

# Evaluation of the nocebo effect during oral challenge in patients with adverse drug reactions

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**Summary.** The nocebo effect is the onset of untoward reactions following the administration of an indifferent substance. The oral challenge with alternative drugs plays a central role in the management of drug allergy and the use of inert substances is part of this procedure. We evaluated the occurrence and clinical characteristics of nocebo effect in patients with adverse drug reactions. Six hundred patients, seen in three different centres (Genoa, Naples and Verona) with a history of reactions to drugs, underwent a blind oral challenge with the administration of an indifferent substance and active drugs. The administration of an inert substance provoked untoward reactions in 54 patients (27%) in Verona, 60 (30%) in Naples and 48 (24%) in Genoa. The overall occurrence of nocebo effect was 27%. The majority of reactions were subjective symptoms (itching, malaise, headache etc), perceived as troublesome by all subjects. The occurrence was significantly higher in women than in men. Our data, collected in a large population, confirm that the nocebo effect occurs frequently in clinical practice. In managing adverse drug reactions through oral challenge the nocebo effect is mandatory to recognize false positive responses .

**Key words:** Placebo effect, nocebo effect, adverse drug reaction, drug challenge

## Introduction

The beneficial action, based on patient's expectation, exerted by an inert substance on the symptoms of a disease, is called placebo effect and it is well known in any medical research field. In recent years an increasing attention has been devoted to the symbolic power of medications in clinical practice (1-3). A "nocebo" effect is also recognized: patients suffering from several illnesses frequently exhibit troublesome symptoms after the administration of inert substances. The response is usually subjective (e.g. nausea, headache, itching, feelings of cold or warmth), but it may also be objective (vomiting, tachycardia, changes in blood pressure, skin rashes). The nocebo effect is influenced by several

factors such as patient's expectation, previous experience, setting, appearance of the drug.

The oral challenge with alternative drugs is a useful procedure for managing adverse drug reactions (ADRs) (4, 5). It involves the administration of a single dose or increasing doses of drugs different in structure from those suspected to have provoked ADR. The aim is to define one or more drugs to be taken safely when needed. In this context, it is important to distinguish those reactions provoked by an active drug from those with a predominantly psychosomatic component (6). This can be made by blindly administering an inert substance (called placebo) in order to exclude psychosomatic adverse reactions. Patients with ADR represent an ideal population to study the nocebo effect, therefore we

aimed at evaluating the occurrence and clinical characteristics of the responses to an inert substance in a large population of patients with ADRs. The patients were studied in three different centres in Italy, following similar procedures.

## Methods

### Patients' selection

Two hundred consecutive outpatients from each center (Genoa, Naples and Verona) with previous adverse drug reactions (ADRs) were evaluated during the oral challenge. We admitted patients with one or more of the following reported ADR: urticaria/angioedema, generalized itching, asthma, respiratory symptoms (cough, chest tightness, wheezing), laryngeal oedema, anaphylaxis. The reliability of ADR history was evaluated by trained allergists, based on the documentation from GPs (or preferably from emergency care units). In particular, ADRs had to occur within 24 hours from the intake of a single drug. In the case of unobservable manifestations (e.g. itching) the reproducibility of symptoms was required in at least two occasions, with the same drug and the same time of onset. Patients with systemic diseases (insulin-dependent diabetes, arrhythmias, chronic obstructive pulmonary disease, uncontrolled asthma) were not admitted. Patients had to be symptom-free at the time of the challenge. All patients signed an informed consent. The Ethical Committees approved the oral challenge with placebo for ADR as part of the routine procedures used in our hospitals.

### Oral challenge

The oral challenge was carried out with one or more alternative drugs, different in structure from those suspected to have previously caused ADR, according to the recommendations of the Italian Society of Allergy and Clinical Immunology (SIAIC), slightly modified (5). Therefore, the challenge was done

irrespective of the mechanism underlying the ADR, but with the only aim to determine a safe drug for each patient to take when needed (7).

Capsules containing different amounts of the active drug (ranging between 1/10 and 1/2 of a single therapeutic dose) or talcum were used in Verona and Naples. All capsules were packed by the hospitals' pharmacists. In Genoa, the active principle at the same dosage was given diluted in 50 mL of 20% glucose solution, which was also used as inert placebo. The challenges were single-blinded and the inert compound always preceded the administration of the active drug(s). Patients were observed for at least six hours after each administration. The challenges were performed at the clinics under continuous medical supervision and with emergency care equipment available.

