

Using the Placebo Effect to Optimize the Treatment of Pain

October 21, 2016

Palliative Care Collaborative, 9th Annual Regional Conference

Thomas R. Palmer M.D.

Henry Ford Hospital Palliative Medicine Service; Detroit, Michigan

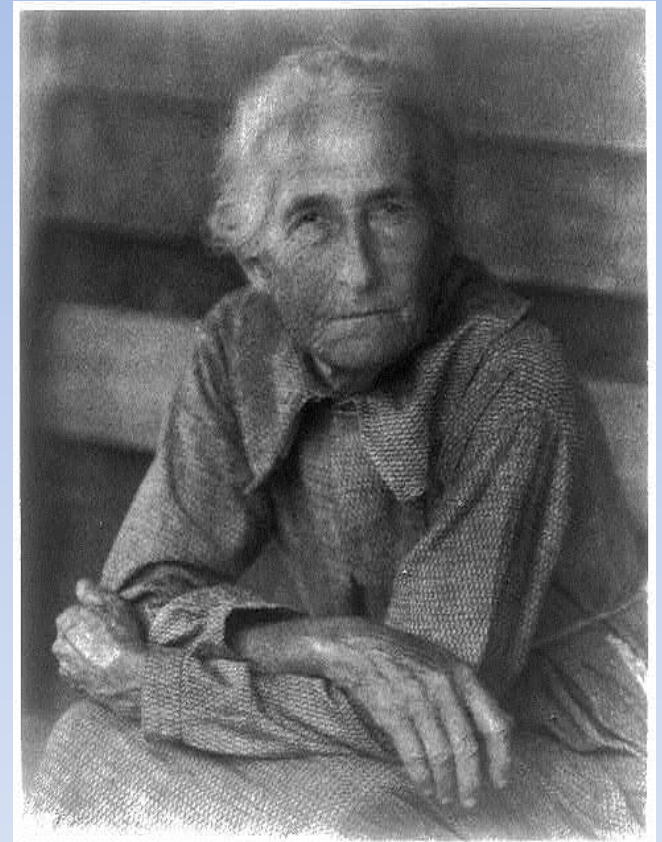
Clinical Associate Professor of Family Medicine, Wayne State University School of Medicine

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



About 13,900 results (0.29 seconds)

 **Lidocaine patch 5% and its positive impact on pain qualities ...**
www.ncbi.nlm.nih.gov/ ... National Center for Biotechnology Information ▾
by AR Gammaitoni - 2004 - Cited by 70 - Related articles
Lidocaine patch 5% and its positive impact on pain qualities in osteoarthritis: results of a pilot 2-week, open-label study using the Neuropathic Pain Scale.

 **Lidocaine patch 5% improves pain, stiffness, and physical ...**
www.sciencedirect.com/science/.../S1063458403002723 ▾ ScienceDirect ▾
by F Burch - 2004 - Cited by 58 - Related articles
Lidocaine patch 5% improves pain, stiffness, and physical function in osteoarthritis pain patients: A prospective, multicenter, open-label effectiveness trial.

 **Lidocaine patch for OA and low back pain? - Medscape**
www.medscape.com/viewarticle/537770 ▾ Medscape ▾
May 12, 2004 - A patch containing 5% lidocaine, currently approved in the US for postherpetic neuralgia, is being tested in knee osteoarthritis and low back ...

Efficacy and Safety of the Lidoderm Patch Applied to ...
<https://clinicaltrials.gov/ct2/show/NCT00589979> ▾ ClinicalTrials.gov ▾
Dec 26, 2007 - Patients with knee pain due to Osteoarthritis (OA) experiencing ... The overall treatment difference for the Lidoderm (lidocaine patch 5%) and ...

 **Lidocaine Patch Found Effective for Knee Pain**
consumer.healthday.com/.../lidocaine-patch-found-effective-for-knee-pa... ▾
Mar 30, 2005 - Osteoarthritis of the knee is a leading cause of disability in the United ... physicians are free to prescribe the lidocaine patch for osteoarthritis of ...

 **List of 41 Common Osteoarthritis Medications - Healthline**
www.healthline.com ▾ Osteoarthritis ▾ Home ▾ Healthline Networks ▾
Oct 29, 2014 - Osteoarthritis is the most common form of arthritis. ... of osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis. ... Lidocaine Patch.

