Placebo Analgesia – Opportunities and Challenges in Clinical Practice

Associate Professor Damien Finniss MB BS, PhD, MSc Med, BPhty, BExSc

Department of Anaesthesia, Royal North Shore Hospital
University of Sydney Pain Management Research Institute
Royal North Shore Hospital

Griffith University School of Rehabilitation Sciences
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 patient's mind, brain and body.

- For clinicians in routine health care practice, the psychosocial context around a patient is able to affect the patient's 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”

Verne et al, Vase et al 2003
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

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 ± 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.
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<td>- What expectations?</td>
<td>- Specify and modulate</td>
<td>- Can we extend duration of placebo component of treatments by focusing on progress, re-aligning expectancies?</td>
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<td>- How have they been shaped?</td>
<td>- Re-establish a positive expectation that is aligned with the treatment</td>
<td>- Specifically setting up a post-treatment review (with the intention of augmenting expectancies for the next treatment).</td>
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<td>- Mutually exclusive?</td>
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<td>- Consistency of information?</td>
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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 (Buckey 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

"Let's try the Good Doctor/Bad Doctor routine."
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)


- 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

Kaptchuk et al 2008
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

- Waiting list (n=87)
- Limited (n=88)
- Augmented (n=87)

Test of trend: \( P<0.001 \); 95% CI 0.18 to 0.90 for limited \( \times \) waiting list; 0.32 to 1.11 for augmented \( \times \) limited

Adequate relief

- Waiting list (n=87)
- Limited (n=88)
- Augmented (n=87)

Test of trend: \( P<0.001 \); 95% CI 2.7 to 30.7 for limited \( \times \) waiting list; 3.2 to 32.3 for augmented \( \times \) limited

Symptom severity

- Waiting list (n=87)
- Limited (n=88)
- Augmented (n=87)

Test of trend: \( P<0.001 \); 95% CI -7.9 to 31.2 for limited \( \times \) waiting list; 16.2 to 63.2 for augmented \( \times \) limited

Quality of life

- Waiting list (n=87)
- Limited (n=88)
- Augmented (n=87)

Test of trend: \( P<0.001 \); 95% CI -2.1 to 3.2 for limited \( \times \) waiting list; 1.7 to 8.8 for augmented \( \times \) 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)
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A separate element to the psychosocial context – conscious boosting of placebo effects

"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

Kaptchuk et al 2010, Plos One
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

Kaptchuk et al 2010, Plos One
Perception of Allocation

Finniss et al 2016, In prep
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Targeted education process

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Delivery of specific ritual (individualised ?)
- Consideration of affective, cognitive components

Reinforcement of placebo responsiveness & context

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**POST TREATMENT**

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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
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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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.

THE POWERFUL PLACEBO

Henry K. Beecher, M.D., Boston
HEALTHCARE SYSTEMS – Training, discipline & institution, financial, consumer

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Patient engagement & self management

RESEARCH – Basic science, translational research to answer clinical questions
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.
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