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Assessment of validity and reliability of Drug Hypersensitivity Quality of Life Questionnaire: The Dutch experience

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Key words

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Summary

Drug Hypersensitivity Quality of Life Questionnaire (DrHy-Q) is the first questionnaire that captures health related quality of life impact in patients with drug hypersensitivity. The aim of this study was to translate and validate the original Italian 15-item DrHy-Q for use among Dutch-speaking residents. We also compared the DrHy-Q scores obtained across countries.

In a prospective cohort study, the Dutch DrHy-Q was completed by 124 patients (65.3% female, age 56.8 ± 14.0) with a confirmed drug hypersensitivity. Median DrHy-Q score was 12 [0-88]. Validity and reliability of the DrHy-Q was confirmed through, 1, confirmatory factor analysis; 2, concurrent validity with a generic health related quality of life questionnaire (RAND-36); 3, internal consistency; and 4, test-retest reliability. A country specific difference in scores was observed.

Introduction

Drug hypersensitivity reactions (DHRs) are the adverse effects of drugs taken at a dose which is tolerated by normal subjects, and which clinically resemble allergy (1). DHRs represent one third of adverse drug reactions and concern more than 7% of the general population (1). Moreover, DHRs are responsible for significant morbidity and possible socioeconomic costs (2). As Health Related Quality of Life (HRQoL) has become an important outcome measure in the treatment of allergic diseases (3,4), the evaluation of HRQoL in patients with drug hypersensitivity is still a widely neglected topic. Even though almost every doctor has encountered a patient presenting with drug hypersensitivity reaction, not many physicians recognize the potential quality of life impact in patients experiencing such reaction as they often appear unexpectedly (2). One of the few studies on the psychometric profiles of patients with DHRs found that patients with drug hypersensitivity had more somatization, reduced HRQoL and more anxiety compared to the general population (5). According to the author standardized questionnaires could help to discover patients who may need psychological support (5).

In 2011, the first standardized, psychometrically robust questionnaire was developed by an Italian group to measure HRQoL impact in patients with drug hypersensitivity, independent of the responsible drug (6). The Drug Hypersensitivity Quality of Life Questionnaire (DrHy-Q) was initially derived from a 34-item pool and scaled down to a 15-item questionnaire and has subsequently been validated for the Italian, Turkish and Spanish population (6-8). Since its first publication, the DrHy-Q has shown to be an appropriate tool for quality-of-life research in patients with drug hypersensitivity and is able to discriminate between number of implicated drugs causing DHRs and severity of DHRs (6,7). In the Turkish population, DrHy-Q was also

able to capture improvement of HRQoL in patients with DHR after diagnostic intervention, and provocation test for finding safe alternative drug or desensitization with culprit drug (7). Furthermore, the DrHy-Q was used to explore HRQoL in patients who experienced an anaphylactic drug reaction in an Italian study and recognized significant HRQoL impairment (9). In the Dutch setting, the DrHy-Q has not been validated yet. Also, an overview of the HRQoL in patients with DHRs across countries has not been established until now.

In this study, we translated the DrHy-Q into Dutch and performed a cross-cultural linguistic adaptation and validation to provide a clinimetrically valid tool for assessing HRQoL in patients with drug hypersensitivity in the Netherlands. We also compared the DrHy-Q scores obtained across countries to investigate cross-cultural differences in HRQoL impact of DHRs.

Methods

Validation of the DrHy-Q followed a two-step procedure:

First: Translation and Pilot Testing of DrHy-Q

The DrHy-Q is composed of 15 questions and standardized response choices arranged in a five-point Likert scale (ea. 1 'not at all' to 5 'very much') (6). The original Italian version of the DrHy-Q (6) was translated into Dutch using a 3-stepwise protocol (10):

1. Forward translation by two professional translators; followed by a reconciliation of the differences between the two forward translations in consultation with the investigators, resulting in a single, provisional Dutch translation. 2. Backward translation by one professional translator with no access to the original Italian version. Added ratings of the backward translation by the original developer of the questionnaire (6), in terms of clarity, common language usage, and conceptual equivalence and subsequent reconciliation of problematic items. 3. Pilot testing (n = 10) of the Dutch version of the DrHy-Q in terms of acceptance and comprehension of the questionnaire content and wording.

