Adherence to inhaled medication in COPD: predictors and outcomes

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**ADHERENCE TO INHALED MEDICATION IN COPD:
PREDICTORS AND OUTCOMES**

PROEFSCHRIFT

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General Introduction

Introduction

The main objective of this thesis is to study adherence to inhaled medication in COPD patients of the "Cohort of Mortality and Inflammation in COPD" (COMIC). The aim is to identify factors associated with adherence to inhaled medication, and to study the impact of adherence on health outcomes. It is important to recognize and understand a non-adherent patient. This understanding can be used to design interventions for optimization of medication adherence in daily clinical practice.

Chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD) is currently the fourth most common cause of death in the world and a major cause of chronic morbidity and mortality. (1) In general, the treatment of COPD is supportive, aimed at relieving patient's symptoms, to decrease the number of exacerbations, and to improve quality of life. (2) Pharmacologic interventions can help to achieve these goals, because appropriate pharmacotherapy can reduce mortality, symptoms, and the frequency and severity of exacerbations, and can improve health status and exercise tolerance. (2-4) Current treatment strategies in COPD include long acting muscarinic agonists (LAMA) like tiotropium, long acting beta agonists (LABA) to relieve dyspnea, inhaled corticosteroids (ICS) to suppress the prominent pulmonary inflammation, and combination drugs. The effectiveness of these inhaled medications is strongly influenced by the patient's therapy adherence.

Definition of adherence

The WHO Adherence Project stated the definition of adherence as "the extent to which a person's behavior - taking medication, following a diet, and/or executing lifestyle changes - corresponds with agreed recommendations from a health care provider". (5) Non-adherence can present itself in different forms and can be unintentional as well as intentional. A person has to obtain the medication to start a therapy. After obtaining, a person can under- or overuse medication or show improper use (for example forgetfulness and alteration of schedules and doses). (6,7)

The various methods of assessing adherence include self-report (questionnaires, diaries, self-report scales), medication measurement (interval pill counts, weighing of MDIs), biochemical validation, electronic medication monitors (pill dispensers, MDIs) and pharmacy refill methods. (8,9) Each method has its strengths and limitations. Self-reporting is frequently inaccurate and has moderate reliability (25-67%) when

compared against more objective measures of adherence such as canister weight. (9) Canister weighing is easy to implement but is not reliable because intentional activation of the device multiple times consecutively over a short period of time, even immediately prior to the visit, can wrongly suggest optimal adherence. Biochemical validation is most scientifically sound, but is expensive and invasive. Electronic monitors provide accurate and reliable records of dosage, but are expensive, subject to malfunction and cannot confirm ingestion. Analysis of pharmacy records is cheap, provides evidence of drug refill patterns, but cannot assess ingestion or pattern of use and 'dose dumping' and may be missing information. (9) Most common are the use of pharmacy records, questionnaires or interviews. (10) In this study we used pharmacy data to record adherence, because Dutch patients traditionally retrieve their medication from one pharmacy thus providing a virtually complete dispensing overview. A method to calculate adherence using pharmacy data is the medication possession ratio (MPR). (11) Theoretical duration of exposure can be calculated using information on dispensing date, total supply, and dosage regimen. The total number of days for which patients has collected medication during follow-up is divided by the total number of days between the first and last medication collection during follow up. This can be expressed as a percentage. In literature there is no consensus on acceptable therapy adherence for COPD, and definitions vary from >70% to >80%. (3,12-17) Krigsmann et al. and Mehuys et al. set the limit for satisfactory refill adherence in COPD patients on 80-120%. (13,18) In order to differentiate low adherence categories and to study overuse as well for the analysis of the COMIC data we introduced four adherence categories. We decided to choose two lower cut-off points to distinguish suboptimal and underuse and an upper cut-off point of 125% for optimal adherence, in order to be able to identify overuse as well. Adherence was deemed optimal if it was 75-125%, sub-optimal between 50-<75%, and poor below <50% (underuse) or above >125% (overuse).

Adherence in COPD

Therapy adherence in COPD is generally poor, varying in studies from 28% to 40% for inhaled corticosteroids (ICS), 29 to 35% for ICS/LABA combinations and 54 to 61% for LABA and LAMA. (12,13,19) Medication adherence in COPD is a complex concept, influenced by multiple factors including patient related, social/environmental and treatment related factors. (6) Patient related factors include health beliefs, cognitive ability, self-efficacy, comorbidities, psychological profile and

conscientiousness. The patient-prescriber relationship, social support, access to medication, device training and follow up are social factors that have to be taken into account. Finally, factors related to treatment are the method of administration (ie inhalation), dosing regimen, polypharmacy and side effects. (6)

Adherence is influenced by patient's perception of the disease. George et al. found that patient beliefs, experiences and behaviors with regards to both disease and treatment were more powerful predictors of medication adherence than sociodemographic and clinical factors in patients with COPD. (20) Next to this, adherent patients had a greater understanding about their illness and the options for managing their illness. (20) And improving knowledge of COPD patients by pharmacists in the pharmaceutical care for patients with COPD (PHARMACOP) trial, showed significantly increased adherence levels. (21) Also satisfaction with and faith in the treating physician were found to be low among less adherent patients compared to highly adherent patients. (20) COPD patients are generally older and often have co-morbidities that require treatment, resulting in polypharmacy, a known factor to increase non-adherence. Also, increasing age can be accompanied by cognitive decline, cognitive impairment (memory loss), difficulty reading small print and difficulty opening containers. (6)

Furthermore, depression is a known factor in non-adherence to medication and the prevalence in COPD can be up to 50%. (22,23) For example Turan et al. found that the presence of depressive symptoms led to decreased adherence in patients with COPD. (24)

Complex multiple drug regimens are often required for adequate management of COPD. Treatment factors thought to influence adherence to inhaled medications include medication and delivery devices, time to onset of symptom relief, symptom severity, regimen complexity (ease of use, dosing frequency, number of medications), cost and adverse effects of medication. (10) Routinization of drug therapy is critical for optimal medication adherence in COPD patients. (20) For example, less adherent patients were more likely to vary their recommended management to suit their lifestyle or based on how they felt. (20)

Type of inhaled medication

Current treatment strategies in COPD contain LAMA and LABA to relieve dyspnea, ICS to suppress the prominent pulmonary inflammation, and combination drugs. (2) Each medication category has its own mechanisms of action and specific adverse effects. Bronchodilators are medications that increase FEV₁ and tend to reduce dynamic hyperinflation at

rest and during exercise, and improve exercise performance. They are most often given on a regular basis to prevent or reduce symptoms.

(2) The principal action of LABA is to relax airway smooth muscle by stimulating beta2-adrenergic receptors. Stimulation of beta2-adrenergic receptors has the potential to precipitate cardiac rhythm disturbances in susceptible patients, and higher doses can induce exaggerated somatic tremor, which can be troublesome in older patients. (2) LAMAs block the bronchoconstrictor effect of acetylcholine on muscarinic receptors. The main side effect is dryness of the mouth. Although occasional urinary symptoms have been reported, there are no data to prove a true causal relationship. (2)

In contrast to LAMA and LABA, ICS (e.g. fluticasone) do not give immediate relief. GOLD guidelines from 2006 and 2011 (current at the time of the data collection of the COMIC cohort) stated ICS use reduces frequencies of exacerbation and improves lung function and symptoms due to their anti-inflammatory effect. (25,26) The current GOLD guideline states that ICS use alone does not modify the long-term decline of FEV₁ nor mortality but that ICS combined with LABA (single and combined preparations) is more effective than the individual components in improving lung function and health status and reducing exacerbations in patients with exacerbations and moderate to very severe COPD. (2) Side effects associated with ICS use are higher prevalence of oral candidiasis, hoarse voice, skin bruising and pneumonia. (2)

Inhaled medication differ in the number of daily doses needed, multiple inhalation moments during the day on the one hand and multiple doses per indigestion moment on the other hand. Frequent daily use and multiple dosing have both shown to have a negative influence on adherence. (8) LAMA, like tiotropium for example, require one inhalation per day whereas the LABA, (e.g. salmeterol) requires inhalation two times per day. In *chapter 2* the differences in adherence to common inhaled medications in COPD is studied in order to see whether medications with various working mechanisms and dosage regimens result in different adherence patterns.

Inhalation devices

A unique feature in the treatment of COPD is the use of inhalation devices to deliver inhaled medication. The devices available are pressurized metered-dose inhalers (pMDI's with or without a spacer), dry powder inhalers (DPI's), soft mist inhalers and nebulizers. Each device has its own distinct properties that have to be taken in to account to achieve successful delivery of the medication in the lungs. Patients need an

adequate cognitive function, dexterity and inhalation strength. (27) Inhaling medication is a difficult task as between 4% and 94% of the patients, depending on the type of inhaler and method of assessment, use their inhaler ineffectively. The most common errors made include failure to exhale before actuation, failure to breath-hold after inhalation, incorrect positioning of the inhaler, incorrect rotation sequence, and failure to execute a forceful and deep inhalation. (28) The effectiveness of an inhaled powdered drug for example depends on the inspiratory flow rate generated by the patient and on the intrinsic resistance of the DPI device. These two forces affect the dose utilization, both the powder disaggregation and dispersion, its penetration into the airways, and finally the efficacy of the treatment. (29) The level of patient satisfaction with their inhaler device for the treatment of COPD is observed to have a positive influence on therapy goals by improving compliance. (10,30) Chrystyn et al. showed that patients' overall satisfaction with their inhaler was significantly associated with treatment adherence and weakly associated with fewer exacerbations. (30) Features of inhalers considered very important by patients with COPD are overall ease of use including ease of holding and carrying, knowing the dose has been taken and a counter to let them know how many doses are left. (7) Chapter 3 studies the influence of type of inhalation device on medication adherence of COPD patients. Do the different features of the inhalers matter with regard to therapy adherence and which device shows the highest adherence?

Health related quality of life

There is a widespread level of impairment of health related quality of life (HRQoL) in patients with COPD regardless of their spirometric stage. (31) Hensch et al. showed that deteriorated HRQoL was predicted by increasing dyspnea, depression/anxiety, increasing number of exacerbations, and decreased exercise capacity. (31) Improving HRQoL is one of the goals in the treatment of COPD. It is feasible that adherence to inhaled medication in COPD and HRQoL are related, as pharmacotherapy can reduce mortality, symptoms, and the frequency and severity of exacerbations. This relationship may be ambivalent. The effect of medication adherence on HRQoL might be a consequence of the effectiveness of the therapy and the negative effects (e.g. side effects, daily life limitation of therapy, social stigma) it can generate. HRQoL might also influence the patterns of patients' drug use as a decreased HRQoL, for example caused by the previously described effect of depression, may lead to non-adherence. Conversely good HRQoL can lead to non-adher-

ence as well when a patient feels well en does not see the need to use medication. Also the dynamics between adherence and HRQoL might differ over time, as the negative effects of medication non-adherence might become dominant in the long run. (32)

Whereas a lot of research has been done on the effect of adherence on HRQoL, the research on the influence of HRQoL on adherence is limited. (32) To measure HRQoL in COPD several tools are available, for example the validated Dutch versions of the Clinical COPD Questionnaire (CCQ) and the EuroQol-5D (EQ-5D) questionnaires. (33-35) It is possible that the scores of these questionnaires can be used to recognize or predict non-adherence in daily practice. Therefore the objective of *chapter 4* is to identify disease-specific and HRQoL factors associated with adherence to ICS and tiotropium.

Non-adherence and patients beliefs and perceptions

As stated above patient related factors influence adherence and include health beliefs, cognitive ability, self-efficacy, co morbidities, psychological profile and conscientiousness. Leventhal proposed a Self-Regulatory Model to obtain more insight in the influence of patient factors on adherence. (36) This model provides a framework for understanding adherence and non-adherence to treatment recommendations, which is based on patient's beliefs of their illness in relation to treatment adherence. (36,37) The model asserts that illness beliefs can be divided into five dimensions: illness identity, time-line, cause, consequences and control-cure. (38) Beliefs about medication were also related to reported adherence, as was shown by Horne et al. for four chronic illness groups (asthma, renal, cardiac, and oncology). Higher medication necessity scores correlated with higher adherence while higher concerns about the risk of dependence or long-term adverse effects correlated with lower adherence. (39) Therefore, Horne et al. designed an extended self-regulatory model of treatment adherence, which incorporates beliefs about treatment as well as illness perceptions. (40) In COPD, disease and medication perception have not been described in much detail, whereas for asthma the model of Horne et al. showed that in asthma patients concerns about potential adverse effects and more negatively perceived consequences of illness were correlated with lower adherence. (40) Although asthma and COPD are both obstructive diseases, asthma shows a more intermittent process whereas COPD is a continuous process. It is possible that COPD patients might have different beliefs and perceptions with regard to their illness and their inhaled medication.

Therefore, in *chapter 5* the perceptions and beliefs in COPD patients with poor adherence (and possible differences between under- or overuse) to ICS are described.

Morbidity and mortality

COPD exacerbations are important events that contribute to a worsening health status, disease progression, and mortality. (41) Various studies have shown that better adherence to inhaled medication in COPD is associated with reduced risk of death and hospitalizations due to exacerbations in COPD. (3,19) The TORCH study showed a significant reduced risk on mortality for adherent patients with the use of fluticasone propionate combined with salmeterol compared to patients with poor adherence (<80%) (HR 0.40; 95% CI 0.35-0.46). (3) Ismaila et al. showed that good adherence to fluticasone/salmeterol (FSC), tiotropium and the combination of these therapies was associated with decreased risks for moderate (mod) and severe (sev) COPD exacerbations. (FSC; ORmod 0.55, ORsev 0.75, Tio; ORmod 0.54, ORsev 0.71 and Tio+FSC; ORmod 0.44, ORsev 0.57). (19) In the studies mentioned above adherence was defined as poor (<80%) or good. In this thesis will be shown that there are also many patients that overuse (>125%) or strongly underuse (<50%) their inhaled medication. It is expected that these patients will have a different risk for COPD exacerbations that need a hospitalization (severe AECOPD) and mortality, compared to patients with optimal (75-125% use) or sub-optimal (50-75% use) adherence. Although the risk on community acquired pneumonia (CAP) is still under debate there is growing evidence for an increased risk. For example recently published results of the UPLIFT-trial showed an increased incidence rate of pneumonia for ICS use compared to no ICS and especially for fluticasone propionate. (42) Next to this Ernst et al. stated that the risk for pneumonia is possibly dose related with a higher dose of fluticasone showing an even higher increased risk of hospitalization for pneumonia. This raises the question whether an increased pneumonia risk could be related to adherence of ICS as well as dosage, with a lower risk for lower adherence and a higher risk for patients that overuse their ICS. Therefore, *chapter 6* contains the results concerning the relationship between therapy adherence with ICS and tiotropium including overuse and morbidity and mortality.

Objectives and outline of this thesis

In *chapter 2* we start with describing the differences in adherence to common inhaled medications in COPD in a population of COPD patients living in the eastern of the Netherlands.

In *chapter 3* we continue the description of our COPD cohort with a focus on the influence of type of inhalation device on adherence of COPD patients to inhaled medication, as the inhalation device is a unique feature in the treatment of COPD.

In *chapter 4* the relationship between Health Related Quality of Life and adherence to ICS and tiotropium are discussed. We conducted a study to identify disease-specific and HRQoL factors that are associated with adherence to ICS and tiotropium in COPD patients.

In *chapter 5* the results of the previous chapters are completed with the COPD patients' point of view on adherence and the disease COPD, studied with in depth interviews.

In *chapter 6* the implications of differences in adherence on morbidity and mortality are studied.

In *Chapter 7* the general discussion is outlined in which we summarize our findings and provide a wider context. This chapter is concluded with recommendations for future research.

In *chapter 8* a summary of findings concludes this thesis.

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Differences in adherence to common inhaled medications in COPD

COPD 2015;12(6):643-8.

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Abstract

Objective: To study differences in adherence to common inhaled medications in COPD.

Methods: Adherence of 795 patients was recorded from pharmacy records over 3 years in the COMIC cohort. It was expressed as percentage and deemed good at ≥ 75 – $\leq 125\%$, sub-optimal ≥ 50 – $< 75\%$, and poor $< 50\%$ (underuse) or $> 125\%$ (overuse). Most patients used more than one medication, so we present 1379 medication periods.

Results: The percentages of patients with good therapy adherence ranged from 43.2 (beclomethasone) - 75.8% (tiotropium); suboptimal from 2.3 (budesonide) - 23.3% (fluticasone); underuse from 4.4 (formoterol/budesonide) - 18.2% (beclomethasone); and overuse from 5.1 (salmeterol) - 38.6% (budesonide).

Patients using fluticasone or salmeterol/fluticasone have a 2.3 and 2.0-fold increased risk of suboptimal versus good adherence compared to tiotropium. Patients using salmeterol/fluticasone or beclomethasone have a 2.3 and 4.6-fold increased risk of underuse versus good adherence compared to tiotropium. Patients using budesonide, salmeterol/fluticasone, formoterol/budesonide, ciclesonide and beclomethasone have an increased risk of overuse versus good adherence compared to tiotropium.

Adherence to inhalation medication is inversely related to lung function.

Conclusion: Therapy adherence to inhalation medication for the treatment of COPD is in our study related to the medication prescribed. Tiotropium showed the highest percentage of patients with good adherence, followed by ciclesonide, both dosed once daily. The idea of improving adherence by using combined preparations cannot be confirmed in this study. Further research is needed to investigate the possibilities of improving adherence by changing inhalation medication.

Introduction

Chronic obstructive pulmonary disease (COPD) is a major cause of chronic morbidity and mortality throughout the world. In general, the treatment of COPD is supportive, aimed at relieving patients symptoms, to decrease the number of exacerbations, and to improve quality of life.

(1) Bronchodilators are the key element in pharmacological management of COPD. (1) In addition, since pulmonary inflammation is prominent in COPD (2), anti-inflammatory drugs such as inhaled corticosteroids are often used.

The effectiveness of inhaled medications is strongly influenced by the patient's drug adherence. Adherence to medication has been shown to be associated with reduced risk of death and hospitalization. (3)

Medication adherence is influenced by patient and medication related factors. Critical patient related factors for optimal medication adherence in patients with COPD are patients' disease and treatment acceptance, knowledge about and faith in the treatment, effective patient-clinician relationship, and routinisation of drug therapy. (4-6) Medication related factors such as frequent daily use and multiple dosing have both shown to have a negative influence on adherence. (7) Patients with COPD often use a medication regimen requiring multiple daily dosages during a prolonged period and often use different medications simultaneously.

All these factors combined can make therapy adherence for COPD patients a difficult task.

Non adherence to inhalation medication can be divided in several categories. The use of medication has to start with obtaining the medication. After obtaining the patient can underuse, overuse or show improper use (for example forgetfulness and alteration of schedules and doses) of the medication. (4,8)

A specific problem with inhalation medication is the use of the device in which the medication is administered. Improving inhalation technique can improve adherence. (9)

Medication adherence with regard to maintenance medication in patients with COPD is generally poor, varying in medication database studies from 28-40% for inhalation corticosteroids, 29-35% for corticosteroid/sympaticomimetic combinations and 54-61% for long acting sympaticomimetics and tiotropium. (10-12)

Many adherence studies use data of one-year follow up and cannot discriminate between asthma and COPD patients. (11,13,14) Medication use in COPD is long- term. We therefore conducted a study to investigate therapy adherence with inhalation medication over a period of

three years in a well defined cohort of confirmed COPD-patients in order to give an estimate on long-term use.

