

Chronic Cough is predominantly a Woman's Issue

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Abstract

Rationale: Women are more sensitive to cough triggers, have a greater cough frequency, and experience more cough-associated symptoms. Previous studies have been unable to consistently demonstrate that chronic cough has a greater impact on certain quality of life domains in women, particularly in functional status, compared to men. The inability to show gender-related differences in quality of life may be due to the small number of men in previous reports.

Objectives: To demonstrate the greater impact of chronic cough on quality of life, particularly the functional domain, in women.

Methods: Patients referred to the Calgary Chronic Cough Clinic completed a cough-specific quality of life questionnaire. They also completed a 0-10 visual analog scale to score the severity of their cough-associated symptoms. The cough-specific quality of life questionnaire and visual analog scale results were analyzed by gender.

Measurements & Results: Data were available from 379 patients including 129 men. The total cough-specific quality of life score was greater, i.e. worse, in women than men (61.7 +/-14.5 versus 52.9 +/-12.8, p<0.001). Physical, psychosocial, functional and extreme physical domain scores were greater in women. Personal safety and emotional domain scores were similar. Using a visual analog scale, women rated urinary and fecal incontinence, nausea and vomiting worse. Chest pain, throat pain, and dizziness were rated similarly.

Conclusions: Cough has a greater impact on quality of life in women, negatively impacting on the functional domain, in addition to the previously reported effects on the physical and psychosocial domains.

Keywords: Chronic cough; Gender issues; Quality of life; Asthma; Gastroesophageal reflux; Rhinitis; Laryngeal irritation

Abbreviations: CQLQ: Cough-specific Quality of Life Questionnaire; CRE: Certified Respiratory Educator; LCQ: Leicester Cough Questionnaire; QOL: Quality of Life; VAS: Visual Analog Scale

Introduction

Women are more likely to seek medical attention for chronic cough, and account for the majority of chronic cough clinical trial participants [1,2]. Moreover, women are more apt to complain of nocturnal and nonproductive cough and experience more frequent cough [3,4]. Acoustic recordings from patients referred for evaluation of chronic cough confirm that women have higher cough rates, particularly at night [5]. These gender-related differences have been shown in chronic idiopathic cough, cough-variant asthma, and chronic cough due to gastroesophageal reflux (GERD) [6,7]. Women taking angiotensin converting enzyme inhibitors are more likely to develop chronic cough [8-10].

Gender-related differences on quality of life (QOL) have been described but, surprisingly, chronic cough did not have a greater impact on the functional domain in women. Kelsall and coworkers were unable to show gender-related differences in Leicester cough questionnaire (LCQ) scores despite objectively proving that women cough more [5]. However, that study was only powered to show differences in cough frequency rather than QOL.

Using their validated cough-specific QOL questionnaire (CQLQ), French and colleagues reported gender-related differences in the physical, extreme physical and psychosocial domains of the CQLQ but not in the functional, emotional or personal safety domains [11]. Among referrals to the Calgary Chronic Cough Clinic, female patients often report a reluctance to participate in social activities such as attending religious services, plays or concerts because of their tendency to cough. Some report work absences and, in some cases, being compelled to leave work permanently because of the negative impact of chronic cough or associated stress incontinence on their ability to work.

Earlier studies were underpowered to demonstrate gender-related differences in the functional QOL domain scores. Only a minority of the subjects were male in the previously published QOL trials, limiting comparison of the gender-specific characteristics. To address this question, the large prospectively-collected Calgary Chronic Cough Clinic database was reviewed to compare the CQLQ functional domain score between women and men.

Methods

Calgary chronic cough clinic

The clinic accepts physician referrals of outpatients for investigation and management of chronic cough. Typical of the Canadian health care system, none of the patients are self-referred. Most are referred by family practitioners, but 16% were referred by specialists including allergists, otolaryngologists, gastroenterologists, and respirologists. The majority had undergone investigations and multiple therapeutic trials prior to referral and nearly half were assessed by at least one consultant previously [1].

