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Placebo Effect In Allergological Study

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Abstract

The placebo effect has been studied and described in several fields. It's used in clinical trials, other areas (pain, cardiovascular development…), and allergological studies. Patients with IgE-mediated allergic diseases are very susceptible to placebo effects. There is also a negative repercussion of the placebo effect, which is the nocebo effect. Some placebo-treated patients will notice subjective symptoms or adverse events because they expect an active medication to have side effects or to worsen their condition.

The target of this study was to clarify the capacity of the placebo effect as a diagnosis or treatment in our Allergy Department patients.

We studied 56 patients who underwent 63 studies in our Allergy Department after giving informed consent for 12 months. They reported different symptoms. In 23 cases, we used a placebo as a diagnostic tool, and in 40 points, we used a placebo to treat the reaction the patient was experiencing.

We consider placebo a diagnostic tool that is very useful to elucidate if the patient is somatising, and given as treatment, we can discriminate between real and unreal allergic reactions.

Keywords: placebo, nocebo, allergy, allergology, drug allergy.

Introduction

Placebo, or *placer* in Latin, means "I will please." The placebo effect includes the psychological and physiological benefits of receiving treatment for a medical problem, independently of the pharmacological effects the prescribed treatment has.

On the other hand, we have the negative repercussion of the placebo effect; this is the nocebo effect ("I will harm"). This is the onset of troublesome reactions after administering an inert substance. Some placebo-treated patients will notice subjective symptoms or adverse events because they expect an active medication to have side effects or to worsen their condition **[1,2]**.

The placebo effect has been studied and described in several fields. Its use is well-known in clinical trials. However, there are reports of its development in pain control and its application to discern the actual effect in cardiovascular, gastrointestinal, and respiratory diseases, psychiatric and neurological disorders, and surgical and other invasive procedures **[3,4,5]**.

Patients with IgE-mediated allergic diseases are very susceptible to placebo effects. The European Academy of Allergy and Clinical Immunology's Task Force has reported a Position Paper reporting several essential topics related to the placebo effect in allergen immunotherapy (AIT) from different perspectives with concern to regulatory aspects of the placebo effect, the underlying neuroimmunological and psychological mechanisms **[6]**.

The responsiveness of allergic reactions to psychological factors is also shown by high placebo response rates in clinical studies with allergic patients, in which placebos are usually used to test the effectiveness of a drug or a treatment **[7,8]**.

In regular allergological studies such as drug and food challenges, a placebo is frequently used to discriminate among subjective symptoms the patient can experience. Drug provocation placebo control test (DPPCT) is commonly used for this purpose in studying drug allergy.

The purpose of our study is to elucidate the capacity of the placebo effect as a diagnosis or treatment in a series of patients referred to our outpatient Allergy Department.

Materials and Methods

We studied 56 patients who underwent 63 studies in our Allergy Department, after giving informed consent, during a period of 12 months, 5 men and 51 women, with a median age of 45,02 (17-74) years.

These patients had previous reactions to different substances: 14 with a beta-lactam antibiotic, 13 NSAID, 6 quinolones, 2 clarithromycin,

2 antiparasitic metronidazole, 2 cotrimoxazole (sulfamethoxazole and trimethoprim), 2 morphic, 2 polyethylene glycol and 2 rifaximin.

Other substances were (11) dexchlorpheniramine, methylprednisolone methylprednisolone, simvastatin, acenocoumarol, methotrexate, iron, diazepam, ranitidine, omeprazole, AIT and air freshener. They reported symptoms such as dyspnoea, pharyngeal discomfort and occupation, abdominal pain, dizziness, nausea, and objective signs such as pruritus, rash, erythema, exanthema, hives, and inflammation.

Results

We used an oral placebo consisting of empty oral capsules and a saline solution as a subcutaneous placebo. We used it to achieve a diagnosis and to treat the patient's symptoms, depending on the case, including the issues of nocebo effects.

Table 1: Placebo for diagnosis.

