International Journal of Chronic Obstructive Pulmonary Disease Dovepress
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REVIEW

# Performance of the Cough and Sputum Assessment Questionnaire (CASA-Q) in COPD: Evidence from Clinical and Online Patient Interaction Studies

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**Introduction:** Patient perception of the burden of chronic bronchitis symptoms in chronic obstructive pulmonary disease (COPD) can be assessed using patient-reported outcome measures (PROMs). The Cough and Sputum Assessment Questionnaire (CASA-Q) was developed and tested for this purpose. This study reviewed the performance of the CASA-Q in published online studies and tested a novel approach to complement traditional methods of qualitative content validation.

**Methods:** A targeted literature search was performed to identify published clinical studies of COPD using the CASA-Q as an endpoint. The performance of the questionnaire was examined in relation to other study endpoints, including clinical and functional measurements and other PROMs. Assessment of the content validity of the CASA-Q was carried out by comparing the content and structure of the questionnaire with published qualitative patient data from previously conducted online social media listening (SML) and online bulletin board (OBB) studies.

**Results:** In the interventional clinical trials, CASA-Q change scores were consistent with study objectives and other endpoints, including $FEV_1$ and other PROMs. Two observational studies showed cross-sectional correlations with other PROMs like the St.-George's Respiratory Questionnaire (SGRQ) and COPD assessment test (CAT) scores. Qualitative data from the SML and OBB patient studies were consistent with the content and structure of the CASA-Q, supporting the content validity of the measure.

**Conclusion:** Results suggest that the CASA-Q is appropriately responsive to changes in cough and sputum symptoms and clinical impact in trials of COPD. The mapping of qualitative findings from online SML and OBB studies to CASA-Q domains and items confirm the content validity of the instrument. These results suggest the CASA-Q can be a valuable tool for evaluating treatment effect in COPD trials.

**Keywords:** patient-reported outcomes, social media, online bulletin board, online community, CASA-Q, chronic obstructive pulmonary disease, content validation, performance, chronic bronchitis

## Introduction

COPD is a common disease with a prevalence ranging from 10% to 15%[1,2] and is the third leading cause of death worldwide.[3] COPD is characterized by persistent respiratory symptoms and airflow limitation due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles/gases, in particular cigarette smoke. Chronic bronchitis, a key phenotype amongst COPD patients, is characterized by chronic cough and mucus.[4]

Chronic bronchitis symptoms in COPD have been linked to increased disease burden and health-care costs due to increased exacerbation rates and severity, disease progression, and potential mortality.[5,6] However, despite various

Received: 8 July 2022
Accepted: 24 November 2022
Published: 10 December 2022



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debilitating effects associated with cough and excess mucus production, current treatments such as smoking cessation, chest or respiratory physiotherapy, expectorants and mucolytics, etc., inadequately manage these symptoms resulting in significant unmet need in patients living with COPD and chronic bronchitis.[7,8] The current therapeutic focus has been mostly on outcomes targeted by existing treatments, such as lung function, exacerbations, and shortness of breath. However, cough and sputum present an important part of the daily symptom burden in patients with COPD with chronic bronchitis,[9,10] and relying on patient-reported improvement in symptoms of cough and sputum along with lung function by $FEV_1$ enables better phenotyping of COPD symptoms. Patient-reported outcomes measures (PROMs) are increasingly used to assess subjective concepts of health and add value to the clinical development and evaluation process. PROMs play a key role in measuring the overall impact of a disease on a patient's health-related quality of life (HRQoL). Understanding patient needs and expectations related to this disease and its treatments is essential to ensure that clinical development addresses what matters to patients.[11]

The cough and sputum assessment questionnaire (CASA-Q) was developed to measure the severity and impact of cough and sputum in patients with COPD and chronic bronchitis.[12] It was developed in accordance with the 2006 US Food and Drug Administration (FDA) draft guidance to industry on the use of PROMs.[13] In keeping with the guidance, the developers of CASA-Q involved patients in the concept elicitation and cognitive debriefing phases to ensure content validity. The questionnaire focuses not only on the severity of physical symptoms of cough and sputum production, but also on the emotional, social, and psychological impact on the patient's life. The psychometric properties were established through an independent validation study and another subsequent study.[12,14]

CASA-Q is a 20-item questionnaire with a 7-day recall period. The development and validation of the instrument have been described in detail,[12] and the responsiveness has also been assessed.[14] The domains include cough symptom severity (COUS) with 3 items, cough impact (COUI) with 8 items, sputum symptom severity (SPUS) with 3 items and sputum impact (SPUI) with 6 items. Each item is answered on a 5-point Likert scale ranging from "never" to "always" for frequency or from "not at all" to "a lot/extremely" for intensity.[14] The CASA-Q does not have a total score, and each domain is scored separately. The scores for each domain range from 0 to 100, with higher scores indicating fewer/less severe symptoms and less impact.

