

**Medication adherence and health-related quality of life among patients
with chronic obstructive pulmonary disease**

NEJC HORVAT

IGOR LOCATELLI

MITJA KOS

ANA JANEŽIČ*

Chair of Social Pharmacy, Faculty of Pharmacy

University of Ljubljana, Askerceva 7, 1000 Ljubljana, Slovenia

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*Correspondence; ana.janezic@ffa.uni-lj.si

This study evaluated medication adherence and health-related quality of life (HRQoL) of Slovenian patients with chronic obstructive pulmonary disease (COPD) and examined factors associated with HRQoL. Demographic and therapy information was gathered from 65 patients through interviews. The St. George's Respiratory Questionnaire and the Morisky Medication Adherence Scale were used to evaluate HRQoL and adherence, resp. A multiple linear regression model was used to assess the association between factors and HRQoL. The mean St. George's Respiratory Questionnaire score (range 0–100, with higher scores indicating lower HRQoL) was 41.4. COPD affected patients' daily activities more than their social and psychological functioning. Slightly more than 53 % of the patients

were optimally adherent, while 12 % were non-adherent. Patients with lower HRQoL had a higher number of medications for concomitant diseases, experienced COPD exacerbation in the last year, and had less education. No statistically significant correlation was found between medication adherence and HRQoL.

Keywords: chronic obstructive pulmonary disease, health-related quality of life, adherence

Uncorrected proofs

Chronic obstructive pulmonary disease (COPD) is a common, preventable and treatable disease. It is characterized by persistent respiratory symptoms, such as shortness of breath, chronic cough and mucus hypersecretion, with airflow limitation due to airway or alveolar abnormalities typically arising from significant exposure to noxious particles or gases (1). COPD was the fourth leading cause of death in 2010, and at that time it was projected to be the third leading cause by 2020. However, this level was already reached by 2012. More than 3 million people died of COPD in 2012, accounting for 5.6 % of all deaths globally (1, 2). In Slovenia, COPD leads to 500–600 deaths yearly, representing 3 % of deaths from all causes (2).

When COPD severity is being assessed, the goals are to determine the level of airflow limitation (characterized by forced expiratory volume in the first second, FEV₁), the risk of future events (*e.g.*, exacerbations) and the impact of the disease on the patient's health-related quality of life (HRQoL) (1). COPD primarily affects the lungs, but it also causes structural and functional changes in other organs, leading to symptoms that have no immediate relationship to expiratory airflow limitation (*e.g.*, fatigue). Consequently, estimating HRQoL is valuable because it reflects the overall impact of the disease and treatment on a patient's life.

One factor that often affects HRQoL of patients undergoing long-term therapies is medication adherence. COPD treatment typically involves multiple medications, which can lead to adherence problems. The chronic nature of the disease and periodic remission of symptoms also contribute to increased risk of adherence issues in patients with COPD (3). Information on HRQoL and adherence is necessary for planning appropriate interventions, but such information is lacking for the COPD population in Slovenia.

Thus, the aims of this study were to evaluate medication adherence and HRQoL of Slovenian patients with COPD and to examine factors potentially associated with HRQoL.

EXPERIMENTAL

A cross-sectional design was used, with eligible patients being recruited in community pharmacies. Demographic characteristics and information about therapy were collected from participants, and they were also asked to complete medication adherence and HRQoL questionnaires.

Sample

Patients who were eligible for the study had to be at least 18 years old, had at least one prescribed inhaler and confirmed that they had COPD. For measurement of adherence, they had to be taking at least one COPD medication intended for regular use for at least 3 months.

Sample size was calculated based on the multiple linear regression requirement of at least 10 subjects per independent variable (4). In addition to adherence score, five other factors that could influence HRQoL (education, age, current smoking status, number of concomitant medications for other diseases, presence of exacerbations) were included. Consequently, a sample of at least 60 patients was required.

Study conduct

From public pharmaceutical institutions (the predominant form of pharmacy ownership in Slovenia, consisting of multiple community pharmacies), 16 of the most frequently visited pharmacies regionally dispersed throughout Slovenia were identified. Community pharmacists in the 16 chosen pharmacies recruited eligible patients when dispensing medication for COPD. Patients who agreed to participate were directed to a pre-trained researcher, who explained the study aims, method and benefits. Participants signed written informed consent.

