

# Review of Symptoms Assessment During Nasal Allergen Provocation in Patients with Allergic Rhinitis

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**Abstract:** *Background:* Allergic rhinitis is the most prevalent allergic disease. Nasal provocation tests (NPTs) may be useful for its clinical diagnostic and therapy monitoring although they are mostly used in clinical research. However, the lack of standardisation in the symptoms assessed and the variety of instruments used make effective comparison between studies difficult. *Objective:* To review the published literature searching for instruments assessing nasal symptoms during NPTs for allergic rhinitis. *Methods:* Pubmed and Embase electronic databases were reviewed, looking for all methods including an instrument assessing symptoms during or following NPTs. Studies on animal models, pediatric subjects, and patients without allergic rhinitis were excluded. Studies were also excluded if they did not assess nasal symptoms during or following the NPT. Only NPT studies performed with allergen extracts or histamine were included. *Results:* A total of 520 studies were retrieved, from which 81 different instruments from 81 studies were included in the present analysis. There was no instrument reporting a validation process for the assessment of symptoms during NPTs. From the remaining instruments, the most common symptoms assessed were rhinorrhea (67), sneezing (70), congestion (67), and nasal pruritus (50). The most frequently used type of scales among those instruments was the four-point Likert scale (39), although different methods were used. *Conclusions:* This review illustrates the large variety of symptoms and methods used to assess the aforementioned NPTs. The lack of validation studies suggests the need to develop and validate a standardized instrument assessing symptoms following NPTs.

**Keywords:** Rhinitis, symptoms, symptom score, allergen challenge, nasal provocation test.

## INTRODUCTION

Several techniques have been developed to study the clinical and pathophysiological mechanisms of rhinitis. Among those being commonly used are direct challenges with histamine or allergens [1]. Nasal provocation tests (NPTs) have the advantage of reproducing an exposure in a controlled setting, making possible the use of the same procedure for all subjects with standardized agents. They are particularly used to assess new treatments of allergic rhinitis [1]. Although rarely performed in clinical practice, NPTs are often used for research purposes on nasal diseases mainly to evaluate efficacy of anti-allergic medication [1-3]. They are also important in the diagnosis of occupational rhinitis.

The evaluation of response during NPTs can be both objective and subjective. With respect to objective methods, biochemical markers measures in nasal secretions have been used [4-6], as well as anterior rhinomanometry, acoustic rhinometry, and rhinostereometry which allow to assess nasal obstruction during NPT [1]. Subjective symptom ratings using Likert or visual analogue scales have been widely used. However, the lack of standardisation in the symptoms assessed and the large spectrum of scales lacking a validation process make effective comparison between studies difficult. Although some scoring systems have been proposed

for standardised quantification of clinical parameters [7-11] and the importance of a rigorous validation process reported, there is, to our knowledge, no “gold standard” for the evaluation of response to NPTs.

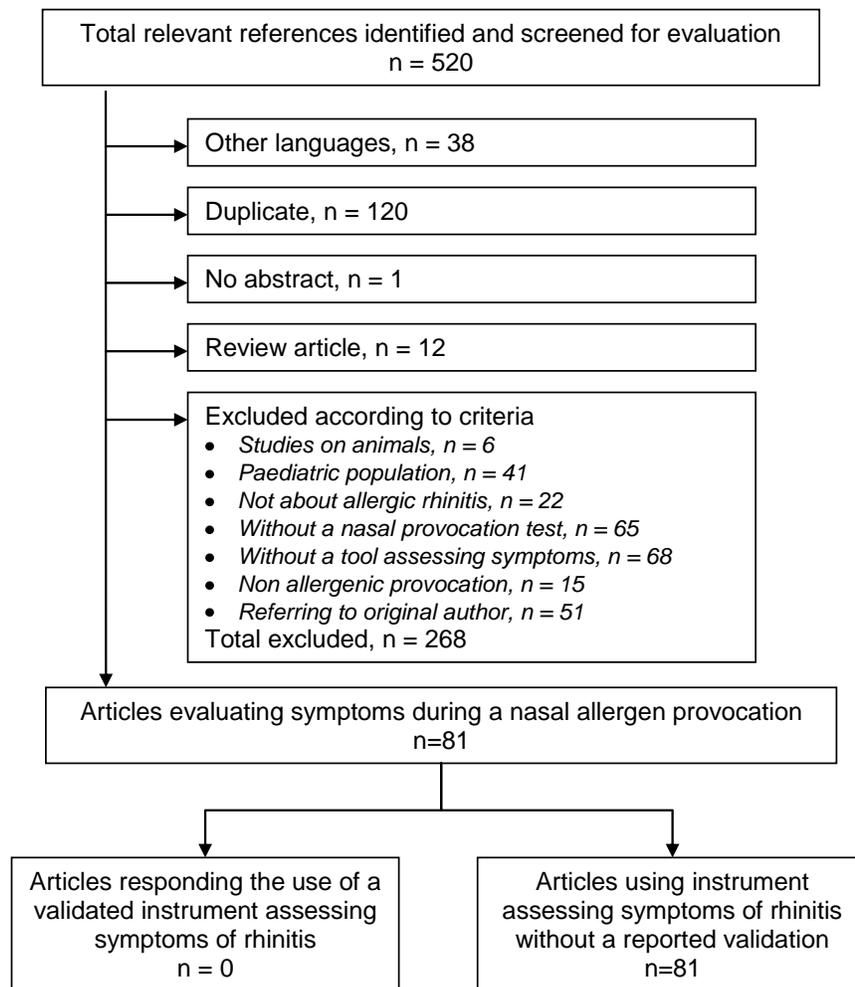
The aim of this work was to review published reports on NPTs, searching for instruments with a reported validation process that evaluated symptoms during or after NPTs and to assess the validation process when available.

