

Validation of a short questionnaire in English and French for use in patients with persistent upper gastrointestinal symptoms despite proton pump inhibitor therapy: The PASS (Proton pump inhibitor Acid Suppression Symptom) test

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BACKGROUND: The management of persistent symptoms during acid suppression therapy in patients with gastroesophageal reflux disease or dyspepsia might be improved if patient-physician communication regarding the presence and character of these persistent symptoms were facilitated.

AIM: To validate a short, simple questionnaire (the Proton pump inhibitor [PPI] Acid Suppression Symptom [PASS] test), in English and French, to identify patients with persistent acid-related symptoms during PPI therapy and document their response to a change in therapy.

METHODS: Patients with persistent acid-related symptoms on PPI therapy were interviewed to produce a draft, five-item questionnaire; content validity was evaluated by focus groups comprising English- and French-speaking patients. Psychometric validity was subsequently evaluated in a multicentre, family practice-based study of English- and French-speaking patients with persistent acid-related upper gastrointestinal symptoms despite PPI therapy. The PASS test, Global Overall Symptom scale, Gastrointestinal Symptom Rating Scale (GIRS), Quality of Life in Reflux and Dyspepsia questionnaire and Reflux Disease Questionnaire were completed at baseline and repeated after one week while patients continued their original PPI therapy. All patients then received esomeprazole 40 mg once daily for four weeks, after which all questionnaires and an evaluation of overall treatment effect were completed.

RESULTS: Content validity was established in 20 English- and 16 French-speaking patients. Psychometric validation in 158 English- and 113 French-speaking patients revealed good-to-excellent test-retest reliability coefficients: 0.76 for English; 0.68 for French. For construct validity, the PASS test showed moderate-to-high correlation with the GIRS scale (0.51 for English; 0.43 for French). After four weeks of therapy, the PASS test score fell to zero in 30% of English- and 33% of French-speaking patients, while the Global

Overall Symptom score fell to one (no symptoms) in 32% of patients (English- and French-speaking); the PASS test demonstrated good responsiveness in comparison with the GIRS, Reflux Disease Questionnaire and Quality of Life in Reflux and Dyspepsia questionnaire.

CONCLUSION: The five-item PASS test is a valid tool for the evaluation of persistent acid-related symptoms in patients receiving PPI therapy. It demonstrates good content validity, test-retest reliability, responsiveness and construct validity in both English and French forms. The PASS test is a simple, clinically applicable tool for the identification of patients with persistent acid-related symptoms during therapy and the assessment of their responses to a change in therapy.

Key Words: *Dyspepsia; Health-related quality of life; Heartburn; Proton pump inhibitor*

Validation d'un bref questionnaire en langue anglaise et en langue française à l'intention de patients qui souffrent de symptômes des voies digestives hautes persistants malgré un traitement par inhibiteurs de la pompe à protons : Le test PASS (pour Proton pump inhibitor Acid Suppression Symptom)

HISTORIQUE : La prise en charge des symptômes persistants malgré un traitement par suppression acide chez les patients qui souffrent de reflux gastro-œsophagien et de dyspepsie pourrait être améliorée si l'on facilitait la communication médecin-patient sur ces symptômes persistants et leur nature.

OBJECTIF : Valider un questionnaire bref et simple (le questionnaire PASS pour Proton pump inhibitor [PPI] Acid Suppression Symptom test) en anglais et en français de manière à identifier les patients qui souffrent de symptômes persistants liés à l'acidité durant leur traitement par IPP et documenter leur réponse à un changement de traitement.

MÉTHODE : Des patients qui souffrent de symptômes persistants liés à l'acidité alors qu'ils se trouvaient sous IPP ont été interrogés afin de produire l'ébauche d'un questionnaire à cinq éléments. La validité du contenu

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a été évaluée par des groupes composés de patients de langue anglaise et de langue française. La validité psychométrique a, par la suite, été évaluée dans le cadre d'une étude multicentrique auprès de cliniques de médecine familiale, chez des patients de langue anglaise et française souffrant de symptômes digestifs persistants liés à l'acidité en dépit d'un traitement par IPP. Le test PASS, une échelle globale d'évaluation des symptômes, l'échelle GSRS (pour *Gastrointestinal Symptom Rating Scale*) et un questionnaire sur la qualité de vie en présence de RGO et de dyspepsie et le questionnaire sur le RGO ont été complétés au départ, puis après une semaine, alors que les patients maintenaient leur traitement original par IPP. Tous les patients ont alors reçu 40 mg d'ésoméprazole, une fois par jour, pendant quatre semaines, après quoi tous les questionnaires et une évaluation de l'effet global du traitement ont été repris.

RÉSULTATS : La validité du contenu a été établie avec la collaboration de 20 patients de langue anglaise et de 16 patients de langue française. La validation psychométrique chez 158 patients de langue anglaise et 113 patients de langue française a révélé des coefficients de fiabilité test-retest de bons à excellents : 0,76 dans le cas de l'anglais, 0,68, dans le cas

du français. Pour ce qui est de la validité conceptuelle, le test PASS a montré une corrélation de modérée à élevée avec l'échelle GSRS (0,51 pour l'anglais, 0,43 pour le français). Après quatre semaines de traitement, le score au test PASS est tombé à 0 chez 30 % des patients de langue anglaise et 33 % des patients de langue française, alors que le score à l'évaluation globale des symptômes est tombé à 1 (aucun symptôme) chez 32 % des patients (de langues anglaise et française). Le test PASS a démontré un bon degré de réactivité en comparaison avec le GSRS, le questionnaire sur le RGO et le questionnaire sur la qualité de vie en présence de RGO et de dyspepsie.

