Mechanisms and Utility of the Placebo Effect in Clinical Research and Practice

Joe Kossowsky, PhD
joe_kossowsky@hms.harvard.edu

Boston Children's Hospital
Until every child is well™

Program in Placebo Studies
& the Therapeutic Encounter
Beth Israel Deaconess Medical Center
Harvard Medical School

Overview

- What is the Placebo Effect?
- Mechanisms of Action & Components
- Pain Perception & Placebo Analgesia
- Acupuncture, Pain, and Placebo Effects
- Conclusions

Terms and Concepts

Placebo: “I shall please”: Placebo domino in regione vivorum; psalm 116, 9th verse

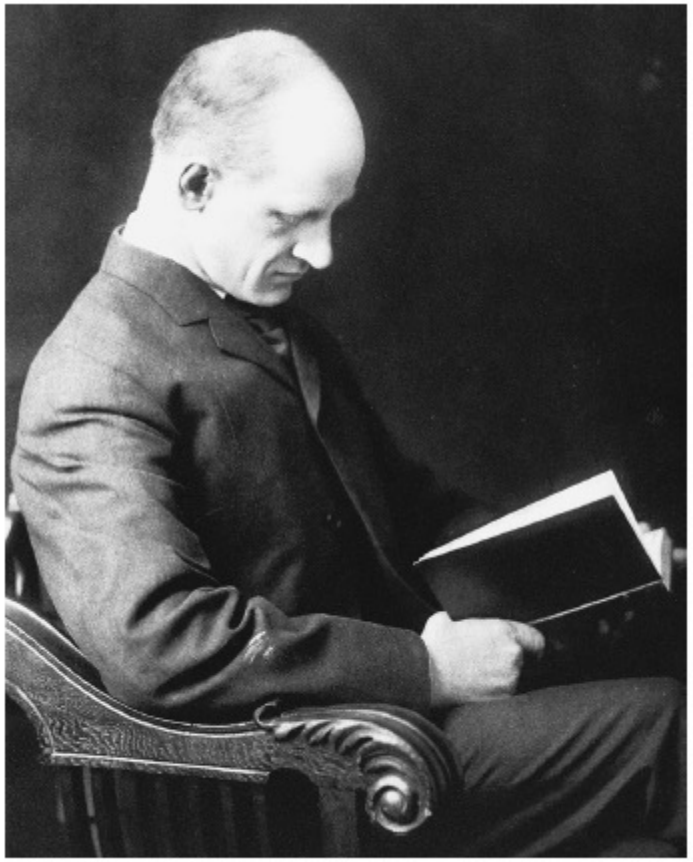
Pure placebo(s): inert intervention (e.g. sugar pill)

Placebo effect(s): a complex and active psycho- and neurobiological phenomenon wherein individuals experience an enhanced benefit via positive expectations and meaning attribution (“meaning response”).

Placebos: Common Clinical Practice, 19th - early 20th Century

- "One of the most successful physicians I have ever known has assured me that he used more bread pills, drops of colored water, and powders of hickory ashes, than of all other medicines put together"
- Thomas Jefferson (1807) on *Pious Fraud*

Early Twentieth Century



Richard Clarke Cabot

Richard Cabot, Professor of Medicine, Harvard Medical School: "[I was] brought up, as I suppose every physician is, to use placebo, bread pills, water subcutaneously, and other devices . . . How frequently such methods are used varies a great deal I suppose with individual practitioners, but I doubt if there is a physician in this room who has not used them and used them pretty often . . . I used to give them by the bushels".

Cabot RC. The use of truth and falsehood in medicine: an experimental study. Am Med 1903.

EFFECTS OF SUGGESTION AND CONDITIONING ON THE ACTION OF CHEMICAL AGENTS IN HUMAN SUBJECTS—THE PHARMACOLOGY OF PLACEBOS [1, 2]

By STEWART WOLF

(From The New York Hospital and Department of Medicine, Cornell University Medical College)

(Received for publication April 18, 1949)

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."[1] 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

Beecher HK. The powerful placebo. JAMA 1955

"It is evident that placebos have a high degree of therapeutic effectiveness in treating subjective responses, [with] decided improvement, interpreted under the unknowns technique [double-masked] as a real therapeutic effect being produced in 35.2 ±2.2% of cases."

National Survey of Placebo Usage

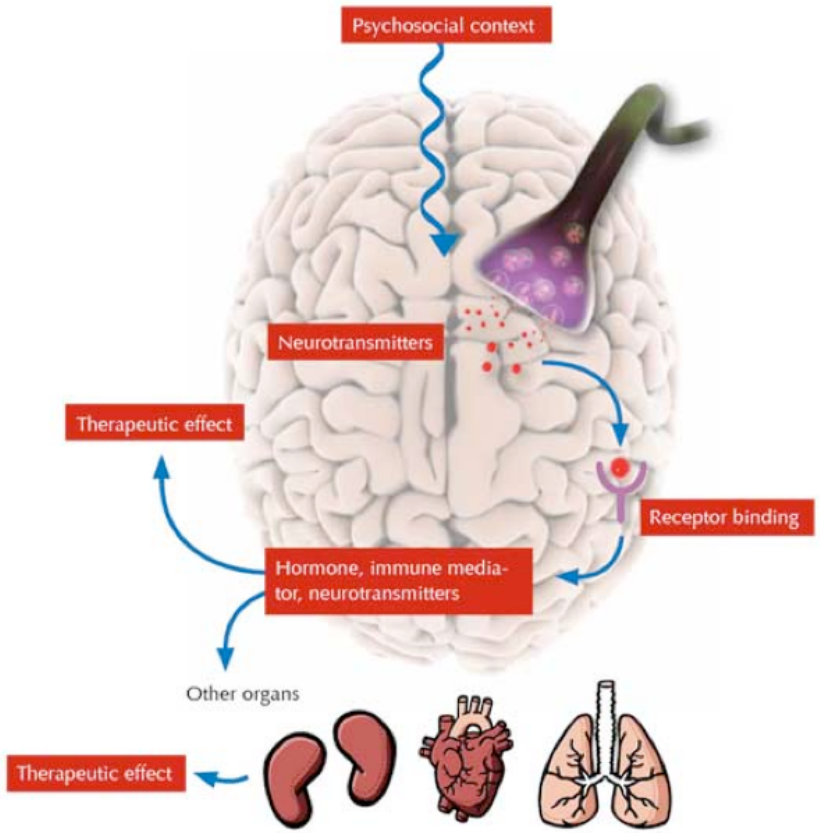
- 50% of US physicians used placebo treatments on a regular basis:
  - 3% saline
  - 2% sugar pills
  - 41% analgesics
  - 38% vitamins
  - 13% antibiotics
  - 13% sedatives

BMJ 2008; 337

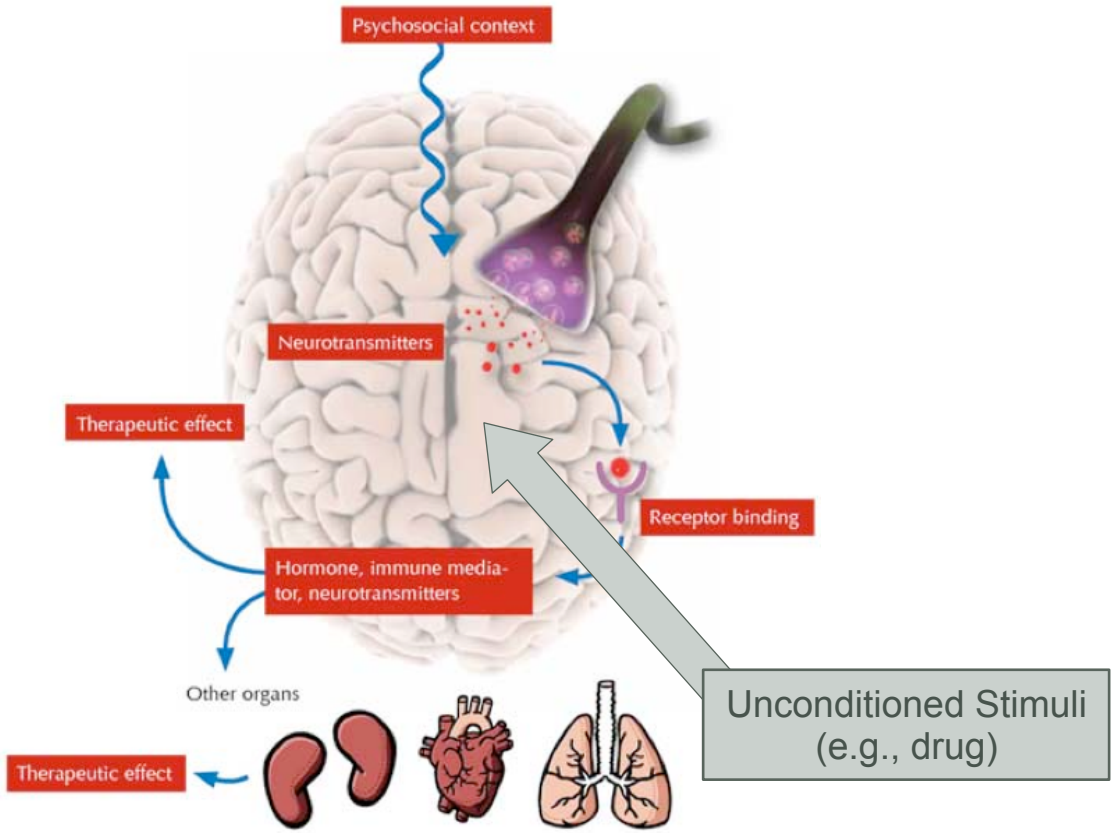
Overview

- What is the Placebo Effect?
- Mechanisms of Action & Components
- Pain Perception & Placebo Analgesia
- Acupuncture, Pain, and Placebo Effects
- Conclusions

