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EDITORIAL

Nocebo effects and psychotropic drug action - an update

Martina Amanzio[a,b] and Sara Palermo[a,b]

[a]Department of Psychology, University of Turin, Turin, Italy; [b]European Innovation Partnership on Active and Healthy Ageing, Brussels, Belgium

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1. Introduction

Randomized Clinical Trials (RCTs) are useful in order to study the role of the patient's psychosocial environment and the context in which therapies are administered on subsequent negative outcomes. The evaluation of adverse events (AEs) in the placebo group, matched with a specific psychotropic drug, provides an important perspective for understanding this phenomenon. These negative outcomes are conceptualized as 'nocebo effects' [1], a clinically salient yet seldom studied phenomena associated with poorer treatment outcomes and treatment discontinuation [2]. There is a need for considerable further research to investigate the nocebo effect within clinical populations, since identifying nocebo responders remains a challenge [1]. One of the populations in which it is important to study the nocebo effect, due to the associated clinical implications, is that of patients with psychiatric diseases – such as major psychotic disorders and mood disorders. Indeed, AEs affect adherence and dropout rates among patients with psychiatric disorders in RCTs [3].

To date, research into RCTs has shown that placebos cause AEs similar to those observed in the active psychotropic drug groups. The AEs reported in the placebo arms of RCTs investigating both a tricyclic antidepressant and a selective serotonin reuptake inhibitor were substantial and similar to those found in the active groups [4]. Therefore, AEs may represent an interesting perspective from which to perform a more in-depth characterization of psychiatric patients who are more likely to have negative outcome expectations, even if the role of prior learning associated with active treatments – in the form of conditioning – cannot be excluded.

Moreover, it has been reported that, in schizophrenic patients, the level of psychopathology, such as the severity of positive symptoms and signs of anxiety and depression, widely affected their perceptions and attribution of bodily sensations to medications [5]. Indeed, a higher level of psychiatric symptomatology makes schizophrenic patients more prone to express AEs manifested as nocebo-like-effects [6].

2. Body

A systematic review that considered placebo-controlled studies of psychotropic drugs – from selective serotonin reuptake inhibitors to tricyclic antidepressants – revealed that placebos produce significant AE rates, similar to those observed in the active drug groups [4]. These different classes of drugs were found to induce different rates of AEs, according to the usual effect of the specific drug [4]. Specifically, if serotonin reuptake inhibitors by themselves are not associated with relevant AEs and tricyclic antidepressants are known to have stronger sedating and cholinergic side effects [7], 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 [4]. This study indicated that many AEs in the placebo group are in line with those found in the active group [4].

Relevant treatment-emergent adverse events have been found in a study by Dodds and collaborators [2], who observed that these were reported by 63.9% of placebo-treated participants, with 4.7% discontinuing the study due to adverse events and 11.2% showing a worsening of the Hamilton Depression Rating Scale total score during placebo treatment [2].

The fact that rates of AEs reported in placebo groups are similar to those observed in active treatment groups was also confirmed by a review of clinical trials of anti-migraine drugs [8].

It was previously suggested that, in psychiatric patients, unfavorable treatment-related expectation effects might be associated with specific psychological and somatic symptoms [5], which can be fully considered as '*nocebo effects*', inducing negative outcome in terms of AEs. Indeed, there was some evidence to support the role of expectation as a cause of nocebo reactions [9]. Understanding the interaction between psychological/psychiatric factors and subjectively reported AEs may represent an interesting perspective through which to evaluate patients who are more likely to have negative outcome expectations [5]. Indeed, in psychiatric patients, the actual level of psychopathology widely affected their perception of bodily sensations and their attribution of these to medications [5]. Essentially, patients with severe levels of positive and anxiety/depressive symptoms may be more likely to report nocebo-like effects of antipsychotics [5]. Moreover, positive symptoms indirectly affect AEs by influencing anxiety symptoms [5]. Considering negative symptoms, a meta-analysis conducted on placebo-controlled, randomized clinical trials of olanzapine for the treatment of bipolar disorder –

CONTACT Martina Amanzio martina.amanzio@unito.it Department of Psychology, University of Turin, Via Verdi 10, Turin 10124, Italy

using data from placebo-treated study participants only – found that 68% of patients reported AEs and that 49.5% of them reported a worsening of symptomatology measured on the Hamilton Depression Rating Scale [9].

To date, few studies have investigated AEs in the placebo arm of RCTs in Schizophrenia Spectrum Disorders (SCD). We recently conducted a meta-analysis considering AEs in the placebo group of double-blind atypical antipsychotic medication trials in SCD patients (the article is part of the research topic 'Nocebo Effects and their Influence on Clinical Trials and Practice: Modulating Factors in Healthy and Pathological Conditions', edited by Frontiers in Pharmacology) [6]. We selected 58 clinical trials describing AEs in SCD placebo groups, which compared atypical antipsychotic medications with placebo. The experimental meta-sample involved a substantial number of subjects, equal to 6,301. The AE profiles of the drug class were clustered using the MedDRA classification and analyzed using a meta-regression approach. The incidence of AEs in the placebo group was substantial and in line with that reported in the active drug group. The proportion of patients in the placebo group with any AE was 66.3% and 7.2% of these withdrew as a consequence of AEs [6]. Moreover, we observed an association between the level of psychiatric symptomatology measured on the Positive and Negative Syndrome Scale (PANSS) and rates of reported AEs [6]. Specifically, higher psychiatric symptomatology, nervous system and gastrointestinal disorders were the most common adverse reactions associated with higher PANSS scores [6]. We concluded that the level of psychiatric symptomatology makes SCD patients more prone to manifest a negative outcome affecting adherence to treatment [6].

