

# Placebo Analgesia – Opportunities and Challenges in Clinical Practice

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## Overview

- Clinically focused talk on placebo analgesia and pain management practice.
- Provide a framework to integrate research on placebo effects to clinical practice
  - *Practical for clinicians*
  - *Useful in developing further clinical questions and ultimately research questions surrounding placebo effects*
- Use selected literature within this framework to demonstrate what is known and what future opportunities and challenges exist.

## Critical Concepts

- When we give a placebo, we are simulating a very specific psychosocial context & therapeutic ritual to see **how** that context affects the patients mind, brain and body.
- For clinicians in routine health care practice, the psychosocial context around a patient is able to affect the patients brain **in addition** to the prescribed treatment (drug, surgery, physical therapy).
- The contextual mechanisms that modulate symptoms are called **placebo effects** because traditionally we have studied them after administering a placebo.
- You **do not** have to give a placebo to generate and maintain placebo effects – these mechanisms are part of routine practice.

# A practical framework for application of research on placebo to clinical practice



## PRE TREATMENT

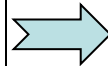
Specific symptoms are and how they started

The process in which the patient enters the health care environment

Intrinsic processes resulting in action to seek treatment

Extrinsic influences that may shape the choice of treatment

Initial interactions with the treatment provider or context



## TREATMENT

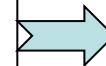
Tablet  
Injection  
Surgery

Physical therapy  
Acupuncture / TENS

Single session  
Series or treatments / program

Duration hours – weeks / months

Delivered (usually) within the same context (therapist, location)



## POST TREATMENT

Follow-up process

Professionals involved

Model of practice – acute vs recurrent vs chronic/persisting

## The framework

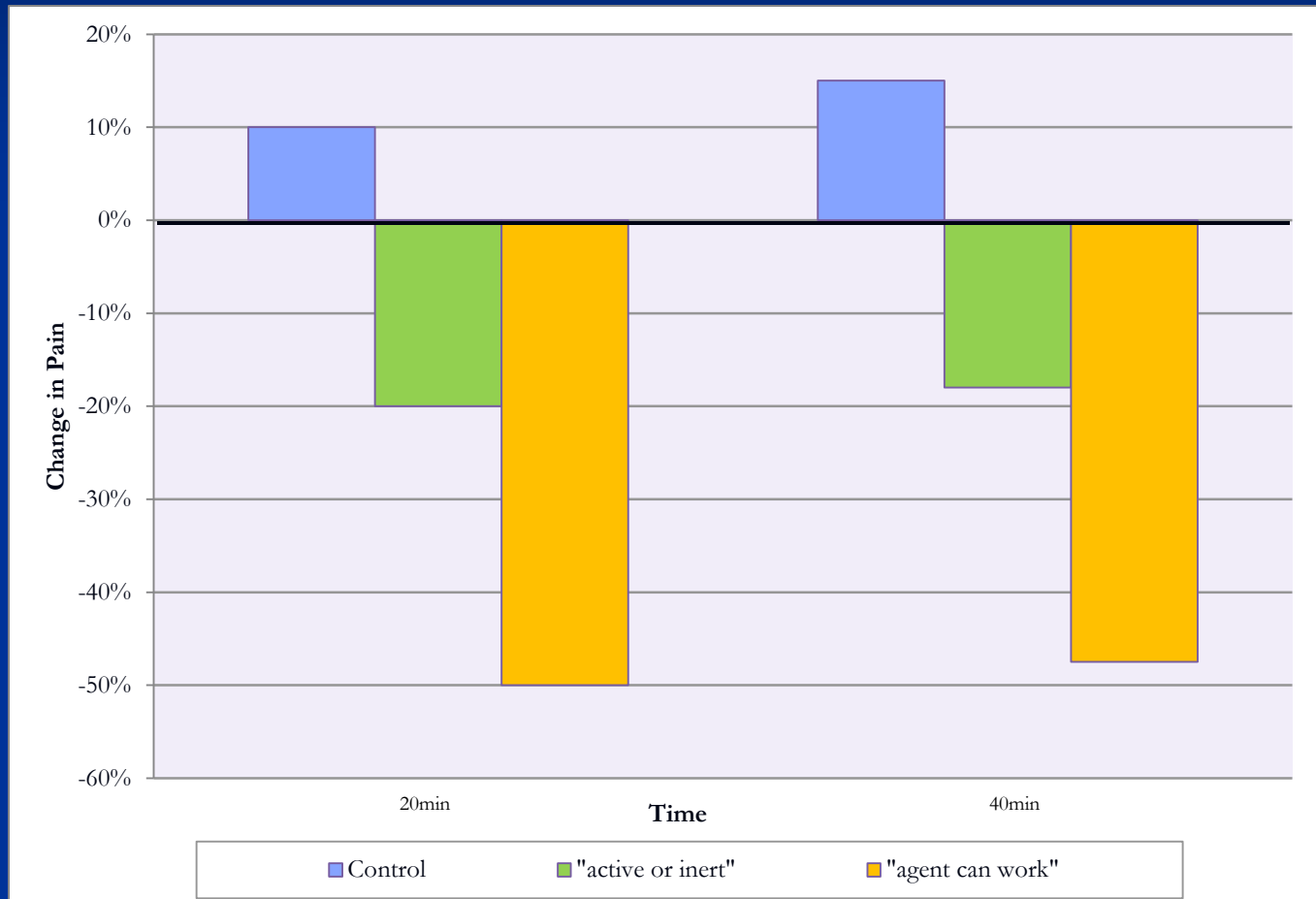
- Expectancies
- Conditioning & Learning
- The Therapeutic Ritual & Doctor-Patient Relationship
- Broader Societal and Health Care Implications
- Present some of the opportunities / challenges concurrently
- Resist the temptation to present the neurobiological research