Second: Field testing, Population and Validation Procedure

Design. A cross-sectional observational study was performed to determine validity and reliability of the DrHy-Q in adult patients with drug hypersensitivity. The DrHy-Q was mailed to all eligible patients (for selection of patients, see below) to be completed at home. Non-respondents received a reminder letter 3 weeks after the initial mailing. All patients who completed the first questionnaire received a second questionnaire within 10 - 14 days for re-test analysis.

Population. All patients aged 18 years and older during study inclusion, who visited the Department of Allergology at the University Medical Center Utrecht, the Netherlands, between January 2007 to November 2015 with confirmed drug hypersensitivity (n = 229) and no ongoing diagnostic involvement, were invited to participate. The diagnostic protocol for ADRs was in accordance with the standard operating procedures recommended by the European Network for Drug Allergy (11). A signed informed consent for medical record release was obtained from participating patients. Data concerning patient's age, gender, concomitant allergic diseases, implicated drugs, symptoms of drug reaction and type of reaction according to the Coombs and Gell classification (12), were collected from patient's medical files. The local Medical Ethics Review Commission confirmed that approval is not necessary (METC protocol nr. 15/729).

Validation procedures. The COSMIN checklist (13) was used to ascertain the methodological quality of the validation procedure and comprised two parts: construct validity and reliability. Construct validity was subdivided in structural validity, convergent validity and discriminant ability. Structural validity was assessed with confirmatory factor analysis (14). Convergent validity of the DrHy-Q was explored by administering the Dutch version of the generic HRQoL questionnaire RAND-36 (15) simultaneously. This health profile measure (16) consists of 36 items divided into nine scales, measuring functional status and well-being: physical functioning, social functioning, role functioning-physical, role functioning-emotional, mental health, vitality, bodily pain, general health and change in health (single item). The scale scores are presented in a 0 - 100-point with a higher score indicating a better HRQoL. The discriminative ability of the DrHy-Q was examined by dividing the study population into number of implicated drug hypersensitivities and severity of DHRs. The reliability of DrHy-Q was investigated by internal consistency (17) and test-retest reliability (18).

Cross-cultural differences in DrHy-Q scores

The total DrHy-Q score of the study populations in Italy (6) and Turkey (7) were compared with our Dutch DrHy-Q scores. The characteristics of implicated study participants were retrieved from the articles and unpublished data were retrieved by correspondence with the study authors.

Analyses

The DrHy-Q scores were converted to a 0 to 100 scale (formula: DrHy-Q = (Σ [items] - 15 / [75 -15]*100), with a higher score indicating a poor disease-specific HRQoL. Missing values were imputed by single imputation using the expectation maximization algorithm (19). Structural validity was assessed by first-order confirmatory factor analyses for categorical data with chi-square goodness-of-fit test and the RMSEA descrip-

tive model fit statistic. Goodness-of-fit cutoff criteria were interpreted as follows: Comparative Fit Index (CFI) > 0.95 suggests good fit, Tucker-Lewis Index (TLI) > 0.095 suggest good fit and root mean square error of approximation (RMSEA) < 0.08 reasonable fit (14). Convergent validity was assessed by calculating Spearman's correlation coefficients between the total score of DrHy-Q and the RAND-36 domains. A weak to moderate negative correlation (-0.20 - 0.40) between DrHy-Q and the generic RAND-36 scales was hypothesized given the specific drug-related nature of the DrHy-Q. The discriminative ability of the DrHy-Q related to number of implicated drug hypersensitivities and severity of DHR were explored using the Mann-Whitney test. The internal consistency was measured by calculating Cronbach's alfa, with a value of ≥ 0.70 indicating adequate inter-relatedness of items (20). The test-retest reliability was assessed by calculating the intra-class correlation coefficient (ICC). ICC values were interpreted as follows: > 0.75 was excellent, 0.40-0.75 was fair to good and < 0.40 was poor (21). Descriptive statistics were used to display cross-country population differences in which DrHy-Q scores were obtained.