The mandate of the clinic is to expedite the safe and effective management of patients suffering primarily from chronic cough who will benefit from the services of a certified respiratory educator. The most common final diagnoses are cough due to upper airway causes, GERD, cough variant asthma, irritable larynx syndrome, also called tic cough, or various combinations of these conditions.

Prior to the initial clinic appointment, patients are assessed to determine whether they can be managed by a certified respiratory educator. This is to insure that patients with potentially life-threatening conditions are seen promptly by a respiratory specialist, yet wait time reductions are achieved for all patients [1,12]. Referrals are screened to identify those with abnormal chest radiographs, hemoptysis, dyspnea, a history of cancer or serious underlying lung disease, other serious comorbid conditions, or systemic symptoms including weight loss, fever, and night sweats, to determine who will be seen semi-urgently by a respirologist [12]. Fatigue is not an exclusion since many cough patients experience sleep disruption. Chest wall pain is also not an exclusion. If laboratory investigations suggest a serious underlying illness, including abnormal blood tests, an abnormal chest computed tomography scan, even if the chest radiograph was reported to be normal, or abnormal sputum cytology, the patient is seen by a respirologist. At first attendance, patients were questioned about concerning symptoms or conditions. If any were present, patients were excluded from the study and were seen by a respirologist. Among the referrals, 52% were excluded because of

concerning symptoms, comorbid conditions, abnormal laboratory or imaging findings. If concerning conditions were not present, patients were randomized to be seen by either a respirologist or a certified respiratory educator.

The clinic database includes information on the patients who participated in a comparative trial of the management of chronic cough by certified respiratory educators or respirologists and clinic patients seen by certified respiratory educators after the study was completed [1]. In addition to a complete medical history, all patients undergo a physical examination, recent chest radiography, and spirometry, and complete the CQLQ. Patients also rate the severity of their cough-associated symptoms including retching, vomiting, chest and throat pain, stress incontinence, and sleep disruption with a visual analog scale (VAS). The study was approved by the University of Calgary/Calgary Zone, Alberta Health Services Conjoint Health Research Ethics Board (Ethics ID E18360). All patients gave written informed consent prior to being screened for study participation and they were free to withdraw from the study at any time.

Statistics

Analyses were performed with SPSS version 15.0 (SPSS Inc, Chicago, Illinois). Normally distributed data were presented as the mean and S.D. Comparison between normally distributed data of the two groups was done by independent t tests. Nonnormally distributed data were expressed as medians and analyzed using a Mann-Whitney U test. Categorical and ordinal patient outcomes were compared by chi square or Fisher’s exact test. For all statistical analyses, p values <0.05 were considered significant.

Power calculations

The power calculations were based on the results of French and colleagues [11]. In their report, women had significantly higher scores in 10 of the 28 CQLQ items. The mean score for stress incontinence was 47% higher in women. The differences in the nine other items ranged from 12 to 19%. The differences between men and women were nearly as great in 6 other items but the study was not adequately powered to demonstrate statistical significance. Based on this study, a sample size of 318 subjects is required to demonstrate a gender-related difference of 10% with an average per item score of 2.0 (95% C.I. 1.9-2.1) with a power of 0.80 and α of 0.05 [11,13].

Results

Patient demographics

Data were collected from 379 patients who completed the CQLQ; 198 study subjects and 181 patients seen subsequently by certified respiratory educators in the Calgary Chronic Cough Clinic [1]. Approximately 66% were female, were an average of 50.8+/-14.1 years, had an average Body Mass Index of 28.4+/-6.0, mean FEV₁ was 98.8+/-15.6 and 97.9+/-17.3 % of the predicted values and FEV₁/FVC was 76% and 75%, in females and males, respectively. Median cough duration was 21 months (mean of 73+/-107 months) (Table 1). The numbers of current, ex- and never smokers and their smoking histories are shown in Table 1.