Methods

Setting and design

This study is part of the Cohort of Mortality and Inflammation in COPD (COMIC) study a single centre prospective cohort study. From December 2005 till April 2010, 795 patients were included with a follow-up period of three years. Patients were recruited at the outpatient clinic of the Department of Pulmonology, Medisch Spectrum Twente Hospital, Enschede, located in the Eastern part of The Netherlands, serving a catchment population of approximately 264,000 persons. The study was approved by the hospital's Medical Ethical Committee (P05-49). 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 GOLD criteria (2) current or ex-smoker; (3) age 40 years or over; (4) no medical condition compromising survival within the follow-up period or serious psychiatric morbidity and, (5) absence of any other active lung disease (e.g. sarcoidosis), (6) no maintenance therapy with antibiotics, (7) and the ability to speak Dutch. Patients were consecutively enrolled when hospitalised for an acute exacerbation of COPD (AECOPD group) or when visiting the outpatient clinic in stable state (stable state group). To be included in the AECOPD group, patients had to be hospitalised for an AECOPD and be able to produce an adequate sputum sample at the day of hospitalisation. To be included in the stable state group patients had to meet the following criteria: no use of antibiotic and/or prednisolon 4 weeks prior to enrolment and no exacerbation less than 4 weeks before study entry. Of the 1503 patients that were screened for eligibility, a total of 795 were included. All surviving patients completed the three-year follow-up period. All patients were treated according to standard care. Demographic data was collected from medical records.

Lung function and smoking status were both determined at baseline. Lung function was measured by spirometry, performed according to standardised guidelines. (15) Forced Expiratory Volume in 1 second (FEV₁) and Vital Capacity (VC) were measured until three reproducible recordings (less than 5% difference) were obtained. Smoking status was determined by the Vlagtwedde questionnaire. (16)

The primary outcome, therapy adherence was recorded from patients' pharmacy records. The patients were not aware that their medication records were going to be used for the monitoring of therapy adherence.

Theoretical duration of exposure 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 medication collection during follow up plus the day's supply of the last refill. (17) This was expressed as a percentage and adherence was deemed good if it was $\geq 75\%$ - $\leq 125\%$, sub-optimal between $\geq 50\%$ - $< 75\%$, and poor below $< 50\%$ (underuse) or above $> 125\%$ (overuse). In literature there is no consensus on acceptable therapy adherence, definitions vary from $> 70\%$ to $> 80\%$ for a clinical research setting. We decided to set the limit for optimal adherence at $\geq 75\%$, which is between these two definitions. Next to this, we decided to choose an upper cut-off point as well for optimal adherence ($> 125\%$), in order to exclude overuse from this category. (3,10,11,18) We excluded medication when it was prescribed once only or was used less than 90 days.

Computerized pharmacy data made it feasible to monitor medication adherence by tracking requests for refills. Computerized drug dispensing histories from Dutch pharmacies are virtually complete and include data concerning the dispensed drug, the prescriber, the dispensing date, the amount dispensed, the prescribed dose regimens, and the estimated duration of use. In The Netherlands, there is a strong pharmacy-patient liaison for reimbursement of prescription drugs, a high degree of computerization, the use of standardized classification and coding systems, and a strong commitment of pharmacists to surveillance of medication. The following bronchodilators were used: salmeterol and tiotropium. Furthermore, the inhaled corticosteroids beclomethasone, ciclesonide, fluticasone and budesonide and the combined preparations of fluticasone/salmeterol and budesonide/formoterol were included in the analyses. Therapy adherence with formoterol was not analysed, because formoterol (unlike salmeterol) can be used on demand as well and this confounds our calculation of adherence. (19)

Statistical analyses

Baseline characteristics are reported as mean with SD for continuous variables, or as numbers with corresponding percentages for categorical or dichotomous variables. Not normally distributed continuous variables are reported as median with corresponding interquartile range (IQR). We investigated the relationship between therapy adherence and type of medication with Nominal Regression analyses. Tiotropium and good therapy adherence were set as reference in the Nominal Regression analyses.

Furthermore potential confounders (age, sex, smoking status, lung function) were first tested for their association with therapy adherence. Associated variables were subsequently tested for their association with type of medication. For categorical variables this association was tested by means of Chi-square tests or Fisher exact tests, as appropriate. For continuous variables this association was tested with an ANOVA or Kruskal-Wallis test as appropriate. Variables that were both associated with therapy adherence and type of medication were all entered in the multivariate Nominal Regression analyses. Subsequently, potentially confounding variables with the highest p-value were eliminated from the model one by one until the fit of the model decreased significantly, based on the -2 Log Likelihood.

All statistical calculations were carried out with the SPSS statistical package (version 21.0) and p-values <0.05 were considered significant.

Results

The study population included 795 patients (Table 1). Patients were predominantly male (61.1%). The mean age of the study population was 68 years. Almost three-quarter of the patients were ex-smokers.

Table 1. Baseline characteristics.

	N= 795 Overall	Good ≥75- ≤125%	Sub-optimal 50-<75%	Underuse <50%	Overuse >125%	P
Age in years (Mean (SD))	67.8 (9.9)	66.5 (9.6)	66.5 (10.3)	64.3 (11.0)	67.2 (9.7)	0.100
Sex (Number of men(%))	486 (61.1)	560 (61.6)	112 (53.6)	62 (53.9)	87 (59.6)	0.102
Smoking status (Number (%))						
Current smoker	212 (26.7)	246 (27.1)	49 (23.4)	45 (39.1)	56 (38.4)	0.001
Ex-smoker	583 (73.3)	663 (72.9)	160 (76.6)	70 (60.9)	90 (61.6)	
Lung function (Mean (SD))						
FEV ₁ in Litres	1.4 (0.6)	1.4 (0.6)	1.4 (0.5)	1.5 (0.6)	1.3 (0.5)	0.001
FEV ₁ % predicted	52.1 (19.4)	51.0 (17.8)	52.4 (18.4)	55.3 (20.1)	47.3 (16.9)	0.004
FEV ₁ /VC ratio	44.5 (13.6)	42.3 (12.6)	45.5 (13.3)	48.0 (15.2)	42.3 (12.7)	0.000

Table 2 displays the number (%) of patients in the subgroups of therapy adherence for the different inhalation medications. Because many patients used more than one type of inhaled medication and since use of one medication in different devices (for example MDI and Diskus) was scored separately during the observation period, data on 1379 periods of medication use are presented. The majority of the study patients

were treated with tiotropium and salmeterol/fluticasone. The percentages of patients with good therapy adherence within the studied medications ranged from 43.2 (beclomethasone) - 75.8% (tiotropium); suboptimal adherence ranged from 2.3 (budesonide) - 23.3% (fluticasone); underuse from 0 (ciclesonide) - 18.2% (beclomethasone); and overuse from 5.1 (salmeterol) - 38.6% (budesonide). All inhaled medications had a median time of use of more than 25 months except beclomethasone (15) and ciclesonide (23.5). The Chi-square test showed an association between therapy adherence and the studied medications ($p < 0.001$).

Table 2. Number (%) of patients in the subgroups of therapy adherence per medication.

Medication	Good ≥ 75 - $\leq 125\%$	Suboptimal ≥ 50 - 75%	Underuse $< 50\%$	Overuse $> 125\%$	Months used median (IQR)
Tiotropium (n=566)	429 (75.8)	68 (12.0)	36 (6.4)	33 (5.8)	28.7 (15.1-35.5)
Ciclesonide (n=22)	15 (68.2)	3 (13.6)	0	4 (18.2)	23.5 (15.8-35.5)
Salmeterol (n=39)	26 (66.7)	6 (15.4)	5 (12.8)	2 (5.1)	27.1 (6.9-35.2)
Fluticasone (n=73)	46 (63.0)	17 (23.3)	4 (5.5)	6 (8.2)	25.7 (12.5-34.9)
Formoterol/ Budesonide (n=91)	56 (61.5)	12 (13.2)	4 (4.4)	19 (20.9)	31.2 (15.9-36.5)
Salmeterol/Fluticasone (n=500)	295 (59.0)	95 (19.0)	55 (11.0)	55 (11.0)	27.5 (13.7-35.0)
Budesonide (n=44)	23 (52.3)	1 (2.3)	3 (6.8)	17 (38.6)	28.2 (17.4-36.7)
Beclomethasone (n=44)	19 (43.2)	7 (15.9)	8 (18.2)	10 (22.7)	15.7 (7.5-31.7)

To compare the four categories of therapy adherence between inhalation medications we used Nominal Regression analyses. Because the highest percentage of patients with good adherence was observed for tiotropium, this medication, including good therapy adherence was set as reference in Table 3. Of the potential confounders listed in Table 1, FEV₁ in litres, FEV₁ % predicted and FEV₁/VC ratio were both associated with type of medication as well as with therapy adherence and were therefore potential confounders that should be entered to the multivariate Nominal Regression analyses. Due to multicollinearity between FEV₁ in litres, FEV₁ % predicted and FEV₁/VC ratio, only the variable with the best model fit was entered to multivariate Nominal Regression analyses, which was FEV₁ in litres.

Compared to tiotropium, patients using fluticasone or salmeterol/fluticasone had a 2.3 and 2.0-fold increased risk of suboptimal versus good adherence (Table 3). Patients using salmeterol/fluticasone or beclomethasone had a 2.3 and 4.6-fold increased risk of underuse versus good adherence. Patients using budesonide, beclomethasone, formoterol/budesonide, ciclesonide and salmeterol/fluticasone, beclomethasone had an increased risk of overuse versus good adherence.

Table 3. Nominal Regression analyses of medication vs. therapy adherence.

		OR	95% CI
Suboptimal (≥ 50 - $<75\%$) (n=209)	FEV ₁ (L) baseline	1.1	0.8 - 1.4
	Ciclesonide	1.3	0.4 - 4.4
	Salmeterol	1.4	0.6 - 3.6
	Fluticasone	2.3	1.3 - 4.3
	Formoterol/Budesonide	1.4	0.7 - 2.7
	Salmeterol/Fluticasone	2.0	1.4 - 2.9
	Budesonide	0.3	0.04 - 2.1
	Beclomethasone	2.3	0.9 - 5.7
Underuse ($<50\%$)(n=115)	FEV ₁ (L) baseline	1.5	1.1 - 2.1
	Ciclesonide	**	**
	Salmeterol	2.1	0.8-5.9
	Fluticasone	1.1	0.4 - 3.2
	Formoterol/Budesonide	0.8	0.3-2.4
	Salmeterol/Fluticasone	2.3	1.5-3.6
	Budesonide	1.6	0.4-5.5
	Beclomethasone	4.6	1.9-11.3
Overuse ($>125\%$)(n=145)	FEV ₁ (L) baseline	0.6	0.4-0.8
	Ciclesonide	3.6	1.1-11.6
	Salmeterol	0.5	0.1-4.1
	Fluticasone	1.6	0.6-4.0
	Formoterol/Budesonide	4.9	2.6-9.3
	Salmeterol/Fluticasone	2.3	1.5-3.7
	Budesonide	9.8	4.7-20.2
	Beclomethasone	7.7	3.3-18.1

Notes: * Good adherence and tiotropium were set as reference. All corrected for FEV₁ in Litres (L) at baseline; **Not possible to calculate

Compared to fluticasone as reference medication, budesonide had a 0.12 fold risk of suboptimal use compared to optimal use; budesonide, formoterol/budesonide and beclomethasone had an increased risk of overuse (6.1, 3.1 and 4.8, respectively) compared to optimal use, and beclomethasone had a 4.3-fold increased risk of underuse.

FEV₁ (L) at baseline was related to poor adherence, both underuse and overuse.

Underuse was associated with a higher FEV₁ at baseline compared to good adherence, while overuse was associated with a lower FEV₁ at baseline compared to good adherence.

Discussion

Therapy adherence to inhalation medication for the treatment of COPD is in our study related to the medication prescribed. The medications dosed once daily, tiotropium and ciclesonide, showed the highest percentage of patients with good adherence. Medication dosed one time daily is a known factor that improves adherence. Adherence declines as the number of daily doses increased. (20)

The percentage of patients with good adherence with tiotropium is high (76%) compared to literature. Ismaila et al found that 61.1% and 62.9% of the tiotropium users showed good adherence. (12) Also for corticosteroids and corticosteroids combined with adrenergics high percentages of good adherence were observed in our study (varying between 59 and 68%). Krigsman et al found that only 28 and 29% of the patients showed good adherence for corticosteroids and corticosteroids combined with adrenergics. (11) Vestbo et al. found that 79.8% of the patient showed good adherence with salmeterol, fluticasone propionate or a combination of these two over a study period of 3 years. However, these patients were aware that their therapy adherence was being monitored and they had to bring all inhalers at every visit to exchange them for new ones. (3)

All three studies used 80% as cut-off point for good adherence. Changing the cut-off in our study to 80% did not influence the 'good' adherence levels (data not shown). Just as Krigsman we decided to choose an upper cut-off point as well, in order to study overuse, another form of therapy non-adherence. Therapy adherence in a clinical trial setting is usually higher because patients are motivated by the clinical setting. In the COMIC study patients were not aware that their medication records were going to be used for the monitoring of therapy adherence.

We therefore do not expect a large influence on therapy adherence as observed by patients participating in a clinical trial setting. In this light the therapy adherence levels found in our study can be considered very high. This is in line with a nationwide observational study that showed higher adherence levels in our region compared to other regions in the Netherlands. (21)

This study showed increased risks of suboptimal adherence, underuse and overuse for investigated inhaled corticosteroids and corticosteroid/sympathomimetic combinations compared to tiotropium with optimal adherence.

These differences can be caused by medication related factors as number of daily doses needed or relief of symptoms. Tiotropium relieves dyspnea whereas corticosteroids do not give immediate relief. (22) The question is whether changing inhalation medication within the same class of medication can improve therapy adherence. For example if a patient shows underuse on beclomethasone would changing therapy to fluticasone improve adherence? This should be evaluated in future studies. Furthermore, could the difference in therapy adherence also be related to the device in which inhalation medication is administered?

Another interesting finding is that the idea of improving adherence by using combined preparations cannot be confirmed in this study. Differences in adherence between the inhaled corticosteroids and the combined preparations lie in the levels of over- and underuse. Adherence is significantly higher in some preparations and numerically but not statistically significant in others. Combining inhalation medication in one device is thought to improve adherence. Yet, guidelines for the treatment of COPD (GOLD, Dutch guidelines of NHG and CBO) do not recommend the use of combined preparations to improve therapy adherence. (23,24) Our study supports this view. Given the observational design of the study it is however possible that the combined preparations were given to patients that had problems with therapy adherence on the sole preparations, thus resulting in an apparently greater rate of adherence in the remaining subjects continuing to use the sole preparations. Similar results were found for the treatment of asthma in children as well as adults. (25)

Therapy adherence to inhalation medication showed to be related to FEV₁ at baseline. Underuse was associated with a higher FEV₁ at

baseline, while overuse was associated with a lower FEV₁ at baseline. It is possible that patients with higher FEV₁ feel less need to use their medication and therefore show lower adherence levels. The opposite can be an explanation for overuse with a lower FEV₁. Turner et al found a relation between good adherence and reduced FEV₁. This is in line with our results. (26)

There are some potential limitations in our study. Therapy adherence can be measured in several ways. Most common are the use of collected pharmacy records, questionnaires or interviews. Pharmacy records give an indication of drug refill patterns but not of the actual inhalation. Patients can decide to collect the medication to appear adherent, but can dump the medication at home. (27) Another problem with regard to the calculation of adherence is that the prescriber can change the dosage regimen without giving a new prescription. The pharmacy records do not reflect the actual use at this point. The data show the maximum levels of drug use among the patients, and it is likely that the inhaled drug volumes are lower than the volumes dispensed by the pharmacy. (28,29)

We excluded medication if it was prescribed only once or for a period of less than 90 days in a period of 3 years. One time only records give no information on therapy adherence. Due to our definition a onetime prescription fill scores 100% therapy adherence. This would distort our results. We studied therapy adherence over a period of three years. Short time use defined as 90 days or less was also excluded. In the Netherlands dispensing medication for chronic use is restricted to 90 days or less. This rule was designed to reduce costs by preventing discarding large amounts of unused drugs. Patients that do not persist with new inhalation medications, a form of failing therapy adherence, were thereby excluded.

In our data a patient using one inhalation medication is registered as two separate episodes, when the inhalation medication is used in two different devices. Although a similar adherence could possibly be expected when patients use the same medication in a different inhaler, our data showed that this is often not the case (data not shown). Therefore, we decided not to combine the episodes to an overall adherence but to use the separate episodes. Next to the above mentioned limitations we were not able to investigate the effects of improving adherence by changing inhalation medication due to the observational character of the study.

Despite these limitations, major advantages of this study compared with previous published studies are the possibility to link adherence to lung function. While other studies with pharmacy data alone lack the possibility to discriminate between asthma and COPD, our patients were all diagnosed with COPD. Many adherence studies use data of one-year follow-up. Medication use in COPD is long-term. We followed our patients for three years, thus giving an estimate on long-term use.

Conclusion

Therapy adherence to inhalation medication for the treatment of COPD is related to the medication prescribed. This study also confirms that dosing a medication one time daily improves adherence and adherence to inhalation medication is related to lung function. Therefore, lung function should be taken into account when therapy adherence is assessed. The assumption that combining two inhalation medications in one device can improve therapy adherence cannot be confirmed. Further research is needed to investigate the possibilities of improving adherence by changing inhalation medication.

Declaration of interest

The authors declare that there are no conflicts of interest. This study was partly supported by an unrestricted research grant of Glaxo Smith Kline.

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The influence of type of inhalation device on adherence of COPD patients to inhaled medication

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Abstract

Objective: To study the influence of type of inhalation device on medication adherence of COPD patients.

Methods: Adherence to inhalation medication of 795 patients was recorded from pharmacy records over 3 years. It was expressed as percentage and deemed good at ≥ 75 – $\leq 125\%$, sub-optimal ≥ 50 – $< 75\%$, and poor $< 50\%$ (underuse) or $> 125\%$ (overuse). Since most patients used more than one device, 1379 medication periods were analyzed.

Results: Patients using a Metered Dose Inhaler (MDI) or Diskus had a 2.3-fold and 2.2-fold increased risk, respectively, of suboptimal adherence versus good adherence, compared to Handihaler and a 2.1-fold and 2.2-fold increased risk, respectively, of underuse versus good adherence compared to Handihaler. Turbuhaler, MDI, Respimat had a 7.9-fold, 3.5-fold, and 2.0-fold increased risk, of overuse versus good adherence compared to Handihaler.

Conclusions: In COPD, adherence to inhalation medication is device-related. Overuse was most pronounced for devices without a dose counter, devices with the ability to load a dosage without actual inhalation, or devices lacking feedback of correct inhalation. The design of the device seems to be related to underuse and overuse of inhaled medication. Future research might investigate whether prescribing a different device with similar medication improves therapy adherence.

Introduction

In the treatment of Chronic Obstructive Pulmonary Disease (COPD), therapy adherence is an important issue. Therapy adherence to medication in COPD has an extra dimension compared to, for example, the treatment of cardiovascular disease, because most medications are inhaled. In order to inhale medication a patient has to use an inhalation device properly for an effective drug delivery to the lung. The cognitive function, dexterity and inhalation strength of a patient have to be adequate to be able to use such an inhalation device successfully. (1) Poor drug efficacy can be caused by a decreased medication delivery associated with incorrect inhaler technique for the device being used.