Patients were asked to provide basic demographic (sex, age, education level, smoking status) and therapy information (therapy duration, names of used medications, dosage, number of concomitant medications for other diseases). Additionally, the presence of exacerbations of COPD in the last year, defined as an emergency room visit, hospitalization or taking an oral glucocorticoid in last year, was identified (1). Patients' COPD diagnosis and therapy information were confirmed by accessing their health records and pharmacy claims data. After an introductory interview, patients immediately self-completed and returned questionnaires that were used to evaluate medication adherence and HRQoL.

The study was conducted in September 2014 and February 2015. The study was conducted in compliance with the Declaration of Helsinki. National Medical Ethics Committee (Komisija RS za medicinsko etiko, Ministrstvo za zdravje, Štefanova 5, 1000 Ljubljana) approved the study.

Questionnaires

The St. George's Respiratory Questionnaire (SGRQ) was used to assess patients' HRQoL. This questionnaire consists of 50 items divided into three components (symptoms, activity and impacts). Items have different response categories. For symptoms, patients took the preceding 12-month period into account. A score for each of the three components was calculated. A total score reflecting the impact of the disease on overall health status was also calculated. Scores ranged from 0 to 100, with higher scores indicating more limitations (lower HRQoL) (5).

Medication adherence was evaluated using the Morisky Medication Adherence Scale (MMAS-8), an eight-item self-reported measure of medication-taking behaviour (6–8). MMAS-8 scores can range from 0 to 8 points. Patients who scored < 6 points, 6 to < 8 points and 8 points were regarded as having low, medium and high adherence, resp. When answering the questions, patients accounted for all the medications they regularly take for COPD.

Statistical analysis

Standard descriptive statistics measures [mean, standard deviation (SD), median, interquartile range (IQR), min, max] were used. The Kolmogorov-Smirnov test was applied to test normality of the distribution of variable scores. To estimate the association between potential predictors and COPD impact on the quality of life, a multiple linear regression model with the patients' HRQoL score as a dependent variable was used. HRQoL scores followed a normal distribution. MMAS-8 score (low, medium, high), education (elementary school, high school, college/university), age, current smoking status (yes/no), number of concomitant medications for other diseases and the presence of exacerbations were set as factors. In cases of categorical variables with more than two categories, dummy variables (dichotomous variables which take the value of either 0 or 1 to indicate absence or presence of some categorical effect) were used. Sex was not included in the model since the preliminary analysis did not show any significant differences in HRQoL scores between male and female patients ($t = 0.472$, $p = 0.639$). The backward method for selection of predictive variables with criterion probability of F -to-remove ≥ 0.1 was employed (one predictive variable was removed at each step based on largest p value of F). Statistical analysis was performed in SPSS v.23, and p -value < 0.05 was considered to indicate statistical significance.

RESULTS AND DISCUSSION

Demographic data

Altogether, 65 patients were recruited at the community pharmacies. Table I presents the patients' demographic and therapy information.

The median number of medications for COPD treatment was two. Patients mostly received anticholinergics (64 %), long-acting β -agonist/anticholinergic combination (50 %) and a combination of inhaled glucocorticoid and long-acting β -agonist (50 %). Very few patients used theophylline (9 %) or oral glucocorticoids (6 %).

HRQoL

Table II presents the scores of the SGRQ per component as well as the total score. Higher scores indicate lower HRQoL. Patients scored best on the "impact" component, which reflects the impact of COPD on social and psychological functioning. Their scores were worse on the "symptoms" component, which indicates the frequency and severity of symptoms. The worst scores were found in the "activity" component, which centers on daily activities that cause breathlessness or are limited by it.

The mean total SGRQ score summarizing the impact of the disease on overall health status was 41.4. Arpinelli *et al.* (9) reviewed studies using SGRQ to measure HRQoL in patients with COPD and reported similar total scores ranging from 40 to 50. The individual component scores were not so unanimous, as reported by Ekici *et al.* (10), but all studies had a similar ordering of components: "activity" scores were highest, followed by "symptoms" and "impact" scores. This finding is not surprising since COPD patients are mostly older patients who also have other non-respiratory diseases (*e.g.*, osteoporosis, cardiovascular diseases, metabolic syndrome, depression). Such comorbidities, paired with dyspnoea, cause these patients to have reduced physical activity, leading to diminished physical condition. This situation is reflected in the lowest HRQoL for the "activity" and "symptoms" components (11).

