

Anxiety and Depression Effects During Drug Provocation Test



Laura Michelina Losappio, MD, PhD^a, Alessandra Cappai, MD^b, Alessandra Arcolaci, MD^c, Iuliana Badiu, MD^d, Patrizia Bonadonna, MD, PhD^e, Elisa Boni, MD^f, Claudia Bussolino, MD^g, Marco Caminati, MD^h, Pietro Galati, MD^h, Enrico Heffler, MD, PhDⁱ, Rossella Intravaia, MD^j, Marina Mauro, MD^k, Ilaria Massaro, MD^l, Antonino Romano, MD^m, Gabriele Rumi, MD^m, Anna Parolo, MDⁿ, Stefano Pizzimenti, MD^o, Michele Nichelatti, PhD^p, and Elide Anna Pastorello, MD^a *London, UK; and Milano, Cagliari, Cuneo, Verona, Casale Monferrato, Torino, Bologna, Catania, Como, Firenze, Roma, and Padova, Italy*

What is already known about this topic? It is well known that an accurate clinical history and a drug provocation test, possibly preceded by the administration of a placebo, are essential for the diagnosis of drug allergy.

What does this article add to our knowledge? There is a strong relationship between symptoms of anxiety and depression and the development of a placebo reaction during a drug provocation challenge.

How does this study impact current management guidelines? We suggest that a validated questionnaire for anxiety and depression would be useful before a drug challenge test to evaluate the possible psychiatric components of a reaction.

^aAllergy and Immunology Unit, Niguarda Ca' Granda Hospital, Milano, Italy

^bSouth London and Maudsley NHS Foundation Trust, London, UK

^cDepartment of Internal Medicine, Allergology and Clinical Immunology, University of Cagliari, Cagliari, Italy

^dAllergy Unit, Santa Croce e Carle Hospital, Cuneo, Italy

^eAsthma Center and Allergy Unit, Verona University Hospital, Verona, Italy

^fAllergy Unit, Santo Spirito Hospital, Casale Monferrato, AL, Italy

^gAllergy and Clinical Immunology Unit, Mauriziano Umberto I Hospital, Torino, Italy

^hAllergy Unit, Sant'Orsola Malpighi Hospital, Bologna, Italy

ⁱDepartment of Biomedical Sciences—Personalized Medicine, Asthma and Allergy Clinic-Humanitas University and Research Hospital, Milano, Italy

^jMedicine Unit, Catania University, Catania, Italy

^kAllergy Unit, ASST Lariana, Sant'Anna Hospital, Como, Italy

^lTransfusion Medicine Unit, Careggi Hospital, Firenze, Italy

^mAllergy Unit, Fondazione Policlinico Universitario A. Gemelli, Sacro Cuore University, Columbus, Roma, Italy

ⁿInter-departmental, Unit of Transfusion Medicine, Padova, Italy

^oImmunology and Microbiology Unit, Agnelli Hospital, Torino, Italy

^pService of Biostatistics, Niguarda Ca' Granda Hospital, Milano, Italy

Junior Member Group of Italian Society of Allergology, Asthma and Clinical Immunology (SIAAIC): Laura Michelina Losappio, Alessandra Cappai, Alessandra Arcolaci, Iuliana Badiu, Elisa Boni, Claudia Bussolino, Marco Caminati, Pietro Galati, Rossella Intravaia, Ilaria Massaro, Gabriele Rumi, Anna Parolo, and Stefano Pizzimenti.

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Corresponding author: Laura Michelina Losappio, MD, PhD, Unit of Allergy and Immunology, Niguarda Ca' Granda Hospital, Piazza Ospedale Maggiore, 3, Milano 20162, Italy. E-mail: losappiolaura@yahoo.it.

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BACKGROUND: Drug provocation test (DPT) represents the gold standard for the diagnosis of drug allergy. A DPT can be performed in a single-blind placebo-controlled manner. In anxiety and depressive disorders, patients need to be evaluated to understand the nature of placebo reactions.

OBJECTIVE: The aim of this study was to evaluate the psychological profile of patients with reactions to placebo during a DPT.

METHODS: We consecutively enrolled patients with suspected drug allergy undergoing a DPT preceded by the administration of the placebo. All patients underwent the Hospital Anxiety and Depression Scale (HADS), a questionnaire aimed to identify anxiety and depression, before the challenge test.