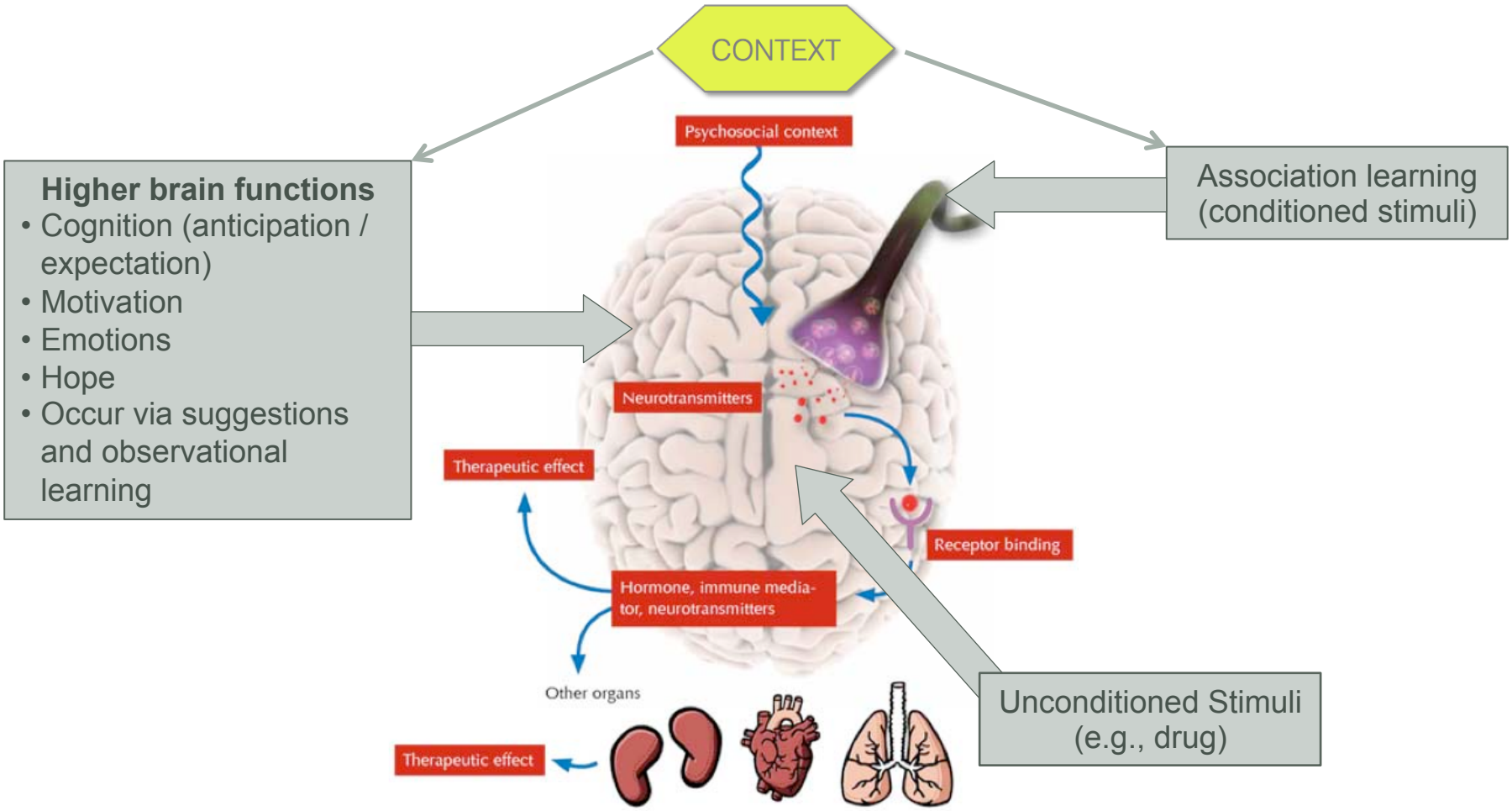
Stimulation of the Psychosocial Context

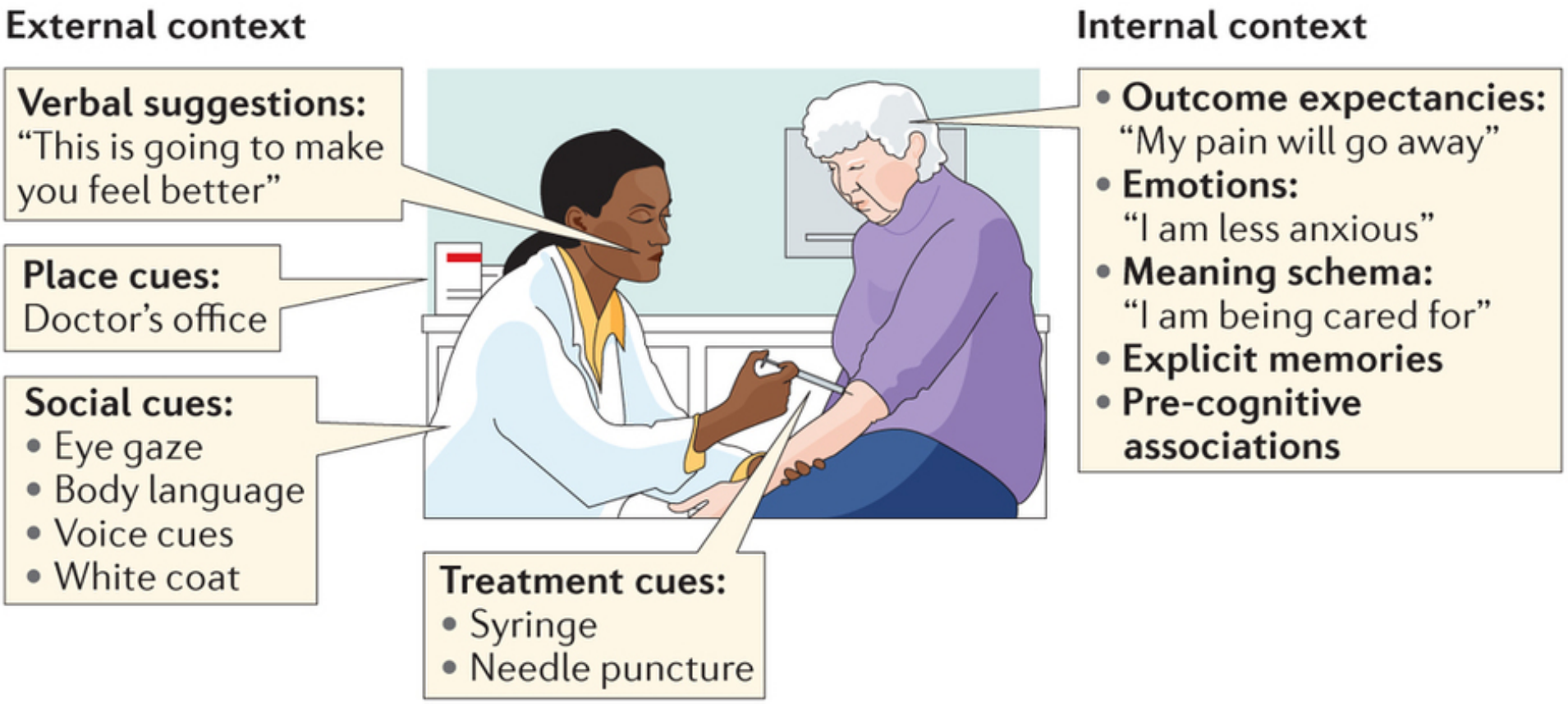


Stimulation of the Psychosocial Context



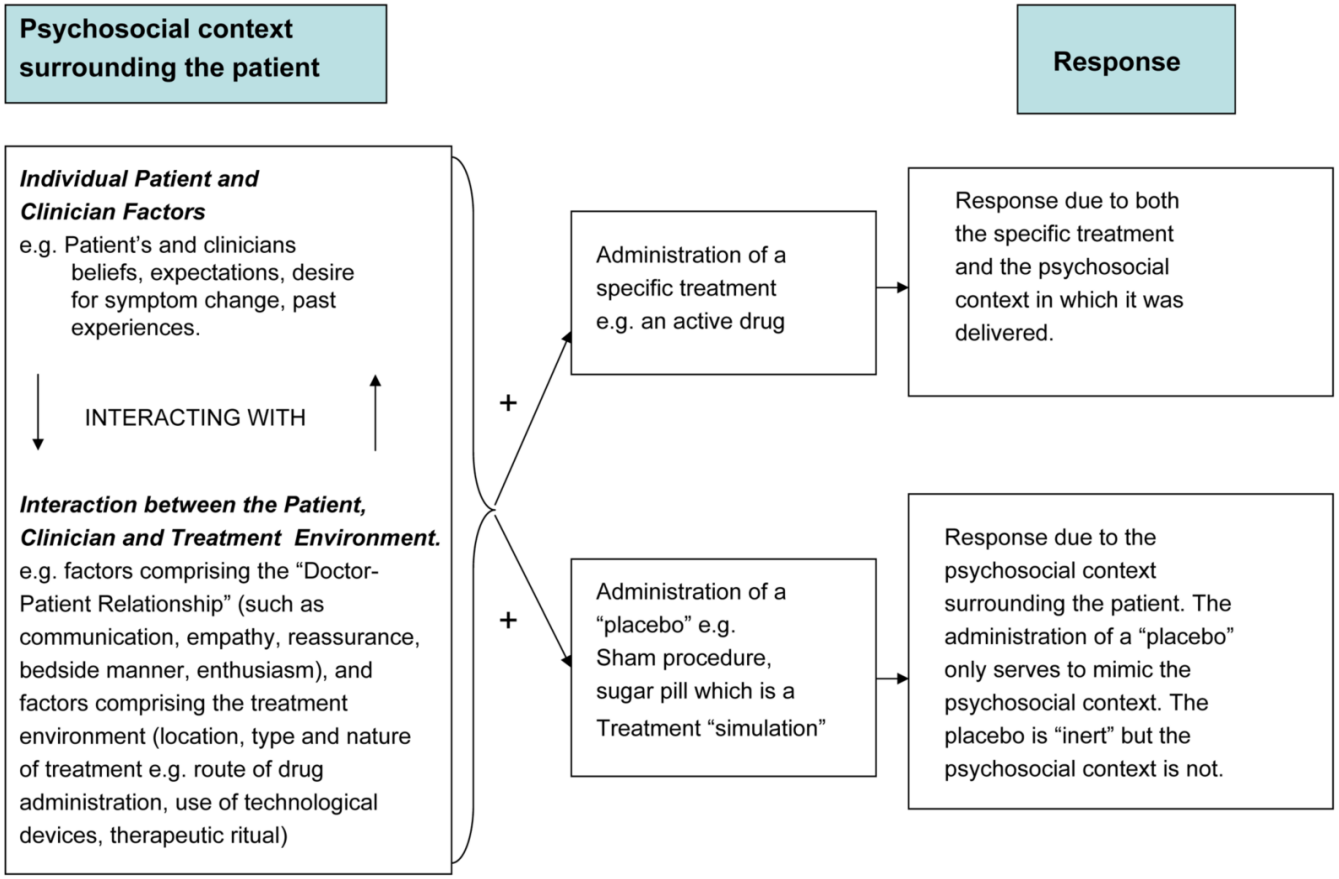
Stimulation of the Psychosocial Context





Wager & Atlas, 2015

Psychosocial Context → Response

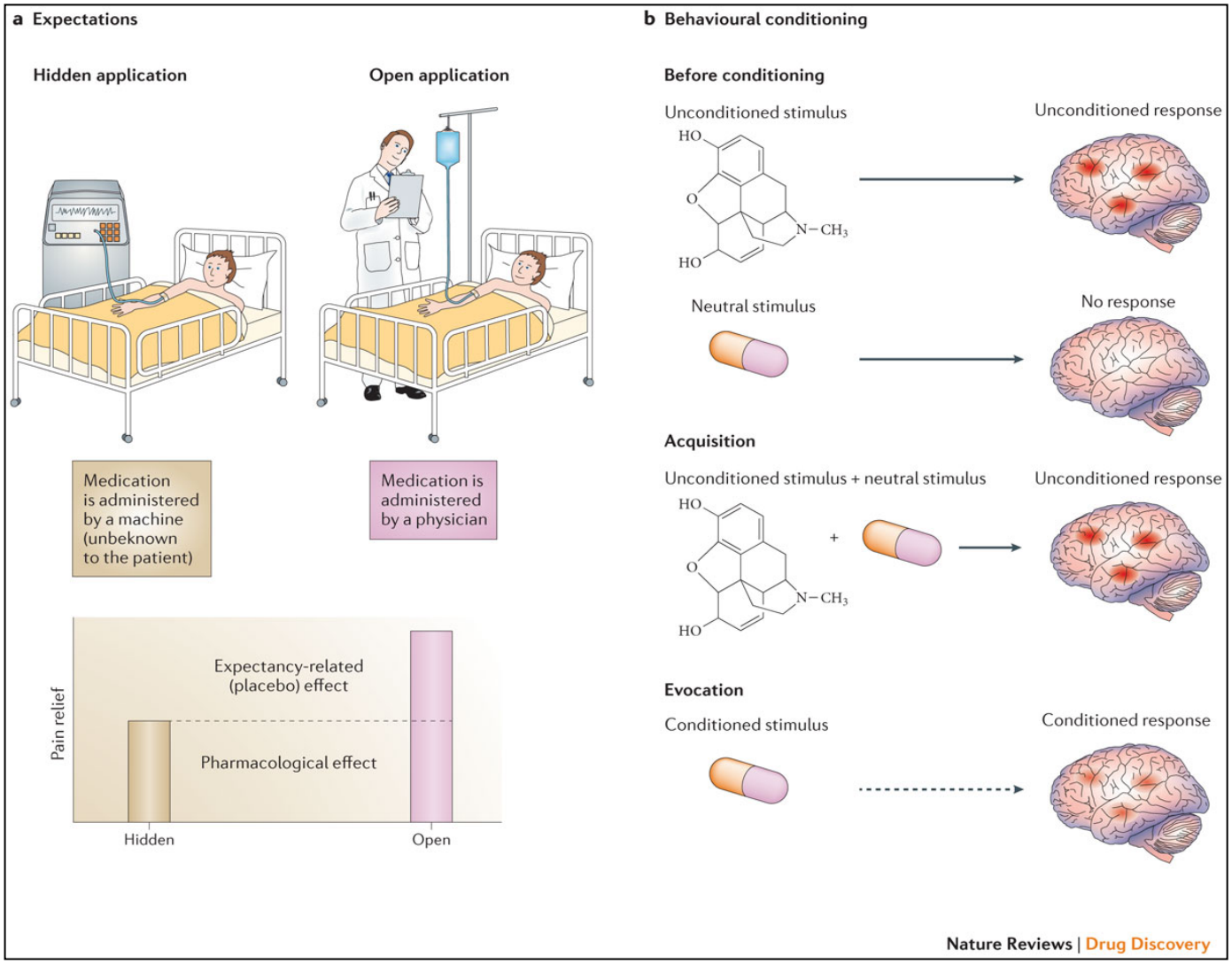


Mechanisms of Action (drug/placebo)

- Expectancy
- Conditioning
- Therapeutic relationship
- Placebo by proxy
  - Expectations of a patient towards his/her treatment occurs in a social context where proxies (family members, caregivers, relatives) respond to symptoms and their improvement and worsening as well

Grelotti & Kaptchuk, 2011; Kaptchuk et al., 2008

Mechanisms: Expectations and Conditioning

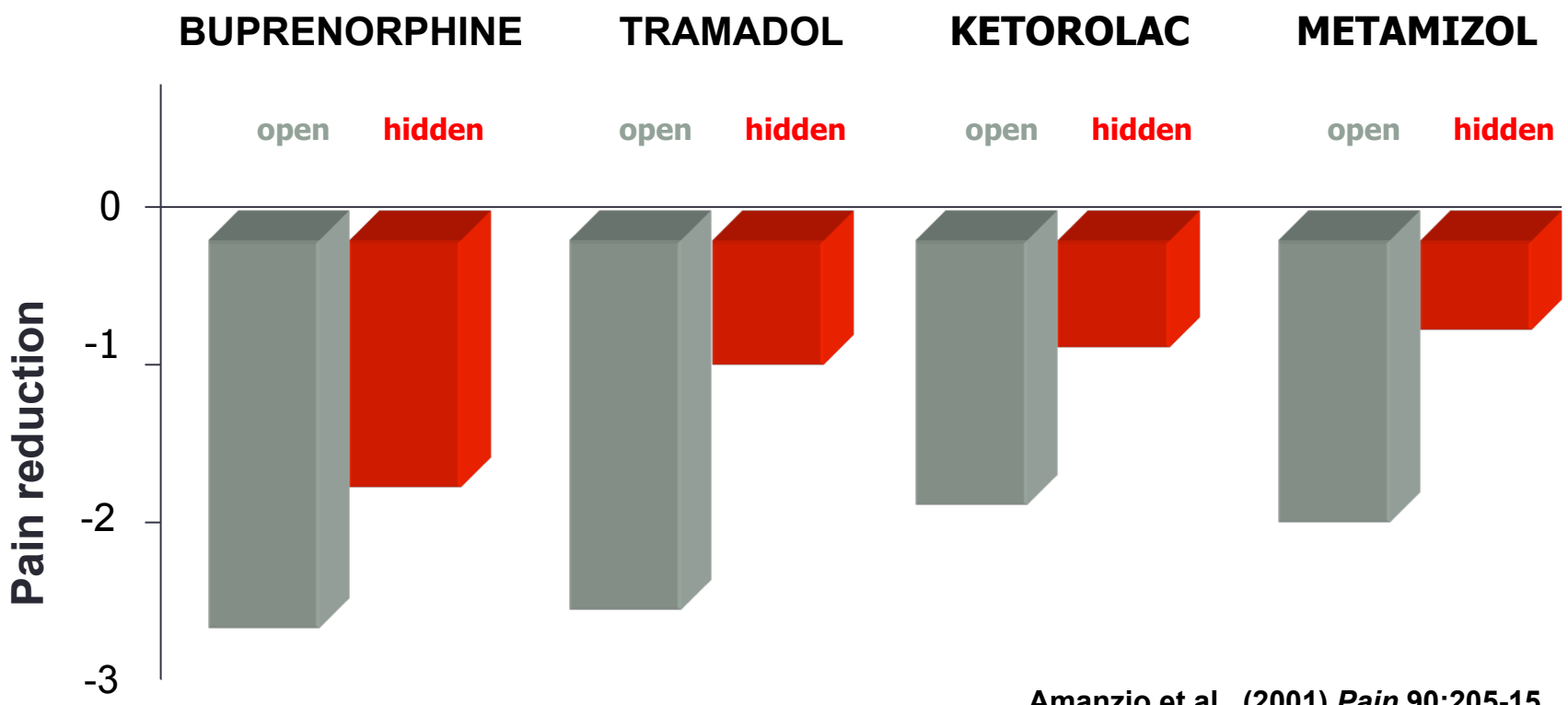


Enck, Bingel, Schledowski & Rief, 2013

Expectation: Open vs. Hidden Administration

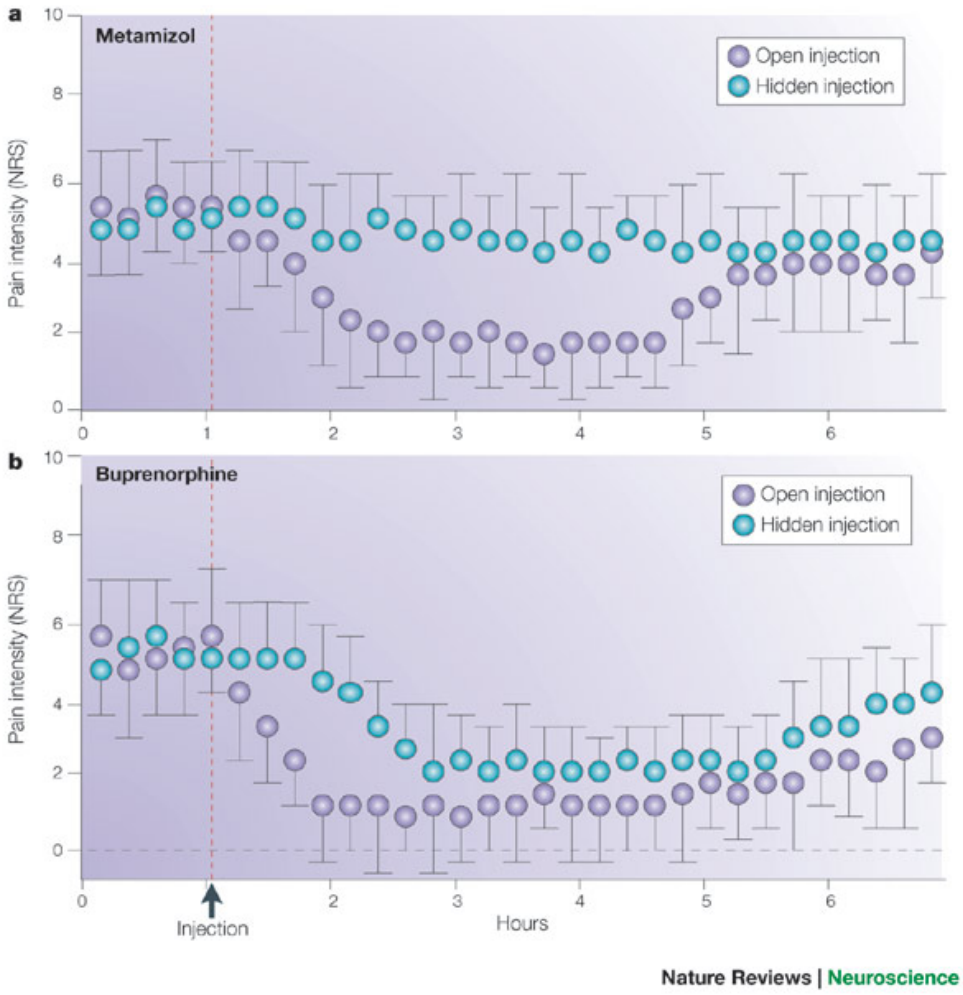
- Comparison of open and hidden administration of medications
- i.e., buprenorphine, tramadol, ketorolac and metamizole for post-operative pain.
- Open injections:
  - “This medication is a powerful painkiller”
- Hidden injections:
  - Patient unaware of drug administration

