

DRUGS AND PLACEBOS: WHAT'S THE DIFFERENCE?

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Defining a drug is not difficult. It is a molecule delivered to the body and producing a biological effect by acting on one or more biochemical pathways, e.g. by binding to a receptor or by modifying the activity of an enzyme. Defining a placebo is quite more complicated. Usually, it is defined as an inert substance with no pharmacological action. However, this is a very superficial and rash definition, for placebos are made of many components, such as words, rituals, symbols, and meanings. Thus, a placebo is not the inert substance alone, but rather its administration within a set of sensory and social stimuli that tell the patient that a beneficial treatment is being given. Indeed, a placebo is the whole ritual of the therapeutic act.

Most of the confusion about the placebo effect derives from the different usage and meaning that it has for the clinical trialist and the neuroscientist. The former is interested in any improvement that may take place in the group of patients who take the inert substance, and this improvement can be due to plenty of factors, such as the spontaneous remission of the disease, statistical regression to the mean, patient's and doctor's biases, and patient's expectations of improvement. By contrast, the latter is only interested in the improvement that derives from active processes occurring in the patient's brain, like expectations of benefit and learning mechanisms. Usually, clinical trials are only aimed at establishing whether the patients who take the true treatment, be it pharmacological or not, are better off than those who take the placebo. Although this pragmatic approach yields fruitful results in the clinical trials setting, it is virtually useless for the neuroscientist who wants to understand what is going on in the patient's brain when a placebo is given, i.e. when a therapeutic ritual is performed without the actual administration of any therapy.

By taking these considerations into account, if the study of the placebo effect is taken over by the neuroscientist, it acquires an important

biological meaning and represents an excellent model to understand how the human brain works. Indeed, the explosion of placebo research over the last couple of decades has taught us that many mechanisms are involved, ranging from modulation of anxiety to activation of reward mechanisms, from classical associative conditioning to social learning, and from genetics to different personality traits (Benedetti, 2020). Therefore, there is not a single placebo effect but many, with different mechanisms across a variety of medical conditions and therapeutic interventions. As occurs for cancer research, in which different mechanisms are responsible for different types of cancer, what we have learned over the past few years is that the question "What is the mechanism of the placebo effect?" is wrong. A better question would be "What are the mechanisms across different conditions?"

One of the most interesting and challenging aspects of placebo research is related to the new emerging concept that placebos activate the same biochemical pathways that are activated by the drugs administered in routine medical practice. This new emerging view is quite an interesting challenge from both an evolutionary and a neurobiological point of view. In other words, humans are endowed with endogenous systems that can be activated by verbally-induced positive expectations, therapeutic rituals, healing symbols, and more in general by social interactions. For example, there is now compelling experimental evidence that placebo analgesia can be mediated by at least two systems: the endogenous opioid system and the endocannabinoid system (Benedetti et al., 2022). In addition, the cholecystokinin system can modulate the opioid system so as to produce placebo responses of different magnitude. Likewise, placebo administration to Parkinson patients induces the release of dopamine in the striatum, and placebos can affect the same brain regions that are the targets of selective serotonin re-uptake inhibitors (SSRI).

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This notion is certainly challenging, and represents an epochal transition from general concepts such as suggestibility and power of mind to a true physiology of the placebo effect.

This new perspective from which placebos are approached and investigated may have profound implications both in routine medical practice and in the clinical trials setting. For example, when morphine is administered, it binds to opioid receptors and inhibits pain transmission, but at the same time the ritual of its administration induces the activation of the same opioid receptors. Similarly, when a SSRI is given, it modulates different brain areas, but at the same time the ritual of its administration may modulate the same areas. Therefore, considering that drugs and placebos share common receptors and biochemical pathways, one of the main challenges is to understand similarities and differences between the action of drugs and that of placebos.

In spite of the common pathways used by drugs and placebos, at least in some conditions such as pain, Parkinson's disease and depression, clearcut differences do exist. These can be summarized as follows: 1) duration of action, 2) variability of effect, 3) magnitude of effect.

- 1) *Duration of action.* In general, the duration of the effect of a drug is longer than that of a placebo. As far as we know today, this holds true for painkillers and anti-Parkinson agents, whereas much less is known about other therapeutic interventions. For example, the effect of apomorphine, a powerful anti-Parkinson drug, lasts on average much more than a placebo.
- 2) *Variability of effect.* The variability of the response is different: the response to a pharmacological agent is usually more constant and less variable.
- 3) *Magnitude of effect.* The effect following placebo administration can be as large as the effect following drug administration. However, it is important to point out that only a small percentage of placebo responders may show such huge effects. If we consider the response variability, the average magnitude is larger for drugs compared to placebos.

