Digestion

Reprinted with permission as:
Digestion 2007;75(suppl 1):55–61
DOI: 10.1159/000101083
Published online: May 4, 2007

Originally published:
Online: May 4, 2005
Digestion 2005;71:145–151
DOI: 10.1159/000085564
Received: March 8, 2005
Accepted: April 19, 2005

Determination of ReQuest™-Based Symptom Thresholds to Define Symptom Relief in GERD Clinical Studies

Vincenzo Stanghellini[a] David Armstrong[b] Hubert Mönnikes[c] Peter Berghöfer[d] Gudrun Gatz[d] Karna Dev Bardhan[e]

[a]S. Orsola-Malpighi University Hospital, Bologna, Italy; [b]McMaster University, Hamilton, Ont., Canada; [c]Department of Medicine, Division Hepatology, Gastroenterology, and Endocrinology, Charité Medical Center – Campus Virchow Hospital, Medical School of Free University and Humboldt University, Berlin, [d]ALTANA Pharma AG, Constance, Germany; [e]District General Hospital, Rotherham, UK

Key Words
Gastroesophageal reflux disease · Symptom thresholds, GERD · Symptom evaluation, GERD-related · ReQuest™ · Reflux questionnaire · Gastrointestinal Symptom Rating Scale · Psychological General Well-Being scale

Abstract
Background/Aims: The growing importance of symptom assessment is evident from the numerous clinical studies on gastroesophageal reflux disease (GERD) assessing treatment-induced symptom relief. However, to date, the a priori selection of criteria defining symptom relief has been arbitrary. The present study was designed to prospectively identify GERD symptom thresholds for the broad spectrum of GERD-related symptoms assessed by the validated reflux questionnaire (ReQuest™) and its subscales, ReQuest™-GI (gastrointestinal symptoms) and ReQuest™-WSO (general well-being, sleep disturbances, other complaints), in individuals without evidence of GERD. ***Methods:*** In this 4-day evaluation in Germany, 385 individuals without evidence of GERD were included. On the first day, participants completed the ReQuest™, the Gastrointestinal Symptom Rating Scale, and the Psychological General Well-Being scale. On the other days, participants filled in the ReQuest™ only. GERD symptom thresholds were calculated for ReQuest™ and its subscales, based on the respective 90th percentiles. ***Results:*** GERD symptom thresholds were 3.37 for ReQuest™, 0.95 for ReQuest™-GI, and 2.46 for ReQuest™-WSO. ***Conclusion:*** Even individuals without evidence of GERD may experience some mild symptoms that are commonly ascribed to GERD. GERD symptom thresholds derived in this study can be used to define the global symptom relief in patients with GERD.

Introduction

Gastroesophageal reflux disease (GERD) is one of the most prevalent gastrointestinal (GI) disorders in Western countries, and is characterized by a heterogeneous symptom pattern. The so-called predominant or typical symptoms of GERD (heartburn, regurgitation) are quite specific but not sensitive for the diagnosis of (acid-related) GERD [1–3]. In addition to the typical symptoms, many patients experience a broad range of different 'atypical' symptoms, mainly with reference to the thorax and abdomen.

KARGER
Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

0012–2823/07/0755–0055$23.50/0

Accessible online at:
www.karger.com/dig

Prof. Vincenzo Stanghellini, MD
Department of Internal Medicine and Gastroenterology, University of Bologna
S. Orsola-Malpighi Hospital, Via Massarenti 9
IT–40138 Bologna (Italy)
Tel. +39 051 636 4101, Fax +39 051 34 5864, E-Mail v.stanghellini@unibo.it

The definition and assessment of GERD symptomatology is complicated by the fact that GERD-related symptoms occur episodically and are affected by external factors such as stress, diet and medication [4]. Furthermore, the perception of symptom severity is purely subjective, and there is no globally accepted term for 'heartburn' (one of the predominant symptoms) in different languages so that symptom terminology cannot be simply translated from one language into another [4].