Open vs. Hidden Administration



Amanzio et al. (2001) *Pain* 90:205-15

Open vs. Hidden Administration



Colloca & Benedetti, 2005

Conclusions: Mechanisms

Psychological

- Verbal instruction that anticipates a benefit
- Developing expectation of analgesia
- Recalling previously acquired pain relief
- Personality traits

Neurochemistry

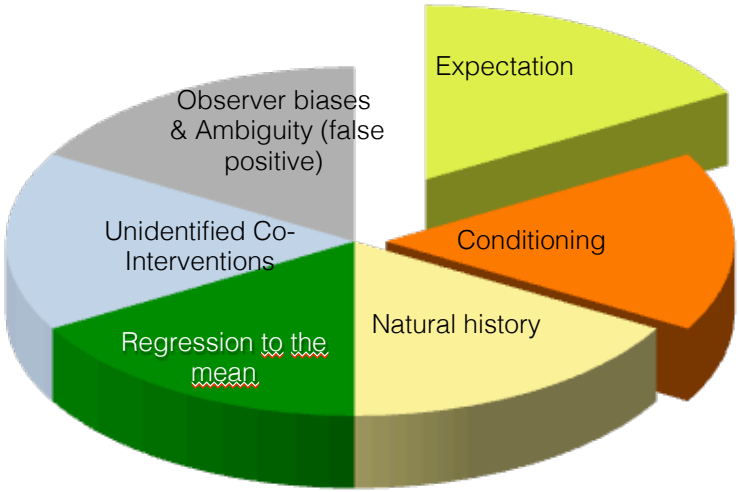
- Release of endogenous neuromodulators: opioids and dopamine
- Antagonized by naloxone

Neurophysiology

- Functional neuroimaging indicating activity changes in the modulatory system

Components of the Placebo Effect

"Apparent placebo effects"
- Artifacts
- Confounding variables



True Placebo Effect

Symptom reduction / "Improvement"

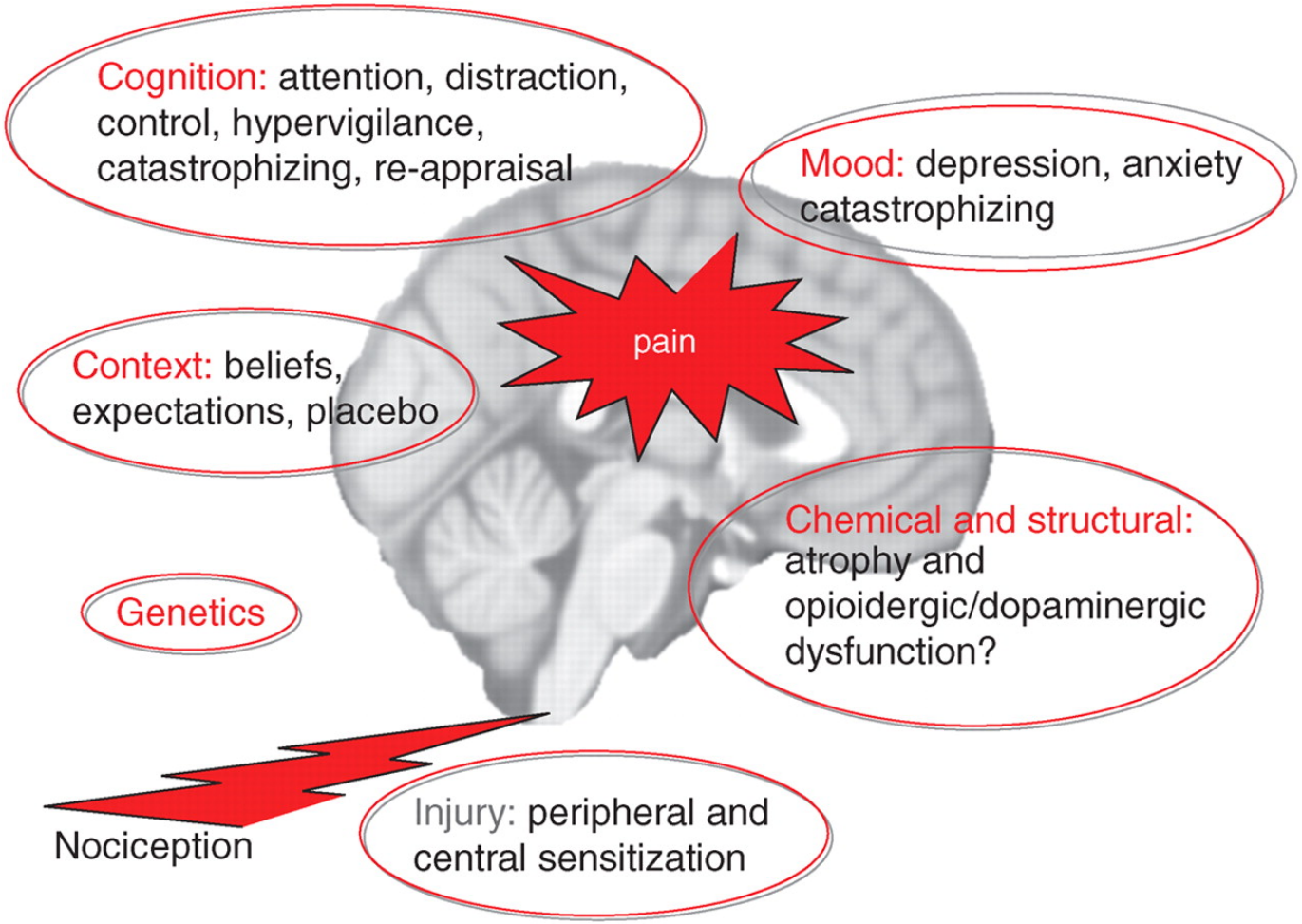
Placebo response (psychophysiological reaction) = Symptom reduction – confounding variables

Control groups (e.g. natural history)

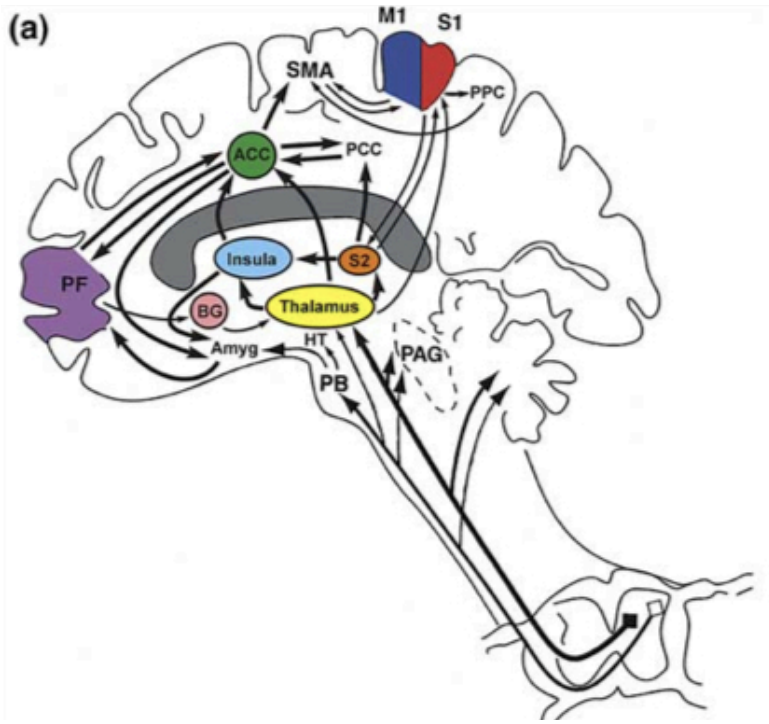
Contents

- What is the Placebo Effect?
- Mechanisms of Action & Components
- Pain Perception & Placebo Analgesia
- Acupuncture, Pain, and Placebo Effects
- Conclusions

Components of Pain Perception: The Pain Matrix



Tracey I, 2008 *Br. J. Anaesth.*



Components of pain perception:

1. **Sensory-discriminative**
   Where and how strong is the stimuli
2. **Affective-motivational**
   How unpleasant is the stimuli
3. **Cognitive-evaluative**
   Memory – previous experiences?

Melzack & Casey, 1968

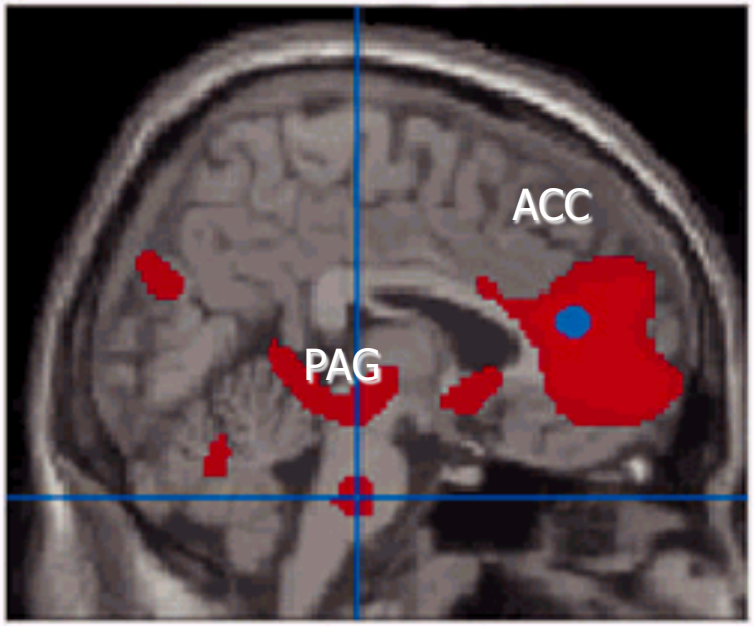
Apkarian et al., 2005 *European J.o. Pain*

The Pain Matrix

- Large distributed brain network
- Sensory component: primary somatosensory (S1) secondary somatosensory (S2), thalamus and posterior parts of insula
- Affective and cognitive component: anterior parts of insula, anterior cingulate cortex (ACC) and prefrontal cortex (PFC)

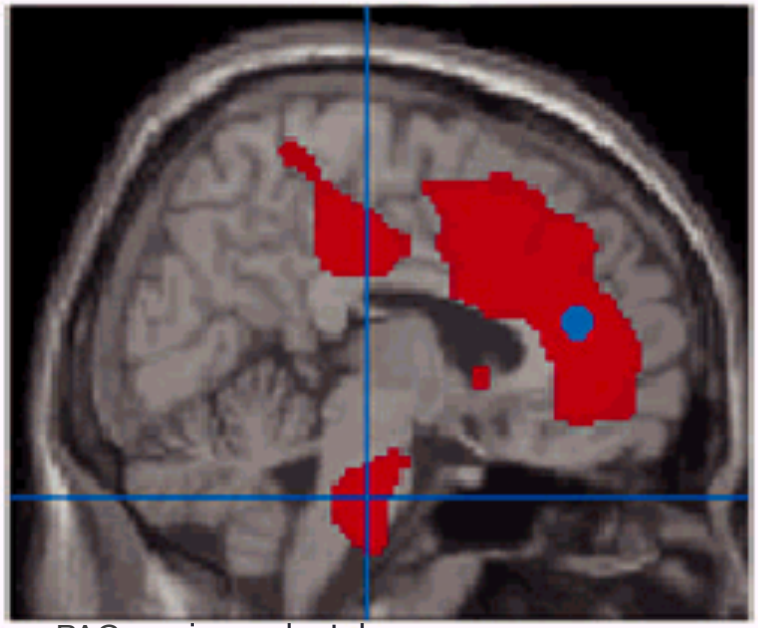
Findings from Functional Imaging

Remifentanil



Petrovic et al., 2002 *Science* 295: 1737-40

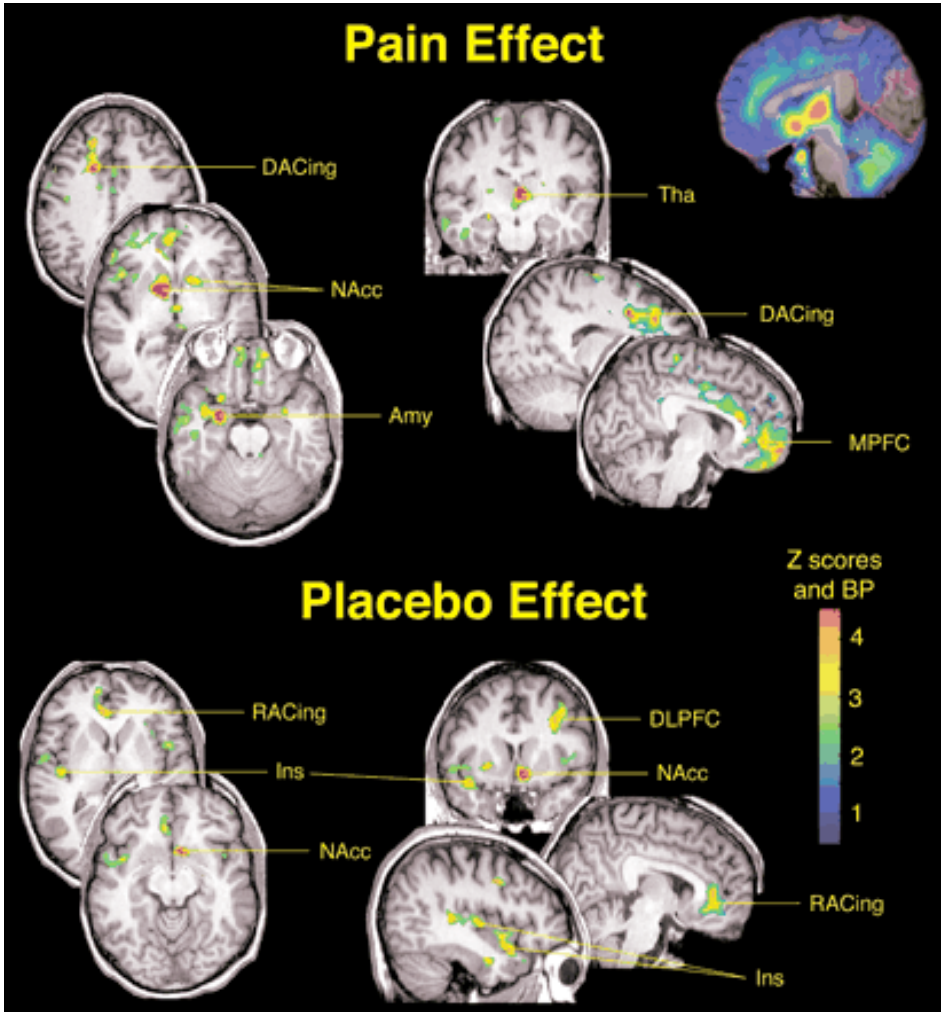
Placebo



PAG: periaqueductal grey
ACC: anterior cingulate cortex

➔ Common neuronal correlate of opioid and placebo analgesia

Placebo Analgesia Activates the Pain Matrix



Findings:
Placebo effect is mediated by endogenous opioid activity on mu-opioid receptors.

