

Quality of life in patients with urticaria and angioedema: Assessing burden of disease

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ABSTRACT

Patients with urticaria and/or angioedema have several reasons to have a poor quality of life (QoL). The intensity of pruritus and density of involvement compromise a patient's lifestyle as well as aggravate stressors that affect physical and psychiatric conditions. The burden of illness is significant in not only costs for emergent practitioner visits, but, often, unnecessary laboratory testing and medication expenses. Questionnaires that assess a patient's QoL serve to document benefit to therapies. Objectively documenting changes that are important to patients with urticaria and/or angioedema allows the patients and clinician to accurately assess effectiveness of therapies over long periods of time. Specific surveys that address urticaria (CU-Q2oL and UAS) and angioedema (AE-QoL questionnaire) allow simplified and sensitive assessments for patients with the corresponding condition. Common components of appropriate surveys assess not only intensity of pruritus and wheals but also impact on sleep, interpersonal relationships, and appearances. In considering the most important aspects of several surveys, an example of a survey is provided that focuses on the patient's perception of how their urticaria and/or angioedema impacts their QoL.

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Since the last publication on quality of life (QoL) in patients with urticaria by the author,¹ several surveys have been published that specifically address issues that are relevant for patients with urticaria and/or angioedema. For the purpose of this article, information found in that article will not be rehashed. Health-related QoL (HRQoL) measurements have taken subjective impressions of medical conditions and converted them to data that assist in decisions on the management of patients. Because of the prevalence of immunologic conditions such as allergic rhinitis and conjunctivitis, asthma, and dermatologic conditions, the use of HRQoL surveys have proven useful in assessing effectiveness of pharmaceuticals as well as therapies for patients. Over the past 10 years, specific surveys assessing dermatologic conditions of urticaria and angioedema have been developed to focus on unique aspects of these conditions. Using these surveys, patients with chronic urticaria have been shown to have their QoL more severely affected than those with rhinitis and asthma.² In evaluating patients with HRQoL, surveys are either generic (e.g., Medical Outcomes Survey Short Form 36 and Medical Outcomes Survey Short Form 12) or specific (e.g., Rhinoconjunctivitis Quality of Life Questionnaire, Dermatology Life Quality Index [DLQI], and

Skindex 29 or Skindex 16).³ In urticaria and angioedema, disease and skin specific instruments afford greater sensitivity to change over time (e.g., Chronic Urticaria and QoL [CU-Q2oL] questionnaire, Urticaria Activity Score [UAS], and Angioedema QoL [AE-QoL] questionnaire).

IMPORTANT ASPECTS OF HRQoL QUESTIONNAIRES

To adequately assess unique aspects of specific medical conditions, surveys should contain certain psychometric characteristics. These include viability (easy to understand and reasonable length that can be completed in a defined session), validity (exact measurements with the capacity to discriminate variables specific to symptom scores), reliability (reproducible), and sensitive to changes (especially to treatments).³

In clinical practice, simplicity of administration and completion of a questionnaire, enhanced by reproducibility and sensitivity to changes, are necessary for a useful survey that can enhance a clinician's ability to assess benefit of a medication or procedure in the treatment of their patient. An example of such a simple questionnaire is the Asthma Control Test, which assesses changes in symptom scores over a defined period of time.

SELECTION OF A SURVEY IN ASSESSING PATIENT'S QoL

Several tools are available for assessing the burden of skin disease to a patient. However, in most instances, differences in content of the survey may not allow for all considerations of the clinician's interest. For in-

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Table 1 Comparison of items contained in DLQI and CU-Q2oL

Item	Question Found In	Importance	Overall Impact
Itch, sore, pain	DLQI, CU-Q2oL	3.61	3.46
Felt embarrassed	DLQI, CU-Q2oL	2.73	2.29
Interfered with shopping	DLQI		
Influenced choice of clothing	DLQI, CU-Q2oL	2.97	1.52
Affected social leisure	DLQI, CU-Q2oL	0.59	1.74
Difficulty with sports	DLQI, CU-Q2oL	3.06	1.77
Difficulty with work or study	DLQI, CU-Q2oL	2.73	1.9
Problems with partner	DLQI		
Created sexual difficulties	DLQI		
Treatment caused problems at home	DLQI, CU-Q2oL	2.19	1.55
Eyes swelling	CU-Q2oL	2.84	2.23
Interferes with sleep	CU-Q2oL	2.98	2.12
Feel nervous	CU-Q2oL	2.95	2.25
Wheals	CU-Q2oL	2.62	2.37
Lips swelling	CU-Q2oL	3.15	1.95
Interferes with eating	CU-Q2oL	3.01	2.1

Source: Refs. 7 and 8.