A $p \leq 0.05$ was considered statistically significant. Statistical analyses were performed using SPSS 23 for Windows 8.1 (SPSS Inc., Chicago, IL, USA), with the exception of confirmatory factor analyses using Mplus Base Program 6.12 for Windows 8.1 (Muthen & Muthen, Los Angeles, CA, USA).

Table 1 *- DrHy-Q scores in respondents with different clinical characteristics of DHR (n = 124).*

Implicated drugs	**n (%)**	**median (minimum - maximum)**
Antibiotics	62 (50.0)	13.3 (0 - 56.7)
Non-steroidal anti-inflammatory drugs	14 (11.3)	15.0 (1.7 - 88.3)
Peri-operative medication[2]	19 (15.3)	10.0 (0 - 68.3)
Steroids	10 (8.1)	11.7 (3.3 - 56.7)
Proton pump inhibitors	5 (4.0)	10.0 (5 - 48.3)
Others[2]	20 (16.1)	10.8 (0 - 83.3)
Number of implicated drugs		
1	81 (65.3)	8.3 (0 - 88.3)[1]
≥ 2	43 (26.7)	18.3 (0 - 83.3)
Type of hypersensitivity reaction		
Type I (immediate-type)	89 (71.8)	11.7 (0 - 88.3)
Type IV (delayed-type)	35 (28.2)	11.7 (0 - 76.7)
Type of symptoms of the drug hypersensitivity reaction[3]		
Skin symptoms	93 (78.8)	11.7 (0 - 88.3)
Angio edema	46 (39.0)	10.0 (0 - 76.7)
Gastrointestinal symptoms	21 (17.8)	17.7 (3.3 - 83.3)
Respiratory symptoms	35 (29.7)	10.0 (0 - 88.3)
Cardiovascular symptoms	42 (35.6)	13.3 (0 - 88.3)

DrHy-Q: Drug Hypersensitivity Quality of Life Questionnaire; DHR: Drug hypersensitivity reaction; n: Number

[1]Mann-Witney U test, significant difference between medians, p = 0.001.

[2]Peri-operative medication: muscle relaxants, patent blue, chlorhexidine, morphine, remifentanyl; Other drugs: radiocontrast media, vaccins, plasma expanders, local anesthetics, anticoagulants, acetominophen, anti-epileptics, triptans, drug additives.

[3]Symptoms of skin: urticaria, pruritis, maculae/papulae, blisters, pustels; Cardiovascular symptoms: drop in blood pressure, shock, anaphylaxis.

Results

Translation

The Dutch DrHy-Q was pilot tested in a sample of 8 patients with DHR visiting the Allergology department for diagnostics, equally representing men and women aged between 21 and 82 years. No unambiguity was reported in terms of acceptance or comprehension of the questionnaire content and wording. This version required no further modifications, and was used in subsequent field testing. The final version of the DrHy-Q is depicted in the appendix.

Field test: study population

A total of 229 patients were identified of whom 217 were eligible for participation. All eligible patients were invited to participate in the study of whom 124 (57%) completed the questionnaire. 65.3% of the respondents were female, with a mean age of 56.8 ± 14.0 years, range [18 - 86]. No dissimilarities in gender were detected between responders and non-responders. Non-Responders, however were significantly younger (49.9 ± 16.0) compared to responders ($p < 0.001$). Detailed clinical characteristics of respondents with the affiliated DrHy-Q scores are depicted in **table 1**.

