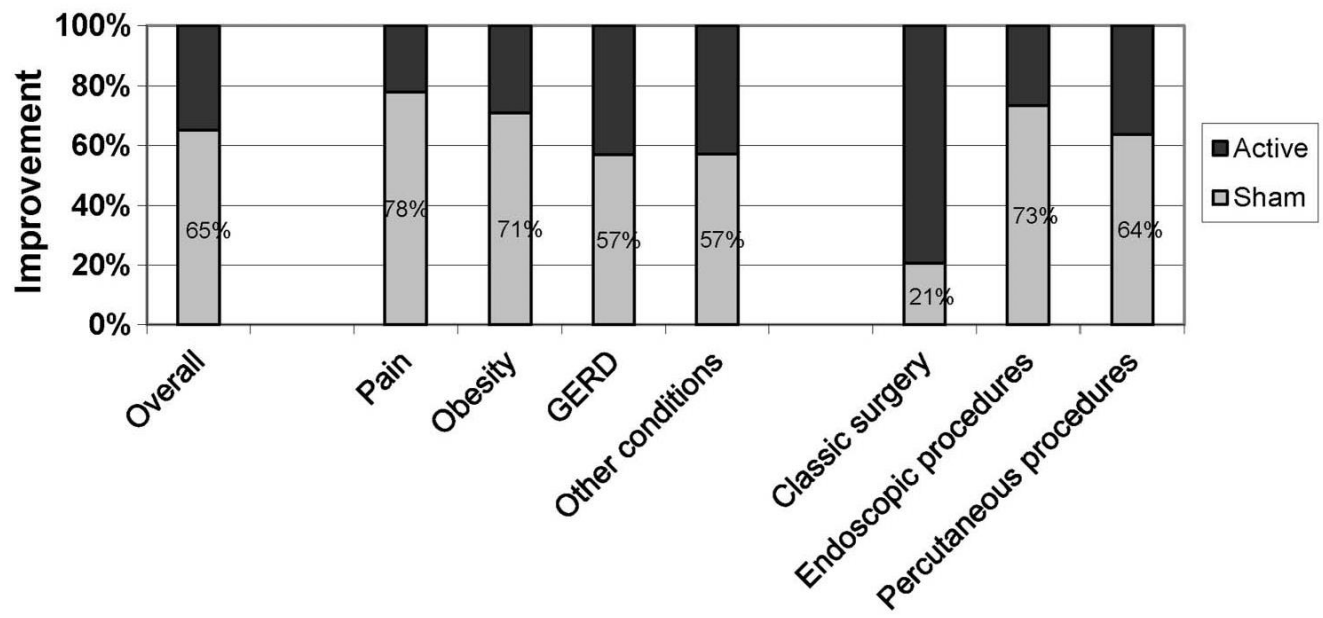


Figure 4 Relative contribution to improvement in the placebo and active treatment groups.

Duration of the placebo effect

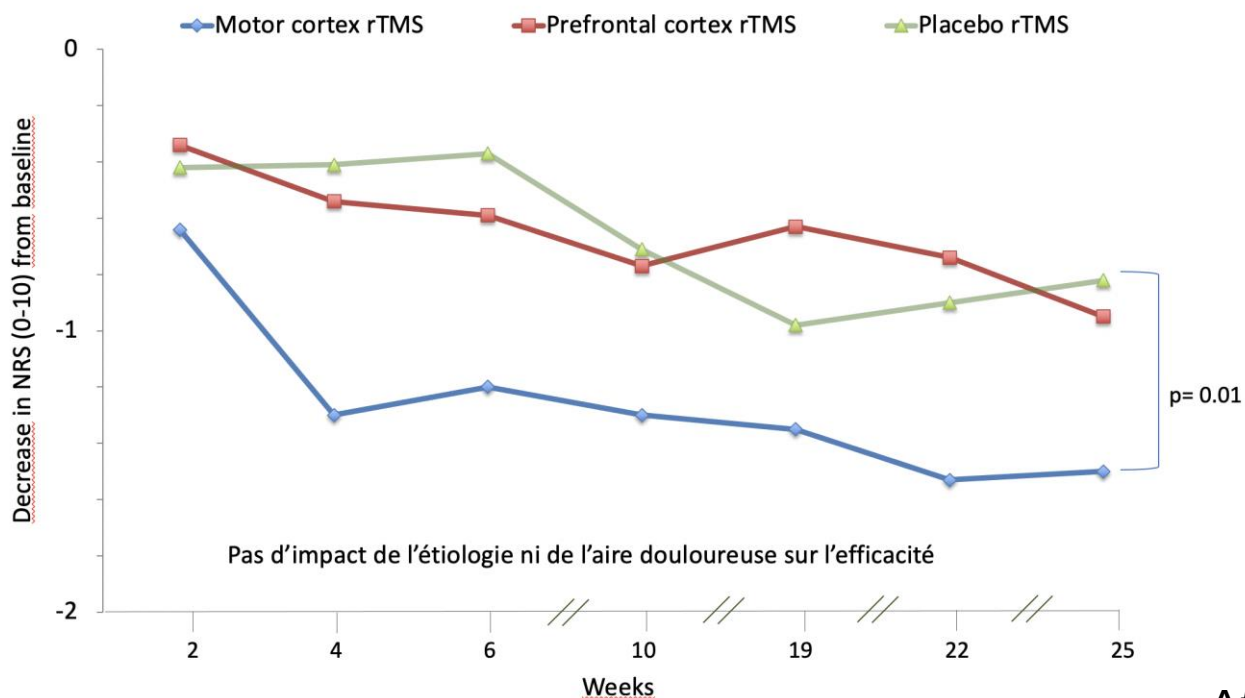
Wartolowska *et al. Trials* (2016) 17:589
DOI 10.1186/s13063-016-1720-7

Trials

REVIEW Open Access

The magnitude and temporal changes of response in the placebo arm of surgical randomized controlled trials: a systematic review and meta-analysis

Karolina A. Wartolowska[1,2*], Benjamin G. Feakins[3], Gary S. Collins[2,4], Jonathan Cook[2], Andrew Judge[2,5], Ines Rombach[1,2], Benjamin J. F. Dean[1,2], James A. Smith[2] and Andrew J. Carr[1,2]



Attal et al., Brain 2021

Factors modulating the placebo effect/response: non verbal cues

Color of the pills

Administration route

Dose

Invasive vs
non invasive treatment

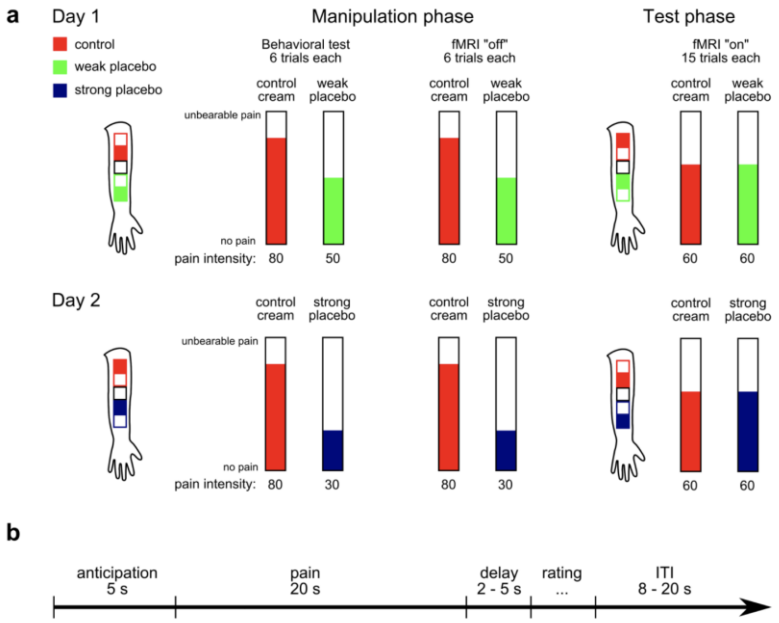
Other factors: price, size and forms, brand-labelled/generic

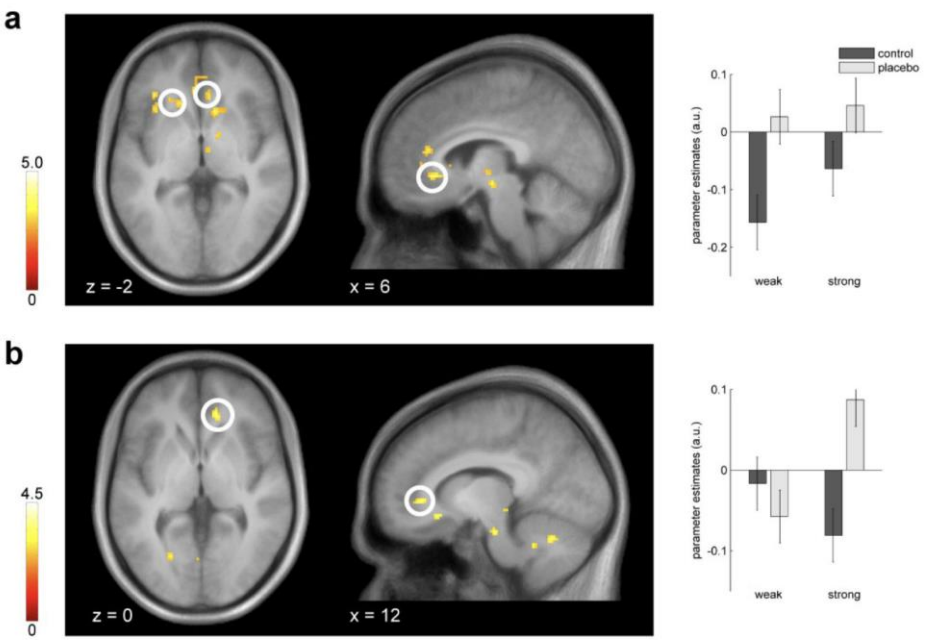
Meissner and Linde, 2018

Neuroimage. 2013 February 15; 67: 227–236. doi:10.1016/j.neuroimage.2012.11.029.

Cortical and subcortical responses to high and low effective placebo treatments

Stephan Geuter, **Falk Eippert**, **Catherine Hindi Attar**, and **Christian Büchel**
Department of Systems Neuroscience, University Medical Center Hamburg-Eppendorf, 20246 Hamburg, Germany



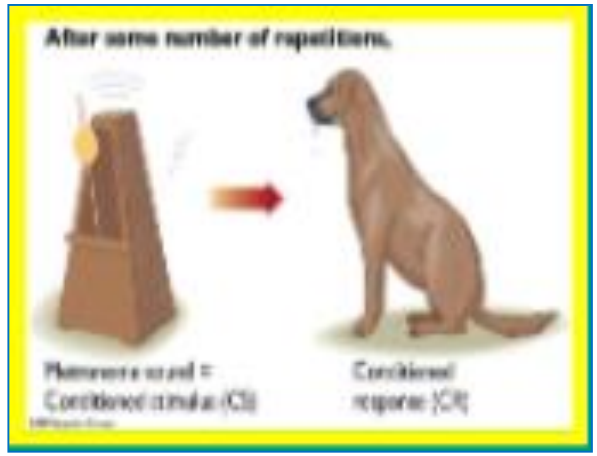


Higher price placebo had stronger analgesic effects and was associated with a stronger activation of brain areas involved in pain modulation.