RESULTS: A total of 196 patients were enrolled into this study: 8 (4%) patients resulted positive to the DPT, 60 (30.6%) demonstrated anxiety or depression based on the HADS, and 54 had at least 1 placebo reaction during drug provocation. There were statically significant correlations between the positivity of the HADS and the finding of a placebo reaction (Fisher's exact test: $P < .001$), and between the latter and a history of severe reactions to drug (Fisher's exact test: $P < .001$).

CONCLUSIONS: There is a significant and strong correlation between the loss of psychic equilibrium and the development of a placebo reaction during a DPT. We suggest the use the HADS or other validated questionnaire in clinical practice before a DPT to evaluate the possible psychiatric components. © 2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2018;6:1637-41)

Key words: Drug allergy; Placebo; Drug provocation test; Anxiety; Depression

Abbreviations used

CI- Confidence interval

DPT- Drug provocation test

ENDA- European Network for Drug Allergy

FEV₁- Forced expiratory volume in 1 second

HADS- Hospital Anxiety and Depression Scale

OR- Odds ratio

Adverse drug reactions are common in clinical practice; they are reported in approximately 10% to 20% of hospitalized patients and 17% to 25% of outpatients. Drugs are responsible of 12.8% of all anaphylaxis.^{1,2} Adverse drug reactions are classified into type A (predictable) and type B (unpredictable); the latter include hypersensitivity reactions and comprise up to one third of all adverse drug reactions. Hypersensitivity drug reactions can be “allergic” if an immunological mechanism is demonstrated; if no immunological mechanism is implicated, they are defined as “nonallergic reactions” (pseudoallergic).^{1,3,4} Moreover, recently the dose-time-susceptibility classification suggests consideration of all the different aspects playing a role in drug allergic reactions, such as genetic, time of exposure, the dose, but the diagnosis is often difficult.⁵ The incorrect diagnosis of drug allergy leads to the increase of health care—related costs, prescription of drugs that are likely a second choice and possibly a less effective treatment, and an increased level of antibiotic resistance.⁶ Accurate identification of the responsible drug is essential for the diagnosis of drug allergy and to avoid the labeling of the patient as “allergic to drugs.” Allergologic workup comprises an accurate clinical history through standardized questionnaires as suggested by European Network for Drug Allergy (ENDA),⁷ plus *in vivo* and/or *in vitro* tests that are available only for some drugs (β -lactams, perioperative drugs, heparins, etc.).^{8,9} To rule out a diagnosis of immune-mediated or non-immune-mediated hypersensitivity drug reactions, the above allergologic workup is completed by the drug provocation test (DPT), which represents the “gold standard.”¹⁰ It consists of a controlled administration of the suspect drug under medical surveillance and permits the determination of tolerance (or the hypersensitivity) to the drug, taking into consideration the individual’s metabolism and immunogenic background. Its implementation is limited by the possibility of severe and unpredictable reactions, and only experienced allergists should perform this test. It should be reserved to limited scenarios: to exclude hypersensitivity in case of equivocal histories of drug reactions, to establish a diagnosis of hypersensitivity drug reactions with negative or nonavailable allergy test results, or to provide alternative safe drugs for the patient,¹⁰ taking into consideration that the risk-benefit ratio of the DPT needs to be evaluated: if the patient does not need or will not likely need the drug in the future, performing a DPT to establish a diagnosis of drug hypersensitivity is risk with no benefit. Detailed recommendations for DPTs have been published,¹¹⁻¹³ and the general principles for DPTs have been outlined by ENDA. Generally, the test should start with the administration of a placebo, followed by a low dose of the suspected culprit drug, carefully increasing up to the maximum single dose. If objective symptoms occur, the test has to be stopped.¹⁴ A DPT can be performed in a single-blind placebo-controlled manner. This is of relevant importance because it has been described that up to 41% of healthy volunteers receiving