Visual analog scale

Using the VAS, women rated urinary (2.7+/-3.0 vs 0.1+/-0.7, p<0.001) and fecal incontinence (0.3+/-1.0 vs 0.0+/-0.2, p<0.001), and nausea and vomiting (2.9+/-3.1 vs 2.0+/-2.9, p=0.007) greater than men. Chest pain (4.1+/-3.2 vs 3.6+/-3.2, p=n.s.), throat pain (3.8+/-2.9 vs 3.2+/-2.7, p=0.06), and dizziness (2.5+/-2.8 vs 2.8+/-3.2, p=n.s.) were rated similarly using the VAS. The VAS results were similar to the CQLQ for nausea and vomiting, urinary and fecal incontinence, and dizziness. Similar to the CQLQ ratings, chest pain was rated higher in women but the difference was not statistically significant. Throat pain also tended to be greater in women.

Total cough specific quality of life (CQLQ) scores

Higher CQLQ scores represent worse QOL. Women had an average total CQLQ score of 61.7+/-14.5 versus 52.9+/-12.8 in men (p<0.001) (Figure 1). Twenty-three of 28 of the CQLQ components were rated worse by women (table 2). In women, CQLQ scores in the physical (20.1+/-5.7 vs 17.3+/-5.2, p<0.001), psychosocial (12.9+/-3.7 vs 11.0+/-3.4, p>0.001), functional (10.4+/-3.9 vs 8.8+/-3.1, p<0.001), emotional (6.0+/-1.9 vs 5.4+/-1.6, p<0.004), and extreme physical (8.2+/-2.7 vs 6.3+/-1.9, p<0.001) domains were rated poorer. The personal safety domain scores were similar in women and men (7.4+/-2.3 vs 7.2+/-2.1, p= 0.39) (Figure 2).

Physical domain

CQLQ scores in eight of the nine components of the physical domain were significantly worse in women; including cough-associated appetite loss, headaches, sweating, voice hoarseness, chest pain, sleep

Table 1: Patient demographics.

Age is expressed in years, gender ratios are expressed as females/males and FEV1 as percent of the predicted value (FEV1%). FEV1/FVC is the ratio of FEV1 to Forced vital capacity (FVC). Smoking status is presented as absolute number (percent of total). One pack year is defined as smoking an average of 20 cigarettes daily for a year and the average and median amounts smoked are presented. Smoking his is based on the patients’ recollection and not on any objective data. Cough durations in months are median and interquartile values. Abbreviations: FEV1%, n.s.: not statistically significant.

| Demographics | Females | Males | p value |
|---|-------------|-------------|---------|
| Number of patients | 250 | 129 | |
| Age | 51.4+/-14.0 | 49.6+/-14.1 | n.s. |
| Body Mass Index | 28.3+/-6.2 | 28.5+/-5.7 | n.s. |
| Current smokers | 19 (7.6%) | 12 (9.3%) | n.s. |
| Pack years smoked Mean, Median | 17.7,6 | 24.8,11.3 | |
| Former smokers | 71 (28.4%) | 36 (27.9%) | n.s. |
| Pack years smoked Mean, Median | 12.7,10 | 16.5,11.1 | |
| Never smokers | 160 (64%) | 81 (62.8%) | n.s. |
| FEV1 (% predicted) | 98.8+/-15.6 | 97.9+/-17.3 | n.s. |
| FEV1/FVC (mean) | 76% | 75% | n.s. |
| Cough duration (median, interquartiles) | 20 (7-120) | 24 (6-96) | n.s. |

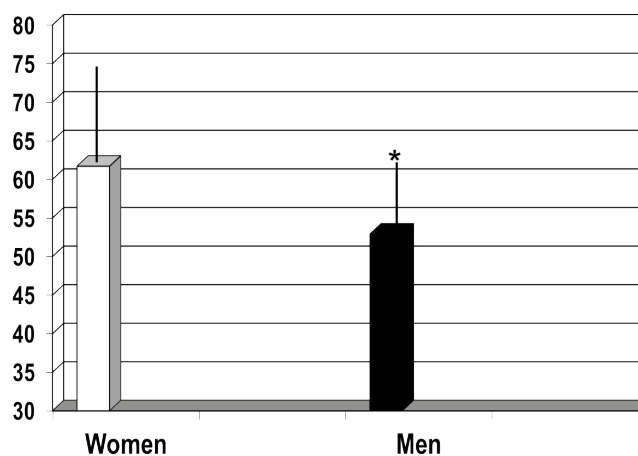


Figure 1: Total cough-specific quality of life. Comparison of the total cough-specific quality of life questionnaire (CQLQ) scores in men and women. A lower score reflects better quality of life. * p<0.001.