## METHODS

### Search Strategy and Inclusion Criteria

A systematic literature search was performed by an information specialist, using Pubmed and Embase databases, to identify reports where the evaluation of symptoms in patients with allergic rhinitis during NPT was assessed, regardless of study design. The following keywords and/or medical heading terms and/or text words were used when applicable: 1) *rhinitis* and 2) *symptoms*, and 3) *evaluation or questionnaire or score or scale or instrument*, and 4) *nasal provocation test or nasal allergen provocation or nasal allergen challenge or nasal challenge*. We analyzed human studies published between 1980 and 2006 written in English or French. Reference lists of included studies and review articles were hand searched afterwards. Studies were included if 1) patients had allergic rhinitis; 2) they included NPTs with allergen extracts or histamine; and 3) they were original publications using tools to assess symptoms during or following NPTs in patients with allergic rhinitis.

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**Fig. (1).** Details of the literature search results.

### Data Extraction and Tool Assessment

The database was analysed independently by two reviewers. General information on the study goal, the study type, the clinical setting, the treatment provided (medical or surgical), and the patient population and inherent characteristics was first collected. Subjects' diagnosis of allergic rhinitis and asthma were also considered. The presence of allergic asthma was noted. The number of symptom evaluation tools used by each study was recorded.

For each symptom assessment instrument used in the studies, information was abstracted on the number of items, the subscales or domains, the scoring method and the mode of administration. If mentioned, the performance characteristics of each instrument including validity, reliability and responsiveness was noted. Therefore, information on nasal and ocular manifestations evaluated by the different tools was precisely noted. Regarding the mode of administration, we noted if the patients completed independently the questionnaire or scale or if an interviewer was involved in the process. If a scale was described, the grading system and the number of items scored were recorded. In the case of visual analog scales (VAS), we were interested in its grading (e.g. 0 to 10, 0 to 100) and the items assessed. Finally, we analyzed

if the VAS assessed the patient's overall feeling of symptoms or precise clinical manifestations.

