Patient Related Outcome Measures

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REVIEW

Is It Time Alpha-1 Antitrypsin Deficiency Had a Specific Patient Reported Outcome Measure? A Review

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Abstract: Alpha-1 antitrypsin deficiency (AATD) is a rare cause of chronic lung and liver disease without its own patient reported-outcome measure (PROM). PROMs for Chronic Obstructive Pulmonary Disease (COPD) are commonly used instead, but AATD differs from COPD in several ways. We reviewed whether the PROMs used in the AATD literature adequately assess quality-of-life in these patients. 11 studies used PROMs as their primary outcomes; 21 included them as secondary outcomes. The St George's Respiratory Questionnaire (SGRQ) was the most commonly used PROM, used by 7 of the 11 primary outcome studies. Others included the COPD Assessment Tool, SF-36, LCOPD, EQ-5D, and the Chronic Respiratory Diseases Questionnaire. Several studies assessed SGRQ as being associated with respiratory disease severity as measured by FEV1% predicted, exacerbation rate, oxygen use and exercise tolerance. However, no studies used PROMs which included assessment of liver-related symptoms, other extra-pulmonary manifestations of AATD, or concerns related to genetics or finances. These factors are likely to have an impact on quality of life in AATD. A specific AATD-PROM is therefore required to holistically address the quality of life effects of an AATD diagnosis.
Keywords: alpha-1 antitrypsin deficiency, COPD, chronic liver disease, rare diseases

Introduction

Alpha-1 Antitrypsin Deficiency (AATD) is a genetic disorder characterized by low circulating levels of alpha-1 antitrypsin (AAT), a protease inhibitor. Circulating AAT levels are dependent on a combination of *SERPINA1* alleles, which exist in the community in M (normal variant), S and Z forms, along with some rarer variants, with ZZ having the lowest circulating AAT levels of the most common phenotypes.[1] AATD is a rare disease, with the ZZ phenotype affecting approximately 250,000 people worldwide, mostly of north and/or western European ancestry.[2] With unopposed protease activity, particularly of neutrophil elastase, pulmonary tissue damage occurs, manifesting as Chronic Obstructive Pulmonary Disease (COPD) and bronchiectasis. Extra-pulmonary effects also occur; polymerisation of misshapen AAT occurs in the liver, leading to hepatocellular death due to protein overload. This causes clinically significant chronic liver disease in a minority of patients.[3] Rarer manifestations have also been reported, including panniculitis and anti-neutrophil cytoplasmic antibody (ANCA) positive vasculitis.[4,5]

Quality of life is known to be impaired in those with AATD across a range of genotypes, particularly with regard to physical activity.[6] Uncertainty about the future regarding disease progression and outcomes can result in anxiety and low mood;[7,8] such uncertainty may be felt more intensely in countries where disease-modifying treatment is not licensed. Consequently, it is important to assess the quality of life when reviewing AATD patients.

In many other chronic diseases, patient-reported outcome measures (PROMs) have become a key tool in monitoring quality of life both clinically, and increasingly in research. They exist as an acknowledgement of the discrepancy between physicians' assessment of objective markers of disease severity, and patients' own impression of the disease's impact on them. Such a discrepancy is seen both in medicine in general, and in COPD.[9,10] Therefore, in AATD it is also possible that subjective symptoms may not fully correlate with objective markers of disease severity.

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Despite their importance in chronic disease management, no dedicated AATD patient-reported outcome measure (PROM) exists. This has two main reasons: firstly, since it is implicated in less than 2% of COPD,[11] AATD is only infrequently encountered in general respiratory clinics, reducing demand for development of a specific PROM – consequently tools such as the COPD assessment tool (CAT),[12] St George's Respiratory Questionnaire (SGRQ),[13] and the less specific EQ-5D-5L score[14] have been used.[15–17] Secondly, in many countries including the UK, AATD-COPD treatment does not differ from treatment for other types of COPD, since specialist treatments such as exogenous replacement (AAT augmentation therapy) are not available. This leads to a perception among those unfamiliar with the disease that AATD is simply a genetic cause of COPD; however, this is likely to be an oversimplification, since AATD differs from usual COPD in a multitude of ways (Table 1), as follows.

