The Placebo Effect

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Overview

• Historical perspective
• Definitions
• Contributing factors
• Proposed mechanisms
• Evidence and biology
• Implications for research and practice
• Conclusions
Historical

- Placere: to please in Latin
- Placebo: “I shall please”
- Psalm 116, verse 9, “Placebo Domino in regione vivorum”
- Dark Ages: fake substances or rituals used by physicians
- 1900’s: placebos used widely
- 1955: Beecher found placebo response rate: 35%
- 1960’s-70’s: placebos felt to have powerful effects
- 1990’s: debate over placebos and definitions

GF Donnelly, Holistic Nurs Prac, 2004
Finniss, D Lancet 2010
Lucan, S Fam Med Feb 2011
Definitions

• Placebo: an intervention designed to simulate medical therapy, but not believed by the investigator or clinician to be a specific therapy for the target condition

• Placebo effect:
  – Change in a patient’s illness attributable to the symbolic import of a treatment rather than a specific pharmacologic or physiological property
  – Beneficial effects that derive from the context of the clinical encounter, including the ritual of treatment and the clinician-patient relationship, as distinct from therapeutic benefits produced by the specific or characteristic pharmacological or physiological effects of medical interventions

• Nocebo: “I shall harm” in Latin
• Nocebo effect: ill-making effects attributed to preparation devoid of active substances

J Turner, JAMA, 1994
Breidert, M Dtsch Arztebl Int 2009
Controversy over definitions

- Placebo: an inert substance.
- The resultant effects are due to complex interactions that result in “nonspecific effects.”
- In 1999, recommendation to call these effects debonafide effects (“derived from good faith” Latin)

GF Donnelly, Holistic Nurs Prac, 2004
Placebo misconceptions

- 1/3 of patients respond to placebos in clinical trials
- Placebo effects are brief
- Placebo responders are of particular personality types and do not have anything wrong with them
- Administering a placebo is “doing nothing”

J Turner, JAMA, 1994
Contributing factors

- Patient factors
- Provider factors
- Patient-provider interaction factors
- Type of illness
- Types of treatments

Kaptchuk T Ann Intern Med 2002; 136
Patient factors

- Patient expectations
- Patient adherence
- Patient preferences
- Patient attitude

Kaptchuk T Ann Intern Med 2002; 136
J Turner JAMA May 1994
Patient expectations

• 1960’s experiment: placebo pill with magnet
• Told that receiving a relaxant, stimulant or placebo
• Gastric motility measured:
  – If believed it was a stimulant, more stomach muscle contractions
  – If believed that it was a relaxant, less contractions

Kaptchuk T Ann Intern Med 2002; 136
Patient beliefs

- Study: Chinese-Americans
- Certain birth years unfavorable
- Examined death certificates in California
- Lower average age of death if born in “unfavorable” years
- Lymphoma patients died at an average age of 59.7 versus 63.6 years in more favorable years
- The stronger the traditional beliefs the more highly these findings correlated

DP Phillips, Lancet, 1993
Patient adherence

• Adhere to placebo 40-75% reduction in mortality

• Explanations
  – adherent have healthier lifestyle
  – adherent to other life prolonging meds
  – protopathic bias
Studies of patient adherence

• RCT’s: coronary artery disease & lipid-lowering agents
  – Divided patients taking placebo into adherent and nonadherent patients
  – Mortality rate 57% higher for nonadherent patients
  – Differences in patients that adhere is so great that it can exceed the benefits of the therapeutic agent alone

Coronary Drug Project, NEJM, 1980
Effects of patient adherence

- Adherence in LV dysfunction trials
- SOLVD – TT, SOLVD- PT
- Lower mortality (total and CVD) and CVD incidents in adherent patients in both groups

A Avins JGIM Aug 2010
Patient attitude

• Experiment: Pain and dispositional optimism
• Dispositional optimism was associated with lower pain ratings in experimental group.