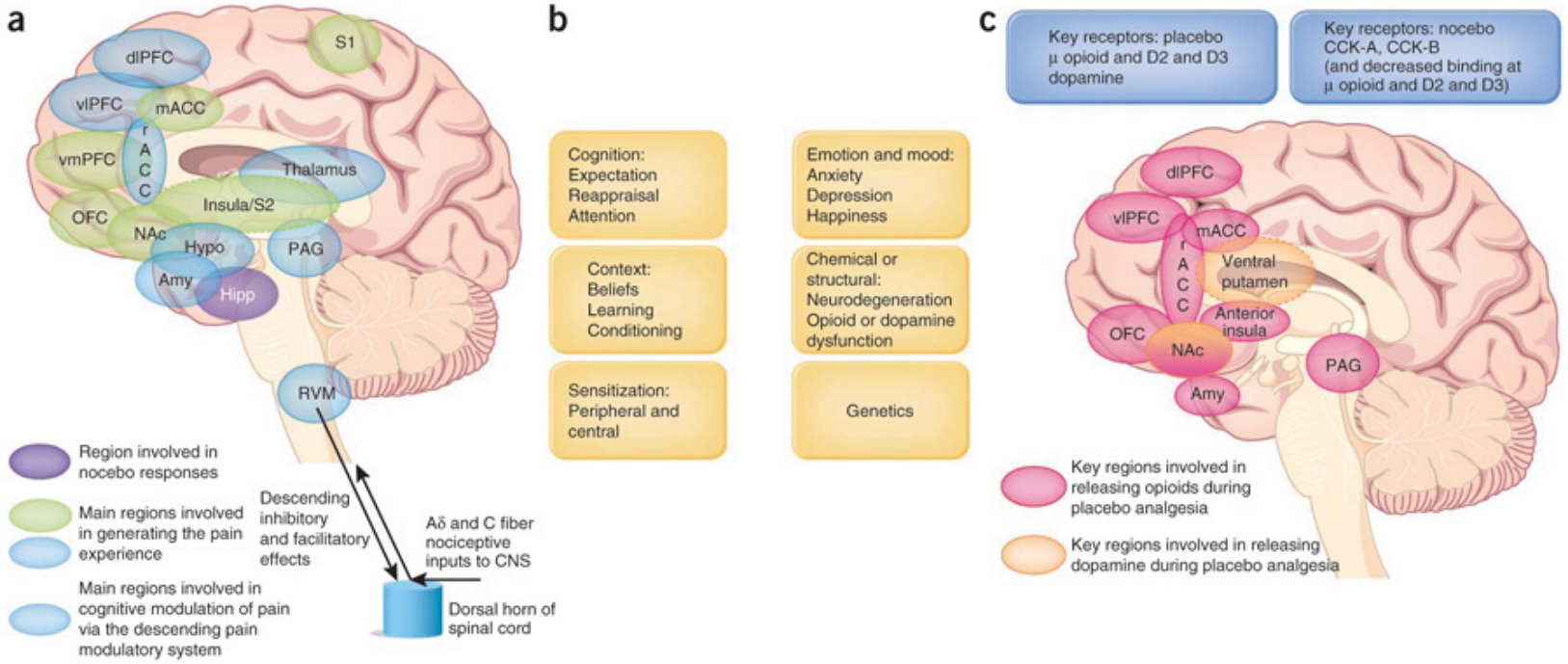
Expectation-induced placebo analgesia activates the pain matrix.

Method: Ligand-PET [^{11}C]Carfentanil Imaging

RACIng: rostral anterior Cingulum
Ins: Insula
NAcc: Nucleus accumbens
DLPFC: dorsolateraler prefrontal Cortex
Amy: Amygdala
Tha: Thalamus

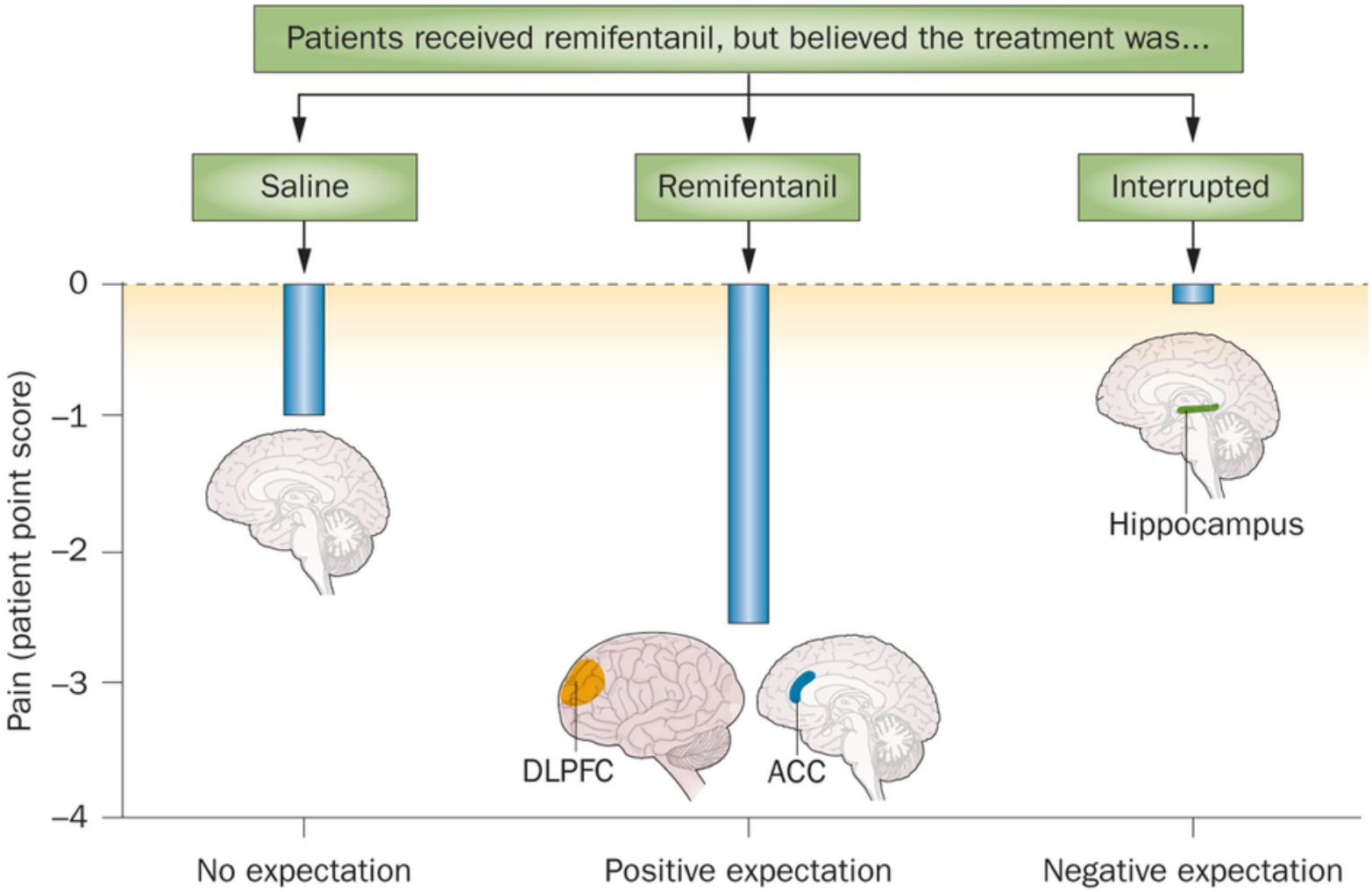
Zubieta et al., 2005 *J. o.Neuroscience*

Key Regions Involved in Pain and Placebo



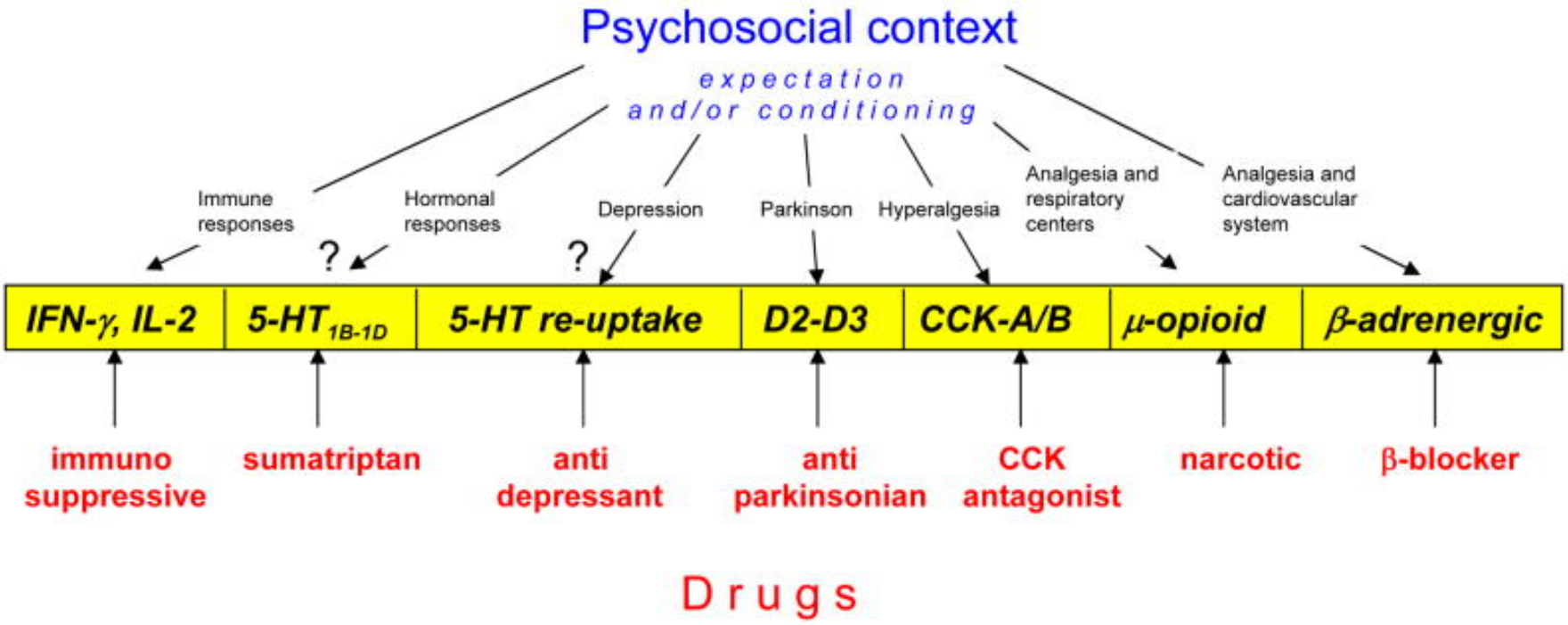
Tracey, I. Nature Medicine (2010)

Nocebo Effects



Bingel et al., 2011

Biological Correlates



Finniss, Kaptchuk, Miller, & Benedetti, F. (2010)

Overview

- What is the Placebo Effect?
- Mechanisms of Action & Components
- Pain Perception & Placebo Analgesia
- Acupuncture, Pain, and Placebo Effects
- Conclusions

BMJ

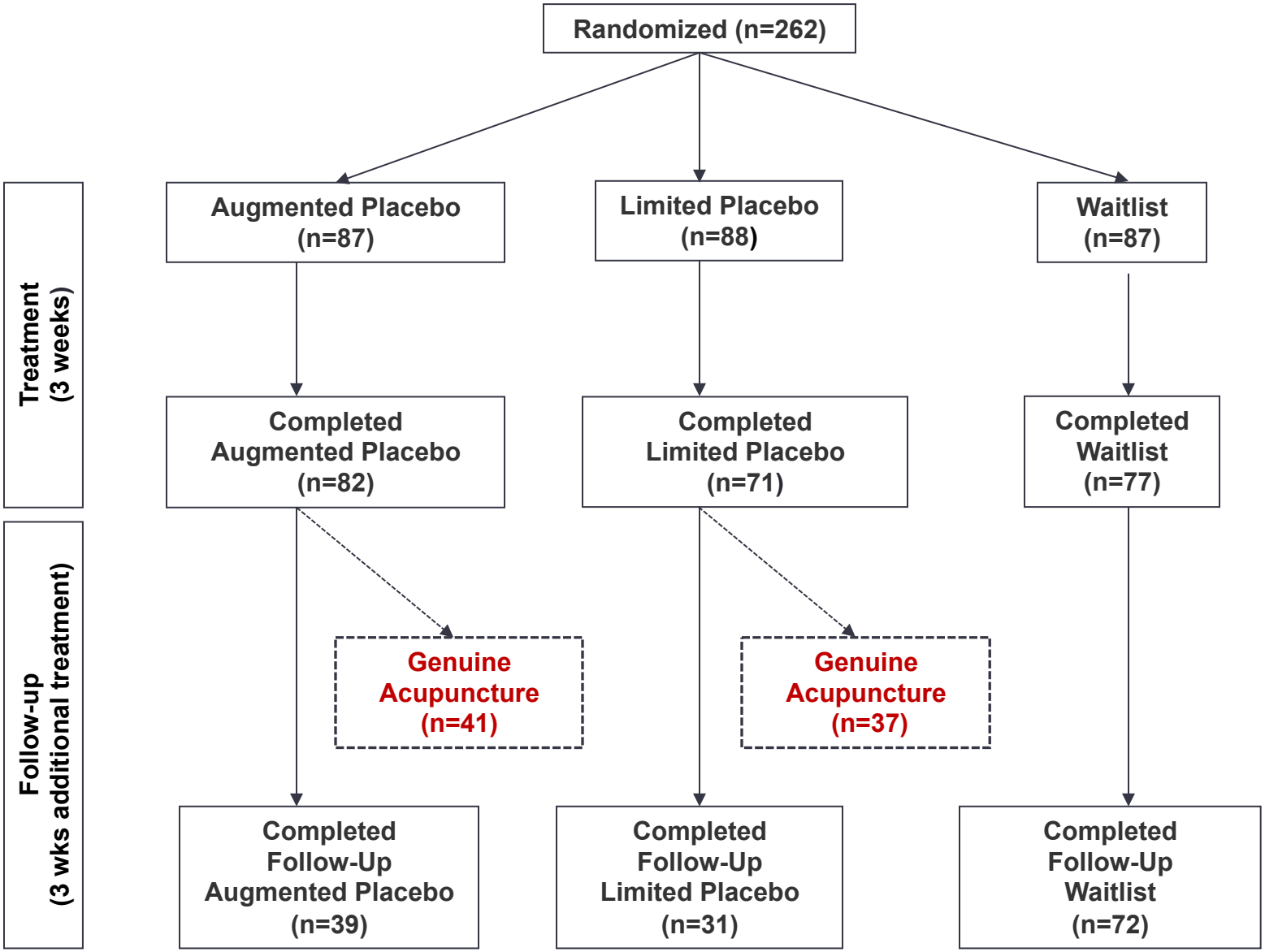
RESEARCH

Components of placebo effect: randomised controlled trial in patients with irritable bowel syndrome