Objectively, emphysema in AATD appears different to usual COPD, with a lower lobe predominance compared to a more widespread distribution in smoking-related lung disease.[18,19] Asthma-like features are less prevalent.[20,21] Patients are younger and less likely to be smokers, with lower rates of cardiac co-morbidities.[22,23] Exacerbations last longer in AATD-COPD than in usual COPD.[24,25] Concomitant liver disease affects a significant minority of patients, and can be independent of lung disease,[3] meaning those without significant emphysema or breathlessness may still require monitoring and treatment.

Furthermore, on a psychosocial level, the earlier age of diagnosis in AATD is likely to bring different considerations, such as impact on careers, physical activity, and family planning.[26,27] Anxiety related to the hereditary nature of the disease is a burden not shared by usual COPD patients.[28] In those who wish to fund AAT augmentation privately, financial matters will be a concern. AATD specialist services are few and far between, requiring long journeys to attend clinics for some patients; those who cannot commit to such travel may be anxious about the quality of their disease management, however comprehensive their local team may be.[29] Given these distinct differences between AATD and usual-COPD, it is reasonable to suggest the need for the development of AATD-specific PROMs for monitoring purposes. This article reviews the use of PROMs in AATD research, and assesses the need for a specific AATD PROM.

Methods

To assess the range of PROMs currently in use in AATD, databases were searched for peer-reviewed articles mentioning alpha-1 antitrypsin deficiency and quality of life scores or patient reported outcome measures. The search strategy included all permutations of "alpha-1 antitrypsin deficiency", and "quality of life" or "patient reported outcomes". PubMed, Embase, and Cochrane databases were searched in April 2024.

Table 1 Major Differences Between AATD and COPD: AATD is Not Simply a Genetic Cause of COPD

	AATD	**Usual-COPD**
Aetiology	Hereditary	Primarily exposure-driven
Age at diagnosis	Younger at diagnosis	Older at diagnosis
Radiological pattern	Lower lobe emphysema	No particular lobar predominance
Liver disease	Affects a minority	No direct association
Asthma-like features	Less common	Significant proportion
Co-morbidities	Lower	Higher
COPD exacerbation duration	Longer	Shorter
Treatment	Specific therapy (AAT augmentation) not licensed in many countries; expensive; many new treatment modalities in clinical trials at present	Licensed and regulated in most countries; cheap; long-established treatment modalities
Service provision	Limited expertise available	Routinely managed by GP and secondary care respiratory services
Implication for future planning	Strong implications for future career/lifestyle/family planning	Average age of diagnosis is closer to retirement age, and after reproductive age

Results were limited to peer-reviewed published research articles of adult patients. Review articles were excluded. Studies with the primary aim of exploring the quality of life of patients with AATD, with or without comparison among genotypes, or to control groups, were included and reviewed. Studies exploring patients' changes in quality of life as secondary outcomes following clinical interventions, or observational studies for other exposures, were reviewed only to assess the popularity of different PROMs selected for these purposes. We then performed a narrative synthesis according to published guidance.[30] The initial theory was that existing questionnaires would not adequately assess quality of life in AATD. Studies were grouped by type of PROM used, and by whether quality-of-life was a primary or secondary outcome of the work, and compared with each other within these groups.

Results

A total of 31 studies were found. 11 studies explored the quality of life of patients with AATD as their primary aim. 20 studies explored patients' changes in quality of life as secondary outcomes. A total of 11 PROMs were reported in these studies and the St George Respiratory Questionnaire (SGRQ) was the most commonly used PROM. Studies included in the review are summarised in Tables 2 and 3. An overview of the PROMs found is highlighted below.