On the other hand, assessment of symptoms as a primary outcome criterion is of increasing importance in clinical studies of patients with GERD, especially endoscopy-negative GERD (enGERD). Hence, a validated, reliable and responsive tool for the measurement of GERD-related symptoms is essential. It has been proposed that a tool for assessment of GERD symptoms, suitable for use as a primary outcome criterion for clinical studies, should meet the following characteristics: (1) be sensitive in patients with GERD; (2) cover the frequency and intensity of typical and atypical GERD symptoms; (3) be multidimensional (cover all symptom dimensions); (4) have proven psychometric properties (validity, reliability and responsiveness); (5) be practical and economical; (6) be self-assessed; (7) use 'word pictures' that are easy to understand for patients; (8) respond rapidly to changes (responsiveness in short time intervals); (9) be usable daily to assess changes during and after therapy, and (10) be valid in different languages for international use [4–6].

A review of the literature revealed that no such tool exists [5] and, consequently, the Reflux Questionnaire (ReQuest™) was developed to meet these criteria. The validity, reliability and responsiveness of ReQuest™ have been documented in international validation studies in both erosive GERD and enGERD [7–9].

If symptom assessment is to be used as a primary outcome criterion in clinical studies, it is necessary to define a level of symptom severity at which a patient can be considered to be adequately treated. The availability of effective treatment led to the approach to consider patients as being adequately treated if they are totally symptom-free (in most cases heartburn only) for a defined period of time. Different definitions of 'complete resolution' of symptoms have been proposed in many clinical trials: all of them were definitions not based on previous experimental observations [10–13]. An innovative approach is the definition of a 'GERD symptom threshold'. This concept aligns with the current clinical practice not to treat patients until complete resolution but rather until symptoms not longer impair the quality of life from the patients perspective. The approach of a GERD symptom threshold is also important due to the fact that also healthy subjects may experience symptoms from time to time, and to prevent over-prescription of therapies.

Therefore, in the present study, we investigated the occurrence of GERD-related symptoms in individuals without evidence of GERD using ReQuest™, as this GERD questionnaire allows valid assessment of the full range of GERD symptoms on a daily basis. The symptom load in individuals without evidence of GERD was calculated using ReQuest™. This sum score was used to calculate a GERD symptom threshold, which can primarily be used to define whether GERD patients are adequately treated in therapeutic studies.

Materials and Methods

Study Design

This study was a 4-day evaluation of GERD-related symptoms in individuals without evidence of GERD. No study medication was administered. Written consent to participate was obtained from each individual. The study was conducted in Germany according to Good Clinical Practice and the Declaration of Helsinki, and was approved by an independent ethics committee.

As this evaluation was to study GERD-related symptoms in individuals without evidence of GERD, special attention was paid to the selection of individuals. To guarantee a selection procedure without selection bias, in the first stage advertisements were placed in local newspapers in randomly chosen cities in Germany. These advertisements included information about the nature and purpose of the evaluation study and asked that the individuals should: (1) be healthy; (2) not consider themselves as suffering regularly from GERD symptoms (heartburn, regurgitation, pain on swallowing, and epigastric pain), and (3) not be taking any medication for GERD.

Individuals further interested in participation in the study based on the information in the advertisements were encouraged to take part in a phone evaluation. During the standardized telephone interview, respondents were screened for the following criteria: (1) a minimum age of 18 years; (2) not regularly suffering from GERD symptoms such as heartburn, regurgitation, pain on swallowing, and epigastric pain within the past 3 months; (3) not being treated with medication for stomach trouble or heartburn; (4) not undergoing endoscopy within the last 12 months, and (5) not have consulted with a gastroenterologist within the past 12 months.

Individuals fulfilling all of these requirements were considered eligible for the evaluation study and received an evaluation kit comprising an individual information sheet, a consent form, a medical evaluation form, ReQuest™, the Gastrointestinal Symptom Rating Scale (GSRS), and the Psychological General Well-Being (PGWB) scale. In the medical evaluation form, individuals were asked whether they had: (1) suffered from heartburn and regurgitation within the past 3 months; (2) seen a specialist for digestive diseases within the past year, or (3) undergone endoscopy or a radiological study of the GI tract (esophagus, stom-

ach, small intestine or colon) within the past year. Furthermore, the medical evaluation form assessed in detail whether the individuals were taking medication for heartburn, medication that assists intestinal motility, or other medication for GI complaints. Only those patients not meeting any of the above-mentioned criteria were eligible for the evaluation and were therefore included in the analyses.