Ted J Kaptchuk, John M Kelley, Lisa A Conboy, Roger B Davis, Catherine E Kerr, Eric E Jacobson, Irving Kirsch, Rosa N Schyner, Bong Hyun Nam, Long T Nguyen, Min Park, Andrea L Rivers, Claire McManus, Efi Kokkotou, Douglas A Drossman, Peter Goldman and Anthony J Lembo

BMJ published online 3 Apr 2008;
doi:10.1136/bmj.39524.439618.25

Flow of Patients in Placebo / IBS Study



Hypothesis: No Treatment < Limited < Augmented

Intake
+
No Treatment

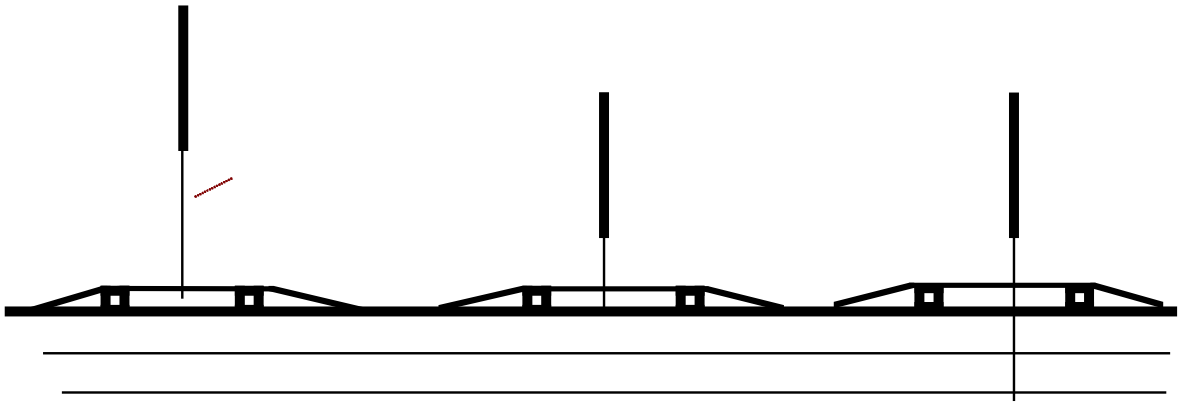
<

Intake
+
Sham Acupuncture
(no engaged care)

<

Intake
+
Sham Acupuncture
(engaged care)

Sham Acupuncture Needle



a) acupuncture needle b) placebo needle c) verum needle

Streitberger. Lancet 1998

Interventions

- Placebo treatments were performed twice a week. At each session, six to eight dummy needles were placed for 20 minutes over predetermined non-acupuncture points on the arms, legs, and abdomen;

Limited Interaction

- Initial visit (duration <5 minutes) during which practitioners introduced themselves and stated they had reviewed the patient's questionnaire and "knew what to do."
- They then explained that this was "a scientific study" for which they had been "instructed not to converse with patients."

Augmented Interaction

- Questions concerning symptoms, how irritable bowel syndrome related to relationships and lifestyle, possible non-gastrointestinal symptoms, and how the patient understood the “cause” and “meaning” of his or her condition.

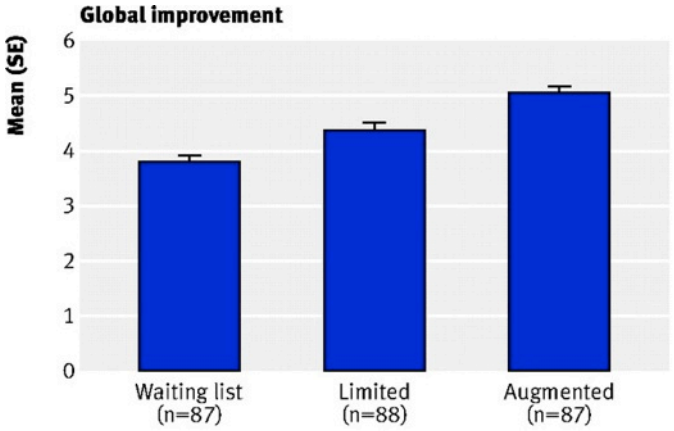
- Behavior:

1. A warm, friendly manner
2. Active listening
3. Empathy
4. 20 seconds of thoughtful silence while feeling the pulse or pondering the treatment plan
5. Communication of confidence and positive expectation

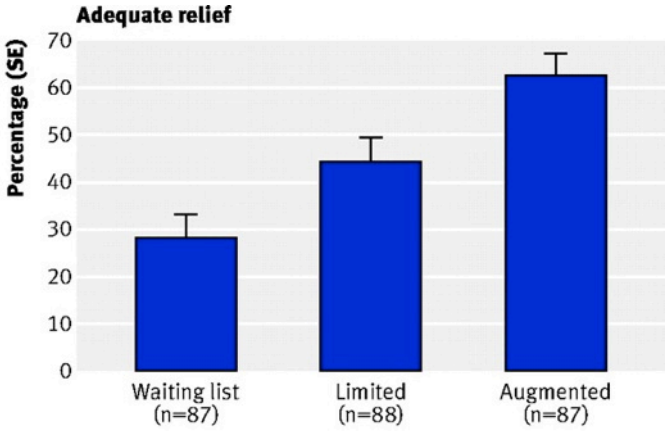
Outcome Measures

- IBS Adequate Relief
- IBS Global Improvement
- IBS Symptom Severity Scale
- IBS QoL

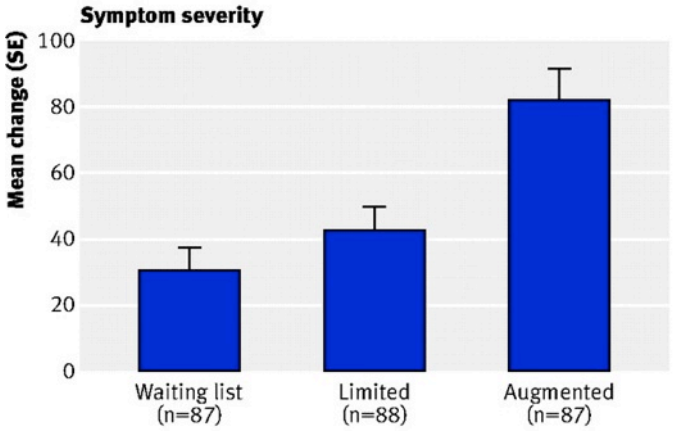
Results



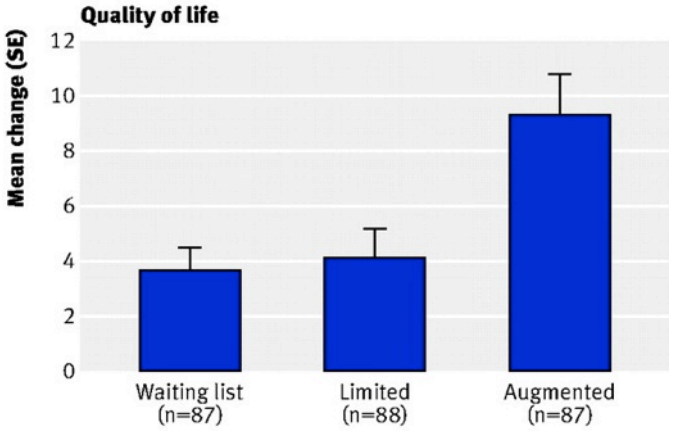
Test of trend: P<0.001; 95% CI 0.18 to 0.90 for limited *v* waiting list; 0.32 to 1.11 for augmented *v* limited



Test of trend: P<0.001; 95% CI 2.7 to 30.7 for limited *v* waiting list; 3.2 to 32.3 for augmented *v* limited

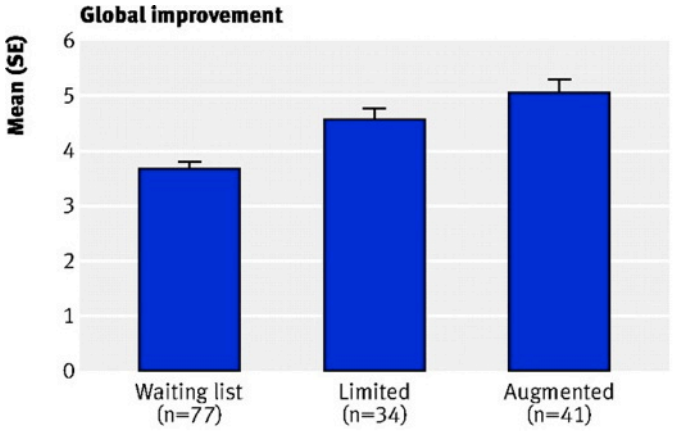


Test of trend: P<0.001; 95% CI -7.9 to 31.2 for limited *v* waiting list; 16.2 to 63.2 for augmented *v* limited

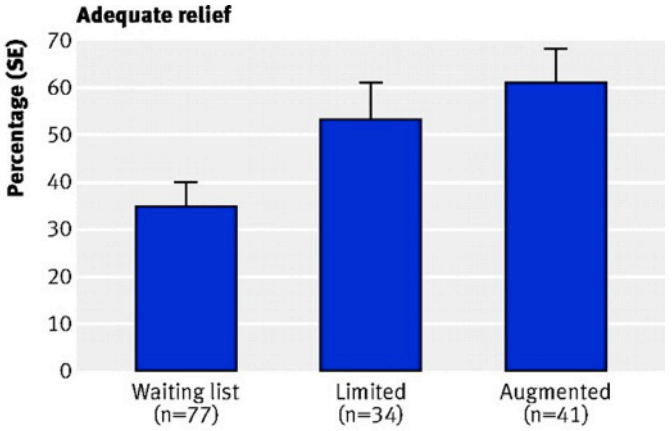


Test of trend: P<0.001; 95% CI -2.1 to 3.2 for limited *v* waiting list; 1.7 to 8.8 for augmented *v* limited

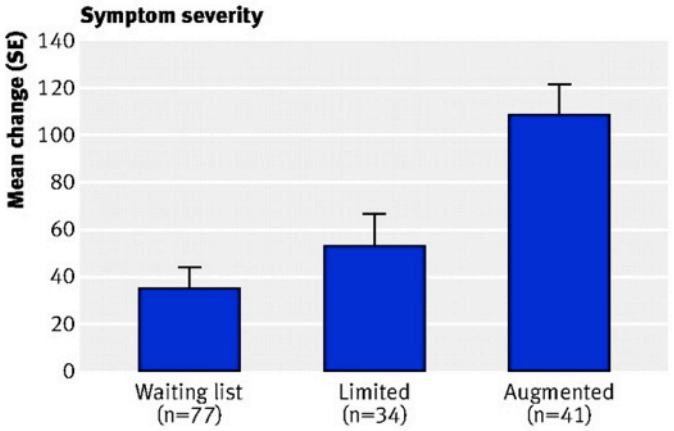
Results



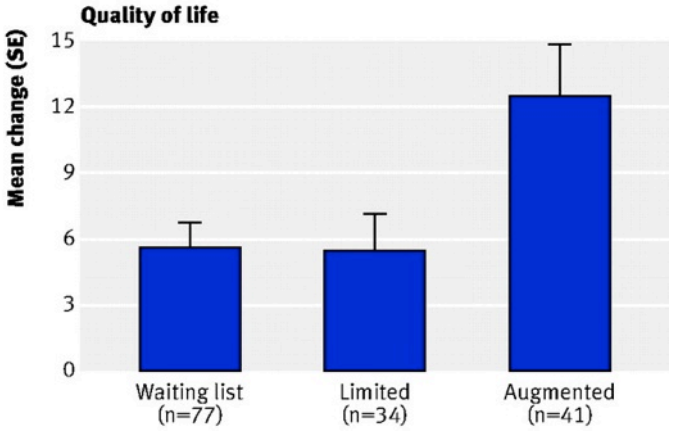
Test of trend: P<0.001; 95% CI 0.5 to 1.4 for limited *v* waiting list; -0.1 to 1.1 for augmented *v* limited



Test of trend: P=0.005; 95% CI -2 to 38 for limited *v* waiting list; -14 to 30 for augmented *v* limited



Test of trend: P<0.001; 95% CI -14.6 to 50.5 for limited *v* waiting list; 15.7 to 95.2 for augmented *v* limited



Test of trend: P=0.002; 95% CI 4.2 to -4.4 for limited *v* waiting list; 0.9 to 13.0 for augmented *v* limited