## Results

Six-hundred outpatients (mean age 42 years, age range 7-76, 418 female and 182 male) underwent the challenge (Table 1). There was no significant difference in demography among the three centres and also the ADRs reported in clinical history were superimposable, with urticaria-angioedema (about 60% of patients) and respiratory symptoms the most frequent ones. The majority of ADRs had occurred with nonsteroidal anti-inflammatory drugs and beta-lactams.

The percentage of patients showing reactions after the inert substance (nocebo effect) was surprisingly high in the three centres: 27% in Verona, 30% in Naples and 24% in Genoa (table 1), with no difference among the hospitals (chi-square,  $p = NS$ ). The prevalence of nocebo effect was significantly higher in women than in men (30% vs 19%;  $p = .01$ ). The majority of the reported symptoms were subjective: itching, dizziness, discomfort, shortness of breath etc. Only 50/162 reactions were objetivable such as tachycardia, cough or skin lesions. (Table 2). No significant pattern of association could be found between the clinical feature of the nocebo effect and the original ADR, in fact the nocebo effect was different from the original reaction in about two thirds of cases. Indeed, out of the 30 patients with skin reaction

Table 1. Demographic and clinical data

	VERONA	NAPLES	GENOA	TOTAL
<b>Patients</b>	200	200	200	600
<b>Age range</b>	9-69 yrs	7-76 yrs	15-72 yrs	7-76 yrs
<b>Male/Female</b>	75/125	49/151	58/142	182/418
<b>Patients reacting to placebo (% of total)</b>	54 (27%)	60 (30%)	48 (24%)	162 (27%)
<b>M/F (%) of patients reacting to placebo</b>	22/32 (40%)	9/51 (18%)	7/41 (17%)	38/124 (23%)

Table 2. Clinical presentation of the reactions to placebo among the populations studied in the three centers

	VERONA	NAPLES	GENOA	TOTAL
<b>Itching</b>	14	23	18	55
<b>Nausea, abdominal pain</b>	13	11	8	32
<b>Headache</b>	5	0	4	9
<b>Dyspnea/cough</b>	6	5	3	14
<b>Hypotension/ tachycardia</b>	1	1	4	6
<b>Erythema, rash</b>				
<b>Urticaria</b>	11	12	7	30
<b>Other (nonspecific malaise)</b>	4	8	4	16
<b>TOTAL</b>	<b>54</b>	<b>60</b>	<b>48</b>	<b>162</b>

to inert substances, 18 had experienced urticaria with the suspected drug. Explaining to patients that their symptoms were induced by an indifferent substance, frequently proved useful. Only 9.3% of patients in Verona, 15% in Naples and 12% in Genoa experienced subsequent symptoms with the verum drug.

## Discussion

The effects of indifferent substances are well known in medical practice. It has been reported that the administration of placebo may produce a beneficial effect in about 35% of patients (1). Indeed, a recent systematic review concluded that the administration of placebo does not significantly differ in clinical efficacy from giving no drug (8), although it has been claimed that patients receiving placebo should be distinguished from those receiving no treatment (9, 10). The clinical aspects of nocebo effect has been extensively considered in a recent review (11), showing that also the nocebo effect is of relevance in many clinical trials. Upon examination of the literature it can be argued that two main factors influence the extent of the nocebo effect: patient's expectation and previous experience of untoward reactions. The real weight of these factors can be measured under controlled conditions (12, 13). Also the setting where the drug is administered, the emotional status of subjects and the appearance of the drug may play a role.

Patients with previous adverse reactions to drugs are particularly susceptible to the nocebo effect, and the blind oral challenge with alternative drugs (4, 5) is an optimal modality to study it in a homogenous population. In fact, all the studied patients had experienced previous side effects and, more or less consciously, they expected new troublesome reactions. In this case, the confounding aspect of non-specific reactions (11, 14) to active drugs

was excluded, since the drugs were not administered to treat an actual disease or symptom. Moreover, the setting of administration was the same (hospital environment) for all patients, as well as the appearance of the drug. In our population, the nocebo effect occurred in 27% of patients. This figure is not so far away from those usually reported for the placebo effect. Moreover, the reactions evoked by the inert substance were of scarce clinical relevance, but perceived as troublesome by all patients. Interestingly, the nocebo reactions were different in their clinical presentation (table 2) from the manifestations of ADR, among which skin and respiratory symptoms were largely predominant. The occurrence of the nocebo effect was independent from social or environmental factors, since the data were superimposable in all three different centres. The nocebo effect was more frequent in women than in men, as previously reported (15). This fact was independent from the unbalanced distribution of ADRs in the general population (182 male VS 418 female).

Our data, collected in a homogeneous population, confirm that the nocebo effect really exists and that it occurs quite frequently. In the case of the oral challenge, used in the management of adverse reactions to drugs, it is helpful to detect false positive responses .

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