International Journal of COPD

Dovepress
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Open Access Full Text Article

ORIGINAL RESEARCH

Quality of life and adherence to inhaled corticosteroids and tiotropium in COPD are related

This article was published in the following Dove Press journal:
International Journal of COPD
26 July 2016
Number of times this article has been viewed

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Background: Poor adherence to inhaled medications in COPD patients seems to be associated with an increased risk of death and hospitalization. Knowing the determinants of nonadherence to inhaled medications is important for creating interventions to improve adherence.

Objectives: To identify disease-specific and health-related quality of life (HRQoL) factors, associated with adherence to inhaled corticosteroids (ICS) and tiotropium in COPD patients.

Methods: Adherence of 795 patients was recorded over 3 years and was deemed optimal at >75%–≤125%, suboptimal at ≥50%–<75%, and poor at <50% (underuse) or >125% (overuse). Health-related quality of life was measured with the Clinical COPD Questionnaire and the EuroQol-5D questionnaire.

Results: Patients with a higher forced expiratory volume in 1 second (FEV_1)/vital capacity (VC) (odds ratio [OR] =1.03) and ≥1 hospitalizations in the year prior to inclusion in this study (OR =2.67) had an increased risk of suboptimal adherence to ICS instead of optimal adherence. An increased risk of underuse was predicted by a higher FEV_1/VC (OR =1.05). Predictors for the risk of overuse were a lower FEV_1 (OR =0.49), higher scores on Clinical COPD Questionnaire-question 3 (anxiety for dyspnea) (OR =1.26), and current smoking (OR =1.73). Regarding tiotropium, predictors for suboptimal use were a higher FEV_1/VC (OR =1.03) and the inability to perform usual activities as asked by the EuroQol-5D questionnaire (OR =3.09). A higher FEV_1/VC also was a predictor for the risk of underuse compared to optimal adherence (OR =1.03). The risk of overuse increased again with higher scores on Clinical COPD Questionnaire-question 3 (OR =1.46).

Conclusion: Several disease-specific and quality of life factors are related to ICS and tiotropium adherence, but a clear profile of a nonadherent patient cannot yet be outlined. Overusers of ICS and tiotropium experience more anxiety.

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

Background

COPD is a major global health problem, currently being the fifth leading cause of morbidity. It is expected to be the third leading cause of mortality in 2020.[1] Treatment of COPD is supportive, aimed at relieving symptoms, decreasing the number of exacerbations, and improving the quality of life.[2] Pharmacotherapy consists of inhaled medications, including short- and long-acting bronchodilators, such as tiotropium bromide, to relieve dyspnea symptoms and inhalation corticosteroids (ICS) to suppress the prominent pulmonary inflammation.[2] Large randomized trials have demonstrated that long-term use of long-acting bronchodilators and ICS reduces symptoms, improves

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Dovepress
http://dx.doi.org/10.2147/COPD.S107303

quality of life and exercise tolerance, reduces number and severity of exacerbations, and may decrease mortality.[3–5]

The effectiveness of inhaled medications is substantially influenced by a patient's therapy adherence. Adherence is essential and seems to be associated with reduced mortality and hospitalization.[6–8] In common with other chronic diseases, therapy adherence in COPD patients is generally poor, varying in studies from 18% to 40% for ICS, 17% to 29% for combination medication, and 13% to 80% for long-acting sympaticomimetics.[9–13] Medication adherence is influenced by patient- and medication-related factors, such as disease- and treatment acceptance, knowledge about and faith in the treatment, effective patient–clinician relationship, routinization of the pharmacological therapy, and side effects.[7,14,15] Medication-related factors, such as frequent daily use, multiple dosing, and side effects, all have a negative influence on adherence.[16,17] COPD patients often have a medication regimen requiring multiple daily dosages during a prolonged period and frequently use more than one medication often in different devices simultaneously, making therapy adherence a difficult task. Next to the above mentioned factors, COPD-specific factors and perceived health-related quality of life (HRQoL) may also be associated with adherence to inhalation therapy.

Understanding of determinants of adherence to inhaled medications is important to help create interventions for improving medication adherence in COPD patients. We therefore conducted a study to identify disease-specific and HRQoL factors that are associated with adherence to ICS and tiotropium in COPD patients.

Methods

Study design

This study is part of the Cohort on Mortality and Inflammation in COPD study. It concerns a single center, prospective, cohort study. From December 2005 till April 2010, 795 patients were included with a follow-up period of 3 years. Patients were recruited at the Department of Pulmonology, Medisch Spectrum Twente Hospital, Enschede. The research protocol was approved by the hospital's Medical Ethical Committee and all patients provided written informed consent.

To be eligible for the study, patients had to meet the following criteria: 1) a clinical diagnosis of COPD, as defined by the Global Initiative for Chronic Obstructive Lung Disease criteria; 2) current or exsmoker; 3) age ≥40 years; 4) no medical condition compromising survival within the follow-up period or serious psychiatric comorbidity; 5) absence of any other lung disease; 6) no maintenance therapy with antibiotics; and 7) the ability to speak Dutch. Patients were consecutively enrolled when hospitalized for an acute exacerbation of COPD or when visiting the outpatient clinic in a stable state.