CONCLUSION : Le test PASS à cinq éléments est un outil valide pour l'évaluation des symptômes persistants liés à l'acidité chez les patients sous IPP. Il fait état de résultats favorables pour ce qui est de la validité du contenu, de la fiabilité test-retest, de la réactivité et de la validité conceptuelle, tant en anglais qu'en français. Le test PASS est un outil simple et facile à appliquer en clinique, pour l'identification des patients qui souffrent de symptômes persistants liés à l'acidité alors qu'ils sont sous traitement et pour l'évaluation de leur réponse au changement de traitement.

Dyspepsia symptoms, including epigastric pain or discomfort, heartburn, abdominal bloating, a feeling of abnormal or poor digestion, early satiety and nausea (1), are reported by up to 40% of the general population. Approximately 10% to 20% of these individuals consult a physician (2,3) and if upper gastrointestinal (GI) endoscopy is performed, the most common diagnoses (reflux esophagitis, duodenal or gastric ulcers, and erosions) are generally amenable to acid suppression therapy (4).

Acid suppression medications are prescribed on a long-term basis to approximately 3% of primary care patients (5,6). Proton pump inhibitors (PPIs) and, to a lesser extent, histamine H₂-receptor antagonists produce symptom relief in a high proportion of patients with reflux esophagitis (7), endoscopy-negative reflux disease (8), peptic ulceration (9,10) and dyspepsia (11,12). However, acid-related disorders are frequently chronic (13,14); up to 90% of patients have recurrent symptoms once they discontinue therapy (5,15) and many patients have persistent symptoms despite continued therapy. Indeed, 15% to 20% of patients receiving PPI therapy are taking double-dose therapy (16). Although this may be unnecessary in some patients, it may also indicate that many patients still experience persistent acid-related symptoms during standard, once-daily PPI therapy. Gastroesophageal reflux disease (GERD) symptoms are associated with a decreased quality of life (17-19) if they are mild and occur on two or more days per week or if they are moderate and occur at least once a week. Furthermore, GERD symptoms are often sufficiently severe to interfere with work and daily activities; in one study (15), up to 50% of patients took over-the-counter medications in addition to their prescribed therapy. Thus, effective symptom control has the potential to produce a significant improvement in quality of life for many patients.

The extent to which patients experience persistent GERD symptoms during therapy is not generally appreciated by physicians, who may tend to overestimate the success of PPI therapy (20,21). As a result, physicians may not elicit, and patients may not report, persistent upper GI symptoms during therapy (20). The management of persistent symptoms in patients taking PPIs might, therefore, be facilitated if there was a standardized, validated tool that could be used to identify patients who still had symptoms and to determine whether these symptoms might respond to a change in acid suppression therapy.

Although there are validated research questionnaires for assessing upper GI symptoms and their response to therapy (22,23), no questionnaire has been designed specifically for clinical practice to identify patients who have persistent symptoms during therapy and to determine whether these symptoms might respond to more effective acid suppression therapy. The aim of the present study was to develop and validate a brief, user-friendly questionnaire that could be used by patients receiving PPI therapy to report the extent of severity of any persistent upper GI symptoms. The present paper describes the development and validation of the PPI Acid Suppression Symptom (PASS) test, in English and Canadian French, in a primary care setting.

METHODS

A literature review did not identify an appropriate, validated clinical assessment tool for use in patients receiving standard PPI therapy.

Identification of relevant symptoms

A telephone survey was conducted, by a third party, to identify the nature and severity of persistent symptoms in patients receiving PPIs. Respondents were selected from a list of adults taking PPIs who had indicated their willingness to participate in market research. Respondents with persistent symptoms despite continued PPI therapy were invited to complete the survey, which was comprised of a structured series of questions to identify each individual's symptoms before the start of therapy, current symptoms, quality of life, preferences and interactions with physicians.

The results of this survey were then summarized and reviewed by a panel of 11 physicians, including gastroenterologists and family physicians, as the basis for developing a short questionnaire that could be used to evaluate persistent symptoms during ongoing PPI therapy.

Construction of initial short questionnaire (PASS test)

Based on the telephone survey, it was determined that there were five major areas of concern with respect to patients' symptoms; each major area was, therefore, addressed with one question (Table 1). The draft PASS test, developed in French and English forms, had five closed 'Yes/No' questions designed to address the presence and impact of upper GI symptoms. The first question asked about the presence or absence of symptoms and the other four questions dealt with specific details.