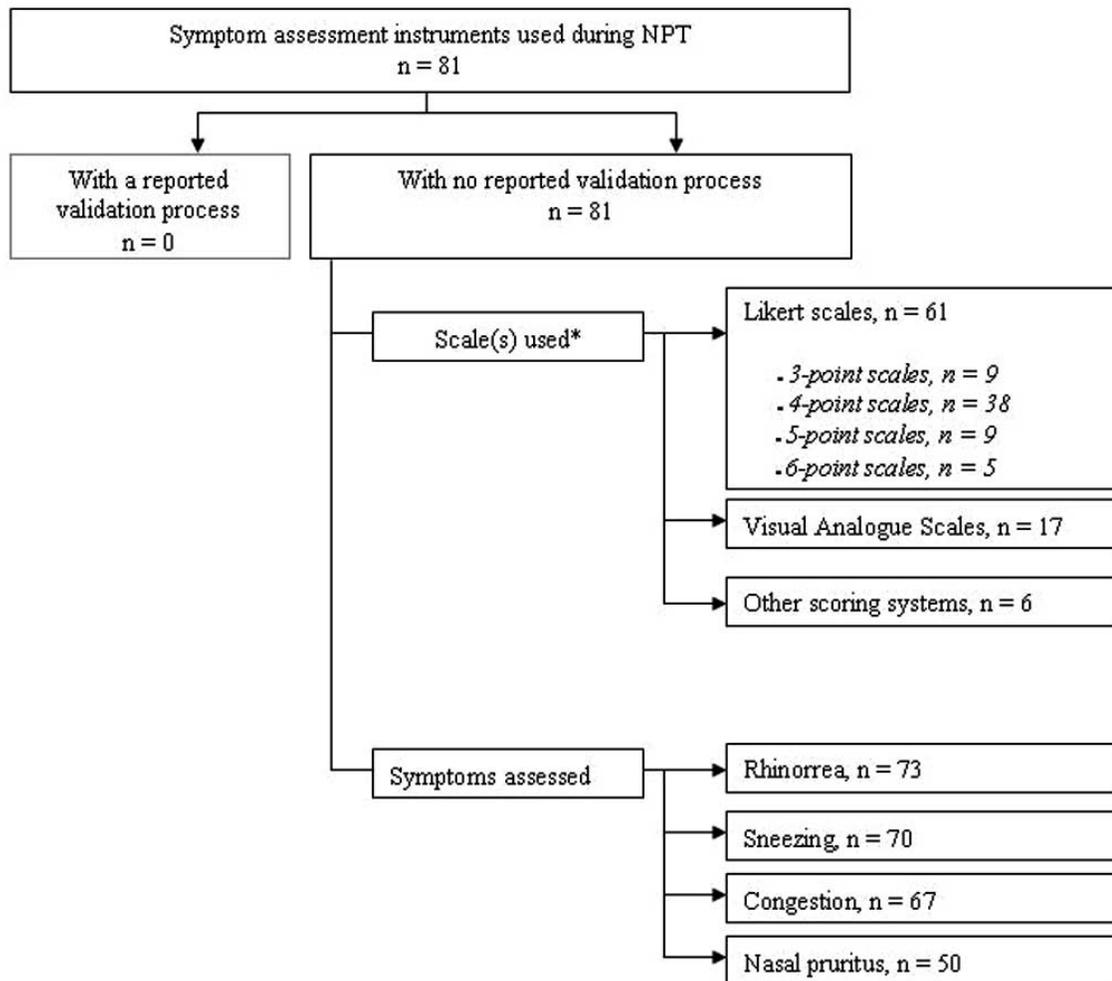
## RESULTS

### Literature Search Results

At first, 520 articles were identified through the query of the Embase and Pubmed databases. We first excluded 120 duplicates, 38 articles in other languages than French or English, 1 without abstract and 12 reviews (Fig. 1). From the remaining 349 articles, we excluded 6 studies on animals and 41 which focused on pediatric patients. We discarded 22 studies on patients without any form of allergic rhinitis and 65 which did not perform a nasal provocation test. Fifteen studies used other substances than allergens or histamine while 68 did not include an instrument to assess symptoms during NPTs. Finally, 51 studies were not the original article describing the instrument used to assess symptoms and referred to previous studies which were included in this analysis. Hence, 81 studies used instruments to assess nasal symptoms following NPTs among subjects with rhinitis.

### Instrument Characteristics

None of these 81 studies used a validation process for their instruments measuring nasal symptoms [9,12-91]. In-



**Fig. (2).** Characteristics of the tools assessing allergic rhinitis symptoms.

deed, we found no description of a validated symptom scoring method. Studies using non-validated tools were reviewed and described in order to find any similarities and repetitive characteristics in nasal symptom assessment which may be useful for further instrument development and validation.

Likert scales were the predominant instrument to assess symptoms following or during NPTs. Sixty one studies included any form of numeric scale while 17 of them used visual analogue scale (VAS). Six studies used other scoring systems, which consisted mostly in a combination of Likert scales depending on the symptom assessed. A scale grading symptoms from 0 to 3 was used in 38 of the 61 studies with Likert scales. Symptom severity was subjectively assessed with the following gradation: 0 corresponded to the absence of symptoms, 1 to mild, 2 to moderate, and 3 to severe symptoms (Fig. 2).