Demographic characteristics were obtained at baseline. Smoking status was determined by the Vlagtwedde questionnaire.[12] Patients were dichotomously categorized as frequent (≥2 exacerbations in the year prior to inclusion in this study) or infrequent (<2 exacerbations in the year prior to inclusion in this study) exacerbators. An exacerbation was defined as a worsening of respiratory symptoms that required treatment with a short course of oral corticosteroids with or without antibiotics. Data on exacerbations and number of hospitalizations 1 year prior to inclusion in this study were recorded from hospital records and dichotomized as ≥1 versus no hospitalizations. Data on the common comorbidities myocardial infarction, congestive heart failure, and diabetes mellitus were obtained from medical records. Lung function was measured by spirometry, performed according to standard guidelines.[10]

Furthermore, HRQoL was measured by means of the validated Dutch versions of the Clinical COPD Questionnaire (CCQ) and the EuroQol-5D questionnaire (EQ-5D). The CCQ is a disease-specific questionnaire consisting of 10 questions that can be combined in a function, mental, and symptom domain.[18,19] It provides an overall score from 0 (very good control) to 6 (extremely poor control). The EQ-5D is a nondisease-specific questionnaire consisting of five domains (mobility, self-care, usual activities, anxiety/depression, and pain/discomfort) and a visual analogue scale.[20] It is used to measure HRQoL in chronic diseases. The questions have three response options (no, some, and extreme problems). In both questionnaires, higher scores indicate a worse experience of health status.

The primary outcome, therapy adherence, was recorded from pharmacy records. The patients were not aware that their medication records were going to be used for monitoring their therapy adherence. Theoretical medication use was calculated using information on dispensing date, total supply, and dosage regimen. We computed the total number of days for which patients had collected medication during follow-up and divided this by the total number of days between the first and last collection during follow-up plus the day's supply of the last refill.[21]

This was expressed as a percentage and was deemed good if it was between ≥75% and ≤125%, suboptimal between ≥50% and <75%, and poor if <50% (underuse) and >125% (overuse). We excluded medication when it

was prescribed only once or when it was used less than 90 days.

Tiotropium was the only long-acting muscarinic agonist used. Furthermore, the ICS beclomethasone, ciclesonide, fluticasone, budesonide, and the combined preparations of fluticasone–salmeterol and budesonide–formoterol were included in the analyses.

Statistical analysis

Baseline characteristics are reported as mean with standard deviation when normally distributed or medians with corresponding interquartile ranges. Nominal variables are reported as numbers with corresponding percentages. To identify a subset of independent continuous variables that are associated with the different types of adherence, analysis of variance tests or Kruskal–Wallis tests were performed as appropriate, with the Tukey HSD and Holm–Bonferroni correction being applied to the significance criterion once pairwise comparisons were made among the study groups. For nominal variables, this association was tested by means of chi-square or Fisher's exact tests. For both medication types, separate multivariate nominal regression models were made. Variables with a significance $P \leq 0.05$ were considered as candidate variables for the multivariate nominal regression analysis and were initially all entered. Subsequently, variables with the highest *P*-values were eliminated step by step, until the fit of the model decreased significantly (based on the likelihood-ratio test). In case of multicollinearity between variables, the variable that produced the best model fit was included in the model. All statistical calculations were carried out with the SPSS statistical package (version 22.0).

Results

Of the 795 included patients, 635 used ICS and 438 used tiotropium. A total of 385 patients used both ICS and tiotropium.

Inhaled corticosteroids

Smoking status, FEV_1 in liters, and the FEV_1/vital capacity (VC) ratio were univariately associated with adherence to ICS (Table 1). Current smoking was more often observed in patients with underuse and overuse. Patients with overuse showed the worst lung function, expressed as a low FEV_1 in liters, while patients with underuse had the highest FEV_1/VC ratio. The number of exacerbations in the year prior to inclusion in this study showed a trend in which underusers were more often infrequent exacerbators. Overall, ≥1 hospital admission in the year prior to inclusion in this study was associated with suboptimal use of medication.

Regarding the CCQ scores, there was a noticeable trend in which patients with optimal adherence scored best on all CCQ questions, indicating a higher quality of life. However, we observed that suboptimal users scored higher on questions 1 (shortness of breath) and 9 (limitations in daily activities) compared to optimal users (Table 2). We also noticed that overusers scored higher on question 3 (being anxious for increased dyspnea) compared to optimal users.

We found no association between adherence to ICS and any of the EQ-5D questions (Table 3).

Multinominal regression analysis with ICS

The multivariate nominal regression model (with optimal adherence set as reference category, see Table 4) showed that an increase of 1 L in FEV_1 was associated with a two-fold lower risk of overuse (odds ratio [OR] =0.49; 95% confidence interval [CI]: 0.25–0.95) compared to optimal use. An increase in 1% of the FEV_1/VC ratio was associated with a 3% higher risk of suboptimal use (OR =1.03; 95% CI: 1.00–1.05) and a 5% higher risk of underuse (OR =1.05; 95% CI: 1.02–1.08) compared to optimal use. Each unit increase on CCQ-question 3 (being anxious for dyspnea) was associated with a 26% higher risk of overuse of ICS (OR =1.26; 95% CI: 1.02–2.91). Finally, patients who were admitted to the hospital 1 year prior to inclusion in this study had a 2.7-fold increased risk of suboptimal use (OR =2.67; 95% CI: 1.48–4.80), compared to optimal use.

