Placebo effects: Scientific advance and potential clinical and ethical implications

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I do not have any financial interests relevant to this meeting, such as a financial relationship with any company or group that may be affected by the topic of this meeting.
Definitions

- **Placebo “I shall please”:** *Placebo domino in regione vivorum* psalm 116, 9th verse

- **Placebo effects:** Neurobiological and clinical changes that are distinct from biases, regression to the mean, natural history, and co-interventions (inclusion of a no-treatment group)

- **Placebo responses:** Unspecific changes in clinical outcomes that may result from patients’ perception of the therapeutic intervention (absence of a no-treatment group)
How to identify a placebo effect...

- Natural history
- Co-interventions
- Regression to the mean
- Biases and false positives
- Hawthorne effect

The placebo component of any intervention

Colloca and Benedetti, Nature Rev Neurosci 2005; 6:545-52
Hidden versus open administration of medication

Positive and negative modulation of post-operative pain

Open-hidden paradigm

## Expectancy-induced analgesia and different painkillers

<table>
<thead>
<tr>
<th>Pain Reduction</th>
<th>BUPRENORPHINE</th>
<th>TRAMADOL</th>
<th>KETOROLAC</th>
<th>METAMIZOL</th>
</tr>
</thead>
<tbody>
<tr>
<td>open</td>
<td>open</td>
<td>hidden</td>
<td>open</td>
<td>hidden</td>
</tr>
<tr>
<td>Pain reduction</td>
<td>-3</td>
<td>-2</td>
<td>-1</td>
<td>0</td>
</tr>
</tbody>
</table>

Amanzio M et al., Pain 2001  
Benedetti F et al., J Neurosci, 2003  
Colloca et al, Lancet Neurol., 2004
**Patient-clinician communication and placebo effects**

**Group 1:** “You are going to feel a big bee sting; this is the worst part of the procedure”

**Group 2:** “We are going to give you a local anesthetic that will numb the area and you will be comfortable during the procedure”

Varelmann et al., Anesth Analg 2010;110:868 –70
Patient-clinician interactions and placebo effects

- **Educate** clinicians and patients about the possible effects of placebo processes

- **Tailor** the information delivery process to the needs of the patient

- **Reframe** the disclosure process, continued attention to ethical approaches surrounding any disclosure

What we have learned…

➢ Placebo effects depend upon the activation of specific physiological mechanisms

➢ Placebo research provides a hint to reconsider the efficacy of interventions and treatments that may work primarily on the basis of placebo mechanisms
How do we identify effective interventions?

Any intervention has efficacy if it is demonstrated in RCTs to be superior to a placebo, no-treatment group and/or usual care interventions

- If an intervention lacks specific efficacy, is it still appropriate to recommend it in daily clinical practice?
Examples of lack of specific efficacy

- Saw palmetto
- Vertebroplasty
- Homeopathy
Saw palmetto
Serenoa repens extract, rich in fatty acids and phytosterols

- Used to treat a variety of conditions, most notably benign prostatic hyperplasia (BPH)
Is saw palmetto effective in controlling BPH?

- Two large scale studies reported no difference in the primary outcome:
  - Saw palmetto vs finasteride (pts: 1098)
    37% vs 39% symptom decrease
  - Saw palmetto vs tamsulosin (pts: 704)
    27% vs 28% symptom decrease
- Costs of saw palmetto are lower than finasteride and tamsulosin

Carraro et al. Prostate 1996; 29:231-40
Vertebroplasty
Injection of cement into spine to stabilize vertebrae fractures

- Observational studies reported immediate pain relief and long-lasting benefit
Is vertebroplasty superior than the sham one?

Sham vertebroplasty consists of a simulation of surgery without injecting any cement

- Results from 2 randomized clinical trials published on NJEM and one open-label trial published on Lancet report no significant differences in pain between true and sham surgery at any measured time points.

Klazen et al., Lancet 2010; 376(9746):1085-92
Buchbinder et al. NEJM 2009; 361(6):557-68
Is it acceptable to recommend this intervention?

Risk-Benefit-Cost profile

- **Safety**
  - No serious complications for sham vertobroplasty
  - No difference in the occurrence of adverse events

- **Benefit**
  - But both true and sham vertobroplasty reduce patients’ pain

- **Costs**
  - Patients treated with vertobroplasty gained on average 120 pain-free days

Is the benefit of homoeopathy a placebo effect?

- Comparison between 110 homoeopathy trials and 110 matched conventional-medicine trials:

  In large trials of higher quality, the odds ratio was 0·88 (95% CI 0·65–1·19) for homoeopathy and 0·58 (0·39–0·85) for conventional medicine.

- A recent veterinary meta-analysis indicates no robust evidence that homeopathy is distinguishable from placebo effects in animals.

Mattie et al., Homeopathy 2015; 104:3-8
Clinical and ethical considerations

- Are interventions working by virtue of placebo responses/effects clinically and ethically acceptable?

- Should clinicians recommend these interventions in addition to, but not instead of, conventional treatments?

- If interventions with equal efficacy than usual care are not given, do we deprive patients of potential benefits?

Conclusive remarks

- It may be acceptable to recommend any intervention with clear favorable risk-benefit-cost profile

- In terms of professional integrity, it may remain potential conflict with evidence-based medicine

- Patients should be transparently informed about the lack of specific efficacy and a potential for unspecific placebo responses.
Thank you for your attention