3. Methodological shortcomings

Methodological shortcomings should be considered in order to consider specific strategies to better study the nature of AEs in the placebo groups and put these observations into practice in order to minimize these effects. We previously highlighted some methodological shortcomings [6,10] with the aim of suggesting how RCTs should be re-outlined and standardized procedures for collecting information on AEs should be pursued in order to obtain the most valid and reliable results [6,10]. Particularly, RCTs need to take important aspects of patients' individual characteristics and context-related factors into greater consideration [10]. Furthermore, it would be essential to concern the strategies to minimize the nocebo effect and improve adherence to drug treatments. In particular:

1) A further natural history group (NH), the so-called 'third arm' of the experimentation, should be added and considered, in order to better study the side effects usually observed in the placebo group, in terms of nocebo effects. This third group would make it possible to study adverse events more accurately, such as the difference between the symptoms collected in the NH group and the side effects presented in the placebo group [11]. As previously noted, the observations achieved through the NH group analysis should be incorporated more frequently into the RCTs, such as in Zelen Design. This would allow monitoring the NH of AEs without randomizing patients into a 'no treatment' control group in order to overcome ethical issues.

2) A whole series of possible intervening factors – still too little considered in RCTs practice – should be taken into consideration.

The general base rate of preexisting symptoms in terms of general complaints, should be considered more rigorously in the population being studied, in order to distinguish drug-associated AEs from the general base rates of symptoms [12]. It would also be important to collect data on previous experiences with side effects (and consequently drop outs) in order to identify those patients with a possible history of complaints not medically explained in the RCT recruitment phase.

Patients characteristics that could represent an important bias factor in the observed results must be evaluated using appropriate assessment scales the presence of: positive symptoms [5,6], mood changes in terms of depression and anxiety, tendency to catastrophize, prior negative experiences with drug treatment, preexisting general medical complaints, and a tendency to somatize, amplify symptoms and show selective attention to bodily sensations [11,13]. Importantly, neuropsychological factors, such as global cognition and executive functions should also be assessed [10,14–16], in order to make an accurate description of the possible presence of mild cognitive impairment.

Another factor to be considered is the chronicity of the disorder. It has been reported that patients who develop most AEs are those who have chronic diseases [10], for example neurological patients with pain conditions or neurodegenerative disorders [10]. It has been suggested that a higher risk of AEs may also be related to illness severity in SCD patients [6]. A context-related factor such as the role of verbal and non-verbal suggestions coming from the examiner in favoring negative outcomes is another issue that should be considered more carefully [10].

Importantly, the use of an additional natural history group (as reported in point #1) – with patients having the same characteristics as those in the other two – should be considered in RCTs in order to monitor the natural history of the disease in terms of a three-arm controlled trial. The homogeneity of the three groups should be ascertained by comparing the data concerning the patients and the context in order to prevent the effect of selection bias on reported AEs [10,11,14,17].

3) Strategies to minimize the nocebo effect and improve adherence to drug treatment should be considered. Explicitly discussing the phenomenon of the nocebo effect with patients could help them become more aware of the 'self-fulfilling prophecies' induced by an incorrect attribution. In this direction, it has been suggested that a training for the prevention of cognitive-behavioral side effects, and a reduction in the expectations of nocebo effects, could be a potential path of health care to improve the quality of life of patients while taking drugs in the long term period [18].

4. Expert opinion

Although some of these variables have been analyzed in RCTs, little information is available about SCD patients. More evidence exists on cancer patients [12]. It is interesting to note that cancer

patients at greater risk of experiencing more severe AEs can benefit from an explicit discussion of the nocebo phenomenon, so that they may become more aware of potential misattribution. In this direction, a cognitive-behavioral AE prevention-training program, optimizing cancer patients' expectations, has been considered as a potential approach for improving quality of life during long-term medication intake [18]. Indeed, negative treatment expectations should be assessed in more detail, in order to provide an objective measure of individual predisposition. The same approach may also be useful in patients with stabilized schizophrenia [6] and chronic diseases. In this direction, a questionnaire designed to predict nocebo effects in outpatients seeking neurological consultation has been published [19]. Although this is an initial and useful tool for detecting potential nocebo effects in clinical practice, more effort should be spent analyzing SCD patients. More research is needed to investigate the association between psychopathology and AEs in order to explain how this negative anticipatory attitude leads patients to experience adverse events. Finally, tailored prevention programs are required to help SCD patients tolerate AEs better.

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