Using the Placebo Effect to Optimize the Treatment of Pain

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Conflicts of interest

• None
Knee pain

- 74 year old lady
- Right knee pain
- Bony enlargement, limited ROM with crepitus
- 3 lidocaine 5% patches on knee
- Asks to continue the patches as they have helped her pain
All patients had pain > 4/10 in a knee. Up to 4 patches per day were applied by the patient to the painful joint.

“Average pain intensity scores were 29% lower after 2 weeks of lidocaine patch 5% treatment ...compared to baseline...P<0.001”
Lidocaine patches to treat osteoarthritic knee or back pain

• Randomized, double blind, placebo controlled studies
  – Unpublished
    • EN-3220-011, 2003: Low back pain
    • EN-3260-001, 2004-5: Knee pain
    • EN-3261-001, 2004-5: Low back pain
  – Published
    • Hashmi JA, et al; 2012: Chronic back pain

• Pain improved in both the placebo patch and lidocaine patch groups. There was no significant difference between them.
Definitions

- **Placebo** - An inert substance or sham procedure given to a patient
  - To try to achieve a beneficial effect for a patient who believes that a helpful treatment is being received
  - To compare its effects with those of a real drug or treatment
- **Placebo effect** – The results of giving a placebo
- **Nocebo** - An inert substance or sham procedure given to a patient which may cause harmful effects due to negative expectations of the patient
- **Nocebo effect** – The results of giving a nocebo
Non placebo phenomena

- Regression to the mean
- Varied temporal patterns of intensity
- Hawthorne effect (observer effect)

A natural history or baseline group is important when assessing placebo effects.
Genesis of the placebo effect?

Inert agent or sham procedure administered to patient

Placebo effect

Incomplete...
Genesis of the placebo effect

Inert agent or sham procedure administered to patient → Psychosocial context → Placebo effect
Psychosocial context surrounding the patient

Individual patient and clinician factors

- Patient’s and clinician’s
  - Beliefs
  - Expectations
  - Desire for symptom change
  - Past experience

Interaction between the patient, clinician, and treatment environment

- Factors in the clinician-patient relationship
  - Communication
  - Empathy
  - Reassurance
  - Bedside manner
  - Enthusiasm
  - Interdisciplinary team

- Factors in the treatment environment
  - Location
  - Nature of treatment
  - Use of technological devices
  - Therapeutic procedure

Based on Finniss DG, et al. *Lancet* 2010
Psychological mechanisms of placebo effect

- Expectation
- Conditioning
- Lessening of anxiety
- Learning
- Motivation
- Somatization
- Reward

Expectation

• Post thoracotomy, all patients on buprenorphine PRN for pain x 3 days

• 3 groups with saline infusion
  – Group 1: Told nothing about any analgesic effect.
  – Group 2: “The infusion is either a powerful pain killer or a placebo.”
  – Group 3: “The infusion is a powerful pain killer.”

Pollo A; Amanzio M; Arslanian A; Casadio C; Maggi G; Benedetti F. Response expectancies in placebo analgesia and their clinical relevance. *Pain*. 2001; 93(1):77-84.
Fig. 3. Total dose of buprenorphine received at the end of the 3-days analgesic treatment in the three groups of patients. The three different verbal instructions about the saline basal infusion produced different buprenorphine intake.

Pollo A; Amanzio M; Arslanian A; Casadio C; Maggi G; Benedetti F. Response expectancies in placebo analgesia and their clinical relevance. *Pain*. 2001; 93(1):77-84.
Open-hidden paradigm for pain

- Patients divided into 2 groups who receive the same analgesic using the same therapeutic protocol
  - One group sees it being given openly, with verbal cues.
  - The other group receives it in a hidden manner, without cues.
- The difference in analgesia is the placebo effect.

