Qualitative Insights on Meaningful Change in Symptoms and Impacts for Patients with Alpha-1 Antitrypsin Deficiency

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Introduction

- Alpha-1 antitrypsin deficiency (AATD)-associated lung disease (LD) is a rare, genetic cause of chronic airflow limitation that is due to a severe "loss of function" deficiency of the alpha-1 antitrypsin (AAT) protein.
- A core symptom of AATD-LD is dyspnea, which can occur at rest or with exertion, causing severe activity limitations.
- Meaningful change for AATD-LD is often evaluated in clinical trials as lung function (forced expiratory volume in 1 second [FEV1]), lung density, and health status decline (St. George's Respiratory Questionnaire for Chronic Obstructive Pulmonary Disease [SGRQ-C]).
  - To date, there has been no research that explicitly characterizes what constitutes a meaningful change directly from the patient perspective.

Objectives

- **The objectives of this study were to identify important symptoms and impacts that patients with AATD-LD experience and gain insights into what patients consider a meaningful change.**

Methods

Study Design

- This was an observational, hybrid, concept elicitation and cognitive debriefing study involving one-on-one telephone interviews.
- Three US clinical sites identified adults (18–80 years old) living with AATD-LD through reviews of medical records and clinical databases.
- Participants were eligible for the study if they had AATD PiZZ, null, or other rare phenotype/genotype; 2) lung disease related to AATD by computed tomography scan; 3) FEV1 percent predicted ≥30% and ≤80% or FEV1/forced vital capacity (FVC) <0.7; 4) non-smoker for at least 12 months; and 5) on stable chronic obstructive pulmonary disease (COPD) medications for at least 6 weeks.

Measures

- Clinical sites completed a brief clinical information form related to diagnosis of AATD-LD, COPD, and emphysema, phenotype/genotype of AATD, comorbidities, and exacerbation history.
- Participants completed a sociodemographic form.
- Two Patient Global Impression of Severity (PGIS) and Patient Global Impression of Change (PGIC) items were included to evaluate the severity of AATD-LD and current shortness of breath related to activities, respectively.
- Qualitative interviews (approximately 90 minutes) were conducted by trained interviewers using a semi-structured interview guide. As part of a larger study, participants were asked about:
  - The symptoms and impacts associated with AATD-LD.
  - What they would consider to be meaningful changes in:
    - Their overall disease and in terms of shortness of breath related to activities.
    - The PGIS and PGIC items.

Analysis

- The interview transcripts were deidentified, coded, and analyzed using a content analysis approach within ATLAS.ti version 22.0.
- Sociodemographic and clinical characteristics were analyzed using descriptive statistics (e.g., mean, SD, frequency).

Results

Sociodemographic and Clinical Characteristics

- Fifteen participants were recruited (53% female), and they had a mean (SD) age of 62.2 (8.8) years. All were White and non-Hispanic (**Table 1**), which is consistent with the disease population.
- The average mean (SD) duration since first AATD-LD diagnosis was 14.9 (11.4) years. Eleven participants (73%) had a FEV1 percent predicted ≥50%.
- Two-thirds of participants (67%) were currently on augmentation therapy, and all participants (100%) were on inhaled medication.

