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# Development and validation of the Drug Hypersensitivity Quality of Life Questionnaire

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**Background:** The impact of drug hypersensitivity has never been considered from the patient's perspective, and no questionnaire is currently available for this purpose.

**Objective:** To develop and validate a questionnaire specifically designed for the assessment of quality of life in patients with drug hypersensitivity entitled the Drug Hypersensitivity Quality of Life Questionnaire (DrHy-Q).

**Methods:** During the development procedure, an initial questionnaire of 34 items was generated and administered to 70 patients; the 20 most important items were detected and converted into questions evaluated with a 5-point Likert scale. This provisional questionnaire then underwent a validation procedure to assess its psychometric properties. The DrHy-Q and the Psychological General Well-Being Index (PGWBI) were completed by 365 patients (67.5% female; mean [SD] age, 40 [15] years).

**Results:** Statistical analysis revealed a 1-dimensional structure for the DrHy-Q that explained up to 50.7% of the total variance and showed good levels of internal consistency for the extracted factor (Cronbach  $\alpha = 0.928$ ). The correlations between the DrHy-Q and the PGWBI scores were low. However, the DrHy-Q scores of patients who experienced anaphylactic shock were significantly higher than the scores from patients with other reactions (analysis of variance;  $F = 5.991$ ;  $df = 4$ ;  $P < .001$ ). The test-retest associations were good ( $R = 0.995$ ;  $P < .001$ ).

**Conclusions:** DrHy-Q met the standards for construct validity, internal consistency, and reliability, indicating that it is appropriate for use alone or in combination with other patient-reported outcome questionnaires to explore the subjective experiences of patients with drug hypersensitivity.

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## INTRODUCTION

*Drug hypersensitivity*, a term suggested by the Review Committee of the World Allergy Organization, refers to “objectively reproducible symptoms or signs initiated by exposure to a defined stimulus at a dose tolerated by normal persons,”<sup>1</sup> independently of the pathogenetical mechanism. Hypersensitivity reactions to drugs affect 10% to 20% of hospitalized patients and more than 7% of the general population.<sup>2,3</sup>

Clinical practice suggests that, from the patient's perspective, drug hypersensitivity is an experience accompanied by intense emotional content. Patients are concerned, anxious, and scared, and drug hypersensitivity may limit enjoyment in their daily life (eg, leisure and holidays). Despite these clinical findings, patient subjectivity has remained unexplored, even when severe systemic reactions have occurred. In con-

trast to other allergic diseases, there are no specific instruments<sup>4–6</sup> to assess health-related quality of life (HRQoL), the impact of the disease and treatment on the patient, as perceived by the patient.<sup>7</sup> The literature available on other allergic diseases (eg, respiratory allergy, allergic skin disorders, food allergy, and insect venom allergy<sup>4,8–10</sup>) demonstrates that the presence of symptoms and exacerbations, the need to take medication, and the necessary changes to habits and lifestyle all negatively affect the patient's life from physical, psychological, and social points of view. Because of the nature of the problem, patients with drug hypersensitivity experience emotions of anxiety, fear, and tension closely related to drug intake, disease management, and present or future physical problems. These emotions, which cover a specific area of the patient's personal experience, can influence life and disrupt daily performance.

Given the preceding factors, we developed and evaluated the psychometric properties of a questionnaire for the assessment of the specific burden of drug hypersensitivity from the patient's perspective. Our goal was to develop a tool that was (1) able to capture HRQoL impact in patients with drug hypersensitivity, independent of the responsible drug; (2) generated and tested in accordance with procedures established and applied to other similar instruments; and (3) designed to be completed by the patient, easy to administer, and easy to score. We have named this new

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tool the Drug Hypersensitivity Quality of Life Questionnaire (DrHy-Q).

## METHODS

The validation process was performed in accordance with published guidelines.<sup>11</sup> It consisted of 2 distinct phases, development and validation, involving different patient groups. Details of the development and validation procedures appear below.

This study was performed according to Good Clinical Practice standards, adhered to the Declaration of Helsinki, and was approved by the local ethics committee. All patients included in this study provided written informed consent.

### *Patients*

Study participants were drawn from 10 Italian allergy units. For both the development and validation phases, the inclusion criteria were adult age ( $\geq 18$  years), diagnosis of drug hypersensitivity according to the standard operating procedures recommended by the European Network for Drug Allergy of the European Academy of Allergy and Clinical Immunology,<sup>12</sup> and the passage of at least 3 months since the last drug reaction.