## Expectancies - words matter !

- Wording or Instruction is critical to expectancies and magnitude of placebo analgesia
- Magnitude of placebo is greater when the context is more similar to the reality of clinical practice (Vase et al 2002)
- Relatively subtle changes in instructions (such as the certainty of receiving a treatment or its benefit) can alter the magnitude of placebo effects.

“ you may receive an active pain reducing medication or an inert placebo agent”

“ the agent you have just been given is known to significantly reduce pain in some patients”





- Expectancy is a complex construct. In pain management, are we talking about expectation of

- Reduced intensity (as reported on a 0-10 scale)?
- A treatment result / reduction in pain ( % reduction in pain)?

- Actually, there is a shift towards other outcomes

- Emotional component – anxiety / negative emotions (***distress***)
- Cognitive appraisal – significance of pain in particular context (e.g. return to work)
- Function / Goal based outcomes

(Atlas & Wager 2012, Neusosci Letters)

- Significant implications for “sensible” modulation of expectancies

- Expectation needs to be matched with experience
- Shapes both future expectations and learning/conditioning processes

- This is almost certainly a ***dynamic*** process

(Vase, Robinson et al, 2005, Pain)

(Finniss et al, 2016, In Prep)

## Verbal suggestions can change meaning of symptoms and treatment

- Information that symptoms are expected “normal” (Egbert 1964, NEJM)

- Egbert et al 1964
- Randomised controlled trial in perioperative medicine (focus on post-operative pain after intra-abdominal surgery)
- Group 1 – usual treatment
- Group 2 – “special care”.
- Information (pre-anaesthetic, day prior)
  - Post operative pain site, likely duration, and that this was “normal”.
  - Specific information about why the pain would be present
  - Advice on strategies to control (not completely alleviate) pain
  - Specific expectation that on day 1 post operation, “complete comfort and relaxation” difficult – medication available on request.
- Visit on afternoon (Day 0) of surgery (information reinforced) and post operative Days 1 and 2 (until no analgesia required).
- Total opioid use (morphine equivalent) measured

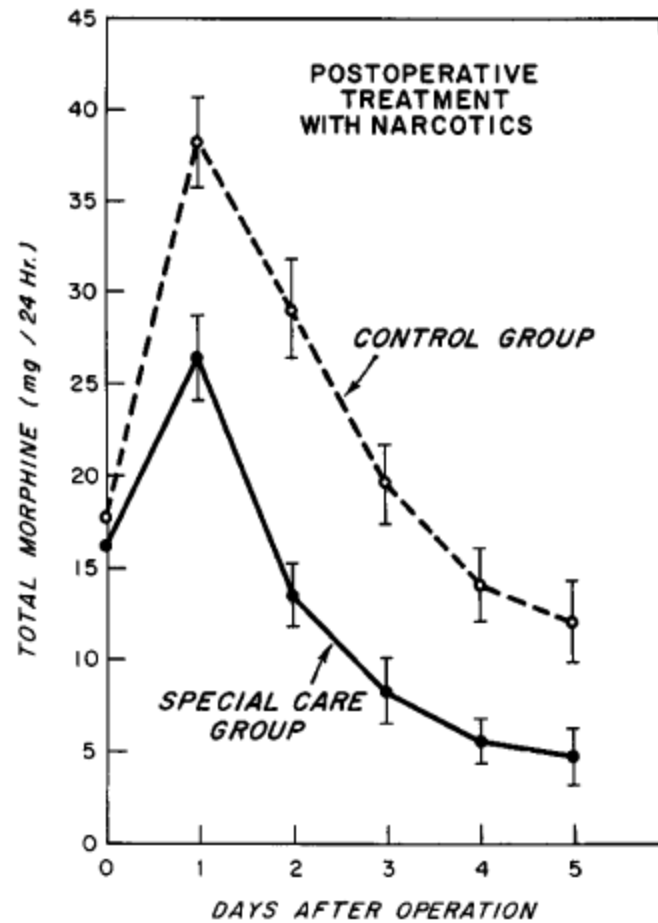


FIGURE 1. Postoperative Treatment with Narcotics (Means for Each Day  $\pm$  Standard Error of the Mean).