placebo capsules reported symptoms such as sedation, irritation, nasal congestion, fever, exanthema, and urticaria.¹⁵ False positive reactions can be due to psychological symptoms. This is the reason why the administration of the placebo should precede the administration of the active molecule. Placebo can be used to distinguish between drug response (behavioral and physical changes in patients taking a drug) and specific drug effect (that portion of the change that is due to the pharmacologic action of a drug). Placebo can be used to explore this distinction because it is chemically inert and without specific pharmacodynamic activity.¹⁶ The most common factors in placebo reactions are well-determined psychological conditions and the fear of experiencing adverse drug reactions based on past personal experience or the experience of people close to them.¹⁷ Many nonspecific factors strongly affect the patient’s psychological responses to drugs,¹⁶ including the demographic and personality characteristics of the patient, nature of the illness, physician-patient relationship, the setting, physician’s and patient’s expectations, and the administration regimen.¹⁸ In anxiety and depressive disorders, patients need to be evaluated to understand the nature of the placebo reactions. Untoward and negative reactions to many different classes of drugs consistently develop in some patients. Anxious patients have been found to experience more side effects when given a placebo than less anxious patients.¹⁹ Anxiety and depression can be measured using the Hospital Anxiety and Depression Scale (HADS),²⁰ which is a validated questionnaire, standardized in several languages including Italian,²¹ as a simple tool to assess the psychological state of hospitalized patients. The HADS is a self-administered measure used to assess the contribution of a mood disorder (especially depression) and/or of an anxiety disorder, in the setting of medical practice.^{22,23} The HADS was developed to provide clinicians with an acceptable, reliable, valid, and easy to use practical tool to identify and quantify depression and anxiety. The HADS can be used in a variety of settings (eg, community, primary care, hospital), and it is not intended as a complete diagnostic tool, but as a means to identify general hospital patients who would require further psychiatric evaluation and assistance.²²

The primary aim of this study was to assess whether anxiety and depression may have influenced symptomatic patients as compared with asymptomatic patients during a drug challenge test, and how psychiatric symptoms influence patients in the development of reactions. A secondary aim was to assess the importance of placebo’s diagnostic role in the allergic test.

METHODS

Patients

One hundred ninety adult outpatients from 7 units of allergy and immunology in Italy were consecutively enrolled in our study. The main entry criterion was a reliable history of suspected drug-induced hypersensitivity reactions including urticaria, angioedema, erythema (possibly associated with gastrointestinal symptoms), asthma, rhinitis, acute bronchospasm, laryngeal edema, and anaphylaxis. The reliability of drug hypersensitivity was evaluated by specialists in allergy and clinical immunology based on patients’ detailed clinical history and/or emergency department visit, and/or hospitalization. The reported symptoms were classified into 3 grades of severity²⁴: grade I, as isolated cutaneous or subcutaneous symptoms (generalized erythema, urticaria, angioedema); grade II, as the presence of gastrointestinal (nausea, vomiting, abdominal pain), respiratory

(dyspnoea, stridor, wheeze, chest, or throat tightness), and/or cardiovascular symptoms (dizziness, diaphoresis), in addition to the grade I symptoms; grade III, as more severe life-threatening cardiovascular or neurological involvement (cyanosis or $\text{SpO}_2 \leq 92\%$, hypotension with systemic blood pressure <90 mm Hg, confusion, loss of consciousness, incontinence), in addition to grade I symptoms. Patients were also investigated for previous history or current psychiatric disorders, including depression and anxiety. The study protocol was approved by the Ethical Committee of Niguarda Ca' Granda Hospital (Milan, Italy) and written signed informed consent was obtained before the challenges by all patients.

Questionnaire

All patients underwent the HADS before the challenge test. A face-to-face interview was performed by a specialist in allergy and clinical immunology. The questionnaire consisted of 2 scales of 7 questions each, assessing the anxiety and the depressive components, respectively. For each question, patients were invited to indicate the best option related to their level of emotional status choosing on a scale from 0 to 3, and only 1 answer was possible for each question. The maximum score for each scale of the questionnaire was 21. A total score ≤ 7 was considered as normal. Figure 1 shows the HADS.²⁰

Drug provocation test

Patients were informed about possible reactions that may occur during the test. DPTs were performed at least 4 weeks after the last episode of a suspected drug reaction. Antihistamines and oral corticosteroids were discontinued at least 7 days before the test.