The CASA-Q was developed by interviews with patients, ensuring the questionnaire measures those concepts most relevant to patients, thus establishing the PROM's clinical relevance and content validity. Content validity of a PROM is emphasized by regulatory agencies, including the US FDA and the European Medicines Agency, and is the yardstick to determine whether a PROM is fit-for-purpose.[15,16] It relies on qualitative research methods, such as interviews or focus groups with patients, caregivers, physicians, and other experts, to identify relevant concepts. It also includes the cognitive interview process to evaluate the patients' comprehension of the instruments' items, wording, recall periods, and format. Rothman et al proposed social media as having great potential to support the content validity of PROMs.[17]

This study addresses two aims: 1) to describe the performance of the CASA-Q in relation to primary endpoints in published COPD clinical studies; and 2) to describe a novel approach for evaluating and documenting content validity using recently published qualitative Social Media Listening (SML)[9] and Online Bulletin Board (OBB)[10] data to determine the extent to which the instrument's content validity remains stable over time (eg, from first publication to date).

# Methods

## Targeted Literature Review of Clinical Studies

A targeted literature review was conducted on the OvidSP database for literature published between 2008 (the year the CASA-Q development study was published) and 2021, including clinical studies and clinical trials registered on clinicaltrials.gov before Nov 2020. The search terms used were "patient-reported outcome", "self-reported outcome", "COPD", "QoL", "HRQoL", "health-related quality of life", and "CASA-Q." Findings by study design and year are presented in Table 1. Publications on the initial development and validation studies by Crawford et al and Monz et al were excluded.[12,14] The retrieved studies were assessed by year, intervention (if applicable) and reported results on primary endpoints CASA-Q domains. For clinical trials, we report the responsiveness of the CASA-Q domains in relation to the primary endpoints.