DrHy-Q scores

The DrHy-Q score in our study population was median 11.7 (min - max: 0 - 88.3). The DrHy-Q scores obtained in the Italian and Turkish populations were: median 36.0 (0 - 73.0) and 32.5 (2.6 - 56.2), respectively. Overview of the demographic and drug hypersensitivity characteristics of the three study populations are clearly depicted in **table 3**.

Outcome validation variables

The rates of missing values for the individual items of the DrHy-Q were consistently low, ranging from 0% to 1.6%, and occurred missing at random. The construct validity was good: CFI 0.992, TLI 0.991 and RMSEA 0.064. The correlation between the DrHy-Q total scores and the RAND-36 domain scores was moderate as expected (**table 2**), representing acceptable divergent validity. The discriminant ability of the DrHy-Q was confirmed for patients with one *vs.* two or more drug hypersensitivities (median, [min-max]: 8.33, [0 - 88.3] vs. 18.33, [0 - 83.3], $p = 0.001$), indicating more impairment in HRQoL in patients with two or more hypersensitivities. No significant differences were detected between severity of HDR symptoms, implicated drug or reaction type (**table 2**). The internal consistency was high, with a Cronbach's alfa of 0.944. The test-retest was assessed in 91 responders (65.9% female, mean age 57.5 ± 13.9 years). The ICC for test-retest reliability was 0.950 ($p = 0.0001$), indicating excellent reliability.

Table 2 - *Convergent validity - Spearman's correlation between the DrHy-Q with the RAND-36 domains.*

		P-value
Physical functioning	-0.26	0.005
Social functioning	-0.36	< 0.001
Role functioning-physical	-0.37	< 0.001
Role functioning-emotional	-0.36	< 0.001
Mental health	-0.39	< 0.001
Vitality	-0.40	< 0.001
Bodily pain	-0.36	< 0.001
General health	-0.35	< 0.001
Change in health	-0.20	0.029

Spearsman's rho test, significant at $p < 0.05$

Discussion

In this study, we have showed that the Dutch DrHy-Q is a valid and reliable tool for assessing quality of life in patients with drug hypersensitivity.

Our findings are in line with previous validation passages of the questionnaire for the Italian and Turkish populations in terms of validation outcomes (6,7). The Dutch DrHy-Q proved the 1-dimensional structure of the original Italian questionnaire, as previously confirmed by the Turkish DrHy-Q (7). The low negative correlations with the RAND-36 domains suggest that the Dutch DrHy-Q is able to capture specific aspects of patient experiences that are barely detectable with a generic tool. This is also in concordance with the findings of the Italian (6) and Turkish (7) DrHy-Q, since both versions showed correlation with the Psychological General Wellbeing Index domains (22), a similar generic HRQoL tool, varying between [min - max] rho 0.002 - 0.143 ($p = 0.001$) and rho = -0.254 - -0.378, respectively ($p = 0.001$).

The Dutch DrHy-Q was able to discriminate between patients with one or more than one implicated drug hypersensitivity reaction. In the Turkish study, a discriminative ability with respect to the presence of respiratory symptoms was also observed (7), but is not confirmed in our study. The discriminative ability between severity of reactions (anaphylactic shock *vs.* other reactions) reported in the Italian validation (6), could also not be seen in our study. A recent additional Italian study (n = 65) showed signifi-

Table 3 - Study population characteristics and DrHy-Q scores obtained in across countries.

	The Netherlands	**Italy**	**Turkey**
Number of patients	124	365	711
DrHy-Q score, *median (min - max)*	12 (0 - 88)	36 (0 - 73)	33 (3 - 56)
Age in years, *median (min - max)*	58 (19 - 87)	46 (18-79)	42 (18 - 78)
Gender, female %	65.3	67.5	73.6
Education, %			
Primary school	4.1	4.0	33.1
High school	64.5	59.0	38.8
University	31.4	37.0	28.1
Concomitant comorbid disease, %	65.3	41	36.5
Number of implicated drug, %			
1	65.3	67.2	44.3
≥ 2	26.7	32.8	53.0
Implicated drugs, %			
Antibiotics	50.0	53.2	38.7
Non-steroidal anti-inflammatory drugs	11.3	21.8	65.9
Others	39.5	25	-
Type of symptoms of the drug hypersensitivity reaction, %			
Skin / Angioedema	86.3	73.4	75.0
Respiratory / Cardiovascular	48.4	26.6	46.4

