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The role of psychosocial context around patient and therapy can be studied through randomized clinical trials. The analysis of the results of clinical trials, and considering the adverse events (AEs) in the placebo groups, provides an important perspective of study for this phenomenon. In double-blind, randomized clinical trials, the side effects reported in placebo-treated groups are not associated with pharmacological treatment, but other factors should be taken into account to explain these symptoms. This phenomenon may be conceptualized as ‘*nocebo effects*’ relating to negative expectations for treatment outcome, even though a role of prior learning in the form of conditioning with active treatments cannot be excluded. This approach makes it possible to observe how associating the placebo groups with a particular drug can cause specific AEs that are consistent with those observed in the active group. This phenomenon was described in a systematic review that examined placebo AEs in tricyclic antidepressant randomized clinical trials. The authors depicted *nocebo effects* in antidepressant placebos similar to the AE profiles of the real drugs, which they were matched with. These key findings contrast with the belief that *nocebo effects were simply nonspecific*. Moreover, they emphasize the need to develop standardized procedures for collecting information about AEs in randomized, double-blind, placebo-controlled trials determining drug efficacy.

The role of psychosocial context around a patient and therapy can be studied through randomized clinical trials (RCTs). The analysis of the results of clinical trials, considering the adverse events (AEs) in the placebo groups, provides an important perspective of study for this phenomenon. In double-blind RCTs, the side effects reported in placebo-treated groups are not associated with pharmacological treatment [1], but other factors should be taken into account to explain these symptoms. The phenomenon observed may be conceptualized as ‘*nocebo effects*’ relating to negative expectations for treatment outcome [2], even though a role of prior learning in the form of conditioning with active treatment cannot be excluded.

This approach makes it possible to observe how associating the placebo groups with a particular drug can cause adverse reactions and dropouts allow

one to answer the question: ‘Are *nocebo*-non-specific effects?’

Interestingly, systematic review studies are the best way to give an objective answer, for example, two studies investigated *nocebo effects* in the placebo groups of RCTs with antimigraine drugs and patients with different levels of cognitive impairment with an anticholinergic drug [2,3]. The analyses demonstrated that patients receiving placebo pills had a high rate of adverse reactions and, interestingly, the side effects matched the AEs in the active treatment groups. For example, the authors observed the placebo group matched with the anticonvulsants drug topiramate showed the high number of dropouts compared with the placebo groups matched with nonsteroidal anti-inflammatory drugs or triptans [2]. This result is consistent with what was observed in the active group [4].

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REVIEWS

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These results were in line with a systematic review that considered placebo-controlled studies of psychotropic drugs, where placebos cause similar AEs to those observed in the active drug groups, which the placebo arm was compared with [5]. Importantly, it is a well-known fact that different psychotropic drugs induce different AEs, for example, for the treatment of anxiety and depressive disorders, different pharmacological agents are used, ranging from selective serotonin reuptake inhibitors to tricyclic antidepressants. These different classes of drugs induce different rates of AEs, even if selective serotonin reuptake inhibitors as a class do not have significant adverse reactions. On the contrary, tricyclic antidepressants have stronger sedating and cholinergic side effects [6]. Consistent with the aforesaid, the authors found higher symptom rates in the placebo groups of tricyclic antidepressant trials when compared with placebo groups of selective serotonin reuptake inhibitor trials, such as: dry mouth (odds ratio [OR]: 3.5; 95% CI: 2.9–4.2), drowsiness (OR: 2.7; 95% CI: 2.2–3.4), constipation (OR: 2.7; 95% CI: 2.1–3.6) and sexual problems (OR: 2.3; 95% CI: 1.5–3.5) [5].

These were the first published studies contrasting with the previously held belief that nocebo effects were simply nonspecific effects. They showed surprising similarities between the active drug group and the corresponding placebo group, which also led to a similar rate of nonadherence to treatment. Additional studies have confirmed these results (see the latest ones): [7–11]. Interestingly, nocebo effects were observed for different pathologies, such as migraine, multiple sclerosis, Parkinson Disease and fibromyalgia [11–14], underlining how different diseases share common risks leading to a negative outcome.

The results emphasize the importance of developing standardized procedures for collecting relevant information in randomized, double-blind, placebo-controlled trials of drug efficacy. In particular, adequate methodology, planning and execution are critical issues in RCTs because different approaches can lead to different results. Specifically, as Häuser *et al.* stated [7], specific strategies to reduce nocebo effects should be further developed in clinical trials and practice to minimize these effects [15]. As rightly observed by Rief *et al.* [5], drug trials should consider the base rates of pre-existing general complaints more rigorously in the population being studied, to distinguish drug-associated AEs from the general base rates of symptoms (see also the article by De La Cruz *et al.* [16]). With this purpose in mind, using an additional natural history group as the trial's so-called third arm is an important factor that should be considered in RCTs. As to the third group, it would be possible to study the AEs because of the nocebo effects as the difference between the symptoms collected in the natural history group and the side effects presented in the placebo group [17]. Indeed, natural course conditions should be incorporated more frequently in RCTs, such as in Zelen Design. This allows the natural history of the disease to be monitored without randomizing patients to a no-treatment controls group to overcome ethical issues [15].

Other important elements that should be taken into account as possible biasing factors in RCTs are represented by patients' characteristics in terms of significant mood changes, tendency to catastrophizing, prior experiences with side effects, pre-existing symptoms and the tendency toward somatization, symptom amplification and selective attention on bodily sensations; all of which were associated with nocebo effects [1,18]. In particular, psychological characteristics, such as depression, anxiety and somatization disorder, were associated with AEs to active drugs and nocebo symptoms [19,20].

It would also be important to collect data on prior therapies that were not successful to identify those patients who have a possible history of medically unexplained complaints in the recruitment phase of RCTs. Importantly, patients who are most at risk of developing nonspecific AEs should be identified through assessing the above-mentioned variables; for an example of specific scales refer [21]. Moreover, it would be important to compare these variables in RCTs (both in the active medication group and in the placebo group) to describe potential differences in these important psychological aspects that may be related to a possible negative treatment outcome. In the future, it would be interesting to test in prospective RCTs the extent to which these psychological variables would be related to the presence/absence of AEs with an overall approach not yet been developed, in order to take into account all these combining factors. This will help to clarify the presence of psychological distress predisposing patients to report nonspecific AEs to an even greater extent. Moreover, discussing the nocebo phenomenon explicitly with patients might help them to become more aware of self-fulfilling prophecies induced by misattribution. In this direction, a cognitive-behavioral side effect prevention training by optimizing patients' expectations was considered a potential pathway in health care to improve a patients' quality of life during long-term medication intake [21]. In line with these suggestions, an assessment of the expectancies related to treatment should be better developed to give an objective measure of the individual predisposition. A questionnaire designed to predict nocebo effects in outpatients seeking neurological consultation has been published recently. Although specificity, positive predictive value and reliability were found to be relatively low, it is an initial and useful tool to detect potential nocebo effects in clinical practice [22]. Tailored prevention programs are required to help patients tolerate AEs better. A future objective should be to explain how this negative anticipation leads to experiencing AEs. So far, their nature is still poorly understood and the existing theories require further replication. Finally, it is important to emphasize the development of standardized procedures for collecting information on AEs in double-blind, placebo-controlled RCTs of drug efficacy. In particular, structured assessment of side effects reports that combined patient and observer ratings for the most valid and reliable results should be preferred [23].

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