 **Lidocaine Patch Reduces Pain, Stiffness in Osteoarthritis ...**
painmedicineweb.com/index.asp?section_id=85&show...id... ▾
Chicago—The lidocaine patch 5% significantly reduced pain and stiffness, and improved physical function, in patients with osteoarthritis (OA), according to a ...



Lidocaine patch 5% improves pain, stiffness, and physical ...
[www.oarsjournal.com/article/S1063-4584\(03\)00272-3/abstract](http://www.oarsjournal.com/article/S1063-4584(03)00272-3/abstract)
by F Burch - 2004 - Cited by 58 - Related articles
Lidocaine patch 5% improves pain, stiffness, and physical function in osteoarthritis pain patients: A prospective, multicenter, open-label effectiveness trial.

 **Ankle Osteoarthritis Medical Treatments - Arthritis-health**
www.arthritis-health.com/.../osteoarthritis/ankle-arthritis-medical-treatme... ▾
A physical therapist can teach an ankle osteoarthritis patient specific exercises to ...
Lidocaine patch 5% and its positive impact on pain qualities in osteoarthritis: ...

 **[PDF] [lidocaine] 5% patch - Amida Care**
www.amidacareny.org/Collateral/...US/Med_Lidoderm_PA_policy.pdf ▾
Jul 20, 2011 - back pain, myofascial pain, osteoarthritis (OA), diabetic neuropathy, and ... and impact on quality of life of the 5% lidocaine patch in diabetic ...

June 26, 2015

OsteoArthritis and Cartilage (2004) 12, 253–255

© 2003 Published by Elsevier Ltd on behalf of OsteoArthritis Research Society International.
doi:10.1016/j.joca.2003.10.007

**Osteoarthritis
and Cartilage**

| **C** R S

**International
Cartilage
Repair
Society**

 **OARSI** OSTEOARTHRITIS
RESEARCH SOCIETY
INTERNATIONAL

Lidocaine patch 5% improves pain, stiffness, and physical function in osteoarthritis pain patients

A prospective, multicenter, open-label effectiveness trial

F. Burch†*, C. Coddington‡, N. Patel§ and E. Sheldon¶

†*Radiant Research, San Antonio, Texas, USA*

‡*Health Research Institute, Oklahoma City, Oklahoma, USA*

§*Cardinal Clinical Research Center, Cudahy, Wisconsin, USA*

¶*Miami Research Associates, Miami, Florida, USA*

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

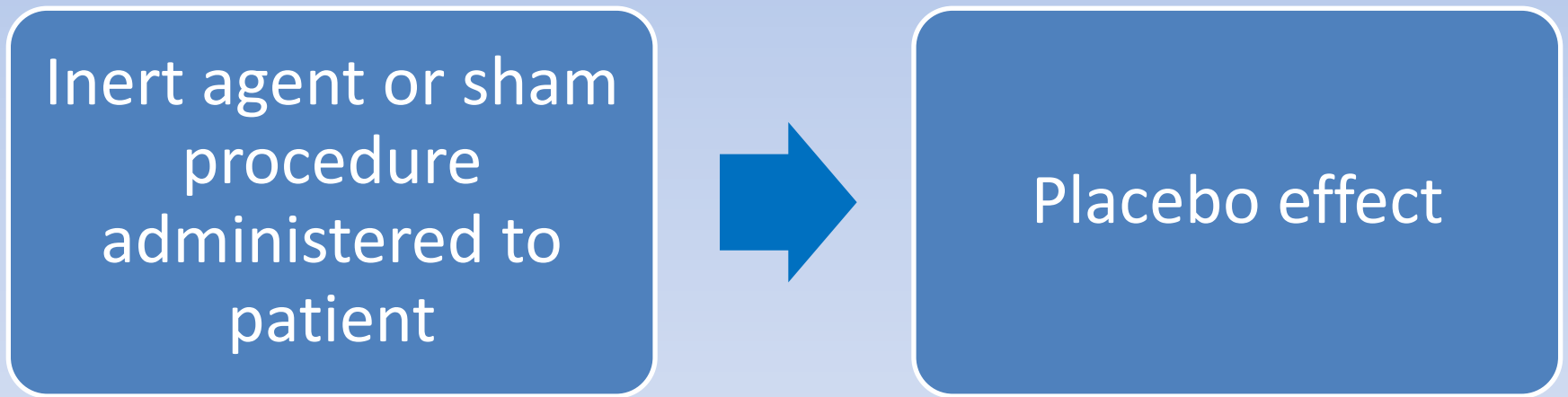
- **Placebo** - An inert substance or sham procedure given to a patient
 - To try to achieve a beneficial effect for a patient who believes that a helpful treatment is being received
 - To compare its effects with those of a real drug or treatment
- **Placebo effect** – The results of giving a placebo
- **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?