TABLE 1
Mean 'Yes' response rates (English [E], French [F]) to five issues related to the use of the Proton pump inhibitor Acid Suppression Symptom (PASS) scale*. PASS content validation questionnaire

PASS question	Percentage answering Yes		Is the question clear and easy to understand?		Is the question vague and confusing?		Is the question related to your experience?		Is this an important complaint?		Do you like the wording?	
	E	F	E	F	E	F	E	F	E	F	E	F
1. Stomach symptoms	100	75	5.7	5.3	2.4	3.1	5.4	5.9	5.7	5.1	5.1	4.8
2. Supplemental medications	65	67	6.5	6.2	2.2	1.8	5.3	6.0	5.6	5.8	5.7	6.4
3. Sleep affected	80	42	6.4	6.7	2.3	1.1	5.7	6.0	5.9	5.8	5.9	6.7
4. Eating or drinking	80	50	6.5	6.8	1.7	1.2	5.9	6.4	6.2	6.2	5.8	6.6
5. Daily activities	50	25	6.4	7.0	2.1	1.8	5.3	5.8	5.8	5.8	6.0	6.3

*Scores on seven-point Likert scale items anchored at each end; 1 = completely disagree; 7 = completely agree

PASS TEST	TEST PASS
<p>Are you taking prescription medication for any of the following stomach problems/symptoms:</p> <ul style="list-style-type: none"> • Stomach pain or discomfort • Heartburn (a burning feeling rising from your stomach or lower chest towards your neck or burning feeling located behind the breastbone which may or may not rise in the chest) • Sour taste in mouth/acid regurgitation (feeling of regurgitation or unpleasant feeling moving upwards to the mouth) • Excessive burping/belching (passing of gas through the mouth) • Increased abdominal bloating (feeling of abdominal distension or fullness) • Nausea (the sensation of needing to vomit) • Early satiety (feeling full just after eating or not able to finish meals) <p>If yes, please complete the following questions:</p> <ol style="list-style-type: none"> 1. Are you still experiencing stomach symptoms? <input type="checkbox"/> Yes <input type="checkbox"/> No 2. In addition to your main medication are you taking any of the following medications to control your symptoms: antacids (e.g. Tums[®], Rolaid[®], Maalox[®]), H₂ blockers (e.g. ranitidine, Zantac[®], Pepcid AC[®]) motility drugs (e.g. Motilium[®]) or others (e.g. Gaviscon[®], Pepto Bismol[®])? <input type="checkbox"/> Yes <input type="checkbox"/> No 3. Is your sleep affected by your stomach symptoms? <input type="checkbox"/> Yes <input type="checkbox"/> No 4. Are your eating and drinking habits affected by your stomach symptoms? <input type="checkbox"/> Yes <input type="checkbox"/> No 5. At any time do your stomach symptoms interfere with your daily activities? <input type="checkbox"/> Yes <input type="checkbox"/> No 	<p>Prenez-vous un médicament sur ordonnance pour vos problèmes d'estomac? OU Prenez-vous un médicament sur ordonnance pour l'un des problèmes (d'estomac) suivants :</p> <ul style="list-style-type: none"> • Douleur/malaise à l'estomac • Brûlures d'estomac (sensation de brûlure remontant de l'estomac ou du bas de la poitrine vers le cou ou sensation de brûlure derrière le sternum qui remonte ou ne remonte pas vers la poitrine) • Goût sur dans la bouche/régurgitations acides (sensation de régurgitation ou sensation désagréable d'un retour d'aliments dans la bouche) • Éructations/rôts excessifs (émission par la bouche de gaz provenant de l'estomac) • Ballonnement abdominal accru (sensation de distension abdominale ou de plénitude gastrique) • Nausées (envie de vomir) • Satiété précoce - sensation que l'estomac est rempli peu après avoir commencé de manger ou impossibilité de terminer les repas – sensation de digestion anormale ou lente) <p>Dans l'affirmative, veuillez répondre aux questions suivantes :</p> <ol style="list-style-type: none"> 1. Éprouvez-vous toujours des symptômes gastriques? <input type="checkbox"/> Oui <input type="checkbox"/> Non 2. En plus de votre principal médicament, prenez-vous l'un des médicaments suivants pour maîtriser vos symptômes : des antiacides (p. ex., Tums[®], Rolaid[®], Maalox[®]), des anti-H₂ (p. ex., ranitidine, Zantac[®], Pepcid AC[®]) des agents favorisant la motilité (p. ex., Motilium[®]) ou autres (p. ex., Gaviscon[®], Pepto Bismol[®])? <input type="checkbox"/> Oui <input type="checkbox"/> Non 3. Votre sommeil est-il perturbé par vos symptômes gastriques? <input type="checkbox"/> Oui <input type="checkbox"/> Non 4. Vos habitudes alimentaires et vos habitudes de consommation de liquides sont-elles perturbées par vos symptômes gastriques? <input type="checkbox"/> Oui <input type="checkbox"/> Non 5. Vos symptômes gastriques interfèrent-ils avec vos activités quotidiennes? <input type="checkbox"/> Oui <input type="checkbox"/> Non

Figure 1) The Proton pump inhibitor Acid Suppression Symptom (PASS) test in English and French

The draft test was validated in two stages with two separate study groups; the first assessed content validity and the second assessed psychometric validity.

Content validity

Content validity was evaluated in English- and French-speaking adults taking PPIs who had indicated their willingness to participate in market research and who were reimbursed for their time. An independent ethics committee (Institutional Review Board Services, Aurora, Ontario) approved the evaluation procedure.

In addition to the draft PASS test, patients completed a content validation questionnaire to evaluate the content of the questions and assess whether the wording was clear, unambiguous and

relevant to their own experience. The PASS test format was finalized based on an analysis of the content validity questionnaire results (Figure 1).

Psychometric validity

Psychometric validation of the PASS test was performed in a three-visit multicentre study at 38 family practice centres across Canada to evaluate 'test-retest' reliability, construct validity and responsiveness. The study protocol was approved by an independent ethics committee (Institutional Review Board Services, Aurora, Ontario); informed written consent was obtained from each patient.