Table 2 Research Studies of Quality of Life in AATD

Authors	Study Design	PROM	PROM Outcome
Knebel et al 1999[31]	Cross-sectional study comparing PROM score with FEV1 and 6-minute walk test	Chronic Respiratory Disease Questionnaire	No relationship between FEV1pp and PROM score
Holm et al 2013[8]	Cross-sectional study of AATD-COPD vs usual COPD	SGRQ, HADS	AATD-COPD patients had poorer PROM scores than usual-COPD
Manca et al 2014[32]	Cross-sectional comparison of multiple PROMs with FEV1, in AATD vs non-AATD COPD	COPDSS, EQ-5D, LCOPD, CAT	COPDSS and LCOPD correlated with FEV1pp, and this correlation was stronger in AATD patients. CAT did not correlate with FEV1.
Luisetti et al 2015[33]	Retrospective cohort study of Italian registry	SGRQ	Poorer PROM scores in index cases, and in those who went on to receive AAT augmentation
Gauvain et al 2015[34]	Cross-sectional study of baseline characteristics compared with PROM	SGRQ	SGRQ score inversely associated with FEV1pp, gas transfer, and 6-minute walk test results
Redondo et al 2017[35]	Cross-sectional study of clinical and demographic data	SF-36	Better PROM score associated with higher FEV1pp and 6-minute walk test
Karl et al 2017[17]	Cross-sectional study of AATD-COPD vs usual-COPD	SGRQ, CAT, EQ-5D-3L	PROM scores did not differ between AATD-COPD and usual-COPD
Stockley et al 2018[36]	Retrospective study of PROM scores influence on outcomes in the UK registry	SGRQ	Annual PROM score associated with FEV1 decline
Werdecker & Bals 2023[37]	Cross-sectional study of the impact of Covid-19, and baseline PROM scores, on AATD patients	SGRQ	Baseline PROM score associated with poorer FEV1pp, stress, and overall well-being
Choate et al 2024[38]	Cross-sectional analysis of the AlphaNet cohort	SF-36	PROM results were associated with exacerbation frequency, mMRC, oxygen use, and productive cough. Physical health was more impaired than mental health.
Choate et al 2024[39]	Retrospective analysis of the AlphaNet cohort (AATD patients on augmentation therapy)	SGRQ	PROM score associated with exacerbation frequency, productive cough, mMRC, and oxygen usage.

Table 3 Choice of PROMs as Secondary Outcome Measures in AATD Research

Authors	Study Design	PROM	PROM Outcome
Hogarth et al 2024[15]	Phase II study of Spiration Valve System in AATD	CAT, SF-36	SVS was associated with better PROM scores
Piloni et al 2023[16]	Cross-sectional study comparing PiZZ, PiMZ and PiMM genotype COPD with PFTs and PROM scores	SGRQ	Significantly differing PROM results between the 3 COPD groups
Ellis et al 2023[45]	Case control study of PROM in AATD patients receiving augmentation therapy vs control	SGRQ	PROM deterioration was greater in the control group vs the treatment group
Everaerts et al 2023[46]	Retrospective non-controlled cohort study of endobronchial valve (EBV) treatment in AATD	SGRQ	EBV treatment was associated with improved PROM score
Schramm et al 2021[47]	Cross-sectional study of PFTs, symptoms, and PROM in AATD compared to non-AATD	SGRQ	Lower PROM scores in AATD group
Annunziata et al 2021[48]	Prospective cohort study of QOL in home AAT augmentation	Abbreviated form of SGRQ	PROM scores improved over 3 months on home augmentation
Crossley et al 2020[49]	Cross-sectional study of CT densitometry in AATD patients	SGRQ, CAT	Correlations between both PROM scores and FEV1pp, FVC, KCO and RV/TLC%
Perotin et al 2018[50]	Retrospective analysis of 6 AATD patients receiving endobronchial coils	SGRQ	Improvement in SGRQ score in most patients.
Bernhard et al 2017;[51,52] Fahndrich et al 2017[53]	Retrospective cohort studies of the German AATD registry	SGRQ	Ex-smoker status reduced the differences in PROM score between PiZZ and PiSZ patients
Lessard et al 2017[54]	Cross-sectional study of MRI biomarkers in AATD patients, ex-smokers with COPD, and never-smokers.	SGRQ	COPD patients had better PROM scores than AATD patients.
Piitulainen et al 2017[23]	Cross-sectional study of Swedish AATD cohort	SGRQ	PiZZ smokers had poorer PROM scores than PiZZ never smokers
Green et al 2016[55]	Retrospective cohort study of CT density decline compared with survival and quality of life scores	SGRQ	No relationship reported between CT density and PROM
Stone et al 2016[56]	Retrospective cohort study of lung transplantation in AATD	SGRQ	Patients undergoing lung transplantation had poorer (pre-transplant) PROM scores than patients not undergoing transplant
McGrady et al 2015[57]	Cross sectional study of WebMD participants reporting COPD.	Bespoke scoring system rated between no impairment, mild, moderate, or severe impairment	AATD patients had lower quality of life than usual COPD patients.
Tanash et al 2015[58]	Cross-sectional studies of Swedish registry	SGRQ	No difference in PROM between genotypes