Table 2: Comparison by gender of the differences in the scores for all 28 items in the 6 domains

The items in each domain are tabulated. The position in the 28 item questionnaire, the item, scores by gender (mean+/-S.D.), and p values determined by chi square or Fischer's exact test are provided.

| Physical domain | Female | Male | p |
|----------------------|-----------|-----------|--------|
| 4. appetite loss | 1.9+/-1.0 | 1.6+/-0.7 | <0.001 |
| 8. headaches | 2.3+/-1.0 | 2.0+/-0.9 | 0.002 |
| 10. dizziness | 2.0+/-0.9 | 1.9+/-0.9 | n.s. |
| 13. sweating | 2.1+/-0.9 | 1.9+/-0.9 | 0.016 |
| 14. hoarseness | 2.7+/-0.9 | 2.4+/-0.9 | 0.003 |
| 15. chest pain | 2.2+/-0.9 | 1.9+/-0.8 | 0.002 |
| 17. sleep disruption | 2.5+/-0.9 | 2.0+/-0.9 | <0.001 |
| 22. ache all over | 2.0+/-0.9 | 1.6+/-0.7 | <0.001 |
| 23. exhaustion | 2.6+/-1.0 | 2.1+/-0.9 | <0.001 |

| Psychosocial domain | Female | Male | p |
|----------------------------------|-----------|-----------|--------|
| 1. others cannot tolerate cough | 2.6+/-1.0 | 2.3+/-1.0 | <0.001 |
| 18. difficulty speaking on phone | 2.5+/-1.0 | 2.2+/-1.0 | 0.003 |
| 24. embarrassed | 2.6+/-1.0 | 2.2+/-1.0 | <0.001 |
| 25. upset by other people | 2.5+/-1.0 | 2.1+/-0.9 | 0.001 |
| 27. self-conscious | 2.7+/-0.9 | 2.3+/-0.9 | <0.001 |

| Functional domain | Female | Male | p |
|------------------------------------|-----------|-----------|-------|
| 2. prolonged absences from work | 2.1+/-1.0 | 1.8+/-0.9 | 0.004 |
| 3. unable to work, volunteer, etc. | 1.8+/-0.8 | 1.6+/-0.7 | 0.012 |
| 19. unable to sing | 2.3+/-1.0 | 1.9+/-1.0 | 0.001 |
| 20. stopped social activities | 1.9+/-0.9 | 1.6+/-0.7 | 0.001 |
| 21. obliged to change lifestyle | 2.1+/-0.9 | 1.9+/-0.8 | 0.007 |

| Extreme physical | Female | Male | p |
|--------------------------|-----------|-----------|--------|
| 5. vomiting | 1.9+/-1.0 | 1.6+/-0.8 | 0.002 |
| 6. retching | 2.5+/-1.1 | 2.3+/-1.0 | 0.035 |
| 11. urinary incontinence | 2.3+/-1.1 | 1.2+/-0.4 | <0.001 |
| 12. fecal incontinence | 1.4+/-0.7 | 1.2+/-0.4 | <0.001 |

| Emotional domain | Female | Male | p |
|-----------------------|-----------|-----------|-------|
| 7. Fear of TB or AIDS | 1.4+/-0.7 | 1.3+/-0.6 | n.s. |
| 16. I broke a rib | 1.4+/-0.6 | 1.2+/-0.5 | 0.014 |

| Personal safety | Female | Male | p |
|--------------------------------|-----------|-----------|------|
| 9. cancer concern | 1.8+/-0.9 | 1.7+/-0.8 | n.s. |
| 26. need for reassurance | 3.1+/-0.9 | 3.1+/-0.9 | n.s. |
| 28. concern of serious illness | 2.5+/-0.9 | 2.4+/-0.9 | n.s. |

Abbreviations: AIDS: acquired immune deficiency syndrome, n.s.: not statistically significant, S.D.: standard deviation, TB: tuberculosis.

disruption, general achiness, and exhaustion (Table 2). Dizziness ratings were similar in women and men (Table 2).

