Placebo response – Is it all in the mind?

Dr Steven Wong

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 $\rightarrow$ placebo response
  – Negative expectation $\rightarrow$ nocebo response

• Conditioning
  – Past experience
Opioid mechanism

• Placebo analgesia response associated with opioid activation in certain brain regions
  – anterior cingulate cortex, periaqeductal gray matter

Amanzio et al, 2001

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!