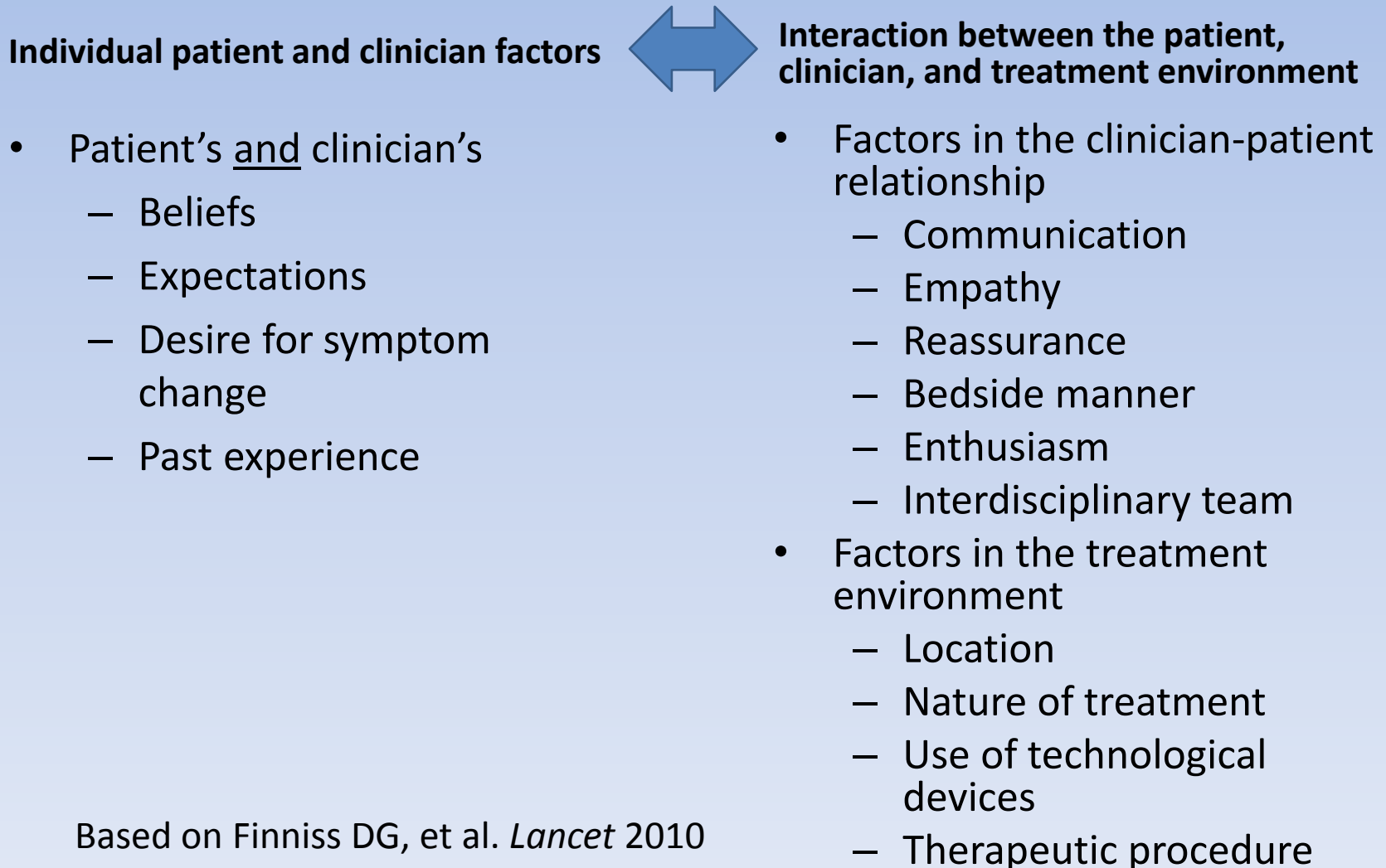


Incomplete...

