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Can placebo challenge test (inducing a "nocebo effect") be a suitable model to assess stress-induced bronchial obstruction? Suggestions from the multidisciplinary Working Groups "Stress-Asthma" and "AAIITO Regione Campania"

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Key words

Adverse drug reaction; anxiety; bronchial asthma; bronchial obstruction; cholinergic tone; depression; increased cholinergic tone; hypersensitivity; nocebo effect; placebo challenge.

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To the Editor,

we read with interest the excellent article of Bizzi *et al.* (1) reporting that female sex, older age and low level of education combined with a depressive tendency seem to be potential risk factors for "nocebo effect" appearing during oral challenge test in patients with drug adverse reactions (ADR).

They demonstrated that 10% of the examined patients reported respiratory symptoms (dyspnea and perception of laryngeal obstruction) as a consequence of the "nocebo effect" and this percentage was quite similar to that found in our previous Italian multicenter study (2). However, since the aim of study was a psychological assessment of these patients, they did not provide comments concerning the association between nocebo effects and respiratory symptoms in patients with ADR.

In other words, are reported respiratory symptoms (in asthmatics with real or "presumed" ADR) the consequence of a real bronchial obstruction, a condition associated to stress or both? It has been also demonstrated that inducible laryngeal obstruction, which is an induced and inappropriate narrowing of the larynx leading to symptomatic upper airway obstruction, can coexist with asthma (3). In fact, in this study, 42% of patients had objective evidence of both conditions, and symptoms possibly attributable to laryngeal obstruction are common (as "nocebo effect") following placebo administration (3).

Based on these premises, we would like to discuss the possibility to use placebo administration as "drug provocation test" and inducing a "nocebo effect", as a potential model to study the role of stress in triggering (or aggravating) bronchial obstruction in asthmatics (with a real or "presumed" ADR).

We have previously shown that about 63% of asthmatic patients reported the usual appearance of at least one non-respiratory symptom (n-RS) before an asthma attack (4). Anxiety, and to a lesser extent depression, represented the most common n-RSs in our study, suggesting that both disorders may have a possible role in the development and triggering of an asthma attack. Several studies have shown that psychological stress may enhance bronchial hyperreactivity through different mechanisms such as mast cell activation, mediator release, inflammation, and impairment of respiratory tolerance (5-7).

Another modality of inducing an increase in airway resistance in asthmatics (but also in healthy individuals) is the use of visual unpleasant stimulations such as bloody or highly-arousal surgery films. Ritz and co-workers (8-10) reported a significant relationship between psycho-social stress and stimulation of the cholinergic system, resulting in an increased airway resistance. The authors demonstrated that unpleasant visual stimulations (*i.e.*, bloody films) can rapidly induce (after 1-2 minutes) a vagal-mediated response associated with an increase of airway resistance assessed by impedance plethysmography and end-tidal PCO_2 by capnometry. In addition, measures of airway inflammation (indirect, fraction of exhaled nitric oxide), reactivity (direct, methacholine challenge), and/or reversibility were also obtained. Therefore, these findings suggest focusing the attention on the potential role of the parasympathetic system as a trigger of bronchial obstruction at least in a group of asthmatics reporting the usual onset of cholinergic-related n-RSs (*i.e.*, stress and/or anxiety) before an asthma attack. We have hypothesized that, in some individuals, this condition of enhanced basal cholinergic tone might play a predominant role in determining airway obstruction, compared with other well-known factors such as allergens, air pollutants, infections, or exercise (a new "asthma phenotype"?) (11).

The vagal hyperactivity induced by anxiety and stress in asthmatics also represents the basis of important considerations by a therapeutic point of view, such as the use of anticholinergic agents (12, 13).

Suggestions from "Asthma-Stress" and "AAIITO Regione Campania" Working Groups

Since organizing bloody films vision could be of difficult feasibility in outpatient settings, the use of placebo administration has the advantage of exploiting the patient's inherent fear of taking drugs and the ambient situation that simulates taking an "active" drug thus inducing a stress status. A subject suffering from asthma and anxiety/depression with a real or "presumed" history of drug-related adverse reaction represents the ideal candidate. Indeed, it is not relevant to have a proven drug allergy, but it is essential that the patient is convinced to be "allergic" to drugs.

The suggested flow-chart to evaluate the possible role of "nocebo effect" in the induction of bronchial obstruction in these asthmatics has been summarized in **figure 1**.

The occurrence of airways obstruction or the worsening of an already present obstruction as assessed by spirometric evaluation, indicates a likely relationship between the parallel onset of stress and bronchospasm. In case of development of an associated onset of other parasympathetic stress-related symptoms (*e.g.*, abdominal pain, reflux, dry mouth etc.), this could support our hypothesis of a possible "asthma phenotype" characterized by a high systemic cholinergic tone.

