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COMMENTARY

Why We should Assess Patients' Expectations in Clinical Trials

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ABSTRACT

Most of the analgesic clinical trials have failed to succeed over the past years because of the occurrence of large placebo responses. Patients' expectations about the therapeutic benefit represent a major determinant of the placebo response. Therefore, assessing patients' expectations should become the rule in any clinical trial. This would allow us to better interpret therapeutic outcomes when comparing placebo and verum groups.

Keywords: Clinical trial; Expectation; Placebo effect

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Failure to demonstrate benefit over placebo in analgesic clinical trials has become the rule over the past years [1, 2]. The number of drugs that are axed after phase II/III clinical trials because they cannot beat placebos is huge. For example, in the past 10 years over 90% of analgesic drugs have been dropped because of the failure to show superiority compared to placebo [3, 4]. Clinicaltrials.gov listed 4152 pain trials in 2011, but in a time span of 3 years only already existing drugs in new formulations or dosage forms were approved [3]. In neuropathic pain, the medication–placebo difference is greater when studies were published earlier, and this is because more recent, longer, and larger trials show higher placebo responses [5, 6]. This lack of superiority of analgesics over placebo and its increase over the past years echo the findings of clinical trials in depression [7], suggesting similarities in patients' placebo responses between pain and psychiatric disorders [8].

One of the most important confounding aspects in clinical trials is patients' expectation, which is a major mediator of the placebo response. The therapeutic outcome can go, at least in part, in the same direction as patients' expectations. There is today compelling evidence that if expectations are not assessed, the interpretation of the outcome may be difficult, or even wrong. A scale for the measurement of patients' expectations about the therapy they are receiving has been developed by Younger et al. [9]. These authors found that this scale can

predict 12–18% outcome variance in patients receiving surgical and pain interventions, and emphasize that it can be used in clinical trials to improve statistical sensitivity for detecting treatment differences. In addition, this study also shows that it is possible to identify patients in the clinical setting with poor expectations about the ongoing therapy.

The design of a clinical trial has been shown to shape the expectations of adults with major depressive disorder. Sneed et al. [10] and Rutherford et al. [11] have found that mean medication response rates in comparator trials (drug vs drug) are significantly greater than the mean medication response rates in placebo-controlled trials (drug vs placebo). Rutherford et al. [12] found that those patients suffering from depression, and who knew that citalopram was the treatment they were receiving, improved more than those who knew that they could receive either verum or placebo.

It is also important to consider what patients believe about their assignment to an experimental group (either placebo or verum). This allows us to better understand patients' expectations of clinical improvement. For example, true acupuncture has been compared to placebo acupuncture, with no significant difference. However, patients who believed they had received true acupuncture improved more than those who believed they had received sham acupuncture, regardless of the real assignment [13]. In addition, when patients are asked whether they trust acupuncture and what they expect from it, patients with positive expectations about acupuncture improve more than those with poor expectations, irrespective of their allocation to true or placebo groups [14]. In other words, what matters is whether patients believe in acupuncture and not whether they actually receive the true or the placebo treatment.

Today, there is also experimental evidence that both positive expectations (placebo effect) and negative expectations (nocebo effect) can be learned through social learning [1]. The observation of the positive effects in other people induces substantial placebo analgesic responses, and these are positively correlated with empathy. Likewise, nocebo effects can be induced by social learning. A recent study investigated the propagation of negative expectations across individuals. In this study [15], a subject received negative information about the occurrence of headache at high altitude. This information was disseminated across many subjects. After 1 week, negative expectations spread across 36 subjects (nocebo group). An increase in headache and prostaglandins was found in this nocebo group when at high altitude compared to a control group. This communication across different subjects produced different outcomes in an aspirin-vs-placebo clinical trial aimed at treating high-altitude headache. Whereas no placebo response was found in the control group, which had not received negative information, large placebo responses were found in the nocebo group, in which both aspirin and placebo reduced pain and prostaglandins. The difference in placebo response between the control and nocebo groups was due to the different baselines of headache and prostaglandins, which were previously induced by the propagation of negative expectations. A placebo effect was present only in the nocebo group because the placebo reduced only the nocebo component of prostaglandins and pain increase.

In this context, it is important to point out that physicians often play a pivotal role in shaping patients' expectations, in both positive and negative directions. For example, Rief et al. [16] have shown that enhancing positive expectations improves the clinical outcomes in invasive medical interventions such as coronary artery bypass graft surgery. The authors provided patients with a psychological intervention to develop realistic expectations about the benefits of surgery and the recovery process; 6 months after surgery, these patients reported lower disability and improved quality of life. In the opposite direction, listing "headache" as a side effect of lumbar puncture treatment, compared to providing no such suggestion, significantly increased the likelihood of postoperative headaches [17]. Also, Amanzio et al. [18] compared the rates of adverse events reported in the placebo arms of clinical trials for three classes of anti-migraine drugs: non-steroidal anti-inflammatory drugs, triptans, and anticonvulsants.

They found that the rate of adverse events in the placebo arms of trials with anti-migraine drugs was high. In addition, the adverse events in the placebo groups corresponded to those of the anti-migraine medication against which the placebo was compared. For example, anorexia and memory difficulties, which are typical adverse events of anticonvulsants, were present only in the placebo arm of these trials.

Important implications of these findings in the clinical trial setting are related to the fact that the interaction among trial participants should be considered as a variable to be controlled for. Participants may be influenced by the observation of the others belonging to the same trial. Communication among patients of the same trial is common, and this may lead to either positive or negative interactions. For this reason, an intriguing question could be what if there were changes in the consenting process to prohibit subjects from interacting with each other? On the other hand, in routine medical practice, doctors should consider the possible negative impact that unsuccessful treatments may have on their patients, when they interact with each other. This holds true in daily life as well, whenever others' suffering and negative outcomes are observed, e.g., through the media.

Indeed, in the era of Health 2.0, or of the patient-centered Web, the exchange of information among patients has become substantially more complex [19]. Online patient communities such as MediGuard and ClinicalResearch are two excellent examples of social tools that promote the awareness of clinical trials and crowd-sourced information exchanges [20]. Since 2009 social media has also been boosted as an avenue for clinical trial recruitment [21] and for sharing information with participants. Several dedicated Web sites, such as Clinicaltrials.gov and the International Clinical Trials Registry Platform (ICTRP), have indeed played crucial roles in helping patients find out about clinical trials (Clinicaltrials.gov website; ICTRP website).

Overall, a better approach to clinical trials should consider patients' expectations as an important element of the therapeutic outcome, thus patients' expectations should be assessed in routine practice. It can be helpful to strategize ways to both randomize patients on the basis of their baseline attitudes and communicate adverse effects at the beginning of each clinical trial, and also to use patients' expectations as co-variables [2]. As a consequence, perceived assignment to either placebo or verum groups could be assessed with a very simple question: Which group do you believe to belong to? Needless to say, this question is related to the assessment of blinding. We strongly believe that this simple way of running clinical trials may better identify the different contributions of placebos and expectations on the one hand and the verum under test on the other.

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