## Verbal suggestions can change meaning of symptoms and treatment

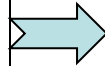
- Information that symptoms are expected “normal” (Egbert et al 1964, NEJM)
- Changing the meaning / context of symptoms can modulate placebo effects (Benedetti 2013)

- Benedetti et al 2013
- Controlled trial – 2 experimental groups
- Assessed pain tolerance (time) to ischaemic arm pain
- Group 1 – Standard instructions about the aversive nature of pain (NEG)
- Group 2 - Specific instructions about the painful stimulus **but** the meaning was changed (POS)
  - Emphasised that the procedure may be beneficial to muscle cells.
  - If repeated many times, and “the longer you can resist”, the larger the beneficial effect.
- Significant differences in pain tolerance between groups.

## PRE TREATMENT

### Expectation

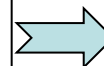
- Assess and establish
- What expectations ?
- How have they been shaped?
- Mutually exclusive?
- Consistency of information ?



## TREATMENT

### Expectation

- Re-establish +/- modify
- Specify and modulate
- Re-establish a positive expectation that is aligned with the treatment



## POST TREATMENT

### Expectation

- Reassess / reinforce
- Can we extend duration of placebo component of treatments by focusing on progress, re-aligning expectancies?
- Specifically setting up a post-treatment review (with the intention of augmenting expectancies for the next treatment).

- Ralphs et al 1994
- In-patient (INPUT) pain management program, London. 4 week CBT & exercise program.
- n=108, randomised to 2 groups. Total opioid dose calculated and converted to daily equivalents (morphine).
- Group 1 – Patient controlled reduction (with reinforcement from team)
- Group 2 – Cocktail reduction – starting at maximum opioid dose, same liquid/taste with graded dose reduction.
- At 4 weeks, additional 21% patients taking the cocktail reduction had ceased all opioids (89%) compared with patient controlled reduction (68%).
- At 6 months, no difference in groups (55% off all opioids) – but the cocktails were not continued outside the program.
- Reduction was linear and not staggered



- Placebo Analgesia is enhanced by pre-conditioning procedures
  - Preconditioning procedure resulted in larger initial placebo response (49.3% vs 9.7%) with a smaller but significant difference some days later (29% vs 18%) (Colloca & Benedetti 2006)
  - Exposure to effective drug “Pharmacological Conditioning” (Amanzio & Benedetti 1999)
- Robust conditioning models exist (for example in performance) (Benedetti et al 2007), (Pollo et al 2008)
- Clinical use of conditioning in dose reduction in pain for some years (Buckley et al 1986, Ralphs et al 1994)
- Social Learning (observation) can result in augmented placebo effects (Colloca & Benedetti, 2009)

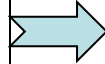
## PRE TREATMENT

### Expectation

- Assess and establish

### Conditioning / Learning

- Careful treatment consideration (past responses or witnessed responses)
- Conditioning procedures



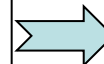
## TREATMENT

### Expectation

- Re-establish +/- modify

### Conditioning / Learning

- Reinforce rationale for treatment (expectancy)
- Conditioning protocols for drug reduction
- Individual vs Group Therapy



## POST TREATMENT

### Expectation

- Reassess / reinforce

### Conditioning / Learning

- Reinforcement schedule
- Specific follow-up procedures to maximise duration of effect
  - *Education*
  - *Reinforcement*
  - *Social / Observational learning*

## The therapeutic ritual & psychosocial context



## Establishing the therapeutic relationship is important

- Egbert et al 1963, JAMA, Randomised Controlled Trial (perioperative medicine) – 2 components
- Component 1 - 4 groups (218 patients)
  - Group 1 – Control
  - Group 2 – Pre-anaesthetic 1hr pre-operation (phentobarbitol) – sedation, hypnosis.
  - Group 3 – Pre-anaesthetic visit (day prior) – time of operation, plan for anaesthetic, likely symptoms and management plan, previous anaesthetic experiences.
  - Group 4 – Pre-anaesthetic visit plus phentobarbitol (combination of groups 2 and 3)
- Assessment of psychological state – anxiety, sedation, “adequacy” of preparation.
- Pre-operative “adequately prepared” (significant differences)  
Control < Phentobarbitol < Pre-anaesthetic visit < Combined visit and drug
- Calming effect (observed “nervous” / reporting feeling “nervous”)  
No differences with drug alone but significant difference control < pre-visit.