The design of the inhaler plays a significant role in the effectiveness of inhaler therapy, with up to 94% of the patients using their inhaler ineffectively. (2) For example the effectiveness of a powdered drug to inhale mainly depends on the inspiratory flow rate generated by the patient and on the intrinsic resistance of the DPI device. These two forces affect the dose utilization, both the powder disaggregation and dispersion, its penetration into the airways, and finally the efficacy of the treatment. (3)

The effectiveness of inhaled medications is also strongly influenced by the patient's medication adherence, which has been shown to be associated with reduced risk of death and hospitalizations due to exacerbations in COPD. (4,5)

Medication adherence can be influenced by patient- and medication-related factors. Patient-related factors are disease and treatment acceptance, knowledge about and faith in the treatment, effective patient-clinician relationships, and routinization of drug therapy. (6-8)

Medication-related factors known to have a negative influence on adherence are frequent daily use and multiple dosing. (9) COPD patients often have a medication regimen that requires multiple daily dosages over a prolonged period of time and they often use various medications simultaneously. All these factors together can make therapy adherence for COPD patients a difficult task.

In COPD and asthma the level of patient satisfaction with their inhaler device is observed to have a positive influence on the treatment goals by improved compliance. (10,11) In a study of Chrystyn et al. it was shown that the principal inhaler attributes influencing overall patient satisfaction were whether it was built to last and would not break easily, whether it was easy to hold and carry, and whether the instructions were simple and easy to follow. (11)

Feedback to indicate correct inhalation is a feature patients also find important. (12) Rau et al. stated, based on a summary of studies, a top three of features an ideal inhaler should possess including: ease of use during an exacerbation, knowing how many dosages are left, and overall ease of use. (13)

We therefore conducted a study to investigate the relationship between therapy adherence and the devices in which inhalation medication for COPD is administered.

Methods

Setting and design

This study is part of the Cohort on Mortality and Inflammation in COPD (COMIC), a single centre prospective cohort study. From December 2005 till April 2010, 795 patients were included with a follow-up period of three years. Patients were recruited at the outpatient clinic of the Department of Pulmonology, Medisch Spectrum Twente Hospital, Enschede, located in the Eastern part of The Netherlands, serving a catchment population of approximately 264,000 persons. The study was approved by the hospital's Medical Ethical Committee. All patients provided written informed consent. (14,15)

To be eligible for the study patients had to have a clinical diagnosis of COPD, as defined by the GOLD criteria. Patients were consecutively enrolled when hospitalized for an acute exacerbation of COPD or when visiting the outpatient clinic in stable state. All surviving patients completed the three year follow-up period and were treated according to standard care. Demographic data was collected from medical records. Lung function and smoking status were both determined at baseline. Lung function was measured by spirometry, performed according to standardised guidelines. (16) Smoking status was determined by the Vlagtwedde questionnaire. (17) The primary outcome, therapy adherence, was recorded from patients' pharmacy records. The patients were a priori not aware that their medication records were going to be used for the monitoring of therapy adherence. Theoretical duration of 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 medication collection during follow up (36 months) plus the days belonging to the last refill. The total follow-up could therefore be prolonged with the days of the last refill. (18) This was expressed as a percentage. Adherence was deemed good if it was ≥ 75 - $\leq 125\%$, sub-optimal between ≥ 50 - $< 75\%$, and poor below

50% (underuse) or above 125% (overuse). In literature there is no consensus on acceptable therapy adherence, with definitions varying from >70% to >80% in clinical research settings. We decided to set the limit for optimal adherence at $\geq 75\%$, which is between these two definitions. Next to this, we decided to choose an upper cut-off point as well for good adherence (at 125%), in order to exclude overuse from this category. (4, 19-21) We excluded medication when it was prescribed once only or was used for less than 90 days. Seven devices were considered in the study; Metered Dose Inhaler (MDI), Autohaler, Respimat and the dry powder inhalers Handihaler, Diskus, Cyclohaler and Turbuhaler. The devices used in this study were prescribed by the physicians. With the current data we have no information on whether each physician has taken the preference of the patient into account.

Therapy adherence with short-acting beta 2- and muscarinic agonists, and formoterol were not analysed because these medications (unlike salmeterol) can be used on demand as well and this confounds the calculation of adherence. (22) Because most patients in the COMIC study were either on combined ICS preparations or on single ICS preparations combined with either long-acting anticholinergic or long acting beta2-agonists, as is recommended for the treatment of COPD, many patients used more than one type of inhaled medication. Since use of one medication in different devices (e.g. MDI and Diskus) was scored separately during the observation period, data on 1379 periods of medication use are presented.

Statistical analyses

Baseline characteristics are reported as mean with SD for continuous variables, or as numbers with corresponding percentages for nominal variables. Not normally distributed continuous variables are reported as median with corresponding interquartile range (IQR).

We investigated the relationship between type of device and therapy adherence with Nominal Regression analyses.

Furthermore, potential confounders (age, sex, smoking status, lung function) were first tested for their association with therapy adherence. Variables associated with adherence were subsequently tested for their association with type of device. For categorical variables this association was tested by means of Chi-square tests or Fisher exact tests, as appropriate. For continuous variables this association was tested with an ANOVA or Kruskal Wallis test as appropriate. Variables that were both associated with therapy adherence and type of device were all entered in the multivariate Nominal Regression analyses. Subsequently, potentially

confounding variables with the highest p-value were eliminated from the model one by one until the fit of the model decreased significantly, based on the -2 Log Likelihood.

Since not all inhaled drug substances COPD patients use, are available in every device, adherence to the type of the device is in some instances identical to adherence with the inhalation medication delivered by this device. It is therefore not possible to study adherence with an inhalation device without the interference of the inhalation medication delivered by the device. Also, because of the strong association between device and medication a statistical correction for the inhaled medication is not feasible because of the phenomenon of multicollinearity.

To compare the four categories of therapy adherence between inhalation devices we used multivariate Nominal Regression analyses. Good adherence was set as reference. Because the highest percentage of patients with good adherence was observed for Handihaler, this device was set as reference in Table 4. We excluded Autohaler and Cyclohaler from these analyses because numbers were too small to obtain reliable estimates. Furthermore, of the potential confounders listed in Table 1, FEV₁ in litres, FEV₁ % predicted and FEV₁/VC ratio were all associated with type of device as well as with therapy adherence and were therefore potential confounders that should be entered to the multivariate Nominal Regression analyses. Due to multicollinearity between these three lung function parameters, only the variable with the best model fit was entered to multivariate Nominal Regression analyses, which was FEV₁ in litres.

All statistical calculations were carried out with SPSS version 21.0. P-values <0.05 were considered significant.

Results

The study population included 795 patients (Table 1). Patients, mean age 68 years, were predominantly male (61.1%). Almost three-quarter of the patients were ex-smokers.

Table 1. Baseline characteristics.

	N= 795 Overall	Good ≥75- ≤125%	Sub-optimal ≤50- ≤75%	Underuse <50%	Overuse >125%	P
Age in years (Mean (SD))	67.8 (9.9)	66.5 (9.6)	66.5 (10.3)	64.3 (11.0)	67.2 (9.7)	0.100
Sex (Number of men (%))	486 (61.1)	560 (61.6)	112 (53.6)	62 (53.9)	87 (59.6)	0.102
Smoking status (Number (%))						
Current smoker	212 (26.7)	246 (27.1)	49 (23.4)	45 (39.1)	56 (38.4)	0.001
Ex-smoker	583 (73.3)	663 (72.9)	160 (76.6)	70 (60.9)	90 (61.6)	
Lung function (Mean (SD))						
FEV ₁ in Litres	1.4 (0.6)	1.4 (0.6)	1.4 (0.5)	1.5 (0.6)	1.3 (0.5)	0.001
FEV ₁ % predicted	52.1 (19.4)	51.0 (17.8)	52.4 (18.4)	55.3 (20.1)	47.3 (16.9)	0.004
FEV ₁ /VC ratio	44.5 (13.6)	42.3 (12.6)	45.5 (13.3)	48.0 (15.2)	42.3 (12.7)	0.000

The devices most used were Handihaler (used for tiotropium) and MDI (used for salmeterol/fluticasone (78.2%), fluticasone (6.2%), ciclesonide (5.4%), salmeterol (4.2%), beclomethasone dipropionate extra fine (2.7%), budesonide (2.0%), and beclomethasone (1.2%)). (Table 2)

We investigated therapy adherence for the different types of inhalers. The results are listed in Table 3. The percentages of patients with good therapy adherence within the studied devices ranged from 38.5 (Cyclohaler) - 77.6% (Handihaler). Suboptimal adherence ranged from 6.7 (Autohaler) - 38.5% (Cyclohaler), while underuse ranged from 5.5 (Respimat) - 26.7% (Autohaler); and overuse from 4.8 (Handihaler) - 26.8% (Turbuhaler). The Chi-square test showed a significant difference in therapy adherence between the studied devices ($p < 0.001$).

Table 2. Prescribed inhalation medication per device.

Device	Medication	Number (%)
MDI	Fluticasone	25 (6.2)
	Salmeterol/Fluticasone	316 (78.2)
	Salmeterol	17 (4.2)
	Budesonide	8 (2.0)
	Beclomethasone	5 (1.2)
	Beclomethasone dipropionate extra fine	11 (2.7)
	Ciclesonide	22 (5.4)
Diskus	Fluticasone	48 (18.9)
	Salmeterol/Fluticasone	184 (72.4)
	Salmeterol	22 (8.7)
Respimat	Tiotropium	128 (100)
Handihaler	Tiotropium	438 (100)
Turbuhaler	Budesonide	36 (28.3)
	Formoterol/Budesonide	91 (71.7)
Cyclohaler	Beclomethasone	13 (100)
Autohaler	Beclomethasone dipropionate extra fine	15 (100)

Abbreviations: *MDI, Metered Dose Inhaler

Table 3. Number (%) of patients in the subgroups of therapy adherence per device.

Device	Good $\geq 75\%$ $\leq 125\%$	Sub-optimal $\geq 50\%$ - $<75\%$	Underuse $<50\%$	Overuse $>125\%$	Months used median (IQR)
Handihaler (n=438)	340 (77.6)	48 (11.0)	29 (6.6)	21 (4.8)	30.8 (17.5-36.1)
Respimat (n=128)	89 (69.0)	20 (15.6)	7 (5.5)	12 (9.4)	20.1 (9.9-29.7)
Diskus (n=254)	159 (62.6)	49 (19.3)	30 (11.8)	16 (6.3)	29.2 (14.2-35.4)
Turbuhaler (n=127)	74 (58.3)	12 (9.4)	7 (5.5)	34 (26.8)	30.6 (17.9-36.5)
MDI (n=404)*	235 (58.2)	74 (18.3)	38 (9.4)	57 (14.1)	25.1 (11.9-34.9)
Autohaler (n=15)	7 (46.7)	1 (6.7)	4 (26.7)	3 (20.0)	15.3 (5.5-31.8)
Cyclohaler (n=13)	5 (38.5)	5 (38.5)	-	3 (23.1)	30.2 (11.0-37.6)

Abbreviations: *MDI, Metered Dose Inhaler

For suboptimal therapy adherence the devices MDI and Diskus differed significantly from the Handihaler compared to optimal adherence. Patients using an MDI or a Diskus had a 2.3 and a 2.2 times increased risk of suboptimal use versus optimal use compared to Handihaler.

Patients using an MDI had a 1.9 times increased risk of suboptimal use versus optimal use compared to Turbuhaler.

Also for underuse MDI and Diskus differed significantly from the Handihaler. With use of MDI or Diskus the risk of underuse was 2.1 and 2.2 times higher compared to the Handihaler and optimal use.

For overuse MDI and Turbuhaler differed significantly from the Handihaler. MDI showed a 3.5 times higher risk while the Turbuhaler showed a 7.9 times higher risk of overuse compared to the Handihaler with optimal therapy adherence.

Next to this MDI differed significantly from Diskus with a 2.1 times increased risk of overuse compared to Diskus with optimal adherence. Turbuhaler showed a 3.9 times increased risk of overuse compared to Respimat and a 2.2 times increased risk of overuse compared to MDI and a 4.7 times increased risk of overuse compared to Diskus with optimal use.

FEV₁ at baseline was related to poor adherence, both underuse and overuse. Underuse was associated with a higher FEV₁ at baseline compared to good adherence, while overuse was associated with a lower FEV₁ at baseline compared to good adherence.

Table 4: Nominal regression analyses of device vs. therapy adherence.

		Odds Ratio	95% CI
Suboptimal (n=203)	FEV ₁ (L) baseline	1.1	0.8 - 1.4
	MDI	2.3	1.5 - 3.4
	Diskus	2.2	1.4 - 3.4
	Respimat	1.6	0.9 - 2.9
	Turbuhaler	1.2	0.6 - 2.3
Underuse (n=111)	FEV ₁ (L) baseline	1.6	1.1 - 2.2
	MDI	2.1	1.2 - 3.5
	Diskus	2.2	1.2 - 3.7
	Respimat	1.0	0.4 - 2.4
	Turbuhaler	1.1	0.5 - 2.6
Overuse (n=139)	FEV ₁ (L) baseline	0.6	0.4 - 0.9
	MDI	3.5	2.1 - 6.0
	Diskus	1.7	0.9 - 3.3
	Respimat	2.0	0.96 - 4.3
	Turbuhaler	7.9	4.3 - 14.4

Notes: Optimal therapy adherence and Handihaler set as reference, corrected for FEV₁ in Litres (L) at baseline;

Discussion

Therapy adherence to inhalation medication for the treatment of COPD is related to the device in which the medication is administered. The highest percentage of optimal therapy adherence was found for the Handihaler (78%). Overuse was found most often for the MDI (14%) and Turbuhaler (27%).

Overuse can be due to both spillage and overdosing. With the Turbuhaler spillage could be caused by the design of the Turbuhaler, since it enables patients to load the device several times by rotating the grip, without actually inhaling. The ability of a device to indicate the release of a dosage without actually inhaling therefore increases the risk of overuse as registered in pharmacy records. Next to this, when a device does not provide feedback on actually inhaling, a patient can feel the need to load a dose and/or inhale again to be sure about taking a dose, which results in overdosing. For example the medication in the Turbuhaler has no taste. This can make a patient insecure about whether they have actually taken the medication. The majority of the Turbuhaler records in our cohort contain budesonide/formoterol (72%). In asthma maintenance therapy this combination can be used on demand

(SMART regimen) when a patient experiences an increase in symptoms due to the short onset of symptom relieve of formoterol. (23) It is possible that this therapy advice is used off-label for the treatment of COPD as well, and because of the high prevalence of symptoms in patients with COPD, this might lead to overuse.

For MDI's overuse might in part be caused by for example "test-puffs" to see whether the device still contains medication. Most MDI's lack a registration of dosages left in the device. Maybe patients discard their MDI too early because they do not know how many dosages are left. This is in line with LaForce et al. who showed that a dose counter relieves anxiety about running out of medication. (24) In the COMIC study population most MDI prescriptions were for the salmeterol/fluticasone combination (78%). This MDI has a counter to register the dosages left in the device. The Respimat has a marker when a patient starts with the last ten dosages. The Turbuhaler has a marker that becomes red when there are approximately 20 dosages left, the least precise indicator of these three inhalers. Despite the counters mentioned above we see overuse happening.

The fact that MDI's are difficult to handle and require critical hand - lung coordination, when not combined with a spacer device, can be a cause of overuse. Many studies have shown that many patients with MDI's make critical inhalation errors that result in reduced delivery of the medication into the lungs. When this is experienced as reduced efficacy, patients might use their inhaler again. The use of a spacer improves drug availability. (25) It is possible that patients showed overuse because they did not use a spacer and therefore experienced reduced efficacy. Although it is common practice in the studied population to prescribe an MDI combined with a spacer including patient instruction, the use of a spacer combined with an MDI could not be derived from our database. The dry powder inhalers, including Diskus, Handihaler, and Turbuhaler, are flow-dependent devices and require minimal coordination. (26) They are also associated with lower rates of incorrect handling, when compared with the MDI device (without spacer). (24)

Diskus and MDI have a higher risk of underuse compared to Handihaler. With an MDI a patient can still actuate the inhaler with little or no drug beyond the maximum number of dosages left in the canister. The pharmacy data show underuse while a patient may believe he is still using his medication properly. This is unlikely to happen with the Diskus once it is empty due to the dose counter. In contrast to the MDI, the Respimat cannot release a mist after the last dosage is delivered,

which prevents patients from using an empty device.

Literature shows that there are aspects in the design of an inhaler that can influence a patient's satisfaction with an inhaler and therefore might influence therapy adherence. A patient's satisfaction with an inhaler is likely to be based on the efficacy of the inhaled medication as well. (10,11)

Previous analyses of the COMIC therapy adherence data showed that therapy adherence to inhalation medication for the treatment of COPD is related to the medication prescribed. The medication dosed once daily, tiotropium and ciclesonide showed the highest adherence. The good results for Handihaler might therefore be influenced by the medication tiotropium. Therapy adherence seems to be influenced by dosage scheme and dosing once daily seems to improve therapy adherence. (27) Also, corticosteroids are not bronchodilators and do not give immediate relief of breathlessness, whereas tiotropium does relieve dyspnea, albeit with a relatively slow onset. (28) The medication inhaled with a Diskus is dosed two times per day and multiple dosing is known to decrease therapy adherence. Salmeterol, inhaled with Diskus, also has a slow onset of effect. To improve adherence numerous combinations of drugs in one inhaler were introduced. But the concept of improving adherence with the combination of drugs in one inhaler could not be supported with the COMIC data. (14)

Unfortunately, not all inhaled drug substances COPD patients use are commercially available in every device so it is not possible to study adherence without the interference of the inhalation medication delivered by the device. However, as can be seen in Table 2, there are several medications that are delivered in multiple devices in which the design of a device can explain aspects of therapy adherence.

Next to the type of device, also FEV_1 at baseline was related to poor adherence, both underuse and overuse. Underuse was associated with a higher FEV_1 at baseline compared to good adherence, while overuse was associated with a lower FEV_1 at baseline compared to good adherence. It is possible that patients with higher FEV_1 show lower adherence levels because they feel less need to use their medication. The opposite can be an explanation for overuse in patients with a lower FEV_1 .

There are some potential limitations in our study. Pharmacy records show maximum levels of medication use in patients. There is no assurance the patient is actually inhaling his medication successfully. Also changes in dosage regimen advised by the prescriber without giving a new prescription are not reflected in the pharmacy data. It is plausible

that the actual inhaled drug volumes are lower than the volumes dispensed through the pharmacy. (29,30)

Despite these limitations, this study has major advantages. The therapy adherence data reflect real life use because of the observational design of the study. Computerized pharmacy data made it feasible to monitor medication adherence by tracking requests for refills. Computerized drug-dispensing histories from Dutch pharmacies are virtually complete and include data concerning the dispensed drug, the prescriber, the dispensing date, the amount dispensed, the prescribed dose regimens, and the estimated duration of use. In the Netherlands, there is a strong pharmacy-patient liaison for reimbursement of prescription drugs, a high degree of computerization, the use of standardized classification and coding systems, and a strong commitment of pharmacists to surveillance of medication.

Next to this, the possibility to link adherence to lung function, the reliable diagnosis of COPD (which studies with pharmacy data alone often lack) and the three year follow up of medication use in COPD is of great benefit.

Conclusion

A striking result was the overuse with MDI and Turbuhaler, which are devices that either have the ability to load a dosage without actual inhalation, don't have a dose counter, or do not provide feedback of an inhalation. Further research is needed to investigate whether improving the design of an inhalation device (for example devices without the ability to load a device without actually inhaling, and devices providing a feedback on correct inhalation) leads to improved adherence.

Declaration of interest

The authors declare that there are no conflicts of interest.

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Quality of Life and Adherence to Inhaled Corticosteroids and Tiotropium in COPD are Related

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Abstract

Background: Poor adherence to inhaled medications in COPD patients seems to be associated with an increased risk of death and hospitalisation. Knowing determinants of non-adherence 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 – $\leq 125\%$, sub-optimal ≥ 50 – $< 75\%$, and poor $< 50\%$ (underuse) or $> 125\%$ (overuse). Health-related quality of life was measured with the Clinical COPD Questionnaire (CCQ) and the EuroQol-5D-questionnaire.