Genesis of the placebo effect



Psychosocial context surrounding the patient



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.”

Expectation

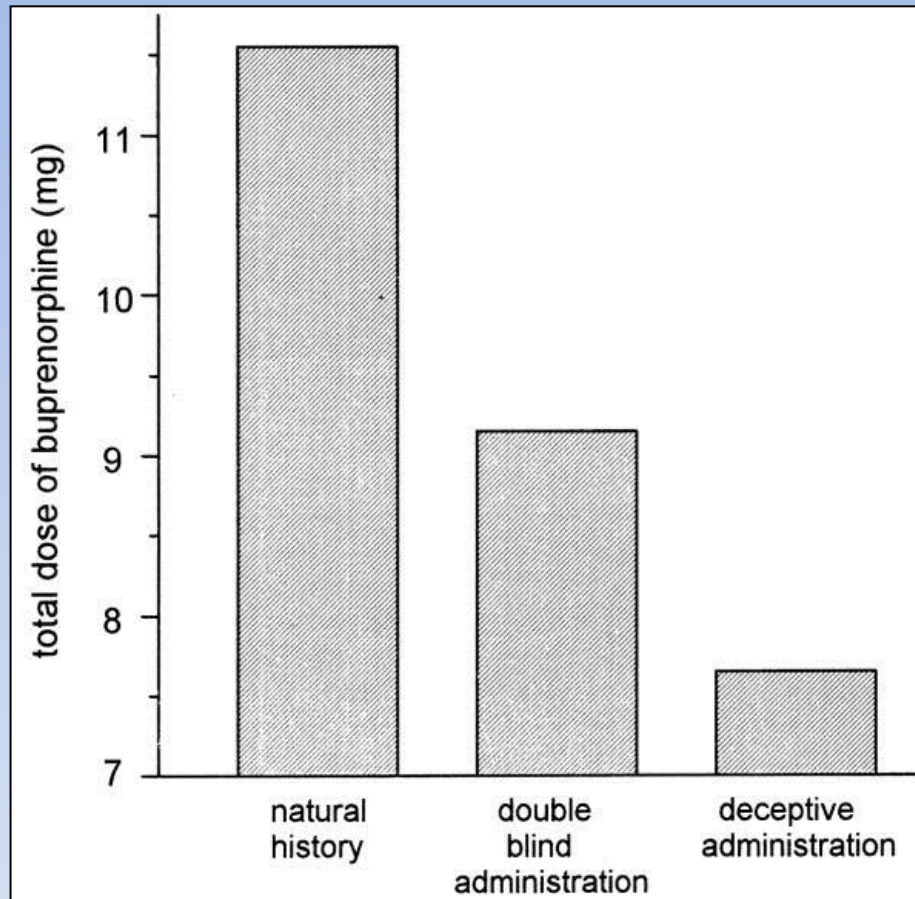


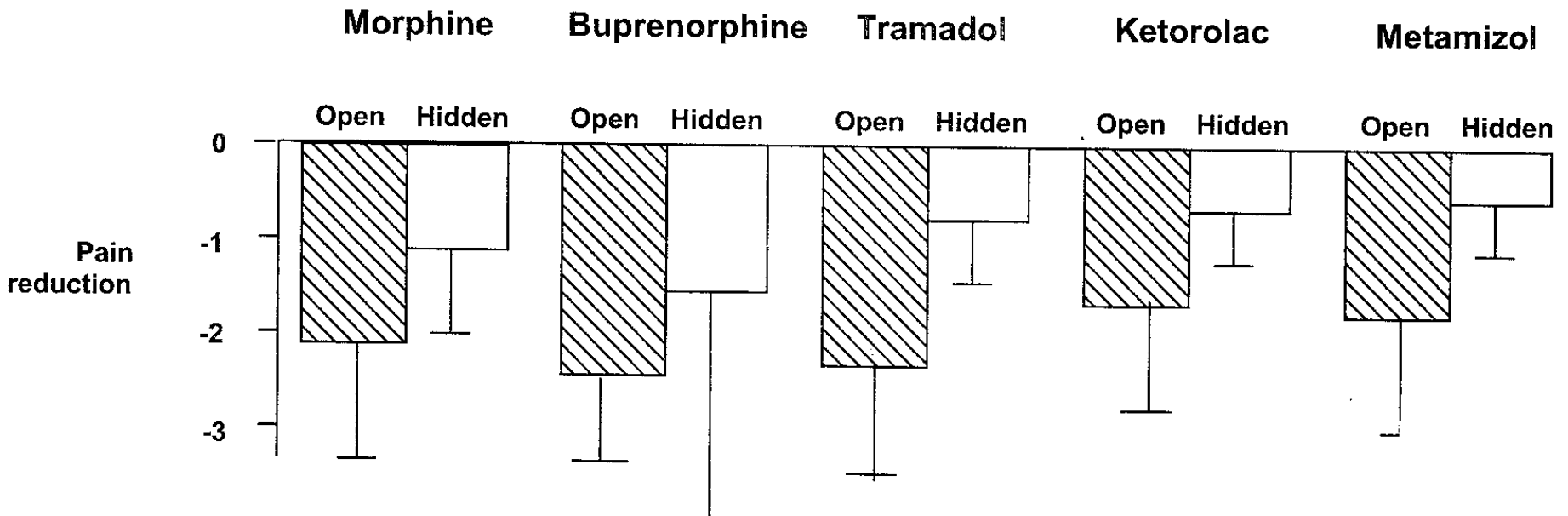
Fig. 3 . Total dose of buprenorphine received at the end of the 3-days analgesic treatment in the three groups of patients. The three different verbal instructions about the saline basal infusion produced different buprenorphine intake.

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. 2

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

Chart from Price DD, et al. A comprehensive review of the placebo effect: recent advances and current thought. *Annual Review of Psychology* 2008; 59: 565-590. based on data from Amanzio et al. 2001

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.