Patients were eligible to participate in the study if they were 18 years of age or older, spoke English or French as a first language, had persistent GI symptoms (including epigastric pain or discomfort, heartburn, acid regurgitation, excessive burping or belching, abdominal bloating, a feeling of abnormal or slow digestion, early satiety and nausea) and had been taking one of the following PPIs at standard once-daily doses for at least the previous eight weeks: omeprazole 20 mg; rabeprazole 20 mg; lansoprazole 30 mg; or pantoprazole 40 mg. Major exclusion criteria included current use of esomeprazole, documented upper GI surgery such as gastric resection, vagotomy, pyloroplasty, hiatus hernia surgery or fundoplication, and the presence of any alarm symptoms requiring investigations.

A history and physical examination were performed in all patients and baseline demographic data were recorded. Adverse events and the use of concomitant medications were recorded throughout the study. PPI use during the week before entry into the study was documented. Patients then completed the PASS test and the Global Overall Symptom (GOS) scale to document the severity of their upper GI symptoms over the previous two days. To demonstrate test-retest reliability of the PASS test, patients were asked to continue their baseline medication for one week (up to 14 days maximum) before they returned to the clinic, at which time they again completed the PASS test, the GOS scale, the Gastrointestinal Symptom Rating Scale (GSRS), the Overall Treatment Evaluation (OTE), the Quality of Life in Reflux and Dyspepsia (QoLRAD) questionnaire and the Reflux Disease Questionnaire (RDQ). Patients were eligible to continue in the study only if they had reported upper GI symptoms of at least mild severity (GOS score of 3 or more) during the last two days before their second visit (24).

Laboratory measurements, including a urine pregnancy test if applicable, were performed at the second visit. All patients then received open label treatment with esomeprazole 40 mg taken each morning, 30 min before breakfast, for the next four weeks. Esomeprazole was chosen because of its superiority, at standard dose, to other PPIs at increasing gastric pH and producing symptom relief for patients with erosive esophagitis (25,26). The patients discontinued other PPIs at this visit but were allowed to continue other medications.

After four weeks, patients returned to the clinic for the third and final visit, at which time all questionnaires administered at the second visit were repeated and compliance was assessed by pill count of returned medication.

The PASS test was evaluated with respect to patients' responses to the individual questions and with respect to the total sum score (minimum score 0: patient has no symptoms; maximum score 5: patient has symptoms requiring supplemental medications and affecting sleep, eating, drinking and daily activities).

The GOS is a seven-point Likert scale, scored from 1 (no problem) to 7 (very severe problem), that measures the overall severity of dyspepsia symptoms (24).

The GSRS includes 15 questions that address GI symptoms in five different domains: reflux, abdominal pain, indigestion, diarrhea and constipation. The GSRS questions are answered using a seven-point Likert-like scale, scored from 1 (no symptoms) to 7 (very severe symptoms) (27,28).

The QoLRAD questionnaire consists of 25 questions in five dimensions (emotions; sleep; vitality; food and drinking habits; and physical and social functioning) that assess the impact of upper GI symptoms on patient quality of life and daily functioning. This questionnaire is a seven-point Likert-like scale, scored

from 1 (severe impact) to 7 (no impact) for each domain. Scores are reported for each domain and overall (29).

The RDQ is a self-administered questionnaire used to measure the frequency and severity of certain patient symptoms: heartburn, regurgitation, epigastric pain, and overall symptoms, over the previous four weeks. Symptom frequency is ranked according to six choices (did not have; less than one day a week; one day a week; two to three days a week; four to six days a week; and daily) as is severity (did not have; very mild; mild; moderate; moderately severe; severe) (30).

The OTE is a 15-point scale that measures the magnitude of change in health status (-7 to -1 is worse; 0 is no change; and 1 to 7 is better). Subjects were first asked to report their symptoms as improved, about the same, or worse when compared with the previous visit. If changed, patients had to indicate the magnitude of change on seven-point scales (1 to 7 or -1 to -7). Patients were then asked to indicate how important the change (if it occurred) was to them on another seven-point scale (31).

Test-retest reliability

Generalizability analysis (G-analysis [32]) was conducted to account for three clearly defined sources of variation that were identified in the present study: assessments at two time points; five test items; and subject characteristics. Intraclass correlation coefficients, representing the ratios of true variance to total variance, were calculated using a repeated measures model to account for the sources of variation. Mean squares from the within-subjects effects were extracted for each of the following – subject*time, subject*item and subject*time*item (error) – to calculate the variances and, consequently, the G coefficients for test-retest reliability and internal consistency (alpha) for the PASS test. The strength of the relationship between each PASS question and the total PASS score was assessed by the total-to-item correlation.

For PASS inter-item analysis, individual phi correlation coefficients were calculated. Correlations were considered low-to-moderate if the coefficients fell between 0.4 and 0.6; moderate-to-high if greater than 0.6; and excellent if greater than 0.8.

Construct validity

Construct validity refers to how well the patient's status is reflected by the PASS test compared with other standard questionnaires. It is determined by the degree of correlation (Spearman's rank correlation ρ) between scores on the PASS scale and those on three other validated scales: GSRS, QoLRAD and RDQ.

Responsiveness and discriminant power

Responsiveness to changes in patients' symptoms due to treatment was evaluated by the use of 'effect size' and symptom improvement. The effect size reflects changes in symptoms standardized by the variability of the change (33). It is calculated using the change in score from pretreatment (visit 2) to four weeks of treatment (visit 3), divided by the baseline SD. Effect sizes between 0.4 and 0.8 were considered moderate-to-good; those greater than 0.8 were considered excellent. For comparison purposes, effect size also was calculated with data grouped by means of GSRS, RDQ and QoLRAD.