**Table 1** Summary of Studies Using the CASA-Q Identified in the Targeted Literature Search and Summary of Main Results

| No | Study (Title, year) | Patient Characteristics | Study design | CASA-Q results | Overall trial results | Ref |
|---|---|---|---|---|---|---|
| **Pharmacological intervention studies** | | | | | | |
| 1 | Withdrawal in Patients with Chronic Obstructive Pulmonary Disease (NCT00975195) **2013** | • Patients had severe or very severe COPD ($FEV_1$ of less than 50% predicted); ≥40 years of age<br>• History of at least one documented exacerbation in the year prior to screening<br>No. of patients= 2488 | • 6-week triple-therapy run-in with LAMA and LABA/ICS (tiotropium and salmeterol/fluticasone propionate).<br>• Patients randomized at Week 0 to either continue triple therapy for 52 weeks or to continue receiving salmeterol and tiotropium (dual bronchodilator therapy) and discontinued ICS stepwise over 12 weeks. ICS completely discontinued by Week 12.<br>• Change in cough and expectoration measured by CASA-Q at baseline and week 12, 18 and 52. | • *COUI Domain*: No change in least squares (LS) mean score of fluticasone maintenance vs fluticasone withdrawal (−4.51 vs −5.54; p =0.4914)<br>• *COUS Domain*: No change in LS mean score of fluticasone maintenance vs fluticasone withdrawal (1.69 vs −3.26: p = 0.3490)<br>• *SPUI Domain*: No change in LS mean score of fluticasone maintenance vs fluticasone withdrawal (4.29 vs −4.15; p = 0.92)<br>• *SPUS Domain*: No change in LS mean score of fluticasone maintenance vs fluticasone withdrawal (−5.10 vs −2.45; p = 0.1241) | • No change in the primary endpoint of time to first moderate/severe on-treatment COPD exacerbation; 107 (94.0 to 124.0) vs 110.0 (99.0 to 120.0) days (95% confidence interval) in the fluticasone maintenance group vs the fluticasone withdrawal group, respectively.<br>• Statistically significant improvements in LS mean trough FEV1 seen in Fluticasone Maintenance group, compared with to Fluticasone withdrawal at week 52 (−0.016 vs −0.059; p = 0.0014) | [26] |
| 2 | Efficacy of Once-Daily QVA149 Compared with Tiotropium Plus Theophylline in Symptomatic Patients with Moderate to Severe COPD. Kirishi et al 2015 | COPD patients with a CAT score of ≥10 or mMRC of ≥ 2 (ie, GOLD category B and D)<br>No. of patients = 35 | • After a four-week run-in period, patients were assigned to once-daily QVA149 (110mg LAMA indacaterol+50mg LABA glycopyrronium; (IND/GLY group) or LAMA tiotropium plus 400mg theophylline (TT group) for 16 weeks)<br>• Cough and sputum symptoms recorded daily by CASA-Q.<br>• Primary endpoint was trough $FEV_1$ response and secondary endpoint was DLCO, CAT score and CASA-Q score. | • Treatment with IND/GLY for 16 weeks improved cough-related domains of CASA-Q (cough symptoms and cough impact, p < 0.001), while the theophylline and tiotropium (TT) arm showed no improvement in the cough-related domains compared to baseline.<br>• Sputum-related domains of CASA-Q (sputum symptoms and sputum impact) remained unchanged in both treatment groups. | • The increase in $FEV_1$ from baseline was higher in the IND/GLY group than in the TT group (week 12: 162 ± 32 mL vs 63 ± 5 mL; week 16: 289 ± 28mL vs 36 ± 21mL, p < 0.01 for each). | [19] |
| 3 | Effect of tiotropium on mucus hypersecretion and airway clearance in patients with COPD. Tagaya et al **2016** | • COPD patients with sputum and cough for at least 8 weeks<br>• Not treated with anticholinergic agents.<br>• Ex-smokers and had not smoked at least for the previous 5 years.<br>No. of patients= 22 | • An open, non-controlled trial. After a 4-week run-in period, all patients received 18 mg LAMA- tiotropium once daily for 8 weeks. Other medications continued without alterations.<br>• Symptoms and their impact associated with cough and sputum were recorded daily, which were then scored according to CASA-Q. | • COUS domain score increased from 45 ± 14 to 64 ± 16 (p < 0.001).<br>• SPUS domain score increased from 47 ± 12 to 64 ±17 (p < 0.001).<br>• COUI increased significantly from 44 ± 13 to 54 ± 12.<br>• SPUI increased from 48 ± 18 to 57 ± 16 (p < 0.05 for both).<br>• The rates of great improvement and improvement were, respectively, 32% and 32% for the COUS domain, 14% and 28% for the COUI domain, 27% and 27% for the SPUS domain, and 23% and 27% for the SPUI domain. | • Tiotropium treatment for 8 weeks compared to baseline increased $FEV_1$/FVC ratio (67 ± 6 vs 64 ± 6, p < 0.05), $FEV_1$ (2.41 ± 0.45 vs 2.26 ± 0.44, p<0.05) and the percentage of predicted $FEV_1$ (63 ± 9 vs 59 ± 11, p < 0.05) | [21] |

(*Continued*)

