



People living with moderate-to-severe COPD prefer improvement of daily symptoms over the improvement of exacerbations: a multicountry patient preference study

Nigel S. Cook ¹, Gerard J. Criner², Pierre-Régis Burgel ^{3,4}, Katie Mycock⁵, Tom Gardner⁶, Phil Mellor⁶, Pam Hallworth⁶, Kate Sully⁷, Sophi Tatlock⁷, Beyza Klein¹, Byron Jones¹, Olivier Le Rouzic^{8,9}, Kip Adams¹⁰, Kirsten Phillips¹¹, Mike McKevitt¹², Kazuko Toyama ¹³ and Florian S. Gutzwiller ¹

¹Novartis Pharma AG, Basel, Switzerland. ²Temple University, Philadelphia, PA, USA. ³Cochin Hospital, Assistance Publique Hôpitaux de Paris, Paris, France. ⁴Université de Paris and Institut Cochin, Inserm U1016, Paris, France. ⁵Adelphi Real World, Macclesfield, UK. ⁶Adelphi Research, Macclesfield, UK. ⁷Adelphi Values, Macclesfield, UK. ⁸La Fondation du Souffle, Paris, France. ⁹Univ. Lille, CHU Lille, Inserm U1019, Lille, France. ¹⁰COPD Foundation, Miami, FL, USA. ¹¹Lung Foundation Australia, Brisbane, Australia. ¹²British Lung Foundation, London, UK. ¹³J-Breath, Tokyo, Japan.

Corresponding author: Florian S. Gutzwiller (florian.gutzwiller@novartis.com)



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There is a need for symptom-focused therapies to deliver meaningful outcomes for people living with COPD <https://bit.ly/3KqcSur>

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Abstract

Introduction This patient preference study sought to quantify the preferences of people living with COPD regarding symptom improvement in the UK, USA, France, Australia and Japan.

Methods The inclusion criteria were people living with COPD aged 40 years or older who experienced ≥ 1 exacerbation in the previous year with daily symptoms of cough and excess mucus production. The study design included: 1) development of an attributes and levels grid through qualitative patient interviews; and 2) implementation of the main online quantitative survey, which included a discrete choice experiment (DCE) to allow assessment of attributes and levels using hypothetical health state profiles. Preference weights (utilities) were derived from the DCE using hierarchical Bayesian analysis. A preference simulator was developed that enabled different health state scenarios to be evaluated based on the predicted patient preferences.

Results 1050 people living with moderate-to-severe COPD completed the survey. All attributes were considered important when patients determined their preferences in the DCE. In a health state preference simulation, two hypothetical health states (comprising attribute levels) with qualitatively equivalent improvements in A) cough and mucus and B) shortness of breath (SOB) resulted in a clear preference for cough and mucus improved profile. When comparing two profiles with C) daily symptoms improved and D) exacerbations improved, there was a clear preference for the daily symptoms improved profile.

Conclusions People living with moderate-to-severe COPD prefer to reduce cough and mucus production together over improvement of SOB and would prefer to reduce combined daily symptoms over an improvement in exacerbations.

Introduction

Regulatory and health technology assessment (HTA) agencies are increasingly interested in gathering the patients' perspective, including patient preferences, to make informed, patient-centred drug licensing and reimbursement decisions [1–3]. Common symptoms of COPD causing disruption of daily activities are shortness of breath (SOB, also referred to as dyspnoea), excess mucus production and cough [4]. These daily symptoms, together with downstream consequences like disturbed sleep and cough-related urinary incontinence, have a significant impact on patients' physical and emotional wellbeing [5–7]. Exacerbations may occur as a less frequent event, due to worsening of several daily symptoms, requiring additional or



adjusted treatment. Acute exacerbations are events which can be life threatening if severe. Hence, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) has recently updated its COPD classification system, with treatment management now including symptom assessment beyond dyspnoea and exacerbations [4]. However, despite various debilitating effects associated with cough and excess mucus production, current available treatments such as smoking cessation, chest or respiratory physiotherapy, or mucolytics in general provide insufficient management of these symptoms, resulting in significant unmet need in these patients [8].

Understanding patient needs and expectations related to disease and treatments is essential to ensure that drug development is addressing what matters to patients [9]. Symptoms like cough, mucus and sleep disturbance have been identified as being important to patients in various qualitative studies, which generally involve smaller sample groups [5, 10, 11]. Though it is important to identify what matters to patients, qualitative studies do not provide insights on how important the management of each symptom (in comparison to other symptoms) is to patients, in particular the relative importance of different attributes (symptoms/disease characteristics) to patients and the trade-offs that patients are willing to make when considering more holistically what matters to them while they seek treatments to alleviate their disease symptoms and improve their quality of life. To address these limitations, quantitative patient preference studies, which are based on the insights gleaned from qualitative research providing a robust and validated scientific approach, are thus recognised by regulatory bodies like the European Medicines Agency (EMA) [12] and US Food and Drug Administration (FDA) [13] as an important input to patient experience data in support of regulatory submissions. Furthermore, large multi-stakeholder initiatives like IMI PREFER are providing guidance for how patient preference studies can support decision-making across the medical product life cycle, including the importance of different clinical end-points to patients, which can inform the design of future clinical trials [14].

