Title: The role of expectations and patients' decision making process

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Abstract

Aim: This work aims at highlighting the role of patient's expectations in regard to experimental drugs and/or medical treatments, analyzing which factors might affect the final clinical outcome (i.e. expected effectiveness).

Results: Current studies suggest that psychological and neurobiological mechanisms intersect in inducing the placebo effect, which might be considered as a positive plus value added to the final collected outcome. Moreover, considering psychological mechanisms, we can identify both the *expectations* and the *classical conditioning*,

Conclusion: A successful relationship between patients and caregivers, which is based on empathy (i.e. the ability to perceive the emotional state of the person we are in contact) can make the difference in the final outcome, increasing the expected effectiveness of the medical treatment.

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1. Introduction

What role does the patient's expectations have in regard to a particular drug or treatment? May they affect the clinical outcome? And what factors may increase the patient's expectations regarding the effectiveness of a drug? This working paper focuses on these open issues, recalling the idea of placebo effect.

In 1811, in Hoopers Medical Dictionary, the placebo was described as a form of *medicine aimed at pleasing the patient than to provide a benefit*. Currently, in the literature, the term "placebo" refers to an inert substance or medical treatment without therapeutic properties. With the term "placebo effect" - derived from the Latin (the future tense of the verb *placere*) - we refer the positive influence exerted by our expectations on a specific drug or treatment without therapeutic effect. This effect is an organic or mental change connected to the symbolic meaning attributed to an event or object in the health sector. But what is the role of expectations in this process? Which are the factors that come into play?

Taking clinical research into consideration, which is the realm of expectations for excellence, authors try to answer these questions by analyzing the "placebo effect". This working paper is organized two main sections: the former introduces the reader in the field of pharmaceutical clinical research; whereas the latter proposes a psychological and neurobiological point of view of the proposed issue. Finally, authors propose some conclusions.

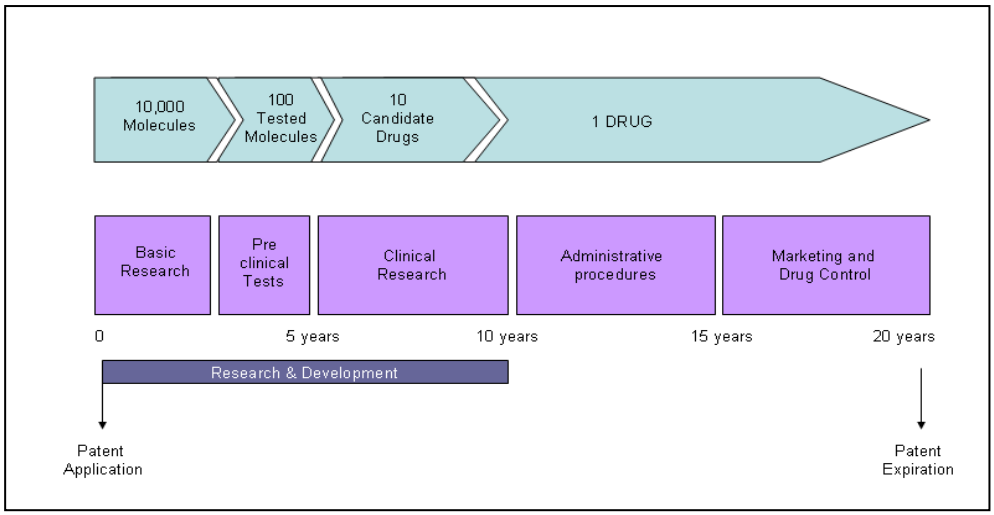
2. Pharmaceutical clinical research and patients' decision making process

Pharmaceutical R&D concerns the development of new products to care patients, such as drugs, vaccine, devices or procedures. In each process, two main parts can be identified. The former (i.e. *basic research*) concerns the drug discovery, that is to say, the designing of new molecules and/or new compounds, as well the study of current knowledge and the available opportunities to increase that level (Criscuolo, 2005). Afterwards, in the latter phase there is the testing of the innovative product on animals (i.e. *pre-clinical test*) and on humans (i.e. *clinical research*) to understand how their bodies respond to the innovative medical treatment. Figure 1 identifies the Research & Development within the production process of

the pharmaceutical industry, suggesting the companies' effort to develop a new product, especially in terms of time.