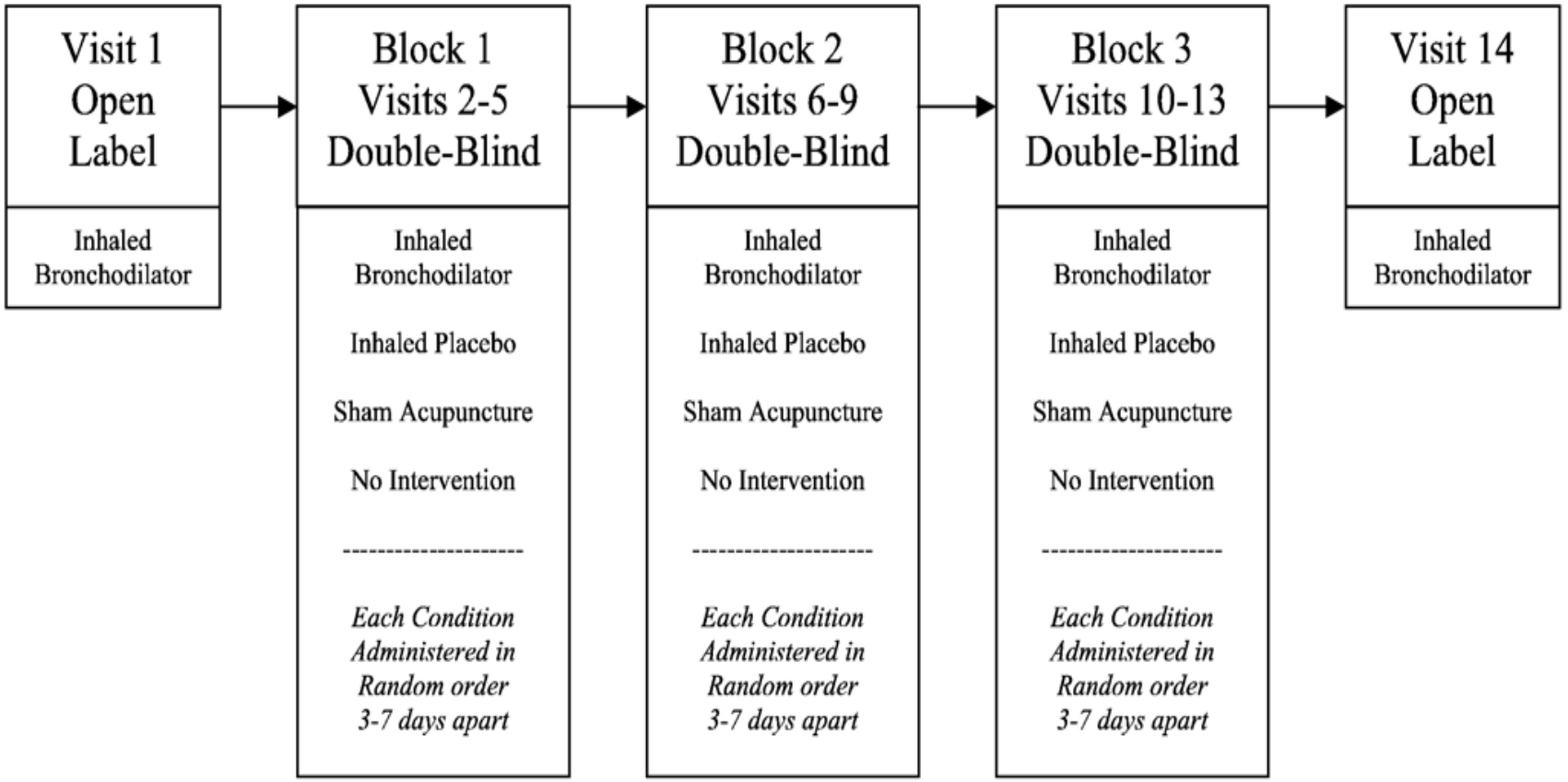
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Active Albuterol or Placebo, Sham Acupuncture, or No Intervention in Asthma

Michael E. Wechsler, M.D., John M. Kelley, Ph.D., Ingrid O.E. Boyd, M.P.H., Stefanie Dutile, B.S., Gautham Marigowda, M.B., Irving Kirsch, Ph.D., Elliot Israel, M.D., and Ted J. Kaptchuk

Asthma Study



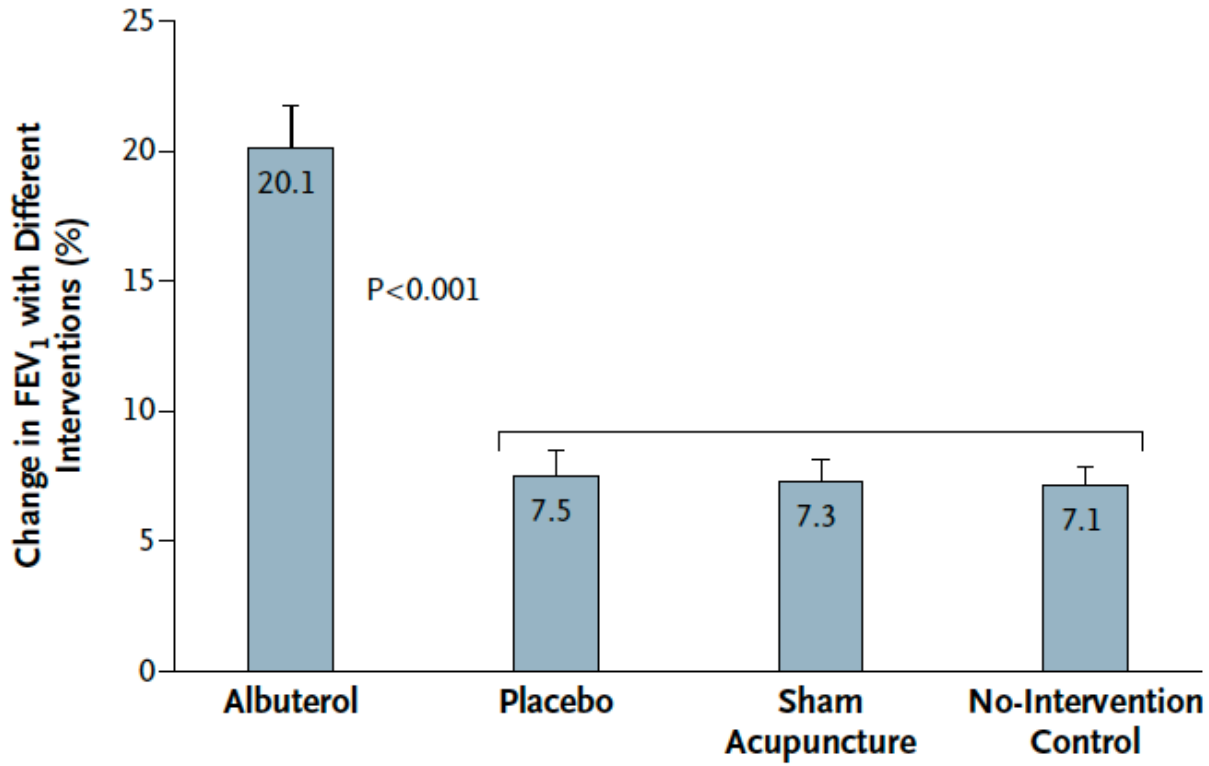


Figure 3. Percent Change in Maximum Forced Expiratory Volume in 1 Second (FEV_1) with Each of the Four Interventions.

The relative improvement in FEV_1 achieved with albuterol was significantly greater than that achieved with each of the other three interventions ($P<0.001$). No other differences among the four groups were significant. T bars indicate standard errors of the mean.

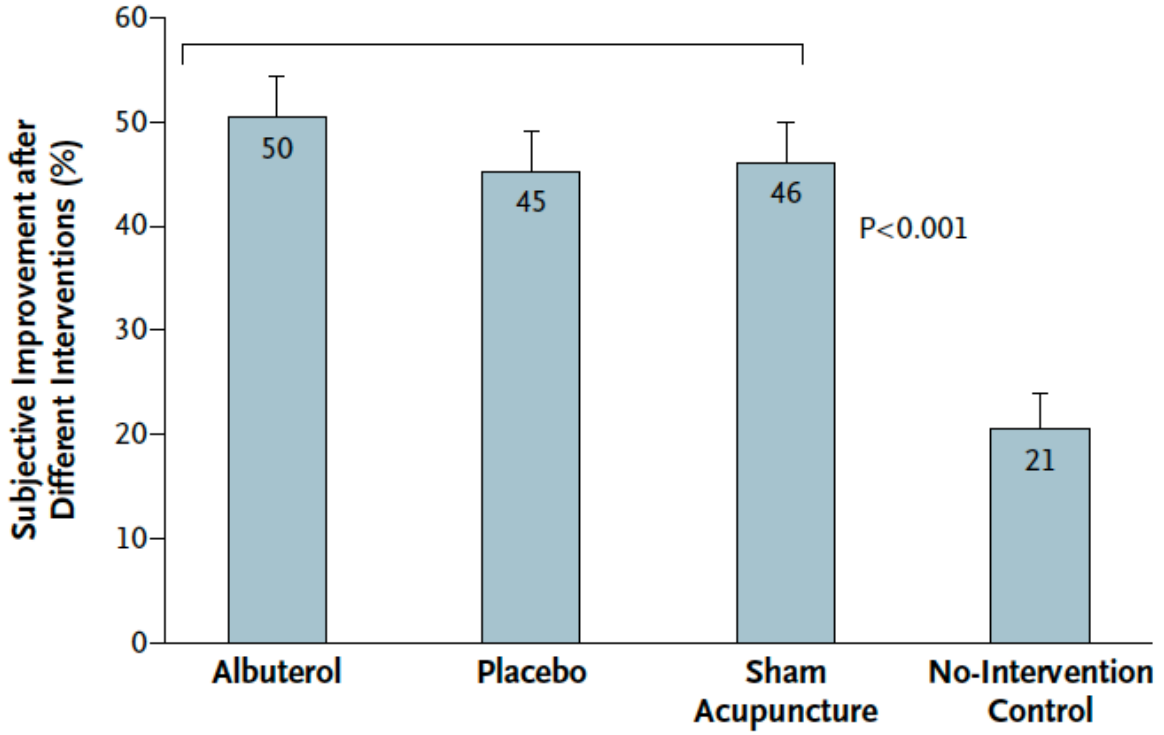
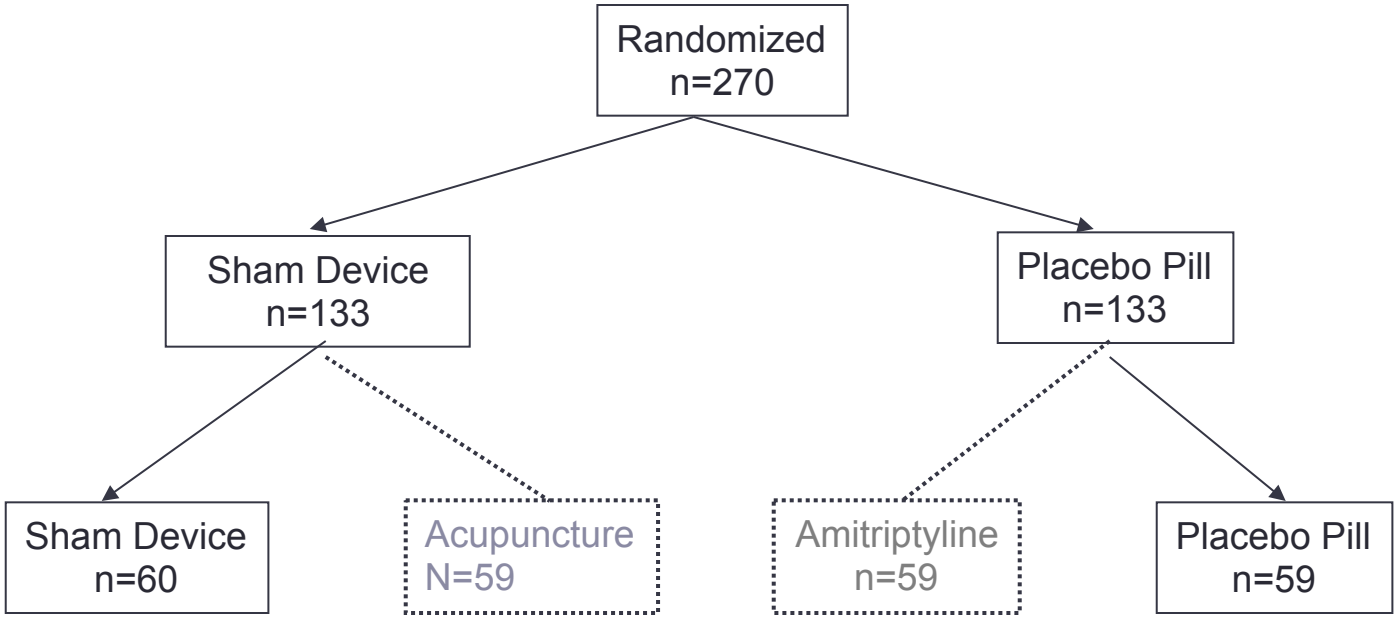


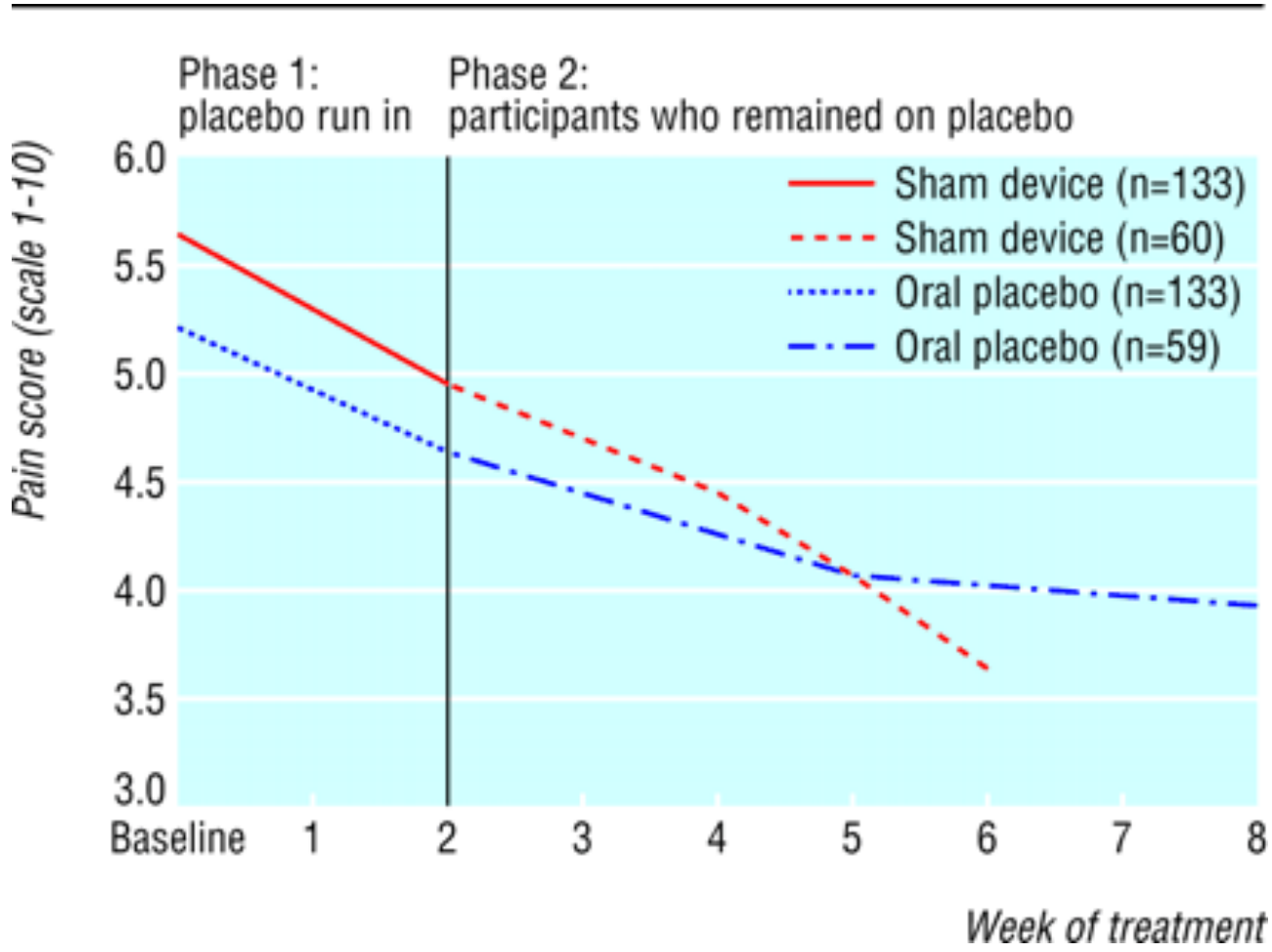
Figure 4. Percent Change in Subjective Improvement with Each of the Four Interventions.