Results: Patients with a higher forced expiratory volume in 1 second (FEV₁)/vital capacity (VC) (OR=1.03) and ≥ 1 hospitalisations 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 FEV₁/VC (OR=1.05). Predictors for the risk of overuse were a lower FEV₁ (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 FEV₁/VC (OR=1.03) and the inability to perform usual activities as asked by the EuroQol-5D questionnaire (OR=3.09). A higher FEV₁/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 non-adherent patient cannot yet be outlined. Overusers of ICS and tiotropium experience more anxiety.

Introduction

COPD is a major global health problem, currently being the fifth leading cause of global 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 quality of life. (2) Pharmacotherapy consists of inhaled medications, including short- and long-acting bronchodilators, such as tiotropium bromide, to relieve dyspnea symptoms, and inhaled 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 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 medication adherence. Adherence is essential and seems to be associated with reduced mortality and hospitalization. (6-8) In common with other chronic diseases, therapy adherence 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 to improve 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

Setting and design

This study is part of the Cohort on Mortality and Inflammation in COPD (COMIC) study. It concerns a single centre, prospective, cohort study. From December 2005 till April 2010, 795 patients were included with a follow-up period of three 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 ex-smoker; (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; (7) and the ability to speak Dutch. Patients were consecutively enrolled when hospitalized for an acute exacerbation of COPD, or when visiting the outpatient clinic in 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 which 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 were recorded from hospital records and dichotomised 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 Euro-QoL-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 non-disease-specific questionnaire, consisting of 5 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 patients' 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 optimal if it was between ≥ 75 and $\leq 125\%$, suboptimal between 50 and 75% and poor $< 50\%$ (underuse) and $> 125\%$ (overuse). We excluded medication when it was prescribed only once or was used for 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 as medians with corresponding interquartile ranges (IQR). 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 patients used tiotropium. A total of 385 patients used both ICS and tiotropium.

ICS

Smoking status, FEV₁ in litres and the FEV₁/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 FEV₁ in litres, while patients with underuse had the highest FEV₁/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 EuroQol-5D questions (Table 3).

Multinomial regression analysis with ICS

The multivariate nominal regression model (with optimal adherence set as reference category, see Table 4) showed that an increase of 1L in FEV₁ was associated with a two-fold lower risk of overuse (odds ratio [OR] =0.49; 95% confidence interval [CI] 0.25-95) compared to optimal use. An increase in 1% of the FEV₁/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 one year prior to inclusion 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 FEV₁/VC ratio was univariately associated with adherence to tiotropium, with underusers having a higher FEV₁/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 EQI-5D question concerning mobility and usual activities used tiotropium more often suboptimally and showed more underuse and overuse (Table 7). Anxiety and depression were associated with suboptimal, underuse and overuse.

Multinomial regression analysis tiotropium

The multivariate nominal regression model (Table 8) showed that an increase of 1% in FEV₁/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 was associated with almost a 1.5-fold increased risk 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 inhaled 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, this is 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 both symptoms and future exacerbations. (4,5) Whereas Cecere et al. and Mehuys et al. 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. (23,24)

Multivariately, the strongest predictors for suboptimal use of ICS were an increase in FEV₁/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 FEV₁/VC ratio. Strong predictors for overuse of ICS were a lower absolute FEV₁, 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 towards 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 decide to 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 FEV₁/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 non-adherence. 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 significant 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 non-adherence. (22) Turan et al. found in 2014 that the presence of depressive symptoms led to decreased adherence in patients with COPD. (28) 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 the adherence, so it is unknown whether the mentioned non-adherence is related to overuse.

Worth mentioning is that we specifically looked at anxiety concerning respiratory symptoms, whereas Snaith et al. looked at anxiety in general according to the Hospital Anxiety and Depression Scale (HADS) questionnaire. (29) Detecting anxiety in COPD is important, since anxiety is a condition that can be effectively treated with pharmacological and non-pharmacological 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. that also found these comorbidities to be poor predictors for adherence. (30,31) Khmour et al. 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. (31)

Our study has several strengths. We defined subgroups of non-adherence, so we could see what type of non-adherence is related to our variables. Just as Krigsman et al. did, we decided to choose an upper cut-off point as well, in order to study overuse. (32) This subdivision shows that non-adherent 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 one-year follow-up. Since medication use in COPD is long-term, we followed our patients for three 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, couldn't be assessed in this study.

Future studies can put more emphasis on these variables to explore them as predictors for non-adherence, 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 non-adherence 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 FEV₁/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 non-adherence in different types of medication classes. Also, further research is required into the role of anxiety in adherence to inhalation medication.

Declaration of interest

The authors declare that there are no conflicts of interest.

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Appendix 1: Tables and figures

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

	Overall N = 635	Good ≥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 men(%))	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
Ex-smoker	459 (72.3)	270 (74.8)	93 (77.5)	38 (62.3)	58 (62.4)	
Packyears	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 litres (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 (%)	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 (%)	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(%)**						0.498
GOLD I	38 (6.1)	23 (6.4)	6 (5.1)	4 (6.8)	5 (5.4)	
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(%)***						0.132
<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)	
≥30.0	168 (26.9)	86 (24.4)	35 (29.4)	21 (34.4)	26 (28.0)	
Exacerbations in the past year (N(%))						0.055
< 2	407 (64.2)	235 (65.3)	72 (60.0)	47 (77.0)	53 (57.0)	
≥ 2	227 (35.8)	125 (34.7)	48 (40.0)	14 (23.0)	40 (43.0)	
≥ 1 Hospital ad- mission (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

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 ¹
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 ^asuboptimal; ^bunderuse; ^cno difference after correction.

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

Appendix 1: Tables and figures

Notes: Holm-Bonferroni correction, there was a significant difference between optimal ^asuboptimal; ^bunderuse; ^cbetween suboptimal and overuse. *One missing lungfunction.

** Seven missing COPD stages. ***Ten missing stages.

Abbreviations: ICS, inhaled corticosteroids; SD; standard deviation; FEV1 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 3. EuroQol-5D scores (range 1-3) per therapy adherence category for ICS users

EuroQol-5D ICS N (%)	Optimal N = 337	Suboptimal N = 112	Underuse N = 53	Overuse N = 83	p-value
Mobility					
1. I have no problems in walking about	114 (61.6)	32 (17.3)	16 (8.6)	23 (12.4)	0.383
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					
1. I have no problems with self-care	231 (61.3)	67 (17.8)	31 (8.2)	48 (12.7)	0.138
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					
1. I have no problems performing usual activities	144 (62.1)	39 (16.8)	17 (7.3)	32 (13.8)	0.375
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					
1. I have no pain or discomfort	159 (57.6)	51 (18.5)	22 (8.0)	44 (15.9)	0.893
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					
1. I am not anxious or depressed	252 (59.7)	79 (18.7)	33 (7.8)	58 (13.7)	0.438
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. Multinomial regression analysis of associated variables per therapy adherence category for ICS users.

	Variable	OR	95% CI	p-value
Suboptimal (≥ 50 - <75%) N= 112	FEV1 in litres	0.90	0.53-1.50	0.660
	FEV1/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
	Ex-smoker	1.00	.	.
	Hospital admission	2.67	1.48-4.80	0.001
	No hospital admission	1.00	.	.
Underuse (<50%) N= 53	FEV1 in litres	0.62	0.31-1.26	0.186
	FEV1/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
	Ex-smoker	1.00	.	.
	Hospital admission	1.83	0.80-4.20	0.153
	No hospital admission	1.00	.	.
Overuse (>125%) N= 83	FEV1 in litres	0.49	0.25-0.95	0.034
	FEV1/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
	Ex smoker	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; FEV₁, forced expiratory volume in 1 second; CCQ, Clinical COPD Questionnaire; VC, vital capacity

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

	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
Ex-smoker	308 (70.3)	241 (70.9)	38 (79.2)	16 (55.2)	13 (61.9)	
Packyears	39.3 (22.8)	37.8 (21.6)	44.5 (26.5)	42.4 (27.3)	45.2 (23.5)	0.138
Lung function						
FEV1 in litres (mean(sd))	1.4 (0.6)	1.4 (0.6)	1.46 (0.5)	1.64 (0.7)	1.31 (0.6)	0.177
FEV1 predicted (%)	52.1 (17.9)	51.7 (17.6)	53.2 (16.7)	59.1 (21.6)	47.4 (17.9)	0.102
FEV1/VC ratio (%)	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 (N(%))**						
<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 ad- mission (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)	0.041b

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 ^b

Notes: *Mean (SD). After Holm-Bonferroni correction, there was a significant difference between optimal and ^asuboptimal; ^bunderuse; ^coveruse; ^dno difference after correction.

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

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

Notes: After Holm-Bonferroni correction, there was a significant difference between optimal and underuse; bno difference after correction. * Four missing COPD stages. **Seven missing BMIs.

Abbreviations: SD, standard deviation; FEV₁, 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 7. EuroQol-5D scores (range 1-3) per therapy adherence category for tiotropium users.

EuroQol-5D Spiriva N (%)	Optimal N = 323	Suboptimal N = 45	Underuse N = 26	Overuse N = 19	p- value
Mobility					
1. I have no problems in walking about	126 (85.1)	9 (6.1)	6 (4.1)	7 (4.7)	0.042
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					
1. I have no problems with self-care	239 (81.3)	30 (10.2)	15 (5.1)	10 (3.4)	0.086
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					
1. I have no problems performing usual activities	154 (85.1)	13 (7.2)	7 (3.9)	7 (3.9)	0.002
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					
1. I have no pain or discomfort	153 (78.9)	21 (10.8)	10 (5.2)	10 (5.2)	0.165
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					
1. I am not anxious or depressed	255 (82.5)	29 (9.4)	14 (4.5)	11 (3.6)	0.003
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.

Table 8. Multinomial 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 indicatie more symptoms. * P-value was 0.049 when building the multivariate model.

Abbreviations: OR, odds ratio; CI, confidence interval; FEV₁, forced expiratory volume in 1 second; VC, vital capacity; CCQ, Clinical COPD Questionnaire.

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Patients with underuse or overuse of inhaled corticosteroids have different perceptions and beliefs regarding COPD and inhaled medication

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Abstract

Background: Therapy adherence in COPD is crucial for treating symptoms, preventing exacerbations and related complications. To achieve optimal adherence, it is important to recognize and understand a non-adherent patient.

Objective: To study perceptions and beliefs regarding COPD and inhaled medication in COPD patients with poor adherence.

Methods: Twenty patients (10 underuse, 10 overuse) were interviewed in semi-structured in-depth interviews, about mental and physical health, illness perceptions, knowledge regarding COPD, and experience with, knowledge of, and acceptance of COPD medication and inhalation devices.

Results: A majority of patients did not fully accept their disease, showed little disease knowledge, and many revealed signs of depressive mood and severe fatigue. Overusers reported more grief about decreased participation in daily life and were more frustrated in general. Underusers claimed using less medication because they felt well, did not want to use too much medication and used their inhalation devices too long. Overusers reported medication “dependency”, they tended to catastrophize when being without medication and discarded inhalation devices too early because they feared running out of medication.

Conclusions: Overusers and underusers showed a different pattern in perceptions and beliefs regarding inhaled medication and COPD.

Practical Implications: It is important to understand the reasons for under- and overuse. Is it related to practical issues regarding knowledge or is it influenced by beliefs and/or anxiety concerning COPD or medication? These issues need to be addressed for improving adherence.

Introduction

In the treatment of COPD, therapy adherence is crucial not only for dealing with symptoms, but also for preventing exacerbations and related complications. Adherence to inhaled corticosteroids (ICS) has, for example, been shown to be associated with reduced risk of death and hospitalization. (1) In order to achieve optimal adherence in COPD patients, it is important to recognize and understand a non-adherent patient. This understanding can be used to guide patients and carers with respect to reaching an agreement with regard to therapy adherence. Non-adherence can present itself in different forms. After collecting (2) medication the patient can underuse, overuse or show improper use of the medication. (3,4) Many adherence studies focus on non-adherence registered as underuse. However, overuse is an important form of non-adherence as well and can be related to different factors.

Therapy adherence in COPD patients is a multifactorial problem. One has to take into account medication, regimen, and patient factors. Adherence to inhaled medication in COPD is related to the type of inhaled medication and to the device with which the medication is inhaled. (5,6) Differences in adherence could be explained, at least partially, by feedback of inhalation, frequency of dosage and the design of the device. (6) Next to these medication factors, known patient factors that affect adherence are higher age, co morbid conditions, polypharmacy, cognitive decline, physical problems as hand-eye coordination and problems with reading small print instructions. (3) In the COMIC cohort study we already showed that a predictor for underuse of ICS was a higher FEV₁, while predictors for overuse were a lower FEV₁, more anxiety for dyspnea as scored with the CCQ, and current smoking (7), so it seems that under- and overusers have different characteristics.

To get more insight in the influence of patient factors on adherence, Leventhal proposed a Self-Regulatory Model. (8) This model provides a framework for understanding adherence and non-adherence to treatment recommendations (9) and is based on patient's beliefs of their illness in relation to treatment adherence. (8) The model asserts that illness beliefs can be divided into five dimensions: illness identity, timeline, cause, consequences and control-cure. (10) In addition to illness beliefs, Horne et al. showed for four chronic illness groups (asthma, renal, cardiac, and oncology) that beliefs about medication were related to reported adherence. Higher medication necessity scores correlated with higher adherence while higher concerns about the risk of dependence or long-term effects correlated with lower adherence. (9)

Therefore, Horne et al. designed an extended self-regulatory model of treatment adherence, which incorporates beliefs about treatment as well as illness perceptions. (11) This model showed that in asthma patients concerns about potential adverse effects and more negatively perceived consequences of illness were correlated with lower adherence. (11)

In COPD, disease and medication perception has not been described in much detail. Which beliefs, experiences, or fears influence the use of inhaled medication? Although asthma and COPD are both obstructive diseases, asthma shows an intermittent process whereas COPD is a continuous process. We therefore believe that COPD patients might have different beliefs and perceptions with regard to their illness and their medication.

Therefore, we aimed to investigate the beliefs and perceptions about 1.) COPD and 2.) the inhalation treatment in COPD patients' non-adherent to ICS.

Using in-depth interviews, this study focuses on which components of the patients' perceptions and beliefs (based on the extended SRM-model of Horne et al.) and practical issues specific for inhaled medication can explain non-adherence to these inhaled medications.

Instead of defining non-adherence only as underuse, we also studied factors related to overuse of ICS. Furthermore, we compared the perceptions of patients with underuse and overuse to see if these perceptions differ. Studying patients' perceptions of both under- and overusers and comparing their perceptions is innovative in this field of research.

Methods

Settings and study population

This study is part of the COMIC (Cohort on Mortality and Inflammation in COPD) study, a single centre prospective cohort study in Medisch Spectrum Twente Hospital, Enschede, the Netherlands. From December 2005 till April 2010, 795 COPD patients were included with a follow-up period of three years. The study was approved by the Medical Ethics Committee Twente (P05-49). All patients provided written informed consent, including consent for collecting all pharmacy records during the studied period. To complement the current data with in-depth interview data this new part of the study was judged not being subject to the Medical Research Involving Human Subjects Act by the Medical Ethics Committee Twente (K15 08). The study was conducted according to the principles of the Declaration of Helsinki. For more detailed information we refer to previous publications. (5,12)

Therapy adherence

Therapy adherence with ICS was recorded from patients' pharmacy records. The patients were not aware that their medication records were used for the monitoring of therapy adherence. Theoretical duration of exposure was calculated using information on dispensing date, total supply, and dosage regimen. This was expressed as a percentage and adherence was deemed good if it was ≥ 75 - ≤ 125 %, sub-optimal between ≥ 50 - < 75 %, and poor below < 50 % (underuse) or above > 125 % (overuse).

Patient selection

In order to study non-adherence ten patients who underused and ten patients who overused their ICS were selected from the COMIC cohort and were invited for an in-depth interview. All patients provided written informed consent. Because the collection of the COMIC data ended in 2014, patients last enrolled in the cohort and still alive, were consecutively first; no further selection criteria were used.

Qualitative Study design

The interviews were conducted by two intensively trained psychology students at the patients' home or at the hospital. The interviews were semi-structured using an interview guide with a structure based on the extended self-regulatory model of Horne et al., supplemented with "Treatment factors" like experience with and acceptance of COPD medication and inhalation device, next to knowledge of the used medication and inhalation device. Self-management information and demographic data concluded the interviews. (Supplement A) Each student interviewed five participants with registered underuse for ICS and five with overuse, while blinded for the adherence pattern of the patient. Patients were sampled until a sufficient number to provide topic saturation (no additional topics emerged during the final phase of analysis) was reached. (13)

Data analysis

The interviews were transcribed verbatim, data were imported in Atlas Ti version 7.5.15. Our approach was initially deductive, based on the above mentioned five dimensions of the extended Self-regulation Model used by Horne et al.: illness identity, time-line, cause, consequences and control-cure. Followed by an inductive phase to reach saturation of analysis. Separate categories regarding specific medication issues in COPD patients were identified and coded, including knowledge and experience

with medication and inhalation devices (for a schematic overview see Figure 1). During the coding process the authors were blinded for the patients' under or overuse. Initially the first author coded four interviews using a concept coding scheme, which was adjusted by discussion in the research team. The coding scheme is added as supplement B. The second author coded four interviews to establish consensus (80% or more was regarded as sufficient). Answers of patients with under- and overuse were grouped for each code to check for different patterns. The first two authors screened the grouped quotations independently for meaningful differences between the two groups. Striking differences in frequencies and/or content of answers were discussed in the research team for consensus.

The results of the interviews are described per dimension of the model (Figure 1). The numbers at the end of the quotations correspond with the patient number.

1. Illness Identity	→ Disease (description)
2. Illness Timeline	→ Complaints / disease symptoms
	→ Curability
	→ Course of the disease over time
	→ Future development/ hope
3. Illness Consequences	→ Physical → Complaints
	→ Limitations
	→ Emotional → Complaints
	→ Limitations
4. Illness Cause	
5. Illness Cure/Control	→ Coping → Psychological
	→ Practical
6. Treatment Necessity	→ Acceptance/non acceptance
	→ Memory; influence on adherence
7. Treatment Concerns	→ Side effects
	→ Dependency
8. Inhaled Medication use	→ Knowledge inhaled medication
	→ Experience with inhaled medication
	→ Daily routine
9. Inhalation Devices	→ Knowledge device
	→ Experience with device

Figure 1: Self Regulatory Model extended with specific COPD treatment topics

Results

The interviewed underusers were more often male, slightly younger and had a better lung function and felt more restricted by their dyspnea (higher mMRC-score) compared to overusers. In both groups one patient had had a severe exacerbation with hospital admission prior to inclusion (Table 1). Patients were treated according to the GOLD guidelines applicable during the time of follow up tot the COMIC cohort (GOLD 2006 and GOLD 2011)

Table 1: Baseline characteristics

	Underuse (n=10)	Overuse (n=10)
Age (Median, range)	58.8 (45-75)	62.0 (54-74)
Sex, number of males (%)	7 (70.0%)	3 (30%)
Smoking status ((N, (%))		
Current smoker	3 (30%)	3 (30%)
Ex-smoker	7 (70%)	7 (70%)
Lung function (Mean (SD))		
FEV ₁ in Litres	1.60 (0.5)	1.3 (0.4)
FEV ₁ % predicted	49.4 (9.5)	53.8 (18.8)
FEV ₁ /VC ratio	46.7 (13.0)	41.5 (11.7)
mMRC score (Mean (SD))	1.3 (0.8)	(1.2)
Patients with one severe exacerbation prior to inclusion	1 (10%)	1 (10%)
COPD stage ((N, (%))		
GOLD I	0 (0%)	1 (10%)
GOLD II	4 (40%)	4 (40%)
GOLD III	6 (60%)	4 (40%)
GOLD IV	0 (0%)	1 (10%)

Abbreviations: FEV₁, forced expiratory volume in 1 second percentage of predicted; mMRC, modified Medical Research Council. GOLD, Global Initiative for Chronic Obstructive Lung Disease.