Geers, A J Pain 2010
Practitioner characteristics

- Physical appearance
- Language
- Attitude
- Expectations
Effects of physician attitude

- RCTs: optimistic/enthusiastic vs neutral/doubtful attitudes
- Increased benefits for patients
- Clinical conditions in which benefits found
  - Pain
  - Psychiatric illness
  - Hypertension
  - Obesity
  - Perimenopausal symptoms

Kaptchuk T Ann Intern Med 2002; 136
J Turner JAMA May 1994
Language

- May cause nocebo effect
- Language “traps”
  - Just
  - Try
Provider expectation

- Double blind RCTs: molar extraction
- Trial 1: placebo or naloxone
- Trial 2: placebo, fentanyl or naloxone
- Dentists knew which trial group patients were in
- Trial 1 patients had more pain than trial 2 patients

RH Gracely, Lancet, 1985
Patient-provider interaction

• Factors that improve relief from symptoms
  – Clear diagnosis
  – Patient reassured
  – Dialogue
  – Agreement

Kaptchuk T Ann Intern Med 2002; 136
Influence of the encounter

- RCT: 200 patients present to PCP
- Randomized to treatment or no treatment
- Randomized again to positive versus negative consultation
- Results: at 2 weeks
  - 64% in positive consultation group
  - 39% in negative group
  - no difference in outcome if treatment given

KB Thomas, British Medical Journal Clinical Research, 1987 May 9
The common cold

• RCT: Provider empathy
• 350 subjects
• Standard or enhanced
• Questionnaires
• 84 pts gave perfect score
  – Cold duration shorter, less severity
  – IL-8 levels higher

Rakel, D Fam Med 2009
Informed consent for invasive procedures

• 159 videos of invasive radiological procedures
• Recorded all statements
• Measured patients' ratings of pain and anxiety
• Warning the patient resulted in greater pain and greater anxiety
• Sympathizing with the patient after a painful event resulted in greater anxiety (P<0.05).

Lang EV, 2005 Mar
Illnesses more likely to have placebo responses

– Chronic GI problems/ IBS
– Back pain
– Chronic pain
– Fatigue
– Arthritis
– Headache
– Cardiovascular dz

– Allergies
– Hypertension
– Insomnia
– Asthma
– Depression
– Anxiety
– Other behavioral issues

Kaptchuk T Ann Intern Med 2002; 136
Asthma

• Randomized, double-blind crossover pilot study
• 46 pts with mild-mod asthma
• Inhaled albuterol vs inhaled placebo vs sham acupuncture vs no intervention
  – Albuterol: 20% increase FEV1
  – 7% increase in FEV1 with inhaled placebo, sham acupuncture, or no intervention
• Patient reports of improvement
  – Albuterol: 50%
  – Placebo inhaler: 45%
  – Sham acupuncture: 46%
  – No intervention: 21%
Type of treatment

- Pills
- Active placebos
- Oral placebo versus injection
- Devices or elaborate procedures
Pill characteristics

• Dosing
• Brand name
• Color

de Craen, Br J of Clin Pharm, dec 1999
Branthwaite, BMJ, 1981
Blackwell, Lancet 1972
Pill color

– Red, yellow, orange associated with stimulant effect
– Blue, green related to sedating effect
– Sedative-hypnotics are more likely to be green, blue or purple

De Craen, BMJ, 1996
Drug information

- Experiment: carisoprodol or placebo
- 3 types of drug info:
  - Relaxant
  - Stimulant
  - No info
- Relaxant group had highest serum concentration of carisoprodol

M A Flaten Psychosomatic Medicine 1999
Injections vs Oral

- Meta-analysis: migraine treatment
- 25.7% had relief with oral placebo
- 32.4% had relief with injecting placebo

De Craen, J of Neurology, 247(3): 183-8, 2000 March
Sham procedures

- 1960’s: sham surgery
  - Angina treatment: bilateral ligation of internal mammary
  - 80% improved
- 1970’s: sham procedures
  - Sham procedure for TMJ
    - 64% had significant symptomatic relief
- Review of disketomies with negative surgical exploration
  - 37% had relief of sciatica
  - 43% had relief of back pain

DE Moerman, Ann Intern Med, 2002
Johnson AG, 22 Lancet, 1994
Oct J Turner, JAMA, 1994
Orthopaedic surgery

• RCT: 180 pts
  – arthroscopic debridement
  – arthroscopic lavage
  – placebo surgery

• Results
  – 165 pts completed trial
  – At 1 and 2 years: no difference between 3 groups