PLACEBO FOR DIAGNOSIS								
Patient	Male/ Female	Age	Suspicious substance (SS)	Symptoms in referred reaction	Placebo	Symptoms with placebo	Resolution Medication	Later tolerance of SS
1	F	52	Amoxicillin	Dizziness, nausea	Oral	Headache	Yes	Yes
2	F	31	Amoxicillin	Scalp pruritus, presyncope, abdominal pain, erythema, dyspnoea	Oral	No symptoms with placebo	No need	No
3	F	70	Amoxicillin-clavulanic acid	Cutaneous erythema and pruritus	Oral	Dizziness	Yes	Yes
4	F	43	Amoxicillin	Bilateral palpebral inflammation	Oral	Sensation of palpebral inflammation	Yes Placebo treatment	Yes
5	F	37	Amoxicillin	Head, otic, facial and general pruritus	Oral	Facial pruritus	Yes Placebo treatment	Yes
6	F	39	Cefuroxime	Abdominal discomfort and syncope	Oral	Paraesthesia in tongue and arms and nausea	Yes Placebo treatment	Yes
7	F	32	Cefuroxime	Maculopapular exanthema with general pruritus	Oral	Burning sensation in arms, palpitations	Yes Placebo treatment	Yes
8	F	74	Acetylsalicylic acid	Hives and pruritus on the back	Oral	General discomfort	No need	Yes
9	F	41	Celecoxib	Facial swelling, interdigital erythema and vesicles	Oral	Generalized pruritus with placebo	Yes Placebo treatment	Yes
10	M	25	Celecoxib	Genital, arms and legs pruritus, facial swelling and dyspnoea.	Oral	Arms pruritus with placebo	Yes	Yes
11	F	72	Metamizole	Maculopapular exanthema	Oral	No symptoms	No need	No
12	M	29	Dexketoprofen	Exanthema and epigastric pain, retrosternal pressure	Oral	No symptoms	No need	No
13	F	18	Levofloxacin	Generalize erythema and pruritus	Oral	Erythematous maculopapular rash and pruritus on left lateral mandibular area with placebo	Yes	Yes
14	F	20	Levofloxacin	Erythema on hands and neckline	Oral	Pharynx and palatine discomfort with placebo	Yes Spontaneously	Yes
15	F	57	Ciprofloxacin	Facial swelling and pharynx discomfort	Oral	Dizziness, pain on neck with placebo	Yes Spontaneously	Yes
16	F	38	Clarithromycin	Generalized erythematous maculopapular rash and pruritus	Oral	Dizziness and perioral erythema with placebo	Yes Spontaneously	Patient refused to complete study
17	F	44	Tapentadole	Micropapular rash and generalized discomfort	Oral	Dizziness and dyspnoea with placebo	Yes Placebo treatment	Yes
18	F	44	Dexchlorpheniramine	Erythema and hives	Oral	Erythema, hives and anxiety	Yes Spontaneously	Yes
19	F	45	Cotrimoxazole	Micropapular rash and pruritus	Oral	Paraesthesia in arms and tongue, nausea.	Yes Spontaneously	Yes
20	F	55	Polyethylene glycol (PEG)	Pharynx discomfort and pruritus, cough, dyspnoea, dysphonia	SC	Pharynx discomfort and pruritus, and cough, with placebo	Yes Placebo treatment	Yes
21	F	68	Rifaximin	Generalized pruritus and hives on legs	Oral	Mild pruritus and macular erythema on left arm with placebo	Yes Spontaneously	Yes
22	F	56	Metilprednisolone	Facial hives and pruritus	Oral	Pruritus on arms	Yes Spontaneously	Yes
23	F	32	Simvastatin	Pharynx discomfort, pain on left arm, generalized discomfort	Oral	No symptoms	No need	No

In 23 cases of reactions to drugs, we used a placebo as a diagnostic tool; **(Table 1)** this is, we gave it to the patients pretending to be the culprit drug of the initial reaction to prove the suspicious drug was not implicated. In 19 cases, we induced a nocebo effect, and the patients experienced different symptoms such as pruritus (7), dizziness (4), nausea (2), paraesthesia (2), pharynx discomfort (2), maculopapular rash (2), erythema (1), general pain (1), urticaria (1), cough (1), palpebral swelling (1), palpitations (1), dyspnoea (1), burning sensation in arms (1), pain (1) and headache (1). In the other 4 cases, the patients did not have any reaction. The referred nocebo effects ceased with no treatment in 12 and placebo treatment in 7 cases. **(Table 1)**

In 40 cases, we used a placebo to treat the reaction the patient was experiencing after giving the suspicious drug in 33 points and a placebo as a diagnosis in 7 cases **(Table 2)**. We shared an oral placebo 6 times and a subcutaneous placebo in 34. We treated different symptoms the patient reported with the substance we had already given: pruritus (22), pharynx discomfort (6), dizziness (5),

inflammation (4), nausea (3), palpitations (2), abdominal pain (2), headache (2), head pressure (1), paraesthesia (1), burning sensation (1), general discomfort (1), cough (1), dyspnoea (1) and erythema (1). **(Table 2)**

The reported symptoms stopped in 36 cases. The four patients **(6, 16, 20 and 23 of table 2)** who didn't respond were treated with methylprednisolone and dexchlorpheniramine, solving the reaction. We could diagnose these patients as allergic to the given drug.