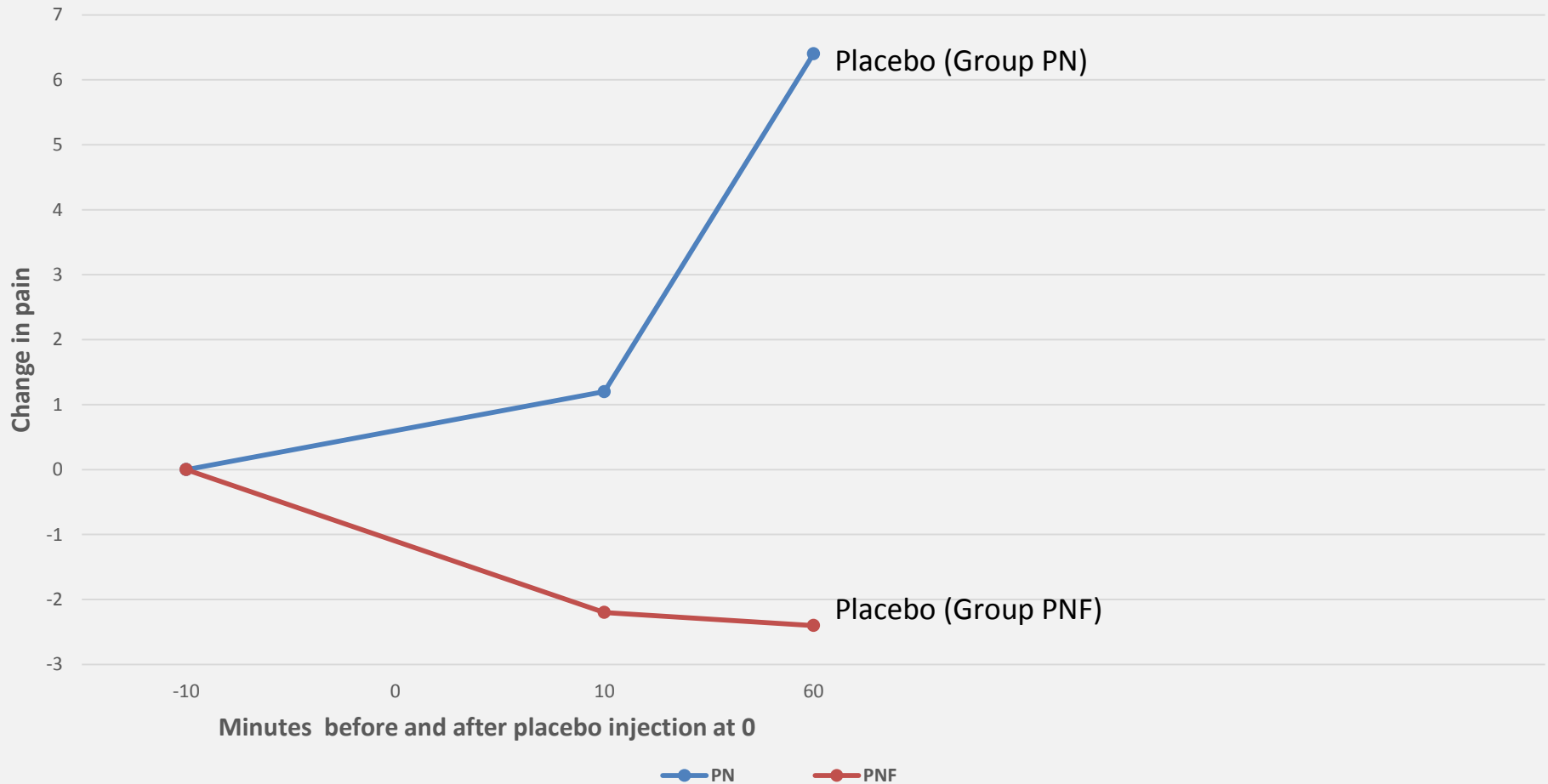
Expectations of clinicians

- 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



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

Gracely RH, et al. Clinicians' expectations influence placebo analgesia. *Lancet* 1985; 1(8419): 43.

Total pain

- Physical
- Psychological 
- Spiritual 
- Social 

Expectation



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?