Patients were also classified after four weeks of treatment as PASS test responders (visit 3 PASS score 0) or PASS test non-responders (visit 3 PASS score greater than 0).

For the analysis, the OTE was collapsed into four different categories: no change (OTE equals -1, 0, +1); small change (OTE

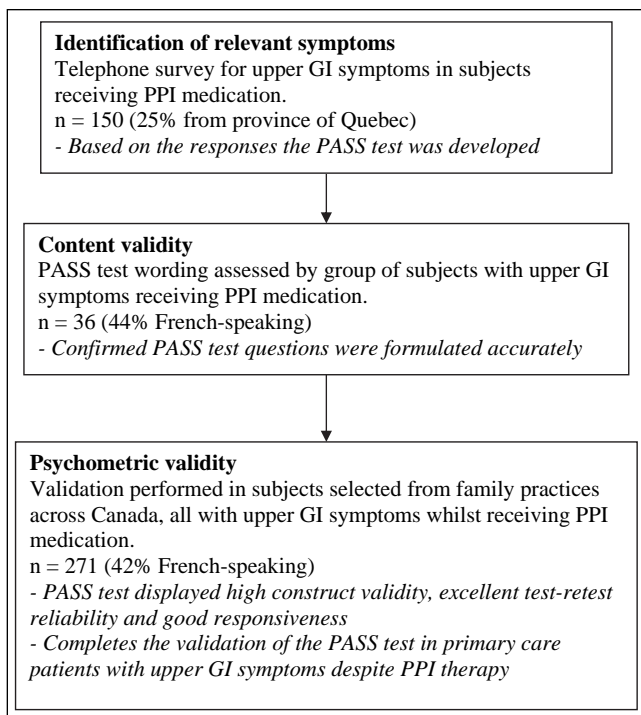


Figure 2 Overview of the process of validation for the Proton pump inhibitor (PPI) Acid Suppression Symptom (PASS) test with the accomplishments of each stage. GI Gastrointestinal

equals -3, -2, +2, +3); moderate change (OTE equals -5, -4, +4, +5); and large change (OTE equals -7, -6, +6, +7) (31,34).

The ability of the PASS test to detect clinical and statistical differences between responders and nonresponders was reported by the use of 95% CI for simple one-way analysis of variance for both the English and the French versions of the PASS test, against each of the validated instruments. CIs not crossing zero were considered statistically significant ($P < 0.05$ or less). No missing values were replaced.

Statistical analysis

Data analysis was performed using SAS (V8.1 2001, SAS Institute Inc, USA). Nominal data were expressed as percentages with ranges and numerical data as means with SDs.

Sample size

Statistical power analysis based on test-retest reliability and anticipated patient dropout rates indicated the need for 200 patients (100 patients each with English or French as their first language) to detect at least a moderate effect size of 0.5, assuming a delta of 0.5 units and an SD of one unit in the PASS test. Two hundred ninety patients from 38 family physician centres across Canada were enrolled to ensure that 200 patients completed the study.

RESULTS

An overview of the validation process for the PASS test is provided in Figure 2.

Initial identification of symptoms and potential PASS questions

Analysis of the telephone survey, completed by 150 patients, indicated that 47% of patients supplemented their PPI with an over-the-counter medication. Stomach-related problems

reported by these patients included sleeping (50%), eating (47%), work or daily activities (23%), social and exercise activities (17% to 18%) and hobbies (15%). The main spontaneously reported GI symptoms were pain or heartburn, indigestion and acid taste or fluid in the mouth or throat, occurring in 65%, 35% and 29% of cases, respectively. The most bothersome symptoms were heartburn (25%) and acid reflux (22%), followed by epigastric or stomach pain (13%).

As a result of this survey, five items were selected for the draft PASS test (Figure 1).

Content validity

The survey was completed in English by 20 patients (mean age 61 years; four men) and in French by 16 patients (mean age 59 years; 10 men). Nineteen patients in the English group and 15 in the French group were taking a PPI one to three times a day before the study.

The main stomach symptom(s) were described as bloating, heartburn, flatulence or gas, regurgitation and discomfort by 75% (15 of 20) and 92% (11 of 12) of the English- and French-speaking groups, respectively. These are consistent with those listed as possible symptoms in the PASS test. The words 'stomach pain or discomfort' and 'heartburn' were well-understood by 95% (19 of 20) of the English-speaking group and 100% (12 of 12) of the French-speaking patients. Fifty per cent (10 of 20) (60% [seven of 12] in the French group) thought that the best definition for heartburn was "a burning feeling rising from your stomach or lower chest toward your neck or a burning feeling located behind the breastbone which may or may not rise in the chest". The terms 'with sour taste', 'excessive burping or belching', nausea and 'increased abdominal bloating' were endorsed by 90% (18 of 20) of the English-speaking patients and 67% (eight of 12) of the French group. The term 'early satiety' was understood by 70% (14 of 20) of the English- and 67% (eight of 12) of the French-speaking group. To the question, "In general, does this list cover the range of symptoms that you experience?", 85% (17 of 20) of the English-speaking patients responded 'Yes', as did 92% (11 of 12) in the French-speaking group.

The term 'stomach problems' for question 1 was considered adequate by 65% (13 of 20) of the English- and 67% (eight of 12) of the French-speaking patients to describe their symptoms.