Medication adherence

The average MMAS-8 score (\pm SD) on a 1–8 scale was 7.3 ± 1.2 . The proportions of patients with high, medium and low adherence rates were 53, 35 and 12 %, resp. No

significant differences in adherence scores were found between male and female patients ($t = 1.345, p = 0.192$).

The current study showed that 53.4 % of the COPD patients were optimally adherent to the treatment (8 points on MMAS-8). Other studies report similar adherence rates of 40–60 % (3). These studies mostly used self-reporting methods for measuring adherence. Patient's self-reports may overestimate their adherence due to social desirability bias, which leads patients to give socially desirable responses rather than responses that reflect their true situation (3). Patients may worry that giving honest answers could influence their relationship with their health-care provider and their future care. Therefore, they give the answers that they think are expected. In this study, this bias was minimized by having researchers rather than health-care providers collect the information. However, an impact on the overestimation of adherence rates cannot be totally ruled out, and the percentage of adherent patients in real-life conditions might be lower than what this study suggests.

Factors related to HRQoL

Table III shows the factors that were used in the final regression model using backward methods for factor selection. The model explained 58.5 % of the variance of HRQoL score ($R = 0.765, p < 0.001$). Four factors were significantly associated with HRQoL: number of concomitant medications (standardized $\beta = 0.36$), presence of exacerbation in the past year (standardized $\beta = 0.32$), education level (standardized $\beta = -0.32$) and current smoking status (standardized $\beta = -0.27$). For each additional medication, the SGRQ score increased by 2.36 points. Patients who experienced exacerbation in the last year had SGRQ scores that were 13.7 points higher on average, indicating lower HRQoL. Patients with university or higher education had lower SGRQ scores than patients with an elementary school education, indicating better HRQoL. Patients who currently smoked displayed SGRQ scores that were 12.5 points lower on average, signifying higher HRQoL. Other factors, including medication adherence, were not significantly associated with HRQoL.

Presence of exacerbations. – The presence of exacerbations increased the SGRQ score by 13.7 points. This finding is in line with other studies, which defined exacerbations similarly and determined their association with HRQoL. Miravittles *et al.* (12) concluded that frequent exacerbations significantly impair HRQoL of patients with moderate COPD.

Education. – People with a university education had SGRQ scores that were 21 points lower on average than people with an elementary school education in this study (adjusted for

other factors). Higher education thus predicted higher HRQoL in patients with COPD. In the study by Miravittles *et al.* (13), patients with a lower education level demonstrated higher prevalence of COPD as well as a higher probability of late diagnosis, suggesting a worse disease course. Consequently, patients with a lower education level had a poorer HRQoL, a finding replicated in this study.

Number of concomitant medications for other diseases. – For each additional medication treating concomitant diseases, the SGRQ score increased by 2.36 points, which indicates a decrease in HRQoL. Comorbidities often accompany COPD since it usually occurs in middle-aged regular smokers (1). Smoking is a risk factor for several diseases. Comorbidities most frequently accompanying COPD are cardiovascular diseases, osteoporosis, anxiety, depression and lung cancer (1). van Manen *et al.* (14) studied the effect of COPD comorbidities on HRQoL and suggested that impairments in social and emotional functioning are exclusively related to the comorbidities and not to COPD itself. COPD principally affects physical functioning, vitality and general health domains.

Smoking status. – Smoking has been shown to have a significant effect on HRQoL of patients with COPD. Since tobacco smoking is considered a primary cause for COPD, smokers are expected to have lower HRQoL. However, smokers had a better quality of life than non-smokers in this study. This seemingly paradoxical finding might be explained by reverse causality. Patients with a worse disease state are more aware of negative smoking effects and therefore quit smoking, while patients whose COPD has not affected their HRQoL might still continue smoking. Because of reverse causality, it would be advisable to check the smoking history of COPD patients and not merely the current smoking status.