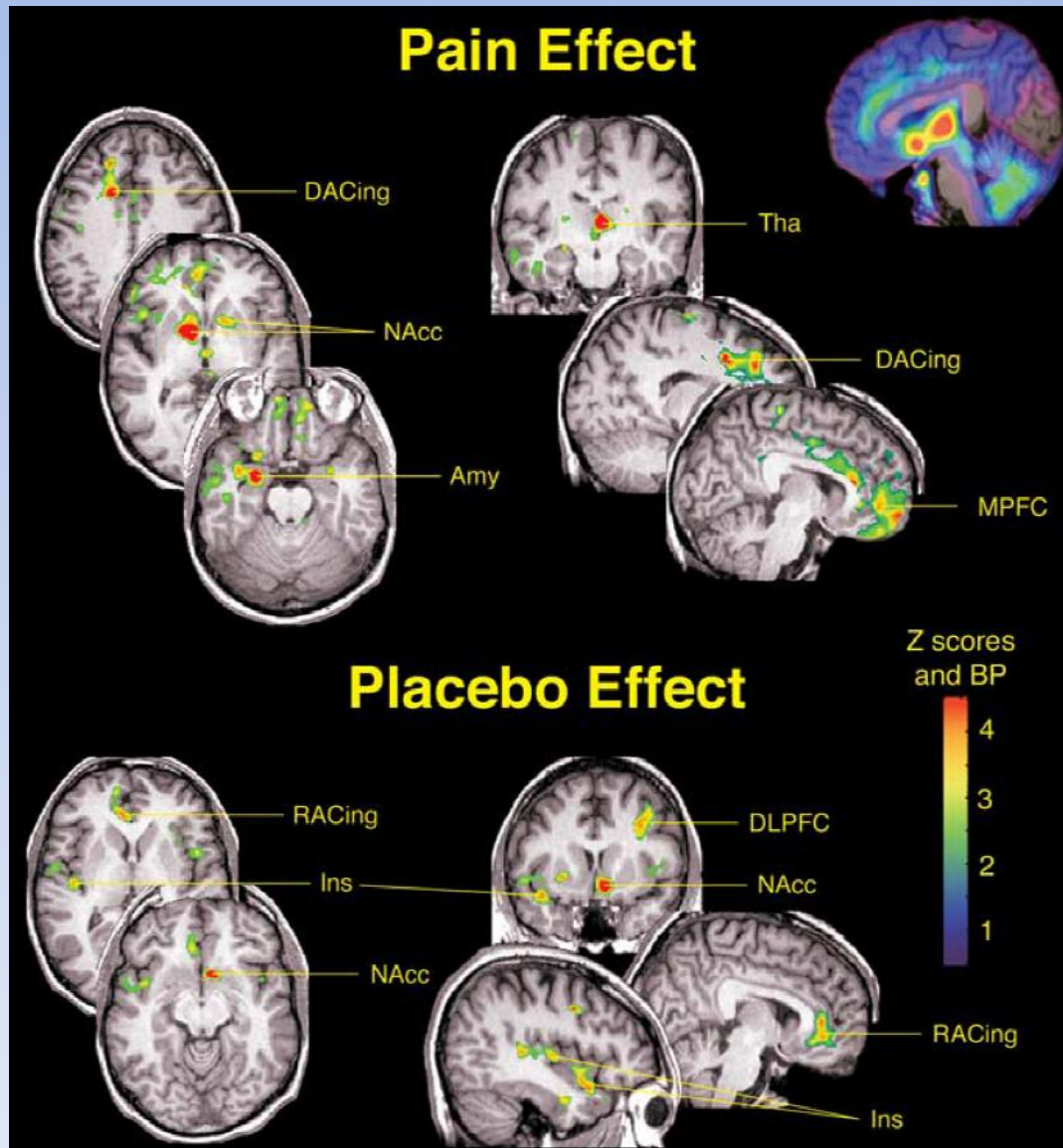
Nocebo effect

- 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

Evidence for opioid mechanisms in placebo analgesia

- Placebo analgesia is antagonized by naloxone.
Levine JD, et al. *Lancet* 1978
- Placebo induced release of endogenous opioids shown by in vivo receptor binding with PET scans. Zubieta JK, et al. *J Neurosci* 2005.

Activation of μ -opioid receptors with placebo



Baseline with no pain was used for comparison

Endogenous opioids when in pain

Endogenous opioids when in pain AND receiving placebo

And the pain was significantly less with placebo

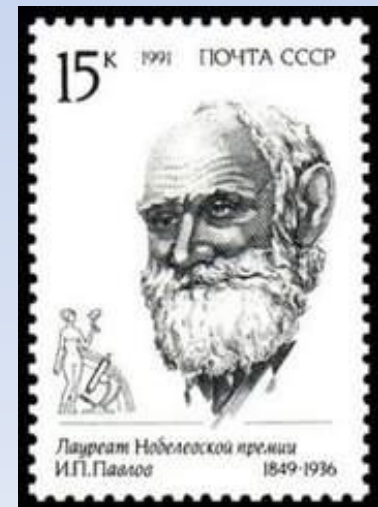
Zubieta JK, Bueller JA, Jackson LR, et al. Placebo Effects Mediated by Endogenous Opioid Activity on μ -Opioid Receptors. *J Neurosci* 2005;25(34):7754-7762.

Conditioning

- Before conditioning
 - Food (US) \Rightarrow salivation (UR)
 - Metronome alone \Rightarrow no response
- During conditioning
 - Food (US) + metronome \Rightarrow salivation (UR)
- After conditioning
 - Metronome alone (CS) \Rightarrow 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

Nonopioid neurotransmitters in analgesic placebo response

- Endocannabinoids

- Ketorolac conditioning Benedetti F, et al. *Nature Med* 2011

- 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
 - Injections better than oral *Kaptchuk TJ, et al. J Clin Epidem 2000*
 - White & gray neutral; blue & green calming; red, orange, and yellow stimulating *de Craen AJ, et al. BMJ 1996*
- Hands on treatments *Kaptchuk TJ, et al. J Clin Epidem 2000*
 - Sham surgery
 - Sham acupuncture
 - Machines, electronic devices

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%

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

Examples of placebos given

- Antibiotics for viral infections40%
- Vitamins23%
- Herbal supplements 12%
- Sub-therapeutic dose of medication 10%
- Ibuprofen for symptoms unrelated to pain. 9%
- Saline infusions or IM injections 6%
- Prepared placebo tablets3%
- Sugar or artificial sweetener pills 2%

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.

