

Placebo response – Is it all in the mind?

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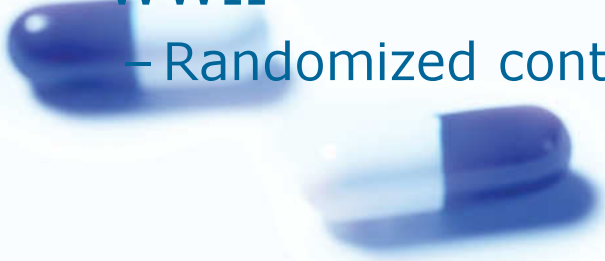
What is a placebo?

- Inert substance “believed to be” devoid of any pharmacological effect
- Usually in the form of a pill
- May also refer to a “sham” procedure



History of placebo

- Widely practised in clinical medicine since 18th Century
 - Latin: “I shall please”
 - Dictionary: “any medicine adapted more to please than to benefit the patient”
- Revived interest in research after WWII
 - Randomized controlled trial



The Powerful Placebo

- “can produce gross physical change”
- “include objective changes at the end organs which may exceed those attributable to potent pharmacological action”



(Beecher, JAMA 1955)

Placebo responding rate

- 30% of patients responded to placebo treatments for pain (no no-treatment groups) (*Beecher, 1955*)
- 26.9% of subjects responded to a placebo analgesic (compared with a no-treatment control group) (*Benedetti, 1996*)

Is the Placebo Powerless?

Meta-analysis of 114 RCTs:

“No significant effects on objective or binary outcomes”

“Possible small benefits in studies with continuous subjective outcomes and for the treatment of pain”

(*Hrobjartsson & Gotzsche, NEJM 2001*)

Magnitude of the placebo analgesic effect

- 2 out of 10 on a VAS / NRS scale
(*Benedetti et al, 1998; Amanzio et al, 2001; Price, 2001*)
- 5 out of 10 in placebo-responders (*Benedetti, 1996*)



Why does placebo have effect?

- Psychosocial context
 - Context of administration
 - Patients' expectation



Placebo effect should be differentiated from

- Natural variations of the disease
- Statistical phenomenon
 - Regression to the mean



Context of administration

- “Open” vs “Hidden” Injections
 - Open administration of a drug is significantly more effective than hidden administration

Amanzio et al 2001; Benedetti et al 2003; Colloca et al 2004; Levine & Gordon 1984



Power of expectation

- “Double-blind” vs “Deceptive” administration of placebo
 - The effect of placebo analgesia was markedly greater when the patients were told that a placebo treatment was a powerful painkiller than when they were told that they might receive either a powerful painkiller or a placebo



Pollo et al, 2001

What are the mechanisms of placebo response?

- Expectancy
 - Positive expectation → placebo response
 - Negative expectation → nocebo response
- Conditioning
 - Past experience



Opioid mechanism

- Placebo analgesia response associated with opioid activation in certain brain regions
 - anterior cingulate cortex, periaqueductal gray matter



Opioid mechanism

- Placebo analgesia response to NSAIDs blocked by opioid antagonists



Amanzio et al, 2001

Non-opioid mechanism

- Serotonin-dependent growth hormone secretion



Benedetti et al, J Neurosci 2003

What are the implications of placebo response?

- Research
- Clinical practice



Implications of placebo response in research

- Psychosocial and environmental context
- Interpretation of results of studies



Implications of placebo response in clinical practice

- Doctor-patient relationship
- Attitude of health-care providers
- Patients' expectation



What are the ethical concerns in using placebo?

- Declaration of Helsinki 1964
 - “Every patient, including those of control group, should be assured of the best current diagnostic and therapeutic method.”
- Use of placebo controls for disorders in which effective treatments exist



Potential negative outcomes of placebo research

- Devoid of effective treatment
- Placebo (sham) surgery



Placebo in clinical care

- Intentional act of fraud
- Psychosocial and environmental context of a therapeutic intervention



Conclusion

- Placebo – not just in the mind
- Biochemical and neuro-anatomical mechanisms
- Psychosocial components of therapy



**To cure seldom,
to care always!**