1. Illness identity

The first dimension of the Self-regulatory Theory is illness identity, how a person views his illness. Most patients could not give a clear definition of COPD. The descriptions vary from emphysema to airway obstruction. The symptom most often described as typical for COPD was dyspnea. (supplementary Table 1) The interview data showed no distinct difference between under- and overusers.

2. Illness Timeline

The factor timeline represents how the patient believes the illness will develop over time. Most patients (14) believed COPD cannot be cured. The most optimistic expectation was that the situation stays stable as long as possible. (supplementary Table 1) There was no visible difference between under- and overusers in beliefs about curability. However, a difference between over- and underusers was a hope for improvement expressed by four patients with overuse versus none of the patients with underuse.

Most patients perceived their condition as stable. (supplementary Table 1) The few patients who experienced improvement in their symptoms had quit smoking or had made a drastic change in lifestyle (e.g. weight loss).

Worrying about the future was similarly distributed between under- and overusers. Half of the patients worried about the future (5 under-, 5 overuse).

3. Illness Consequences

This component comprises patients' beliefs about the severity of their illness and its impact on physical, social and psychological functioning. Physical problems mentioned most were dyspnea, shortness of breath, fatigue and cough. These symptoms influenced every day activities in COPD patients. Patients experienced problems with walking (long) distances and walking stairs was mentioned several times as being extremely difficult. (supplementary Table 1)

There was no difference between under- and overusers in described symptoms or problems with every day activities.

Most patients (under and overusers) experienced limitations in their daily life activities. They cannot do all the things they were used to do. Overusers were more explicit in their grief about being limited in participating in daily life. More patients with overuse reported irritable mood (2 under-, 5 overuse)

Some patients experienced anxiety or fear for dyspnea. (3 under-, 2

overuse) Half of the interviewed patients (4 under-, 6 overuse) experienced a depressive mood; other patients reported no signs of a depressive mood.

4. Illness Cause

For the cause of COPD the majority of patients mentioned smoking as a possible cause (8 underuse, 8 overuse) next to a hereditary component, or a genetic predisposition for lung disease (4 underuse, 6 overuse) and environmental factors like pollution. (supplementary Table 1) Differences between under- and overusers were not detected.

5. Illness Control/Cure

These are the patients' beliefs about the amenability to control or cure their illness. This component contains quotations on acceptance of the disease and coping with COPD by adapting behavior and using tools to improve daily life.

Only four patients described clearly that they accept their COPD (3 under-, 1 overuse). Seven patients reported accepting their disease, but only since they feel that they have no other choice. (4 under-, 3 overuse). And eight patients cannot accept their disease (3 under-, 5 overuse). Overall patients with overuse were less able to accept their disease. (supplementary Table 1)

Most patients used tools and devices to support their daily life activities; for example riding an e-bike. Next to this, patients paced activities in order to participate in daily life. (supplementary Table 1) There were no differences between under- and overusers.

Many patients had social support in their close network. Help from a partner, family or friends. For example; partners or guests smoking outside the house because they do not want to burden the patient. When needed, the pharmacy offered support by delivering medication at home. (supplementary Table 1)

6. Necessity of pharmacological treatment

This component shows the quotations of the patients concerning beliefs about the necessity of the medication and attitude of the patients towards the medication. None of the patients completely accept their inhalation treatment. Underusers claimed using less medication because they feel well or because they do not want to use too much medication. Overusers reported using medication took too much time, being forced to think of the use of medication all day long and its effect on daily life

activities. (supplementary Table 1)

Some patients experienced memory problems. Most of them claimed this did not affect their medication use. The patients that acknowledged they sometimes forgot to use their medication were mostly underusers. Overusers claimed they did not forget, because they needed the medication. (supplementary Table 1)

7. Treatment concerns

The next quotations show the possible concerns for adverse effects and the side effects patients experienced. Some patients reported that they experienced side effects and in a few cases they received substitution medication to overcome this. Mentioned side effects were hoarseness, irritation of the throat and coughing. (supplementary Table 1) Differences between under- and overusers were not detected. Underusers believed they needed the inhaled medication in order to experience less symptoms. In contrast, overusers reported medication “dependency” in the sense that they tend to catastrophize when being without medication, e.g. patients reported they do not go anywhere without their medication, they feel safe when carrying their medication and some claimed that they panic when they forgot to take the medication with them. (supplementary Table 1)

8. Inhaled medication use

This component contains the results concerning knowledge of the effect of, and experiences with the use of inhaled medication. The knowledge regarding the inhaled medication was diverse. Most patients were able to describe the expected effect of medication for example anti-inflammatory or for relieving dyspnea. However, some patients were not able to describe which effect belonged to which medication. Especially overusers reported knowledge of their medication that was wrong. For example saying medication was anti-inflammatory while it was a short acting beta-agonist, or thinking a medication was short acting (had to be taken every few hours), while it was long acting and had to be used once or twice a day. (supplementary Table 1)

A striking result was the perception of several patients (4 under- , 2 overuse) that the medication was not able to prevent exacerbations or to slow down disease progression which is the main reason for prescribing ICS in COPD. (supplementary Table 1)

Although the knowledge of the used inhaled medication is diverse and sometimes incorrect, all patients experienced positive effects of the medication.

Most patients claimed that they used their medication in a daily routine (9 under-, 8 overuse). Two patients with overuse described they did not have fixed times on which they took their medication. (supplementary Table 1)

9. Inhalation devices

The knowledge about functioning/handling of the inhalation devices was low. Especially knowledge on how to determine that a device was empty was stated incorrectly by many patients. Patients with registered overuse seemed to discard their inhaler too early just to be sure they inhaled medication. (supplementary Table 1)

With a Metered Dose Inhaler (MDI) a patient can still actuate with little or no drug beyond the maximum number of dosages left in the canister. Patients with registered underuse answered they used their MDI until it stopped, which is using the inhaler too long after it has released its last dosage.

Patients using devices with a dose counter knew when their device was empty. Next to this, there were patients that were able to use devices without a dose counter by using a note on the calendar reminding them when to discard the device. (supplementary Table 1)

In contrast with the lack of knowledge on the function of the device, patients experienced the use of the device overall as easy. Some patients had negative experiences with a specific device, for example not having enough inspiratory flow to inhale the medication. One patient claimed he did not like the spacer. And a patient with overuse claimed an MDI did not release the dosage as wanted. (supplementary Table 1)

Discussion:

Aim of this study was to investigate the beliefs and perceptions about 1.) COPD and 2.) the inhalation treatment in COPD patients, non adherent to ICS.

Our main findings with regard to beliefs and perceptions about COPD were that many patients did not accept their disease, showed little knowledge regarding their disease, and many showed signs of depression and fatigue. Overusers reported more grief about losing participation in daily life and were irritable more often. Main findings for beliefs and perceptions about the inhalation treatment were that underusers claimed using less medication because they felt well, did not want to use too much medication and used their inhalation devices too long after they were empty. Overusers reported medication "dependency" in the sense that they tend to catastrophize when being without medication

and discarded inhalation devices too early because they feared to run out of medication.

These differences and the abovementioned practical issues provide possible explanations for the registered under- and overuse.

The majority of the non-adherent patients were not able to accept their disease and the accompanied treatment. This finding is in line with Menckeberg et al. (14) who showed a relation between ICS user attitudes and adherence in asthma. Adherence rates in pharmacy records were highest for the patients accepting treatment. It is possible that the registered non-adherence could be (partially) explained by this non acceptance of both the illness and its treatment.

Next to this, George et al. showed that adherent patients had a greater understanding about their illness and the options for managing the illness. (15) The interviewed COMIC patients showed that they had little knowledge on COPD and the way in which they can manage the disease by themselves. There was a lack of knowledge on which medication does what, and when it should be used. Next to this, external factors, like genetic predisposition and pollution, were frequent mentioned as causes of their disease. Although, smoking was mentioned most often, almost none of the patients acknowledged smoking as the real cause of their COPD. Jessop et al. showed that asthma patients who believed that their asthma had been caused by external factors were less likely to adhere. (16) Perhaps this is the case in COPD patients as well.

Furthermore, also depression is a known factor in non-adherence to medication. (17) Turan et al. found that the presence of depressive symptoms led to decreased adherence in patients with COPD. (18) Half of our non-adherent patients also reported depressed mood which is in line with the review of Mikkelsen et al. that reported a prevalence of depression up to 50% in COPD patients. (19)

Zooming in on COPD patients with underuse and overuse, the findings of the previously published COMIC data showed that underusers have a better lung function, which might lead patients to use less medication, since they might experience fewer respiratory symptoms. This is in line with the finding in the interviews, in which underusers claimed using less medication because they feel well. Instead overusers showed a real medication "dependency" which fits with the worse lung function that was previously observed in overusers. This worse lung function, higher dependency and increased anxiety for dyspnea or experienced symptoms might trigger overconsumption, and could also partly be an expla-

nation for discarding devices too early. Next to this, the construction of the device and the (lack of an) empty signal might lead to a premature discard. LaForce et al. for example, showed that a dose counter relieves anxiety about running out of medication. (20)

The lack of a dose-counter could have had the opposite effect in underusers. Underusers reported lower medication dependency and used their MDI until it stopped, which is using the inhaler too long.

Limitations and strengths:

A strong point of this study is the qualitative design with in-depth interviews using the theoretical model for self-regulation and the fact that the authors were blinded for under- or overuse during the interview and coding process.

Saturation of topics was reached with the twenty conducted interviews. Using a top down analysis, followed by a bottom up approach ensured an optimal extraction of results, describing issues related to inhaled medication use in COPD patients.

A weakness in this study is the omission of data on patients with optimal use, which would represent an extra comparison group to validate the conclusions. Next to this the interview data and pharmacy data were not collected in the same research period. Although this is a weakness, given the stability of medication intake in chronic disease this limitation should not be overestimated. The interview questions did not solely focus on ICS-use as patients were asked to describe which medication they used and for what reason. The results showed that many patients had little knowledge COPD patients have on their treatment. Another limitation could be that the number of used inhalers and the complexity of the medication regimen were not specifically addressed, as they can influence adherence. Next to this the level of patient education was not measured. But because the COMIC cohort study is a single centre study we assume that with regard to the level of patient education we have included a rather homogeneous group of patients. Detection of differences between under- and overusers with qualitative designs and relatively small sample sizes is difficult, but it gives indications of underlying cognitive and behavioral causes which could inspire future research on differentiating under- and overuse for inhaled medication in COPD with experimental designs to shed light on causal mechanisms.

Conclusion

Non-adherence in COPD is a multifactorial problem encompassing behavioral issues possibly caused by perceptions and knowledge of patients. Underusers and overusers showed a different pattern in perceptions and beliefs on inhaled medication.

Practical Implications:

When under- or overuse is detected, for example in a pharmacy, it is important to investigate the underlying reasons. Is the under-or overuse related to practical issues regarding knowledge on the inhaled medication or device or is the adherence influenced by beliefs and/or anxiety concerning COPD or medication? These issues need to be addressed when we want to improve therapy adherence.

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Supplementary table 1: Quotes for the topics emerged from the in-depth interviews.

Topic	Quote (under- or overuse; patient number) (A=answer, Q=question)
Illness Identity	<p>A: Yes .. COPD .. airway constriction .. small airways or something like that. In general. And regarding inflammation .. that .. according to me then. under593.</p> <p>A: It is a pulmonary emphysema. As a result of which the lung vesicles have broken. So it absorbs less oxygen into the blood. under722</p> <p>A: Yes .. I'm always very short of breath. over355</p> <p>A: Tightness of the chest. That is a very big complaint under722</p>
Illness Timeline	<p>And we will not get better, we all know that. under313</p> <p>It will only be getting worse, not better. over767</p> <p>No, you can uuh... by using good medications .. you can keep it like this for a while, but you can't heal it. over358</p> <p>Q: And do you think it could get better than it is now?</p> <p>A: Yes, perhaps there will be better medicine at some point. over345</p> <p>Q: And do you think your COPD complaints can become less?</p> <p>A: Do hope so. over355</p> <p>A: At the moment, it is quite stable. under593.</p> <p>A: Well .. I feel very well as it is. It stays a bit stable over664</p> <p>A: Naah, it has become much less since I no longer smoke under207</p> <p>A: Because my COPD category has greatly improved because I lost a lot of weight. under501</p> <p>A: Yes. Not for the past years, but it happened that I've been so out of breath a couple of times at night.. that I think well .. what's the world coming to? under593</p> <p>A: Nah, I'm not worried about it. If I worry, it won't help anyway. over504</p> <p>A: Yes. I worry about that sometimes. over664</p>
Illness Consequences	<p>Dyspnea</p> <p>During showering it is the worst. Then I'm completely out of breath under207</p> <p>When I walk a few meters I'm already out of breath . over355</p> <p>Well, it limits me in everything, I'm always wheezy. over504</p> <p>Always short of breath. over664</p> <p>Fatigue</p> <p>I'm exhausted. That's actually the case with everything I do. under207</p> <p>Yes, it is also tiring.. yes, of course. over358</p> <p>Cough</p> <p>A: Well, sometimes when I'm very short of breath and I have to cough a lot, then those lungs start to hurt so badly. over345</p> <p>A: Yes, coughing. over504</p> <p>Problems with every day activities</p> <p>If you're somewhere ... ooh, you need to go one floor up .. then you will not just take the stairs. That doesn't work anymore. That is taboo. under362</p> <p>For example, if I walk to the toilet, I can't even do that, that's hardly possible anymore ... over355</p> <p>A: And I like gardening a lot. But if I'm busy for 5 minutes or 10 minutes then I'll sit down now and then. over625</p> <p>If I for once want to do the dishes, I may have to lie down for an hour first. A couple of hours or so, sleep first. over767</p> <p>And then my grandchildren, I can't do anything with them really. And then they ask: "Grandma, why can't you do anything?" ... That is SO hard ... over355</p> <p>It restricts so much in your daily life, in your doings, in your existence. That is difficult sometimes. over625</p>

Illness Cause

Maybe you're somewhat eeuh .. Yes, somewhat more irritable, yes. That might be possible. **under207**

Q: And have you been a bit more irritated, annoyed or angry compared to before, lately?

A: Actually yes. Because I had a clash with my son recently. **over625**

You're so limited. At first, if you got it, in the beginning it was quite heavy. That was frightening. That's really frightening. Yes. **under362**

And because of that I also carry some of that anxiety with me ... Of being alone and being short of breath. **over625**

Q: The following questions are about how you have felt lately. Have you occasionally suffered from gloomy, depressive feelings or hopelessness, lately?

A: Yes .. yes .. yes .. for sure. **over345**

No .. Nooo .. That is not the case at all. No **over504**

Smoking:

Well, they told me it comes from smoking. Well, I guess it is.. **under313**
And if you also smoke, and you already have bad lungs.. I did not smoke much at all, but that's definitely the reason, the smoking. That's bad.

over358

Hereditary:

It will also be something hereditary. My father had it too. **under593**

It's hereditary. It's in the genes I think. **over710**

Environment:

I grew up in the Ruhr Area (Germany). Maybe also because of that air.

under362

And particles in the air. At my work, my father had his own company, who was a car painter yes ... Without something in front of the mouth and when they blew their noses .. you had to see the shit that was in there. And you just inhale that. **over358**

Illness Control/ Cure

Acceptance:

But I just accept it. I have no trouble with that. **under207**

And it took a long time before I thought what a pity that I can't do things anymore. But I think now if I do something and get tired, then I'm going to sit down. **over625**

Non acceptance:

A: I just can't accept it. Just not. No, I could never sit still before. I still don't, I still have a lot of problems with that. **under460**

Q: Can you cope with the fact that you have COPD or is it difficult?

A: Well, that's hard, yes. I would prefer not to have it .. And that I can just do everything. **over664**

Practical coping:

Cycling is OK, but then, I have an electric bike. **under313**

Every so often I will sit down for a while, where there is a possibility to sit.

under460

We love to ride a bike and an electric bike is nice. **over345**

I cannot make an appointment for tomorrow, because tomorrow .. I have to wait for the morning first and then I can say, well.. I will do this or that.

over358

Because you are looking for shops where the shopping cart is very close to the parking lot. So if you have such a cart, it will be fine. **over750**

Support:

Q: And do you get help with collecting the medication?

A: It will be delivered and if not my daughter-in-law will pick them up.

over504

Nobody smokes in this house and where I go to, no one else does too.

under362

I have a wonderful wife. She supports me in everything. **under460**

Necessity
Pharmacological
Treatment

I am glad I have it, because if I do not use it, I'm a lot more breathless. And I have no problems with it. **under501**

A: Yes, that's OK, I don't think it is that difficult either. If I don't do it, I'm getting breathless, right .. No, that's absolutely fine you know. **over345**

Non acceptance of necessity of treatment:

Q: What do you think about your medication?

A: I think it's terrible.. **over664**

A: Yes, it takes a lot of free time and yes, I'm getting tired of it. I am really fed up with it (...)

A: Yes, it is very difficult. You have to take them, but I would rather throw them out of the window. Otherwise I would bring harm upon myself.

over767

Reported underuse:

Actually four times, but because I take a double dose in the morning.. Of course I should not have too much of it. That's why I often do it three times.

under362

In the evening, I sometimes forget the inhaler because it is just going well, and I can permit myself to (...)

A: And if I notice it's going less good, I'll use it more often again. **under501**

A: Yes. meaning.. The pharmacy says to me: You need to use your inhalation more often, because you take too little. Well, that is just what I will not do then. **under690**

Look, you should not take too much medicine. **under593**

Reported overuse:

I have puffers with me. Just in case. At times I take a puff more than is prescribed **under719**

Memory:

And does that also affect your medication intake for example? That you forget that by mistake?

A: No, no. **under207**

Q: Okay. Can you remember things well?

A: No. Not at all. I really don't. It's just a sieve. That is difficult yes.

Q: Okay. Does this also affect the medication intake?

A: Yes, of course. **under362**

When I was still working, I forgot it sometimes. **under460**

A: Nooo, I'll never forget that. I can't do without that. **over345**

Q: Okay. And with the medication? Do you ever accidentally forget to use your medication?

A: It happens every once in a while. That I think: "Did I take it, or not?"

over625

Side effects:

Getting hoarse. **under593**

Like that Spiriva ... the disadvantage is that it irritates the throat immediately. **under719**

Once I had a medicine that made me cough. **over358**

Medication dependence:

So I think I could not live without those medications anymore. **under501**

Very important. Yes, very important. I couldn't live without those medications, I think. **over345**

That medicine? Because you need it. If I go out and I notice that I do not have that thing, I panic. **over358**

Yes, no but, especially those. I always have one in the car for that reason.

But if I go out, I'll put it in my pocket, because you never know what will happen with the effort. **over668**

It gives you some sense of safety when you have it with you. **over750**

Treatment concerns

Inhaled medication use

Correct knowledge:

I use medication to widen the airways and anti-inflammatory. **under460**

And this is more for anti inflammatory, that's Seretide. **over345**

A: The medications are to keep it stable. **over625**

Wrong knowledge:

It was Ventolin and that was an inflammatory inhibitor **over625**

Q: And is one of that medication also for when you get out of breath that you can use it at that moment?