Table 2: Placebo as treatment.

PLACEBO AS TREATMENT								
Patient	Male/ Female	Age	Suspicious substance (SS)	Symptoms in referred reaction	Symptoms in study workout	Placebo	Resolution	Tolerance of SS
1	F	43	Amoxicillin	Bilateral palpebral inflammation	Sensation of palpebral inflammation with placebo	SC	Yes	Yes
2	F	37	Amoxicillin	Head, otic, facial and general pruritus	Facial pruritus with placebo	SC	Yes	Yes
3	F	54	Amoxicillin	Pruritus and hives in arms and legs	Pruritus in arms and legs with SS	SC	Yes	Yes
4	F	30	Amoxicillin	Generalized hives	Otic, facial and pharynx pruritus with SS	Oral	Yes	Yes
5	F	54	Amoxicillin-clavulanic acid	Conjunctival erythema, facial inflammation, pruritus in arms	Dizziness, nausea, headache with SS	SC	Yes	Yes
6	F	62	Amoxicillin-clavulanic acid	Facial inflammation, general erythema and pruritus.	Facial inflammation and discomfort with SS	SC	No	No
7	F	37	Amoxicillin	Scalp pruritus, facial and general pruritus	Generalized pruritus with SS	Oral	Yes	Yes
8	M	41	Amoxicillin	Generalized pruritus	Abdominal pruritus with SS	SC	Yes	Yes
9	F	41	Amoxicillin-clavulanic acid	Pharynx inflammation, dyspnoea, dysphagia	Pharynx discomfort with SS	SC	Yes	Yes
10	F	39	Cefuroxime	Abdominal discomfort and syncope	Paraesthesia in tongue and arms and nausea with placebo	Oral	Yes	Yes
11	F	32	Cefuroxime	Maculopapular exanthema with general pruritus	Burning sensation in arms and palpitations with placebo	SC	Yes	Yes
12	F	62	Celecoxib	Palms and soles pruritus, cutaneous paraesthesia and dysphagia	Facial and ears pruritus with SS	SC	Yes	Yes
13	F	41	Celecoxib	Facial swelling, interdigital erythema and vesicles	Generalized pruritus wit placebo	SC	Yes	Yes
14	F	51	Celecoxib	Generalized urticaria and facial swelling	Feeling of inferior lip swelling with SS	SC	Yes	Yes
15	F	49	Etoricoxib	Anaphylaxis	Nausea with alternative drug	SC	Yes	Tolerated AD
16	F	28	Acetylsalicylic acid	Urticaria and lips angioedema	Pharynx discomfort with SS	SC	No	No
17	F	38	Naproxen	Generalized urticaria and abdominal pain	Pruritus on arms, back, abdomen	SC	Yes	Yes
18	F	59	Dexketoprofen	Generalized micropapular exanthema	Pruritus with SS	SC	Yes	Yes
19	M	22	Desketoprofen	Erythema and pruritus on arms, legs and trunk	Pharynx discomfort with SS	SC	Yes	Yes
20	F	32	Meloxicam	Facial swelling	Lingual pruritus with SS	SC	No	No
21	F	54	Moxifloxacin	Dyspnoea, pharyngeal occupation, palmoplantar, otic and pharynx pruritus	Palpebral swelling and epigastric pain	SC	Yes	Yes
22	F	59	Moxifloxacin	Erythematous maculopapular rash and pruritus on legs	General pruritus with SS	SC	Yes	Yes
23	F	17	Moxifloxacin	Head and arms pruritus and erythema on arms	Head and arms pruritus and erythema on arms with SS	Oral	No	No
24	F	46	Clarithromycin	Generalized erythematous rash and pruritus	Dizziness with SS	SC	Yes	Yes
25	F	45	Metronidazole	Micropapular rash	Dizziness and discomfort with SS	SC	Yes	Yes
26	F	53	Metronidazole	Facial erythematous rash and generalized pruritus	Tongue and lips pruritus with SS	Oral	Yes	Yes
27	F	44	Morphine	Dizziness, nausea, erythema	Dizziness and nausea with SS	Oral	Yes	Yes
28	F	44	Tapentadole	Micropapular rash and generalized discomfort	Dizziness and dyspnoea with placebo	SC	Yes	Yes
29	F	55	Polyethylene glycol (PEG)	Pharynx discomfort and pruritus, cough, dyspnoea, dysphonia	Pharynx discomfort and pruritus, and cough, with placebo	SC	Yes	Yes
30	F	51	Polyethylene glycol (PEG)	Facial heat and erythema, warmth sensation, generalized erythema	Pharynx discomfort and ocular pruritus.	SC	Yes	Yes
21	F	45	Cotrimoxazole	Micropapular rash and pruritus	Mild pruritus with SS	SC	Yes	Yes
32	F	54	Acenocumarol	Cutaneous pruritus	Head pressure with SS	SC	Yes	Yes
33	F	51	Methotrexate	Abdominal discomfort, erythema on the back, pruritus on the back and arms.	Headache, palpitations with SS	SC	Yes	Yes
34	F	68	Rifaximin	Generalized pruritus and hives on legs	Abdominal pain with SS	SC	Yes	Yes
35	F	48	Iron	Generalized pruritus, hives on glutei	Pruritus on lips and neck with SS	SC	Yes	Yes
36	M	51	Diazepam	Thorax exanthema, warmth sensation, shortness of breath	Pruritus with SS	SC	Yes	Yes
37	F	43	Ranitidine	Generalized pruritus	Generalized pruritus with SS	SC	Yes	Yes
38	F	41	Omeprazole	Facial inflammation and interdigital erythema	Generalized pruritus with SS	Oral	Yes	Yes
39	F	19	Olive tree pollen immunotherapy	Muscle weakness	Generalized discomfort	SC	Yes	Yes
40	F	50	Air freshener	Pharyngeal swelling feeling, facial and neck pruritus.	Pharyngeal discomfort and facial pruritus with SS.	SC	Yes	Yes