The symptoms most frequently evaluated were, in order of prevalence, rhinorrhea (73), sneezing (70), nasal blockage (67), and nasal pruritus (50). The prevalence of these four upper airway symptoms was clearly higher compared to the others. Tearing (12) and itching of the eyes (9) as well as bronchial symptoms (6) were the following most prevalent symptoms assessed during NPTs. Bronchial symptoms, relating to lower airway symptoms, included cough, wheezing,

and shortness of breath. In 39 studies, the symptom evaluation tool was auto-administered. Nineteen studies used an interviewer to complete the symptom assessment tool. Twenty three studies did not mention the mode of administration.

## DISCUSSION

This review confirms the lack of standardization and validity assessment of the different tools used to assess the upper airway response to nasal allergen challenges. No validation process for an instrument was found following the review of 81 original manuscripts meeting the previously described criteria. Nevertheless, the publications using non-validated tools were reviewed to find any common characteristics in nasal symptom assessment.

When analysing data extracted from the non-validated tools, the four-point Likert scale was the most commonly used instrument to assess symptoms following NPTs. Likert scales and VAS allow the subjects to report the frequency or intensity of their symptoms. Moreover, these last have been reported as having relatively comparable reliability and responsiveness [92,93]. Otherwise, Likert scales may be easier to administer and interpret and therefore may be preferable for use in clinical trials [93-95].

Rhinorrhea, sneezing, nasal congestion, and nasal pruritus were the most frequently evaluated symptoms. Even though these results come from studies which lacked a validation process, the four symptoms most frequently assessed during or after NPTs correspond to the definition of allergic rhinitis according to the Allergic Rhinitis and its Impact on Asthma workshop report [96]. Allergic rhinitis may be described as a complex condition characterized by paroxysms of sneezing, rhinorrhea, nasal obstruction, and itching of the eyes, nose, and palate [97]. In a more recent evaluation of clinical parameters for the definition of allergic rhinitis, Ng *et al.* suggested that the most important factors to be considered in the diagnosis of allergic rhinitis are those related to nasal and ocular symptoms; for example, the symptoms of rhinorrhea, sneezing, sniffing, impaired sense of smell, blocked nose, watery eyes, red eyes, mouth breathing, and itchy nose [98]. Therefore, the symptoms commonly assessed in studies using NPTs seem to be relevant in the evaluation of patients with allergic rhinitis and should be included in an evaluation tool.

Another important finding of the study was the diversity of the methods to assess symptoms. In some instances, the same author used different instruments to evaluate symptoms during NPTs. However, the use of more than one instrument to assess symptoms following NPTs was rarely noted. Multiple scales could be used to assess the various components of the nasal response. On one side, specific symptoms could, for instance, be individually assessed with a Likert scale. In addition, it could be of interest to have a composite measurement of the disease control and stability of subjects, for example, by adding a more objective measure (ex. Nasal peak flow).

As shown in this review, there is no consensus or gold standard for the establishment of upper airway symptoms following NPTs. The data collected in this study are most valuable for the future construction and validation of a new symptom score as they reflect the perception of most authors on rhinitis' key features. This review stresses the need to develop and most importantly, validate a common tool to assess severity and evolution during or following NPTs in patients with allergic rhinitis. Since no standardized and common tool has been produced for this purpose, the evaluation and comparison of studies using various methods to assess NPTs remain difficult and less reliable. In addition, like other chronic diseases, allergic rhinitis requires adequate monitoring of symptoms in order to provide adequate treatment. The tool developed for evaluation of symptoms following NPTs could also be useful in the assessment of rhinitis control.

#### POTENTIAL FINANCIAL CONFLICTS OF INTERESTS

**Advisory Boards:** L.-P. Boulet (Altana, AstraZeneca, GlaxoSmithKline, Merck Frosst, Novartis); **Lecture fees:** L.-P. Boulet (3M, Altana, AstraZeneca, GlaxoSmithKline, Merck Frosst, Novartis); **Sponsorship for investigator-generated research:** L.-P. Boulet (AstraZeneca, GSK, Merck Frosst, Schering); Research funding for participating in multicenter studies: L.P. Boulet (3M, Altana, AsthmaTx, AstraZeneca, Boehringer-Ingelheim, Dynavax, Genentech, GlaxoSmithKline, IVAX, Merck Frosst, MedImmune, No-

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