On the 1st day of the evaluation, individuals were instructed to complete the long version of ReQuest™, the GSRS and the PGWB scale. On the 2nd and 3rd days, individuals were asked to complete the short version of ReQuest™ and, finally, on the 4th day, the long version of ReQuest™ was completed.

ReQuest™

ReQuest™ is a self-assessed, dimension-orientated scale designed to evaluate the treatment response in patients suffering from erosive GERD or enGERD on a frequent, e.g. daily, basis. ReQuest™ has been validated in GERD and enGERD both nationally and internationally [7–9]. It comprises a short and a long version; both versions assess seven dimensions of GERD (acid complaints, upper abdominal/stomach complaints, lower abdominal/digestive complaints, nausea, sleep disturbances, other complaints and general well-being). The intensity is measured on a 100-mm visual analogue scale and the frequency (except general well-being) on a 7-point Likert scale, ranging from 0 to more than 10 times per day. Additionally, the long version asks for the occurrence of symptom descriptions known to be typical of the corresponding dimension.

Two validated subscales of ReQuest™ exist: ReQuest™-GI and ReQuest™-WSO. ReQuest™-GI comprises the dimensions of acid complaints, upper abdominal/stomach complaints, lower abdominal/digestive complaints and nausea, while ReQuest™-WSO comprises general well-being, sleep disturbances and other complaints. The minimum sum score for ReQuest™ and its subscales is 0. The maximum sum score for ReQuest™ is 46.28. For ReQuest™-GI and ReQuest™-WSO, the maximum sum scores are 30.77 and 15.51, respectively.

GSRS and PGWB Scale

The GSRS comprises 15 items assessed on a 7-point scale ranging from 0 (no complaints at all) to 6 (very severe complaints). The PGWB scale comprises 22 items assessed on a 6-point scale ranging from 0 (most negative option) to 5 (most positive option).

Statistical Analyses

The main objective of this evaluation was to determine the upper limit of a range of GERD symptom scores (afterwards termed a 'GERD symptom threshold') by means of ReQuest™ to distinguish between individuals with and without clinically relevant GERD symptoms, as compared with the same symptoms in individuals without evidence of GERD. This was achieved by first adding the scores for the 7 dimensions on all 4 days to create a sum score for all participants of the study. Additionally, the ReQuest™-GI score and the ReQuest™-WSO score were calculated separately, by taking the respective dimensions into account.

The score for each dimension of ReQuest™ is calculated by the weighted product of $score_{intensity}$ and $score_{frequency}$. The general well-being dimension is the weighted $score_{intensity}$. The sum of all scores of the dimensions is the ReQuest™ sum score, which is the basis for calculating the GERD symptom threshold.

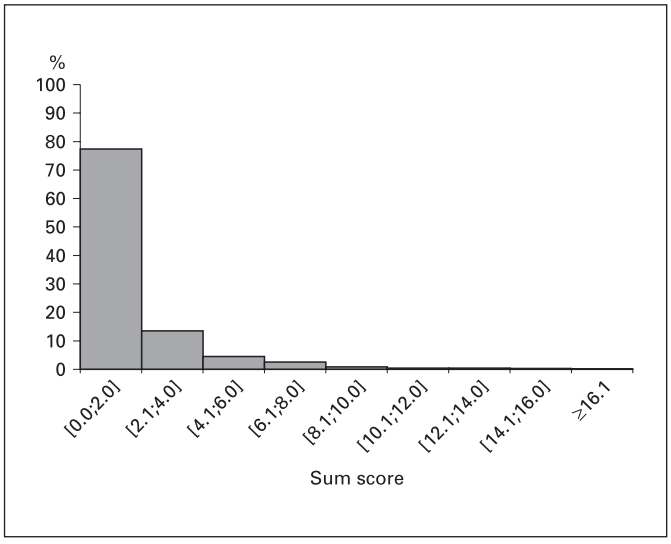

Fig. 1. Empirical frequency distribution of the ReQuest™ sum scores on days –4.