Understanding the formation of placebo responses: Psychological theories

Verbal suggestion/expectations - anticipating a clinical benefit induces a placebo response – the patient experiences a health outcome and a change in the state of disease and illness

Conditioning – like Pavlov's dogs, a patient responds to stimuli which accompany the administration of a therapy because she/he has experienced benefit from such therapy in the past



Mostly based on experimental studies

Pain 128 (2007) 264–271

PAIN

www.elsevier.com/locate/pain

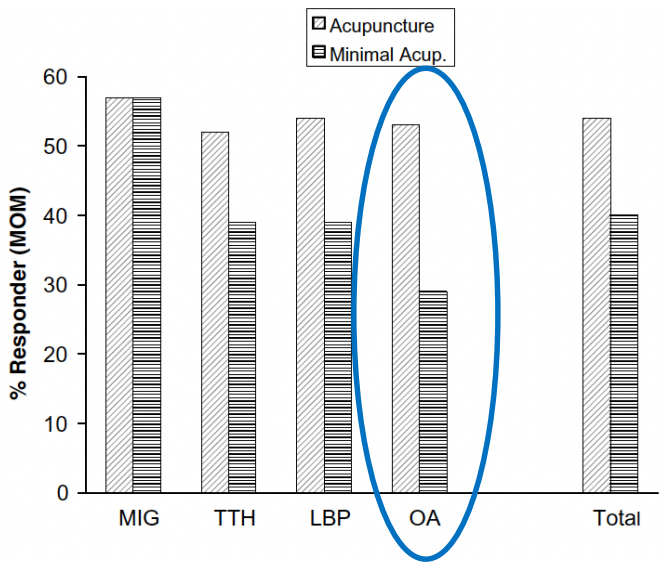
The role of expectations

The impact of patient expectations on outcomes in four randomized controlled trials of acupuncture in patients with chronic pain

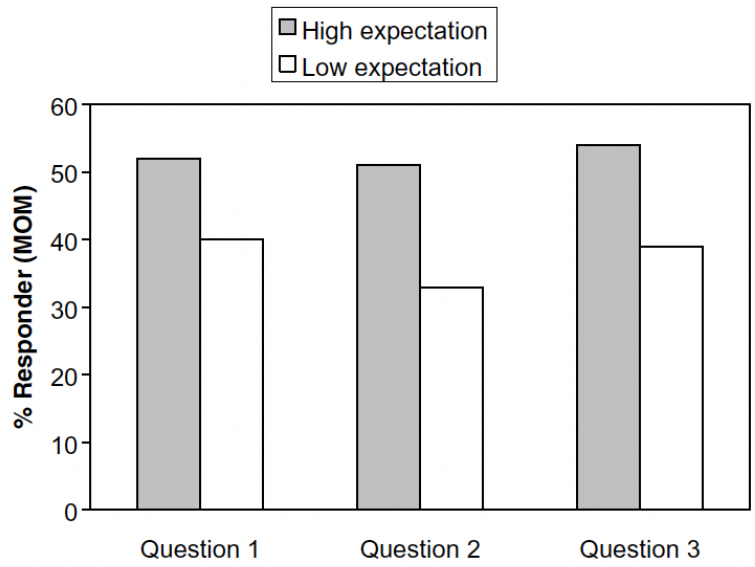
Klaus Linde [a,*], Claudia M. Witt [b], Andrea Streng [a], Wolfgang Weidenhammer [a], Stefan Wagenpfeil [c], Benno Brinkhaus [b], Stefan N. Willich [b], Dieter Melchart [a,d]

[a] *Centre for Complementary Medicine Research, Department of Internal Medicine II, Technische Universität München, Kaiserstr. 9, 80801 Munich, Germany*
[b] *Institute of Social Medicine, Epidemiology, and Health Economics, Charité University Medical Centre, Berlin, Germany*
[c] *Institute of Medical Statistics and Epidemiology, Technische Universität München, Munich, Germany*
[d] *Division of Complementary Medicine, Department of Internal Medicine, University Hospital Zurich, Switzerland*

Received 27 June 2006; received in revised form 14 November 2006; accepted 4 December 2006



Significant difference only in OA patients



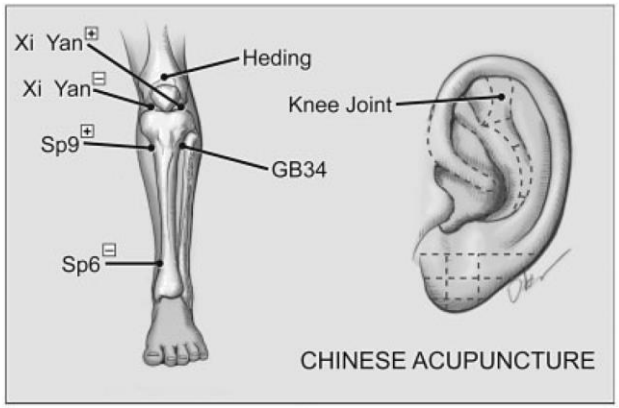
Significant effects of expectations in both sham and acupuncture groups

Arthritis Care & Research
Vol. 62, No. 9, September 2010, pp 1229–1236
DOI 10.1002/acr.20225

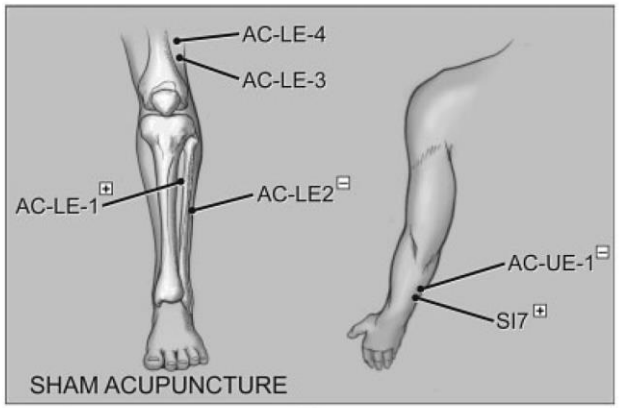
ORIGINAL ARTICLE

A Randomized Controlled Trial of Acupuncture for Osteoarthritis of the Knee: Effects of Patient-Provider Communication

MARIA E. SUAREZ-ALMAZOR,[1] CAROL LOONEY,[1] YANFANG LIU,[2] VANESSA COX,[1] KENNETH PIETZ,[3] DONALD M. MARCUS,[3] AND RICHARD L. STREET, JR.[4]



A



B

Table 2. Outcome measures by acupuncture treatment group*

	Baseline		4 weeks		6 weeks		3 months			Waiting list		
	TCA	Sham	TCA	Sham	TCA	Sham	TCA	Sham	P†	Baseline	3 months	P‡
J-MAP§	4.4 ± 1.3	4.4 ± 1.3	3.3 ± 1.3	3.4 ± 1.3	3.1 ± 1.3	3.3 ± 1.4	3.3 ± 1.4	3.4 ± 1.5	> 0.20	4.3 ± 1.2	4.2 ± 1.3	0.0003¶
WOMAC pain§	44.5 ± 18.4	45.0 ± 18.2	31.8 ± 17.5	32.6 ± 17.2	28.1 ± 18.4	28.9 ± 18.6	30.8 ± 17.9	31.0 ± 19.1	> 0.20	44.1 ± 15.2	42.4 ± 16.8	0.0002¶
WOMAC function§	42.9 ± 19.0	44.6 ± 18.1	32.3 ± 17.7	34.1 ± 17.1	29.5 ± 17.8	31.4 ± 18.5	31.2 ± 17.9	32.1 ± 18.3	> 0.20	40.1 ± 16.5	41.7 ± 18.0	0.0003¶
SKIP#	n/a	n/a	4.15 ± 0.68	4.10 ± 0.68	4.13 ± 0.80	4.04 ± 0.79	4.00 ± 0.85	3.95 ± 0.78	> 0.20	n/a	n/a	n/a
VAS pain§	58.3 ± 22.3	57.4 ± 23.5	34.8 ± 25.9	38.2 ± 25.4	29.0 ± 26.3	32.5 ± 27.8	36.2 ± 28.5	36.7 ± 29.0	> 0.20	54.6 ± 21.3	53.2 ± 24.3	0.0001¶
SF-12 PCS#	35.0 ± 9.9	33.5 ± 8.7	38.5 ± 10.0	37.7 ± 9.1	40.5 ± 10.0	39.0 ± 9.9	39.5 ± 9.7	38.7 ± 10.1	> 0.20	35.3 ± 8.4	35.8 ± 8.9	0.11
SF-12 MCS#	52.3 ± 9.4	53.4 ± 9.3	53.9 ± 8.3	54.2 ± 8.9	53.4 ± 7.9	54.0 ± 8.7	54.1 ± 8.2	53.2 ± 8.9	> 0.20	53.7 ± 10.7	51.6 ± 9.8	0.11
TUG, seconds§	13.9 ± 7.3	13.4 ± 5.5	n/a	n/a	12.2 ± 4.3	12.2 ± 5.0	11.9 ± 4.1	12.1 ± 5.4	> 0.20	12.3 ± 3.3	12.2 ± 3.5	> 0.20
ROM, degrees#	105.7 ± 13.7	105.7 ± 13.1	n/a	n/a	106.1 ± 12.8	106.7 ± 13.1	106.2 ± 12.1	106.5 ± 12.6	> 0.20	105.7 ± 13.0	104.9 ± 13.7	> 0.20

* Values are the mean ± SD. SKIP = Satisfaction with Knee Procedure; n/a = not administered. See Table 1 for additional definitions.
† For repeated-measures models testing for difference in means across time excluding the waiting list group.
‡ Including the waiting list group.
§ Improvement is seen as negative differences.
¶ Statistically significant ($P \leq 0.05$).
# Improvement is seen as positive differences.