PSYCHOMETRIC VALIDITY

Demographics and baseline characteristics

Overall, 158 English-speaking patients (mean age 56 years, 41% male) and 113 French-speaking patients (mean age 58 years, 31% male) participated in this phase of the study. The educational backgrounds for the English-speaking group were college or university (36%), high school (47%) and elementary school (17%); the corresponding figures for the French-speaking group were 31%, 53% and 16%, respectively.

At baseline, all patients had GOS scores of at least 3 (of 7 possible), with a median GOS score of 4 for both the English- and French-speaking groups. There were no significant differences in demographics between the English and French patient groups. All patients were receiving PPI therapy at baseline: omeprazole (37%), pantoprazole (31%), lansoprazole (16%) and rabeprazole (16%). Two hundred forty-nine patients of the initial 271 remained in the study for four weeks after visit 2 and

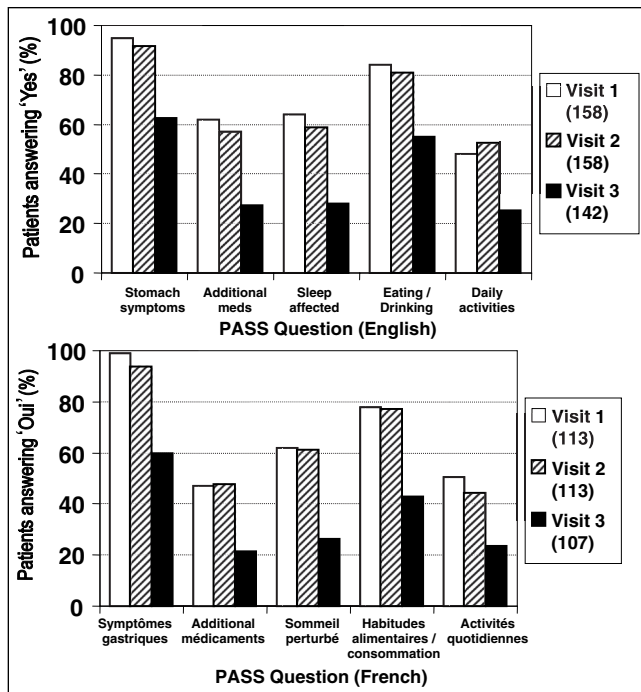


Figure 3) The percentages of patients answering 'Yes' to each question, at the three visits, for English- (upper panel) and French-speaking (lower panel) patients. Meds Medications; PASS Proton pump inhibitor Acid Suppression Symptom test

completed the follow-up assessments. Except for two patients (with a compliance rate of less than 80%), all patients had a high compliance rate with the medication during the four-week treatment phase.

Mean total PASS scores were 3.5 (SD 1.2) and 3.4 (SD 1.4) for visits 1 and 2, respectively, in the English group; and 3.4 (SD 1.2) and 3.3 (SD 1.3), respectively, in the French group. After the four-week treatment, at visit 3, the mean total PASS scores had fallen to 2.0 (SD 1.7) and 1.7 (SD 1.7) in the English and French groups, respectively. The proportions of patients answering 'Yes' to the individual questions were comparable at visits 1 and 2 but fell markedly by visit 3 (Figure 3).

Test-retest reliability and internal consistency

Test-retest analysis correlation coefficients were calculated for all patients in each group by comparing study results obtained at visits 1 and 2. Test-retest coefficients were 0.76 and 0.68 for the English and French versions of PASS test, respectively, indicating good-to-excellent reliability.

Internal consistency measurement by means of G-analysis gave results in the moderate range (between 0.50 and 0.48) for English and French. Assessment of internal consistency at visit 2, which was performed by comparing scores for individual items with the summed scores for the other four items, indicated a low-to-moderate correlation (0.15 to 0.46) for all items in both languages.

Construct validity

The PASS test scores were compared with baseline scores for the comparator scales (GSRs, QoLRAD and RDQ) to evaluate construct validity (Table 2).

The PASS test score from visit 2 showed moderate-to-high correlation with the overall GSRs scale in both languages

TABLE 2
Correlation coefficients ($P < 0.0001$ unless otherwise reported) for Proton pump inhibitor Acid Suppression Symptom (PASS) questionnaire scores compared with domain and overall scores for other scales by language and visit

SCALE, Language	Domains	PASS total (visit 2)	PASS total (visit 3)
GSRs			
English	Diarrhea	0.36	0.35
	Indigestion	0.42	0.59
	Constipation	0.22 ($P=0.0060$)	0.40
	Abdominal pain	0.56	0.76
	Reflux	0.40	0.70
	GSRs overall	0.51	0.74
French	Diarrhea	0.17 ($P=0.0753$)	0.20 ($P=0.0321$)
	Indigestion	0.34 ($P=0.0002$)	0.51
	Constipation	0.23 ($P=0.0158$)	0.29 ($P=0.0022$)
	Abdominal pain	0.32 ($P=0.0005$)	0.55
	Reflux	0.35 ($P=0.0002$)	0.63
	GSRs overall	0.43	0.62
QoLRAD			
English	Emotional distress	-0.52	-0.74
	Sleep disturbance	-0.57	-0.70
	Food or drink problem	-0.51	-0.80
	Physical or social	-0.49	-0.71
	Vitality	-0.52	-0.75
French	Emotional distress	-0.41	-0.63
	Sleep disturbance	-0.50	-0.74
	Food or drink problem	-0.43	-0.63
	Physical or social	-0.38	-0.57
	Vitality	-0.31 ($P < 0.001$)	-0.63
RDQ			
English	Heartburn	0.32	0.56
	Regurgitation	0.36	0.55
	Epigastric pain	0.42	0.63
	GERD	0.37	0.64
	Overall RDQ	0.41	0.68
French	Heartburn	0.25 ($P=0.0016$)	0.55
	Regurgitation	0.30 ($P=0.0013$)	0.55
	Epigastric pain	0.22 ($P=0.0196$)	0.54
	GERD	0.34 ($P=0.0003$)	0.69
	Overall RDQ	0.37	0.69