Tiotropium

The tiotropium group showed similar baseline characteristics compared to patients in the ICS group, except for a prominent higher percentage of optimal adherence in this group (78%). Table 5 shows that only FEV_1/VC ratio was univariately associated with adherence to tiotropium, with underusers having a higher FEV_1/VC ratio compared to optimal users.

Regarding the CCQ scores, tiotropium showed the same trend as ICS in which patients with optimal adherence scored better on every question. Nevertheless, suboptimal users had significantly higher scores on question 1 (shortness of breath in rest) (Table 6). In contrast to ICS adherence, underusers instead of overusers scored significantly higher on question 3 (anxiety for increased dyspnea). The symptom domain and total CCQ scores were also associated with underuse of medication, but overuse was also related to higher scores on the symptom domain. Patients with a higher score on the EQ-5D questions concerning mobility and usual activities

Table 1 Descriptive demographics for the study population at baseline who use ICS

Characteristics	Overall N=635	Optimal ≥75%–≤125% N=361	Suboptimal 50%–<75% N=120	Underuse <50% N=61	Overuse >125% N=93	*P*-value
Age in years, mean (SD)	67.1 (9.7)	67.5 (9.7)	66.4 (9.7)	65.6 (11.0)	67.4 (8.9)	0.414
Sex, number of males (%)	377 (59.4)	221 (61.2)	68 (56.7)	34 (55.7)	54 (58.1)	0.735
Smoking status, N (%)						
Current smoker	176 (27.7)	91 (25.2)	27 (22.5)	23 (37.7)	35 (37.6)	0.016
Exsmoker	459 (72.3)	270 (74.8)	93 (77.5)	38 (62.3)	58 (62.4)	
Pack-years, N (%)	38.3 (22.6)	38.4 (22.7)	39.8 (23.2)	36.6 (23.4)	36.8 (21.3)	0.743
Lung function*						
FEV_1 in liters, mean (SD)	1.4 (0.6)	1.4 (0.5)	1.4 (0.6)	1.4 (0.7)	1.2 (0.5)	0.047[c]
FEV_1 predicted, mean (SD)	51.2 (18.4)	51.1 (18.0)	53.1 (19.6)	53.1 (20.3)	47.7 (16.9)	0.151
FEV_1/VC ratio, mean (SD)	43.5 (13.3)	42.4 (12.6)	45.6 (13.8)	47.9 (16.1)	42.4 (12.6)	0.005[b]
COPD stage, N (%)**						
GOLD I	38 (6.1)	23 (6.4)	6 (5.1)	4 (6.8)	5 (5.4)	0.498
GOLD II	270 (43.0)	154 (43.0)	58 (49.2)	26 (44.1)	32 (34.4)	
GOLD III	254 (40.4)	147 (41.1)	38 (32.2)	23 (39.0)	46 (49.5)	
GOLD IV	66 (10.5)	34 (9.5)	16 (13.6)	6 (10.2)	10 (10.8)	
BMI, N (%)***						
<22.0	101 (16.2)	48 (13.6)	22 (18.5)	13 (21.3)	18 (19.4)	
≥22.0–<30	356 (57.0)	218 (61.9)	62 (52.1)	27 (44.3)	49 (52.7)	0.132
≥30.0	168 (26.9)	86 (24.4)	35 (29.4)	21 (34.4)	26 (28.0)	
Exacerbations in the past year, N (%)						
<2	407 (64.2)	235 (65.3)	72 (60.0)	47 (77.0)	53 (57.0)	0.055
≥2	227 (35.8)	125 (34.7)	48 (40.0)	14 (23.0)	40 (43.0)	
≥1 Hospital admission, N (%)	93 (14.7)	39 (10.8)	30 (25.0)	10 (16.4)	14 (15.1)	0.002[a]
Comorbidities, N (%)						
Heart failure	100 (15.8)	57 (15.8)	17 (14.2)	8 (13.1)	18 (19.4)	0.692
Ischemic heart disease	26 (4.1)	14 (3.9)	7 (5.8)	2 (3.3)	3 (3.2)	0.743
Diabetes mellitus	36 (5.7)	18 (5.0)	8 (6.7)	3 (4.9)	7 (7.5)	0.756
mMRC score, mean (SD)	1.80 (1.3)	1.69 (1.3)	1.99 (1.3)	1.96 (1.2)	1.93 (1.3)	0.073

Notes: After Holm–Bonferroni correction, there was a significant difference between optimal and [a]suboptimal; [b]underuse; [c]between suboptimal and overuse. *One missing lung function. **Seven missing COPD stages. ***Ten missing BMIs.
Abbreviations: ICS, inhaled corticosteroids; SD, standard deviation; FEV_1, forced expiratory volume in 1 second; GOLD, Global Initiative for Chronic Obstructive Lung Disease; VC, vital capacity; mMRC, modified Medical Research Council; BMI, body mass index.