Whereas duration, variability and magnitude have to do with efficacy, several considerations can be made on toxicity as well. Indeed, placebos may produce negative effects. These are called nocebo effects and represent the evil twins of placebo effects (Benedetti, 2020). In analgesic clinical trials for migraine, patients who receive the placebo often report a high frequency of adverse events. These negative effects correspond to those of the anti-migraine medication against which the placebo is compared. For example, anorexia and memory difficulties, which are typical adverse events of anticonvulsants, are present only in the placebo group of these trials, which suggests that the adverse events in placebo arms of clinical trials of anti-migraine medications depend on the adverse events of the active medication against which the placebo is compared. These findings are in keeping with the important role of expectation in the placebo/nocebo phenomenon, such that sometimes what the patients expect they get, for example by reading the possible side effects described in the informed consent. The dropouts in clinical trials due to nocebo effects are a crucial aspect that may confound the interpretation of many clinical trials.

Much less is known about the biological mechanisms of nocebos, mainly due to the ethical limitations of giving negative information to patients. Today we know that anticipatory anxiety plays a key role in the

nocebo response, and anxiety triggers the activation of cholecystokinin that in turn facilitates pain transmission (Benedetti et al., 2022).

Similarities and differences between drugs and placebos are not only confined to the classical clinical setting. For example, placebo can reproduce some effects of recreational drugs and cognitive performance-boosting drugs. Moreover, placebos may also show effects similar to those of the ergogenic drugs used in sport to increase physical performance. This raises important ethical and legal issues for anti-doping agencies, since placebos, that are detectable neither in blood nor in urine, have been found to increase performance in some conditions. So the question is: Is it ethical to use placebo procedures in sport to mimic the ergogenic action of drugs?

Several important questions also arise as to how to exploit the placebo effect in routine clinical practice. However, two opposite questions can be posed, depending on the setting where placebos are administered. In fact, in routine clinical practice one wants to maximize the placebo effect, so that the main question which physicians are interested in is "How can we decrease variability and increase duration and magnitude of placebo effects?". By contrast, in the clinical trials setting we want to minimize the placebo response in order to better emphasize the drug effect, so that clinical trialists would like to answer the question "How can we decrease variability, duration and magnitude of placebo effects?".

Today we are in a good position to partially solve these two questions. Indeed, it is possible to manipulate, at least in part, the placebo response in both directions. First, by using a learning procedure, we can decrease variability and increase duration and magnitude. To do this, a pharmacological pre-conditioning is carried out, whereby a real drug is administered for several days in a row, and then it is replaced with a placebo. By using this approach, most patients show huge placebo responses, which indicates that learning plays a key role in the placebo effect. This is desirable in routine medical practice, for it is possible to reduce drug intake in the long run. Second, by using a negative conditioning procedure, whereby there is a mismatch between what the patient expects and what he gets, it is possible to decrease the magnitude of the placebo effect. This is what would be necessary in the clinical trials setting, in which subjects with low placebo responses can be better compared with subjects who take the active treatment. Unfortunately, this negative conditioning procedure can only control for the learning component of the placebo effect, but it has no effect on spontaneous remission and regression to the mean.

A better understanding of the similarities and differences between drugs and placebos represents an important challenge for future research that will surely lead to better medical practice and better interpretation of clinical trials. The crucial starting point is the understanding of the biological underpinnings of placebos and their relationship to drug action. As far as we know today, at least two possibilities can be envisaged. Drugs and placebos can act either on the same receptors or, otherwise, on the same type of receptor but in different regions of the central nervous system, for example in pain. There is some experimental evidence that the second mechanism is more likely. For example, narcotics bind to the *mu* opioid receptors in one region of the brain, whereas placebos act, through the activation of endogenous ligands, on *mu* opioid receptors in a different region, with an overall additive effect.

In spite of these recent insights into the neurobiol-

ogy of placebos effects, there is a paradox in placebo research: the more we know about placebos, the more difficult our correct communication to the general public seems to be. Indeed, there is a danger around the corner (Benedetti, 2019). Robust placebo responses can be triggered by the very ritual of the therapeutic act, thus any therapeutic ritual can in principle activate those biochemical mechanisms that I have described in this editorial. If fake pills prescribed by doctors can lead to positive expectations and outcomes, so talismans handed out by quacks and bizarre rituals performed by shamans may induce positive expectations as well. There is today a growing tendency to justify bizarre procedures and healing practices by claiming that they may really induce positive expectations and outcomes. After the discovery that placebos and positive expectations activate endocannabinoids, I was contacted by plenty of quacks with weird and eccentric proposals aimed at enhancing expectations, beliefs, trust and hope. These individuals often claim that any procedure that increases expectations and beliefs is justified, no matter where it comes from, either a real doctor or a quack. This is really a worrisome future perspective that I think we should avoid by boosting good communication be-

tween science, ethics and media. The results of placebo research should be better explained to both journalists and general public, because the social impact could be devastating and the credibility of modern medicine itself could be undermined. The future ethical/biological debate promises to be exciting and stimulating, for we are dealing with foibles and vulnerable aspects of human beings, namely, expectations, beliefs, trust, hope and suggestibility. Understanding their underlying biology is exciting but may turn out to be dangerous and alarming if badly exploited.

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