The purpose of the present research with COPD patients was to provide supportive evidence to the selection of phase III clinical trial end-points for future studies in COPD, to reflect end-points that matter most to patients. Patient preference studies such as this COPD study, performed early in the product development life cycle (phase I to II), can inform discussions with stakeholders such as HTA and regulatory bodies during the development of clinical study protocols [15–18].

Our patient preference study sought to quantify the preferences of people living with moderate-to-severe COPD (defined as having ≥ 1 COPD exacerbations in the past year) regarding improvement of various symptoms, the impact on their quality of life and evaluation of whether preferences vary with certain respondent characteristics. The primary objective of this study was to analyse preference for improvement of mucus production, (chronic) cough and SOB in addition to downstream impacts on sleep and urinary incontinence, compared to improvement of exacerbations.

Exploratory objectives sought to assess how stated preferences may vary according to disease severity and the level of patient activation using the Patient Activation Measure-Questionnaire (PAM-Q).

This study is an IMI PREFER consortia case study, a collaborative research project of the Innovative Medicines Initiative.

In this manuscript, the word “patients” is sometimes used to refer to those people living with COPD, for ease of reading.

Methods

Design of the patient preference study

A review of methodological best practice guidelines [1, 19, 20] deemed a discrete choice experiment (DCE) to be the most methodologically robust approach to evaluate the relative importance of the needs and preferences of people living with COPD. A DCE is a technique widely used in healthcare to assess patient preferences for the management of a variety of conditions including COPD to determine how patients choose, for example, between two treatment options [21, 22].

The findings from extensive patient qualitative research [5, 10], evidence from clinical guidelines [4], and methodological best practice [1, 19, 20] informed the initial identification of attributes and levels for inclusion in the DCE, with levels of each attribute describing changes in symptom severity. These inputs were reviewed by clinical experts and patient group representatives from five countries to finalise the design of the patient preference study prior to pilot-testing (figure 1). The National Institute for Health and Care Excellence (NICE) provided advice on the study design and statistical analysis [23].