**Table 1** (Continued).

| No | Study (Title, year) | Patient Characteristics | Study design | CASA-Q results | Overall trial results | Ref |
|---|---|---|---|---|---|---|
| 4 | A randomized, phase III trial of once-daily fluticasone furoate/ vilanterol 100/25 μg versus once-daily vilanterol 25μg to evaluate the contribution on lung function of fluticasone furoate in the combination in patients with COPD. Siler et al **2017** | • COPD patients; ≥40 years<br>• Post-albuterol $FEV_1$ ≥30 and ≤70% of predicted and a $FEV_1$/ forced vital capacity (FVC) <0.70 at screening<br>• ≥1 COPD exacerbation in past year | • Phase IIIa study (clinicaltrials.gov NCT02105974) was a multi-centre, randomized, stratified (reversibility status), double-blind study.<br>• After a 2-week single-blind run-in period, patients were randomized to either ICS fluticasone furoate (FF) 100mg + LABA vilanterol (VI) 25 mg combination once daily or VI 25 mg once daily for 12 weeks. | • There was a nominal statistical difference in favour of the vilanterol 25 μg group for adjusted mean change from baseline at day 84 for SPUS (– 3.02 [95% CI –5.09 to – 0.95; p = 0.004]) and SPUI (–2.14 [95% CI –3.91 to – 0.37; p = 0.018]).<br>• There were no statistically significant differences between groups in adjusted mean change from baseline at treatment day 84 for COUS (– 0.02 [95% CI –1.96 to 1.93; p = 0.987) and COUI (–0.18 [95% CI 1.94 to 1.57; p = 0.837]). | • Statistically significant improvements at all timepoints in the FF/VI 100/25 μg group, compared with the VI 25 μg group<br>• At day 84, FF/VI 100/25 μg group showed a statistically significant adjusted mean treatment difference of 34 mL over the VI 25 μg group in change from baseline trough $FEV_1$ (95% CI 14–55; p = 0.001) | [20] |
| 5 | Effect of hypertonic saline on mucociliary clearance and clinical outcomes in chronic bronchitis. Bennett et al 2020 | • COPD patients with chronic bronchitis symptoms, age 40–80 years, $FEV_1$ /FVC <0.70 and $FEV_1$ 35–80% of predicted. GOLD II, n=17. GOLD III, n=5. No. of patients= 22 | • Patients randomized in a double-blinded, crossover study. Each treatment period was 2 weeks long, with an intervening 2–4-week washout period.<br>• Study agents included inhaled hypertonic saline (7% NaCl) and hypotonic saline (0.12% NaCl) delivered twice daily | • No effects of hypertonic saline or control solutions were observed on CASA-Q scores | • No significant $FEV_1$ changes were observed to either study post-treatment (57.6 ±13.6 vs 58.0±12.5; 0.12% hypotonic and 0.7% hypertonic saline, resp.) | [23] |
| **Non-pharmacological interventional studies** | | | | | | |
| 6 | Minimal Clinically Important Differences for Patient-Reported Outcome Measures of Cough and Sputum in Patients with COPD. Rebelo et al **2020** | • COPD patients with predicted $FEV_1$ 50.4±19.4%<br>• Patients stable over the previous month No. of patients = 49 | • All participants completed a 12-weeks community-based pulmonary rehabilitation program | • Changes in CASA-Q COUS domain correlated significantly with changes in SGRQ (s=−0.322, p = 0.040), CAT (r=−0.378, p=0.015) and patients' GRC for cough (s = 0.317, p = 0.043).<br>• Changes in CASA-Q COUI domain correlated significantly with patients' GRC for cough (s = 0.464).<br>• Changes in CASA-Q sputum domains, both symptoms and impact, correlated significantly with changes in SGRQ (s=−0.398 and r=−0.407, respectively). | • Significant improvements were found in CASA-Q COUI domain; ΔCOUI score (± SEM) is 3.1 [−3.1;9.4], p = 0.034.<br>• The AUCs' discrimination ability was not acceptable for CASA-Q SPUI using SGRQ and for CASA-Q's COUS using patients' GRC for cough as anchors (ie, AUC<0.7).<br>• MCID as per ROC analysis is 4.2 for both cough and sputum symptom domains and 4.7 for cough impact.<br>• Pooled MCID for the CASA-Q subscales were 10.6 for COUS; 10.1 for COUI; 9 5 for SPUS and 7.8 for SPUI | [22] |

(*Continued*)

**Table 1** (Continued).

| No | Study (Title, year) | Patient Characteristics | Study design | CASA-Q results | Overall trial results | Ref |
|---|---|---|---|---|---|---|
| **Observational studies** | | | | | | |
| 7 | Impact of current cough on health-related quality of life in patients with COPD. Deslee et al 2016 | • COPD patients in stable condition with no exacerbations in the previous month<br>No. of patients = 148 | • A cross-sectional study to assess cough and sputum production within the past 7 days using the CASA-Q and other outcome measures | • Univariate analyses showed each CASA-Q domain score associated with the total SGRQ score: COUS (R = −0.391), COUI (R = −0.586), SPUS (R = −0.263), and SPUI (R = −0.481, p < 0.0001 for all)<br>• Multivariate analyses with all CASA-Q domains considered without other variables, showed both COUS and COUI scores statistically associated with total SGRQ score. | • The median values for the CASA-Q assessing cough and sputum in the previous 7 days were 70.8 (50.0–91.7) for COUS, 84.4 (59.4–100.0) for COUI, 66.7 (41.7–88.1) for SPUS, and 87.5 (66.7–100.0) for SPUI.<br>• Scores of the four CASA-Q domains was significantly lower with the presence of chronic bronchitis (p < 0.0001), indicating more cough and sputum symptoms and symptom impact in the presence of chronic bronchitis | [24] |
| 8 | Gastroesophageal reflux symptoms and nasal symptoms affect the severity of bronchitis symptoms in patients with chronic obstructive pulmonary disease. Hasegawa et al 2018 | • Patients with stable COPD diagnosed according to the GOLD criteria<br>No. of patients = 99 | • This cross-sectional study was conducted as part of a prospective observational study. | • The COUS and SPUS scores in the CASA-Q were significantly associated with the CAT1 score ($\rho$ = −0.66, p = 0.0001) and the CAT2 score ($\rho$=−0.63, p = 0.0001), respectively. | • The median and interquartile range of the COUS and the SPUS scores were 83.3 (66.7–91.7) and 83.3 (66.7–100), respectively.<br>• The median scores of the impact domains of the CASA-Q were 100, suggesting the presence of a ceiling effect for these domains | [25] |