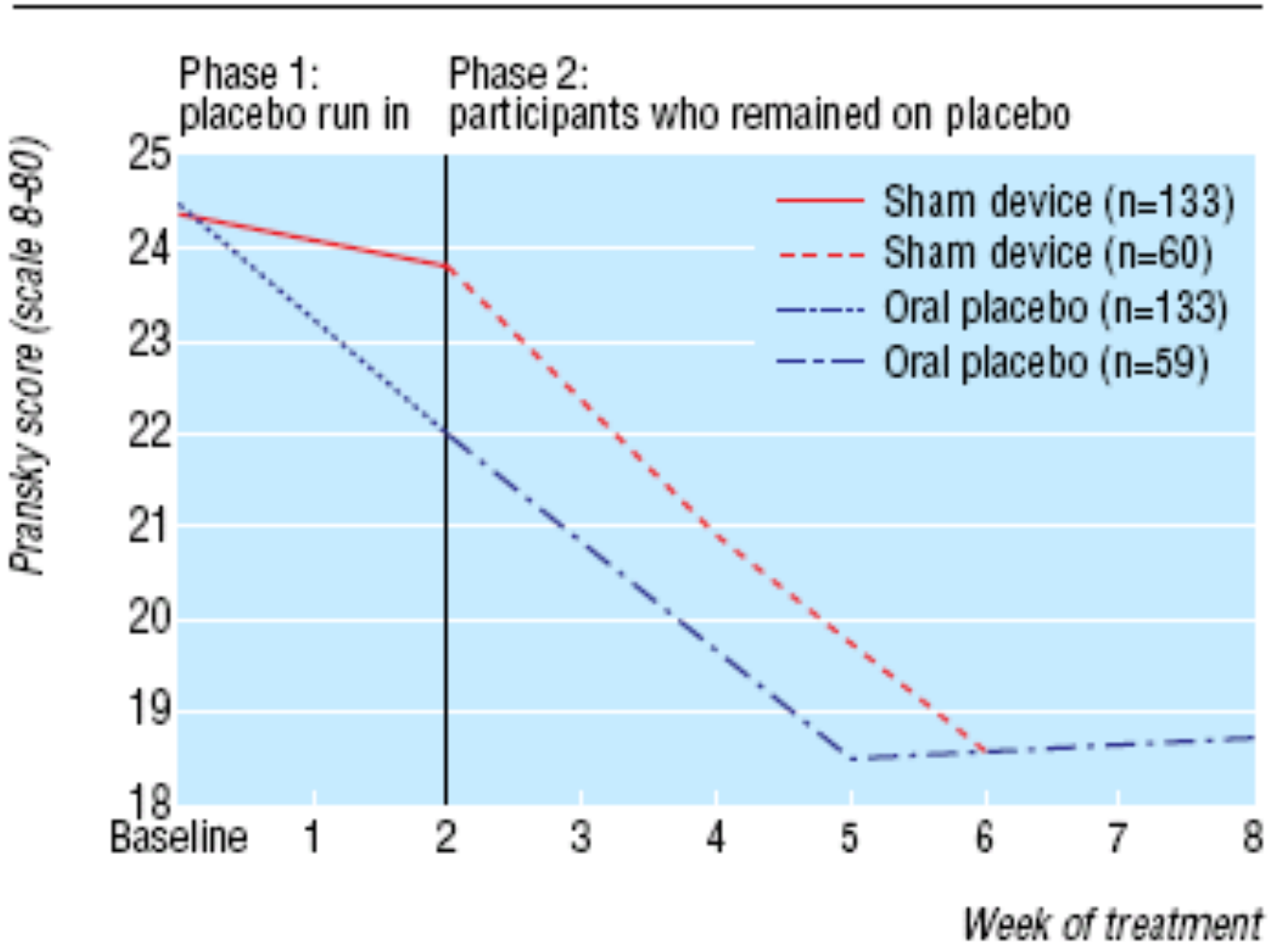
The relative improvement in subjective outcomes, assessed with the use of a visual-analogue scale (with 0 indicating no improvement and 10 indicating complete improvement), was significantly greater with the albuterol inhaler, the placebo inhaler, and sham acupuncture interventions than with the no-intervention control ($P<0.001$). No other differences among the four groups were significant. T bars indicate standard errors of the mean.

Sham device *v* inert pill: randomised controlled trial of two placebo treatments

Ted J Kaptchuk, William B Stason, Roger B Davis, Anna T R Legedza, Rosa N Schnyer, Catherine E Kerr, David A Stone, Bong Hyun Nam, Irving Kirsch, Rose H Goldman




Phase 1:
placebo run in
Phase 2:
participants who remained on placebo
Pain score (scale 1-10)
6.0
5.5
5.0
4.5
4.0
3.5
3.0
Baseline
1
2
3
4
5
6
7
8
Week of treatment
Sham device (n=133)
Sham device (n=60)
Oral placebo (n=133)
Oral placebo (n=59)


Phase 1:
placebo run in
Phase 2:
participants who remained on placebo
Pransky score (scale 8-80)
25
24
23
22
21
20
19
18
Baseline
1
2
3
4
5
6
7
8
Week of treatment
Sham device (n=133)
Sham device (n=60)
Oral placebo (n=133)
Oral placebo (n=59)

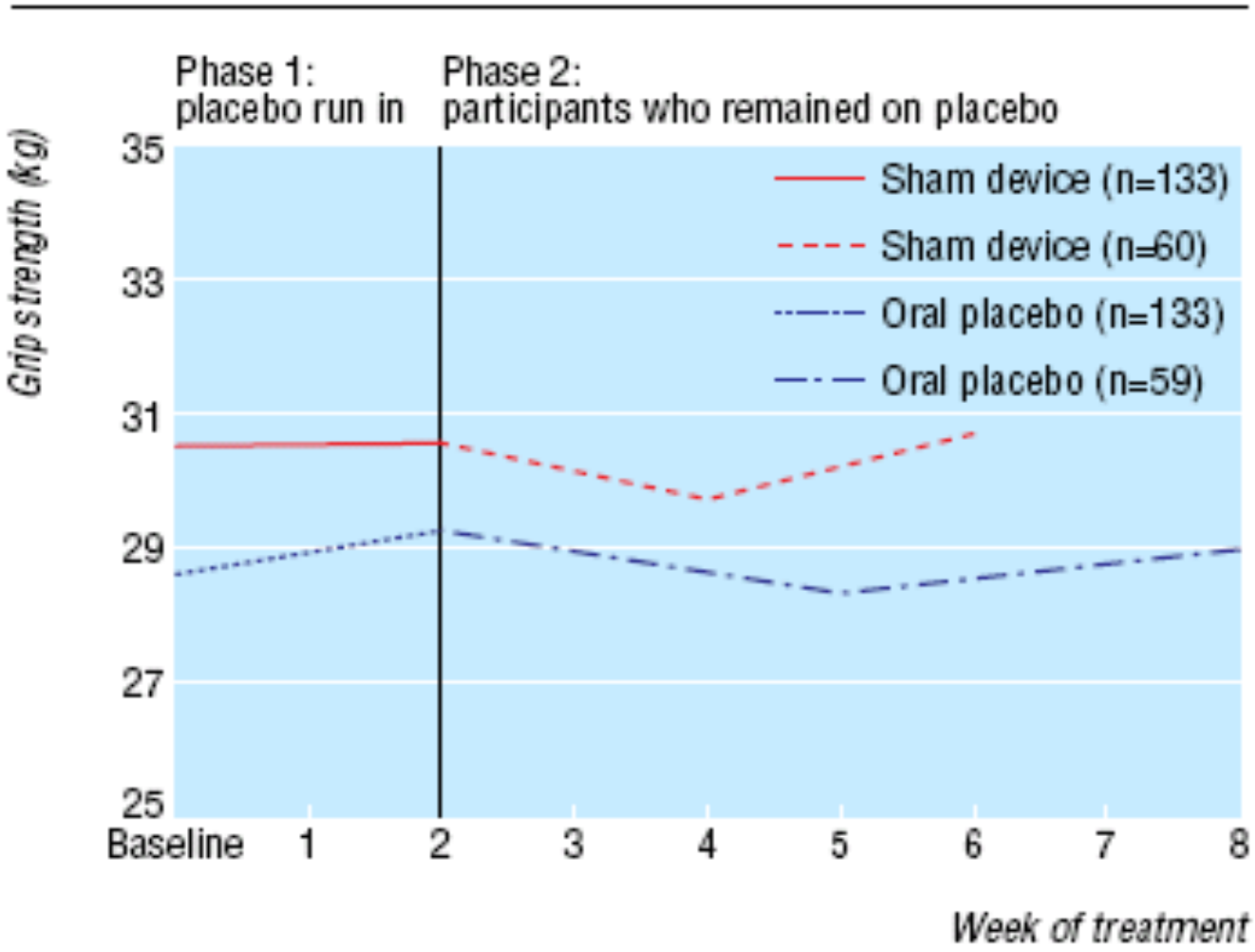

Phase 1:
placebo run in
Phase 2:
participants who remained on placebo
Grip strength (kg)
35
33
31
29
27
25
Baseline
1
2
3
4
5
6
7
8
Week of treatment
Sham device (n=133)
Sham device (n=60)
Oral placebo (n=133)
Oral placebo (n=59)

Table 4 Side effects from placebo treatments at two weeks

Side effect	No (%) of participants
Sham acupuncture	
Pain during treatment	19 (15)
Increased pain after "removing" needle	12 (10)
Redness or swelling	4 (3)
Other	13 (12)
Placebo pill	
Drowsiness	25 (20)
Dry mouth	23 (19)
Restlessness	9 (7)
Dizziness	6 (5)
Headache	5 (4)
Anxiety	5 (4)
Nightmares	4 (3)
Nausea	4 (3)
Frequent urination	2 (2)
Skin rash	3 (2)

Sham Device vs. Inert Pill: Conclusions

- A validated sham acupuncture device has a greater placebo effect on subjective outcomes than oral placebo pills
- A placebo analgesia effect beyond the natural evolution of a disease is detectable over time
- Adverse events and nocebo effects are linked to the information provided to patients

East Asian Medical Theory: Accounting for Placebo Effects

- Acupuncture represents a co-mingling of:

  得　气 (obtain the qi)

  治　神 (treat spirit)

OR: Acupuncture represents a co-mingling of:

A. needling factors (technical physical details of acupuncture) &

B. psychosocial factors

Tao Liu eCAM 2008

Concluding Remarks

- East Asian medicine understands healing as the interaction of “intervention” with how the practitioner aligns the patient to receive, absorb and transform different energy.

- “Intervention” is a unity of the “method” and “practitioner.”

Concluding Remarks

- Placebo studies elucidates the elaborate drama that surrounds pills and procedures that includes a mixture of symbols, words and behaviors mingled with hope, uncertainty, fear, empathy, and trust.

- Placebo studies has begun to elucidate some of the underlying biology of placebo responses.

- Placebo studies directly addresses the enduring moral practices of caring, the expressions of kindness and decency and the commitment to be present.

Thank you for your attention

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Randomized Trial of Vertebroplasty for Osteoporotic Spinal Fractures

David F. Kallmes, M.D., Bryan A. Comstock, M.S., Patrick J. Heagerty, Ph.D., Judith A. Turner, Ph.D., David J. Wilson, F.R.C.R., Terry H. Diamond, F.R.A.C.P., Richard Edwards, F.R.C.R., Leigh A. Gray, M.S., Lydia Stout, B.S., Sara Owen, M.Sc., William Hollingworth, Ph.D., Basavaraj Ghdoke, M.D., Deborah J. Annesley-Williams, F.R.C.R., Stuart H. Ralston, F.R.C.P., and Jeffrey G. Jarvik, M.D., M.P.H.

2009; 361: 569


Saint Marys
Hospital
Mayo Eugenio Litta
Children's Hospital

OPEN ACCESS Freely available online

PLOS | ONE

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

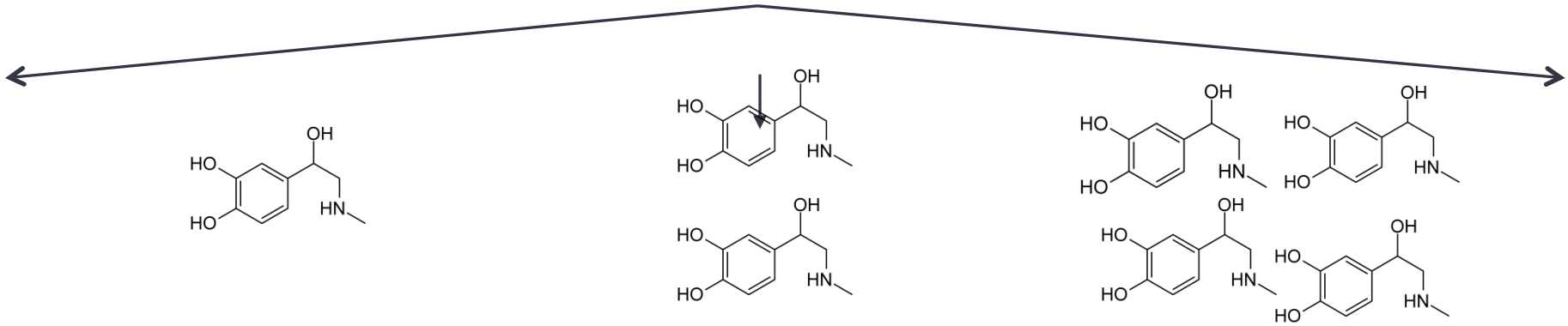
Kathryn T. Hall[1,2]*, Anthony J. Lembo[2,3], Irving Kirsch[2,4], Dimitrios C. Ziogas[5], Jeffrey Douaiher[6], Karin B. Jensen[2,7], Lisa A. Conboy[2], John M. Kelley[2,7,8], Efi Kokkotou[2,3], Ted J. Kaptchuk[1,2]