In the second step, the empirical percentiles of ReQuest™ and its subscales were calculated from these data on day 1 of the evaluation. The 90th percentile was set as the GERD symptom threshold; that is, 90% of the ReQuest™ and ReQuest™ subscale sum scores fell below this value.

Data derived from both GSRS and PGWB were analyzed in a descriptive manner.

Other statistical information such as demographic data and sum scores on day 1 are descriptive only and were not analyzed further.

Results

A total of 479 individuals were screened in this evaluation, 385 of whom were eligible for analysis. Demographic characteristics are presented in table 1.

Figure 1 shows the distribution of ReQuest™ overall sum scores in the population studied on the 1st to 4th days of the evaluation. The bars show the percentage of sum scores falling in each score category. Only 7% of the data are equal to 0. A total of 80% of the sum scores fall below the GERD symptom threshold.

On the basis of the ReQuest™ overall sum score, an individual can be classified as being without clinically relevant GERD symptoms if the sum score is within a range of 0 to 3.37, which corresponds to the 90th percentile determined in this study. The 90th percentiles for the ReQuest™-GI and ReQuest™-WSO scores were calculated as 0.95 and 2.46, respectively. The ReQuest™ overall

Table 1. Demographic data of eligible individuals

Parameter	Male	Female
Gender	146 (37.9%)	239 (62.1%)
Mean age, years	40.6 ± 13.6	38.2 ± 12.3
Mean height, cm	180.5 ± 7.1	167.7 ± 6.2
Mean weight, kg	82.4 ± 17.3	65.5 ± 13.0
Mean body mass index, kg/m^2	25.3 ± 5.1	23.3 ± 4.2
Smoking behavior		
Daily smoker	70 (18.2%)	
Occasional smoker	43 (11.2%)	
Non-smoker	271 (70.6%)	
Alcohol consumption		
Daily	25 (6.5%)	
Never/occasional	360 (93.5%)	

Values are the mean ± standard deviation or the number of individuals with percentages in parentheses.

Table 2. The sum scores of ReQuest™ and its subscales corresponding to different percentiles on day 1

Empirical percentile	ReQuest™	ReQuest™-GI	ReQuest™-WSO
90th	3.37	0.95	2.46
91st	3.62	1.12	2.64
92nd	4.09	1.29	3.11
93rd	4.48	1.38	3.23
94th	4.88	1.53	3.33
95th	5.04	1.73	3.68
96th	5.69	2.24	4.20
97th	6.53	2.40	4.71
98th	7.62	3.60	5.49
99th	9.54	4.39	6.52

ReQuest™-GI = Subscale of ReQuest™ comprising acid complaints, upper abdominal/stomach complaints, lower abdominal/digestive complaints, nausea; ReQuest™-WSO = subscale of ReQuest™ comprising general well-being, sleep disturbances, other complaints.

Table 3. Summary statistics for the sum scores of the different questionnaires on day 1 of the evaluation

Score	n	Mean sum score (CI)	SD	Minimum	Maximum
PGWB sum score	385	83.67 (82.29; 85.05)	13.78	31	110
GSRS sum score	385	7.12 (6.43; 7.82)	6.94	0	40
ReQuest™ sum score	363[a]	1.45 (1.26; 1.65)	1.86	0	15.85
ReQuest™-GI sum score	374[a]	0.33 (0.24; 0.43)	0.94	0	11.14
ReQuest™-WSO sum score	372[a]	1.11 (0.98; 1.25)	1.30	0	8.67

SD = Standard deviation; CI = confidence interval; ReQuest™-GI = subscale of ReQuest™ comprising acid complaints, upper abdominal/stomach complaints, lower abdominal/digestive complaints, nausea; ReQuest™-WSO = subscale of ReQuest™ comprising general well-being, sleep disturbances, other complaints; n = number of individuals; PGWB = Psychological General Well-Being scale; GSRS = Gastrointestinal Symptom Rating Scale.

[a] As missing data were not replaced on day 1, different numbers of individuals filled in the ReQuest™ and its subscales.

sum score, the ReQuest™-GI sum score, and the ReQuest™-WSO sum score corresponding to further upper limits between the 90th and 99th percentiles were calculated (table 2). The choice of the percentile depends on the desired accuracy.