DLQI = Dermatology Life Quality Index; CU-Q2oL = Chronic Urticaria and Quality of Life questionnaire.

stance, the Short Form (36) Health Survey (SF-36) encompasses excellent psychometric assessment for most medical conditions but lacks specificity in addressing unique aspects of dermatological conditions.

The DLQI, developed in 1994 by Finlay and Kahn, assesses an individual's disability of the following domains: daily activities, leisure, work and school, symptoms and feelings, interpersonal relationships, and the effects of treatment on daily symptoms. Measured over the impressions by the patient of the previous week, it assesses the intensity of each domain using a linear scale of a score of 0 (not at all) to 3 (very much impact). The higher the score, the greater the disability.⁴ It can be completed in 5 minutes. However, the use of the DLQI lacks consideration of emotional or mental health aspects, lack of consideration of itch-scratch problems, and the patient's perceived social stigmatization limits its use.⁵

The Skindex-29, developed by Chen *et al.* in 1997, attempts to reduce the burden of respondents. It assesses across symptoms (10 questions), emotions (7 items), and functions (12 items). Like the DLQI, it can be completed in a reasonable amount of time by patients. Several variations of this survey exist, depending on the intent and whether the level of bother is considered (Skindex-16) or psychosocial and symptoms (Skindex-17).⁵

In addressing urticaria and/or angioedema specifically, other survey instruments should be considered. The DLQI may not be accurate in reflecting the burden of a patient's illness across a wide spectrum of fluctuations in their symptom scores.⁶ For that reason, other surveys have been developed.

The CU-Q2oL Survey was revised from an original 37-item survey to 23 items (CU-Q2oL) of most significance with answers on a 5-point Likert scale (1, not at all, to 5, very much). Like the aforementioned surveys, it takes 5 minutes to complete. It is useful in evaluating the burden of chronic urticaria and HRQL and to detect changes induced by treatment. Table 1 outlines several items found between the DLQI and CU-Q2oL. Based on an assessment of importance to the patient found in Baiardini's article,⁸ an assessment of the overall impact in a patient's QoL with urticaria can be considered. Subjects' assessments of importance of an item correlated well with that item's impact on their QoL. Note that several physical signs such as swelling of eyes and lips, wheals, interference with sleep, and eating were considered in the CU-Q2oL but not in DLQI because the latter was not specific for urticaria. Likewise, social interactions and interpersonal relationships (*e.g.*, sex and partner relations) received less impact for patients with urticaria compared with other dermatologic conditions where shopping and clothes selection may be important (*e.g.*, psoriasis).

A separate QoL survey for angioedema (AE-QoL Questionnaire) has recently been defined.⁹ Although urticaria patients with angioedema were included in the analysis, the majority of patients enrolled had angioedema alone—either from hereditary angioedema or angioedema without urticaria. Based on item impact analysis, 17 items were included in the final survey (Table 2). As with CU-Q2oL survey, the importance of limitations in choosing clothing, sporting activities, or preference for being alone were not selected by subjects with angioedema as having much impact on their

Table 2 Comparisons of CU-Q2oL and AE-QoL

Item	Found In	Cronbach's Coefficient
Impairment with work	CU-Q2oL	0.828
	AE-QoL	0.896
Impairment with physical activities	CU-Q2oL	0.794
	AE-QoL	0.896
Impairment with social relationships	CU-Q2oL	0.832
	AE-QoL	0.896
Impairment with spare time	CU-Q2oL	0.780
	AE-QoL	0.896
Difficulties in falling asleep	CU-Q2oL	0.795
	AE-QoL	0.870
Awakening in the night	CU-Q2oL	0.764
	AE-QoL	0.870
Feeling tired due to sleep disturbance	CU-Q2oL	0.808
	AE-QoL	0.870
Difficulties concentrating	CU-Q2oL	0.684
	AE-QoL	0.870
Embarrassed due to symptoms	CU-Q2oL	0.744
	AE-QoL	0.825
Embarrassed to go into public places	CU-Q2oL	0.772
	AE-QoL	0.825
Troubled by drug side effects	CU-Q2oL	0.732
	AE-QoL	0.825
Limitations in eating	CU-Q2oL	0.514
	AE-QoL	0.851

Source: Adapted from Refs. 8 and 9.