### *Development Procedure*

To ensure the inclusion of items appropriate and relevant for patients with adverse drug reaction (ADRs) in the DrHy-Q, the generation and selection of items, as well as item pretesting, were based on current guidelines.<sup>11</sup> An initial list of problems was generated based on 2 sources. First, a panel of clinical and research experts in immunology, allergy, and psychology was asked to identify troublesome problems for patients with ADRs, leading to the creation of 28 relevant items. Second, exploratory semi-structured interviews were performed with 50 patients with drug hypersensitivity, who were excluded from subsequent validation phases of the study. These patients were asked to describe the areas of their lives that were impaired by drug hypersensitivity. An initial list of 33 items was created that maintained, whenever possible, patient expressions. By combining the elements identified by specialists and patients, a total of 45 items passed the generation phase of this study. Finally, items were eliminated that were redundant, ambiguous, difficult to understand, or expressed in negative form, resulting in a generation-phase list of 34 items.

The 34 generation-phase items were administered, during 2 months, to 70 consecutive outpatients with drug hypersensitivity who were excluded from subsequent questionnaire validation phases. The patients indicated which items they had experienced (the response options were yes or no) and the importance of each selected item on a 5-point Likert scale (0 indicating not important and 4 indicating very important). In this first phase, on the basis of the responses, we calculated the percentage of patients

who answered yes for each item (range, 0%–100%), the mean importance value attributed to each item identified as a problem (range, 0–4 points), and the overall importance score for the item, defined as the product of the frequency and the mean importance value divided by 100 (range, 0–4). This first phase resulted in a questionnaire in which patients used a 5-point Likert scale (1 indicating not at all to 5 indicating very much) to indicate the extent to which they have been troubled by each problem. Questions and scores were formulated so that higher scores reflected worse HRQoL. We presented the items resulting from the item reduction phase to an additional 15 patients to test the wording of questions and to identify possible patient difficulties.

### *Validation Procedure*

In the validation phase, participants completed the Psychological General Well-Being Index (PGWBI)<sup>13</sup> in addition to the preliminary DrHy-Q. The PGWBI is a brief self-administered questionnaire that contains 22 items rated on a 6-point scale; higher scores indicate better quality of life. Six mood states are evaluated with the PGWBI: anxiety, depressed mood, positive well-being, self-control, general health, and vitality. Each item is scored from 0 to 5 points, leading to a total score between 0 and 110 points, with higher values indicating more positive responses. The PGWBI has been extensively used as an indicator of HRQoL in patients with chronic conditions.<sup>14–16</sup>

The validation phase was aimed to evaluate the following psychometric properties of the DrHy-Q. The acceptability of the DrHy-Q was verified through assessment of the completeness of data and the score distributions. Missing responses were evaluated according to the percentage of patients who had completed responses for all DrHy-Q items; ideally, less than 20% of the items should lack responses. Ceiling and floor effects were calculated from the proportion of patients with the minimal and maximal scores for each item, respectively.

The validity of the DrHy-Q was assessed with 3 different analyses. Factorial analysis (extraction of main components with eigenvalues  $>1$ ) was performed on the DrHy-Q to ascertain whether the factorial structure was congruent with our hypothesis (construct validity); the maximum likelihood factor analysis was adopted. In the absence of a “gold standard” for assessing HRQoL in patients with ADRs, we assessed divergent validity with a generic HRQoL measure by calculating the Spearman correlation coefficient between the DrHy-Q scores and the PGWBI domain scores. Because drug hypersensitivity is a specific health aspect, we did not expect the new questionnaire to be correlated with the generic HRQoL measures. Discriminant validity, the instrument’s ability to differentiate between populations that are known or expected to differ, was evaluated by comparing DrHy-Q scores from patient groups with different allergic reactions; 1-way

analysis of variance was used to test the differences among these independent groups.