Clinical research is aimed at collecting clinical evidence of these innovative products, which is essential to obtain manufacturing authorization from national drug agencies and thus to make profit on patients and their diseases. The research activity is conducted in phases. Each phase has a different purpose and helps scientists answer different questions. In details, there are three phases in pharmaceutical clinical research with, according to the National Health Institute, the following features: "…Studies of phase I in which researchers test an experimental drug or treatment on a small group of healthy people (20-80) for the first time to evaluate its safety, determine a safe dosage range, and identify side effects... in phase II trials, the experimental study drug or treatment is given to a larger group of people (100-300) to see if it is effective and to further evaluate its safety… in phase III trials, the experimental study drug or treatment is given to large groups of people (1,000-3,000) to confirm its effectiveness, monitor side effects, compare it to commonly used treatments, and collect information that will allow the experimental drug or treatment to be used safely…".

Figure 1: Production process of the pharmaceutical industry



Source: Les Entreprises du Médicament (LEEM)[3]

Both physicians and general practitioners can be involved in pharmaceutical clinical research as medical researchers. They have to present the experimental medical treatments to patients (research subjects), as well as the alternative current treatment; afterwards they will treat subjects according to the clinical trial, collecting, at the end of the process, all required

[3] For a deeper analysis see the LEEM report entitled "L'industrie du médicament en France, réalités économiques", 2008 Edition.

clinical evidence. Before the enrolment of research subjects, an informed consent session is necessary in order to guarantee the patient's freedom of choice (i.e. being involved in the research activity or not). Indeed, after a discussion with the physician, all patients have to sign the informed consent to be treated (Faden et al. 1986; Braddock et al. 1997). According to Appelbaum et al. (1982), Daugherty (1999), Emanuel (1995) and Miller (2000), this section is persistently affected by a relevant and unsolved ethical issue: therapeutic misconception, that is to say, patients' inability to understand their involvement in a trial and the expected and unexpected adverse events.[4] Taking Prospect Theory into account, Kahneman and Tversky (1979) suggest how choices could be affected by specific framing exerted by those who want people to make given choices. According to Sankar (2004), one potential explanation for patients' misconception is precisely the *framing* phenomenon, that is to say, a specific behavior on the part of the physician during the informed consent session in order to involve patients in a clinical trial, creating expectations in the experimental treatment.

From a psychological and neurobiological point of view, which might be the effect of these expectations on research subjects? Is admissible a relation between the output of the clinical trial (i.e. effectiveness of the experimental medical treatment) and the necessary expectations to involve patients in the research activity?

Next section highlights the role of expectations in the placebo effect, as well as in the patients' decision making process.

3. Psychological and neurobiological mechanisms behind patients' expectations

Current studies (Benedetti *et al.*, 2005, 2010) suggest that psychological and neurobiological mechanisms intersect in inducing the placebo effect. Benedetti et al. (2005) notes that there are two psychological mechanisms at the basis of this effect. The first mechanism concerns *expectations* whereas the second deals with the mechanism of *classical conditioning*, which is also denoted *Pavlovian conditioning*.

First of all, it's important to point out that the term *expectation* is not a unique term, that is to say it can be considered from multiple perspectives. In general, the expectation allows the body to prepare for addressing an event and, for this reason, an important evolutionary value

[4] Seeing the issue from another prospective, it concerns the inability to understand the sharing of risks between companies

can be recognized. However, as well suggested by Price *et al*. (2008), the expectation often works alongside the *motivation* and *memory*; whereas, according to Frank (1971), the concept of *hope* is also fundamental in the healing process.

The expectation of a benefit, as observed by Benedetti (2010), leads to an effective reduction of symptoms through the activation of the brain mechanisms of *reward*, in which the frontal lobes have an important role, allowing the anticipation of a pleasant event.