A: Yes, the Seretide. **over664**

A: The Spiriva every 3 to 4 hours really. **over664**

If I have a cold, I take an extra Seretide. Then I can cough better. **over710**

Q: But do you think that those exacerbations can be prevented by the treatment?

A: No, I do not think so. **under460**

Do you think the treatments can reduce the sudden exacerbations? That it will occur less often ..

A: No, I would not know how that would be possible. **under501**

Positive experience:

A: Yes, that is the relief of the tightness of the chest. It certainly does. **under460**

It gives a little relief; I get somewhat less short of breath. So I have some help from that. **under480**

Well, and then I take those medications, I have such an extension and you blow it in and you get air again. And that's really nice! **over345**

Yes, you get a somewhat less short of breath and it gets lighter. **over504**

Daily routine:

A: Yes, that is automatic, but yes, I've been using those things for so many years now. Really, that just is automatic. **under719**

A: Yes, it's definitely a routine .. I do not have to think about it. **under313**

A: Yes, all goes automatic. **over664**

A: In the morning, I use them and that's always a fixed pattern. **over710**

No routine:

Q: At which times do you take the medication?

A: Well, that can be at any time of the day. **over504**

A: No. No fixed times. In the morning before I get out of bed I take this and that keeps on working around the clock and then at night it has stopped working sometimes and sometimes not. And then I will add this, but for the rest .. **over750**

Inhalation devices

Discarding too early:

Q: Do you see whether the inhaler is empty?

A: I can feel it .. when I think: he's going a little bit difficult. Then I spray once and then oh god, there are one or two left. I'll do that more often. Then it's empty. **over358**

A: Well, I see that with the Oxis, there's a little thing that indicates that. It shows a red signal: if it's at the top, then I can still take it a few more times, but if it's in the middle, I'll throw it away. Sometimes I think I throw it away too soon, but then I'm afraid I'm not getting enough. **over625**

If only very little is coming out, I just throw it away. And then I put a new one in. **over345**

Discarding too late:

A: Well, if nothing is coming out anymore then it's time to get a new one. **under719**

A: Yes, then I shake it and think well .. there could be nothing more in there.. I've also tried to weigh once, but that did not work .. with such a household weighing scale ... and that's not working, but I'll take a look and if something is still coming out then I know that it's still good. **under719**

Knowledge device (when empty):

A: If that piece turns red, it's empty **under207**

Q: And how do you see whether the inhaler is empty?

A: That is on the backside. There is a counter. **under501**

In the end, I think, "well, I don't think there's anything left...". I look at the number of times you have to use them, well that's just per month. Then I just write the date there ... Is the date due then I will throw them away and I take a new one. **under313**

A: Look, here it says: 5 more puffs. Do you see that? That is the Seretide..

Q: Yes ..

A: Well, then I can throw it away when it's empty and get a new one.

over345

A: Well.. the Spiriva .. It will turn completely red .. Then you cannot turn anymore. **over345**

A: The Flixotide .. There I always write down when I start. **over625**

Positive experience:

Just easy to use yes. **under207**

No. No, no, but yes, because of years of medication use, especially in the field of COPD, it's just routine and it's not hard and there are no difficulties. **under460**

A: No, it's all very easy to use. **over345**

Negative experience:

I have that, but I only used that because the other one was one that I had to inhale.. I did not have the strength for that. **under313**

Well, I don't like such a spacer. **under719**

It just seemed like that thing was empty and then I will have used it a few times for nothing. That is very annoying. Then I spray it under the table, you know. There was nothing left anymore. A week ago or so I had tried that and then one still came out. That is very disadvantageous. **over767**

Supplement A: Interview Schedule

Start

Entry, acquaintance, thanking for cooperation, provide opportunity to ask questions, informed consent, explain process, start interview ...

General introductory

How do you experience living with the disease COPD?

Person-related factors

Knowledge of disease and medication

To begin with, I would like to ask some questions about the disease COPD

- Can you explain what the disease COPD implies?
 - > What are the symptoms that occur in COPD?
 - > What symptoms do you experience yourself?
- > To what extent does COPD limit you in your daily life?
- > What do you think are the reasons that cause the disease COPD?
 - *Is smoking cited as a cause? Then:*
 - > Do you smoke?
 - > Did you smoke?
 - > Do people smoke in your vicinity?
 - *If smoke is not mentioned as a cause, ask later in the interview.*
- > Do you think the disease can be cured?
- > How serious is your illness?

Stimulation of knowledge and perception

Now that we talked about COPD, I would like to ask some questions about whether and how the doctor, pulmonary nurse or other health care provider has given information about the disease COPD.

- Who do you see as your main caregiver?
 - > Explain main caregiver if needed
- Did you receive information from your care provider about COPD, to gain knowledge about the disease?
 - > If so, how?
- Have you been explained what the treatment can do for you? How treatment can help?
 - > If so, how? Who gave you this information?

- Did you receive advice regarding a healthy lifestyle and was it fit for you?

-> If yes, what advice have you received? And how did you fit this in?

Depression

Besides the above questions, now I would like to ask some general questions about how you feel lately.

- Did you suffer from gloomy or depressive feelings or even hopelessness, this last month?

- Did you experience loss of interest or pleasure in doing certain activities, this last month?

- Did you suffer from tiredness, last month?

-> If yes:

- Is that because of complaints that have to do with COPD?

- Is it because you are worrying about, for example, the course of the disease?

- Is it because you are afraid you will be short of breath at night or have fear of other symptoms that can occur with COPD?

- Are you more irritable lately, touchy or angry compared to before?

Physical performance

- Can you remember things well or do you have the feeling sometimes that you forget things by mistake?

-> If yes:

You just mentioned that you accidentally forget things lately; does that affect the intake of medication?

Treatment Factors

Confidence in treatment and outcome

Now that we have talked about COPD in general, whether and how the doctor, pulmonary nurse or other health care provider has given you information about COPD and how you feel lately, I would like to talk about the treatment and about the course of the disease.

- How do you experience the treatments you undergo?

-> Is it easy or difficult to live according to the prescribed treatment?

- What is easy / difficult?

- How many different types of treatments do you undergo?

- > Which of these treatments are easy to maintain? Why?
- > What treatments are more complicated? Why?
- > Is the combination of treatments easy to maintain?
- (Possibly: What is difficult for you?)
- Do you think that the treatment can prevent the sudden outbreaks?
- Do you think that the symptoms that you are experiencing may diminish?
- > Can this be due to the treatment that you follow?
- Other factors?
- Are you worried about the course of the disease and associated symptoms?
- > Does the treatment that you get (partly) take away your concerns?

Acceptance of disease and treatment

I would also like to know what your feelings are regarding COPD and its treatment.

- What kind of feeling do you experience suffering from COPD?
 - Can you put up with the fact that you have COPD?
 - Do you think it is therefore better to try to 'embrace' the disease by learning to cope with it?
- Do you agree with the prescribed treatment?
 - > Do you have a say in the treatment you receive?

Relationship between the patient and health care provider

Regarding your treatment I would like to ask you some questions about the relationship between you and your health care provider

- How is the relationship between you and your health care provider?
 - > Can you and dare you to discuss everything with your health care provider?
 - > Do you feel that the caregiver knows you well and understands you?
 - > Do you accept what the caregiver tells you and recommend you?
 - > Can you work together with your health care provider; do you feel that your opinion also counts/is being considered?

Medical factors

We talked earlier about the treatment of COPD in general. Now I would like to talk about one specific part of the treatment. The following ques-

tions are about the medication you use.

- Which medication do you take for the disease COPD?

If the respondent knows this, then:

-> Can you tell what effect does the medication have and what are they meant for?

If the respondent does not know this:

Use

- Could you show what medications you are taking?

-> How do you take this medication?

- Do you have an idea whether the medication is used in a correct way?

-> What do you think about your medication?

-Why?

-Are there any positive or negative effects?

-> How important is it to take the medication according to you?

Why?

-> If yes / no:

-Why?

-> Have you received explanations about the medication that the caregiver has prescribed?

-> Do you know whether there are other medications for COPD?

Or did you use other medicines in the past?

Frequency of use

-> At what times do you take the medication?

- Do you experience the medication as something automatic, hence as a routine, or do you need to think about it carefully every time again to take the (different) medication in time and in the right way?

Difficulties inhaled medication

We have just discussed all kinds of medication for COPD. Now I would like to talk for a moment about the inhaled medication. The following questions are about that.

- How do you experience the use of the inhaled medication?

-> Why?

- How do you know if you have used the correct dosage?

- How do you see whether the inhaler is empty?

- How could the use of inhaled medication be made easier?

Medications other disorders

- Do you also use other medication for other conditions (diseases)?
 - > If yes, how many other medications do you use daily?
 - > How many times a day do you use this medication?
 - > Can you use all these medications at the same fixed time? Or are there different times that you should use this medication?
- We have now talked about the use of medications. With the medication there is always an insert and I would like to ask the following question about the insert.
- Do you read the package insert of your medications?
 - > If yes, what do you think of the instructions?
 - Are the letters big enough, or would you prefer that the letters would be something bigger?
 - Is the text understandable, or would it be better if the text could be simpler?
 - > If not, why not?

Self-management

So far we talked about the treatment and medication of COPD. Furthermore I would like to ask what

you can do yourself to manage your illness in the right direction?

- How do you do that?
- Are you being guided in this by the caregiver?
 - > If not:
 - Why not?
 - Do the caregivers try to stimulate you (to be able) to manage eventually?

Demographic data

Besides the questions we have just asked you, we would also like to collect some basic information to get a better picture of the people who cooperated on this study.

1. You are man / woman
2. What's your birth year?
3. What is your highest level of education?
4. Are you still working? How many hours a week?
5. With how many people do you live together?
6. Do you get help collecting your medication?
7. Do you get help in taking your medication?

Just ask these questions if the question has not been discussed in the section "person-related factors".

2. In addition to your age, I would also like to ask whether you smoke?
 -> If not, have you smoked?
3. Do people smoke in your vicinity?

Supplement B: Codingscheme

Coding scheme	1st level	2nd level
Identity	1.1 What encompasses COPD	1.1.1 Irreversible damage to the lungs (irreversible obstruction).
		1.1.2 Emfysema
		1.1.3 No idea
		1.1.4 Losing participation in daily life
Timeline	1.2 Complaints/disease symptoms	1.2.1 Dyspnea
	2.1 Curability	2.1.1 Not curable
		2.1.2 Maybe curable
		2.1.3 I do not know if COPD is curable
	2.2 Experienced disease over time	2.2.1 Worse
		2.2.2 Stable (no improvement)
		2.2.3 Improvement/relief of com complaints
		2.2.4 Ups and downs
	2.3 Expectations about the clinical course /future development of COPD	2.3.1 Positive: No worries about the clinical course
		2.3.2 Negative: Worries about the clinical course
		2.3.3 No idea about future development/clinical course
		2.3.4 Hope for improvement
Cause	3.1 Causes of COPD	3.1.1 Smoking
		3.1.2 Genetic/Hereditiy
		3.1.3 Unknown
		3.1.4 External factors (pollution, asbestos)
		3.1.5 Unhealthy lifestyle

Coding scheme	1st level	2nd level
Consequences (personal impact)	4.1 Emotional complaints	4.1.1 Loss of joy /interest in Life
		4.1.2 Gloomy, depressive feelings and hopelessness
		4.1.3 Irritable, angry
		4.1.4 Anxiety
	4.2 Emotional limitations	4.2.1 Have to quit smoking
		4.2.2 Sadness about losing participation in daily life
	4.3 Physical complaints	4.3.1 dyspnea, shortness of breath
		4.3.2 Fatigue
		4.3.3 Cough
	4.4 Physical limitations	4.4.1 Problems with every day activities
5. Control/Cure	5.1 Coping	5.1.1 Psychological adjustment to the disease (including acceptance)
		5.1.2 Behavioral adjustment to the disease (use of (medical) aids, practical adjustments)
		5.1.3 Seek social support
		5.2.1 Acceptance of treatment
		5.2.2 Problems with acceptance of treatment (nonacceptance)
	5.2 Treatment	5.2.3 Influence memory on adherence
		6.1.1 Knowledge on effect of inhalation treatment
		6.1.2 No/wrong knowledge on effect of inhalation treatment
		6.2.1 Positive effect (less complaints, less worries)
		6.2.2 Side effects (negative effect)
6. Treatment/ Medication	6.2 Experience inhalation treatment	6.2.3 No effect / no improvement
		6.2.4 Dependency (fear of being out of medication)
		6.3.1 Knowledge on correct use of device
		6.3.2 No/wrong knowledge on correct use of device
	6.3 Knowledge inhalation device	6.4.1 Good experience / easy to use
		6.4.2 Bad experience/ problems with use
	6.4 Experience inhalation device	6.5.1 Yes, routine (incl. knowledge correct dosing scheme)
		6.5.2 No routine
	6.5 Routinely use of medication	

The association between Poor Therapy Adherence to Inhaled Corticosteroids and Tiotropium and Morbidity and Mortality in Patients with COPD

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Abstract

Aim: To study the association between therapy adherence to inhaled corticosteroids (ICS) and tiotropium on the one hand and morbidity and mortality in COPD on the other hand.

Methods: Therapy adherence to ICS and tiotropium over a three-year period of respectively 635 and 505 patients was collected from pharmacy records. It was expressed as percentage and deemed optimal at 75–125%, sub-optimal at 50–75%, and poor at <50% (underuse) or >125% (overuse). The association between adherence and time to first hospital admission for an exacerbation (AECOPD), community acquired pneumonia (CAP), and mortality was analysed, with optimal use as the reference category.

Results: Suboptimal and underuse of ICS and tiotropium were associated with a substantial increased mortality risk: hazard ratio (HR) ICS 2.9 (95%CI 1.7–5.1) and 5.3 (95%CI 3.3–8.5), HR Tiotropium; 3.9 (95%CI 2.1–7.5) and 6.4 (95%CI 3.8–10.8) for suboptimal and underuse, respectively. Suboptimal and overuse of tiotropium were also associated with an increased risk of CAP, HR 2.2 (95%CI 1.2–4.0) and 2.3 (95%CI 1.2–4.7), respectively. Non-adherence to tiotropium was also associated with an increased risk of severe AECOPD: suboptimal HR 3.0 (95%CI 2.01–4.5), underuse HR 1.9 (95%CI 1.2–3.1), and overuse HR 1.84 (95%CI 1.1–3.1). Non-adherence to ICS was not related to time to first AECOPD or first CAP.

Conclusions: Poor adherence to ICS and tiotropium was associated with higher mortality risk. Next to this, non-adherence to tiotropium was associated with higher morbidity. The question remains whether improving adherence can reduce morbidity and mortality.

Introduction

COPD management aims at reducing symptoms, exacerbations and mortality by giving appropriate pharmacotherapy. (1-3) Treatment strategies contain long acting muscarinic agonists (LAMA) like tiotropium, inhaled corticosteroids (ICS), long acting beta agonists (LABA) and combination drugs.

Several studies have described the risk of pneumonia associated with ICS use. The Towards a Revolution in COPD Health (TORCH) study was the first to show an increased risk of pneumonia for ICS users and recently the Understanding Potential Long-Term Impacts on Function with Tiotropium (UPLIFT) also showed higher incidence rates of pneumonia for ICS users. (4-6) The magnitude of this risk, the effects of different preparations and doses, and the mechanism of this effect remain unclear. (7,8) Although the risk-benefit ratio for ICS is under debate, the GOLD guidelines still suggest considering the use of ICS in patients with severe airflow limitation or for those who are at high risk of exacerbations. (9,10)

The effectiveness of inhaled medications is strongly influenced by the patient's medication adherence, with better adherence showing reduced risk of death and hospitalization due to COPD exacerbations for fluticasone/salmeterol and tiotropium. (2,3,11) In most of these studies adherence was defined as poor (<75 or <80%) or good. In the Cohort on Mortality and Inflammation in COPD (COMIC) cohort we have however shown that there are also many patients that overuse (>125%) or strongly underuse (<50% use) their ICS and despite the high percentage of optimal use with tiotropium, underuse and overuse are observed for this medication as well. (12) It is expected that these patients will have a different risk for a COPD exacerbation that needs hospitalisation (severe AECOPD), community acquired pneumonia (CAP) and mortality compared to patients with optimal (75-125% use) or sub-optimal (50-75% use) adherence. Therefore, in this manuscript the association between therapy adherence (underuse, sub-optimal use, optimal use, and overuse) with ICS and tiotropium and time to first hospital admission for a severe AECOPD, CAP, and mortality is described.

Methodes

Settings and study population

This study is part of the Cohort on Mortality and Inflammation in COPD (COMIC) study, a single centre prospective cohort study in Enschede, the Netherlands. Of the 1503 patients that were screened for eligibility from December 2005 till April 2010, 795 COPD patients were included. All surviving patients completed the three year follow-up period. All patients provided written informed consent, including consent for collecting pharmacy records during the studied period. The study was approved by the Medical Ethics Committee Twente (P05-49) and was conducted according to the principles of the Declaration of Helsinki. For in- and exclusion criteria see previous publications. (12-14)

Baseline measurements

Demographic data was collected from medical records at baseline. Data on common comorbidities myocardial infarction (MI), congestive heart failure (HF), and diabetes mellitus (DM) were obtained from medical records. Lung function was measured by spirometry, performed according to standardised guidelines. (15) The modified Medical Research Council dyspnea grade (mMRC) was obtained at stable state. (16)

Therapy adherence

Therapy adherence was recorded from patients' pharmacy records. If patients used more than one medication delivery system or switched between various brands of ICS (including combination preparations) during follow up, adherence data were combined for the calculation of the therapy adherence of ICS. For adherence to tiotropium, prescriptions of Handihaler and Respimat were used.

Theoretical duration of exposure 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 medication collection during follow up plus the day's supply of the last refill. We excluded patients when medication was prescribed once only or was used less than 90 days. We set the limit for optimal adherence at ≥ 75 . Next to this, we decided to choose two lower cut-off points to distinguish suboptimal and underuse and an upper cut-off point as well for optimal adherence ($>125\%$), in order to be able to identify overuse. (2,17-19) Adherence was deemed good if it was 75-125%, sub-optimal between 50- $<75\%$, and poor below $<50\%$ (underuse) or above $>125\%$ (overuse). (12)

Since adherence can change over time, adherence was computed for 6 month intervals. For each 6 month period, the total number of days for which patients had collected medication was divided by the total number of days between the first and last medication collection during these 6 months and multiplied by 100. (20) If a refill period went over a 6 month boundary the prescription was taken into account in both intervals.

Morbidity and Mortality

Morbidity was defined as time to first hospitalisation for a severe AECOPD and time to first CAP. An AECOPD was defined as an acute negative change from baseline, reported by the patient, in dyspnea and/or sputum volume and/or colour of sputum (yellowish or greenish sputum) and/or cough, which may warrant additional treatment of prednisolone with or without antibiotics by a physician in a patient with underlying COPD. CAP was defined as an acute respiratory tract illness associated with radiographic shadowing on a chest radiograph consistent with infection which was neither pre-existing nor of any other known cause. (21) All X-rays were double-read by a radiologist and a pulmonary physician. In case of doubtful shadows in the report, the X-ray was presented to another pulmonary physician for final judgment. Survival was based on all-cause mortality. Date of death was verified from the municipal administration.

Statistics

Baseline characteristics are reported as mean with standard deviation (SD) or median with interquartile range (IQR) for continuous variables. Categorical variables are displayed as numbers with corresponding percentages. Differences in baseline characteristics between the adherence categories measured in the first 6 month period, were analysed by ANOVA or Kruskal-Wallis test for continuous variables and Chi-square tests for categorical variables.