The scale homogeneity (internal consistency) was computed using the Cronbach correlation coefficient on the extracted factors. Measures with reliability of 0.50 to 0.70 or greater have been recommended to compare the groups.<sup>17</sup>

The test-retest ability of the DrHy-Q was ascertained to determine whether the questionnaire would provide the same results when used repeatedly in stable conditions. A randomized group of 40 patients were assessed at baseline and after 1 week, in the absence of any clinical or personal significant change. The 2 score sets were analyzed by the *t* test for paired samples.<sup>17</sup>

## RESULTS

### Development Procedure

Seventy patients completed the generation-phase questionnaire of 34 items. Most of these patients (61.4%) were female, and the mean (SD) age was 43.8 (9.5) years, ranging from 21 to 73 years. Clinical manifestations of immediate and nonimmediate hypersensitivity reactions included cutaneous, respiratory, and cardiovascular symptoms. The items that scored higher than an arbitrary cutoff of 1.5 points (14 items) were excluded from the version of the questionnaire carried forward to the pretesting phase; therefore, the items that were retained were the items scoring highest in impact (Table 1). The participants in the pretesting phase (9 women and 6 men; mean [SD] age, 44.8 [8.4] years; age range, 19-68 years)

Table 1. Development Procedure: Results of Item Reduction (70 Patients)

| Item                                                                                                    | Frequency,<br>% | Mean<br>importance | Overall<br>impact |
|---------------------------------------------------------------------------------------------------------|-----------------|--------------------|-------------------|
| I would like the allergist's opinion before taking drugs prescribed by other specialists                | 62.87           | 2.93               | 1.87              |
| I feel different from others                                                                            | 71.42           | 2.51               | 1.79              |
| <b>I feel unluckier from others</b>                                                                     | <b>30.00</b>    | <b>2.44</b>        | <b>0.73</b>       |
| Even a little discomfort for me is a problem                                                            | 74.28           | 2.84               | 2.11              |
| I talk to others about my allergy problem                                                               | 78.57           | 1.94               | 1.52              |
| My job efficiency is affected by the problem of my allergy to drugs                                     | 75.71           | 2.93               | 2.21              |
| <b>I feel helpless</b>                                                                                  | <b>34.28</b>    | <b>1.89</b>        | <b>0.64</b>       |
| <b>I sleep badly</b>                                                                                    | <b>40.00</b>    | <b>1.43</b>        | <b>0.62</b>       |
| <b>I feel embarrassed in relationships with others</b>                                                  | <b>31.43</b>    | <b>2.56</b>        | <b>0.80</b>       |
| Since I am unable to take drugs every illness limits me more than other people                          | 75.71           | 3.44               | 2.60              |
| <b>I have difficulties concentrating</b>                                                                | <b>24.28</b>    | <b>2.12</b>        | <b>0.51</b>       |
| My family is aware of my problem                                                                        | 77.14           | 1.96               | 1.51              |
| <b>My allergy problem interferes with my sexual life</b>                                                | <b>31.42</b>    | <b>1.44</b>        | <b>0.45</b>       |
| I feel anguished due to my problem of allergy reaction                                                  | 62.85           | 2.94               | 1.84              |
| <b>I feel ill</b>                                                                                       | <b>27.14</b>    | <b>3.15</b>        | <b>0.85</b>       |
| <b>I am restricted in my nutrition from fear of substances I might be allergic to</b>                   | <b>18.57</b>    | <b>3.34</b>        | <b>0.62</b>       |
| My partner is conscious of my problem                                                                   | 64.28           | 3.15               | 2.02              |
| I'm afraid of being I am afraid of being administered a drug during an emergency to which I am allergic | 77.14           | 3.21               | 2.48              |
| <b>I feel I can't cope with my allergy problem</b>                                                      | <b>34.28</b>    | <b>2.16</b>        | <b>0.74</b>       |
| For each disease I would be confident that there is a drug that I can safely take                       | 91.42           | 3.42               | 3.13              |
| I am afraid I could not deal with the pain                                                              | 90.00           | 3.18               | 2.86              |
| I feel anxious due to my problem of allergy reaction                                                    | 85.71           | 3.48               | 2.98              |
| <b>My problem influences my relationships with other people</b>                                         | <b>31.14</b>    | <b>3.12</b>        | <b>0.97</b>       |
| I'm in a bad mood due to my problem of allergy reaction                                                 | 72.85           | 3.4                | 2.48              |
| I feel frightened due to my problem of allergy reaction                                                 | 88.57           | 3.28               | 2.90              |
| I worry every time I take a drug different from ones that cause my allergic reactions                   | 81.42           | 3.04               | 2.48              |
| <b>I feel tired during the day because I sleep badly at night</b>                                       | <b>25.71</b>    | <b>2.33</b>        | <b>0.60</b>       |
| I give up leisure activities (sport, vacations, trips) because of my problem                            | 67.14           | 2.45               | 1.64              |
| The idea of taking a medicine makes me feel anxious                                                     | 75.71           | 2.31               | 1.74              |
| My family doctor is aware of my problems                                                                | 68.57           | 3.34               | 2.29              |
| <b>I'm annoyed by frequent medical controls</b>                                                         | <b>27.14</b>    | <b>1.98</b>        | <b>0.53</b>       |
| <b>Due to my allergic problem I am never quiet</b>                                                      | <b>48.57</b>    | <b>2.12</b>        | <b>1.02</b>       |
| The problem of adverse reaction to drugs affects my life                                                | 91.43           | 3.12               | 2.85              |
| <b>I spend too much money for it</b>                                                                    | <b>22.86</b>    | <b>2.14</b>        | <b>0.49</b>       |