- Part 2 (Separate trial)
- 232 patients randomised to 2 groups (pre-anaesthetic visit day prior)
- Same outcome measures
- Group 1 – Informative pre-anaesthetic visit
  - Colourless information
- Group 2 – Supportive pre-anaesthetic visit
  - Same information but delivered in a supportive way (no detail of how)
- All patients received phentobarbital 1hr pre-op
- No significant difference between type of anaesthetic visit (but the visits were demonstrated to be significantly beneficial in Part 1)
- Raises some questions about **what** components of the therapeutic encounter (particularly pre-treatment) are important in **which** patients

## Psychosocial context augmentation

- Trial of “components of placebo effects” on 262 adults with IBS
- Intervention: 6 week trial, two phases of 3 weeks
- Phase I – 3 groups
  - I: Natural History / Wait List
  - II: “Limited Placebo acupuncture”
  - III: “Augmented Placebo acupuncture”
- 2 x 20min sessions per week for 3 weeks

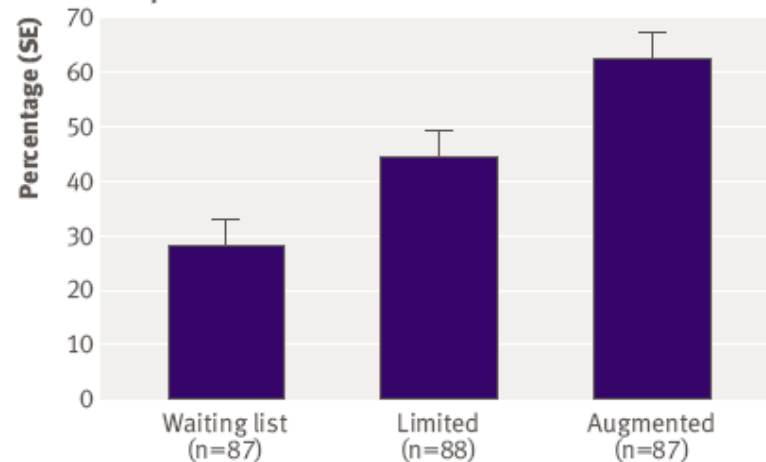
- How did the placebo groups differ?
- Limited placebo acupuncture
  - Clinician met patient, instructed (confidence) “knew what to do”, read file / notes.
  - Scientific study, therefore not allowed to interact during the treatment
  - Needles placed, clinician left the room
- Augmented placebo acupuncture
  - Clinicians coached on both discussion points and behaviours
  - Discussed symptom questions, effect of symptoms on patient (life, relationships), cause and meaning of illness, any other related symptoms
  - Behaviours included being friendly/warm, active listening (asking for clarification), empathy, thoughtful silence, confident delivery of expected outcomes

### Global improvement



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

### Adequate relief



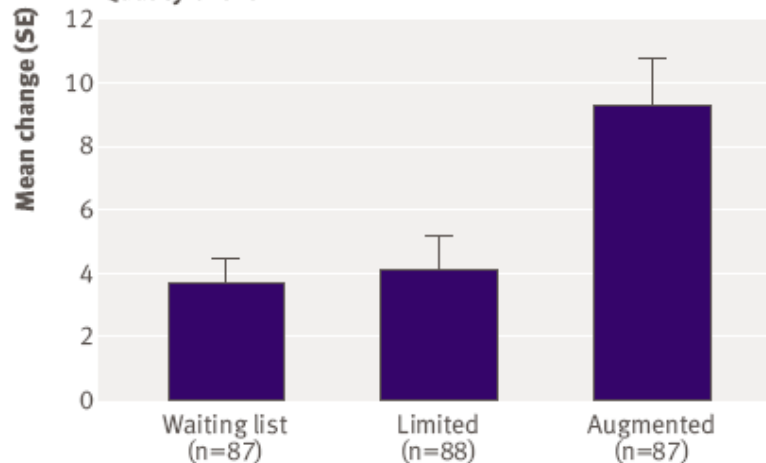
Test of trend:  $P < 0.001$ ; 95% CI 2.7 to 30.7 for limited v waiting list; 3.2 to 32.3 for augmented v limited