(*Continued*)

Table 3 (Continued).

Authors	Study Design	PROM	PROM Outcome
Chapman et al 2015[44]	RCT of AAT augmentation therapy vs placebo	SGRQ	No significant difference in PROM scores between intervention groups
Campos et al 2009[59]	Prospective Cohort Study of PROM score stratified by age	SGRQ, SF-36	Older patients had better PROM scores and FEV1 decline
Campos et al 2009[42,60]	Prospective cross-over Cohort Study of PROM score in a patient self-management program	SGRQ, SF-36	Better SGRQ activity domain decline in intervention phase; poorer SGRQ scores with higher exacerbations
Dirksen et al 2009[43]	RCT of AAT augmentation therapy vs placebo	SGRQ	No significant difference in PROM score deterioration
Holme & Stockley 2007[61]	Cross-sectional study comparing CT densitometry, PROM and FEV1	SGRQ	Lower PROM score in those with abnormal lung function vs severe

St George Respiratory Questionnaire (SGRQ)

The SGRQ is by far the most commonly used PROM in the available literature. It has 2 sections: the first consists of questions about the last 3 months, with the patient asked to report the frequency and duration of cough, phlegm, shortness of breath, wheezing, and exacerbations. The second section asks about the impact of the respiratory disorder and treatment on work and day-to-day living. Elevated scores have been associated with more severe lung function baseline measurements and decline, and higher exacerbation rate. The maximum score is 100: a difference of 4 points or more is considered clinically significant, except in severe COPD, where this threshold may be higher.[40,41]

SGRQ has been used in the study of QoL in AATD. In 2013, Holm et al[8] found that AATD patients had higher SGRQ scores than non-AATD COPD patients, by 4.75 points on average, using multivariate regression analysis which accounted for age, smoking history, and oxygen use, and limited the AATD to those with a "severely deficient" genotype. Scores were also higher in those with shorter education duration, and uncoupled persons. However, since this study used a pre-existing cohort, results could not be adjusted for severity of COPD, as spirometry data was not available. When adjusting for COPD severity, Karl et al's 2017 study found no significant differences in SGRQ between 131 AATD-COPD patients and 2049 usual-COPD patients.

In the Italian registry, Luisetti et al[33] found higher SGRQ scores in index cases (the first case in a family) (mean 41.2, SD 24.4) vs non-index cases (mean 6.2, SD 8.3), but this was not adjusted for the presumed lower age of non-index cases, who will have been identified from family screening processes.

Gauvain et al[34] summarised health-related QoL in the patients with COPD in their French AATD registry, and found SGRQ score was associated with shortness of breath, 6-minute walking distance, FEV1 and gas transfer, but not with age or current smoking. Stockley et al[36] went into temporal detail, and found that SGRQ score was relatively stable over time, was greater for patients with COPD than those without, and correlated with FEV1 decline. Choate et al in 2024 also studied SGRQ score over time, and found long-term stability of SGRQ score, as well as an association between SGRQ decline and exacerbation frequency and use of oxygen.[39] Like Holm et al, their study also used the AlphaNet cohort, a health management organization for United States patients with AATD who are prescribed augmentation therapy,[42] and therefore could not be adjusted for COPD severity. However, due to its stability over time, both Stockley et al and Choate et al concluded that SGRQ score is not a suitable choice for a primary outcome measure in AATD research trials.

