Placebo effect in clinical scales for CNS diseases

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What is Placebo?

• The term Placebo is medically used to designate a biologically inert substance or a sham surgical intervention that produces a placebo effect, which is defined as a favourable outcome in the course of a disease state, such as:
  - the relief of various types of pain (headache, neuropathic pain);
  - improvement of manifestations of Parkinson's disease;
  - reduction of the seizure frequency in epilepsy;
  - alleviation of symptoms in multiple sclerosis;
  - fortunate impact on mood disorders.

• Nocebo phenomena are opposite to placebo phenomena. In this case, the pathogenic effects of imagination, negative expectations and beliefs creates harmful effects in a patient.
What is Placebo?

• It is a well recognized **biological phenomenon**, controlled by the brain, but poorly understood.

• Randomized, double blind, *placebo-controlled* trials have become the gold standard for the comparison of a new drug in clinical trials.

• The word comes from the Bible:
  
  “Placebo Domino in regione vivorum”

  ↓

  “I shall be pleasing in the lord in the land of the living”
History of Placebo = History of Medicine

• Until the early 20th century, most treatments were placebo.
Psychological aspects of placebo effects

• Several psychological mechanisms seem to contribute to the appearance, enhancement or duration of the placebo effects:
  – **classical conditioning** such as doctor-patient relationship, the trial site, the aspect of the pill, the route and the frequency the treatment is given.
  – **cognitive factors**, such as expectation, desire and reward.
Neurobiological basis of placebo effects

- The recent developments in brain imaging (PET, fMRI) enabled a better understanding of the neurobiological mechanisms underlying the placebo effects.

- Some of the discovered psycho-neuro-immune pathways involved are:

## Endogenous opioid pathways

- Today a consensus was reached that the endogenous opioid system, by the activation of its μ-opioid receptors, is the main mediator of the placebo effects in various types of pain.

<table>
<thead>
<tr>
<th>Receptor</th>
<th>CNS location</th>
<th>Response on activation</th>
</tr>
</thead>
<tbody>
<tr>
<td>μ</td>
<td>Brain (laminae III and IV of the cortex, thalamus, periaqueductal gray), spinal cord (substantia gelatinosa)</td>
<td>μ₁: supraspinal analgesia, physical dependence; μ₂: respiratory depression, miosis, euphoria, reduced gastrointestinal motility, physical dependence</td>
</tr>
<tr>
<td>κ</td>
<td>Brain (hypothalamus, periaqueductal gray, claustrum), spinal cord (substantia gelatinosa)</td>
<td>Spinal analgesia, sedation, miosis, inhibition of antidiuretic hormone release</td>
</tr>
<tr>
<td>δ</td>
<td>Brain (pons, amygdala, olfactory bulbs, deep cortex)</td>
<td>Analgesia, euphoria, physical dependence</td>
</tr>
</tbody>
</table>

Dopamine pathways

- The activation of dopaminergic system when giving placebo has been documented by using PET with the D2/D3 receptor-labeling radiotracer [11C] raclopride. One study performed on healthy subjects proved that intravenous placebo induced dopamine release at the basal ganglia level.

[Halita 2008] Effects of intravenous placebo with glucose expectation on human basal ganglia dopaminergic function.

Serotonin pathways

- The serotoninergic system seems involved in the placebo effects observed in depressive patients. One study using PET showed regions of change overlapped in brain glucose metabolism induced by placebo versus fluoxetine.

Neurological disorders and placebo effects

**Parkinson's disease**

- The symptoms of Parkinson's disease result from the death of dopamine-generating cells.
- A severity rating method known as the Unified Parkinson's Disease Rating Scale (UPDRS) is the most commonly used metric for clinical study.

[Benedetti 2004] Placebo-responsive Parkinson patients show decreased activity in single neurons of subthalamic nucleus.
• PET images of a representative patient with Parkinson disease. Each image pixel represents the binding potential (BP$_{ND}$) of [11C] raclopride.

• A decrease in raclopride BP$_{ND}$, indicating an increase in dopamine release in this region.

Chances of receiving active Levodopa were:
• Group A = 25%
• Group B = 50%
• Group C = 75%
• Group D = 100%

All subjects received placebo!

[Lindstone 2010] Effects of Expectation on Placebo-Induced Dopamine Release in Parkinson Disease
The expectation of improvement triggered by the administration of placebo produces the release of dopamine in the striatum, as shown by PET using raclopride, and this supplemental dopamine leads to the alleviation of motor symptoms in Parkinson's disease.
Migraine

- Migraine is a condition that causes attacks of headaches. Other symptoms such as feeling sick (nausea) or being sick (vomiting) are also common.

- Unfortunately, all these studies cannot distinguish between real placebo responses and spontaneous remissions, thus the presence of a real psychobiological placebo phenomenon in migraine is not definitive.

Epilepsy

- Significant improvements in frequency of seizures, usually defined as a 50% reduction, are not uncommon in placebo arms of anticonvulsant trials.

- These benefits occur even in animals!

- However, the disease course is relatively unpredictable and no trials have directly evaluated the placebo effect with a natural history control.

Conclusion

• Studying the placebo effect in neurological disorders might provide better clues to a deeper understanding of the mechanisms involved, as it has been demonstrated by using performant-imaging techniques in the last several years.

• As we have seen with *migraine* and *epilepsy*, many neurological diseases show improvements in placebo groups, but the mechanisms are not known.

• *Parkinson's disease* has emerged as an interesting model for understanding the neurobiology of the placebo effect. The same experimental approach should be extended to other neurological conditions, such as Tourette’s syndrome, multiple sclerosis...
PHARMACOLOGICAL
DRUG TRIAL RESULTS

OUR TRIALS SHOW THAT
THE NEW DRUG PERFORMS
NO BETTER THAN PLACEBO

MAYBE WE SHOULD
INVEST IN PLACEBOS

CHRIS MADDEN