### Symptom severity



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

### Quality of life



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



# Many factors identified as being important in Clinician-Patient Interaction – some examples

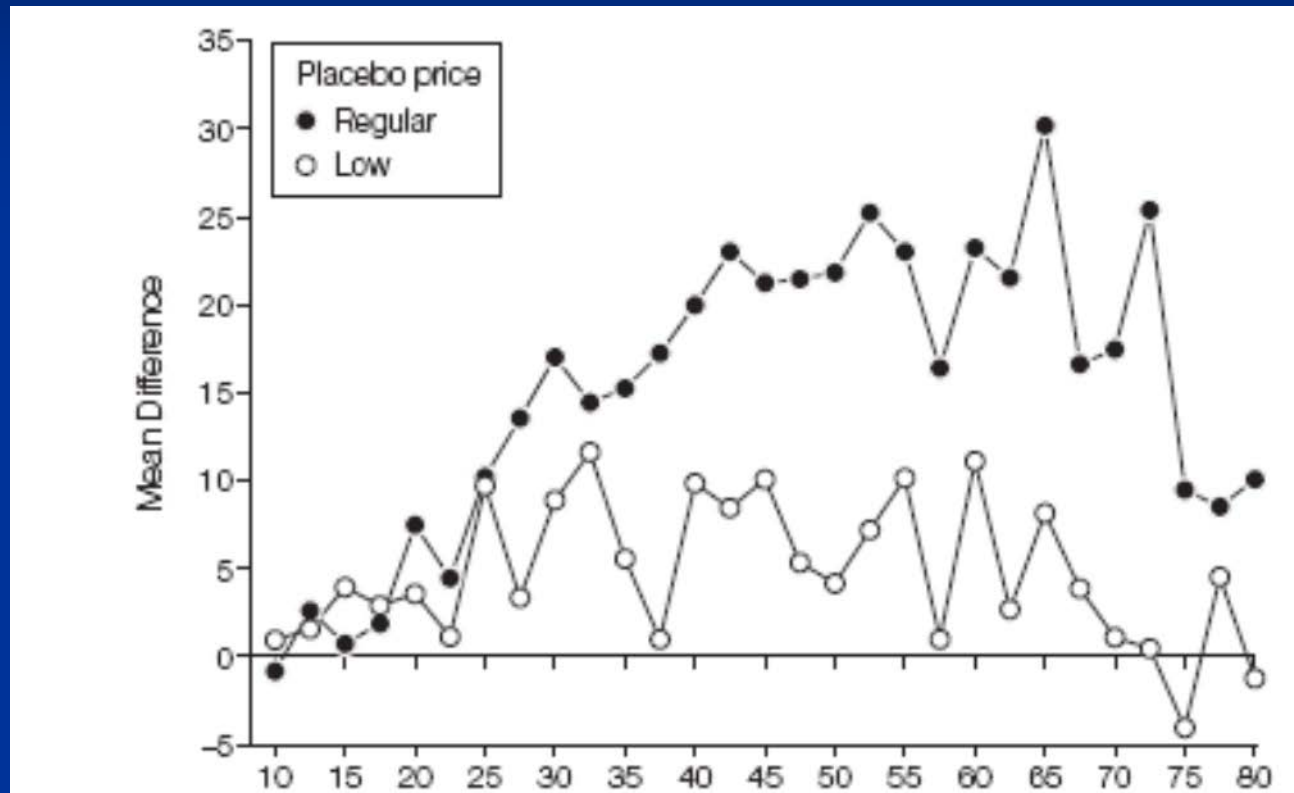
- Prospective research (e.g. Farin et al, J Behav Med, 2013)
  - 688 patients attending pain rehabilitation program
  - Trust, satisfaction (explanation of symptoms, empathy and effort to arrange therapy)
  - Satisfaction associated with better outcomes (6 months post-treatment)
- Systematic reviews (e.g. Pincus et al, Pain, 2013)
  - Affective components (rapport, empathy)
  - Cognitive components (explanation of information)
- Narrative reviews (Benedetti, Physiol Rev, 2013)
  - Neuroscience of the Doctor-Patient relationship
  - Empathy, compassion, hope
  - Non –verbal (facial expression, eye contact, gestures & posture, touch)

## Other aspects about the therapeutic context



- Waber et al 2008, JAMA
- 82 patients, experimental pain.
- Randomised to two different treatments
- “New opioid analgesic, approved by the FDA, similar to codeine but faster action”
- Group 1: “The price of the pill is \$2.50 per pill”
- Group 2: “The pill is discounted to \$0.10 per pill (no reason why)”

24% less patients responded to the discounted placebo (85% vs 61%)



Significant differences in mean difference between pre-post pain tolerance

## Far more complexity to the clinical context

- High tech placebos work better than low tech (Kaptchuk 2000)
- Two placebo tablets are better than one & four better than two (Blackwell et al 1972; de Craen 1999; Moerman 2000).
- Frequency of placebo dosing may be associated with improved outcomes (de Craen 2001)
- Route of administration alters placebo effects (de Craen 2000)
- Placebos show different efficacy when tested against each other (Kaptchuk 2006)

## PRE TREATMENT

### Expectation

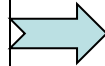
- Assess and establish

### Conditioning / Learning

- Careful treatment consideration (past responses or witnessed responses)
- Conditioning procedures

### Establishing the therapeutic ritual

- What might be needed (choice, route of administration)



## TREATMENT

### Expectation

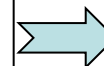
- Re-establish

### Conditioning / Learning

- Reinforce rationale for treatment
- Conditioning protocols for drug reduction
- Individual vs Group Therapy

### Delivery of specific ritual (individualised)

- Consideration of affective, cognitive components



## POST TREATMENT

### Expectation

- Reassess / reinforce

### Conditioning / Learning

- Reinforcement schedule
- Specific follow-up procedures (social learning)

### Post treatment interaction

- Target expectation & learning
- Availability for follow-up, help, arranging further referrals

## A separate element to the psychosocial context – conscious boosting of placebo effects

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search ID: rman2358

"You know that guy you prescribed placebos for? — he paid his bill with Monopoly money."