Sham and acupuncture induced similar effects, but in both groups the analagesic effects were directly related to expectations and "acupuncturists' style"

BMJ Open

Development of the generic, multidimensional Treatment Expectation Questionnaire (TEX-Q) through systematic literature review, expert surveys and qualitative interviews

Jannis Alberts ,[1] Bernd Löwe ,[1] Maja Alicia Glahn,[1] Keith Petrie ,[2] Johannes Laferton ,[3] Yvonne Nestoriuc ,[4,5] Meike Shedden-Mora [1]

CLINICAL TRIALS ARTICLE

Clinical Trials 2012; **0:** 1–10

Development of the Stanford Expectations of Treatment Scale (SETS): A tool for measuring patient outcome expectancy in clinical trials

Jarred Younger, Vanisha Gandhi, Emily Hubbard and Sean Mackey

	Strongly Disagree	Moderately Disagree	Slightly Disagree	Agree Nor Disagree	Slightly Agree	Moderately Agree	Strongly Agree
1. This treatment will be completely effective	o	o	o	o	o	o	o
2. I am worried about my treatment.	o	o	o	o	o	o	o
3. My condition will be completely resolved after treatment	o	o	o	o	o	o	o
4. I have fears about this treatment	o	o	o	o	o	o	o
5. I have complete confidence in this treatment	o	o	o	o	o	o	o
6. I am nervous about the negative effects of this treatment	o	o	o	o	o	o	o

7. What treatment are you going to receive?

_____

8. What specific benefits (if any) do you expect to receive from this treatment?

_____

9. What specific harms or negative side-effects (if any) do you think may occur because of this treatment?

_____

10. Have you ever received this treatment before? ☐ Yes ☐ No

Table 3 Illustrative TEX-Q items for each subscale

Expected benefits												
How much relief in your symptoms do you expect from the treatment?												
No relief	□	□	□	□	□	□	□	□	□	□	□	Complete relief
	0	1	2	3	4	5	6	7	8	9	10	
Expected positive impact												
How much improvement do you expect in your ability to do your daily activities (eg, occupation, household, social life)?												
No improvement	□	□	□	□	□	□	□	□	□	□	□	Complete improvement
	0	1	2	3	4	5	6	7	8	9	10	
Expected harm												
To what extent do you expect risks from your treatment?												
No risks	□	□	□	□	□	□	□	□	□	□	□	Extreme risks
	0	1	2	3	4	5	6	7	8	9	10	
Expected negative impact												
How much do you expect the treatment will reduce your quality of life?												
Not at all	□	□	□	□	□	□	□	□	□	□	□	Extremely
	0	1	2	3	4	5	6	7	8	9	10	
Desired benefits												
How much benefit do you hope for from the treatment?												
No benefit	□	□	□	□	□	□	□	□	□	□	□	Extreme benefit
	0	1	2	3	4	5	6	7	8	9	10	
Desired impact												
How much improvement do you hope for considering your emotional state?												
No improvement	□	□	□	□	□	□	□	□	□	□	□	Extreme improvement
	0	1	2	3	4	5	6	7	8	9	10	
Feared harm												
To what extent do you fear risks from the treatment?												
No risk	□	□	□	□	□	□	□	□	□	□	□	Extreme risk
	0	1	2	3	4	5	6	7	8	9	10	
Feared negative impact												
How much do you fear the treatment will limit your day-to-day responsibilities (eg, at home, at work, in the family)?												
Not at all	□	□	□	□	□	□	□	□	□	□	□	Extremely
	0	1	2	3	4	5	6	7	8	9	10	
Process-related expectations												
To what extent do you expect to be satisfied with the treatment procedure or process?												
Not at all	□	□	□	□	□	□	□	□	□	□	□	Extremely
	0	1	2	3	4	5	6	7	8	9	10	
Expected behavioural control of the treatment												
To what extent do you expect your own behaviour to influence the success of the treatment?												
Not at all	□	□	□	□	□	□	□	□	□	□	□	Extremely
	0	1	2	3	4	5	6	7	8	9	10	

TEX-Q, Treatment Expectation Questionnaire.

Other studies have reported variable effects of expectations in clinical studies

Haanstra *et al. Health and Quality of Life Outcomes* 2012, **10**:152
http://www.hqlo.com/content/10/1/152

HEALTH AND QUALITY OF LIFE OUTCOMES

RESEARCH Open Access

Systematic review: Do patient expectations influence treatment outcomes in total knee and total hip arthroplasty?

Tsjitske M Haanstra[1*], Tobias van den Berg[1], Raymond W Ostelo[1,2], Rudolf W Poolman[3], Ilse P Jansma[4], Pim Cuijpers[5] and Henrica CW de Vet[1]

Complementary Therapies in Medicine (2015) **23**, 185–199

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journal homepage: www.elsevierhealth.com/journals/ctim

Measuring expectations of benefit from treatment in acupuncture trials: A systematic review☆

Stephanie L. Prady[a,*], Jane Burch[b], Laura Vanderbloemen[c], Simon Crouch[a], Hugh MacPherson[a]

CrossMark

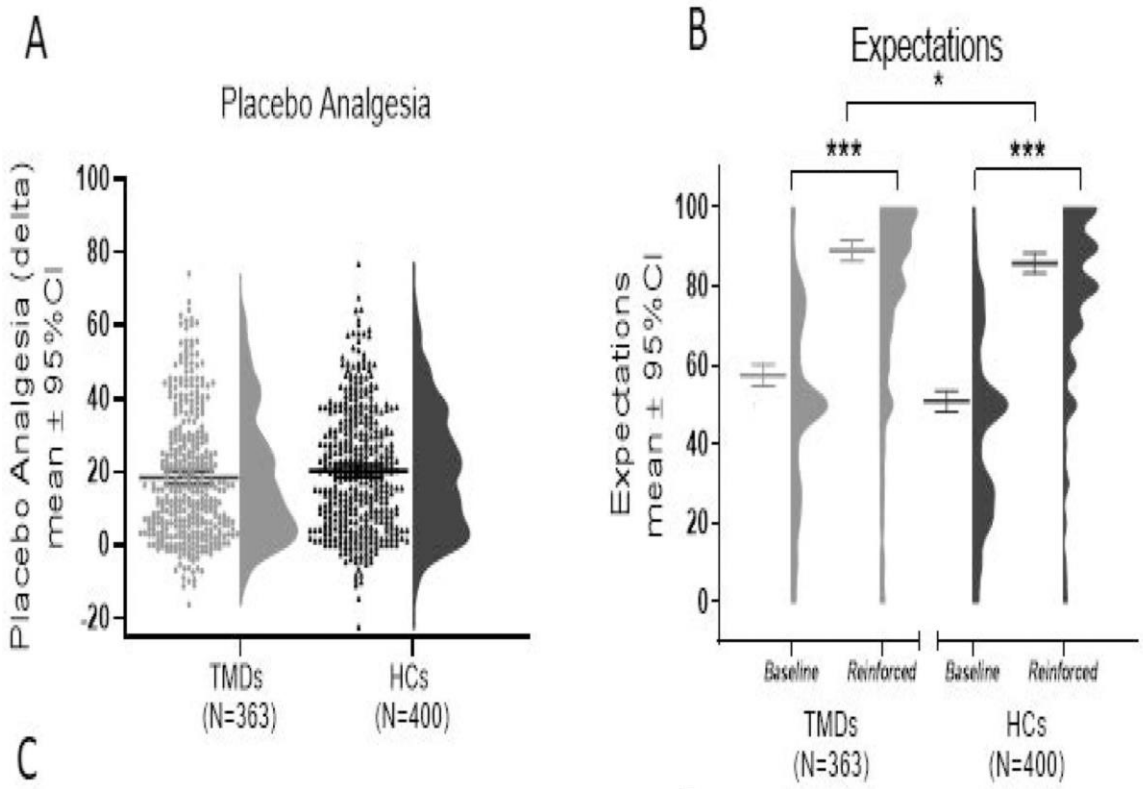
Importance of unconscious expectations?

Published in final edited form as:
Psychother Psychosom. 2020 ; 89(6): 371–378. doi:10.1159/000507400.

Prior therapeutic experiences, not expectation ratings, predict placebo effects: An experimental study in chronic pain and healthy participants

Luana Colloca[1,2,3], **Titilola Akintola**[1,3], **Nathaniel R Haycock**[1], **Maxie Blasini**[1], **Sharon Thomas**[1], **Jane Phillips**[4], **Nicole Corsi**[1], **Lieven A. Schenk**[1,3], **Yang Wang**[1,3]

[1]Department of Pain and Translational Symptom Science, University of Nursing, University of Maryland, Baltimore, US



Similar placebo analgesia in TMD patients and HCs but, in patients, analgesia was not mediated by expectations

The role of classical conditioning has been well established in experimental setting, but less in clinical studies

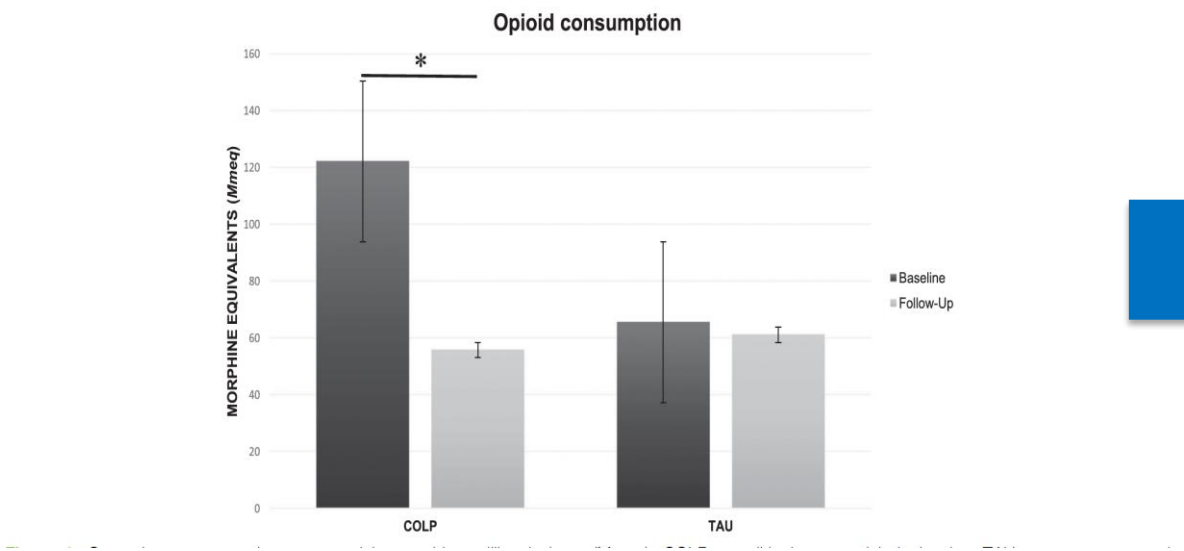
Pharmacology
Brief Report

OPEN

PAIN REPORTS®

Conditioning open-label placebo: a pilot pharmacobehavioral approach for opioid dose reduction and pain control

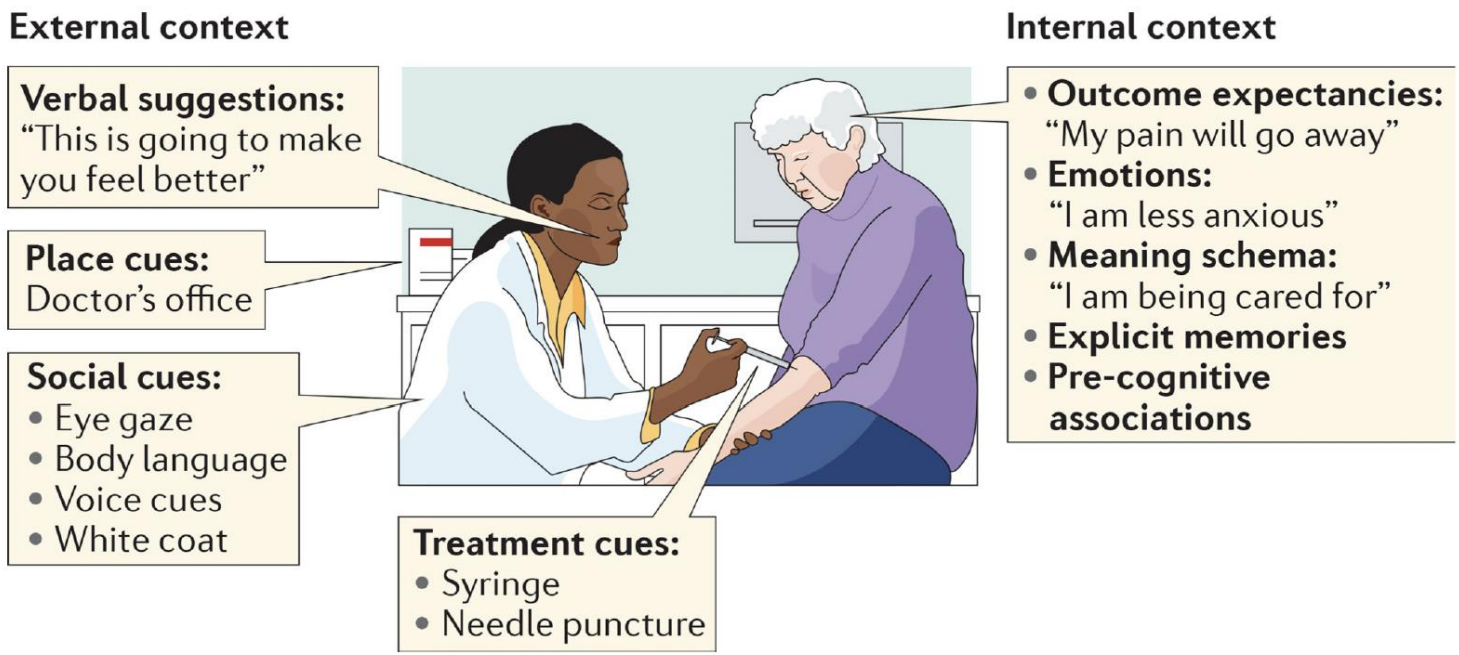
Leon Morales-Quezada[a,*], Ines Mesia-Toledo[a], Anayali Estudillo-Guerra[a], Kevin C. O'Connor[a], Jeffrey C. Schneider[a], Douglas J. Sohn[a], David M. Crandell[a], Ted Kaptchuk[b], Ross Zafonte[a]