JB Moseley, NEJM, 2002
Back surgery

- Lumbar spinal stenosis
  - improvement of 64-68%

- Source of benefits?
  - Specific effects of procedure vs placebo effect + natural history of the illness

Turner JA, JAMA, 1992 Aug 19
What is the mechanism of the placebo effect?
Causes of clinical improvement

- Natural history of illness
  - Regression to the mean
  - Specific effects of treatment
  - Nonspecific effects of treatment (i.e. placebo effect)

J. Turner, JAMA 1994
Theories of placebo effect

- Decreased anxiety
- Expectations of patient and practitioner
- Conditioning/learning
- Endorphins

J Turner JAMA May 1994
Pharmacokinetics of placebos

- Time-effect curves
- Peak and increased effects with increasing doses
- Body’s responses, not actually properties of the placebo itself

J Turner JAMA May 1994
Experiments on the placebo effect
Opioid-mediated effects

- Placebo analgesia more likely if
  - Previous successful analgesic experience
  - Side effects from the actual medication
- Experiment: post-op patients treated with buprenorphine
  - Variation in opioid responsiveness
  - Variation in respiratory depression
- Patients who had respiratory depressive symptoms to buprenorphine
  - Similar symptoms to placebo
  - Unrelated to variability in responsiveness to opioid

More on post-op patients

- Patients s/p thoracotomy
- Treated with buprenorphine for 3 days
- Given basal IV saline infusion, divided into 3 groups
  - Group 1: natural history group
  - Group 2: double-blind
  - Group 3: deceptive
- Results
  - deceptive group asked for the least amount of buprenorphine
- Each group had equivalent analgesic, yet groups with larger placebo effect required less additional opiate
Hidden injections of medications

- Hidden injections: buprenorphine, tramadol, ketorlac, and metamizole
- Hidden injections less effective and less variability in response than if given openly
- Response variability to analgesics may be due to placebo effects (nonspecific effects)
- Though ketorlac is nonopioid NSAID, its effectiveness reduced if given hidden
- If openly given with naloxone, diminished effects
- Opioid placebo effects even with nonopioid drugs

Amanzio, Pain, 2001
Expectations and conditioning

• Experiment: induced ischemic arm pain
• Expectations: told that receiving potent analgesic, but received saline injection
• Conditioning: pain induced; patient conditioned with morphine or ketorolac, then given saline on later injection
Conditioning to an opiate
Conditioning + expectations to opiate
Conditioning to ketorolac
Conditioning + expectations to ketorolac
Results

• If patient had large response to analgesic, then larger placebo response
• Expectations + morphine conditioning blocked by naloxone
• Morphine conditioning alone blocked by naloxone
• Expectations + ketorolac conditioning partially blocked by naloxone
• Ketorolac conditioning insensitive to naloxone blockade
• Expectations created placebo responses blocked by naloxone
• Conditioning created placebo responses blocked by naloxone only if conditioned with opiate

Amanzio, J Neurosci, 1999
Competitive sports

- Study: 4 groups; pain induced during “training phase”
- Group A and B: training without morphine
- Group C and D: training with morphine
- Competition day:
  - Group A given nothing
  - Group B, C told given morphine, but given saline
  - Group D told given morphine, but given naloxone
Results

• Group C (conditioning + placebo) performed considerably better than other groups.
• Group B (placebo alone) performed slightly better than control group.
• Group D (conditioning + naloxone) performed no better than control group A.
• Subjects given morphine during training phase had induced opioid-mediated increase of pain endurance and physical performance.
• Is this ethical or is it doping?

Benedetti J Neuroscience 2007
Nocebo effects

- Experiment: pts with mild post-op pain
  - increase their pain for 30 minutes
  - actually given saline and told it would increase pain
- Nocebo effect: patients pain increased
- If given CCK antagonist proglumide, then no nocebo effect
- Naloxone did not reverse the proglumide blocked nocebo effect (nonopioid mechanism)
- Patients’ negative expectation of pain caused anticipatory anxiety, then increase CCK and increases pain levels
- CCK antagonist will prevent anxiety-induced hyperalgesia

F Benedetti Pain 71(2): 135-40, 1997 June
Benedetti J Neuroscience 2006
Colloca L. Current Opinion in Anesthesiology 2007
Biology and Evidence
Biological evidence