Table 1. Sociodemographic and Clinical Characteristics

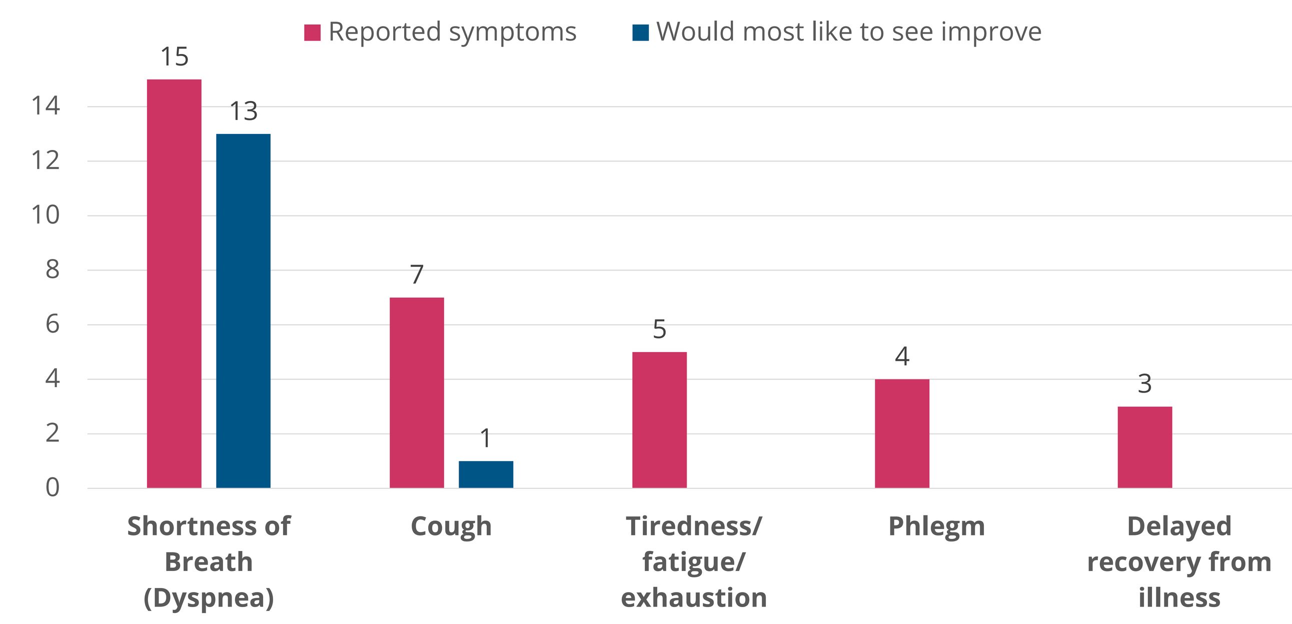
Sociodemographic Characteristics	Total (N=15)
Age, years	
Mean (SD)	62.2 (8.8)
Median [Min-Max]	66.0 [45.0–72.0]
Sex assigned at birth, n (%)	
Male	7 (46.7%)
Female	8 (53.3%)
Ethnicity, n (%)	
Not Hispanic or Latino	15 (100%)
Racial background, n (%)	
White	15 (100%)
Highest level of education, n (%)	
Secondary/high school	3 (20.0%)
Some college/university	4 (26.7%)
College/university degree (BA, BS)	7 (46.7%)
Postgraduate degree (MA, PhD)	1 (6.7%)
Time Since AATD-LD diagnosis (years)	
Mean (SD)	14.9 (11.4)
Median [Range]	16.8 [2.9–49.2]
Time Since COPD/emphysema diagnosis (years)	
Mean (SD)	10.8 (7.5)
Median [Range]	8.1 [0.9–22.4]
Number of moderate/severe AECOPD episode(s) in past 12 months, n (%)	
None	7 (46.7%)
1	2 (13.3%)
2	4 (26.7%)
>2	2 (13.3%)

Abbreviations: AATD-LD = alpha-1 antitrypsin deficiency lung disease; AECOPD = acute exacerbation of chronic obstructive pulmonary disease; COPD = chronic obstructive pulmonary disease

Patient-reported Symptoms and Impacts

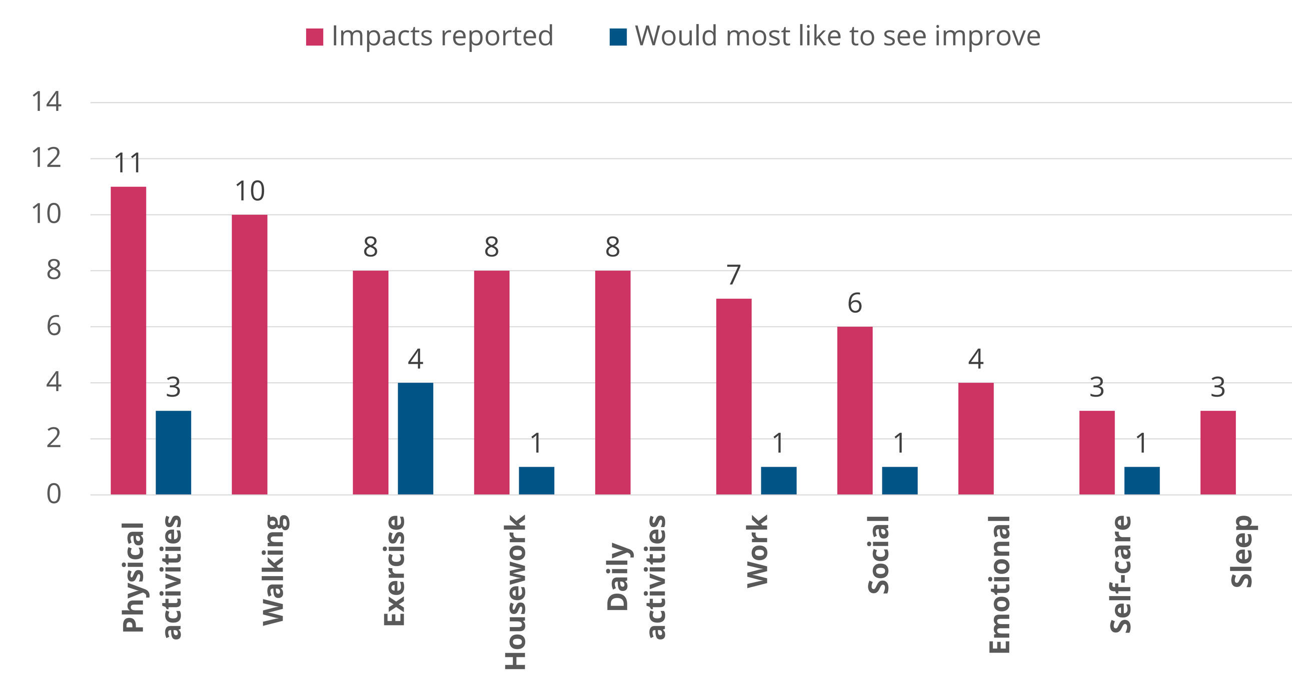
- Nineteen unique symptoms were reported; all participants (100%) reported shortness of breath as a symptom, and 13 (87%) indicated this is the symptom they would most like to see improved (**Figure 1**).
- Participants reported a range of impacts, with physical activities (n=11, 73%), walking (n=10, 67%), exercise (n=8, 53%), housework (n=8, 53%), daily activities (n=8, 53%), work (n=7, 47%), social (n=6, 40%), and emotional (n=4, 27%) impacts commonly mentioned (**Figure 2**).
- Physical activities/exercise (n=7, 47%) were most commonly identified as the impacts that patients would most like to see improved (**Figure 2**).