It is possible to decrease opioids consumption, by pairing opioids with placebo administration

Main determinants of the placebo effect

- Clinical encounter
- Patient-physician relationship (attention, empathy, trust, competence, proximity, etc.)
- Quality of the doctor-patient communication (verbal and non verbal)
- Associative processes
- Medical Ritual

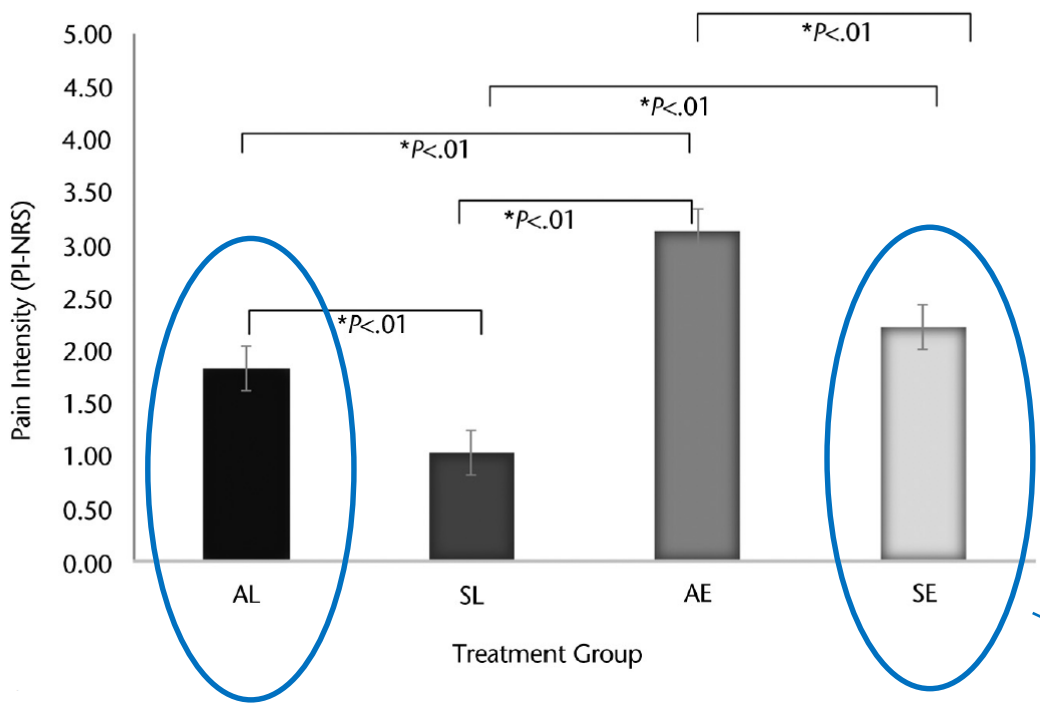


How to investigate further the role of contextual factors?

Enhanced Therapeutic Alliance Modulates Pain Intensity and Muscle Pain Sensitivity in Patients With Chronic Low Back Pain: An Experimental Controlled Study

Jorge Fuentes, Susan Armijo-Olivo, Martha Funabashi, Maxi Miciak, Bruce Dick, Sharon Warren, Saifee Rashiq, David J. Magee, Douglas P. Gross

Four groups of LBP patients receiving active or sham electrotherapy associated with enhanced or limited TA



High TA increased the effects of both sham and active electrotherapy

Sham treatment with enhanced TA was better than active treatment with low TA

Are there predicting factors of the placebo effect ?

- Learning and conditioning: prior experiences of pain and of treatment
- Patients characteristics (extraversion, agreeableness, openness, less emotional distress or catastrphizing)
- Practitioner characteristics (expectancy of pain relief, empathy)
- Verbal suggestions (Vase et al., 2003; Verne et al. 2003)
- Patients-practitioner relationship (Kaptchuk et al., 2008)

Patients expectations about pain relief: are they predictive?

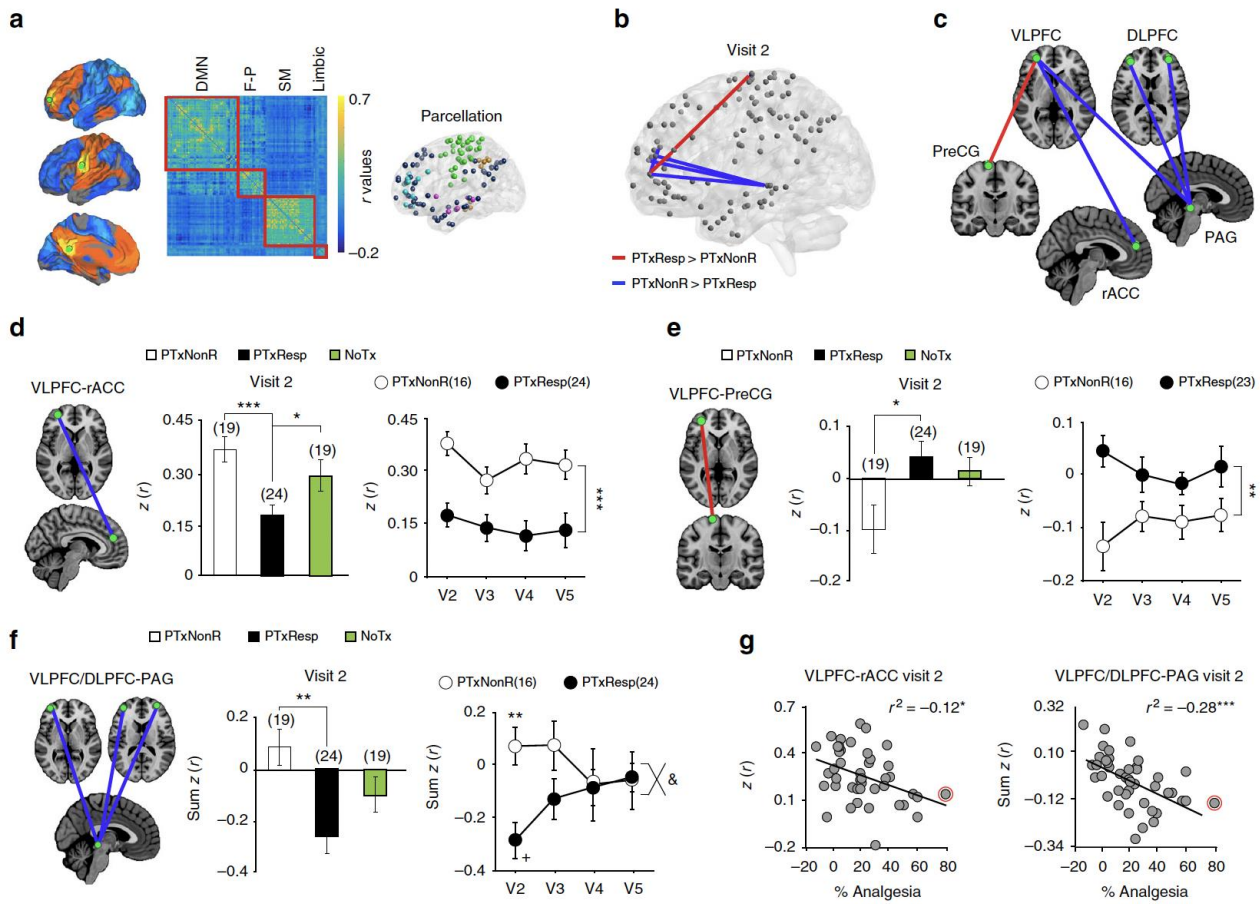
nature COMMUNICATIONS

ARTICLE

DOI: 10.1038/s41467-018-05859-1 OPEN

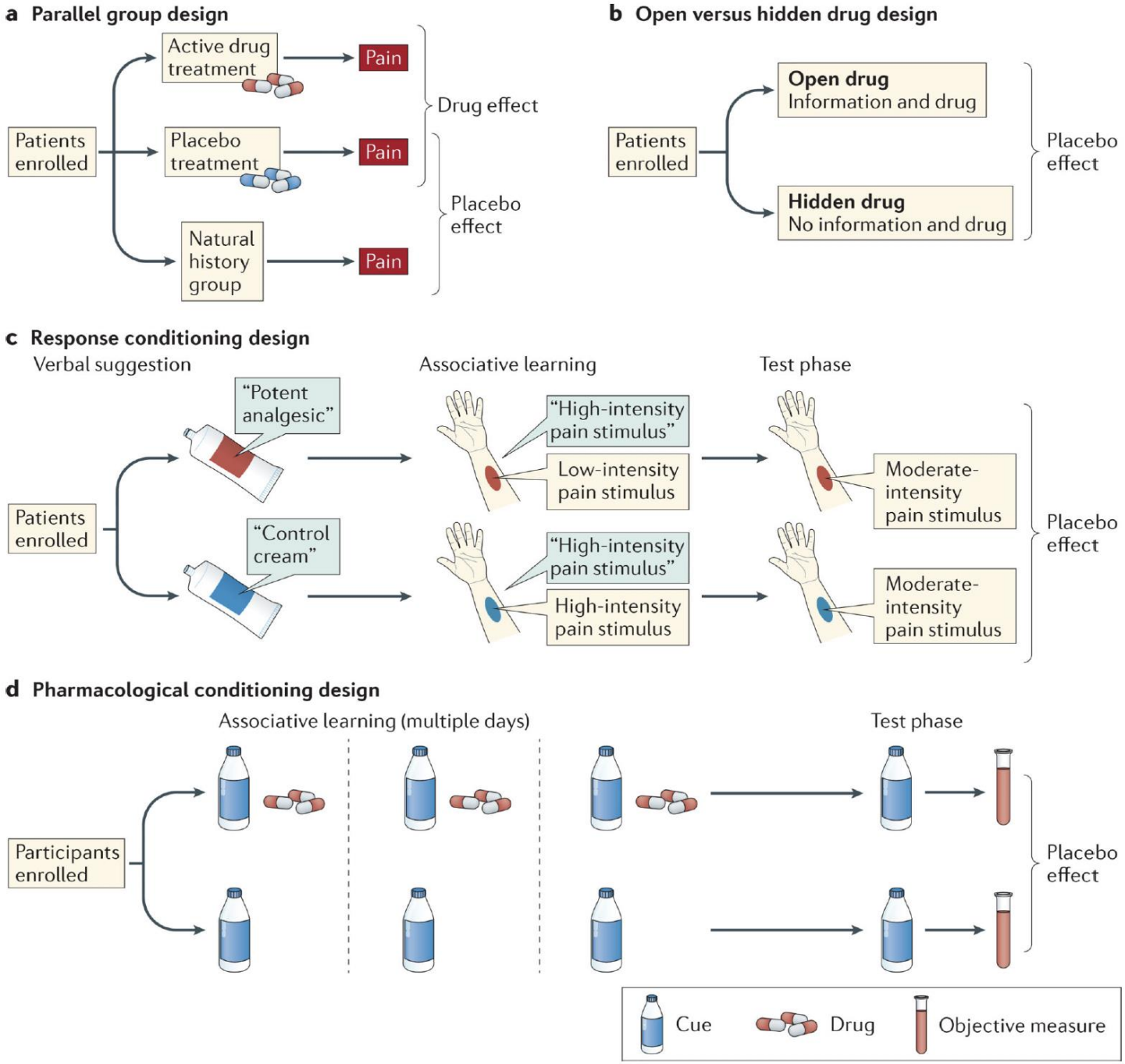
Brain and psychological determinants of placebo pill response in chronic pain patients