- Functional MRI:
  - placebo response in distinct areas of brain
  - those with strongest enhancement on imaging with greatest pain relief

Wager, Science 303, 1162–1167; 2004
Wager PNAS 2007
Antidepressants

• PET scans in hospitalized patients with depression
• Fluoxetine vs placebo
• PET scans of placebo responders:
  – metabolic increases and decreases in several regions similar to fluoxetine
  – fluoxetine also had additional areas of increase

HS Mayberg, Am J Psych, 2002
Several reviews of placebo effect

• Placebos no more effective than no treatment at all
• Exception: studies with subjective pain ratings subjectively
• Small benefits in continuous subjective outcomes and for treatment of pain

Hrobjartsson A J Intern Med 2005
Hrobjartsson A Cochrane Database Syst Rev 2004
Limitations on research

• Evidence for placebo effects
  – RCT placebo-controlled
  – Lab experiments to look at placebo effects
• Placebo effect may be more a component of healing
Implications for research design
Clinical trials

- Random assignment aims to reduce systematic bias between groups.
- In clinical trials, both providers and patients know that there is actual treatment and a placebo.
- If either patient or provider guesses which treatment the patient received, then these expectations (of the patient or provider) can bias the study.
- Control treatments must be as similar to active treatment as possible to prevent this bias.
- Trials in which the control treatment is more similar to active treatment have shown less benefit.
Novel study designs

- Balanced placebo design
- Half balanced placebo design*
- Balanced cross-over design
Implications for practice
Clinical practice

• If the patient and/or the practitioner perceive a given treatment as being effective, then there will be placebo effects (expectations).

• Placebo effects act synergistically with active treatment effects.

• Most likely to get these placebo effects if:
  – Anxious patient
  – Perception of physician as being great/an expert
  – Belief by patient and provider that treatment is highly effective
  – Treatment is impressive and expensive
Primary care

• Survey of 1000 family practitioners
• 43% response rate
• 56% used placebos
• Reasons for use
• Ethics of use
• 97% believed that placebos have therapeutic effects
• Providers also believed their practices can promote placebo effect

Kermen, R, Fam Med Oct 2010
Ethics of using placebos

• Calling placebo pill medicine is deceptive.
• Placebo effects may be less powerful than what we believed.

Kupferschmidt CMAJ Jul 2011
Nocebo phenomenon

• Adverse effects caused by placebos
• More common in women than men
• About ¼ patients report adverse effects
• Types of side effects:
  – headache
  – drowsiness
  – weakness
  – dizziness
  – Nausea

AJ Barsky, JAMA, 2002
Side effects

• Patients may discontinue placebos due to these side effects
  – Study on pain
  – 13/58 stopped the placebo due to adverse effects
  – 3 patients claimed that placebo had permanently worsened their pain

• Side effects of actual medications may be due to nocebo phenomenon rather than from the medication itself

AJ Barsky, JAMA, 2002
Nocebo Factors

- Patient’s expectations of adverse effect
- Prior conditioning
- Patient traits: anxiety, depression, tendency to somatize
- Situational factors

AJ Barsky, JAMA, 2002
Conclusions

• Most patients will improve regardless of the treatment given for most illnesses.

• Placebos are substances or procedures not known to have any therapeutic effect on the clinical conditions.

• Placebo effects are produced by many factors including patient factors, provider factors, provider-patient interaction, characteristics of the placebo, and the type of illness.

• Response to a placebo can occur in actual cases of pain or other illness.

• No personality type is characteristic of placebo responders.
Conclusions

• Prior conditioning to a medication affects the placebo response as do expectations. Expectations and conditioning will lead to a stronger placebo response.
• The biological basis of the placebo effect is still unclear, but both opioid and non-opioid mechanisms seem to occur.
• Placebo effects can enhance the therapeutic effects of a proven treatment.
• Nocebo phenomenon may contribute to intolerance to medications.
• Placebos are widely used by providers.


References


References

References


• Kermen R, Hickner J, Brody H, Hasham I. Family physicians believe the placebo effect is therapeutic but often use real drugs as placebos. Fam Med. 2010 Oct;42(9):636-42.


• Lucan SC. Which "placebo effect"? (and why it matters). Fam Med. 2011 Feb;43(2):125.


References

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