**Abbreviations**: AUC, area under the curve; CAT, COPD assessment test; COUI, cough impact domain; COUS, cough symptoms domain; DLCO, diffusing capacity of lung for carbon monoxide; $FEV_1$, forced expiratory volume in one second; GOLD, Global Initiative for Chronic Obstructive Lung Disease; GRC, global rating of change scales; ICS, Inhaled corticosteroid; LABA, Long-Acting Beta-Agonists; LAMA, long-acting muscarinic antagonist; MCID, minimal clinically important difference; ROC, receiver operating characteristic; SGRQ, St. George's Respiratory Questionnaire; SPUI, sputum impact domain; SPUS, sputum symptoms domain.

## Content Validity Using Patient Insights from Social Media Listening (SML) and Online Bulletin Board (OBB)

Content validity for CASA-Q was initially established by Crawford et al in 2008.[12] Applying the approach proposed by Rothman et al,[17] the content validity of the CASA-Q was assessed using the information provided in the publications pertaining to qualitative data obtained from SML[9] and OBB[10] studies. The SML study was conducted to gather COPD patients' perspectives on symptoms, diagnosis and comorbidities associated with COPD and its impact on patients' quality of life, while the OBB study was used as a qualitative research tool to evaluate the effect of cough and mucus on COPD patients with persistent cough and excessive mucus. The methodology and results of SML and OBB have been previously published[9,10] and are summarized in the results section.

Insights available in the two publications resulting from the qualitative SML and OBB studies regarding topics related to cough and mucus mattering most to patients living with COPD were first grouped by a study team member into the four CASA-Q domains. In a second step, this grouping was checked by a second reviewer. The final grouping was unanimously endorsed by the study team. Next, the qualitative data grouped under the four CASA-Q domains were mapped to the items in each of those domains where they fitted best according to the judgement of a study team member. This mapping was again reviewed by a second reviewer. The final mapping was unanimously endorsed by the study team. For example, insights (eg, patient quotes) as reported in the two SML and OBB publications related to mucus

characteristics (eg, frequency of bringing up mucus) were grouped under the sputum symptoms (SPUS) domain. Similarly, insights from the qualitative studies associated with cough (eg, frequency of coughing) were grouped under the cough symptoms (COUS) domain. Finally, the qualitative findings related to physical, emotional and functional disturbances due to mucus and cough were grouped into the sputum impact (SPUI) and cough impact (COUI) domains, respectively.

# Results

## Responsiveness of CASA-Q in COPD Studies

The targeted literature search identified nine studies of COPD where the CASA-Q had been used as an endpoint. A study by Goosens et al mentioned the use of CASA-Q, but CASA-Q-related results were not available in the publication and were therefore excluded.[18] Of the remaining eight studies, seven were identified from published literature[19–25] and one was reported on "ClinicalTrials.gov".[26] Five studies assessed pharmacological interventions,[19–21,23,26] one study was a non-pharmacological study,[22] while two were non-interventional or observational.[24,25]

### Pharmacological Intervention Studies

The CASA-Q was used in five pharmacological interventional studies (Table 1; presented in chronological order).

The WISDOM trial (NCT00975195) used the CASA-Q as part of a trial assessing lung function changes and exacerbations upon stepwise inhaled corticosteroid (ICS) withdrawal.[26] There was a significant improvement in mean trough $FEV_1$ in ICS maintenance group compared to the withdrawal group, but no change in time to exacerbations or in the cough and sputum-related CASA-Q domains was observed between both arms.