Table 2 CCQ scores (range 1–6) per therapy adherence category for ICS users

CCQ Median (IQR)	Optimal N=332	Suboptimal N=111	Underuse N=53	Overuse N=83	*P*-value
CCQ-1	1.0 (0.0–2.0)	1.5 (0.0–2.0)	1.0 (0.0–3.0)	1.0 (0.0–3.0)	0.007[a]
CCQ-2	4.0 (2.0–6.0)	5.0 (3.0–6.0)	4.0 (2.0–6.0)	5.0 (3.0–6.0)	0.323
CCQ-3	0.0 (0.0–1.0)	0.0 (0.0–1.0)	0.0 (0.0–1.0)	0.0 (0.0–2.0)	0.015[b]
CCQ-4	0.0 (0.0–2.0)	0.0 (0.0–2.0)	0.0 (0.0–2.0)	0.0 (0.0–2.0)	0.399
CCQ-5	2.0 (1.0–3.0)	2.0 (1.0–3.0)	2.0 (1.0–3.0)	2.0 (2.0–3.0)	0.479
CCQ-6	2.0 (1.0–3.0)	2.0 (1.0–3.0)	2.0 (0.0–3.5)	2.0 (1.0–3.0)	0.589
CCQ-7	4.0 (2.0–5.0)	4.0 (2.0–6.0)	4.0 (3.0–6.0)	4.0 (3.0–6.0)	0.246
CCQ-8	2.5 (1.0–4.0)	3.0 (2.0–5.0)	3.0 (1.0–5.0)	3.0 (2.0–4.0)	0.083
CCQ-9	1.0 (0.0–3.0)	2.0 (0.0–4.0)	2.0 (0.0–3.0)	1.0 (0.0–3.0)	0.039[a]
CCQ-10	0.0 (0.0–2.0)	1.0 (0.0–3.0)	1.0 (0.0–2.0)	1.0 (0.0–3.0)	0.167
Domain 1 symptom*	2.45 (1.3)	2.52 (1.2)	2.47 (1.3)	2.56 (1.2)	0.868
Domain 2 function*	2.19 (1.5)	2.58 (1.6)	2.55 (1.4)	2.50 (1.6)	0.049[c]
Domain 3 mental	0.0 (0.0–1.0)	0.5 (0.0–1.5)	0.5 (0.0–1.5)	0.5 (0.0–2.0)	0.112
CCQ Total*	1.78 (1.0)	1.97 (1.1)	1.95 (0.9)	2.04 (1.1)	0.086

Notes: *Mean (SD). After Holm–Bonferroni correction, there was a significant difference between optimal and [a]suboptimal; [b]overuse; [c]no difference after correction.
Abbreviations: CCQ, Clinical COPD Questionnaire; ICS, inhaled corticosteroids; IQR, interquartile range; SD, standard deviation.

Table 3 EuroQol-5D scores (range 1–3) per therapy adherence category for ICS users

EuroQol-5D ICS	Optimal, n (%) N=337	Suboptimal, n (%) N=112	Underuse, n (%) N=53	Overuse, n (%) N=83	*P*-value
Mobility					0.383
1. I have no problems in walking about	114 (61.6)	32 (17.3)	16 (8.6)	23 (12.4)	
2. I have some problems in walking about	219 (56.3)	76 (19.5)	37 (9.5)	57 (14.7)	
3. I am confined to bed	4 (36.4)	4 (36.4)	0 (0.0)	3 (27.3)	
Self-care					0.138
1. I have no problems with self-care	231 (61.3)	67 (17.8)	31 (8.2)	48 (12.7)	
2. I have some problems with self-care	91 (53.5)	35 (20.6)	18 (10.6)	26 (15.3)	
3. I am unable to wash or dress myself	15 (39.5)	10 (26.3)	4 (10.5)	9 (23.7)	
Usual activities					0.375
1. I have no problems performing usual activities	144 (62.1)	39 (16.8)	17 (7.3)	32 (13.8)	
2. I have some problems performing usual activities	164 (56.2)	56 (19.2)	30 (10.3)	42 (14.4)	
3. I am unable to perform usual activities	29 (47.5)	17 (27.9)	6 (9.8)	9 (14.8)	
Pain/discomfort					0.893
1. I have no pain or discomfort	159 (57.6)	51 (18.5)	22 (8.0)	44 (15.9)	
2. I have moderate pain or discomfort	129 (57.3)	44 (19.6)	24 (10.7)	28 (12.4)	
3. I have extreme pain or discomfort	49 (58.3)	17 (20.2)	7 (8.3)	11 (13.1)	
Anxiety/depression					0.438
1. I am not anxious or depressed	252 (59.7)	79 (18.7)	33 (7.8)	58 (13.7)	
2. I am moderately anxious or depressed	67 (50.8)	27 (20.5)	18 (13.6)	20 (15.2)	
3. I am extremely anxious or depressed	17 (58.6)	5 (17.2)	2 (6.9)	5 (17.2)	
Measuring scale (VAS)*	61.9 (16.3)	61.5 (15.6)	59.8 (14.4)	60.2 (14.9)	0.718

Notes: *Mean (SD). Higher outcomes indicate more symptoms.
Abbreviations: ICS, inhaled corticosteroids; VAS, visual analogue scale (range 1–100); SD, standard deviation.