Bold type indicates low-importance items (overall impact < 1.5).

Table 2. Demographic and Clinical Characteristics of 365 Participants in the Validation Phase

| Characteristic           | Participants, % |
|--------------------------|-----------------|
| Sex                      |                 |
| Male                     | 32.5            |
| Female                   | 67.5            |
| Education                |                 |
| Primary school           | 4.0             |
| Secondary school         | 18.0            |
| High school              | 41.0            |
| Academic degree          | 28.0            |
| Postgraduate             | 9.0             |
| Type of reaction         |                 |
| Bronchospasm             | 5.9             |
| Edema of the glottis     | 3.4             |
| Urticaria and angioedema | 61.1            |
| Maculopapular reactions  | 12.3            |
| Anaphylactic shock       | 17.3            |

demonstrated ease in understanding all items; therefore, no changes were made, and the questionnaire was carried forward to the validation phase.

### Validation Procedure

Cutaneous reactions, specifically urticaria, angioedema, and macular or maculopapular exanthema, were the most frequently reported reactions (73%) (Table 2). Approximately 17% of patients had experienced an anaphylactic reaction. A smaller percentage of patients had bronchospasm and edema of the glottis.

Of the 365 patients included in the validation process, 33 questionnaires (9.0%) lacked at least 1 response; item 20 ("My partner is conscious of my problem") had the highest proportion of missing responses (5.4%). The items included in the preliminary questionnaire did not exhibit any relevant ceiling or floor effect, with the exception of the items "I am restricted in my nutrition from fear of substances I might be allergic to" and "I'm in a bad mood," which showed a relevant floor effect (36.3% and 34.8%, respectively).

Factor analysis revealed a 1-dimensional structure that explained up to 50.7% of the total variance. On the basis of the eigenvalues, this solution was deemed appropriate.

Table 3. Spearman Correlations Between DrHy-Q Scores and PGWBI Dimensions

| PGWBI dimension     | DrHy-Q score          |
|---------------------|-----------------------|
| Anxiety             | $R = 0.012; P < .001$ |
| Depressed mood      | $R = 0.081; P < .001$ |
| Positive well-being | $R = 0.104; P < .001$ |
| Self-control        | $R = 0.058; P < .001$ |
| General health      | $R = 0.143; P < .001$ |
| Vitality            | $R = 0.002; P < .001$ |

Abbreviations: DrHy-Q, Drug Hypersensitivity Quality of Life Questionnaire; PGWBI, Psychological General Well-Being Index.

Table 4. Drug Hypersensitivity Quality of Life Questionnaire Scores in Patients With Different Allergic Reactions

| Reaction                 | Mean (SD) score |
|--------------------------|-----------------|
| Anaphylactic shock       | 47.17 (11.87)   |
| Bronchospasm             | 41.25 (10.92)   |
| Urticaria and angioedema | 37.68 (12.95)   |
| Maculopapular reactions  | 35.76 (10.34)   |
| Edema of the glottis     | 25.50 (2.89)    |

Five items were excluded because they were not allocated in the extracted dimension: "My family doctor is aware of my problems," "I talk to others about my allergy problem," "My partner is conscious of my problem," "My family is aware of my problem," and "My job efficiency is affected by my problem of allergy to drugs." The correlations between the DrHy-Q and the PGWBI scores were low (Table 3). DrHy-Q scores (Table 4) from patients who experienced anaphylactic shock were significantly higher than patients with other reactions (analysis of variance,  $F = 5.991$ ;  $df = 4$ ;  $P < .001$ ), indicating that the DrHy-Q was able to distinguish patients with reactions of different severity. In addition, the internal consistency reliability for the extracted factor exceeded the minimum reliability stan-