GERD Gastroesophageal reflux disease; GSRs Gastrointestinal Symptom Rating Scale; QoLRAD Quality of Life in Reflux and Dyspepsia; RDQ Reflux Disease Questionnaire

(0.51 and 0.43) and moderate QoLRAD correlation (0.38 to 0.57) depending on the domain and language. Some domains in each scale correlated better than others with the total PASS test score. For visit 3, all correlations were higher, reflecting the treatment response. In all instances, the sign of the correlation was in the appropriate direction. However, weak-to-mild correlation was found for RDQ with lower values for the French version than the English. Again for visit 3, there was a substantial increase in correlation between PASS test scores and RDQ, both for total score and all domains. There was a poor correlation between the PASS test scores and the acid-independent GSRs dimensions of constipation and diarrhea.

TABLE 3
Effect sizes for Proton pump inhibitor Acid Suppression Symptom (PASS) test responders (PASS score = 0) and PASS test nonresponders (PASS score > 0) for the Gastrointestinal Symptom Rating Scale (GSRS), Quality of Life in Reflux and Dyspepsia (QoLRAD) and Reflux Disease Questionnaire (RDQ) by domain after four weeks of treatment

SCALE, Domain	English		French	
	Non-responders	Responders	Non-responders	Responders
GSRS				
Diarrhea	-0.17	-0.68	-0.27	-0.44
Indigestion	-0.45	-0.96	-0.69	-1.20
Constipation	-0.26	-0.55	-0.21	-0.71
Abdominal pain	-0.43	-1.04	-0.61	-1.14
Reflux	-0.61	-1.20	-0.70	-1.38
QoLRAD				
Emotional distress	0.50	0.92	0.51	1.31
Sleep disturbance	0.49	0.93	0.47	1.27
Food or drinking problem	0.69	1.29	0.62	1.53
Physical or social	0.35	0.68	0.35	1.15
Vitality	0.55	1.08	0.48	1.45
RDQ				
Heartburn	-0.49	-1.00	-0.46	-1.21
Regurgitation	-0.53	-0.95	-0.38	-1.12
Epigastric pain	-0.41	-0.95	-0.53	-1.29
GERD	-0.56	-1.04	-0.49	-1.34

GERD Gastroesophageal reflux disease

Greater symptom severity, recorded by the GOS score at baseline, was associated with higher total PASS scores (data not shown). Similar trends were observed for the other validated scales.

Responsiveness and discriminant validity

The PASS results showed that 42 (30%) and 35 (33%) patients in the English- and French-speaking groups, respectively, were ‘PASS test responders’ on a per protocol analysis; ie, they had complete resolution of their symptoms (PASS test score 0) at the end of treatment.

Most of the effect sizes for individual domains of the three validated scales GSRS, RDQ and QoLRAD were moderate-to-good for PASS test responders in both the English- and French-speaking groups (Table 3) and responders’ effect sizes were, on average, two to three times higher than the effect sizes for the PASS test nonresponders.

The first PASS question provided the greatest observed response reduction (-1.25 and -1.68 for English and French, respectively), with other questions providing responses in the range of 0.45 to 0.85 (data not shown), comparable to the individual domain responses for all three validated scales. Despite the small number of subjects in some response classes, greater improvement was observed in those PASS test responders who had also reported a larger overall treatment effect (Figure 4). For PASS test responders, a large overall treatment effect was associated with an effect size of -2.95 (-3.67/1.24) and -3.22 (-3.90/1.21) for the English and French groups, respectively.

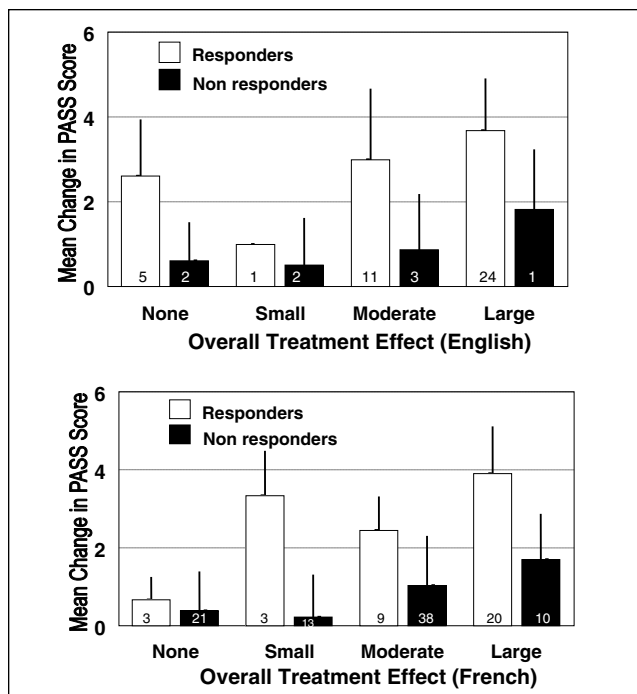


Figure 4) Mean change in Proton pump inhibitor Acid Suppression Symptom (PASS) total score (line indicates SD) for PASS test responders and nonresponders, stratified by degree of change in overall treatment effect (n in each column) after four weeks of treatment at visit 3 for both English- (upper panel) and French-speaking (lower panel) patients