In a study comparing indacaterol/glycopyrronium (IND/GLY) vs tiotropium plus theophylline, Kirishi et al reported a higher increase in $FEV_1$ in the IND/GLY group compared to the comparator group.[19] In the IND/GLY group, CASA-Q cough symptom and cough impact domains improved, with tiotropium plus theophylline showing no improvement in the cough-related domains compared to baseline. Sputum-related domains remained unchanged in both groups.

A study by Tagaya et al, testing the effect of tiotropium on mucus hypersecretion and airway clearance, showed an improvement in $FEV_1$ and $FEV_1$/FVC with tiotropium. Similarly, a significant improvement in all four CASA-Q domains compared to baseline was observed.[21]

The study by Siler et al, comparing effects on lung function with fluticasone furoate (FF) plus vilanterol (FF/VI) to VI alone, found that FF/VI improved trough $FEV_1$. There was a nominal difference in favor of the VI group for SPUS and SPUI domains but no difference for the COUS and COUI domains of the CASA-Q were observed.[20]

Bennett et al assessed the effect of hypertonic saline on mucociliary clearance and clinical outcomes in COPD patients with chronic bronchitis. They found that hypertonic saline does not result in any significant $FEV_1$ changes. Similarly, no effect was observed on CASA-Q domains.[23]

### Non-Pharmacological Interventions

CASA-Q was used in one non-pharmacological intervention study (Table 1).

Rebelo et al measured cough and sputum change using the CASA-Q after a 12-week pulmonary rehabilitation program.[22] The study observed a significant improvement in the COUI domain, which correlated with the patients' global rating of change scales (GRC) for cough. The changes in COUS domain correlated significantly with the St. George's respiratory questionnaire (SGRQ), the COPD Assessment Test (CAT) and the patients' GRC for cough. Changes in both CASA-Q sputum domains (SPUI and SPUS) significantly correlated with the change in SGRQ.

## Validation of CASA-Q in COPD Studies from Observational Studies

Published results from two observational studies provided insight into the validity of CASA-Q scores (Table 1). Deslee et al assessed the impact of cough and sputum on HRQoL in patients with COPD and found that all CASA-Q domain scores were significantly lower in a subset of patients with chronic bronchitis. Multivariate analysis of all CASA-Q domains considering all other clinical variables found that the COUI score was significantly associated with the SGRQ

score,[24] indicating the adverse impact of cough was associated with an impairment in overall health status in these patients.

An observational study examining the impact of gastroesophageal reflux symptoms on cough and sputum symptoms reported a significant cross-sectional correlation between the COUS and SPUS scores and the CAT cough and sputum item scores,[25] offering further support of the relationship between cough and sputum impact and overall COPD health status.

## Mapping Qualitative Patient Insights to CASA-Q Items and Domains

Methods and results of the two qualitative SML and OBB studies used to further assess content validity of the CASA-Q have been reported elsewhere.[9,10] The main findings are summarized here for convenience: In these studies, patients emphasized that high symptom load and poor HRQoL associated with COPD significantly disrupted patients' lives on multiple levels. The SML study reported that relief from cough, mucus, and shortness of breath were the most valuable aspects of disease management from the patients' perspective. In the OBB study, the patients mentioned that COPD has an impact on both proximal concepts, ie, those which directly affect health such as persistent cough and difficulty clearing sputum and also more distal concepts, ie, those that indirectly affect health such as a low emotional and social well-being.[10] Cough and mucus impeded physical activities and social interactions, which influenced the patient's relationships with friends and family, and their daily tasks and routine, thus impacting their overall functional, emotional, social and economic quality of life.[10]

The results of thematically grouping qualitative data from the SML and OBB studies to the four CASA-Q domains are presented in Table 2.