Table 5. Cronbach  $\alpha$  Correlation Coefficient on Factorial Score

| Item                                                                                     | $\alpha$ coefficient if the item is excluded |
|------------------------------------------------------------------------------------------|----------------------------------------------|
| I would like the allergist's opinion before taking drugs prescribed by other specialists | 0.566                                        |
| I feel different from others                                                             | 0.709                                        |
| Even a little discomfort for me is a problem                                             | 0.816                                        |
| Since I am unable to take drugs every illness limits me more than other people           | 0.685                                        |
| I feel anguished due to my problem of allergy reaction                                   | 0.782                                        |
| I am afraid of being administered a drug during an emergency to which I am allergic      | 0.682                                        |
| For each disease I would be confident that there is a drug that I can safely assume      | 0.599                                        |
| I am afraid I could not deal with the pain                                               | 0.659                                        |
| I feel anxious due to my problem of allergy reaction                                     | 0.804                                        |
| I'm in a bad mood due to my problem of allergy reaction                                  | 0.714                                        |
| I feel frightened due to my problem of allergy reaction                                  | 0.790                                        |
| I worry every time I take a drug different from ones that cause my allergic reactions    | 0.783                                        |
| I give up leisure activities (sport, vacations, trips) because of my problem             | 0.558                                        |
| The idea to take a medicine makes me feel anxious                                        | 0.599                                        |
| The problem of adverse reaction to drugs affects my life                                 | 0.842                                        |

dard of 0.50 to 0.70 recommended for group comparison (Table 5), with a Cronbach  $\alpha$  of 0.928.

Finally, the preliminary DrHy-Q was completed twice by 40 participants (26 women and 14 men) with a mean (SD) age of 41 (14.6) years. The test-retest associations for the preliminary DrHy-Q were good ( $R = 0.995$ ;  $P < .001$ ).

## DISCUSSION

HRQoL has become an important outcome measure in allergic diseases, and many specific questionnaires are available to evaluate the impact of allergy.<sup>4</sup> HRQoL is also a crucial outcome in drug hypersensitivity because this kind of allergic reaction potentially affects the patient's experience in terms of fear, anxiety, thoughts, and expectations. Oude Elberink<sup>18</sup> highlights the paradox of a disease, such as drug hypersensitivity, in which patients infrequently experience symptoms but report HRQoL problems because of the continuous vigilance required to prevent unintentional exposure. The impact of drug hypersensitivity has never been studied from the patient's perspective, and no questionnaire has been made available. For these reasons, we developed and validated a specific HRQoL questionnaire that takes into account the recent suggestions of a position paper addressing to patient-reported outcomes in allergy.<sup>19</sup>

This study used a 15-item tool, the DrHy-Q, that is simple, is easy to administer, and requires a few minutes to complete without any assistance. Patients reported appreciation after responding to the questionnaire because it was useful in detecting and monitoring patient perspectives on their allergies. The statistical analyses provided evidence that our questionnaire met the standards for good construct validity, internal consistency, and reliability. The low correlations with PGWBI (Table 3) suggested that the DrHy-Q was able to capture specific aspects of patient experiences that are barely detectable with generic tools.

In the generation phase of the development procedure, we incorporated information from both patients and experts in drug hypersensitivity management to create a large list of possible questionnaire items. The extensive subsequent development and validation steps followed a widely used method. The large sample size (485 patients) is another strength of the current study. However, our study design did not allow us to explore the sensitivity of DrHy-Q to changes after interventions (eg, causal diagnosis and desensitization), the potential difference between drugs or pharmacological classes in affecting HRQoL, or the role of clinical data (potential differences among patients who experienced only 1 hypersensitivity reaction vs those with recurrent reactions). Moreover, because longitudinal data were not used, we were unable to calculate the minimal important difference. Finally, we were unable to assess DrHy-Q use in patient subgroups known to possess characteristics that may influence HRQoL, such as psychiatric comorbidity.

Validation is an iterative process, and this study constitutes the first phase in that process. Further work is planned to examine responsiveness in a clinical trial population and to explore the relationship of the DrHy-Q to other clinical factors (such as responsible drug and number of allergic reactions) and psychological factors (such as mood states). The DrHy-Q is a tool that can be used alone or in combination with other patient-reported outcome questionnaires to explore the subjective experience of patients with drug hypersensitivity.

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