The results obtained with ReQuest™ were compared with those of two other questionnaires. Table 3 summarizes the sum scores for each questionnaire on day 1 of the study. The results indicate that even individuals without evidence of GERD experience slight symptoms that are usually ascribed to gastroesophageal reflux, as the scores of ReQuest™, its subscales, and GSRS were slightly above 0. However, all the scores were near the minima of the respective scale, with the exception of the PGWB sum score which measures general psychological well-being rather than symptoms of GERD.

Furthermore, it should be noted that age, weight, height, body mass index, and gender appeared to have no significant effect on the ReQuest™ sum score in this group of subjects who had no evidence of GERD, which

is different from patients with GERD, where these factors were considered to influence the symptomatology [14, 15].

Discussion

In the past, the success of drug treatment in patients with GERD has been evaluated using the healing of esophagitis as the main outcome criterion. However, in recent years, the impact of treatment on GERD-related symptoms has become increasingly important. Finally, in enGERD patients, relief of symptoms is the only criterion which can be used for treatment success.

Despite the growing importance of symptomatic outcomes in clinical studies, in a recently published review Sharma et al. [16] showed that, until now, there has been no concerted attempt to optimize and standardize methods of symptom evaluation. Comparisons of the results from different trials are very difficult due to variations in symptom evaluations with respect to the: (1) types of symptoms evaluated (a single symptom such as heartburn, or various symptoms such as GI symptoms); (2) definition of treatment success (complete absence or subjective reduction); (3) time periods of symptom assessment; (4) scales used, and (5) type of assessment (patients' self-assessment, investigator assessment). To date, the complexity of GERD symptoms is not completely understood, but it is clear that as a sole criterion, heartburn is not sufficient to judge treatment success, and that the criteria for its assessment have to be established (e.g. when and by whom symptoms should be assessed) in order to make reliable statements about treatment success [4].

A literature survey revealed that a validated, responsive and reliable tool for monitoring GERD patients' symptomatology during treatment was lacking [5]. To remedy this gap, we developed and validated the ReQuest™ questionnaire, both nationally and internationally [7–9]. The ReQuest™ questionnaire enables the assessment of symptoms in patients with GERD, and the evaluation of treatment success, both objectively and prospectively, by fulfilling the requirements mentioned elsewhere [5], e.g. multi-dimensional and self-assessed symptoms on a daily basis.

The results of the present study indicate that even individuals without evidence of GERD experience symptoms comparable to those experienced by individuals with documented GERD. This is in accordance with the literature [3] from which it is known that various factors such as lifestyle and heavy meals can facilitate or even provoke GERD symptoms in individuals without evidence of GERD. However, it can be concluded from the results of the present evaluation that the severity and frequency of the symptoms are so limited that the individuals do not suffer as a result of the condition, i.e. the symptoms do not have a significant effect on their quality of life. Furthermore, they do not seek medical help, i.e. they do not consult the health care system and therefore save costs, and they do not take medication such as antacids for symptom relief. Obviously, these individuals can tolerate their symptoms, as their impact is below a subjective threshold of impairment.

Assuming that individuals without evidence of GERD do not suffer from GERD-related symptoms, the GSRS and ReQuest™ scores would be expected to show that these individuals are totally free of symptoms; however, the scores observed in this study were above 0. According to Enck et al. [17] the patients in this evaluation were not impaired in their quality of life as the mean of the PGWB score determined in this evaluation was above the threshold determined in their study ($83.67 > 79.11$). This clearly indicates that individuals in this evaluation, although experiencing slight symptoms of GERD, were not impaired in their quality of life. In another study [18], the threshold for the PGWB score was estimated at 102.94 in a randomly selected population in one city in Sweden, suggesting that regional differences in the patients' self-assessment are responsible for the different thresholds. In our national validation study for ReQuest™, we estimated a mean PGWB sum score of about 70 in patients suffering from GERD (70.37 in the 20-mg pantoprazole group; 69.66 in the 40-mg pantoprazole group) at the baseline visit (data on file). This value rose to nearly 80 (77.50 and 79.43, respectively; data on file) at the end of treatment. Therewith, values at the end of treatment were slightly below the thresholds determined in this evaluation.