Kong et al. (2007) and Scott et al. (2008) show the changing of neurotransmitters in the brain according to the perceived event. If the expectation is positive, neurotransmitters that mediate the complex feelings of pleasure and pain will increase, as well as those neurotransmitters involved in anxiety and panic will decrease. In particular, we can identify these types of neurotransmitters:

1. serotonin, which regulates mood, will increase (i.e. the better the mood, the lower the perception of pain);
2. dopamine will increase;
3. adrenaline will decrease, as well as all mediators of anxiety, fear and stress.

Considering the target of this work and the role of expectations in the collected effectiveness of experimental drug, dopamine is the key factor of patients' positive feed back. Indeed, the neurotransmitter is produced when there is a chance of gratification in the short run and its presence contributes to support a *too long* and *complex* number of personal actions. In other words, the goal needs a boost motivation (which is given by the neurotransmitter) and when it is reached, the production of dopamine is inhibited (which is the reason of the gap, in terms of joy and satisfaction, between foretasting one thing and getting it). At the same time, endogenous *opioids* will increase, that is to say the organic and natural chemicals are produced by the brain (and equipped with analgesic and physiological properties similar to those of morphine), which mitigate significantly the perception of pain. These changes have been amply demonstrated in numerous studies over the years. Indeed, the technique of functional magnetic resonance imaging (fMRI) have shown the activation of specific brain areas (Kong et al., 2007).

The second psychological mechanism concerns the mechanism of classical conditioning, which has been denoted *Pavlovian conditioning*. The repeated association between the hospital environment (e.g. a syringe or medical staff) and the medical treatment (e.g. the drug contained in the syringe) can induce a conditioned response. In other words, after repeated

(unexpected adverse events) and research subjects (expected adverse events). For a deeper analysis, see Ippoliti (2013).

associations, the mere sight of the syringe or the physician will be sufficient to induce the reduction of patients' symptoms. This is the mechanism suggested by the physiologist Ivan Petrovich Pavlov.

Considering an experimental treatment, which are the determinants of the placebo effect? This is the main question of the proposed preliminary work and, according to the aforementioned considerations, the next section will propose some conclusions.

4. Conclusions

According to Benedetti, Chicken, Lopiano et al. (2003), expectations play an important role in the placebo response of conscious processes (i.e. pain and motor performance), whereas the conditioning is responsible for the placebo response of not aware processes (i.e. secretion of hormones and immune responses).

The key factor is the relationship between the physician and the patient. Indeed, the positive effect has already start before the proposal to be involved in an experimental activity or to be treated with the current medical treatment. Moreover, the physicians' consciousness of the expected positive impact of the experimental treatment can increase its degree on the research subjects. The placebo response might be amplified, therefore, by the physician's expectations on the effectiveness of the experimental drug, as well it has been demonstrated by double-blind studies in which this positive effect decreases if the medical researcher is not aware of the patient's treatment (i.e. the experimental drug or the placebo).

As pointed out by Conti (2008), the enthusiasm of the physician in the proposal of the medical treatment, as well as his/her empathic attitude and/or the atmosphere are the main determinants of the placebo response. A sick person, who is asking for help, will activate the motivational system of attachment (Liotti, 2001), i.e. he/she will look for the proximity of a con-specific protection, identifying potential *supplier* of help. What makes the difference in a successful relationship between patients and caregivers (in our case, between the medical researcher and research subject), is the empathy, which is the ability to perceive the emotional state of the person we are in contact. In other words, thanks to its mirror neurons (Rizzolatti, 2008), the empathic physician feels the patients' suffering, accepting and validating the subject's emotional state. The patient will recognize these emotions, with an evident biochemical response that will activate *opioids* or *endogenous cannabinoids*.

Obviously, this phenomena will allow the patient's trust in the physicians' decision/suggestions, amplifying the already positive emotions has been experienced in the care relationship by the subject (thanks to his/her mirror neurons).
Of course, if the physician demonstrates a negative attitude towards the experimental drug, the patient will feel this emotional level, decreasing the expected effectiveness of the experimental drug. In other words, working on the physicians' perception of the research activity, there would be possibilities to work on the collected final outcome of the experimental activity (Ippoliti, 2012)

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