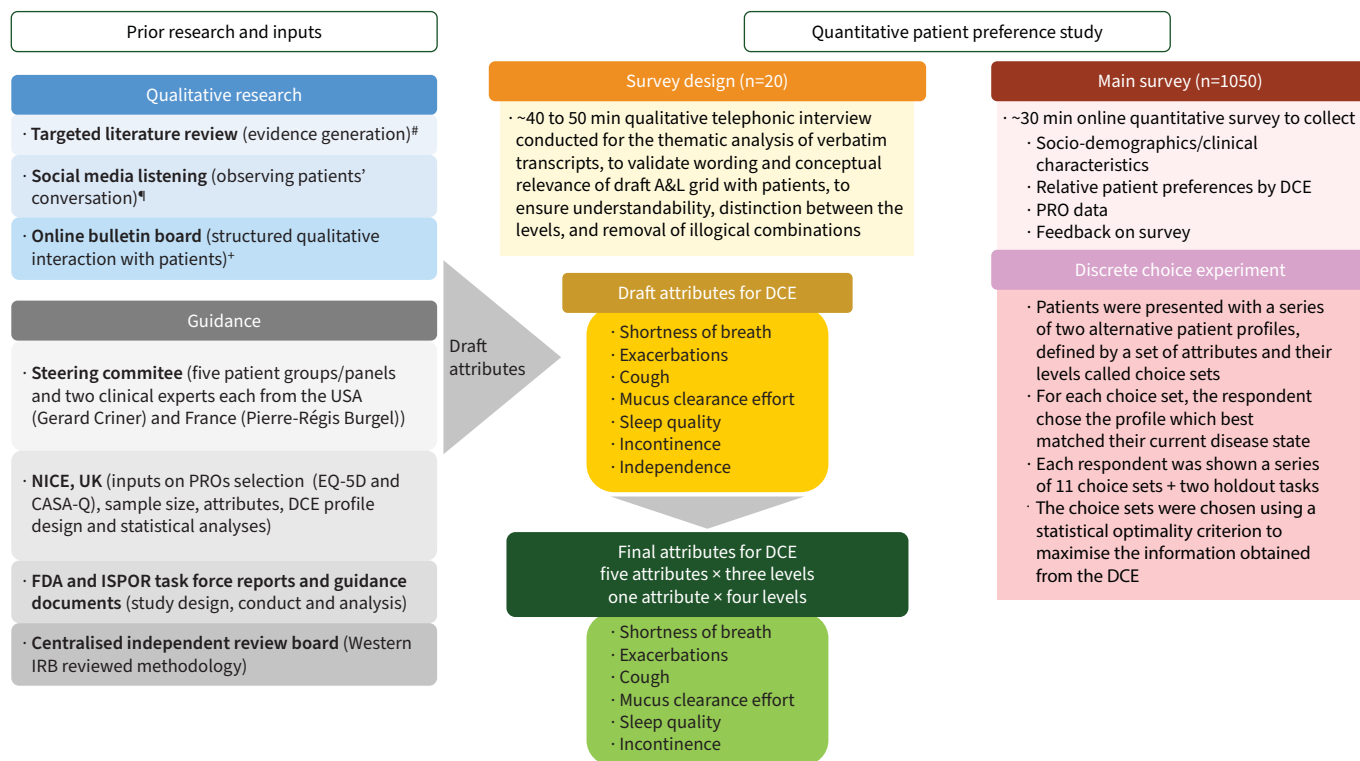


FIGURE 1 Design of quantitative patient preference study. PRO: patient-reported outcome; EQ-5D: European Quality of Life Questionnaire; CASA-Q: Cough and Sputum Assessment Questionnaire; DCE: discrete choice experiment; FDA: Food and Drug Administration; ISPOR: International Society for Pharmacoeconomics and Outcomes Research; NICE: National Institute for Health and Care Excellence; IRB: independent review board; A&L: attributes and levels. [#]: to assess existing evidence on patients' preferences in terms of types and amount of evidence available and objectives and outcomes of earlier research; [¶]: to gain more information on what affects and motivates patients, their questions, pains, experiences, concerns and the way they communicate about their disease; [†]: to explore the disease experience, understand the priorities, detect potentially hidden aspects and further understand the communication.

Patient-reported outcome (PRO) measures, such as the COPD Assessment Test (CAT) [24], the Patient Activation Measure (PAM-Q) [25, 26], the Cough and Sputum Assessment Questionnaire (CASA-Q) [27] and the European Quality of Life Questionnaire (EQ-5D-3L), and questions on socio-demographic and clinical characteristics were included as part of the online quantitative survey to explore possible heterogeneity of the preferences expressed based on pre-specified subgroups. Data for the qualitative and quantitative phases were collected during February–May and September–December 2019, respectively. The study was reviewed and granted exemption by a centralised independent review board (Western IRB, USA). Participants were asked to provide voluntary online consent to participate before enrolling in the study.

Details on insight gathering from social media listening [10] and online bulletin board studies [5] are presented in supplementary Appendix A.

Patients and sample size calculation

Details on patient characteristics were self-reported. Participants were included in the study if they were aged ≥ 40 years with diagnosis of COPD by a healthcare practitioner and had moderate-to-severe COPD defined as having had ≥ 1 COPD exacerbation in the past year, along with daily symptoms of cough and excess mucus production. Moderate exacerbation was defined (based on GOLD criteria) as worsening of COPD in terms of exaggeration of symptoms requiring treatment with antibiotics and/or corticosteroids. Severe exacerbation was defined as worsening of COPD that requires hospitalisation [4]. Patients were excluded if they had participated in a COPD patient survey in the past 3 months.

Primary recruitment was conducted *via* patient support groups, and participation was voluntary. Patient groups in the UK, USA, France and Australia leveraged their patient networks for the recruitment. Supplementary recruitment *via* patient panels was introduced once patient group recruitment was saturated,

with participation compensated at fair market value to encourage patient involvement. In Japan, participants were recruited only through patient panels.

A specified minimum of 120 participants from each country was required for the design, meeting statistical properties of balance and orthogonality of the DCE. The target sample counts for each country were based on simulations of the design efficiencies within the Lighthouse Studio Software [28]. Using a total of 120 patients, each presented with 11 choice tasks, enabling a balanced DCE to be used. The “balanced DCE” means design is created with the aim that each respondent views each level of each attribute in combination with every other level of other attributes an equal (balanced) number of times.

Data collection

During pilot-testing of the survey (phase I), qualitative 40- to 50-min telephone interviews were conducted with participants living with COPD to validate wording, conceptual relevance of draft attributes, and to ensure understand ability and distinction between the attribute levels with participants. The methodological approach of the interview was in line with best practice guidances [13, 19], including the use of broad open-ended questioning to elicit spontaneous data, the “think aloud” feedback process, and presenting interviewees with a “dummy” DCE task.

Phase II was the main quantitative survey of ~35-min duration. All participants were provided with the relevant instructions and a link to the online survey. Although participants were requested to take the survey at one sitting, they could take breaks whenever needed by keeping the survey screen active.