Expectation, postoperative pain


Pain rating scale 0-10
Expectations of clinicians

• 60 dental patients had unilateral upper & lower wisdom teeth removed under 2% lidocaine local

• An injection was given and pain score obtained 10 min before & after, and 1 hour after

• All patients were told that they would receive either a placebo (saline), a narcotic analgesic (fentanyl), or a narcotic antagonist (naloxone) and that these might not have an effect on, decrease, or increase their pain.

Expectations of clinicians

- Clinicians gave drugs and questionnaire
- Clinicians knew there were 2 groups & who was in each group
  - PN : May get placebo or naloxone
  - PNF: May get placebo, naloxone, or fentanyl
- Comparing only those who got placebo, pain in PNF placebo group was significantly less at 1 hour than in the PN placebo group. (p<0.01)

Expectations of clinicians

**Change in pain rating index between baseline (10 min before injection) and 10 and 60 minutes after**

- **Placebo (Group PN)**
- **Placebo (Group PNF)**

**PN**=Group that could have either received placebo or naloxone

**PNF**=Group that could have received placebo, naloxone, or fentanyl

Total pain

- Physical
- Psychological
- Spiritual
- Social

Cicely Saunders
Headache

• 35 yo lady with long history of headaches
• She has previously tried many different medications and seen multiple clinicians with no improvements
• DX: chronic tension-type headaches
• What are her expectations regarding the treatments to be prescribed?
• What are your expectations?
Nocebo effect

- Negative expectations may be formed from
  - Previous experiences
  - Observing another person experiencing symptoms
  - News media reports
  - Switching to a generic medication
  - The informed consent process

Based on Faasse K, Petrie KJ. *Postgrad Med J* 2013
Evidence for opioid mechanisms in placebo analgesia

- Placebo analgesia is antagonized by naloxone.

Activation of $\mu$–opioid receptors with placebo

Endogenous opioids when in pain

Baseline with no pain was used for comparison

Endogenous opioids when in pain AND receiving placebo

And the pain was significantly less with placebo

Conditioning

• Before conditioning
  – Food (US) → salivation (UR)
  – Metronome alone → no response

• During conditioning
  – Food (US) + metronome → salivation (UR)

• After conditioning
  – Metronome alone (CS) → salivation (CR)

US = Unconditioned stimulus
UR = Unconditioned response
CS = Conditioned stimulus
CR = Conditioned response

Ivan Pavlov
Conditioning causes opioid mediated placebo effect on pain tolerance

- 4 teams training for pain competition: A, B, C, D
  - Weekly “training sessions” & 4th week competition
  - None given morphine week 1
  - Weeks 2 & 3 Groups A & B given no treatment and C & D given morphine (0.14 mg/kg) before training
  - Week 4: Group A no treatment, B & C placebo, and D getting naloxone
  - Group C tolerated pain significantly longer than all other groups suggesting that the conditioned placebo response was due to endogenous opioids

Components of analgesic placebo effect

- Placebo response is divided into opioid and non-opioid components. Fields HL, Levine JD. *West J Med* 1984
  - Expectation: activates opioid systems
    - Blocked by naloxone Amanzio M, Benedetti F. *J Neurosci* 1999
  - Conditioning: may activate both opioid and non-opioid subsystems Amanzio M, Benedetti F. *J Neurosci* 1999
    - Placebo response where morphine was used for conditioning is blocked by naloxone
    - Placebo response where ketorolac was used for conditioning is not totally blocked by naloxone
Nonopiod neurotransmitters in analgesic placebo response

- Endocannabinoids
  - Ketorolac conditioning  

- Cholecystokinin
  - Nocebo effect

- Dopamine
  - Mediates pleasure
  - Pain processing
Other conditions responsive to the placebo effect

- Bipolar disorder
- Depression
- Panic disorder
- Social phobia
- Urinary flow in BPH

- Allergic rhinnitis
- Asthma
- Irritable bowel syndrome
- Parkinson disease
- Sports performance
Factors that contribute to the efficacy of placebos

• Price
  – Costlier medication works better  Andrade C. J Clin Psych 2015

• Form and color
  – Capsules better than tablets

• Hands on treatments
  – Sham surgery
  – Sham acupuncture
Placebos: pills and procedures