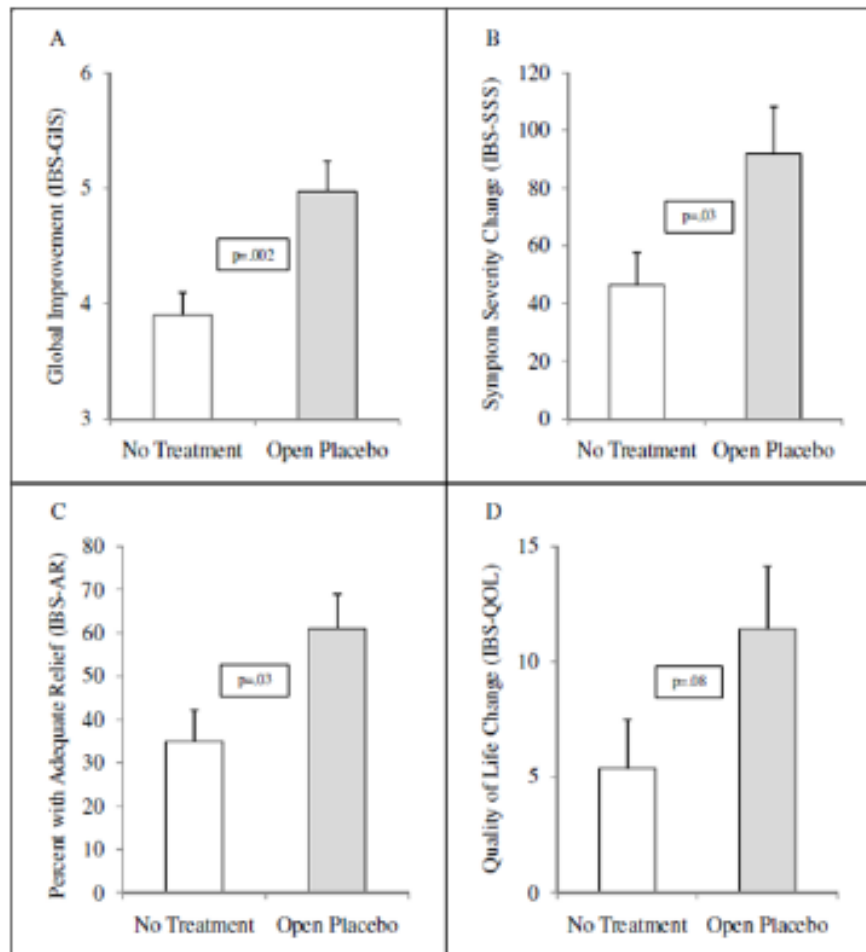
## Unblinded placebo opens new perspectives

- RCT
- 80 patients IBS divided into 2 groups
- Group 1: No treatment control
- Group 2: Open administration of placebo
- Primary measures taken at 3 weeks

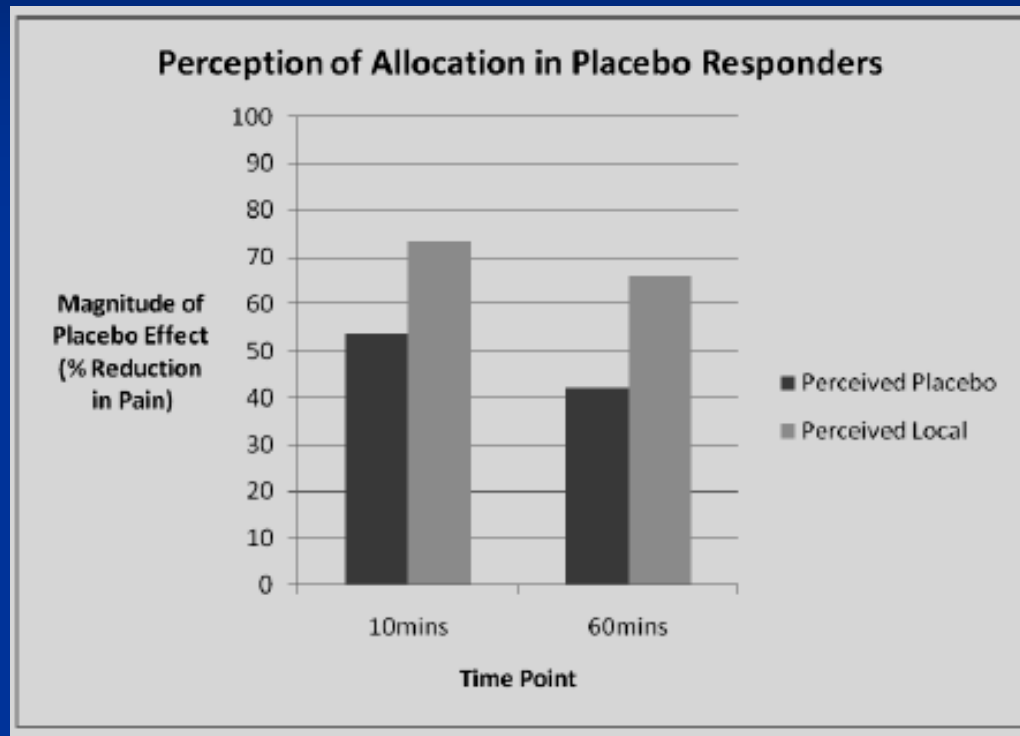


## Unblinded placebo opens new perspectives

- Patients were invited to participate in a study of a “novel mind-body therapy”
- Would receive placebo (inert) “sugar” pills that are known to have “self healing properties”
- 15 min specific information, encompassing
  - 1) Placebo is powerful
  - 2) Human Body can respond automatically “like Pavlov's dogs”
  - 3) Positive attitude helps (but not necessary)
  - 4) Taking pills faithfully is critical