DrHy-Q: Drug Hypersensitivity Quality of Life Questionnaire; n: Number

cant higher DrHy-Q scores (mean 62.8 ± 12.1) in patients with drug induced anaphylactic shock, strongly implicating the influence of severity of reaction on HRQoL (9). Possibly, the smaller sample size in our study explains why a discriminative ability with respect to severity of the reaction could not be observed with the Dutch DrHy-Q. Also a 42.9% drop-out rate in enrolling patients, including 8.9% returning a blanc questionnaire, has to be taken into account. Yet, this percentage of drop-outs is considered as expected in mail based questionnaires (23).

In this study we also observed a country specific difference in total DrHy-Q scores. We found a considerably lower median DrHy-Q score in our population compared to the Italian and Turkish populations, with scores of 36 and 32.5, respectively (6,7). This observed difference in DrHy-Q values could be attributed by several contributing factors. First, the investigated populations showed several differences leading to lower comparability. Participants of our study had completed their diagnostic work-up and counseling before study inclusion compared to the possible heterogeneous group in the other countries. Since it is shown that the DrHy score is sensitive to diagnostic interventions (pre-intervention score 33 vs. post-intervention score 29; p = 0.008) in the Turkish population (7), this could explain the lower DrHy-Q value to some extent. Furthermore, participants of this study were of higher age compared to those in the other populations and had more comorbid diseases, both variables which are known to influence generic HRQoL tools (15). Within our study, only the impact of comorbid disease on DrHy-Q was observed.

Differences in drug consumption between countries also might cause the difference in DrHy-Q scores and is illustrated by the antibiotic Defined Daily Dose (DDD) consumption between the three countries. As antibiotics account for the majority of drug hypersensitivities (2) the antibiotic Defined Daily Dose (DDD) consumption between the three countries was compared. Recent reports showed an antibiotic use of 9.4 DDD per 1000 inhabitants per day in the Netherlands versus 13.9 - 16.7 DDD per 1000 inhabitants per day in Italy and 42.3 DDD per 1000 inhabitants per day in Turkey in the past several years (24,25). This higher intention of drug consumption might increase the perception of impairment in patients with (antibiotic) drug hypersensitivities and thus differences in DrHy-Q scores. Finally, also social and cultural differences could influence HRQoL perception and

could explain a lower DrHy-Q score. This assumption is already established in different validated HRQoL questionnaires for use in allergic diseases, such as asthma (26) and food allergy (27), in which Dutch participants show a favorable health perception compared to other populations.

Our study has some limitations. The small sample size and tertiary setting compromises the value of this dataset for establishing DrHy-Q norm scores for the general Dutch population and for different age and gender strata. The frequency of patients diagnosed with a NSAID drug hypersensitivity was low in this study population compared previously published analyzed population. Since many patients have been referred by other departments from our tertiary university hospital, reference bias could explain the relative low frequency of NSAID hypersensitivities compared to particularly antibiotic hypersensitivities. Ethnic differences in the population were not assessed, as well as the responsiveness of the Dutch DrHy-Q in diagnostic interventions. Both topics are of interest for further research. For future studies, a multi-center design and larger sample sizes in comparable population are needed to investigate cross country comparability. In addition, further studies are needed to explain country specific differences in drug hypersensitivity related quality of life as this study only described a qualitative analysis since statistical comparison was not possible. In conclusion, the Dutch version of the DrHy-Q has shown to be a practical, reliable, and valid instrument for evaluation of drug hypersensitivity related quality of life in the Netherlands.

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