Adherence. – No significant relationship was found between medication adherence and HRQoL of patients with COPD in this study. Similar results were reported by Boland *et al.* (15), even after adjusting for disease severity, demographics and health lifestyle variables. The lack of significant relationship might also be due to a small sample size or the categorization method. Although the association was not significant, the multiple linear regression coefficient suggests that less adherent patients experienced higher levels of HRQoL. Again, this finding might be due to reverse causality, with improved HRQoL possibly serving as a trigger for non-adherence in patients with COPD. Restrepo *et al.* (3) investigated common causes of poor adherence in patients treated for COPD. The most prominent cause was feeling well and consequently deciding to skip medications or forgetting to take doses.

Limitations

This study has several possible limitations. A self-reported indirect measure of adherence was used, which might overestimate adherence rates. No single method for measuring adherence is considered a gold standard, and a combination of methods is advised to correctly validate adherence rates. A cross-sectional method for measuring adherence and HRQoL was employed. A longitudinal study would be a more reliable method to better understand the relation between these two variables. This approach would also allow for better control of reverse causality.

CONCLUSIONS

More than half (53.4 %) of the Slovenian patients with COPD were optimally adherent to their treatment. COPD predominantly influenced patients' daily activities, while their social and psychological functioning was less impaired. Patients' HRQoL was negatively affected by an increasing number of concomitant medications, exacerbations in the past year and lower education level. Medication adherence did not show a significant association with HRQoL.

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Uncorrected proofs

Table 1. Demographic and therapy information of 65 included patients

Characteristic	% or mean (\pm SD) or median (IQR)
Sex ($N = 65$)	32.3 % female, 67.7 % male
Age ($N = 64$)	mean 70.1 (\pm 10.3) yrs
Education level ($N = 65$)	
Elementary school	15.4 %
High school	70.8 %
College/university	13.8 %
Current smoker ($N = 65$)	24.6 %
Duration of COPD treatment ($N = 61$)	
< 1 years	10.8 %
1–5 years	40.0 %
6–10 years	21.5 %
> 10 years	21.5 %
No. of medications for COPD ($N = 65$)	median 2 (1)
No. of concomitant medications for other diseases ($N = 57$)	median 3 (4)
Exacerbations in the past year ($N = 65$)	
Emergency room visits	20.0 %
Hospitalisation	23.1 %
Oral glucocorticoid treatment	23.1 %
At least one of the above (emergency room visit, hospitalisation or oral glucocorticoid treatment)	38.5 %

COPD – chronic obstructive pulmonary disorder, IQR – interquartile range

Table II. Means, standard deviations and ranges of the SGRQ individual component scores and the total score

	Component			Total
	Symptoms	Activity	Impacts	
Mean	49.8	53.7	31.6	41.4
Standard deviation	24.6	25.4	20.1	19.9
Min–max	0–95.0	0–93.3	0–73.7	2.0–79.4

SGRQ – St. George’s respiratory questionnaire

Table III. Multivariate regression of HRQoL on patients' demographic data, adherence and exacerbations^a

	B ^b	95 % confidence interval	Standardized β^c	p-value
Constant	42.25	25.05, 59.44		
Presence of exacerbation	13.74	3.68, 23.80	0.32	0.009
Current smoker	-12.45	-23.82, -1.08	-0.27	0.033
Education (high school vs. elementary school)	-12.24	-25.65, 1.17	-0.26	0.072
Education (university vs. elementary school)	-20.85	-40.40, -1.30	-0.32	0.037
Adherence (low vs. high)	-14.12	-29.53, 1.30	-0.22	0.071
No. of concomitant medications for other diseases	2.36	0.69, 4.03	0.36	0.007

HRQoL – health-related quality of life

^a Backward method for selection of factors with criterion probability of F -to-remove ≥ 0.1 was used. Excluded variables: age, dummy variable medium vs. high adherence due to criterion probability of F -to-remove < 0.1 .

^b Unstandardized B coefficient indicates the individual contribution of each factor to the model. It represents the value for the regression equation for predicting the dependent variable from the factor.

^c Standardized β coefficient presents the number of standard deviations that the outcome will change as a result of one standard deviation change in the factor. It allows comparisons of the magnitude of the coefficients to identify which has more of an effect on the dependent variable.