

DEVELOPING OF A NEW TOOL FOR EVALUATION OF THERAPEUTIC ADHERENCE IN COPD

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Abstract

Patients-reported outcomes can be used to measure health concepts that cover the full spectrum of human functioning. The objective of this study was to develop and validate a tool that could be used in assessment the adherence patients with chronic obstructive pulmonary disease (COPD). In the second part of the questionnaire we used EQ-5D-5L. COPD is characterized by progressive limitation of the respiratory flow which is not totally reversible. Pharmacological therapy is the basis for COPD treatment and includes inhaled bronchodilators such as β_2 adrenergic agonists (e.g. olodaterol) and anticholinergic agents (e.g. tiotropium). Being a new treatment on the reimbursement list in Romania, the treatment with a fixed dose combination of olodaterol and tiotropium was one of the inclusion criteria of patients with COPD in this study. The tool has good measurement properties and provides a valid and reliable measure of COPD-specific adherence.

Rezumat

Instrumentele de măsurare a rezultatelor raportate de pacienți sunt folosite în domenii largi din sănătate. Scopul acestui studiu a fost de a dezvolta și valida un instrument pentru evaluarea aderenței la tratament a pacienților cu boală pulmonară obstructivă cronică (BPOC). În a doua parte a chestionarului a fost folosit EQ-5D-5L. BPOC se caracterizează prin limitarea progresivă și doar parțial reversibilă a fluxului respirator. Terapia farmacologică reprezintă baza tratamentului pentru BPOC și cuprinde bronhodilatatoarele inhalatorii, precum agoniștii β_2 adrenergici (ex. olodaterol) și agenții anticolinergici (ex. tiotropiu). Fiind un medicament nou introdus pe listele de medicamente gratuite și compensate din România, tratamentul cu o combinație în doză fixă de olodaterol și tiotropiu a fost unul dintre criteriile de includere a pacienților cu BPOC în acest studiu. A fost dovedit că instrumentul dezvoltat oferă o modalitate validă și fiabilă de evaluare a aderenței specifice pacienților cu BPOC.

Keywords: adherence, chronic obstructive pulmonary disease, quality of life

Introduction

Patients-reported outcomes (PROs) are standardized measures directly reported by the patient that feature the patient's perception of the impact of disease and treatment on health and functioning. Frequently, PROs ensure information that would otherwise be difficult to quantify, such as in the case of symptom burden, social participation, treatment adherence or pain. Not least, PROs reflect the values and priorities of patients. PROs can be designed to comprehensively assess the overall health-related quality of life (HRQoL) or with a specific focus on a particular disease. PROs are required to estimate health outcomes of Chronic

Obstructive Pulmonary Disease (COPD), facilitating the information collection and improving communication between patient and clinician.

According to World Health Organization and Global Initiative for Chronic Obstructive Lung Disease, COPD is a preventable and treatable lung disease that is characterized by airflow limitation and persistent respiratory symptoms. It is not totally reversible and is associated with significant concomitant chronic diseases. The clinical symptoms are dyspnoea, cough and/or sputum production, wheeze, and intermittent exacerbations or “flare-ups”. Tobacco smoking is the primary cause of COPD, then the considerable

exposure to noxious gases/particles and genetic abnormalities [2, 8, 9].

COPD is a major cause of morbidity and mortality and is predicted to be the third leading cause of death worldwide by 2020 [5, 14]. COPD becomes apparent in middle to older age, but is now considered to have origins in early life [15].

COPD has substantial economic and social costs. These include both direct costs related to medical management and indirect costs related to disability, lost revenue from not attending work, and caring for patients. In Europe, 6% of the health budget is used for direct costs related to respiratory diseases, just over half of which are related to COPD [8].

The pharmacological treatment is mainly based on inhaled therapy and includes bronchodilators (short- and long-acting beta 2 agonists, short- and long-acting muscarinic antagonists, and combinations of beta 2 agonists and antimuscarinic agents), corticosteroids and combinations of corticosteroids with other agents. Oral drugs (methylxanthines and a phosphodiesterase 4 inhibitor) are adjunctive medications which may be recommended [12].