A challenge test was started with placebo and was continued with the administration of increasing 4 number doses of drug starting from a low dose until reaching the maximum single dose. Before the challenge, blood pressure and forced expiratory volume in 1 second (FEV_1) were measured, the oral cavity and skin were carefully inspected for preexisting lesions. During the challenge test, blood pressure, FEV_1 values, and skin, ocular, nasal and bronchial reactions were monitored by a medical doctor or a trained nurse. A positive reaction for bronchospasm was defined as a decrease in FEV_1 of at least 15% with respect to the baseline value. Patients who developed clinical symptoms after the administration of placebo but not the suspected drug were evaluated as nonallergic to the suspected drug, whereas patients who developed objective symptoms (urticaria, angioedema, pruritus, erythema, gastrointestinal symptoms, asthma, rhinitis, acute bronchospasm, laryngeal edema, and anaphylaxis) after the administration of the suspected drug were considered to have a positive test. Subsequently, we divided the study population into 2 groups: group A, which included subjects with clinical symptoms after the administration of placebo, and group B, including patients with no reaction to the placebo. Patients were observed for at least 8 hours after the DPT, and any subjective or objective symptoms were recorded by the attending physician. All doses were administered at 20-minute intervals unless symptoms appeared.

Statistical methods

All data were analyzed using descriptive statistics. Variables normally distributed (after checking with the Shapiro-Wilk test) were summarized as mean and standard deviation, whereas nonnormal variables were described by median and range. Cross-tabulation between categorical variables was checked by Fisher's exact test, and the association between binary endpoints and binary, or discrete,

Hospital Anxiety and Depression Scale

~ Scoring Sheet ~

	Yes definitely	Yes sometimes	No, not much	No, not at all
1. I wake early and then sleep badly for the rest of the night.	3	2	1	0
2. I get very frightened or have panic feelings for apparently no reason at all.	3	2	1	0
3. I feel miserable and sad.	3	2	1	0
4. I feel anxious when I go out of the house on my own.	3	2	1	0
5. I have lost interest in things.	3	2	1	0
6. I get palpitations, or sensations of 'butterflies' in my stomach or chest.	3	2	1	0
7. I have a good appetite.	0	1	2	3
8. I feel scared or frightened.	3	2	1	0
9. I feel life is not worth living.	3	2	1	0
10. I still enjoy the things I used to.	0	1	2	3
11. I am restless and can't keep still.	3	2	1	0
12. I am more irritable than usual.	3	2	1	0
13. I feel as if I have slowed down.	3	2	1	0
14. Worrying thoughts constantly go through my mind.	3	2	1	0

Anxiety 2, 4, 6, 8, 11, 12, 14

Depression 1, 3, 5, 7, 9, 10, 13

Scoring 3, 2, 1, 0 (For items 7 & 10 the scoring is reversed)

GRADING: 0 - 7 = Non-case 8 - 10 = Borderline case 11+ = Case

FIGURE 1. Hospital Anxiety and Depression Scale questionnaire.

or continuous regressors was analyzed using the logistic regression and Wald's test to verify the statistical significance.

RESULTS

Study population

A total of 196 patients (148 females [75.5%]; median age of 47 years [range 18-85 years]) presenting with a positive clinical history of suspected drug allergy were enrolled into this study. Ninety-one patients (46.4%) reported a history of allergic reactions to nonsteroidal anti-inflammatory drugs, 94 (47.9%) to antibiotics, and 11 (5.6%) to both drug classes. According to the severity of the reaction, 17 (8.6%) patients were of grade III, 56 (28.6%) of grade II, and 123 (62.7%) of grade I. Fifteen patients were known to have anxiety and 2 depression, all already on treatment for these diseases.

HADS questionnaire

Sixty patients (30.6%) (90% females) had an abnormal HADS score: 22/60 (36.7%) for depression, 26/60 (43.3%) for anxiety. Of 60 patients, 12 (20.0%) with an abnormal HADS score were positive for both components. There was a statistical association between the abnormal HADS score and female gender (Fisher's exact test, $P = .002$).

TABLE I. Positive challenge to drug, with provocative threshold dose and elicited symptoms presented for 8 of 196 study patients

Patient	Challenge with drug		
	Challenge drug classes	SYM	NPD
1	NSAIDs	E	4
2	β -Lactams	E, P	4
3	β -Lactams	U	2
4	Macrolides	U, P	2
5	NSAIDs	E, A	2
6	NSAIDs	E, P	2
7	β -Lactams	E, P	3
8	NSAIDs	U, P	2

A, Asthma; E, erythema; NPD, number provocation dose; NSAID, nonsteroidal anti-inflammatory drug; P, pruritus; SYM, challenge symptoms; U, urticaria.