Common items found in both surveys.

CU-Q2oL = Chronic Urticaria and Quality of Life questionnaire; AE-QoL = angioedema quality of life.

QoL. Those items that did were grouped according to specific domains (*e.g.*, functioning, fatigue/mood, fears/shame, and food). Comparisons between the urticaria and AE-QoL surveys are noted in Table 2.

In assessing internal consistency, surveys use analysis of Cronbach's correlation coefficient. Coefficients <0.6 are undesirable, 0.65–0.7 are minimally acceptable, 0.7–0.8 are respectable, 0.8–0.9 are excellent, and >0.9 are excessive consistency.¹⁰ Examples of correlation coefficients for CU-Q2oL and AE-QoL are found in Table 2. Within each survey, domains were defined by items that best correlated with them. Differences between CU-Q2oL and AE-QoL were found in higher correlation coefficients for pruritus and swelling in CU-Q2oL (not defined specifically in AE-QoL survey, although the latter defined the effect that swelling had on fears and shame domain).

When both surveys were used in conjunction with SF-36, correlation using Pearson correlation coefficient (*r*) to evaluate convergent validity showed significant (between $p < 0.01$ and $p < 0.001$) correlations for most

domains. The exception in correlation occurred with the "food" domain of AE-QoL (measuring limitations in selection of and eating foods) and the "looks" domain of the CU-Q2oL (which assessed embarrassment, use of cosmetics, and choosing clothes).^{8,9}

The usefulness of having a specific QoL questionnaire affords the opportunity to assess, from a patient's perspective, the impact of their disease on them over time. Such questionnaires are brief and easily completed (within 5 minutes) to aide in the management of patients. Comparisons of treatments can also use these questionnaires to tailor benefit from what the patient desires. However, although assessment of public embarrassment played a pivotal role in these surveys, out-of-pocket expenses were relatively ignored. Whether governmental support for health insurance (in Europe) may have reduced the impact in the countries where the surveys were developed remains to be considered. In one study, the financial impact of patients with chronic spontaneous urticaria was estimated to be >\$2000 per year—mostly from four direct (*e.g.*, medication, laboratory costs, and out-patient or emergency room visits) and two indirect health care costs (travel and lost wages due to time off for evaluations).¹¹ In assessing the economic impact for countries based on point prevalence of chronic spontaneous urticaria of 0.5–1%, based on the previous studies, total annual costs for chronic urticaria in the United States alone would range from \$2.5 to 5 billion and in Europe, between 5 and 10 billion Euros.¹²

In a study between subjects in Australia and Sri Lanka, similar questions were posed as found in the CU-Q2oL.¹³ Differences between patient populations revealed that those sampled in Sri Lanka perceived greater effect of chronic urticaria on their home or work activities, affecting mood, and put limits on selection of food, whereas Australians felt more fatigue because of poor sleeping affected by urticaria. In this study, patients who were >40 years old and had their urticaria for >1 year had trends toward worse perception of their urticaria for most of the questions posed in the modified CU-Q2oL survey.

In a separate Brazilian study, which used only SF-36 and DLQI, information was obtained that although women are more likely affected by urticaria, in the DLQI survey, only leisure domain (*e.g.*, effects on shopping, choice of clothing, or activities at home) was significantly different.¹⁴ Women also scored worse on the SF-36 for vitality, role emotional and mental health domains compared with men. Patients with a better education level were more affected in daily activities and leisure domains as well as overall score of the DLQI and worse on the social functioning of the SF-36. In contrast to the Australian study¹¹ using a modified CU-Q2oL survey, this Brazilian study defined that newer patients (those having urticaria for <1 year) had

Table 3 UAS (the cumulative total over 7 days is UAS7)

Score	Number	Duration	Size of Hives	Angioedema	Intensity of Pruritus
0	0	None	None	None	None
1	<10	<1 hr	<1 cm	1/day	Mild
2	10–50	1–3 hr	1–3 cm	2–3/day	Moderate
3	>50	>3 hr	>3 cm	>3/day	Severe

Source: Adapted from Ref. 16.