Long-acting inhaled bronchodilators, both beta 2 agonists (LABAs) and antimuscarinic agents (LAMAs), are indicated for moderate to severe COPD to alleviate symptoms, diminish exacerbation frequency and also to enhance quality of life and health status [18]. Fixed-dose combinations of inhaled LABAs and LAMAs are frequently recommended due to (a) achieving maximal and sustained bronchodilation, and (b) using the lowest effective doses and reducing side effects from monotherapy [3, 18]. Combinations ensure a complementary action on lung function as LAMAs operate mainly within the proximal sections of the lung and LABAs typically within the distal sections [3]. Most of the international COPD clinical practice guidelines mention the importance of “reduced symptoms, reduced exacerbation risk and improved quality of life” [13].

The aim of this study was to develop an instrument that could be used in assessing the quality of life and adherence patients with COPD. Medication non-adherence affects the health of patients [17]. Non-adherence in patients with COPD has a number of causes that are related to the characteristics of the patients, the disease and the therapies [1].

The price of the therapy is also a factor that influences the adherence. Reimbursement policy as well as pricing for drugs and implications of Health Technology Assessment (HTA) in Romania help patients benefit from innovative treatments [10]. The objectives of health policies are to assure availability and accessibility for patients to treatments and medicines [4]. The values of pharmacy's break-even point varied according to any crisis aggravation. There is a continuous increase of the number of positions occupied by reimbursed medicines and it was confirmed that generic

formulations, having foreign Marketing Authorization Holders, exceeded the ones having Marketing Authorization Holders located in Romania [16].

A fixed dose combination of olodaterol and tiotropium, received marketing authorization from Romanian National Drug and Medical Devices Agency in 01.04.2015 [7] and was introduced on reimbursement lists on 2017.

The research question of this tool is about finding connections between the treatment adherence, factors that could influence adherence and quality of life for patients with COPD. There are many collection methods for adherence data: self-reported method, administrative claims, pharmacy claims, prescription refill record, electronic medical records, clinical measures, pill counts, therapeutic drug monitoring or patient's appointment records. Electronic data are very hard to find and access in Romania, so the best measurement for treatment adherence remains the use of questionnaires. Moreover, a questionnaire helps health providers to find also why the patient is non-adherent, not only the fact that the patient is adherent or not.

Materials and Methods

The study was approved by the Ethics Committee of the University of Medicine and Pharmacy of Craiova, Romania.

The instrument has three parts: Adherence Part, Factors Part and Quality of Life Part. The adherence Part aims to collect data about treatment adherence of patients with COPD that have treatment with the fixed dose combination of olodaterol and tiotropium. The second part contains 9 statements about factors that could influence adherence to the specified bronchodilator treatment. The third part uses EQ-5D-5L Proxy 1 – Paper version (in MS Word format) from EuroQol Research Foundation [6]. We used the five-level version of the EQ-5D for increasing sensitivity and not failing to capture important aspects of health in COPD.

There were two important steps in validating this instrument. First was achieving face validity, when attention was directed to its flow, format, length and its mode of administration. The second step was to be pilot tested and validated in order to evaluate if it is measuring the factors we supposed to measure and is it doing it reliably.

After the initial pool of questionnaire was written in the first step, qualified experts reviewed the items. The initial questionnaire had 12 statements (Table I). After reviewing, the final questionnaire had 9 statements (Table II), ensuring that the items do not contain content that may be perceived as offensive or biased by a particular subgroup of respondents or with repetitive statements.

Formulating the questions is critical and we have taken into consideration appropriateness of the content, level of sophistication of language, type and form of sentences. The language should be at the level of understanding of the responders. It is essential to formulate the questions in a way that they can easily be understood by the patients and should be according to their educational level and culture [11].

Table I

Initial statements of the questionnaire

Q1	<i>I was away from home</i>
Q2	<i>I was too busy</i>
Q3	<i>I didn't notice any differences without treatment</i>
Q4	<i>I was too tired</i>
Q5	<i>The device makes me think I am sick</i>
Q6	<i>I am not feel very sick without the spray</i>
Q7	<i>I was afraid of becoming spray addict</i>
Q8	<i>I feel depressive</i>
Q9	<i>I was nauseous</i>
Q10	<i>The treatment is very expensive</i>
Q11	<i>I take to many medicines</i>
Q12	<i>I was thinking about the side effects of the drug</i>

In the second step, the questionnaires were self-administrated in a medical office or a community pharmacy. This mode is less sensitive to information bias and interviewer effect, but we were careful not influence the answers. The main advantages of this type of questionnaire application is that it can reach a large sample size, cover wide geographical area and population which is sometimes difficult to reach, excellent for capturing sensitive topics and cheaper as compared to others. Also, a qualified person was near the patient to answer questions if something was unclear.