According to our previous study (11), a simple question exploring the presence of vagal-related n-RSs during the collection of anamnestic data could help identify asthmatics with an imbalance between sympathetic and parasympathetic systems. These individuals could benefit of a further diagnostic evaluation *e.g.*, oxygen and methacholine inhalation, neck suction, slow deep breathing assessed by multiple frequency Forced Oscillation Technique (FOT), measurement of resting heart rate and pupillometry of a possible higher basal cholinergic tone (14), Laryngeal Dysfunction Questionnaire (LDQ) (15) which might be elevated by a "nocebo effect" induced-psychological distress. Following this hypothesis,

our suggested procedure (**figure 1**) could be a useful method to assess if an induced stress is able to start or increase airway obstruction in the single asthmatic patient. This demonstration could have important diagnostic (*e.g.*, for asthma phenotyping), preventive (*e.g.*, for avoidance of stressing situations) and therapeutic consequences such as the importance of psychological support in these individuals. In addition, since the degree of cholinergic tone is likely to be different among asthmatics, we believe it is not possible to rule out that the effectiveness of anticholinergic agents such as tiotropium could be greater in patients with an increased degree of cholinergic tone (11-13). This potential increased responsiveness to tiotropium may be usefully exploited also in the event of poor treatment efficacy or occurrence of adverse events with the use of long-acting β_2-adrenoceptor agonists (LABAs) (16).

In conclusion, the currently available literature indicates that anxiety and related psychological disorders should be considered as mechanisms that might trigger airway inflammation, the onset of asthma attacks, and the severity of respiratory symptoms. We believe that our suggested diagnostic procedure could be a useful model to assess the relationship between an induced stress/anxiety condition and the onset or aggravating bronchial obstruction in asthmatics (with a real or "presumed" ADR). Further studies should be planned to confirm our hypothesis in clinical practice.

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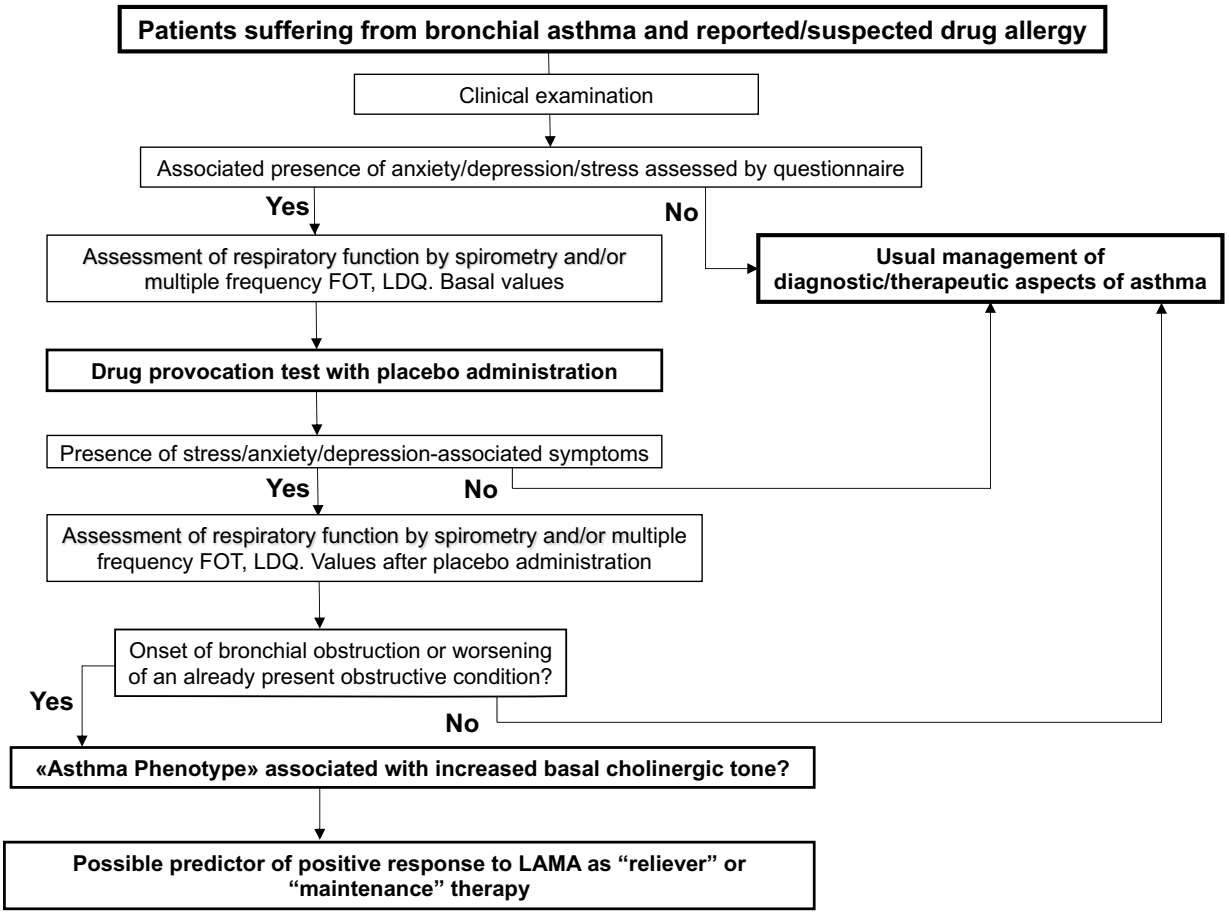
Conflict of interests

The authors declare that they have no conflict of interests.

Figure 1 *- Suggested flow-chart to evaluate the possible role of "nocebo effect" in the induction of bronchial obstruction in asthmatics suffering from anxiety/depression.*



FOT: forced oscillation technique; LAMA: long-acting muscarinic antagonist; LDQ: laryngeal dysfunction questionnaire.

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