Etienne Vachon-Presseau[1], Sara E. Berger[1,2], Taha B. Abdullah[1], Lejian Huang[1], Guillermo A. Cecchi[2], James W. Griffith[3], Thomas J. Schnitzer[4,5] & A. Vania Apkarian[1,5,6]



Specific brain connectivity patterns can predict the placebo effect

Study designs used to analyse the placebo effect

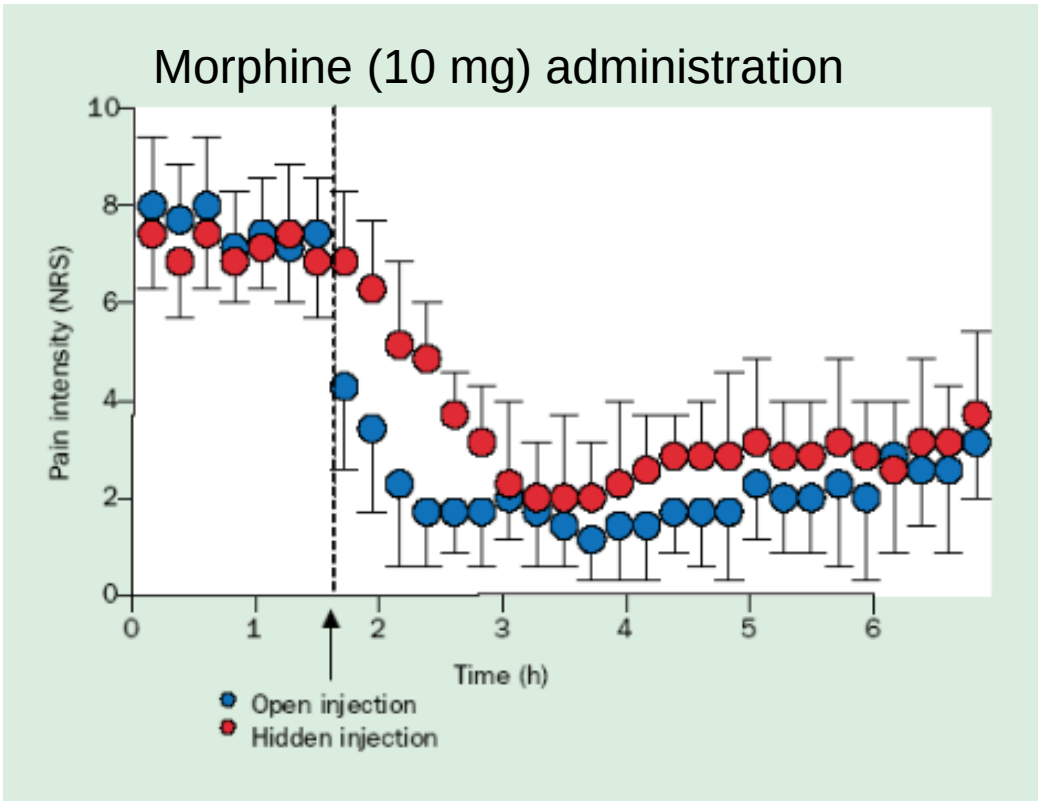


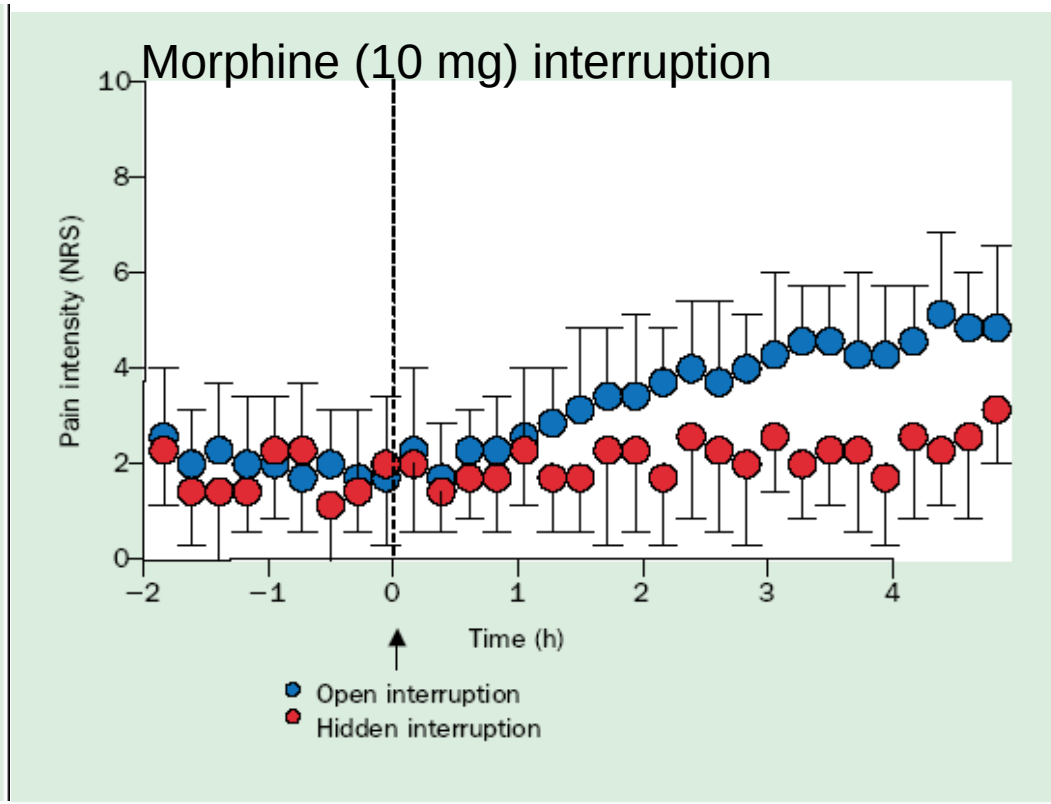
Which study design to better assess the placebo and non specific effects?

Most of the RCTs analyzed the placebo response, but not the placebo effect

- Open-hidden treatment
- Balanced-placebo design
- Double-blind vs decetptive
- Dose-Extending placebo design
- Open label design