Psychosocial domain

All five psychosocial domain components, including intolerance of the cough by friends and relatives, difficulty speaking on the telephone, concern by others, embarrassment, and self-consciousness, were significantly worse in women (Table 2).

Functional domain

The effects of cough on all five CQLQ components of the functional domain were greater in women. Prolonged absences from work, inability to work or volunteer, inability to sing or attend social activities and obligation to change lifestyle were worse in women (Table 2).

Extreme physical domain

Women rated the effects of cough on urinary and fecal incontinence and on vomiting and retching worse than did men (Table 2).

Emotional and personal safety domains

Although the difference in the emotional domain score was statistically significant, it was relatively small and may not be clinically relevant. The differences in the individual items in the emotional domain, 'I broke a rib' and 'I have a fear that I might have AIDS or tuberculosis' were relatively small (Table 2). Fears that the cough represented a serious illness were similar in men and women as was the need for reassurance (Table 2). Fear that cough was due to cancer or another serious condition, was similar in men and women (Table 2).

Discussion

The impact of chronic cough is evaluated by its severity, associated-symptoms, and by its detrimental effect on lifestyle and QOL. Both the CQLQ and LCQ were developed to evaluate cough-specific QOL [14]. The recently published American College of Chest Physicians cough guidelines endorse use of both the LCQ and CQLQ, 'they are the most extensively studied and commonly used previously validated and reliable cough-specific health-related QOL questionnaires to assess the impact of cough' [15,16]. The LCQ contains 19 questions covering the physical, psychological, and social QOL domains [14]. It is not as comprehensive as the CQLQ nor does it assess the functional impact of cough to the same extent despite inquiring whether cough has hampered the ability to work or perform daily tasks in the previous two weeks and whether it has interfered with conversation or talking on the telephone. Although the LCQ correlated with the VAS-scored cough severity [14], it did not show gender-related differences in any of the major domains but in the study that evaluated gender-related differences it was not powered for that purpose with only 86 patients and only 29 male participants [5].

The CQLQ was chosen to analyze the impact of chronic cough on QOL in CCCC since it is more comprehensive than the LCQ, evaluating 28 items covering six domains including questions on stress incontinence which is common in our female patients. It also contains five questions that specifically address the effect of chronic cough within the functional domain. Moreover, the CQLQ was validated in a North American population with similar demographics to our patients; primarily female, middle-aged, and upper airway cough syndrome was the most common etiology [2].

CQLQ domain scores

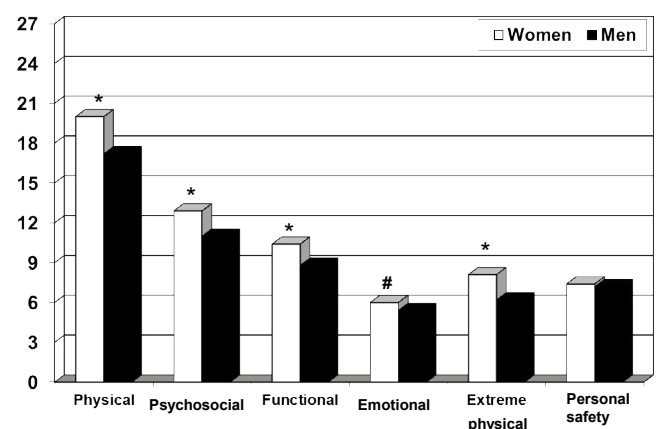


Figure 2: Scores for the individual domains of the cough-specific quality of life (CQLQ) in men and in women. The 6 domains are physical, psychosocial, functional, emotional, extreme physical and personal safety. $p < 0.001$, # $p < 0.01$.