Table 4 Multinominal regression analysis of associated variables per therapy adherence category for ICS users

Variable	OR	95% CI	*P*-value
Suboptimal (≥50%–<75%) N=112			
FEV_1 in liters	0.90	0.53–1.50	0.660
FEV_1/VC ratio	1.03	1.00–1.05	0.024
CCQ-3	1.10	0.92–1.32	0.310
Smoker	0.78	0.46–1.32	0.351
Exsmoker	1.00		
Hospital admission	2.67	1.48–4.80	0.001
No hospital admission	1.00		
Underuse (<50%) N=53			
FEV_1 in liters	0.62	0.31–1.26	0.186
FEV_1/VC ratio	1.05	1.02–1.08	0.001
CCQ-3	0.94	0.71–1.23	0.645
Smoker	1.47	0.78–2.80	0.237
Exsmoker	1.00		
Hospital admission	1.83	0.80–4.20	0.153
No hospital admission	1.00		
Overuse (>125%) N=83			
FEV_1 in liters	0.49	0.25–0.95	0.034
FEV_1/VC ratio	1.02	0.99–1.04	0.221
CCQ-3	1.26	1.05–1.52	0.015
Smoker	1.73	1.02–2.91	0.040
Exsmoker	1.00		
Hospital admission	1.43	0.69–2.93	0.336
No hospital admission	1.00		

Abbreviations: ICS, inhaled corticosteroids; OR, odds ratio; CI, confidence interval; FEV_1, forced expiratory volume in 1 second; CCQ, Clinical COPD Questionnaire; VC, vital capacity.

used tiotropium more often suboptimally and showed more underuse and overuse (Table 7). Anxiety and depression were associated with suboptimal use, underuse, and overuse.

Multinominal regression analysis tiotropium

The multivariate nominal regression model (Table 8) showed that an increase of 1% in FEV_1/VC ratio was associated with a 3% higher risk of suboptimal use (OR =1.03; 95% CI: 1.01–1.06) and a 4% higher risk of underuse (OR =1.04; 95% CI: 1.01–1.07) compared to optimal use. Each unit increase in CCQ-question 3 score was associated with almost a 1.5-fold increased risk of overuse of tiotropium (OR =1.46; 95% CI: 1.07–2.00). Patients' scoring being unable to perform usual activities had a 3.1-fold increased risk of showing suboptimal use (OR =3.09; 95% CI: 0.95–10.06) instead of optimal use.

Discussion

This analysis was designed to determine COPD-related factors that are associated with adherence to inhalation medication. Therapy adherence to both ICS and tiotropium showed to be related to various disease-specific and HRQoL factors.

In our study, 57% of the patients who use ICS and 78% of the patients who use tiotropium showed optimal adherence, which is higher than reported in literature. However,

Table 5 Descriptive demographics for the study population at baseline who use tiotropium

Characteristics	Overall N=438	Good ≥75%–≤125% N=340	Suboptimal 50%–<75% N=48	Underuse <50% N=29	Overuse >125% N=21	*P*-value
Age in years, mean (SD)	65.5 (9.7)	65.9 (9.4)	64.4 (10.6)	62.9 (11.2)	65.8 (10.9)	0.366
Sex, number of men (%)	269 (61.4)	214 (62.9)	25 (52.1)	15 (51.7)	15 (71.4)	0.247
Smoking status, N (%)						
Current smoker	130 (29.7)	99 (29.1)	10 (20.8)	13 (44.8)	8 (38.1)	0.124
Exsmoker	308 (70.3)	241 (70.9)	38 (79.2)	16 (55.2)	13 (61.9)	
Pack-years, N (%)	39.3 (22.8)	37.8 (21.6)	44.5 (26.5)	42.4 (27.3)	45.2 (23.5)	0.138
Lung function						
FEV_1 in liters, mean (SD)	1.4 (0.6)	1.43 (0.6)	1.46 (0.5)	1.64 (0.7)	1.31 (0.6)	0.177
FEV_1 predicted, mean (SD)	52.1 (17.9)	51.7 (17.6)	53.2 (16.7)	59.1 (21.6)	47.4 (17.9)	0.102
FEV_1/VC ratio, mean (SD)	43.8 (13.1)	43.0 (12.6)	47.0 (13.4)	49.7 (16.6)	41.8 (12.2)	0.013[a]
COPD stage, N (%)*						
GOLD I	29 (6.7)	21 (6.2)	2 (4.2)	4 (14.8)	2 (9.5)	0.617
GOLD II	191 (44.0)	148 (43.8)	24 (50)	13 (48.1)	6 (28.6)	
GOLD III	175 (40.3)	139 (41.1)	17 (35.4)	8 (29.6)	11 (52.4)	
GOLD IV	39 (9.0)	30 (8.9)	5 (10.4)	2 (7.4)	2 (9.5)	
BMI**						
<22.0	65 (15.1)	48 (14.4)	8 (16.7)	4 (13.8)	5 (23.8)	0.882
≥22.0–<30	254 (58.9)	198 (49.5)	26 (54.2)	19 (65.5)	11 (52.4)	
≥30.0	112 (26.0)	87 (26.1)	14 (29.2)	6 (20.7)	5 (23.8)	
Exacerbations in the past year, N (%)						
<2	293 (66.9)	229 (67.4)	27 (56.3)	24 (82.8)	13 (61.9)	0.111
≥2	145 (33.1)	111 (32.6)	21 (43.8)	5 (17.2)	8 (38.1)	
≥1 Hospital admission, N (%)	47 (10.7)	33 (9.7)	6 (12.5)	6 (20.7)	2 (9.5)	0.313
Comorbidities, N (%)						
Heart failure	77 (17.6)	60 (17.6)	7 (14.6)	6 (20.7)	4 (19.0)	0.914
Ischemic heart disease	17 (3.9)	11 (3.2)	3 (6.3)	1 (3.4)	2 (9.5)	0.406
Diabetes mellitus	30 (6.8)	22 (6.5)	2 (4.2)	5 (17.2)	1 (4.8)	0.129
mMRC score, mean (SD)	1.69 (1.2)	1.60 (1.2)	1.87 (1.2)	2.12 (1.2)	2.16 (1.3)	0.041[b]