Discussion

Placebo as a diagnostic tool is well known, and there are many reports of the nocebo effect related to drug allergy studies. The DPPCT is a common practice in the allergological study of drug reactions. Different articles concerning the nocebo effect during challenge or provocation drug tests have been reported **[9,10,1].** They studied the factors that lead to a nocebo effect in patients undergoing drug provocation tests. Baybek et al. observed a majority of subjective influences, and many patients had abnormal results on the hospital anxiety depression questionnaire **[9]**.

The nocebo effect occurs frequently in clinical practice, and subjects with high education, non-atopy, and older drug hypersensitivity reaction history seem more likely to experience the nocebo effect during oral drug provocation tests **[10,11]**. These risk factors should be considered and managed accordingly to successfully complete the drug provocation procedure. Our patients with nocebo effect due to the placebo given as a diagnostic tool had similar characteristics.

Medical treatments have specific effects (pharmacodynamics) and nonspecific effects related to the psychocognitive impacts, patients' perceptions and expectations, and variations of the symptom's severity and psychosomatic **[12]**.

In managing adverse drug reactions through oral challenge tests, the nocebo effect is mandatory to recognize false positive responses **[10,11]**.

Placebo and nocebo effects are linked to the patient's expectations and beliefs about the drug they think they are receiving or taking.

Patient hopes about the treatment and conditionings are cognitive factors involved in the placebo response in different diseases and physiological systems. The psychological mechanisms activate intricate neurobiological phenomena as distinct brain areas activation and peripheral physiology, including the release of endogenous substrates **[13,14]**.

When we give the placebo, pretending it is the drug that produced the patient's reaction, many patients have symptoms. In most of our cases, 19 out of 23 patients experienced symptoms similar to the ones they had taking the drug. This makes us be on the watch for a possible unreal reaction in these patients when giving them the natural medicine afterward. So, if they again report symptoms with the suspected drug as with the placebo, we can anticipate the referred symptoms to stop spontaneously without using placebo treatment. Many patients do not experience symptoms when given the actual drug after first having symptoms with the diagnostic placebo.

Allergic responses of type 1 hypersensitivity, including asthma, are affected by psychological factors such as stress and anxiety and can be controlled by interventions other than conventional drug therapy **[15]**.

In our study, most of the patients experienced symptom relief after administering the placebo as treatment.

In our opinion, trained nurses are crucial in giving the placebo with confidence, particularly when it is used as treatment, speaking and soothing the patient, and providing them a feeling of security. They also watch the patients closely and have a close relationship with them and their companions to know how to approach them.

We should be pretty sure the patient is somatising, and it is not a natural reaction when deciding to give a placebo as treatment. When the patient's symptoms don't disappear with the placebo treatment, we use standard drugs such as antihistamines and corticosteroids, as we did in of the 40 patients, with good results.

Conclusion

We consider placebo treatment helps allergological studies discriminate between real or unreal reactions.

As a diagnosis given before the suspicious substance, a placebo helps identify symptoms from possible somatization.

Allergologists and qualified nurses form a team in these studies, and in Allergy Departments, they have a significant role in giving the placebo and managing it individually for each patient.

Contribution

All coauthors have contributed to the article according to the requirements approved by the International Committee of Medical Journal Editors (ICMJE).

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