Challenge tests

Based on the placebo challenge's results, patients were grouped as follows: 54 (27.5%) patients (85.2% females) with a placebo-induced reaction and 142 (72.4%) without any reaction to the placebo administration. There was a statistical association between the prevalence of a placebo-induced reaction and female gender (Fisher's exact test, $P = .025$). Of 54 patients, 32 (59.3%) with placebo-induced reactions complained of pruritus, 19 (35.2%) of pruritus and asthenia, 2 (3.7%) of asthenia, and only 1 (1.8%) complained of respiratory symptoms. All these symptoms resolved spontaneously in few minutes, and the affected patients were able to continue the test and underwent a challenge with drugs. One hundred eighty patients had a negative challenge to drug, whereas 8 (4.1%) had a positive result. Table I shows the positive challenge to drug, with provocative threshold dose and elicited symptoms. Because of a low number of positive challenge tests, we did not consider this group for statistical analysis.

Relationship between the study parameters

In our study population, patients with known anxiety and/or depression reported being in good control by treatment, and we did not find an association between having these conditions and positivity to placebo challenge (Fisher's exact test: $P = .254$); we observed a nonsignificant tendency of an association between being affected by anxiety and/or depression and abnormal HADS scores (Fisher's exact test: $P = .052$). Moreover, a history of an adverse reaction to more than 1 drug was not related to positivity to placebo (Fisher's exact test: $P = .999$). On the other hand, we found a significant association between positivity to placebo and a history of severe reactions to drug (Fisher's exact test: $P < .001$). Specifically, a 1 unit increase of the severity grade of the drug reaction symptoms to drugs, corresponded to a significant increase in the odds of developing placebo reactions (odds ratio [OR] = 2.0; 95% confidence interval [CI] for OR: 1.3-3.2; Wald's test: $P = .003$). There was a significant relationship between abnormal HADS scores and positivity to placebo (abnormal HADS corresponded to 81.7% positivity and 18.3% negativity to placebo, whereas normal HADS corresponded to 3.7% positivity and 96.3% negativity to placebo; Fisher's exact test: $P < .001$). In particular, abnormal HADS corresponded to a highly significant increase in the odds of developing placebo reactions (OR = 116.7; 95% CI for OR: 38.6-353.0; Wald's test: $P < .001$).

DISCUSSION

The relationship between psychiatric disorders and adverse drug reactions has been widely investigated, but it is still not totally understood. Anxiety and depression have been associated with dysregulation in secretion of cortisol and catecholamines, and to abnormal immune response.²⁵ These alterations may be related to a variety of symptoms, from pruritus to bronchospasm. A history of an adverse reaction to drugs significantly elevates anxiety in patients and affects therapeutic decisions. This study investigated the connection between anxiety and/or depression and the results of placebo challenges. The main finding of our study is the strong association between the positivity of the HADS questionnaire and a placebo-induced reaction: to our knowledge, this is the first report of this kind of finding. Moreover, we found an association between the positivity of placebo challenge and a history of severe drug reactions. Our findings are in line with another study that observed that DPTs themselves could cause significant anxiety in patients with drug hypersensitivity, and that anxiety levels decreased after a negative test.²⁶ There is still no clear understanding of the reasons behind this, and whether patients with previous "bad experiences" may be more prone to develop anxiety or if having anxiety traits may be the trigger to develop adverse reactions. To have a clearer picture about this specific issue, and to be able to target effectively primary symptoms, it would therefore be important to establish longitudinally whether psychiatric symptoms precede or follow any adverse drug reaction. In line with previous research,²⁷ cutaneous symptoms were the most common reaction to placebo challenge.

We observed an association between female gender and placebo-induced reactions, which is comparable with previous results in DPTs,²⁸ and our findings confirm the connection between psychic equilibrium and allergic reactions.²⁹

In conclusion, considering the findings of this study, we suggest the use of the HADS questionnaire to screen patients who will undergo a drug challenge.

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