Notes: After Holm–Bonferroni correction, there was a significant difference between optimal and[a] underuse;[b] no difference after correction. *Four missing COPD stages. **Seven missing BMIs.

Abbreviations: SD, standard deviation; FEV_1, forced expiratory volume in 1 second; VC, vital capacity; COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease; mMRC, modified Medical Research Council; BMI, body mass index.

Table 6 CCQ scores (range 1–6) per therapy adherence category for tiotropium users

CCQ Median (IQR)	Optimal N=320	Suboptimal N=45	Underuse N=26	Overuse N=19	*P*-value
CCQ-1	1.0 (0.0–2.0)	2.0 (0.0–2.5)	1.0 (0.0–4.0)	1.0 (0.0–3.0)	0.004[a]
CCQ-2	3.0 (2.0–6.0)	4.0 (2.0–6.0)	4.5 (2.75–6.0)	5.0 (3.0–6.0)	0.512
CCQ-3	0.0 (0.0–1.0)	0.0 (0.0–1.0)	1.0 (0.0–2.0)	0.0 (0.0–2.0)	0.003[b]
CCQ-4	0.0 (0.0–1.0)	0.0 (0.0–2.0)	0.5 (0.0–2.25)	0.0 (0.0–2.0)	0.225
CCQ-5	2.0 (1.0–3.0)	2.0 (1.0–3.0)	3.0 (1.75–4.0)	3.0 (2.0–5.0)	0.030[d]
CCQ-6	2.0 (0.0–3.0)	2.0 (0.5–3.0)	2.5 (1.0–5.0)	3.0 (2.0–5.0)	0.005[c]
CCQ-7	3.0 (2.0–5.0)	4.0 (2.0–6.0)	5.0 (2.75–6.0)	3.0 (3.0–5.0)	0.114
CCQ-8	2.0 (1.0–4.0)	3.0 (2.0–4.0)	3.0 (2.0–4.0)	3.0 (1.0–4.0)	0.316
CCQ-9	1.0 (0.0–2.0)	1.0 (0.0–3.0)	1.0 (0.0–3.25)	2.0 (0.0–5.0)	0.091
CCQ-10	0.0 (0.0–2.0)	1.0 (0.0–2.0)	1.0 (0.0–3.0)	0.0 (0.0–2.0)	0.154
Domain 1 symptom*	2.27 (1.2)	2.48 (1.3)	2.99 (1.6)	3.05 (1.4)	0.002[b,c]
Domain 2 function*	2.02 (1.4)	2.43 (1.4)	2.61 (1.7)	2.45 (1.5)	0.060
Domain 3 mental	0.0 (0.0–1.0)	0.5 (0.0–1.5)	1.0 (0.0–2.125)	0.0 (0.0–2.0)	0.064
CCQ Total*	1.64 (1.0)	1.93 (1.1)	2.28 (1.3)	2.23 (1.1)	0.001[2]

Notes: *Mean (SD). After Holm–Bonferroni correction there was a significant difference between optimal and[a] suboptimal;[b] underuse;[c] overuse;[d] no difference after correction.

Abbreviations: CCQ, Clinical COPD Questionnaire; IQR, interquartile range; SD, standard deviation.