Werdecker and Bals in 2023 demonstrated a positive correlation between SGRQ score and negative emotions, stress, and deterioration of health status following the Covid-19 pandemic, although they reduced health status to a binary outcome of "unchanged" or "worsened" based on an unpublished questionnaire.[37] They also found that SGRQ mediated the relationship between FEV1 and stress, although stress had also been reduced to a binary outcome of "yes" or "no", and is itself a subjective term.

Many studies have used SGRQ score as a secondary outcome in observational studies, or interventional trials. Overall, these studies would suggest that SGRQ is a useful tool in assessment of QoL in AATD, showing significant results in various trials including augmentation, endobronchial valves and coils (Table 3), with the notable exception of 2 studies of augmentation therapy: Dirksen et al in 2009[43] and Chapman et al in 2015,[44] who both found no significant differences in SGRQ scores between intervention and control groups; however both these studies had relatively small numbers (65 and 180 individuals respectively). By contrast, Ellis et al's 2023 case-control study of AAT augmentation included 541 patients, and did find reduced SGRQ score decline in those who had received AAT augmentation.[45]

COPD Assessment Tool

This questionnaire uses Likert scales to assess various chest-related and functional symptoms.[12] It is much shorter than the SGRQ and SF-36, and therefore easier to perform in clinic, but contains less functional assessment than longer questionnaires.

Manca et al assessed CAT score in their study of 2014,[32] but found it did not associate with FEV1% predicted, despite the COPD Severity Score, EQ-5D and LCOPD score (Table 4) both having significant associations with this outcome measure. Karl et al also used CAT score in their article analysing healthcare-related costs, but only to compare AATD patients against COPD patients, finding no significant difference in CAT, SGRQ or EQ-5D between the 2 groups.[17]

Sf-36

A less commonly used measure of quality of life in AATD has been the SF-36 score. Unlike the SGRQ, the SF-36 is not focused only on chest symptoms, aiming to be holistic by assessing the following 9 domains: physical functioning, role limitations due to physical health, role limitations due to emotional problems, energy and fatigue, emotional well-being, social functioning, pain, general health, and change in health.[86]

The SF-36 has been used to study quality-of-life in AATD. In a cross-sectional study of 26 patients in 2017, Redondo et al[35] found several aspects of SF-36 score to correlate with disease outcomes, including the "physical health" domain with FEV1 and mMRC score, the "role limitation due to physical health" domain with mMRC score, and the "bodily pain" domain with 6 minute walk test. However, they did not analyse the total SF-36 score in comparison to outcomes. If only some domains associate with disease outcomes, rather than the total score, its use by clinicians less familiar with the score may be limited.

Choate et al assessed the use of the SF-36 score in the AlphaNet cohort, and found both the mental health components and the physical health components to be associated with MRC shortness of breath score and exacerbation rate.[38]

Other PROMs

Other COPD PROMs used by AATD studies included the Chronic Respiratory Disease Questionnaire, the COPD severity score (COPD-SS) and the LCOPD score. Generic or mental health PROMs used included the EQ-5D and HADS scores. These other PROMs are summarised in Table 4.

PROMs in AATD Liver Disease

Although articles focused on quality of life in AATD liver disease were not excluded from the search criteria, no such articles were identified. This may be because liver disease in alpha-1 antitrypsin deficiency is less common than lung disease, only affecting 10–35% of those with the most severe PiZZ genotype,[87,88] and highlights this under-researched area.

PROMs as Secondary Outcomes in AATD Research

A variety of studies have used PROMs as secondary outcomes in AATD research. SGRQ is again the most common, with 18 of the 20 articles (85.7%) identified using this PROM. Three of these also used another PROM: two used the SF-36 score, one used the CAT score. Two further papers opted not to use the SGRQ: Hogarth et al in 2024[15] used the CAT and SF-36 scores; and McGrady et al[57] used a bespoke scoring system.