The minimal clinically important difference has not been determined with the CQLQ. In a previous report, the CQLQ score did not change in patients whose cough did not improve after eight weeks of treatment, decreased an average of 10.4 in patients whose cough improved, and decreased 14.8 in those whose coughs resolved [1]. The mean gender difference was 8.8 ($p < 0.001$), similar to the difference reported in patients whose cough improved.

In health status studies, a quotient of the score difference divided by the standard deviation > 0.5 , the effect size, is considered clinically significant [17]. In this study the effect size of the gender difference was > 0.6 , suggesting that it was clinically significant.

French et al reported that the total CQLQ score and the physical, psychosocial, and extreme physical domain scores were worse in women but there were not gender-related differences in the other domains; functional, emotional, and personal safety [18]. That report included data from a study with 154 subjects, including 38 males and data from another 18 men with chronic cough; a total of 56 males [11].

The present study found significant gender-related differences in 23 of 28 CQLQ items (Table 2). Even when the rigorous Bonferroni correction, is applied to adjust for multiple comparisons, differences remain statistically significant for 18 items. The clinic data confirm that most patients referred for evaluation of chronic cough are female and that chronic cough has a greater impact on their QOL [3-5]. Earlier reports were inadequately powered to demonstrate gender-related differences in the functional and emotional domains [11,18]. Since chronic cough has a greater impact on the physical, extreme physical, and psychosocial CQLQ domains in women, it would be anticipated to have a greater effect on the functional domain. In the current report, there were gender-related differences in the physical, extreme physical, psychosocial and in the functional domain.

An important difference from previous reports was that this study was adequately powered to show differences in the functional domain in items such as prolonged absences from work and social activities, lifestyle disruption, physical complaints such as fecal incontinence, hoarseness, and sleep disruption, and inability to sing. These were all significantly worse in women. Moreover, women reported greater difficulty talking on the telephone, which interfered with their ability to work in certain professions.

The quotient of the functional domain score difference between the genders and the standard deviation, 1.6/3.1, was greater than 0.5 suggesting that the difference is also clinically significant [17].

One would anticipate that the greater physical, psychosocial and functional impacts of chronic cough would affect women more and be reflected in the emotional domain score. Although statistically significant, the absolute difference between the gender scores was small and possibly not clinically relevant, although only two questions are included in this domain.

Fears of personal safety were similar in men and women. Even though the consequences of cough were greater in women, they were as confident that their lives were not in danger.

Anger, anxiety, and frustration are common in these patients and may contribute to their perceptions of how the cough disrupts their lives [18]. Similar to patients in other specialized cough clinics, our patients represent the more severe end of the spectrum [19]. The frequent doctor visits, clinical investigations, medication use, adverse effects, and cost of medications, both over-the counter and prescribed, contribute to the detrimental effect on QOL [19].

Summary

Chronic cough patients suffer from anxiety and depression related to the physical, psychosocial, and functional impact of their condition [20,21]. Women are more likely to complain of chronic cough or

associated symptoms such as stress incontinence, more likely to seek medical attention and to be referred to a consultant for assessment of the cough [11]. In addition to a greater sensitivity to cough stimuli, the adverse effects of chronic cough on health-related QOL are greater in women [11,18].

Cough has a significantly greater impact on their QOL and it is important to understand the gender-related differences in chronic cough and its complications in order to properly evaluate, treat and support these patients.

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Conflicts of Interest

None of the authors have conflicts of interest regarding the contents of this manuscript.

Authors Contributions

S. K. Field: Study design, data collection, analysis & interpretation, manuscript preparation

Diane P. Conley: Study design, data collection and analysis, manuscript approval

Leslie Paramchuk: Data collection, manuscript approval

Richard Leigh: Study design, data collection & interpretation, manuscript preparation

Brandie L. Walker: Data collection and interpretation, manuscript preparation

Robert L. Cowie: Study design, data collection & interpretation, manuscript preparation

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