Profile-matching exercise

Prior to the DCE, participants were asked to complete a profile-matching exercise to define their own “current” disease state/baseline profile. Based on selecting levels from the attributes and levels grid created for the DCE, this exercise helped orient participants to the different options in the discrete choice exercise but was also used to create an individual “DCE index” (how they rated their health state relative to the best/worst health states based on the six attributes tested: SOB, exacerbations, cough, mucus clearance effort, sleep quality and urinary incontinence). We also analysed preference based on patient current symptom profile (from the matching exercise), *e.g.* for those participants experiencing SOB at rest versus upon strenuous exercise, *etc.*

Discrete choice experiment

Two holdout cards were included in the DCE choice task, and displayed the same task for every respondent; these holdout cards were not included in the modelling estimation but were used to check the validity of the model. The DCE design was optimised using a D-optimal design strategy that exchanges one by one the profiles in each choice set using a point-exchange algorithm to yield an optimal design. Participants were asked to choose their preference between two hypothetical disease states created with attributes and their levels using two full profile design cards called choice sets (table 1). For each choice

TABLE 1 Example of choice task for COPD disease state profiles as seen by the patients: patients are asked to select their preference between the disease states of patient A or B

	Patient A	Patient B
When waking up on a typical morning:	You feel rested	You do not feel rested at all
On a typical morning:	It is not at all difficult to bring up mucus	It is a little difficult to bring up mucus
On a typical day:	You experience shortness of breath when washing (e.g. taking a shower) or dressing Your cough does not interrupt/disturb any of your usual activities COPD symptoms are causing a few drops of urine leakage	You experience shortness of breath when sitting or lying down Your cough interrupts/disturbs most of your usual activities COPD symptoms are causing a few drops of urine leakage
During a typical year:	Never experience any COPD flare-ups/exacerbations	You experience one or more COPD flare-ups/exacerbations that require a hospital stay or visit

set, the respondent chose the profile which best matched their current disease state. Each respondent was shown a series of 11 choice sets and two holdout tasks with different profiles.

After the DCE task, PRO questionnaires were administered to collect patients' clinical (CAT and CASA-Q), attitudinal (PAM-Q) and overall health status (EQ-5D (3L)) information.

Data collected from this quantitative survey were analysed using IBM SPSS v7.5 data collection survey reporter software, and p-values were reported where required. Hierarchical Bayesian analysis with effects-coding parameterisation (subject to acceptable model fitting as confirmed by multinomial logistic regression) was undertaken on the preference data to robustly estimate (using Gibbs sampling) the relative value each respondent places on an attribute level (*i.e.* the part-worth utilities). The study used an orthogonal design to ensure attributes and levels were being tested independently from one another – the important contributions of the individual features can be isolated from the rest of the effects presented simultaneously as part of the DCE. In order to simulate the potential benefits to be derived from therapeutic modalities on the health state/symptom profile, a sensitivity analysis was conducted, based on the relative importance preference weights.

Preference share for different health states

A simulator tool was developed (built in Microsoft Excel 2016) using hierarchical Bayesian analysis data to predict “preference shares of the study population” (expressed as a percentage) for input profiles. Profile scenarios were simulated in which the health states across different attributes were altered from the average patient (“DCE index”), to demonstrate the potential symptom improvement offered, and in turn generate a preference share.

COPD severity

Severity of COPD was determined using four variables: 1) self-reported perceived COPD severity by participants; 2) number of exacerbations in previous year; 3) CAT total score; and 4) CASA-Q domain and overall scores.

Impact of disease severity and patient activation levels on patient preference

The impact of severity of COPD and level of patient activation on patient preference was also assessed using the PAM-Q. The 10-item PAM-Q evaluates patients' ability to manage their own health by assessing three key domains: knowledge, skills and confidence. Scoring of the PAM-Q enabled patients to be grouped into four activation levels: patients with low activation (level 1) are typically passive recipients of care and do not believe in an active patient role, while those with high activation (level 4) are proactive participants in the care process and actively engage in healthy behaviours [25, 26].

Results

Phase I: pilot-testing

The results of this phase are reported in supplementary Appendix B.

Phase II: online quantitative survey

Demographics and clinical characteristics

1050 participants (USA n=400, UK n=200, France n=150, Australia n=150 and Japan n=150) completed the survey, 51% men and 49% women; 86% were either current or ex-smokers. Commonly self-reported comorbidities were asthma (44%), hypertension (40%), allergies (34%) and depression/anxiety (25%). In the past year, 47% of participants experienced ≥ 2 exacerbations that led to hospitalisation. It was observed that 35% participants reported “a great deal/a very great deal of mucus” brought up when coughing in the last 7 days. Details are presented in table 2.