Figure 1. Participant-reported AATD-LD Symptoms



Abbreviation: AATD-LD = alpha-1 antitrypsin deficiency lung disease

Figure 2. Participant-reported AATD-LD Impacts



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Patient-reported Description of Meaningful Change

- When asked about what they would consider a meaningful change in their AATD, nearly all participants reported an improvement in the ability to engage in physical activities, particularly in conjunction with a reduction in shortness of breath.
- Participants were asked if it would be meaningful for their condition to remain stable. Almost all participants (n=14, 93%) reported that if their condition remained stable, they would consider that to be meaningful.
- Only one participant (7%) mentioned stability would not be meaningful due to how impactful the condition was on their quality of life.

"I would want to see, first off, a treatment that would hold my level of lung capacity at its current level, in other words not become worse. And I think that's about all I can hope for. Because short of a lung transplant, I don't believe there is anything that can improve my lung function. Most I can really hope for is to maintain the function I have."

300-003

Meaningful Change on the PGIS and PGIC

- Participants were asked to describe the smallest change on the PGIS and PGIC that they would consider meaningful.
- Most participants reported that a 1-point improvement on the PGIS and "minimally improved" on the PGIC represents a meaningful change category.
  - Almost all participants (93%) reported a 1-point improvement on the PGIS-Overall and PGIS-Activity would be a meaningful change.
  - One participant (7%) each on the PGIS-Overall and the PGIS-Activity responded to the question, without describing a category improvement.

"I think I would have less reliance on O_2. I don't know if that's possible. Maybe if I'm able to exercise more or make myself exercise more, then some of my symptoms could be partially abated. Because a lot of it has to do with endurance and so it's a two-edged sword. I know I need to build my endurance, but it's really hard to do that. And, yeah, I think mild is, would be having more endurance…"

100-006

"Well, because then you're going to have increased lung improvement."

200-004

- More than half the participants (60%) reported "minimally improved" on the PGIC-Overall would be a meaningful change. Five participants (33%) mentioned "much improved" would be meaningful; one participant (7%) stated "no change" would be meaningful.

"I guess noticing that I didn't have to stop, or I didn't have to labor with my breathing to accomplish something that I had started having trouble with."

100-005

Limitations

- The results of this study should be interpreted considering the sample size (N=15). While this is a robust sample for a qualitative study in a rare condition, additional research to confirm the results may be helpful.

Conclusions

- **Shortness of breath is a core symptom of AATD-LD and a key consideration for symptom improvement.**
- **Participants experienced a range of impacts and reported a range of impacts they would want to see improved.**
- **Most participants with AATD-LD indicated that achieving stability (i.e., no longer experiencing decline) would be meaningful to them.**
  - **In chronic conditions that are characterized by worsening health status, interrupting or slowing the rate of decline may represent a meaningful treatment benefit; these patients do not always expect to experience improvements in their condition.**
- **These results may be useful for subsequent work to select anchor categories and establish thresholds for meaningful change and/or to inform the selection of appropriate endpoints for drug development.**

Disclosures

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