# Perception of Allocation



PL = 73% (28.9)

PP = 54 % (28.1)

\* p = .014

PL = 66% (23.3)

PP= 42 % (24.6)

\* p = .001

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### Targeted education process

## TREATMENT

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### Conditioning / Learning

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- Individual vs Group Therapy

### Delivery of specific ritual (individualised ?)

- Consideration of affective, cognitive components

### Reinforcement of placebo responsiveness & context

## POST TREATMENT

### Expectation

- Reassess / reinforce

### Conditioning / Learning

- Reinforcement schedule
- Specific follow-up procedures (social learning)

### Post treatment interaction

- Target expectation & learning
- Availability for follow-up, help, arranging further referrals

### Patient engagement & self management

## Can we encourage changing of beliefs about placebo ?

- Buchbinder (2001)
- Mass public education strategy about low back pain
- 2 year program, 2 states of Australia (1 intervention, 1 control)
- Baseline measurement of beliefs about back pain with follow-up post campaign
  - n=2400 (general public)
- 3 months intensive media at start and end of 2 years, maintenance phase in the middle
  - TV and radio advertising in prime time
  - Sports persons and significant public figures who had managed back pain successfully
  - Billboards, posters.

## The messages

- “delivered sharply focused and unambiguous messages”

*Spine is strong*

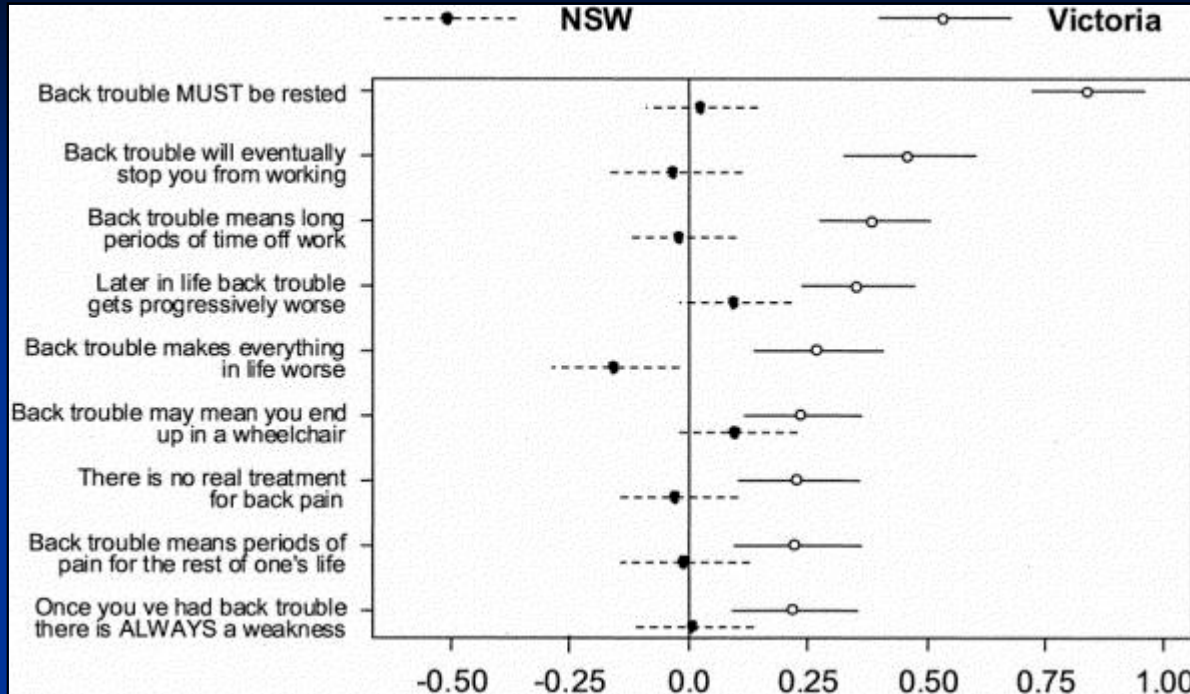
*Self coping is important*

*Investigations are often not helpful*

*Surgery may not be the answer*

*Staying active and not resting too long will help*

Figure 1



2001 Volvo Award Winner in Clinical Studies: Effects of a media campaign on back pain beliefs and its potential influence on management of low back pain in general practice.

Buchbinder R; Jolley D; Wyatt M

Spine. 26(23):2535-42, 2001 Dec 1.

Figure 1 . Average change (95% confidence interval) in the scores for individual items on the Back Beliefs Questionnaire between Surveys 1 and 3 in New South Wales and Victoria.