Primary objective

Profile-matching exercise

The majority of participants across all countries identified the middle level of the six attributes as most closely representing their current health state, except urinary incontinence where the lowest level was most commonly selected (figure 2). Of note, 54% (n=568; males n=238 (41.9%); females n=330 (58.1%)) of participants indicated during this profile-matching exercise that they experience urinary incontinence to some extent, due to their COPD (40% “COPD symptoms are causing a few drops of urine”; 14% “COPD symptoms are causing urine leakage which makes my underwear wet”). Furthermore, the proportion of patients who experienced SOB during strenuous activity (walking uphill/upstairs), during light activity (short walk on level ground), when washing (taking shower) or dressing, or at rest (sitting or lying down)

TABLE 2 Demographics and clinical characteristics of participants who completed the online survey

Parameters	Quantitative phase II (n=1050)
Age, years, mean±sd	
At survey	60.5±11.0
At diagnosis	53.6±11.3
Time since diagnosis, years, mean±sd	7.2±7.0
Age groups %	
40–59 years	45
60–79 years	50
>80 years	5
Sex, male %	51
Country n (%)	
USA	400 (38.1)
UK	200 (19.0)
France	150 (14.3)
Australia	150 (14.3)
Japan	150 (14.3)
Body mass index % (n=954)	
Underweight (<18.5 kg·m ⁻²)	4
Healthy (18.5–24.9 kg·m ⁻²)	44
Overweight (25.0–29.9 kg·m ⁻²)	28
Obese (>30 kg·m ⁻²)	24
Smoking status %	
Current smokers	29
Ex-smokers	57
Never-smokers	14
Comorbidities %	
Asthma	44
Hypertension	40
Allergies	34
Depression/anxiety	25
Gastro-oesophageal reflux disorder	22
Sleep disturbance	31
Diabetes	17
Obesity	16
Osteoporosis	16
Urinary incontinence	15
Rheumatology disease	15
COPD severity (self-perceived) %	
Mild	11
Moderate	54
Severe/very severe	35
Severity derived from PRO instruments[#], mean±sd	
CAT score	25.0±6.67
CASA-Q score	50.3±20.9
Exacerbations in the past 12 months[¶] %	
0	29
1	24
2	22
≥3	25
Amount of mucus when coughing in the past 7 days %	
A great/very great deal	35
Some/a little	62
None at all	3
Asthma/respiratory allergy %	
Since childhood	23
Since adulthood	42
No allergy	35
Educational qualification (higher college or university degrees) %	
USA	68
UK	48

Continued

TABLE 2 Continued	
Parameters	Quantitative phase II (n=1050)
France	72
Australia	59
Japan	86
Employment status %	
Retired	42
Currently full time	34
Other (working part time, home maker, on sick leave, student and unemployment)	24

PRO: patient-reported outcome; CAT: COPD Assessment Test; CASA-Q: Cough and Sputum Assessment Questionnaire. #: CAT scores range from 0 to 40; higher scores denote a more severe impact of COPD on a patient's life; and CASA-Q domain scores range from 0 to 100, with higher scores associated with fewer symptoms/less impact due to cough or sputum. *: that required hospitalisation; higher scores denote a more severe impact of COPD on a patient's life.

was 30.8%, 38.9%, 25.8% and 4.6%, respectively. Over a quarter of the cohort experienced dyspnoea when washing/dressing or at rest.

From the profile-matching exercise, we were able to segregate the respondent population according to the severity of each COPD symptom, as they reported for their current condition. This allowed us to perform an analysis of preferences according to severity of individual symptoms experienced (e.g. for those participants experiencing SOB at rest versus SOB upon strenuous exercise). However, we did not see any obvious difference in preferences expressed when analysed in this manner by severity of symptoms experienced.

Preference weights from the discrete choice experiment

The estimated mean zero-centred preference weights together with the standard deviations and confidence intervals from the hierarchical Bayesian model are given in figure 3. All the estimated coefficients are significantly different from zero (p<0.05), indicating that all attributes were considered important when