- Systemic review of 79 RCTs of migraine prophylaxis using active vs. placebo treatments
- Meta-analyses compared the success of various placebos used in the trials
- If the frequency of headaches was reduced by 50%, they were responders

% of PLACEBO RESPONDERS IN TRIALS USING
- Placebo pills......................22%
- Sham acupuncture............38%
- Sham surgery....................58%

Meissner K, et al; 2013
Types of placebos

• Pure placebo
  – Sugar or starch pill

• Impure placebo
  – Penicillin for viral infection
  – Lidocaine 5% patch for osteoarthritic pain

• Placebo effect augmenting the action of a beneficial medication or procedure
Placebo use in clinical practice

• Survey to 970 members of AAFP
  – Family physicians
• 412 (43%) returned survey
• 56% reported prescribing or using placebos
  – 19% over ten times per year
  – 27% one to ten times per year
  – 10% less than once per year

Kermen R, et al. *Fam Med* 2010
Examples of placebos given

- Antibiotics for viral infections ......................40%
- Vitamins .................................................................23%
- Herbal supplements .............................................12%
- Sub-therapeutic dose of medication ...........10%
- Ibuprofen for symptoms unrelated to pain. 9%
- Saline infusions or IM injections .................6%
- Prepared placebo tablets ................................3%
- Sugar or artificial sweetener pills ...............2%

Kermen R, et al. Fam Med 2010
Expectation in acupuncture

- Real vs. sham acupuncture compared in 2 studies
  - Wisdom tooth removal: No significant difference in analgesia between real & sham groups. Patients who believed they were in the real treatment group had significantly greater analgesia compared to those who thought they were in the sham (placebo) group. Bausell RB, et al. Eval Health Prof 2005

  - Pooled analysis of 4 RCTs. 3 of 4 trials had shown no significant difference in analgesia between real and sham groups. Those who thought acupuncture was an effective or highly effective therapy had significantly greater improvement than those who were more skeptical. Linde K, et al. Pain 2007

  - It didn’t matter whether they had real or sham Rx, what mattered was whether they expected a benefit from acupuncture.
Ethics of the placebo effect

• Can pure placebos or impure placebos ever ethically be used?
• If it helps, why worry?
  – Why not use lidocaine patches for osteoarthritis?
• What should I tell the patient?
• How much information should be given when obtaining informed consent?

• “In the clinical setting, the use of a placebo without the patient’s knowledge may undermine trust, compromise the patient-physician relationship, and result in medical harm to the patient.”

• “Physicians can avoid using a placebo, yet produce a placebo-like effect through the skillful use of reassurance and encouragement.”
Psychosocial context surrounding the patient

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Maximizing the placebo effect in treating pain

- Spend time with the patient, listen
- Carefully examine the patient, hands on
- Let the patient know your diagnosis and educate them regarding it.
- Discuss the prescribed treatment and the benefits you expect from it in a positive, honest manner
Maximizing the placebo effect in treating pain (continued)

• Discuss possible adverse effects realistically, but emphasize how the benefits outweigh the risks
  – Anticipate and prevent side effects

• Anticipate concerns
  – Generic vs. brand name
  – Cost of medication
  – Concerns about addiction with opioids for cancer or end of life pain

• Schedule follow up visit
Uncontrolled metastatic cancer pain

• 50 yo man has lung cancer with liver metastases. C/o severe 10/10 pain RUQ not controlled by scheduled MS Contin 30 mg po q 8 hours and Norco 5/325 1-2 po q 4 hours PRN.

• On exam: liver is enlarged with an irregular edge, very tender to palpation.
Summary

• The placebo effect is a real psychobiologic process involving endogenous opioids and other neurotransmitters.
• The placebo effect can be used to enhance the pharmacological effectiveness of analgesics.
• The placebo effect is maximized through optimization of psychosocial factors in the clinical encounter.
Questions?