Table 4 Patient Reported Outcome Measures Used in AATD

Name (Max. Score)	Symptoms Assessed	Strengths	Weaknesses	Validated Groups
SGRQ (100])	Cough, phlegm, shortness of breath, wheezing, social impact	Covers multiple domains High consistency and test-retest reliability[62] Widely used in many clinical trials Available in other languages[63]	Lacking assessment of non-chest domains such as fatigue level. Lengthy administration Trend bias could be induced due to the presence of non-polar questions. No adjustment for age, sex and other co-morbidities.[64] Cannot be used clinically to measure the changes in QoL of AATD patients when placed on therapeutic therapy.[39] Patients' response to SGRQ is dependent on their cultural background and geographical location.[65]	Validated in 2 separate groups: firstly 40 COPD and 20 asthma patients; secondly 141 patients with "chronic airways obstruction"[13]
CAT (40)	Cough, phlegm, chest tightness, breathlessness, activity limitation, sleep, energy levels.[12]	Short and simple (8 items questionnaire) making it quick and easy to use and it has been validated across many languages and cultures.[66] Ability in discriminating different levels of patient responses Responsive to change in COPD health status[67] Can also be utilized in patients with mild airflow obstruction, and has the ability to differentiate patients according to sexes and frequency in experiencing exacerbations.[68]	Limited scope – mostly respiratory symptoms only	First validated by 1503 COPD patients from Europe and USA in the study by Jones et al, 2009.[12] Later validated as an effective assessment of fatigue in COPD patients.[69]
COPD Severity Score (COPD SS) (35)	Breathlessness, oxygen use, hospitalisations.[70]	Simple and quick. Can differentiate COPD severity levels[71] Can predict exacerbation treatment failure[72]	No assessment of functional status and exercise capacity	Validated in 837 COPD patients >40 years old[71]

(*Continued*)

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Table 4 (Continued).

Name (Max. Score)	Symptoms Assessed	Strengths	Weaknesses	Validated Groups
EQ-5D (NA, EQ VAS = 100)	The 5 main domains are: Mobility, Selfcare, Usual Activities, Pain/Discomfort and Anxiety/Depression	Holistic assessment of quality of life Simple, therefore easy to administer and comprehend	May lack sensitivity in the cases of milder COPD and asthma patients[73,74] Could be more holistic by considering fatigue, cognitive function, and vision[75] Not specific to AATD symptoms	Initially validated in 40 patients with a mixture of arthritis, diabetes and asthma.[14] Later validated in 616 COPD patients[76]
LCOPD (Living With COPD questionnaire) (22)	Breathlessness, fatigue, cough, sputum production, sleep disturbance, emotional well-being and social functioning.	37 COPD patients were included in the design process Easy to complete COPD-specific Relatively holistic assessment	Not widely adopted since release in 2011	Validated in 307 COPD patients from both the USA and UK.[77] Later validated in 408 COPD patients, and found to differentiate severity of airflow obstruction.[78]
SF-36 (100)	General QoL Measures 8 main domains: physical functioning, role limitations due to physical problems, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and general mental health.	Comprehensive High internal consistency[79] Can be used in other diseases Available in multiple languages: Mandarin, Danish, French and Australian	Not able to capture AATD-specific aspects of QoL[38] Time-consuming to administer Does not correlate with SGRQ[80]	Initially validated in 1980 randomly selected primary care patients in the UK[81] Later validated in 50 male COPD patients as associating with degree of breathlessness[82]
Chronic Respiratory Disease Questionnaire (100)	Assesses 4 main domains: dyspnea, fatigue, emotional mastery and function.	Relatively holistic Validated in AATD patients[31]	Not specific to COPD or AATD	Initially validated in 13 patients with "chronic airflow limitation" or pulmonary fibrosis[83] Later validated in severe COPD patients, and found to correlate well with SGRQ[84,85]