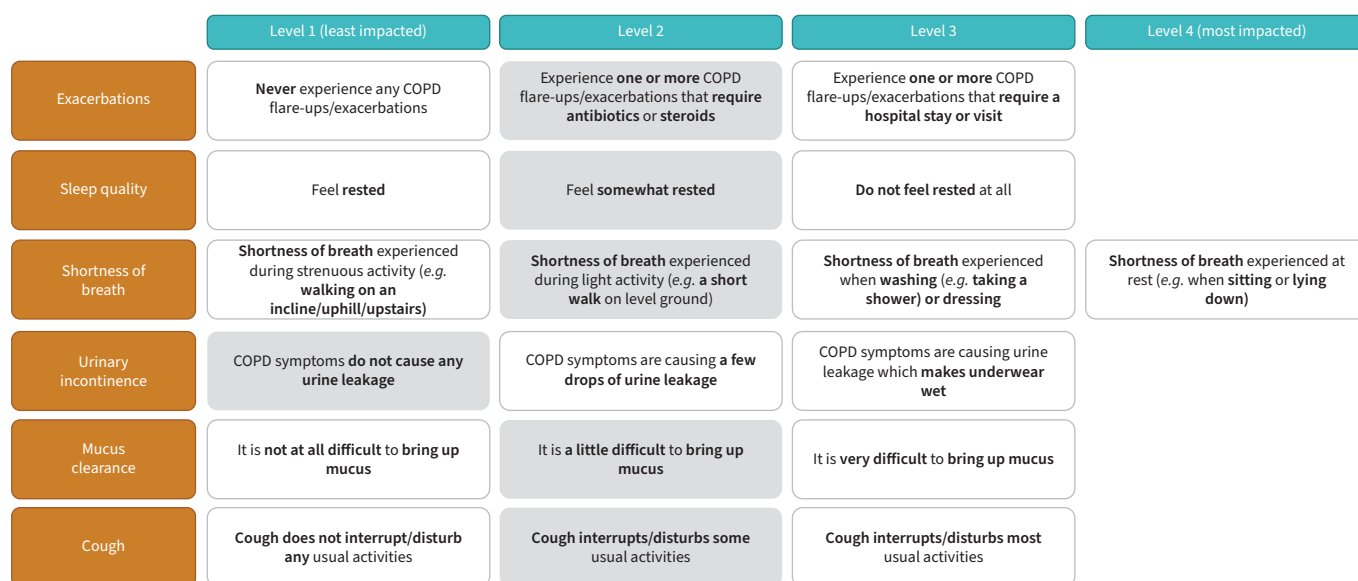


FIGURE 2 Profile-matching showing average patient profile, selected by patients to best match themselves at time of completing the questionnaire (summing results over all countries). Shaded boxes show the median level selected by patients for each attribute as that matching their current health state. Percentages of selected levels by attribute (level 1/level 2/level 3/level 4 (for shortness of breath)): exacerbation 14%/64%/23%; sleep quality 17%/51%/32%; shortness of breath 31%/39%/26%/5%; urinary incontinence 46%/39%/14%; mucus clearance 22%/57%/21%; cough 29%/54%/17%.

	Level 1 (least impacted)	Level 2	Level 3	Level 4 (most impacted)
Exacerbations	Never experience any COPD flare-ups/exacerbations	Experience one or more COPD flare-ups/exacerbations that require antibiotics or steroids	Experience one or more COPD flare-ups/exacerbations that require a hospital stay or visit	
Mean preference weight (sd) Upper CI/lower CI	0.72 (1.03) 0.78/0.66	0.15 (0.39) 0.18/0.13	-0.88 (1.01) -0.82/-0.94	
Sleep quality	Feel rested	Feel somewhat rested	Do not feel rested at all	
Mean preference weight (sd) Upper CI/lower CI	0.56 (0.64) 0.59/0.52	0.22 (0.32) 0.24/0.20	-0.77 (0.75) -0.73/-0.82	
Shortness of breath	Shortness of breath experienced during strenuous activity (e.g. walking on an incline/uphill/upstairs)	Shortness of breath experienced during light activity (e.g. a short walk on level ground)	Shortness of breath experienced when washing (e.g. taking a shower) or dressing	Shortness of breath experienced at rest (e.g. when sitting or lying down)
Mean preference weight (sd) Upper CI/lower CI	0.57 (0.53) 0.60/0.54	0.30 (0.37) 0.33/0.28	-0.14 (0.35) -0.12/-0.17	-0.73 (0.67) -0.69/-0.77
Urinary incontinence	COPD symptoms do not cause any urine leakage	COPD symptoms are causing a few drops of urine leakage	COPD symptoms are causing urine leakage which makes underwear wet	
Mean preference weight (sd) Upper CI/lower CI	0.50 (0.61) 0.53/0.46	0.16 (0.34) 0.18/0.14	-0.65 (0.60) -0.62/-0.69	
Mucus clearance	It is not at all difficult to bring up mucus	It is a little difficult to bring up mucus	It is very difficult to bring up mucus	
Mean preference weight (sd) Upper CI/lower CI	0.36 (0.35) 0.38/0.34	0.13 (0.28) 0.15/0.12	-0.50 (0.41) -0.47/-0.52	
Cough	Cough does not interrupt/disturb any usual activities	Cough interrupts/disturbs some usual activities	Cough interrupts/disturbs most usual activities	
Mean preference weight (sd) Upper CI/lower CI	0.30 (0.37) 0.32/0.28	-0.02 (0.30) -0.00/-0.04	-0.28 (0.37) -0.26/-0.30	

FIGURE 3 Preference weights. CI: confidence interval; SD: standard deviation.

participants determined their preferences in the DCE (*i.e.* there is a difference between the levels within each attribute).