PLoS 2012

COMT val158met
rs4680

valine
high-activity

methionine
low-activity



val/val
high-activity
***less* dopamine**

val/met

met/met
low-activity
***more* dopamine**

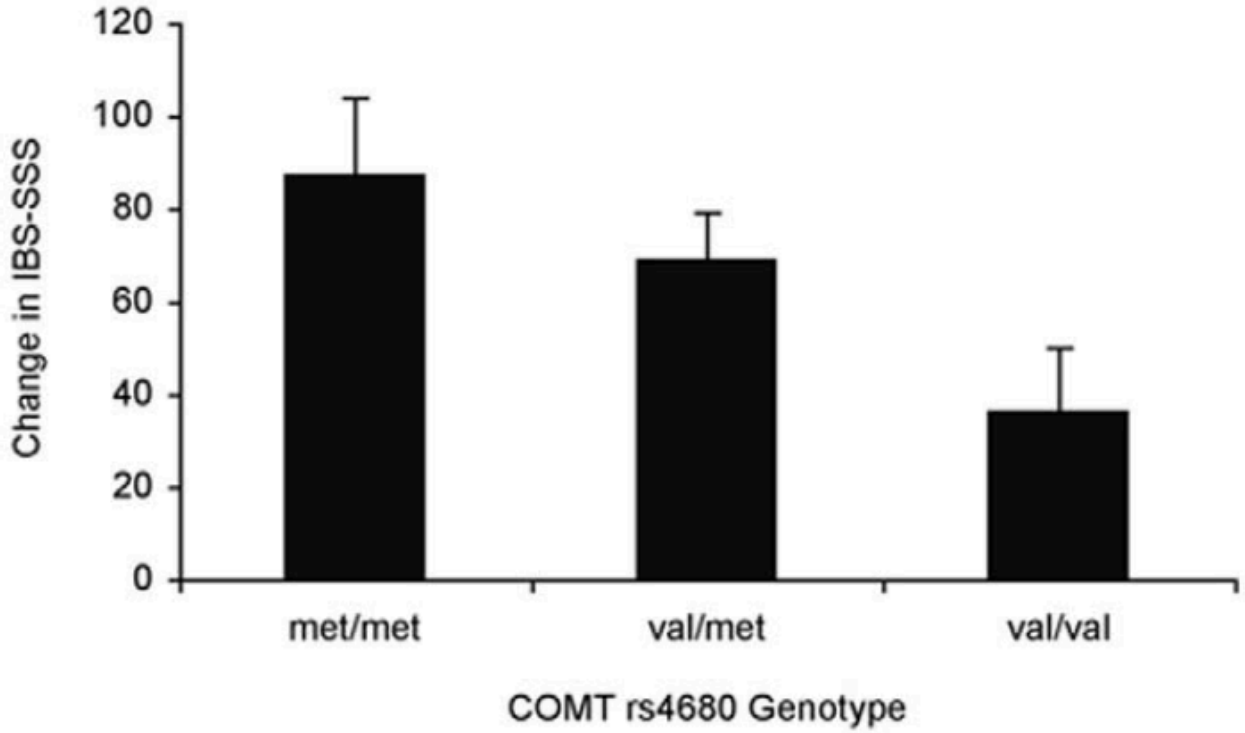
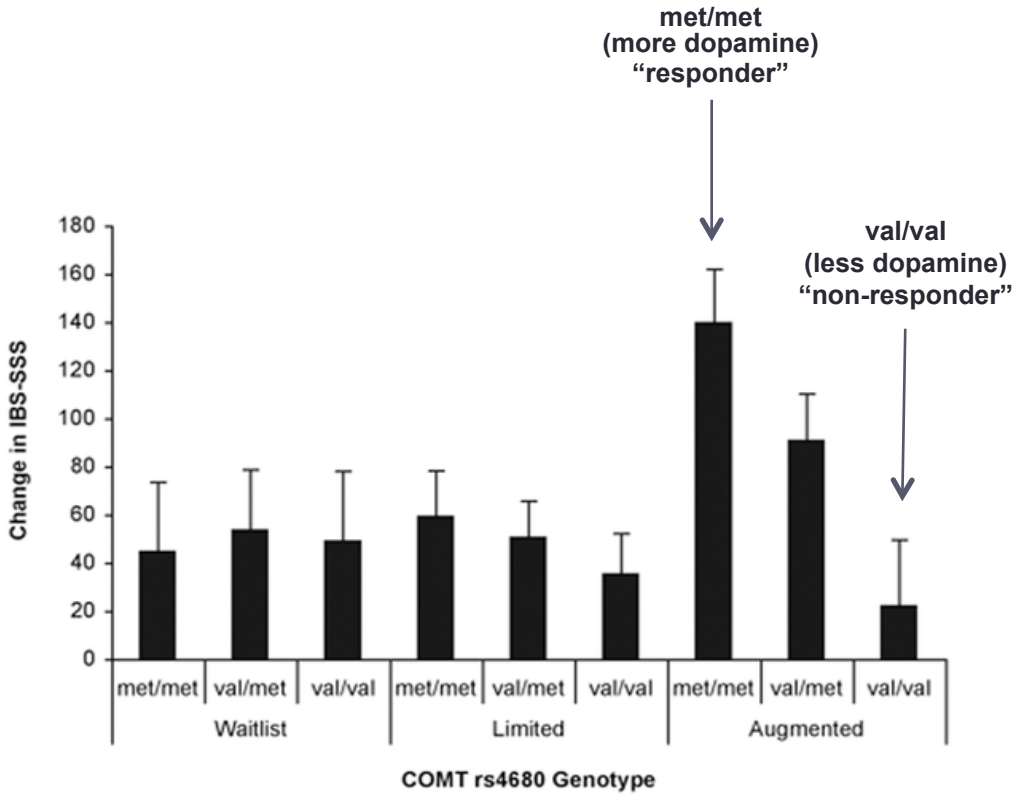


Figure 1. Effect of COMT genotype on change in IBS-SSS. Number of val158met met alleles showed a significant linear effect on IBS-SSS (beta = 0.17; p = .032). IBS-SSS includes abdominal pain severity, abdominal pain frequency, abdominal distention severity, dissatisfaction with bowel habits, and disruption of quality of life. Change in IBS-SSS = (IBS-SSS at baseline – IBS-SSS at 3-weeks). Regression model included COMT genotype (number of met alleles) and baseline IBS-SSS. Error bars indicate the standard error of the mean. N = 104.
doi:10.1371/journal.pone.0048135.g001

Catechol-0-Methyltransferase (COMT) genotype is associated with IBS placebo response



COMT genotype (β = 0.19; p = .02)
COMT genotype x treatment arm (β = 0.17; p =.035)
(N=104)

PLOS ONE

OPEN ACCESS Freely available online

PLoS one

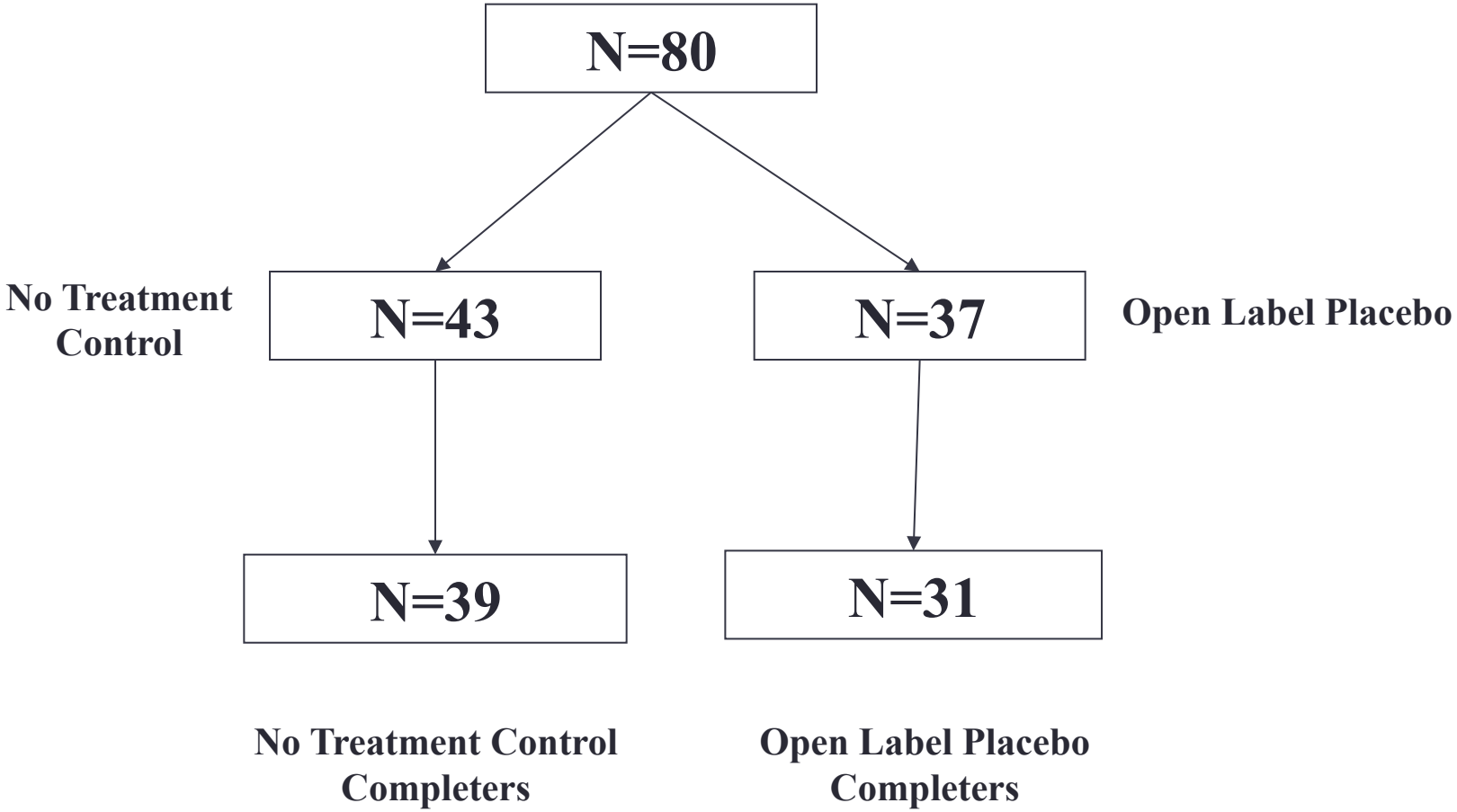
Clinical Trial

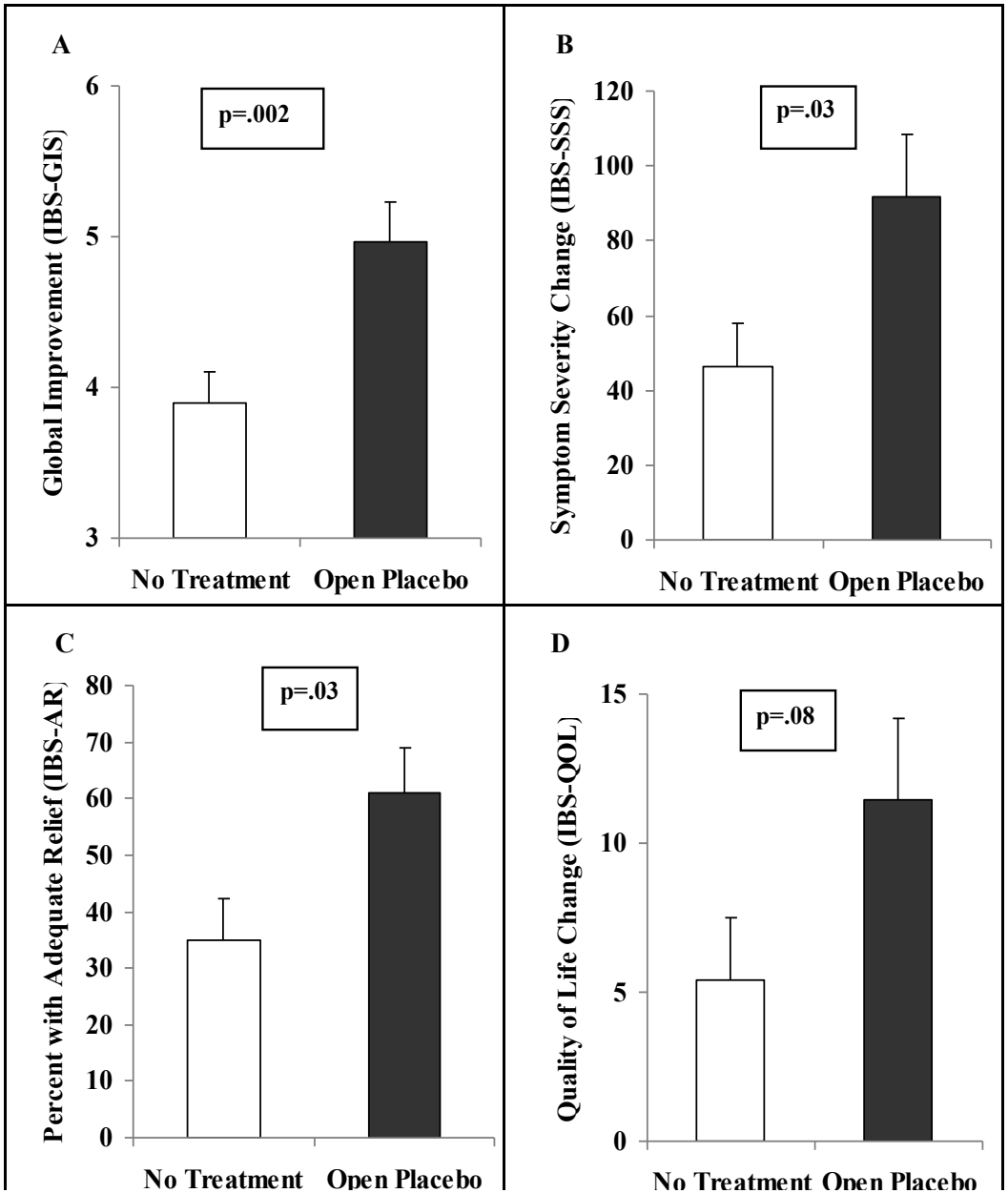
Placebos without Deception: A Randomized Controlled Trial in Irritable Bowel Syndrome

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]


PLACEBO

Open-Label Placebo in IBS: Study Flow




A
Global Improvement (IBS-GIS)
6
5
4
3
p=.002
No Treatment
Open Placebo
B
Symptom Severity Change (IBS-SSS)
120
100
80
60
40
20
0
p=.03
No Treatment
Open Placebo
C
Percent with Adequate Relief (IBS-AR)
80
70
60
50
40
30
20
10
0
p=.03
No Treatment
Open Placebo
D
Quality of Life Change (IBS-QOL)
15
10
5
0
p=.08
No Treatment
Open Placebo

Legal and Ethical Considerations

- Placebos arms are not acceptable particularly when there is an effective intervention to avoid significant morbidity or mortality
  - i.e. ALL, meningitis, status epilectus, status asthmaticus
- Placebo may be acceptable if
  - No commonly accepted therapy
  - Commonly used therapy is of questionable efficacy
  - Commonly used therapy has significant side effects
  - Disease has spontaneous exacerbations and remissions
  - Placebo is an add-on to established therapy

(AAP Committee on Drugs, 1995)

Placebo Response Rate in Children

	MDD (%)	OCD (%)	AD (%)	ADHD (%)
Children	60	40	42	20-30
Adolescents	49	32	32	
Pooled	50	31	40	
Adults	38	23	33	10

(Cohen et al., 2008; Waldbush et al., 2009; Wilens et al., 2002)

Placebo Response Rate in Children

- Epilepsy
  - Children had a significantly higher placebo response rate in comparison with adults (19.0 vs. 9.9%)
  - but not to medication (37.2 vs. 30.4%)(Rheims et al., 2008)
- Migraines
  - Children had a significantly higher placebo response rate in comparison with adults (57.5% vs. 29.9%)
  - responses depends in part on the route of administration (Kossowsky et al., in preparation; Loder et al., 2005; Sun et al., 2013)
- Functional abdominal pain
  - Children have a high placebo response rate (around 50%) (Kossowsky et al., in preparation)
- Placebo Analgesia
  - comparable to adults (Krummenacher, Kossowsky et al., submitted)