Discussion

Currently, the vast majority of research uses COPD-specific PROMs to assess the impact of lung disease in AATD. The strengths of this approach are that they are generally well validated for patients with COPD, in both stable and exacerbating patients. They are generally widely used, and easy to complete. They have also been widely translated and validated in these translations, making them more accessible to different patient populations. There is evidence that they correlate well with the progression of emphysema clinically, which is a key marker of AATD disease progression.[55] Although the validity of SGRQ for COPD assessment has been doubted,[65] several studies reviewed here have shown that, in alpha-1 antitrypsin deficiency, SGRQ score correlates with FEV1% predicted, exacerbation rate, oxygen requirement, MRC breathlessness score, gas transfer impairment, 6-minute walk test score, phlegm production, and stress levels, suggesting it is a valid way of assessing COPD severity in AATD.

Much of the research into PROMs in AATD relies on pre-existing cohorts, particularly the AlphaNet cohort, which features in many of the studies reviewed here. The use of such cohorts provides numerous practical advantages, but will naturally select the most motivated patients, who may have been exposed to a high level of information in conferences, awareness days and other research, meaning they may not be representative of all AATD patients. AlphaNet participants also tend to be on augmentation. Studies which rely on responding to questionnaires sent by post risk exclusion of the sickest patients who cannot get out to post items, and those which use digital means of data collection risk other exclusions (eg by age or socio-economic status).

Overall, the studies in this review appear to support the use of some existing PROMs in AATD assessment, including SGRQ and SF-36. However, since the PROMs used are not designed for the patient population affected by AATD, they will not have been able to assess the quality-of-life effects of extra-pulmonary AATD-specific issues, and SGRQ has proven insensitive to change in RCTs of the only licensed therapy for AATD lung disease (augmentation). This is a key weakness, especially as we move into an era where showing patient centred efficacy is important – more sensitive scores are needed for use in future trials. Furthermore, AATD patients vary from COPD patients in a number of key ways (Table 1), many of which are not assessed by the PROM scores mentioned in this review – none of them assess the impact of liver disease, the implication of hereditary disease, or the financial dilemma when disease-modifying treatment is not subsidised. If patients are not asked these questions, confirmation bias can influence the interpretation - we might be falsely reassured by better PROM scores.

The paucity of PROMs assessing liver disease in AATD is a particularly clear limitation to a holistic assessment, as a diagnosis of chronic liver disease can be expected to have a high impact on patients. At the less invasive end of the scale, more stringent alcohol and fluid intake restrictions may impact social plans; in more severe disease, invasive endoscopies, biopsies or even liver transplants would clearly influence quality of life. Additionally, social stigma and lack of effective treatments for end-stage liver disease have been shown to have a negative effect on quality of life in other forms of chronic liver disease.[89] Furthermore, a significant minority of AATD patients with biopsy-proven liver fibrosis have only mildly impaired FEV1.[88] Such patients would therefore be expected to have low SGRQ and CAT scores despite the burden of liver disease; in fact, it has been proven that there is no relationship between CAT score and non-invasive liver fibrosis.[90] Therefore, there is an unmet need for an AATD-specific PROM to assess this and other extra-pulmonary manifestations of AATD. This has been identified as a priority by the 2017 ERS statement on areas for future research in AATD.[91]

Conclusions

The most commonly used PROMs in AATD are sufficient to assess the COPD element of AATD, but may lack sensitivity, and there is a need for a PROM which includes the extra-pulmonary quality of life effects of a diagnosis of AATD.

Abbreviations

AAT, Alpha-1 Antitrypsin; AATD, Alpha-1 Antitrypsin Deficiency; ANCA, Anti-Neutrophil Cytoplasmic Antibody; CAT, COPD Assessment Tool; COPD, Chronic Obstructive Pulmonary Disease; COPD-SS, COPD Severity Score; EBV,

Endobronchial Valve; FEV1, Forced Expiratory Volume in 1 second; LCOPD, Living with COPD; PROM, Patient-Reported Outcome Measure; SF-36, Short Form 36; SGRQ, St George's Respiratory Questionnaire.

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.

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