Changes in preference weights (utilities) for equivalent improvements in cough and mucus combined were higher (more valued) than those for SOB alone. As a result, if these improvements were included in a health state preference simulation (with two profiles: A) cough and mucus improved and B) SOB improved) there was a clear preference for the cough and mucus improved profile (figure 4a). When comparing two profiles, C) daily symptoms (excess mucus production, cough and SOB) improved and D) exacerbations improved, there was a clear preference for the daily symptoms improved profile. Effects of different improvements of attributes are shown in figure 4b. Adding any other symptom (*e.g.* urinary incontinence or sleep quality) to mucus, cough and SOB alleviation would increase the preference for the “symptom improved health state” (profile C) even more.

Exploratory objectives

Data from all four variables of COPD severity were summated into one “factor” to represent disease severity (low, medium or high severity). This enabled three equally sized ($n=350$ in each group) patient severity groups to be generated for which preference scores were further analysed. Overall, preferences were consistent across the three severity groups (not significantly different – results not shown). Mean scores on CASA-Q individual domains were: cough symptoms domain 46.5; cough impact domain 51.6; sputum symptoms domain 48.1; and sputum impact domain 50.0.

Furthermore, both the Pearson’s and Spearman’s matrix showed a high degree of correlation (values close to ± 1) between the severity assessment parameters (supplementary Appendix C).

PAM-Q data allowing calculation of activation level were available for 899 participants. The responses of 151 participants were removed from the analysis (59 outliers and 92 invalid surveys) based on Insignia

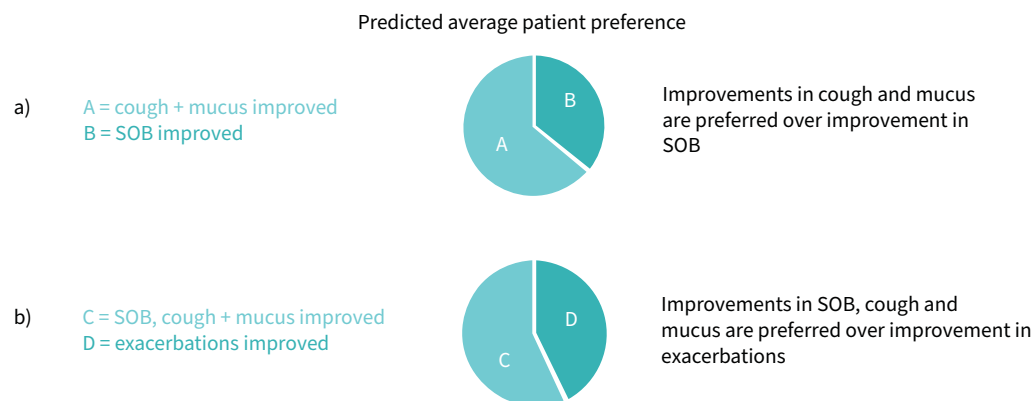


FIGURE 4 Impact of attributes improvement on patient preference (events of daily living). a) Improvement in cough and mucus *versus* improvement in shortness of breath (SOB); b) improvement in daily symptoms (excess mucus production, cough and SOB) *versus* improvement in exacerbations.

Health scoring guidelines [29]. Almost half of participants were scored as activation level 3 (n=446, 46.8%), indicating that, in relation to their COPD, they were considered as “taking action and gaining control”. A quarter of participants were at level 4 (n=225, 25.0%), the highest level of activation, described as participants “maintaining behaviours and pushing further”. The remaining participants were split fairly evenly between level 1 (“disengaged and overwhelmed”; n=113, 12.6%) and level 2 (“becoming aware but still struggling”; n=117, 13.0%). No evidence of an association of preferences with activation level was observed.

Discussion

The findings from this patient preference study indicate that analysis of changes in preference weights (utilities) for improvements in cough and mucus combined are higher (more valued) than those for SOB alone. Furthermore, improvement in daily symptoms (SOB, cough and mucus) were valued more compared with improvement in exacerbations alone.

The preference share and sensitivity analysis shows the considerable value patients place on the improvement of symptoms to achieve a health state where clinical end-points like cough, mucus, SOB, sleep and incontinence would be improved. These results are consistent with GOLD-informed COPD management strategy guidelines [4].