The data obtained using ReQuest™ and GSRS are in accordance with those from another study showing that all individuals suffer from GI symptoms from time to time [19].

Although the inclusion criteria for this study were strict, we cannot completely rule out the possibility that some individuals with symptoms caused by GERD may have been enrolled. However, given this possibility, it is important to mention that such individuals obviously did not suffer severely enough from the condition to seek medical help.

The GERD symptom threshold, calculated as the 90th percentile of the ReQuest™ score in this population with-

out evidence of GERD, can be used as a criterion for symptom relief in the treatment of patients suffering from GERD. The GERD symptom thresholds for the two subscales of ReQuest™ (ReQuest™-GI and ReQuest™-WSO) can also be used as outcome criteria when focusing specifically on either GI symptoms or quality of life. Depending on the requirements or desired accuracy, the GERD symptom thresholds could also be selected corresponding to either the 95th percentile (5.04) or the 99th percentile (9.54). The higher the percentile (90th, 95th or 99th), the fewer patients (10, 5 or 1%, respectively) can be classified as not clinically suffering from symptoms due to the higher GERD symptom thresholds.

With reference to the GERD symptom thresholds derived from the present study, two other treatment studies in GERD patients (data on file) are worth noting. In a study to assess symptom relief, the measurement error was used to calculate the GERD symptom threshold, while in a study to assess the healing of esophageal lesions, the sensitivity of the former version of ReQuest™ was used. In the first study, the measurement error was calculated using standard mathematical methods, whereas the sensitivity in the second study was defined as a conditional probability (not-ill former ReQuest™ version/not-ill standard (endoscopy)). In comparison to the GERD symptom threshold in ReQuest™ of 3.37 in the present study, both of these studies showed GERD symptom thresholds that fall within a narrow range (symptom study, measurement error 3.88; healing study, sensitivity 3.09).

To our knowledge, no other comparable study has been conducted with the aim of defining a certain symptom level to enable a distinction between individuals with clinically relevant GERD symptoms and the same symptoms in individuals without evidence of GERD.

As individuals without evidence of GERD experience GERD-related symptoms, it is clearly inappropriate to use 'being free of symptoms' as a criterion of treatment success in clinical studies of patients with GERD. Rather, a symptom threshold has to be defined showing that, in the majority of the population, a symptom load below this threshold is not viewed as an impairment in quality of life or as a necessity to seek medical treatment. This GERD symptom threshold concept corresponds to common clinical practice aiming to avoid over-treating patients. Based on the present data, these thresholds can rationally be defined for treatment studies in patients with GERD using the ReQuest™ sum score as an outcome criterion. Thus, the determination of GERD symptom thresholds offers further opportunities such as the establishment of new primary endpoints for clinical trials, for instance time to first (below GERD symptom threshold) and sustained symptom relief (below GERD symptom threshold until end of study) as indicators for the time that is needed for effective treatment. These parameters directly reflect the patients' primary concerns, i.e. fast symptom relief, and further confirm the clinical relevance of the GERD symptom threshold concept.

Finally, this new scientific concept provides the opportunity to distinguish between individuals with clinically relevant GERD symptoms, compared with such symptoms in individuals without evidence of GERD, allowing the valid, objective and prospective definition of symptom relief in clinical studies.

Acknowledgement

We thank the IFE Institute for Research and Development, Essen, Germany, for supporting this project.

References

1 Guedon C: How to diagnose gastroesophageal reflux? Part 1. Diagnostic value of symptoms. Interpretation and role of endoscopy (in French). Gastroenterol Clin Biol 1999;23:S202–S207.

2 Wiklund IK, Glise H: Quality of life in different gastrointestinal conditions. Eur J Surg 1998;582(suppl):56–61.

3 Dent J, Brun J, Fendrick AM, Fennerty MB, Janssens J, Kahrilas PJ, Lauritsen K, Reynolds JC, Shaw M, Talley NJ, on the behalf of the Genval Workshop Group: An evidence-based appraisal of reflux disease management – The Genval Workshop Report. Gut 1999;44(suppl 2):S1–S16.