The Open-Hidden administration paradigm

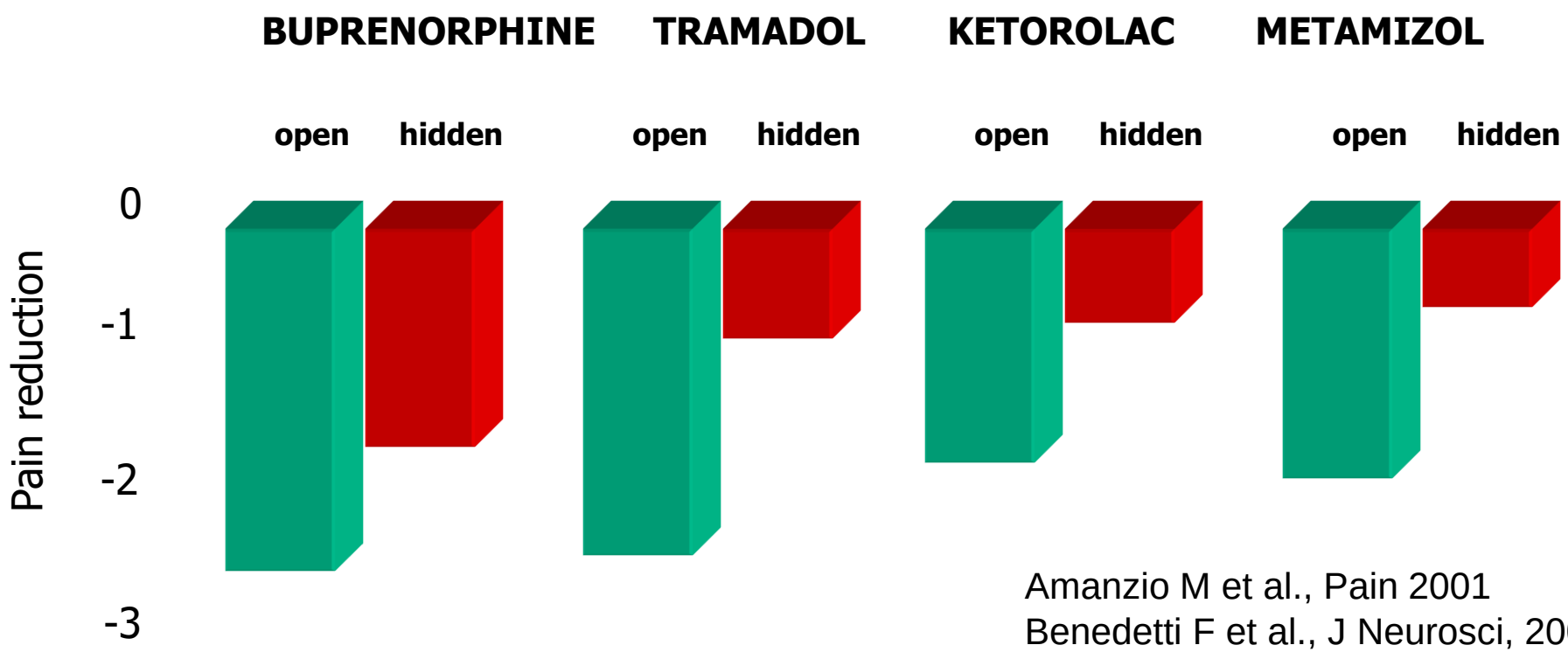




Colloca L, et al. Lancet Neurol. 2004;679-84

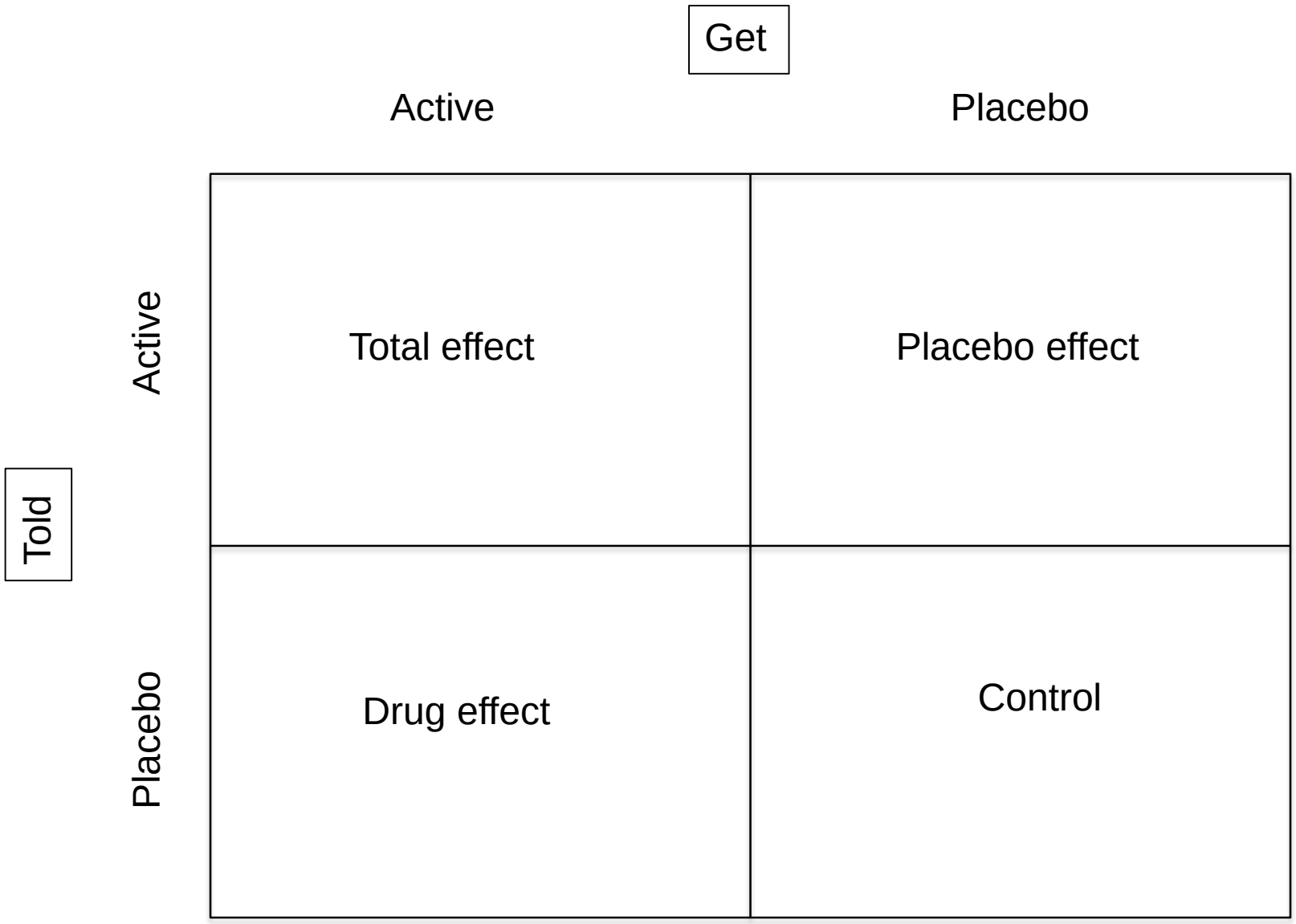
Placebo effects without any placebos

Open-hidden paradigm



Amanzio M et al., Pain 2001
Benedetti F et al., J Neurosci, 2003
Colloca et al, Lancet Neurol., 2004

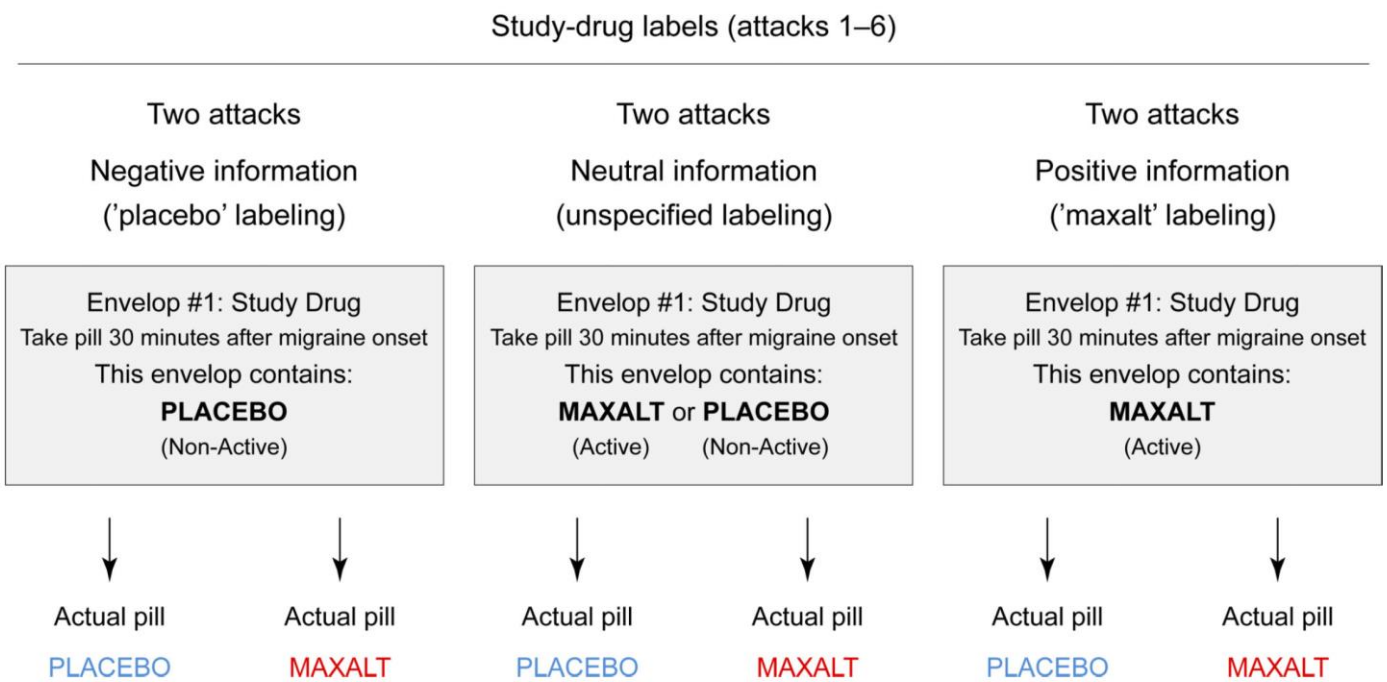
The balanced-placebo design: control for the role of verbal information



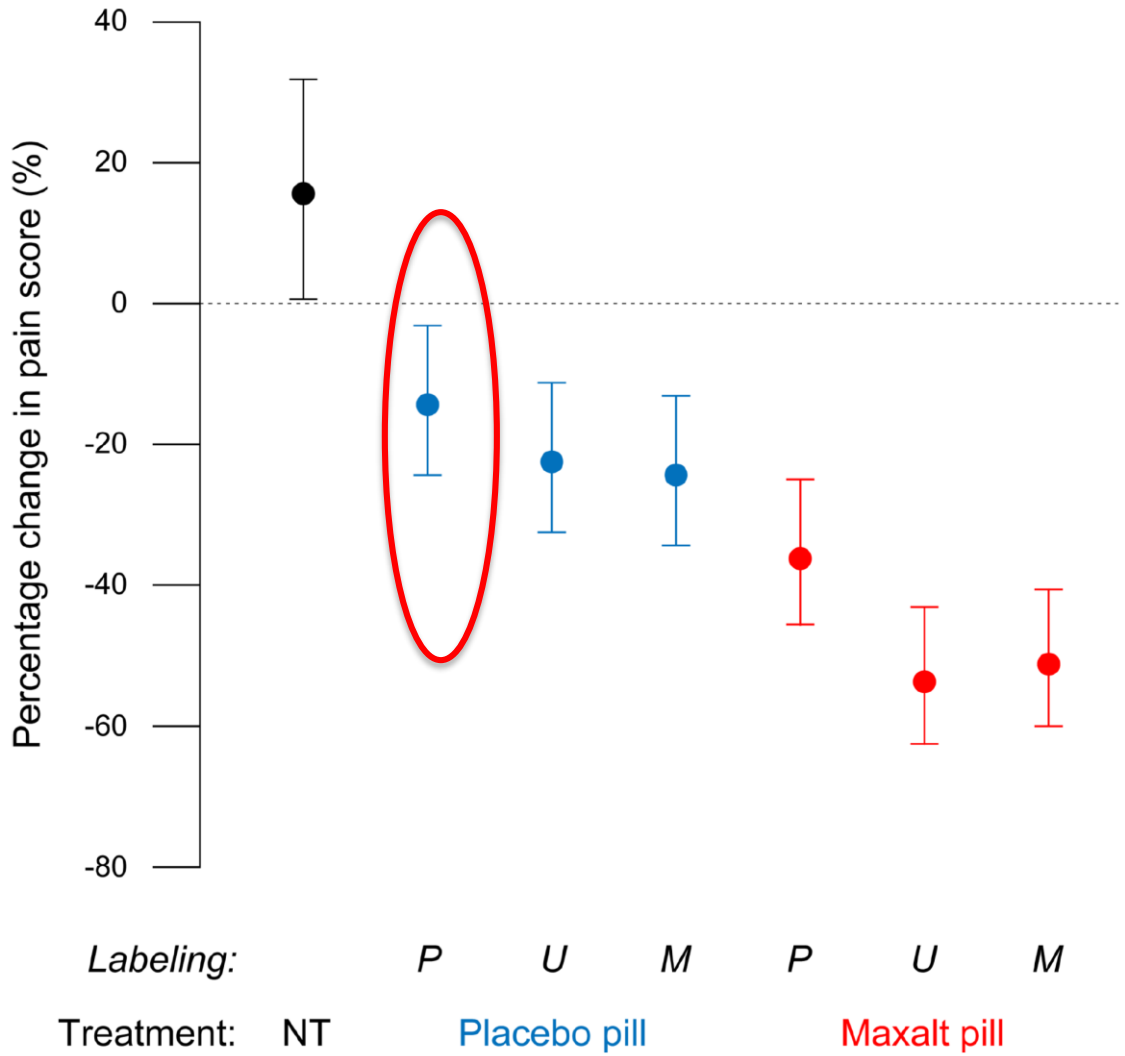
Published in final edited form as:
Sci Transl Med. 2014 January 8; 6(218): 218ra5. doi:10.1126/scitranslmed.3006175.

Labeling of Medication and Placebo Alters the Outcome of Episodic Migraine Attacks

Slavenka Kam-Hansen[1], **Moshe Jakubowski**[2], **John M. Kelley**[3,4,5], **Irving Kirsch**[5,7], **David C. Hoaglin**[6], **Ted J. Kaptchuk**[5,*], and **Rami Burstein**[2,*]



Results



1 - The placebo presented as active was similar to the active presented as placebo

2 - More than 50% of the active drug effects can be attributed to the placebo effect

3 - The placebo presented as placebo was better than no treatment.