Table 7 EuroQol-5D scores (range 1–3) per therapy adherence category for tiotropium users

EuroQol-5D Tiotropium	Optimal, n (%) N=323	Suboptimal, n (%) N=45	Underuse, n (%) N=26	Overuse, n (%) N=19	*P*-value
Mobility					0.042
1. I have no problems in walking about	126 (85.1)	9 (6.1)	6 (4.1)	7 (4.7)	
2. I have some problems in walking about	194 (74.6)	35 (13.5)	20 (7.1)	11 (4.1)	
3. I am confined to bed	3 (60.0)	1 (20.0)	0 (0.0)	1 (20.0)	
Self-care					0.086
1. I have no problems with self-care	239 (81.3)	30 (10.2)	15 (5.1)	10 (3.4)	
2. I have some problems with self-care	72 (72.0)	13 (13.0)	8 (8.0)	7 (7.0)	
3. I am unable to wash or dress myself	12 (63.2)	2 (10.5)	3 (15.8)	2 (10.5)	
Usual activities					0.002
1. I have no problems performing usual activities	154 (85.1)	13 (7.2)	7 (3.9)	7 (3.9)	
2. I have some problems performing usual activities	152 (76.4)	25 (12.6)	14 (7.0)	8 (4.0)	
3. I am unable to perform usual activities	17 (51.5)	7 (21.2)	5 (15.2)	4 (12.1)	
Pain/discomfort					0.165
1. I have no pain or discomfort	153 (78.9)	21 (10.8)	10 (5.2)	10 (5.2)	
2. I have moderate pain or discomfort	136 (81.9)	15 (9.0)	9 (5.4)	6 (3.6)	
3. I have extreme pain or discomfort	34 (64.2)	9 (17.0)	7 (13.2)	3 (5.7)	
Anxiety/depression					0.003
1. I am not anxious or depressed	255 (82.5)	29 (9.4)	14 (4.5)	11 (3.6)	
2. I am moderately anxious or depressed	59 (67.0)	13 (14.8)	10 (11.4)	6 (6.8)	
3. I am extremely anxious or depressed	7 (50.0)	3 (21.4)	2 (14.3)	2 (14.3)	
Measuring scale (VAS)*	64.2 (15.6)	60.7 (13.5)	57.9 (17.8)	60.5 (18.0)	0.115

Notes: *Mean (SD). Higher outcomes indicate more symptoms.
Abbreviations: VAS, visual analogue scale (range 1–100); SD, standard deviation.

this is in line with a nationwide observational study that showed higher adherence levels in our region compared to other regions in the Netherlands.[22] Lately, emphasis has been placed on enhancing therapy adherence because there seems to be an evident reduction in symptoms and future exacerbations.[4,5] Whereas Cecere et al[23] and Mehuys et al[24] found demographic factors predictive for therapy adherence to long-acting beta-agonists, we did not find any demographic factors predictive for adherence to ICS and tiotropium.

Table 8 Multinominal regression analysis of associated variables per therapy adherence category for tiotropium users

Variable	OR	95% CI	*P*-value
Suboptimal (≥50%–<75%) N=45			
FEV_1/VC ratio	1.03	1.01–1.06	0.015
CCQ-question 3	1.06	0.81–1.39	0.661
Usual activities score 1	1.00	–	–
Usual activities score 2	1.68	0.79–3.57	0.181
Usual activities score 3	3.09	0.95–10.06	0.061*
Underuse (<50%) N=26			
FEV_1/VC ratio	1.04	1.01–1.07	0.018
CCQ-question 3	1.32	0.93–1.87	0.119
Usual activities score 1	1.00	–	–
Usual activities score 3	3.07	0.71–13.22	0.133
Overuse (>125%) N=19			
FEV_1/VC ratio	0.99	0.96–1.03	0.633
CCQ-question 3	1.46	1.07–2.00	0.043
Usual activities score 1	1.00	–	–
Usual activities score 2	0.81	0.26–2.48	0.711
Usual activities score 3	3.29	0.70–15.53	0.133

Notes: Higher scores on usual activities indicate more symptoms. **P*-value was 0.049 when building the multivariate model.
Abbreviations: OR, odds ratio; CI, confidence interval; FEV_1, forced expiratory volume in 1 second; VC, vital capacity; CCQ, Clinical COPD Questionnaire.

Multivariately, the strongest predictors for suboptimal use of ICS were an increase in FEV_1/VC ratio and ≥1 hospital admissions in the year prior to inclusion in this study. An important predictor for underuse of ICS was an increase in FEV_1/VC ratio. Strong predictors for overuse of ICS were a lower absolute FEV_1, a higher score on CCQ-question 3 concerning anxiety for dyspnea, and a current smoking status. These findings suggest that a better lung function predisposes patients to decreased use of their medication, whereas a worse lung function predisposes patients to overuse. However, predictors were measured at baseline, while overuse was determined over the 3-year follow-up period. Overuse could indeed be already present before the follow-up. Infrequent exacerbations were not significantly associated with adherence, but showed a trend toward underuse. This can possibly be explained by the fact that COPD patients who do not experience frequent exacerbations and/or have a better lung function experience less respiratory symptoms and therefore use less inhaled medications.

With regard to tiotropium, multivariately, strong predictors for suboptimal use were a better lung function and the inability to perform usual activities as asked by the EQ-5D whereas a higher FEV_1/VC ratio also was a predictor for

underuse. The association between therapy adherence and lung function corresponds with our findings in the ICS group. Overuse was again strongly associated with a higher score on CCQ question 3 concerning anxiety for dyspnea.