Our COPD study population was broadly representative of people living with moderate-to-severe COPD in the general population (with the proviso that participants were required to have chronic cough and sputum to meet recruitment criteria), with slight differences: the patient population in our study was slightly younger compared to the real-life COPD population (mean age: 60.5 years *versus* 71 years [30]) and 44% who participated in the survey self-reported to have asthma as a comorbidity, compared with 20–40% in the general COPD population [31, 32]. In the general COPD population, ~62% of people are reported to experience >1 exacerbation annually [33], while in our study 71% had ≥ 1 exacerbation; and 70–90% of participants in the general COPD population are smokers [32, 34], compared with 86% in our study. Also, the population included in this study had higher levels of education compared to the general COPD population, which may reflect their interest in participating in such surveys and they may be members of patient support groups [35]. SOB was not one of the screening questions *per se*, but the first screening question was “Have you been diagnosed (by a doctor or healthcare provider) with COPD?” – SOB is part of the definition of COPD, and hence implicit in this question, and we also gathered information on SOB in the profile-matching exercise.

Only 15% of participants spontaneously reported at the beginning of the survey that they experience urinary incontinence as a medical problem. However, when questioned about urinary incontinence in relation to their COPD health profile, 54% of participants indicated that COPD symptoms caused urine leakage to some or a great extent. A reason for this discrepancy could be the stigma associated with urinary incontinence.

During the profile-matching exercise, most participants stated they experience difficulty in bringing up mucus and that cough disturbs their usual activities. In the clinical setting, participants typically report

SOB and sputum symptoms; however, they do not always acknowledge the association of these symptoms with a coughing reflex (expert opinion, unpublished data). Literature suggests that symptoms as investigated in our study are intertwined: cough and mucus can impact sleep quality and can cause incontinence and SOB [5, 11, 36]. Other studies have shown that both cough and mucus are associated with COPD disease worsening and exacerbations [37, 38].

In this study, the assessment of COPD severity through four different means showed a good overall consistency across the different severity measures; we are not aware of previous research that has looked at the consistency of different methods to determine COPD severity.

Our findings of patient activation levels were consistent with those reported by MÜLLEROVÁ *et al.* [39], with about 28% of patients scoring level 1–2 and about 73% scoring level 3–4. Patient preferences in our study did not vary with activation levels.

Our study results cannot be directly compared with previously published quantitative patient preference studies as these studies focused on product features instead of disease symptoms and other attributes such as side-effects and/or convenience factors [40, 41]. The quantitative COPD preference study by GOOSSENS *et al.* [42] differed from the present study both in terms of experimental design and attributes investigated. To our knowledge, the current study, across five countries, is the first such study to attempt derivation of preference weight from a patient perspective and provide clinical data on new therapeutic offerings, in terms of the value these profiles would afford people living with COPD [42].

The study has some limitations, First, DCE was designed based on the assumption that the attributes are operating independently, and the research confirmed that the attributes have been considered independent in the context of its meaning for the DCE. In a disease like COPD, this is a challenge as individual symptoms such as cough, SOB and mucus are interconnected, and deterioration of symptoms leads to COPD exacerbation [43]. Second, it is true that through the requirement to have access to an online platform, we may have limited the ability of some patients to participate; however, since recruitment was through patient support groups primarily and then supplemented through patient panels, one would expect all of these patients to have internet access, so it is unlikely that many patients would have been excluded through this approach. Also, online surveys may have limitations, especially for an ageing population. However, literature has been published to indicate that results are similar for online and other survey administration routes in the elderly [44, 45]. Third, study eligibility criteria for study participation was patient self-reported. Since recruitment was *via* COPD/respiratory patient support groups or COPD patient panels, this should ensure correct inclusion into the study; however, participants who are registered with support groups or panels for research purposes may also be more engaged with their disease management, which could influence their preferences. Finally, as this study was conducted across five countries, there was climate variability; for example, Australia will be having its summer while it is winter in the other countries studied. However, in general the results suggest there is not much difference in preferences across these countries.

Despite these limitations, we think that our simulation model, built from DCE data and relative importance and weights derived from patient research, provides a unique way in which to assess different profiles and determine the patient value that would be derived from alleviation of different symptoms to a greater or lesser extent. We also believe that this study will make an important contribution in terms of informing the decision to include different patient-relevant end-points (cough, mucus, sleep disturbance and incontinence) in future COPD clinical trial designs, in addition to traditional end-points. The same has recently been emphasised by GOLD in its COPD classification system [4] and ongoing CoreCOPD group [46], which also aims to harmonise and inform future clinical trial design in COPD.

Conclusions

The study showed that people living with moderate-to-severe COPD would prefer to reduce cough and excess mucus production together over improvement of SOB and prefer to reduce combined daily symptoms over an improvement only in exacerbations. Hence, there is clear value in symptom-focused therapies to deliver meaningful outcomes for people living with COPD. This study also showed that gathering patients' insights *via* a structured and systematic preference approach is viable in early drug development and may benefit decision-making by multiple stakeholders.

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