4 Moss SF, Armstrong D, Arnold R, Ferenci P, Fock KM, Holtmann G, McCarthy DM, Moraes-Filho JP, Mutschler E, Playford R, Spechler SJ, Stanghellini V, Modlin IM: GERD 2003 – A consensus on the way ahead. Digestion 2003;67:111–117.

5 Stanghellini V, Armstrong D, Mönnikes H, Bardhan KD: Systematic review: Do we need a new gastro-oesophageal reflux disease questionnaire? Aliment Pharmacol Ther 2004;19:463–479.

6 Armstrong D, Mönnikes H, Bardhan KD, Stanghellini V: The construction of a new evaluative GERD questionnaire – Methods and state of the art. Digestion 2004;70:71–78.

7 Bardhan KD, Stanghellini V, Armstrong D, Berghöfer P, Gatz G, Mönnikes H: Evaluation of GERD symptoms during therapy. Part I. Development of the new GERD questionnaire ReQuest™. Digestion 2004;69:229–237.

8 Mönnikes H, Bardhan KD, Stanghellini V, Berghöfer P, Bethke TD, Armstrong D: Evaluation of GERD symptoms during therapy. Part II. Psychometric evaluation and validation of the new questionnaire ReQuest™ in erosive GERD. Digestion 2004;69:238–244.

9 Bardhan KD, Stanghellini V, Armstrong D, Berghöfer P, Gatz G, Mönnikes H: International validation of ReQuest™ in patients with endoscopy negative gastroesophageal reflux disease. Aliment Pharmacol Ther 2004;20:891–898.
10 Castell DO, Kahrilas PJ, Richter JE, Vakil NB, Johnson DA, Zuckermann S, Skammer W, Levine JG: Esomeprazole (40 mg) compared with lansoprazole (30 mg) in the treatment of erosive esophagitis. Am J Gastroenterol 2002;97:575–583.
11 Talley NJ, Lauritsen K, Tunturi-Hihnala H, Lind T, Moum B, Bang C, Schulz T, Omland TM, Delle M, Junghard O: Esomeprazole 20 mg maintains symptom control in endoscopy-negative gastro-oesophageal reflux disease: A controlled trial of 'on-demand' therapy for 6 months. Aliment Pharmacol Ther 2001;15:347–354.
12 Dettmer A, Vogt R, Sielaff F, Luhmann R, Schneider A, Fischer R: Pantoprazole 20 mg is effective for relief of symptoms and healing of lesions in mild reflux oesophagitis. Aliment Pharmacol Ther 1998;12:865–872.
13 Hatlebakk JG, Hyggen A, Madsen PH, Walle PO, Schulz T, Mowinckel P, Bernklev T, Berstad A, on behalf of the Norwegian Heartburn Study Group: Heartburn treatment in primary care: Randomised, double blind study for 8 weeks. BMJ 1999;319:550–553.
14 Mathus-Vliegen EM, Tytgat GN: Gastroesophageal reflux in obese subjects: Influence of overweight, weight loss and chronic gastric balloon distension. Scand J Gastroenterol 2002;37:1246–1252.
15 Ter RB, Johnston BT, Castell DO: Influence of age and gender on gastroesophageal reflux in symptomatic patients. Dis Esophagus 1998;11:106–108.
16 Sharma N, Donnellan C, Preston C, Delaney B, Duckett G, Moayyedi P: A systematic review of symptomatic outcomes used in oesophagitis drug therapy trials. Gut 2004; 53(suppl 4):58–65.
17 Enck P, Dubois D, Marquis P: Quality of life in patients with upper gastrointestinal symptoms: Results from the Domestic/International Gastroenterology Surveillance Study (DIGEST). Scand J Gastroenterol 1999; 231(suppl):48–54.
18 Dimenas E, Carlsson G, Glise H, Israelsson B, Wiklund I: Relevance of norm values as part of the documentation of quality of life instruments for use in upper gastrointestinal disease. Scand J Gastroenterol Suppl 1996; 221:8–13.
19 Huang JQ, Hunt RH: pH, healing rate and symptom relief in patients with GERD. Yale J Biol Med 1999;72:181–194.