After grouping the qualitative data by CASA-Q domains, the SML and OBB findings were then mapped to the individual items in each CASA-Q domain. In this process, all original items from the CASA-Q could be matched to important aspects of disease voiced by the patients themselves (as presented in SML and OBB findings). This is consistent with the original qualitative work supporting content-validity of the CASA-Q. As shown in Figure 1, in the SPUI domain, the items about "annoyance by phlegm", "avoidance of public places", "interruption of usual activities" and "to bother other people" were supported by feedback received from patients from the OBB, while "breathing difficulty" and "interfering with speaking ability" were supported by findings from SML. Similarly, qualitative data from the SML and OBB corresponded to the items in the remaining domains of the CASA-Q, such as items on "thickness", "frequency" and "difficulty bringing up sputum" in the SPUS domain and items "tired after coughing", "avoidance of public places", "interruption of usual activities", "sleep interference" and "bothering other people" in the COUI domain. The items from the COUS domain such as "bouts of cough" and cough during the day and mornings were also supported by findings from the SML/OBB qualitative data.

**Table 2** Social Media Listening and Online Bulletin Board Findings Grouped Under the CASA-Q Domains Based on Closest Symptom or Concern Match

| CASA-Q Domains | Sputum Symptoms (SPUS) | Sputum Impact (SPUI) | Cough Symptoms (COUS) | Cough Impact (COUI) |
|---|---|---|---|---|
| ***Social media listening and online bulletin board findings*** | • Difficulty in mucus clearance<br>• Exhaustion resulting from ridding mucus | • Depression/ frustration<br>• Low self-esteem<br>• Embarrassment<br>• Low emotional well-being<br>• Low social well-being<br>• Impact on social interactions<br>• Impact on intimate relationships<br>• Impact on normal functioning | • Persistent cough (with or without mucus) | • Tiredness<br>• Loss of energy<br>• Embarrassment<br>• High anxiety<br>• Impact on mobility/physical activity<br>• Impact on routine tasks<br>• Impact on social interactions<br>• Lack of sleep<br>• Discomfort in talking to others |

**Abbreviations**: COUS, CASA-Q domains: cough symptoms; COUI, cough impact; SPUS, sputum symptoms; SPUI, sputum impact.

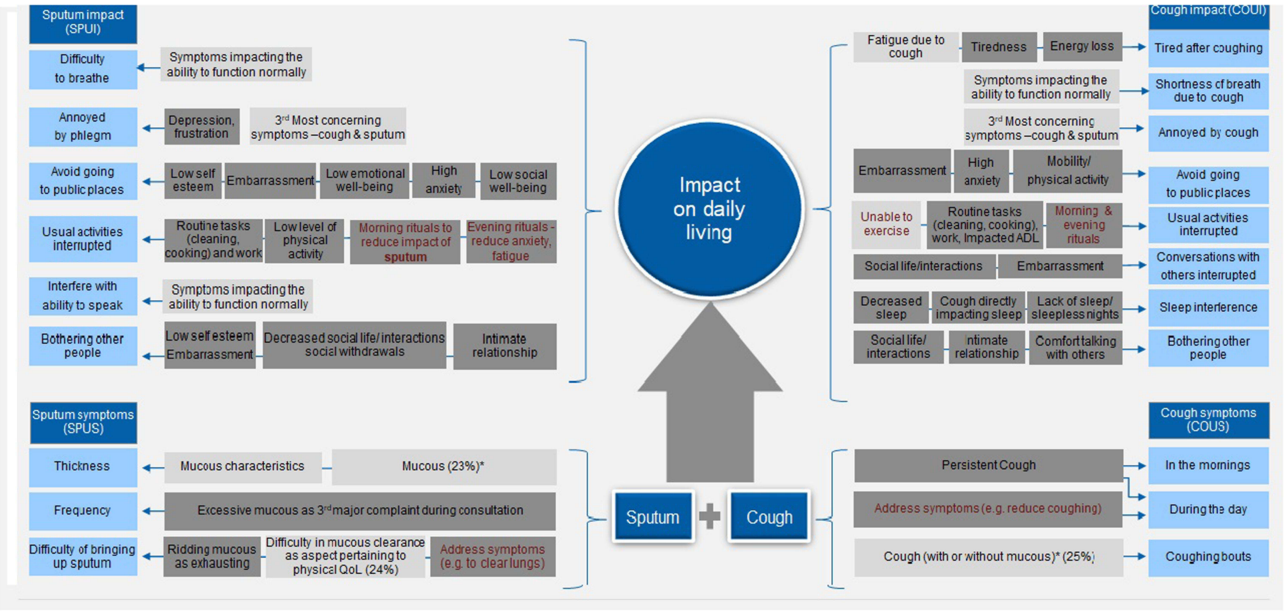


**Figure 1** Interlinkage between insights from SML and OBB with CASA-Q items: The qualitative findings obtained from the SML and OBB (in the light and dark gray boxes) were mapped against corresponding items of the CASA-Q (light blue boxes), illustrating the content validity of the CASA-Q.
**Notes**: CASA-Q domains, CASA-Q Items, Online Bulletin Board, Social Media Listening. **A:** Behavioral/lifestyle adaptations. * % of patients who mentioned these as the most bothersome, which become severe as the disease progresses.