Research Paper

PAIN

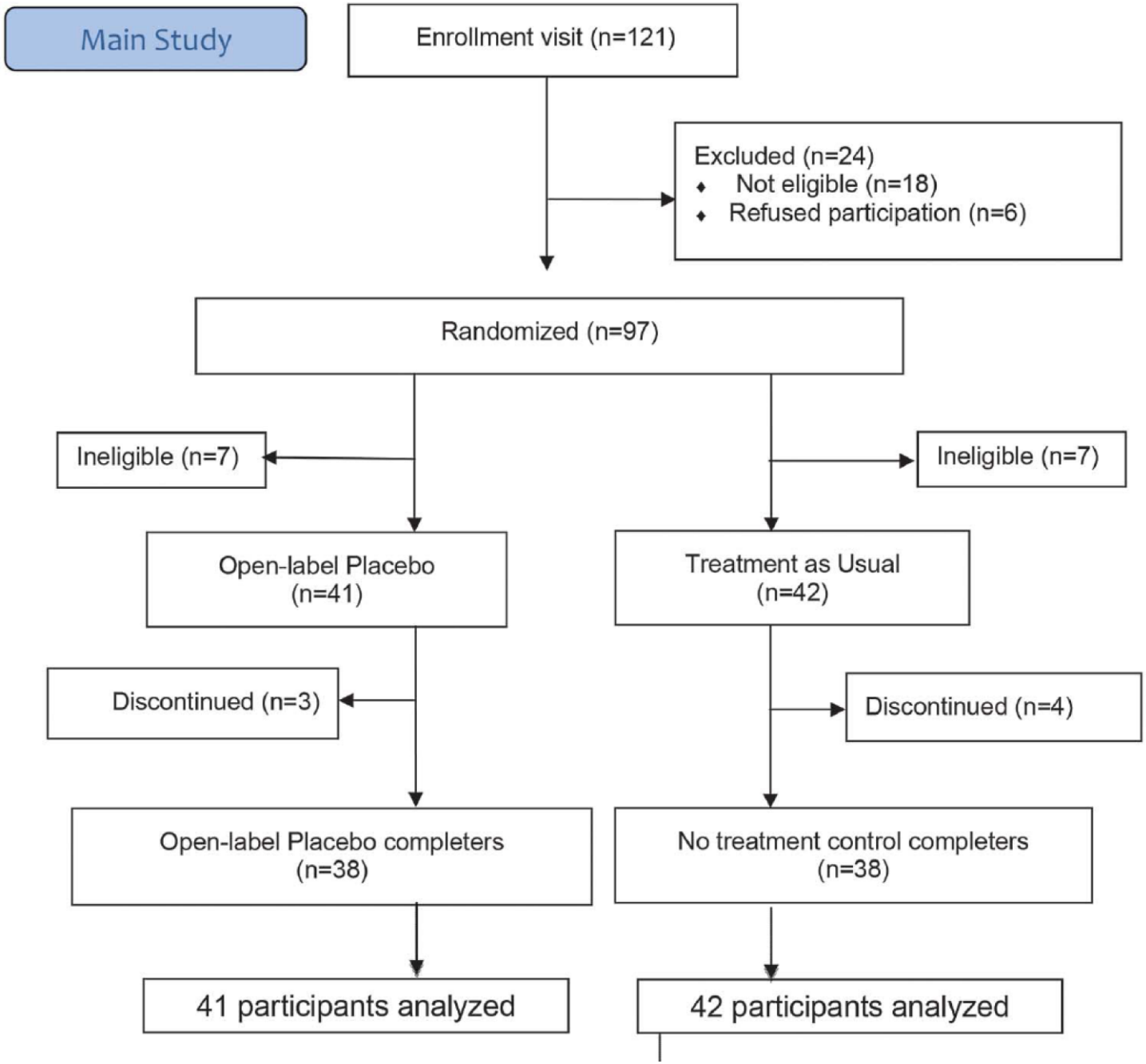
OPEN

Open-label placebo treatment in chronic low back pain: a randomized controlled trial

Cláudia Carvalho[a,*], Joaquim Machado Caetano[b], Lidia Cunha[c], Paula Rebouta[c], Ted J. Kaptchuk[d], Irving Kirsch[d]

Is it possible to induce a placebo effect
without diceiving the patients?

Flow chart


Main Study
Enrollment visit (n=121)
Excluded (n=24)
Not eligible (n=18)
Refused participation (n=6)
Randomized (n=97)
Ineligible (n=7)
Ineligible (n=7)
Open-label Placebo (n=41)
Treatment as Usual (n=42)
Discontinued (n=3)
Discontinued (n=4)
Open-label Placebo completers (n=38)
No treatment control completers (n=38)
41 participants analyzed
42 participants analyzed

Results

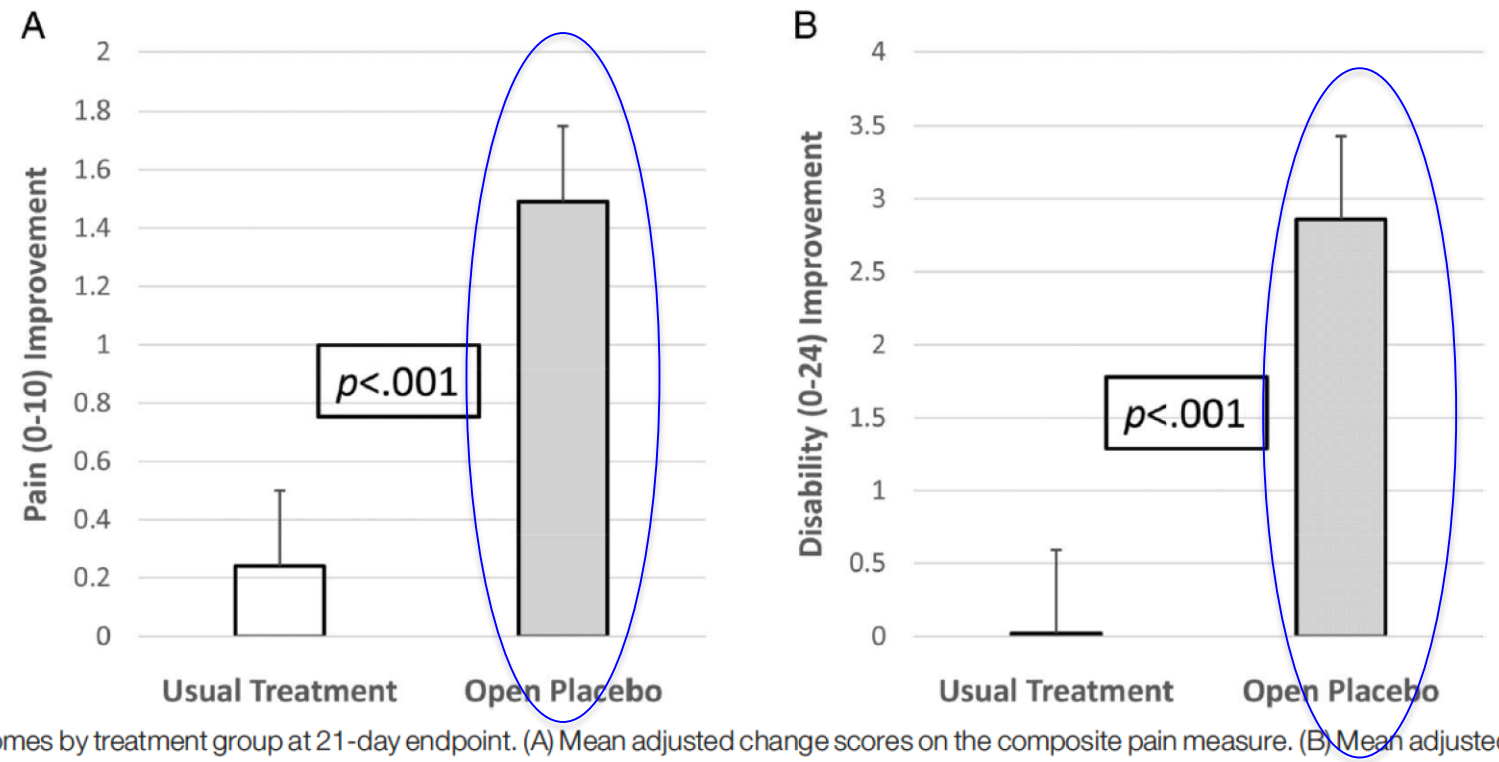


Figure 2. Outcomes by treatment group at 21-day endpoint. (A) Mean adjusted change scores on the composite pain measure. (B) Mean adjusted change scores on the 24-item Roland–Morris Disability Questionnaire. Error bars represent standard errors of the mean.

Effects on pain

mean = 30 %

Effects on function

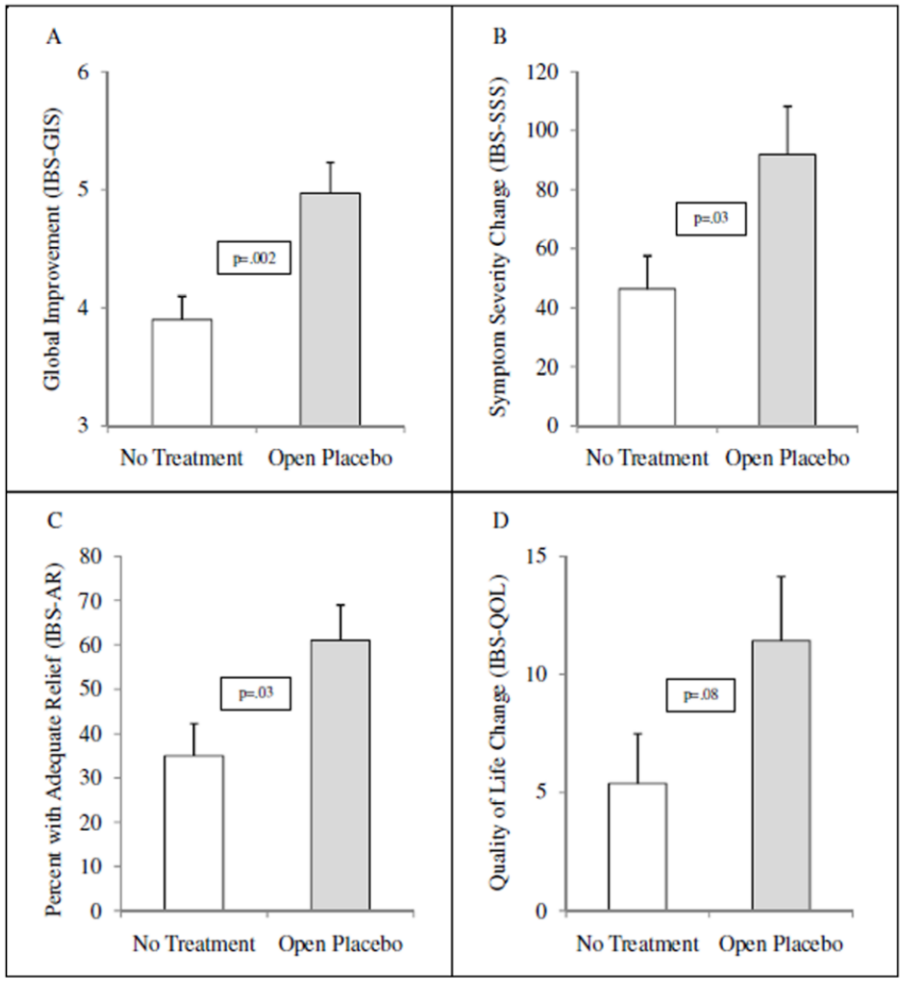
OPEN ACCESS Freely available online

PLoS one

Placebos without Deception: A Randomized Controlled Trial in Irritable Bowel Syndrome