To assess the relationship between therapy adherence to ICS, time to first severe AECOPD, time to first CAP and time to death Cox regression was used with time-varying coefficients. (22,23) The same analyses were conducted for tiotropium.

For each separate multiple variable Cox-regression model, all baseline characteristics (Table 1, Table 2) that were associated with both the studied adherence of the model and either time to severe AECOPD, CAP or mortality at $p < 0.10$, were entered as potential confounders.

All statistical calculations were carried out with the SPSS statistical package (version 21.0) and R (version 3.4.1). (24)

Results

Baseline characteristics

Table 1 shows the baseline characteristics of patients using ICS and Table 2 of tiotropium. 635 Patients used ICS with an overall median duration use of 32.5 months (IQR 20.5-36.6), varying per ICS preparation between 9.3-31.2 months (Table 3). 505 Patients used tiotropium with an overall median duration use of 30.0 months (IQR 15.0-35.0), (Respimat 20.1 months (IQR 9.9-29.7), Handihaler 30.8 months (IQR 17.5-36.1)).

Table 1. Baseline characteristics patients using inhaled corticosteroids (including combined preparations);

	ICS N=635	Optimal ≥75- ≤125% N=365	Suboptimal ≥50- <75% N=92	Underuse <50% N=75	Overuse >125% N=103	P
	Overall	Adherence category First 6 months of ICS use				
Age in years (Mean (SD))	67.1 (9.7)	66.2 (9.5)	69.1 (10.3)	67.1 (9.8)	68.5 (9.6)	0.035
Sex (Number of men (%))	377 (59.4)	221 (60.5)	61 (66.3)	39 (52.0)	56 (54.4)	0.187
Smoking status (Number (%))						
Current smoker	176 (27.7)	86 (23.6)	25 (27.2)	21 (28.0)	44 (42.7)	0.002
Ex-smoker	459 (72.3)	279 (76.4)	67 (72.8)	54 (72.0)	59 (57.3)	
Lung function (Mean (SD))						
FEV ₁ in Litres	1.4 (0.56) ¹	1.4 (0.55)	1.3 (0.66)	1.3 (0.59)	1.3 (0.46)	0.035
FEV ₁ %predicted	51.2 (18.4) ¹	52.3 (17.7)	49.4 (20.5)	50.1 (21.1)	49.7 (16.8)	0.379
FEV ₁ /VC ratio	43.5 (13.3) ¹	43.5 (12.3)	42.7 (14.2)	45.6 (16.1)	42.8 (13.8)	0.483
mMRC (Mean (SD)) ²	1.8 (1.26)	1.6 (1.2)	2.0 (1.3)	2.2 (1.3)	2.0 (1.3)	0.000
Tiotropium use, N (%)	440 (69.3)	265 (72.6)	70 (76.1)	40 (53.3)	65 (63.1)	0.002
Comorbidities, N (%)						
Heart failure	100 (15.8)	52 (14.2)	19 (20.7)	11 (14.7)	18 (17.5)	0.460
Myocardial infarction	26 (4.1)	8 (2.2)	8 (8.7)	4 (5.3)	6 (5.8)	0.016
Diabetes Mellitus	36 (5.7)	16 (4.4)	5 (5.4)	5 (6.7)	10 (9.7)	0.220

Notes: 1 Lung function measurements of 634 patients (1 patient with optimal use missing) 2 mMRC data available of optimal use N=328, suboptimal N=86, underuse N=68, overuse N=97

Abbreviations: ICS, inhaled corticosteroids; SD, standard deviation; FEV₁, forced expiratory volume in 1 second; VC, vital capacity; mMRC, modified Medical Research Council.

Table 2. Baseline characteristics patients using tiotropium;

Adherence category First 6 months	Tiotropium N=505	Optimal ≥ 75- ≤ 125% N=360	Suboptimal ≥ 50- < 75% N=64	Underuse < 50% N=36	Overuse > 125% N=45	P
	Overall	Adherence category First 6 months of tiotropium use				
Age in years (Mean (SD))	66.0 (9.8)	65.9 (9.4)	67.1 (11.1)	64.0 (11.1)	66.8 (9.8)	0.443
Sex (Number of men (%))	310 (61.4)	222 (61.7)	38 (59.4)	21 (58.3)	29 (64.4)	0.932
Smoking status (Number (%))						
Current smoker	149 (29.5)	94 (26.1)	24 (37.5)	14 (38.9)	17 (37.8)	0.073
Ex-smoker	356 (70.5)	266 (73.9)	40 (62.5)	22 (61.1)	28 (62.2)	
Lung function (Mean (SD))						
FEV ₁ in Litres	1.4 (0.56)	1.4 (0.56)	1.4 (0.53)	1.7 (0.66)	1.3 (0.46)	0.021
FEV ₁ % predicted	51.7 (17.7)	51.9 (17.7)	51.1 (16.0)	57.1 (21.1)	47.1 (16.3)	0.090
FEV ₁ /VC ratio	43.5 (12.8)	43.4 (12.5)	43.2 (13.2)	47.9 (16.3)	51.7 (17.7)	0.097
mMRC (Mean (SD)) ¹	1.71 (1.2)	1.59 (1.8)	1.93 (1.17)	2.00 (1.37)	2.15 (1.41)	0.007
ICS use, N (%)	440 (87.1)	316 (87.8)	55 (85.9)	30 (83.3)	39 (86.7)	0.876
Comorbidities, N (%)						
Heart failure	86 (17.0)	67 (18.6)	4 (6.3)	7 (19.4)	8 (17.8)	0.108
Myocardial infarction	18 (3.6)	10 (2.8)	3 (4.7)	1 (2.8)	4 (8.9)	0.161
Diabetes Mellitus	35 (6.9)	21 (5.8)	4 (6.3)	6 (16.7)	4 (8.9)	0.100

Notes:¹ MMRC data available of optimal use N=334, suboptimal N=59, underuse N=33, overuse N=39

Abbreviations: ICS, inhaled corticosteroids; SD, standard deviation; FEV₁, forced expiratory volume in 1 second; VC, vital capacity; mMRC, modified Medical Research Council.

Table 3: Inhaled corticosteroids that were investigated:

Medication	Months used median (IQR)
Ciclesonide (n=22)	23.5 (15.8-35.5)
Fluticasone (n=73)	25.7 (12.5-34.9)
Formoterol/Budesonide (n=91)	31.2 (15.9-36.5)
Salmeterol/Fluticasone (n=493)	27.4 (13.2-34.7)
Budesonide (n=44)	28.2 (17.4-36.7)
Beclomethasone (n=44)	15.7 (7.5-31.7)
Formoterol/Beclomethasone (n=8)	9.3 (4.0-16.5)

Of the baseline characteristics, FEV₁ percentage of predicted, (FEV₁%) age and mMRC were associated ($p < 0.10$) with therapy adherence to ICS (Table 1) on the one hand, and with time to first severe AECOPD, time to first CAP (except for mMRC) and time to death on the other hand (data not shown) and were therefore included in these models as potential confounders. Next to this, for the models on time to first severe AECOPD and CAP also myocardial infarction was included, while for the time to death model tiotropium use was included as additional confounder.

FEV₁% and mMRC were associated ($p < 0.10$) with therapy adherence to tiotropium (Table 2) on the one hand, and with time to first severe AECOPD, CAP and time to death on the other hand (data not shown) and were therefore included as potential confounders in the tiotropium models.

ICS

Time to first severe AECOPD:

The median duration use (until event or end of follow up) was 24 months (IQR 12-36). Analyses showed no increased risk of a hospital admission for severe AECOPD for non-adherent ICS use. Unadjusted: suboptimal use; HR 1.3 (95%CI 0.9-1.8), underuse HR 1.0 (95%CI 0.7-1.4), overuse; HR 1.4 (95%CI 1.0-2.0).

Adjusted: suboptimal use; HR 1.2 (95%CI 0.8-1.8), underuse HR 0.8 (95%CI 0.5-1.2), overuse; HR 1.2 (95%CI 0.8-1.7). (Table 4) A lower FEV₁% and a higher mMRC score at baseline were associated with a higher risk of hospital admission for a severe AECOPD: HR 2.04 (95%CI 1.43-2.50) and HR 1.4 (95%CI 1.2-1.5), respectively.

Time to first CAP:

The median duration use (until event or end of follow up) was 30 months (IQR 18-36). There was no relationship between the different adherence categories and the risk of CAP. Unadjusted: suboptimal use; HR 1.1 (95%CI 0.7-1.7), underuse HR 1.2 (95%CI 0.8-1.8), overuse; HR 1.1 (95%CI 0.7-1.7). Adjusted: suboptimal use; HR 1.0 (95%CI 0.6-1.6), underuse HR 1.1 (95%CI 0.7-1.7), overuse; HR 0.9 (95%CI 0.6-1.5). (Table 4) A higher FEV₁% at baseline was associated with a lower risk of CAP: HR 0.7 (95%CI 0.5-0.97)

Mortality:

The median duration use (until event or end of follow up) was 36 months (IQR 24-36). Unadjusted analysis showed a significant increased mortality risk for patients with suboptimal (HR 2.5; 95%CI 1.5-4.2) or underuse (HR 5.0; 95%CI 3.2-7.6), compared to optimal use. This risk increased to 2.9 (95%CI 1.7-5.1) for suboptimal and to 5.3 (95%CI 3.3-8.5) for underuse compared to optimal use after correction (Table 4). A higher mMRC score was also associated with a higher mortality risk HR 1.2 (95%CI 0.99-1.4).

Tiotropium**Time to first severe AECOPD:**

The median duration use (until event or end of follow up) was 24 months (IQR 12-36). Patients with suboptimal, under- or overuse of tiotropium had a significantly increased risk of a hospital admission for severe AECOPD compared to optimal use with an unadjusted HR of 3.1 (95%CI 2.2-4.5), 1.8 (95%CI 1.2-2.9) and 2.4 (95%CI 1.5-3.8), respectively. After correction, the risk of suboptimal and underuse remained almost the same at respectively 3.0 (95%CI 2.0-4.5) and 1.9 (95%CI 1.2-3.1), while the risk for overuse decreased to 1.8 (95%CI 1.1-3.2) (Table 5). Next to this, a lower FEV₁% and a higher mMRC score at baseline were associated with a higher risk of hospital admission for a severe AECOPD with respectively a HR of 2.0 (95%CI 1.4-2.5) and HR 1.4 (95%CI 1.2-1.6).

Time to first CAP:

The median duration use (until event or end of follow up) was 30 months (IQR 12-36). Patients showing suboptimal or overuse of tiotropium had an unadjusted increased risk for CAP compared to optimal use with a HR of 2.3 (95%CI 1.3-3.9) and 2.2 (95%CI 1.1-4.4), respectively. The 2-fold increased risk of CAP for suboptimal and overuse remained after correction with a HR of 2.2 (95%CI 1.2-4.0) and 2.3 (95%CI 1.2-4.7) respectively (Table 5). A higher FEV₁% at baseline was also associated with a lower risk of CAP HR 0.6 (95%CI 0.4-0.9).

Mortality:

The median duration use (until event or end of follow up) was 36 months (IQR 24-36). Both suboptimal and underuse of tiotropium were associated with a significant increased risk of mortality (Table 5). Unadjusted analysis showed a 4.1 fold (95%CI 2.4-7.3)

increased risk of dying in suboptimal users and a 5.6 fold (95%CI 3.4-9.1) increased risk for underusers compared to optimal users (Table 5). After correction suboptimal use showed a 3.9 fold (95%CI 2.1-7.5) and underuse a 6.4 fold (95%CI 3.8-10.8) increased mortality risk. (Table 5) Furthermore, a lower FEV₁% and a higher mMRC score at baseline were associated with a higher mortality risk with a HR of 3.3 (95%CI 2.0-5.0) and 1.2 (95%CI 0.99-1.5), respectively.

Table 4: Univariate and Multivariate Cox regression analysis with time-varying coefficients of therapy adherence to inhaled corticosteroids.

	Adherence category / confounder	Univariate			Multivariate		
		HR	95%CI	P	HR	95%CI	P
Hospital admission	Suboptimal	1.3	0.9-1.8	0.135	1.2	0.8-1.8	0.382
	Underuse	1.0	0.7-1.4		0.8	0.5-1.2	
	Overuse	1.4	1.0-2.0		1.2	0.8-1.7	
	FEV ₁ %				0.5	0.4-0.7	<0.001
	Age				1.0	1.0-1.0	0.295
	mMRC				1.4	1.2-1.5	<0.001
	MI				1.9	1.1-3.4	0.032
Pneumonia	Suboptimal	1.1	0.7-1.7	0.918	1.0	0.6-1.6	0.940
	Underuse	1.2	0.8-1.8		1.1	0.7-1.7	
	Overuse	1.1	0.7-1.7		0.9	0.6-1.5	
	FEV ₁ %				0.7	0.5-1.0	0.007
	Age				1.0	1.0-1.0	0.026
	MI				1.9	1.1-3.5	0.047
Mortality	Suboptimal	2.5	1.5-4.2	<0.001	2.9	1.7-5.1	<0.001
	Underuse	5.0	3.2-7.6		5.3	3.3-8.5	
	Overuse	1.2	0.6-2.3		0.9	0.4-2.1	
	FEV ₁ %				0.3	0.2-0.5	<0.001
	Age				1.1	1.0-1.1	<0.001
	mMRC				1.2	1.0-1.4	0.009
	Tiotropium use				1.2	0.8-1.8	0.635

Notes: Optimal use set as reference category

Abbreviations: FEV₁%, forced expiratory volume in 1 second percentage of predicted; mMRC, modified Medical Research Council; MI, myocardial infarction.

Table 5: Univariate and Multivariate Cox regression analysis with time-varying coefficients of therapy adherence to Tiotropium

	Adherence Category/ confounder	Univariate			Multivariate		
		HR	95%CI	P	HR	95%CI	P
Hospital admission	Suboptimal	3.1	2.1-4.5	<0.001	3.0	2.0-4.5	<0.001
	Underuse	1.8	1.2-2.9		1.9	1.2-3.1	
	Overuse	2.4	1.5-3.8		1.8	1.1-3.2	
	FEV ₁ %				0.5	0.4-0.7	<0.001
	mMRC				1.4	1.2-1.6	<0.001
Pneumonia	Suboptimal	2.3	1.3-3.9	0.014	2.2	1.2-4.0	0.018
	Underuse	1.5	0.8-2.8		1.7	0.9-3.2	
	Overuse	2.2	1.1-4.4		2.3	1.2-4.7	
	FEV ₁ %				0.6	0.3-0.9	0.001
	mMRC				1.2	1.0-1.4	0.057
Mortality	Suboptimal	4.1	2.4-7.3	<0.001	3.9	2.1-7.5	<0.001
	Underuse	5.6	3.4-9.1		6.4	3.8-10.8	
	Overuse	1.7	0.7-4.4		1.1	0.3-3.7	
	FEV ₁ %				0.3	0.2-0.5	<0.001
	mMRC				1.2	1.0-1.5	0.060

Notes: Optimal use set as reference category

Abbreviations: FEV₁, forced expiratory volume in 1 second percentage of predicted; mMRC, modified Medical Research Council.

Discussion

Suboptimal and underuse of ICS and tiotropium were associated with a substantially increased mortality risk compared to optimal use. Suboptimal and overuse of tiotropium were also associated with an increased risk of CAP. Next to this non adherence to tiotropium was associated with an increased risk of hospital admission for a severe AECOPD. An independent association between adherence to ICS and hospital admission for a severe AECOPD or CAP could not be demonstrated.

A lower FEV₁% at baseline was associated with a higher risk of hospital admission for a severe AECOPD, CAP, and dying, while a higher mMRC score was associated with a higher risk of severe AECOPD and a higher risk of dying in both ICS and tiotropium users.

The current results on decreased mortality risk in patients that are adherent to ICS are in line with the TORCH study which showed a borderline significant reduced risk on mortality with the use of Fluticasone propionate combined with salmeterol. (2) This risk seems even more increased in underusers (<50%), who show an almost two-fold increased mortality risk than suboptimal users (50-75%), which implies the need to make also a distinction in type of non-adherence. Our study results were not in line with Ismaila et al. who showed that reduced adherence to fluticasone/salmeterol was associated with increased risks for moderate and severe COPD exacerbations. (11) Overall optimal adherence in the COMIC cohort study was much higher (58% vs 35%) and Ismaila et al. could not correct for lung function and mMRC, which can possibly explain the observed differences.

The increased risk for CAP in ICS users as shown in for example the TORCH study (HR 1.5 for patients with adherence >80% compared to non ICS use), could not be confirmed. (4,6) A possible explanation could be that the COMIC study lacks statistical power due to the low number of CAP's. Furthermore, TORCH investigated a specific dosage, namely 500µg fluticasone twice daily, whereas in the COMIC study also lower dosages were used. This is supported by the findings of Ernst et al., who suggested that there was a dose-related increase for pneumonia. (25) Furthermore, the diagnosis of pneumonia was X-ray confirmed in the COMIC cohort, which was not the case in the TORCH study. This could have led to misclassification of CAP in the TORCH study.

Both suboptimal and underuse of tiotropium were associated with a significant increased mortality risk compared to optimal use.

Furthermore, non-adherence to tiotropium compared to optimal use was associated with an increased morbidity risk. These effects could possibly be caused by the fact that the patient misses the protective effect of tiotropium as studied in the UPLIFT study and shown by Ismaila et al. (3,11).

The risk even seems to increase as adherence rates decrease, with higher risks in underusers than suboptimal users. A reason for taking less tiotropium could be that the patient is feeling well and does not see the need for using tiotropium. This is supported by the results that underuse is associated with better lung function at baseline.

Whether the association between overuse of tiotropium and increased risk of severe AECOPD and CAP was caused by the medication or the underlying disease, although we corrected for lung function and mMRC, cannot be ruled out due to the observational nature of the data. Since overuse is associated with lower lung function and higher mMRC it seems that overuse is related to COPD severity, which could explain the increased risk. Overuse could be due to an overall poor health condition, which results in feeling the need to use more medication. Another reason why patients can become overusers is an incorrect inhalation technique, since this can diminish the effect of the inhaled medication. Overuse can therefore be seen as a compensatory mechanism for not experiencing any relief of the medication used. Unfortunately there are no data available on inhalation technique in the cohort. Also lack of knowledge could be a reason for overuse. When a patient does not know what to expect from for example an ICS and experiences no immediate benefit he could inhale again because the symptoms are not yet relieved. Also as shown previously, adherence to inhaled medication is related to the device in which the medication is delivered. (26) For example, if a device does not provide inhalation feedback and a patient is not confident about having taken a dose he can decide to inhale again to be sure. (26) Non-adherence can also be a general behaviour, influenced by a patient's beliefs on their illness in relation to treatment recommendations. In COPD, disease and medication perception has not been described in much detail and future research with for example in-depth interviews could provide more insight.

An advantage of the data of the COMIC cohort is the chance to assess the effect of ICS and tiotropium in real life COPD out-patients and not in a selected trial population. Also in the cohort a valid diagnosis of COPD, lung function data, comorbidity data and an X-ray confirmed pneumonia is present. The possibility to correct for lung function, comorbidities

and mMRC in the analyses is another asset of this study. Finally, the follow-up of three years and determining the adherence over 6 month periods thus following adherence development over time, is a strong point as well.

A limitation of pharmacy data is that they only give an indication of drug refill patterns, but not of the actual inhalation. The data show the maximum levels of drug use among the patients, and it is likely that the inhaled drug volumes are lower than the volumes dispensed by the pharmacy. Patients can collect the medication to appear adherent and dump the medication, or store it in different places for convenience without actually using the medication. (27-29) An electronic counting device with flow meter could help to analyze and tackle this problem. However, these devices were not yet available at the start of this cohort.