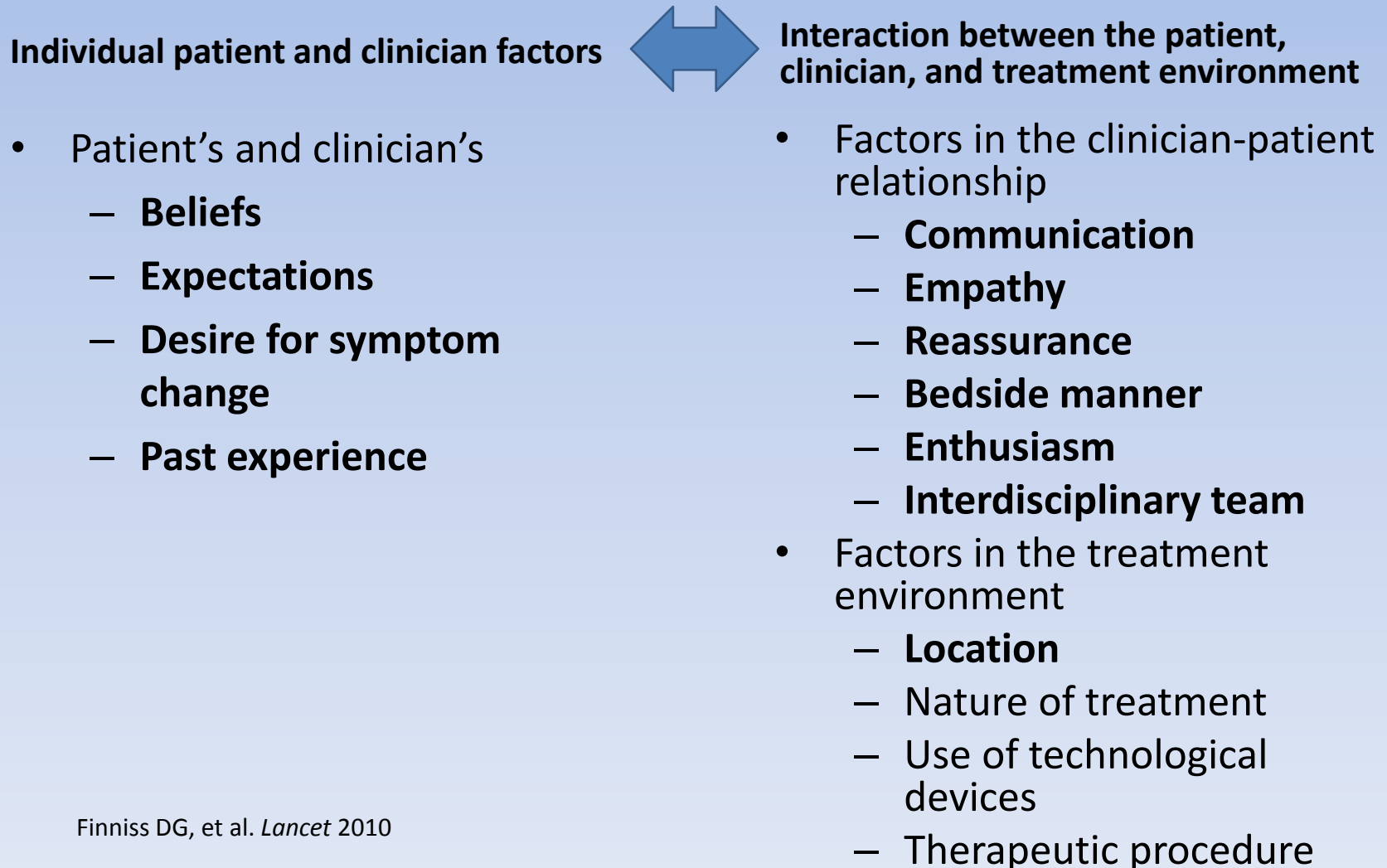
Ethics of the placebo effect

- 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?

Placebo use in clinical practice: AMA Council on Ethical and Judicial Affairs, 2008

- “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



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?