Our results demonstrate that in a large cohort of patients with COPD, adherence to inhaled medications is in fact class-dependent. This means that adherence to inhaled medications depends on the type of medication.[25] However, in our study we only used ICS, merged into one group, and tiotropium. We did not include short-acting beta-2-agonists, such as salbutamol, which are frequently used among patients with COPD because therapy adherence with these medications is not possible to determine, being used as needed. Also, it is important to notice that adherence to one type of medication does not automatically mean adherence to another type of medication.

The relationship between adherence and HRQoL may be ambivalent. A better HRQoL may lead to nonadherence. Contrary, the effect of adherence on HRQoL might be a consequence of the negative effects that it can generate.[26] With regard to quality of life and therapy adherence, we noticed that two questions concerning respiratory symptoms (shortness of breath in rest and anxiety for dyspnea) were associated with adherence to ICS and tiotropium. Patients experiencing more shortness of breath in rest were univariately more likely patients with suboptimal adherence to ICS and tiotropium. We cannot fully explain this association and wonder whether it concerns a chicken-and-egg situation. It is also possible that patients with suboptimal use do not optimally benefit from the therapy and therefore experience more shortness of breath in rest. The same explanation can be posed for the total CCQ score regarding tiotropium. It is possible that patients who show underuse experience more shortness of breath in rest, resulting in higher total CCQ scores, indicating a worse quality of life.

While depression and anxiety often coexist, they are separate conditions, but many COPD patients suffer from both.[27] A remarkable finding in our study is the significantly increased scores on the question concerning anxiety for dyspnea in overusers of ICS and tiotropium. Several studies have already demonstrated the relation between depression and nonadherence.[22] Turan et al[28] found in 2014 that the presence of depressive symptoms led to decreased adherence in patients with COPD. However, they did not find a significant association between anxiety and adherence, which is in contrast with our study, nor did they include overuse in measuring adherence, so it is unknown whether the mentioned nonadherence is related to overuse. It is worth mentioning that we specifically looked at anxiety concerning respiratory symptoms, whereas Snaith et al[29] looked at anxiety in general according to the Hospital Anxiety and Depression Scale (HADS) questionnaire. Detecting anxiety in COPD is important, since anxiety is a condition that can be effectively treated with pharmacological and nonpharmacological interventions and consequently might reduce overuse.

We observed no association between presence of one of the recorded comorbidities and therapy adherence. This is consistent with a study of Huetsch et al[30] that also found these comorbidities to be poor predictors for adherence.[31] Khdour et al[31] found a relation between presence of comorbidities and adherence, but included more comorbidities than we did in our study and put these comorbidities together as a dichotomous variable.

Our study has several strengths. We defined subgroups of nonadherence, so we could see what type of nonadherence is related to our variables. Just as Krigsman et al[32] did, we decided to choose an upper cut-off point as well, in order to study overuse. This subdivision shows that nonadherent patients differ in profile, which helps us to examine patterns of different medication use between patients. Furthermore, our use of pharmacy refill records for estimating adherence could be seen as a strength. This method allowed us to obtain objective data and avoid recall and social desirability biases. Also, this method of monitoring is an accurate measurement of adherence compared to self-report. A downside of this method is that it measures medication acquisition, but not actual medication consumption. It is likely that patients who regularly refill their medications are using them, but this cannot always be verified. In general, adherence is higher in clinical trial settings because patients are motivated to take their medication in correct doses at correct times. Since our patients were not in a clinical trial and since they were not aware that their medication records were going to be used for monitoring their therapy adherence, adherence in our study can be considered very high. Next to this, many adherence studies use data of 1-year follow-up. Since medication use in COPD is long-term, we followed our patients for 3 years, thus giving an estimate on long-term use. Finally, we applied a very comprehensive and complete database of 795 patients complemented with accurate completeness of associated pharmacy data.

Despite these advantages, some limitations of our study should be noted. The information available for our analyses was limited to the variables included in the database. The impact of other variables possibly associated with adherence, such as side effects from therapies, inconvenience in the form of frequent or complex medication dosing regimens, and patient's beliefs, could not be assessed in this study.

Future studies can put more emphasis on these variables to explore them as predictors for nonadherence, possibly by means of in-depth interviews, where a closer look may be taken why patients do not adhere. Also, interventions that are developed to improve adherence may need to be adapted to incorporate different types of nonadherence in different types of medication.

Conclusion

This study confirms that several quality of life factors and disease-specific factors are related to ICS and tiotropium adherence, but a clear profile of the patient who shows underuse or overuse cannot yet be outlined. A better lung function, expressed as a higher FEV_1/VC ratio, was in both groups associated with more suboptimal use and more underuse. Overusers of ICS and tiotropium experience more anxiety symptoms and more physical symptoms. Further research is needed to investigate more variables associated with the different types of nonadherence in different types of medication classes. Also, further research is required into the role of anxiety in adherence to inhalation medication.

Acknowledgment

This study was partly supported by an unrestricted research grant from GlaxoSmithKline.

Disclosure

The authors report no conflicts of interest in this work.

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