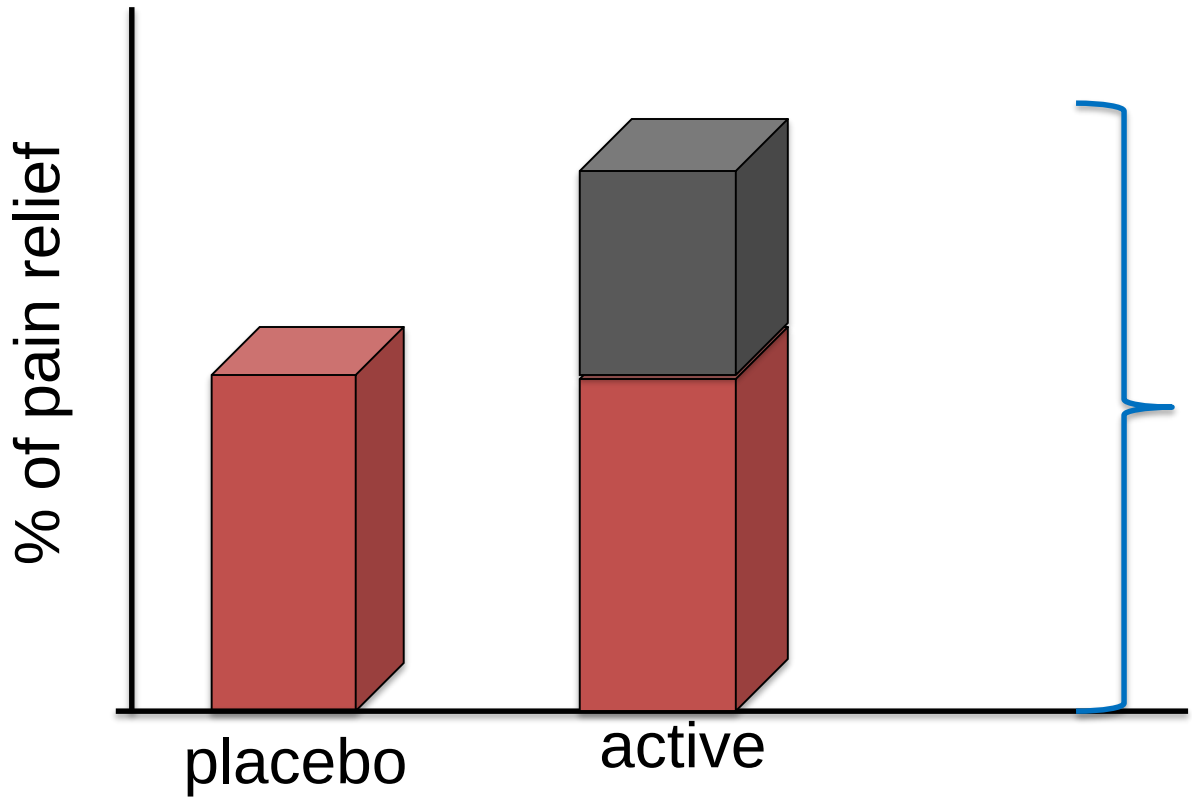
Ted J. Kaptchuk[1,2]*, Elizabeth Friedlander[1], John M. Kelley[3,4], M. Norma Sanchez[1], Efi Kokkotou[1], Joyce P. Singer[2], Magda Kowalczykowski[1], Franklin G. Miller[5], Irving Kirsch[6], Anthony J. Lembo[1]

1 Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts, United States of America, **2** Osher Research Center, Harvard Medical School, Boston, Massachusetts, United States of America, **3** Psychology Department, Endicott College, Beverly, Massachusetts, United States of America, **4** Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, United States of America, **5** Department of Bioethics, National Institutes of Health, Bethesda, Maryland, United States of America, **6** Department of Psychology, University of Hull, Hull, United Kingdom



Satisfactory pain relief in 59% of the patients

Is the additivity assumption true?



The drug effect is the sum of the placebo and specific effects

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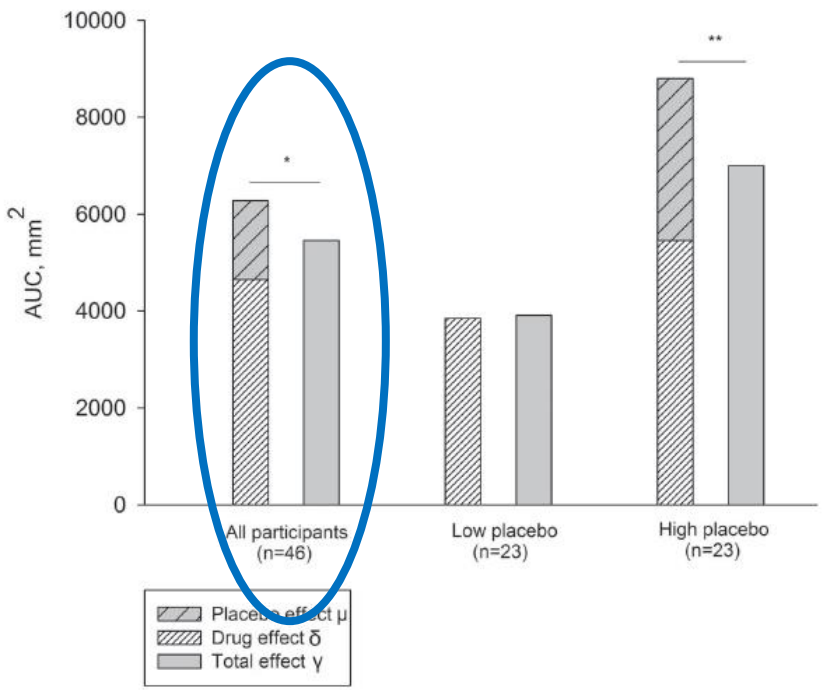
PLOS ONE

Randomised Controlled Trials May Underestimate Drug Effects: Balanced Placebo Trial Design

Karen Lund[1]*, Lene Vase[2], Gitte L. Petersen[2], Troels S. Jensen[1], Nanna B. Finnerup[1]

1 Danish Pain Research Center, Aarhus University Hospital, Aarhus, Denmark, **2** Department of Psychology, School of Business and Social Sciences, Aarhus University, Aarhus, Denmark



The total effect was lower than placebo + drug effect

Figure 3. Subadditive placebo and drug effects. Mean area under the curve (AUC) for the sum of the drug effect and the placebo effect (δ+ μ) and for the total treatment effect (γ) for all participants and for the groups with low and high placebo effects.* P<0.05, ** P<0.01.
doi:10.1371/journal.pone.0084104.g003

Has the placebo effect increased over the last decade?

- This has been reported in studies related to antidepressants, antipsychotics (e.g. Bridge et al., 2009 Agid et al., 2014)

- Suggested reasons: the most recent studies were associated with larger sample sizes, longer duration of the study, increase in the number of sites, less un-blinding, etc.

Is it the same in pain studies?

Research Paper

PAIN®

Increasing placebo responses over time in U.S. clinical trials of neuropathic pain

Alexander H. Tuttle[a], Sarasa Tohyama[a], Tim Ramsay[b], Jonathan Kimmelman[c], Petra Schweinhardt[d], Gary J. Bennett[e], Jeffrey S. Mogil[a,*]

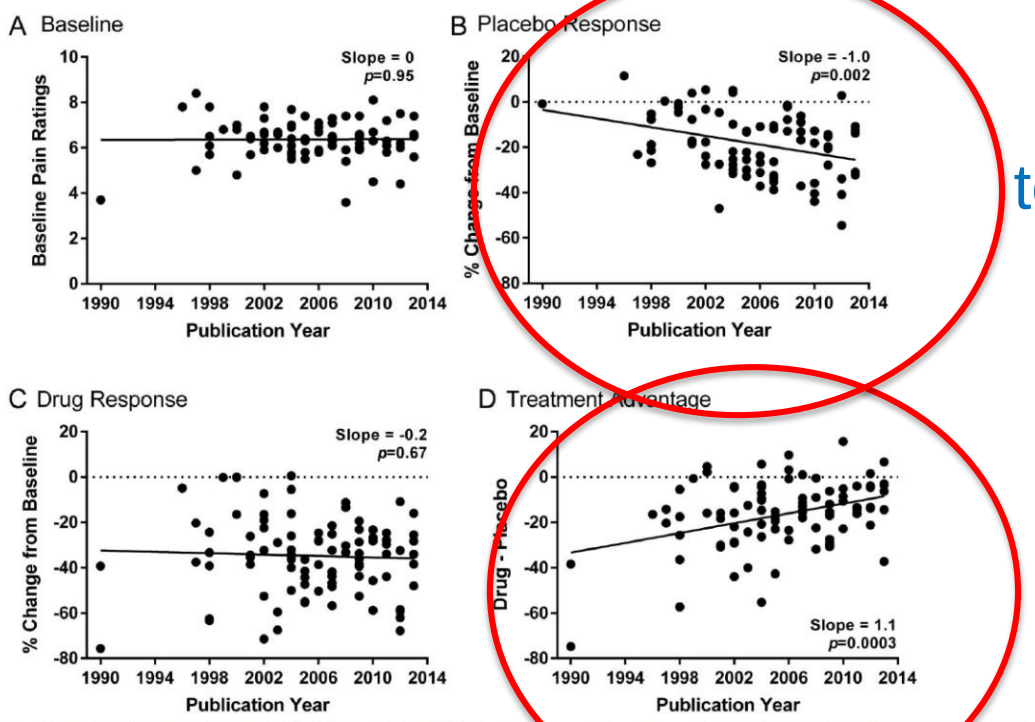


Figure 2. Trends in neuropathic pain trials over the period 1990 to 2013. (A) No change over time was observed in baseline (predrug) pain ratings. Placebo response increased significantly over time (B), but treatment (drug) response (C) did not. Treatment advantage (drug–placebo) decreased significantly over time (D). All *P* values are uncorrected but, in graphs (B) and (D), remain highly significant after Bonferroni correction for multiple comparisons.

Only in the US
a recent analysis tend
to contradict these results

The trend was mainly due
to the studies performed
up to 2000

Is it possible to reduce the placebo effect by excluding the placebo responders?

- Placebo run-in phases,
- Enriched enrollment,
- Randomized withdrawal, etc.

overall, these approaches have not been successful

The placebo effects might be related to the drug effect

The large variability of the placebo responses which might be related to the fact that the response to placebo is more a state than a trait

Conclusions

- Unspecific effects represent a large proportion of the observed responses in pain studies.

- It is important to distinguish placebo effect and placebo response.

- Major improvement in our understanding of the mechanisms of placebo analgesia, but most of the studies were done in healthy volunteers.

- Several factors influence the placebo effect, but no reliable predictors have been identified so far.

- Expected level of pain relief and desire for pain relief seem to be major determinants (predictors?) of the placebo effect.

- Is the placebo effect a state or trait?