The questionnaire was tested on a sample of responders. This was an opportunity for us to know if there is confusion about any items, and whether respondents have suggestions for possible improvements of the items.

The responders were patients with COPD from different counties from Romania, without limitations of studies, socio-professional level or marital status. To be included in the study, patients had to be treated with the fixed dose combination of olodaterol and tiotropium.

The adherence value was calculated as proportion of days covered (PDC): numerator is the sum of days covered by the bronchodilator treatment and the denominator is 30 days.

We tested the validity (a measure of the degree of validity – an instrument is said to be valid if it is

able to measure what is to be measured or desired) of our questionnaire using SPSS Statistics 20. If the significance value $p < 0.05$ for every items, then the instrument is declared valid.

Reliability is the degree to which an instrument is free from random error. We measured internal consistency reliability using Cronbach's Alpha and reproducibility using a Pearson correlation. If Cronbach's Alpha > 0.9 , it's very high reliability (for a value < 0.5 = low reliability). Reproducibility establishes the stability of an instrument over time in a stable population.

Results and Discussion

After reviewing, the final questionnaire had 9 statements, ensuring that the items do not have content that may be perceived as offensive or biased by a particular subgroup of respondents or with repetitive statements. Table II presents the nine statements.

Table II

Final statements of the questionnaire

Q1	<i>I was too busy</i>
Q2	<i>I didn't notice any differences without treatment</i>
Q3	<i>I was too tired</i>
Q4	<i>The device makes me think I am sick</i>
Q5	<i>I was afraid of becoming spray addicted</i>
Q6	<i>The treatment is very expensive</i>
Q7	<i>I take too many medicines</i>
Q8	<i>I was thinking about the side effects of the drug</i>
Q9	<i>Other reasons</i>

The format, order, spacing and grouping of all the statements are very important features in overall layout of the questionnaire and have a direct effect on the responses and time spent by the patient to provide it. This is one of the reasons for why from 12 initial statements in the Second part; we have only 9 statements left.

The statements are simple, clear and easy to understand, using minimum of words and space. For example, for the statement about smoking, it could be unclear "Have you ever smoked?". The answer must be useful for the investigator, so the statement about smoking has three answers: "Never", "I do not smoke anymore" and "Number of cigarettes *per* day: ____". Some patients might have different reasons for non-adherence. All the 8 statements are common reasons for non-adherence. We decided to have a question where patients could have the option for other reasons not to respect the treatment every day. So, the Q9 is "Other reasons: _____".

Fifty-one patients completed the study questionnaire. The characteristics are summarized in Table III.

Table III

Clinical and sociodemographic characteristics of responders

Parameter		
Age (years)	Mean $\pm$ SD	65.29 $\pm$ 11.99
	Range	40 - 90
Sex (%)	Male	64.7%
	Female	35.3%
Education	Low	35.3%
	Medium	58.8%
	High	15.9%
Place of living	Urban	41.18%
	Rural	58.82%
Civil status	Married	76.5%
	Unmarried	5.9%
	Divorced	5.9%
	Widow/Widower	11.7%
Job	Employed	11.76%
	Unemployed	0%
	Retired	88.24%
Smoking habits (%)	Never	31.58
	Quit smoking	35.29
Number of cigarettes for those who smoke	Mean $\pm$ SD	12.8 $\pm$ 7.01
	Range	4 - 20
Adherence	Mean $\pm$ SD	91% $\pm$ 11.49%
	Range	67 - 100
Quality of Life	Mean $\pm$ SD	71.25% $\pm$ 15.86%
	Range	50 - 100

Quantitative data are expressed in mean $\pm$ standard deviation (SD). Qualitative data are expressed in percentage.

Validity was analysed and significance levels were less than 5% for all 8 statements so the items are all valid. Regarding reliability, Cronbach's alpha was 0.68, so the questionnaire items were reliable. The low correlations between total score of the statements and the degree of the disease (-0.12) suggest that there are no significant differences between groups classified by grade of severity of COPD and our questionnaire score.

Conclusions

The results obtained from this study indicated the tool is a valid and reliable measure of COPD-specific adherence and factors that could influence it. The responders had to complete the questionnaire by themselves and the items were written in a way that can be easily understood by the majority of the responders. The items are simple, short and written in a language familiar to target responders. The questionnaire contains sufficient items to measure the factors that could influence the non-adherence and the quality of life and it is not so long that responders experience fatigue or loss of motivation in completing the questionnaire.

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