## Discussion

Results of published studies using the CASA-Q to assess cough and sputum symptoms showed that CASA-Q scores are appropriately responsive to change with treatment, moving in the same direction as other endpoints, such as $FEV_1$ and SGRQ. In addition, the content of the CASA-Q was supported by data from recently conducted qualitative online patient studies, suggesting that since CASA-Q's development in 2008, the questionnaire continues to be content valid.

The WISDOM trial demonstrated that the stepwise withdrawal of inhaled corticosteroid treatment did not increase the risk of exacerbations as assessed by no difference in time to first exacerbation compared to the corticosteroid-continuation group. In line with the stability of the clinical parameters in the corticosteroid withdrawal group, no changes in cough and sputum on the CASA-Q were observed. Similarly, for the other interventional studies, the CASA-Q scores moved in the same direction as the clinical measurements, in line with the study design and pharmacological intervention's mechanism of action.

The non-pharmacological pulmonary rehabilitation study showed strong correlation between change in CASA-Q domain scores and change in SGRQ and CAT reference tests supporting the responsiveness of the CASA-Q in COPD symptom evaluation.[22] The two observational studies showed moderate or strong correlations between the CASA-Q domain scores and the SGRQ and CAT reference tests.[24,25] These studies offer further support for the validity of the CASA-Q and suggest that reducing symptom impact should improve health status.

Qualitative data from the SML and OBB online patient studies were consistent with the content and structure of the CASA-Q, supporting the content validity since its development. The instrument continues to capture constructs important to patients. Published findings of the qualitative data obtained with the SML and OBB studies confirmed the impact of cough and sputum symptoms and concerns of COPD patients. The fact that all items of the CASA-Q could be matched with findings from these recent qualitative studies shows that the method proposed by Rothman et al[17] can be applied in practice and suggests that the content validity of the CASA-Q remains stable over time.

## Limitations

The results presented here are based on published studies reporting results of CASA-Q in COPD patients. There were limited trials using the CASA-Q to evaluate the effects of treatment on the severity and impact of cough and sputum.

Content validity evaluation using online patient interactions was limited to secondary analyses of the published results from two previously conducted qualitative studies, namely social media listening and online bulletin boards.

## Conclusion

Findings from this literature review suggest CASA-Q can detect changes in cough and sputum symptoms and impact in therapeutic trials of COPD, with observational studies showing a correlation between symptom impact and health status. The successful mapping of qualitative findings from online SML and OBB studies to CASA-Q domains and items suggests that since its development, the CASA-Q remains content valid. Findings of this study suggest that online qualitative data can be used as a promising new additional tool to bolster, rather than replace, qualitative interviews and focus groups, playing a key role in understanding and documenting content validity of PROMs over time. Based on its development history and the evidence presented here, the CASA-Q is a valid and responsive measure of cough and sputum on the lives of people with COPD suitable for use in clinical trials.

## Abbreviations

CASA-Q, Cough and Sputum Assessment Questionnaire; COPD, chronic obstructive pulmonary disease; PROMs, patient-reported outcome measures; SML, social media listening; OBB, online bulletin board; SGRQ, St.-George's Respiratory Questionnaire; CAT, COPD assessment test; HRQoL, health-related quality of life; ICS, inhaled corticosteroid; IND/GLY, indacaterol/glycopyrronium; FF, fluticasone furoate; VI, vilanterol.

## Data Sharing Statement

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

## Acknowledgements

Boehringer Ingelheim is the copyright holder of the CASA-Q.

## Funding

This study was funded by Novartis Pharma AG, Basel, Switzerland.

## Disclosure

Francesco Patalano, Carolina Hache, Abhijit Pethe, Harneet Kaur, Tasneem Arsiwala, and Florian S. Gutzwiller are full-time employees of Novartis. Nuzhat Afroz was a full-time employee of Novartis when the study was conducted. Nancy Kline Leidy is employed by Evidera/ PPD. The authors report no other conflicts of interest in this work.

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