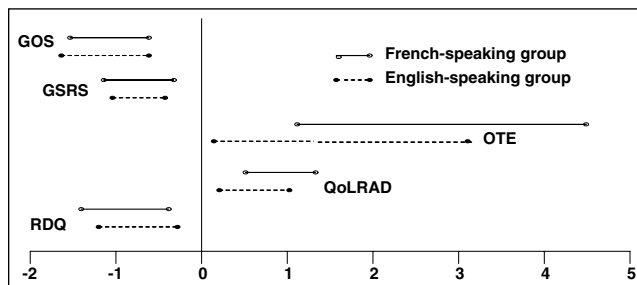


Figure 5) Difference in scores (95% CI) between Proton pump inhibitor Acid Suppression Symptom test responders and nonresponders. The solid lines indicate responses from the French-speaking group and the dashed lines indicate responses from the English-speaking group. GOS Global Overall Symptom scale; GSRS Gastrointestinal Symptom Rating Scale; OTE Overall treatment effect; QoLRAD Quality of Life in Reflux and Dyspepsia questionnaire; RDQ Reflux Disease Questionnaire

After patients switched their PPI medication at visit 2, 54% (77 of 142) in the English-speaking group and 69% (74 of 107) in the French-speaking group experienced symptom relief with esomeprazole based on their GOS response. In both linguistic groups, 32% of patients had a total resolution of their symptoms at the end of four weeks.

The response to treatment, calculated as the difference between scores at baseline and after treatment for all comparator scales, was significantly greater in patients defined as PASS test responders than in PASS test nonresponders (Figure 5). All scales in the plot show that patients had an improvement

in the severity of symptoms (scored by PASS) after using esomeprazole.

Safety

Reported adverse events were mostly mild-to-moderate and transient, and none was considered to be causally related to esomeprazole therapy.

DISCUSSION

The PASS questionnaire was developed using established methodology to address the identified need for a simple clinical tool. The concerns and therapeutic needs of patients with persistent acid-related symptoms despite ongoing PPI therapy were first documented and, based on this, a list of questions was developed to assess content validity in focus groups. Five major areas or domains of interest or concern to patients were identified; therefore, the PASS questionnaire was designed as a short five-question questionnaire. With respect to content validity, the focus group members' responses were all in the good-to-excellent range, indicating that the PASS questions were clear, relevant to their experience, easy to understand and suitable for the development of a questionnaire. Acknowledging the importance of linguistic and cultural differences in Canada, the French and English versions were developed separately, rather than by back-translation from one language to the other.

Psychometric validation of the questionnaire focused on construct validity, test-retest reliability and responsiveness in French and English populations. The construct validity data indicate that the PASS questionnaire can detect ongoing symptoms in domains of importance to patients; this is confirmed by strong correlations between the PASS scores and other validated outcome measures including the GOS score for dyspepsia symptom severity, the QoLRAD, RDQ and GSRS questionnaires and the OTE questionnaire.

The PASS questionnaire demonstrated excellent test-retest reliability when comparing questionnaire scores from the baseline visit with those obtained one week later. It also demonstrated good responsiveness in detecting a significant change in health status. Because the PASS test questionnaire was designed to pose a very limited number of questions – each question intended to address an independent aspect of the patient's symptoms – there was, as expected, low internal consistency and this was confirmed by the G-analysis.

Approximately 30% of the patients reported complete resolution of their symptoms, based on their PASS and GOS scores. Because this was an open label treatment study, one cannot conclude that esomeprazole was superior to the previous PPI therapy but the data suggest that persistent symptoms will respond to a change in PPI therapy in a substantial proportion of patients. Further, double-blind studies are needed to determine the extent to which more potent acid suppression will produce symptom resolution in patients with persistent symptoms on standard PPI therapy.

SUMMARY

The present paper presents the development and validation of a short, five-question tool to identify patients with persistent acid-related symptoms; test scores correlate well with accepted validated scales and the new, short questionnaire

shows a good response to a four-week course of acid suppression therapy with a PPI. The test has good test-retest reproducibility and responsiveness.

In its current form, the PASS questionnaire allows patients to record their current symptoms easily and it facilitates communication with their physicians; the questionnaire also allows physicians to rapidly assess their patients' symptom status during PPI therapy. As such, it should help physicians to identify patients with upper GI, acid-related problems that require rescue medication or a change in acid suppression therapy, and it may also be helpful in assessing the patients' response to treatment.

In the future, the PASS questionnaire may also be developed as a simple diagnostic test, to differentiate between those patients who have symptoms that will respond to an increase in acid suppression therapy and those patients who have other, possibly functional symptoms that are not acid-related. This test would be beneficial in clinical practice but it might also help to determine, from a payer's perspective, whether an increase in acid suppression therapy is appropriate. Finally, it may be useful to monitor symptom response in large-scale clinical trials designed to assess the effect of changing therapy for patients with persistent reflux- or acid-related symptoms.

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