- Significant improvement in beliefs about low back pain in intervention state (Victoria). Control group (NSW) essentially the same (possibly a little worse)
- Results maintained 3 years later (Buchbinder 2005)

# HEALTHCARE SYSTEMS – Training, discipline & institution, financial, consumer

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### Expectation

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### Establishing the therapeutic ritual

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### Patient engagement & self management



**THE DOCTOR HIMSELF AS A THERAPEUTIC  
AGENT \***

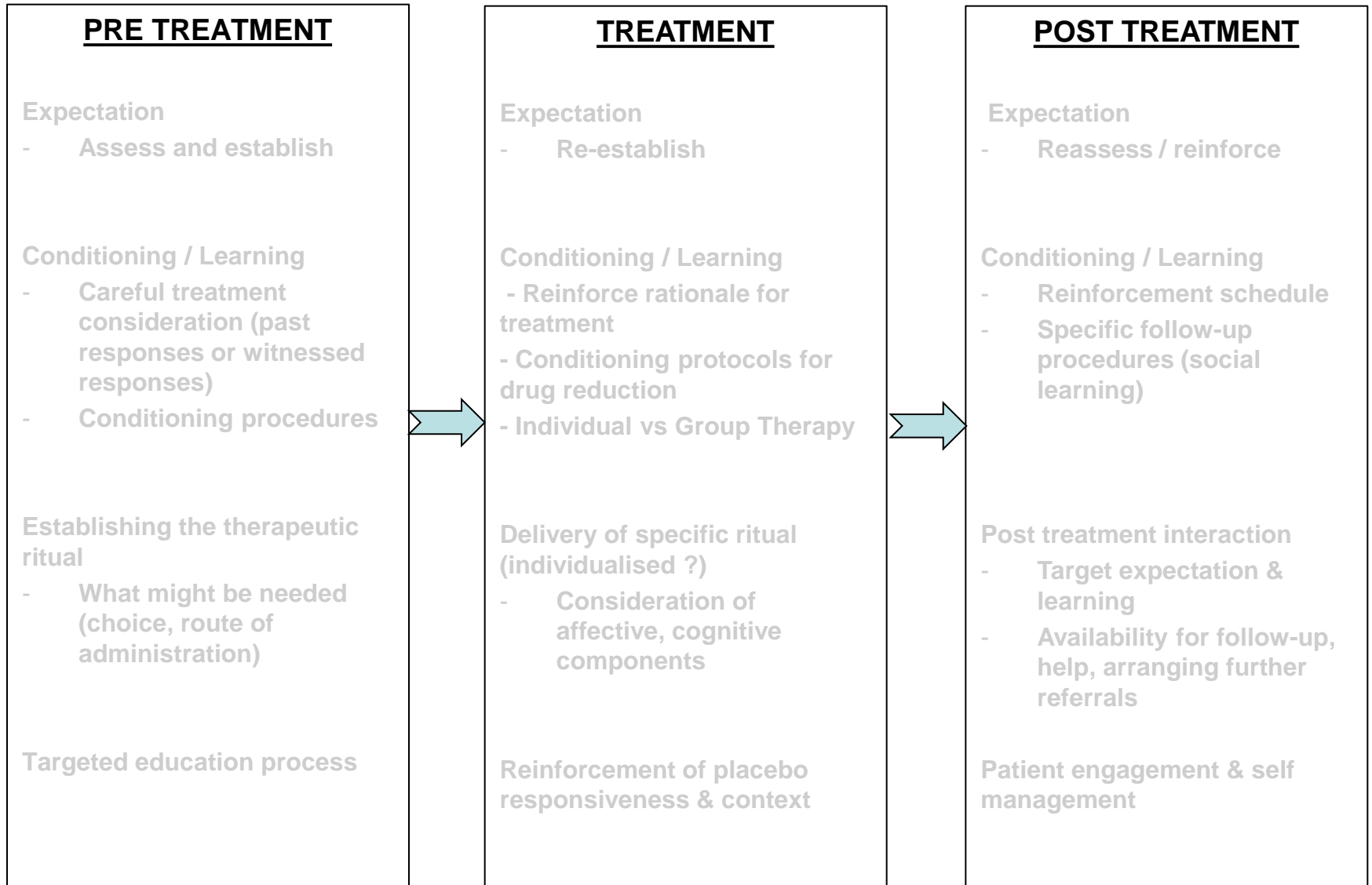
By W. R. HOUSTON, F.A.C.P., *Austin, Texas*

\* Read at the St. Louis meeting of the American College of Physicians, April 19, 1937.  
1416

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

**THE POWERFUL PLACEBO**

*Henry K. Beecher, M.D., Boston*



# Conclusions

- Placebo effects are integral to clinical health care
- Bidirectional relationship between basic science research on placebo and clinical practice
  - Translating basic science research to improve therapeutic outcomes
  - Understanding clinical practice as to apply to researching the mind-brain-body interaction
- Broad health care delivery & societal implications
- Clinical framework needed to apply research on placebo to practice – particularly placebo over the continuum of care.

# Acknowledgements

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