UAS = Urticaria Activity Score.

a poorer QoL with significant effects seen in leisure, personal relationships, and overall score for the DLQI survey and social functioning for the SF-36.

In another study from Brazil, a modified DLQI with 10 questions and scored from 0 (not at all) to 3 (very much), patients were affected mostly by skin inflammation and embarrassment, with interference in activities such as home, work, or study. Interference with interpersonal relationships, sports, or sex was not a significant problem for most patients. In this study, patients with angioedema and urticaria had worse QoL compared with those who had urticaria alone.¹⁵

CLINICAL SCORING SYSTEMS

Another method for defining a patient's QoL involves the use of the UAS (or UAS obtained over 7 days [UAS7]).¹⁶ Developed to assess disease activity, it is an accurate method of defining frequent changes in urticaria with or without angioedema over a brief period of time. Assessments of urticaria number, size, pruritus, duration, and presence of angioedema are assessed on a daily basis. The details of UAS are shown in Table 3.

To validate UAS7 as a QoL measurement, the survey was compared with DLQI domains in the same patients. In patients who were compliant in maintaining their data entry, correlation with DLQI total score was achieved. In noncompliant patients, the score for the number of erythemas varied but the remainder of sampling scores correlated well with the DLQI. The authors concluded that the UAS best reflected a patient's QoL when averaged over 4 consecutive days or summed after 7 days.¹⁶

USING THE SURVEYS

Examples of studies that use QoL surveys to define differences are mostly pharmaceutical based. One study evaluated any differences in QoL measurements with results comparing autologous plasma skin test (ASST) and autologous plasma skin test intradermal testing in patients with chronic autoimmune urticaria.¹⁷ Disease activity was assessed by UAS7, and QoL impairment was assessed by DLQI and CU-Q2oL. There were no significant differences between ASST (+

or –) and autologous plasma skin test (+ or –) in regard to disease duration, presence of antithyroid antibodies, UAS7 scores, DLQI, or CU-Q2oL scores. However, the ASST had higher sensitivity and accuracy in this study.

In comparison with bilastine and levocetirizine in the treatment of urticaria, there was no significant differences amid any of the domains documenting improvement with either medication versus placebo alone (ANOVA analysis).³

In another study aimed to define the effect of therapy for urticaria on three different survey results, the UAS7, CU-Q2oL, and DLQI were all compared simultaneously before and after treatments.¹⁸ Patients who were surveyed had been treated for their urticaria before enrolling. The initial UAS7 score was low (18.7 out of a maximum of 42) but improved by 21% with further therapy ($p = 0.02$). However, over the period of 4 weeks to 3 months after start of therapy, the DLQI failed to show significant differences ($p = 0.23$). Furthermore, only 29% who showed improvement had a change of 2.24 (total) or more points in their DLQI, a score that would attach significant change. In contrast, the CU-Q2oL, although only 15% change, was less variable and achieved significance ($p = 0.001$). Of the domains within the CU-Q2oL, 69% had significant improvement in itching/embarrassment, sleep, and mental status after therapy ($p = 0.001$).¹⁸ Correlation was better between the CU-Q2oL and UAS7 compared with DLQI and UAS7 ($r = 0.39$, $p = 0.005$, versus $r = 0.33$, $p = 0.02$, respectively).

Significant correlations in CU-Q2oL domains were found with UAS7 for functioning, itching/embarrassment, and mental status whereas those for sleep, swelling/eating, and limits did not correlate significantly.

Recently, two articles have been published using QoL surveys in assessment of improvement in urticaria with omalizumab. In a retrospective review, patients treated for 24 weeks with omalizumab showed significant improvement in their UAS (12.11 ± 1.97 before and 2.7 ± 4.23 after; $p = 0.001$) and CU-QoL (34.65 ± 13.58 to 60.88 ± 11.11 ; $p = 0.004$). The dosage of systemic corticosteroids, antihistamines, and other immunomodulators were all significantly reduced. The au-

Table 4 Example of a survey for clinical use based on select questions from referenced surveys

Score Question	1	2	3	4	5
How bad is the itching?	None	Mild	Moderate	Severe	Unbearable
How many hives do you have?	None	Few	Several	Most of my body have hives/swelling	Unbearable
Do you have swelling of your skin?	No	Once a day	Two to three times per day	Three times a day or more	Unbearable
How long do the hives or swelling last?	None	Less than 1 hour	1–3 hours	3 to 24 hours	Unbearable
How big are your hives on average?	None	Tiny bumps	Smaller than a dime	A dime to quarter size	Unbearable
Are you embarrassed by your hives or swelling?	Not at all	A little	Somewhat	A lot	Unbearable
Do you feel nervous from your hives/swelling?	Not at all	A little	Somewhat	A lot	Unbearable
Do your hives/swelling interfere with sleep?	Not at all	A little	Somewhat	A lot	Unbearable
Are you tired from lack of sleep?	Not at all	A little	Somewhat	A lot	Unbearable
Do your hives/swelling interfere with eating?	Not at all	A little	Somewhat	A lot	Unbearable
Do your hives/swelling interfere with work?	Not at all	A little	Somewhat	A lot	Unbearable
Do your hives/swelling interfere with social activities?	Not at all	A little	Somewhat	A lot	Unbearable
Do your hives/swelling interfere with sports?	Not at all	A little	Somewhat	A lot	Unbearable
Do your hives affect your mood?	Not at all	A little	Somewhat	A lot	Unbearable
Do you have trouble concentrating?	Not at all	A little	Somewhat	A lot	Unbearable

Source: Adapted from CU-Q2oL/AE-QoL surveys and UAS and Refs. 8, 9, and 16.

CU-Q2oL = Chronic Urticaria and Quality of Life questionnaire; AE-QoL = angioedema quality of life; UAS = Urticaria Activity Score.

thors found a higher prevalence of personal or family history of atopy in those patients with urticaria who responded to omalizumab compared with those who did not.¹⁹

In another study using omalizumab for patients uncontrolled with optimal antihistamine and montelukast combinations, both UAS7 and CU-Q2oL were used to show improvement in the subjects' QoL. Patients received 300 mg of omalizumab subcutaneously at 4-week intervals over 24 weeks. Using a patient urticaria diary that catalogued their hives, significant changes were seen in UAS7 at week 12 of patients given omalizumab compared with placebo (–19 versus –8.5, respectively; $p < 0.001$), change in weekly number of hives score (–10.4 versus –4.5, respectively; $p <$

0.001), patients with UAS7 < 6 at week 12 (132 versus 10, respectively; $p < 0.001$), and change in CU-Q2oL from baseline compared with placebo (–29.3 versus –16.3, respectively; $p < 0.001$).²⁰

PUTTING SURVEYS INTO CLINICAL PRACTICE

With the number of surveys available, clinicians can select specific components that work best for their practice. Although the example survey in Table 4 has not been subject to intensive analysis as a single survey, its components have and have shown reproducibility and reliability. Surveying patients at time intervals to define their QoL can objectively define therapeutic(s) benefit or lack of benefit. A reasonable

interval for having the patient complete such surveys may be every 2–4 weeks.

CONCLUSION

The use of QoL surveys is useful in defining changes in a patient's symptoms over a period of time. Based on current surveys available, choosing a broader-based urticaria (CU-Q2oL) or angioedema (AE-QoL) survey along with a measurement tool (*e.g.*, UAS7) for allowing the patient to catalog daily changes due to therapy can provide objective documentation for the clinician. Compared with surveys outlined in older reviews,¹ newer surveys allow for the definition of what is important to the patient. Customization of the surveys can be performed within reason for a clinician's own practice, eliminating such questions that may have no relevance on the management of a patient's urticaria or angioedema (*e.g.*, shopping). As the therapies for urticaria and angioedema become more expensive, adequate documentation based on surveys will provide more objective evidence that may be required by managed care before, during, and after the treatment.

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