Another possible limitation is the fact that this is a single-center study which may affect external validity since the adherence in this centre seems somewhat better compared to other regions in the Netherlands. (12)

Previously published main determinants of non-adherence in this cohort were lung function and having more anxiety for dyspnea (measured with the Clinical COPD Questionnaire question 3). (14) An interesting additional outcome measure for future research would be to study the change in morbidity of patients based on longitudinal symptom and quality of life assessments.

The described results raise questions about what should be done next. Patients that do not use their medication as prescribed, might need extra attention because diverting from optimal adherence is significantly associated with morbidity and mortality. The community pharmacy can play an important role in recognising these patients because adherence to medication starts with filling a prescription. In case of non-adherence there should be a reflection on adherence and a starting point for further support and guidance towards optimal use of medication.

Conclusion

Poor adherence to ICS and tiotropium was significantly associated with a substantial higher mortality risk. Non-adherence to tiotropium was also associated with an increased risk of severe AECOPD and CAP. In contrast to this an independent association between adherence to ICS and severe AECOPD or CAP could not be demonstrated. Future research is warranted to confirm these associations and to study whether improving adherence reduces mortality and morbidity.

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General Discussion

7

General Discussion

The main objective of this thesis is to study adherence to inhaled medication in COPD patients, to identify factors associated with adherence to inhaled medication, and to study the impact of adherence on health outcomes. In this chapter, we will summarize our findings and review them in a wider context. Additionally, practical implications and recommendations for future research will be addressed.

Adherence in COPD

Non-adherence in COPD is a complex puzzle with many pieces and THE non-adherent COPD patient does not exist. In this thesis, we studied patterns of adherence to inhaled medication and their corresponding inhalation devices. The percentage of patients with good adherence described in *chapter 2* was high, compared to literature, especially keeping in mind that the study was carried out in real life COPD patients who were not aware that the pharmacy data were going to be used to study adherence. For example the percentage of patients with good adherence with tiotropium was 76% whereas Ismaila et al found around 62%. (1) Also for corticosteroids and corticosteroids combined with adrenergics high percentages of good adherence were observed in our study (varying between 59 and 68%) whereas in literature percentages from 28% to 40% for ICS and 29 to 35% for ICS/LABA combinations are described. (2,3) In Twente, a region in the eastern part of the Netherlands, these results are in line with a national observational study that showed higher adherence levels in this region compared to other regions in the Netherlands. (4)

We have shown that non-adherence can present itself in many ways and different types of non-adherence seem to correspond with different patient characteristics. Although in literature, there is no consensus on acceptable therapy adherence in COPD patients, and definitions vary from adherence of >70% to >80% as good adherence, most studies define only two categories: adherent or non-adherent. Supplementary categories for low adherence (under- and suboptimal use) and non-adherence by overuse, introduced in this thesis (*chapter 2, 3, 4, 5 and 6*) proved to be very informative and provided new insights into adherence in COPD. We found that risks of morbidity and mortality increased when adherence decreased and in the overuse group these risks increased as well. These differences are important in developing strategies for each category to improve adherence.

Adherence to Inhaled medication

GOLD guidelines state that each pharmacologic treatment regimen should be individualized and guided by the severity of symptoms, risk of exacerbations, side effects, co-morbidities, drug availability and cost, and the patients' response, preference and ability to use various drug delivery devices. (5) Adherence starts with the prescribing of a treatment. In *chapter 2* we observed that medications dosed once daily, tiotropium and ciclesonide, showed the highest percentage of patients with good adherence. This is in line with a study of Claxton stating that medication dosed once daily is a known factor improving adherence since adherence declined as the number of daily doses increased. (6) This is also supported with the interview data as described in *chapter 5*, where patients stated that medication use was a breach in daily life activities because they were being forced to remind the use of medication all day long and also because they experienced that inhaling of medication took too much time.

Another important aspect of inhaled medication in relation to adherence is the relief of symptoms that patients experience after inhalation. (3) Tiotropium, which showed to have the highest adherence percentages in *chapter 2*, does indeed relieve dyspnea within 30 minutes after inhalation. (7) This relief of symptoms is not experienced with ICS except for combination preparations containing ICS and LABA components in which the LABA component relieves dyspnea within for example 20 minutes (salmeterol). Although a substantial amount of patients in the COMIC cohort used such a combination preparation (fluticasone/salmeterol) this did not result in a higher optimal adherence rate compared to the separate ICS preparation (fluticasone). The idea of improving adherence by combining two medications in one device could therefore not be confirmed in this thesis. This might be caused by a kind of selection bias when a prescriber chooses a combination preparation for a patient with a problematic or suspected low adherence. In this way a combination preparation is introduced to a patient with a tendency for low adherence. The past few years many new combination preparations for inhaled medications, containing two or even three components with different mechanisms of action, have been introduced on the market. In the in-depth interviews (*chapter 5*) patients (overusers) stated that inhaling medication took too much time and the effect of complex medication dosing schemes interfered with daily life activities. So, the idea of combining preparations in one device still seems to be a sensible addition to the current therapy options.

In contrast to the combination fluticasone/salmeterol, the combination preparation formoterol/budesonide showed a numerically but not statistically significant higher percentage good adherence compared to budesonide alone (*chapter 2*). However, both formoterol/budesonide and budesonide alone showed a high percentage of overuse compared to fluticasone/salmeterol. Formoterol/budesonide can be used on demand (SMART regimen) in asthma therapy when a patient experiences an increase in symptoms due to the short onset of symptom relief of formoterol. (8) It is possible that this therapy advice is also used off-label for the treatment of COPD and might lead to overuse.

In *chapter 5* the interview data showed that the non-adherent patients had little knowledge of COPD and how to manage their COPD. In addition, there was a lack of knowledge about the mechanisms of action of medication, and when which medication should be used. For example, the misconception of patients that their medication was anti-inflammatory instead of a short acting beta-agonist, lead to underuse as it was used on demand. Other patients were overusers by thinking a medication was short acting and had to be taken every other hour, while it was long acting and had to be used once or twice daily (*chapter 5*). Next to this, it is plausible that when patients do not know what to expect from for example an ICS and experiences no immediate relief they might inhale once again because the symptoms were not yet relieved. Educating COPD patients on COPD and their inhaled medication can improve adherence, as was shown by the PHARMACOP trial in which a pragmatic pharmacist care program improved the pharmacotherapeutic regimen. (9) In addition, many patients stated that they did not accept their disease. Menckeborg et al. showed for asthma patients that adherence rates for ICS in pharmacy records were highest for patients accepting treatment. (10) It is possible that the registered non-adherence could be (partially) explained by this non-acceptance of both the illness and its treatment. Next to this, George et al. showed that adherent patients had a greater understanding about their illness and the options for managing their illness. (11) When we take into account that many COPD patients have low levels of health literacy, it seems that the information the patients receive does not result in acceptable knowledge levels, consequently resulting in non-adherence to inhaled medication. Studies of COPD patients with hypoxemia have found impairments in abstract reasoning, memory, speed of performing and co-ordination of simple motor tasks. (12,13) Furthermore Liesker et al. found that also non-hypoxemic COPD patients have impaired cognitive performance in tasks

primarily evaluating the speed of information processing, although their memory and mental flexibility were relatively undisturbed. (14) This raises the question what proper information should look like. Perhaps medication should have an indication or pictogram that shows the effect of the medication. Although lower education levels and functional illiteracy, which can result in non-adherence, are common in COPD patients, education level can also have opposite effects as shown by the Copenhagen General Population Study. This study showed that a higher education level was associated with decreased adherence, possibly explained by the fact that highly educated individuals may choose to rely more on their own judgment and, consequently, adjust dosages to perceived symptoms rather than simply follow a fixed-dose regimen. (15)

Finally, we have to take into account the possibility that high percentages of overuse are caused by the device in which the medication is administered. The influence of the design of the device on adherence will be discussed in the next paragraph.

Adherence and inhalation device

Another important step in prescribing therapy for COPD is selection of the device in which the medication is administered because therapy adherence to inhaled medication and the device are related (*chapter 3*). The highest percentage of optimal therapy adherence described in *chapter 3* was 78% for the Handihaler. However, this result cannot be seen as solely contributed by the device. One has to take into account the fact that the Handihaler is used for tiotropium, a medication with dyspnea relieving effect and once daily dosing. In addition, overuse was found most often in the MDI (14%) and Turbuhaler (27%). Overuse can be due to both spillage and overdosing. With the Turbuhaler overuse could be caused by the off label SMART regimen as described above. Next to this, spillage could be also caused by the design of the Turbuhaler, since it enables patients to load the device several times by rotating the grip, without actually inhaling. With a Diskus this is less likely because a patient has to close the device completely before another dose can be loaded. With an MDI, it is also possible to actuate a dose without inhaling. So, the ability of a device to release a dosage without actually inhaling increases the risk of overuse as registered in pharmacy records. In addition, most MDI's do not have a dose counter to indicate how many dosages are left, and perhaps patients perform "test puffs" to verify that there is still medication left in the MDI. The recent designed Respimat inhaler,

which cannot release additional medication after the last dosage is delivered, might prevent this kind of overuse. In *chapter 5* patients stated that they discarded a device because they were not sure the device was empty or not, thus resulting in registered overuse in the pharmacy data.

An explanation for underuse with an MDI can be that a patient can still actuate the inhaler with little or no drug beyond the maximum number of dosages left in the canister, which is not signaled by lack of a dose counter. The pharmacy data will register underuse while a patient may believe he/she is still using the medication properly. This was confirmed with the interview data in *chapter 5* where underusers stated to use their MDI until it stops, which is using an inhalation device too long after it is empty. In *chapter 5* patients described putting a reminder on their calendar to replace an MDI for inhaled medication with a regular dosing scheme. In the pharmacy, this advice could be given to support patients with their adherence. In addition, when a device does not provide feedback on actually inhaling, a patient can feel the need to load a dose and/or inhale again to be sure about inhaling a dose, which results in overdosing. For example, the medication in the Turbuhaler has no taste in contrast to the medication in the Diskus, which can be tasted distinctly after inhalation. It is plausible this can make a patient insecure about whether or not they have actually taken the medication, resulting in an extra inhalation just to be sure.

Another aspect that could influence adherence is incorrect inhalation technique. Studies have shown that many patients mishandle their inhalation devices. Melani et al. found at least one critical error among a substantial amount of users for several devices, ranging from 12% for MDI's, 35% for Diskus and Handihaler and 44% for Turbuhaler. (16) Critical inhalation errors are errors that result in reduced delivery of medication into the lungs. (16,17) It is possible that a patient does not benefit from the medication due to a poor technique and feels the need to repeat inhalation in order to reach a desired effect, resulting in registered overuse. Although manufacturers have recognized the problem of difficult inhalation devices and introduced new inhalers like Ellipta and Genuair, which showed fewer critical inhalation errors compared to devices like Diskus and Turbuhaler, older devices including MDI are still widely used and new devices with the possibility of critical inhalation errors like Elpenhaler are introduced. (18-20) Spacers can be used to minimize problems with lung-hand coordination with an MDI and increase lung deposition. (21) However, not every patient uses a spacer, which was shown by the statement in *chapter 5* of a patient that he

“just doesn’t like his spacer”. Because there were no data available on inhalation technique and spacer use could not be derived from our database, the influence of inhalation technique and spacer use on adherence could not be studied in this thesis.

The past few years, after the data collection of the COMIC cohort ended, many patents of inhaled medication have expired and generics have been introduced to the market. Although at the introduction of different inhaled therapy options manufacturers chose color-coding for their devices like blue for short acting beta 2 mimetics (SABA) and brown for ICS, the generic manufacturers introduced a wide range of new devices and new colors for their devices. This made it difficult for COPD patients to recognize their medication by color and appearance. These changes could result in non-adherence because we have shown that patients already had little knowledge on the mechanisms of action of medication, and when which medication should be used. To support patients in their medication use, remembering which medication does what, each category of inhaled medication should have a distinct color scheme. All the issues stated above tell us that an inhalation device should be designed in such a way that patients should be able to load a device only once prior to inhaling with as little handling steps as possible, the device should give feedback on inhaling, and it should be compulsory for manufacturers to put a dose counter on their device. In case of suspicion of overuse an electronic counting device with flow-meter could help to analyze and tackle this problem. (22,23)

Patient related factors

Differentiating therapy adherence into four instead of just two adherence categories turned out to be very informative as different patient characteristics were related to different non-adherence categories. Defining non-adherence solely as using less than 80% of prescribed doses ignores the fact that patients with suboptimal adherence are different from patients that use even less medication. Defining optimal adherence as >80% without setting a maximal optimal level leaves non-adherence in the form of overuse undetected while these patients can have serious problems that deserve attention. In *chapter 2 and 3* for example, we have shown that FEV₁ levels at baseline were related to poor adherence, both underuse and overuse, but in different ways. While underuse was associated with a higher lung function at baseline compared to good adherence, overuse was associated with a lower lung function at baseline compared to good adherence.

In *chapter 4* lung function showed even to be an independent predictor for adherence to both ICS and Tiotropium. It is possible that patients with a better lung function feel less need to use their medication and therefore show lower adherence levels. This assumption was supported by the interview data in *chapter 5* where underusers stated they used less medication because they felt well and did not want to use too much medication.

Various disease-specific and HRQoL factors showed in *chapter 4* to be related to therapy adherence to both ICS and tiotropium. In this chapter, we studied whether HRQoL measurements could predict non-adherence and observed that having more anxiety for dyspnea was a predictor for overuse. Since overuse was also more prevalent in patients with a worse lung function and a higher mMRC, it seemed that overuse was related to disease severity. It is important to take into account the fact that registered overuse not necessarily means overconsumption but can also result from discarding an inhalation device before it is empty. As was shown in the in depth interviews in *chapter 5*, where patients admit to discarding devices before they are empty because they are afraid to run out of their inhaled medication. This is also supported by the tendency of overusers to catastrophize when the inhaled medication is not at hand (patients returning home to pick up their forgotten inhalation device), as described in *chapter 5*.

In *chapter 4* current smoking was shown to be a predictor for overuse but not underuse. Perhaps current smoking increases dyspnea and therefore increases the need for inhaled medication use. In literature, smoking is associated with non-adherence in the form of lower adherence, this association could not be confirmed with the COMIC data. (24,25)

Anxiety and depression are both known factors that increase non-adherence independent of lung function. (26) It is a very relevant co-morbidity in COPD and in *chapter 5* we showed that many of the interviewed patients had signs of depression and fatigue. In addition, overusers reported more grief about losing participation in daily life and were more often irritable. It is therefore important to recognize depression in COPD patients. Next to this, 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. Data on anxiety as co-morbidity were not available for the COMIC cohort and therefore the influence of anxiety on adherence could

not be studied. We did find that fear of dyspnea was a predictor for overuse, but fear of dyspnea and anxiety are not necessarily the same. We do not know whether patients experiencing anxiety are also patients with high scores on fear of dyspnea. Future research could focus on the differentiation and/or potential overlap between anxiety in general and fear of dyspnea specifically.

Fatigue has also been shown to be associated with medication non-adherence. (27) Physical health, including fatigue and physical functioning is an important domain of HRQoL in patients with COPD. (28) Perhaps fatigue can be a predictor for non-adherence as well, because many of the interviewed patients in *chapter 5* showed signs of fatigue. In the current study, except for the twenty interviewed patients, no data were available on depression and/or fatigue. Future research could investigate the role of these factors on adherence in COPD in more detail.

Morbidity and mortality

Regarding adherence and risk of having a severe COPD exacerbation that needs hospitalization (AECOPD), an independent association with adherence to ICS could not be demonstrated, whereas non-adherence to tiotropium was associated with an increased risk. For tiotropium the risk even seems to increase as adherence rates decrease, with higher risks in underusers than suboptimal users. A reason for taking less tiotropium could be that the patient is feeling well and does not see the need for using tiotropium. This is supported by the results that underuse is associated with better lung function at baseline. Whether the association between overuse of tiotropium and increased risk of severe AECOPD and CAP was caused by the medication or the underlying disease, although we corrected for lung function and mMRC, cannot be proven due to the observational nature of the data. Since overuse is associated with lower lung function and a higher mMRC score at baseline, it seems that overuse is related to COPD severity, and consequently could explain the increased risk. Overuse could be due to an overall poor health condition, which results in feeling the urge to use more medication.

LABA/ICS combinations are indicated for patients with severe to very severe COPD and a history of repeated exacerbations. (5) In *chapter 6* we could not demonstrate an independent association between adherence to ICS and a hospital admission for a severe AECOPD. This raises the question whether the patients treated with ICS had an indication for ICS use; in other words were they severe COPD patients,

the ones with a history of a high frequency of exacerbations? Literature suggests that an informative relationship exists between pretreatment blood eosinophil levels and reduction in the frequency of COPD exacerbations with ICS/LABA treatment. Pavord et al. concluded in a review of studies of fluticasone/salmeterol (FS) in patients with COPD executed by to prove whether blood eosinophil levels $>2\%$ were associated with a greater reduction in exacerbation rates with ICS therapy, that FS was associated with significant reductions in exacerbation rates versus tiotropium and placebo. (29) In contrast, none of the treatment comparisons (FP versus placebo, versus fluticasone or salmeterol alone, or versus tiotropium) in the $>2\%$ eosinophils subgroup were statistically significant for time to first moderate/severe exacerbation, but this analysis was limited by lack of power resulting in wide 95% CI margins. (29) Unfortunately, pretreatment blood eosinophil levels were not available for the COMIC cohort, therefore this line of thought could not be studied and in our analyses, and so we could not correct for exacerbation rate or blood eosinophil levels.

With regard to adherence and CAP, an independent association with adherence to ICS could not be demonstrated. Whereas suboptimal use and overuse of tiotropium were associated with an increased risk of CAP, the COMIC data could not confirm the increased risk of pneumonia by use of ICS as shown in other studies, such as the TORCH study. (30) Our assumption that a higher intake (overuse) might result in a higher pneumonia risk and less medication use (suboptimal use and underuse) in a lower pneumonia risk was not confirmed. The results of the in depth interviews in *chapter 5* showed that overuse registered in pharmacy records not necessarily means overconsumption (e.g. devices discarded before they were empty), which means that the patient might not have received a higher dosage that could result in a higher pneumonia risk. Observational studies showing an increased risk of pneumonia with ICS use are possibly affected by the fact that patients with COPD who use ICS have more severe COPD and severe COPD in itself results in an increased pneumonia risk. In our analyses, we corrected for lung function, thus taking a marker for severity of COPD into account. Furthermore, the diagnosis of pneumonia was X-ray confirmed in the COMIC cohort, which was not the case in the TORCH study. This could have led to misclassification of CAP in the TORCH study.

With regard to adherence and mortality, suboptimal use and underuse of ICS and tiotropium were associated with a substantially increased

mortality risk compared to optimal use. For ICS this risk seems even more increased in underusers, who show an almost two-fold increased mortality risk compared to suboptimal users, which implies the need to make a distinction in type of non-adherence. In addition to the adherence data, a lower lung function at baseline was associated with a higher risk of hospital admission for a severe AECOPD, CAP, and dying. Next to this, a higher mMRC score at baseline was associated with a higher risk of severe AECOPD and a higher risk of dying in both ICS and tiotropium users (*chapter 6*).

Overall, non-adherence is related to increased morbidity and mortality risks. The results seem to implicate that a worse COPD status, as might be expected, increases morbidity and mortality risks.

Innovative in this thesis is the differentiation of non-adherence, especially for patients that use less than optimal. Not only underuse but also suboptimal use showed increased risks, which should be subject to further research into how to optimize adherence in these patients and potentially lower their risks. This trigger for optimization of adherence will be mainly new for suboptimal patients who are nowadays often not confronted with their lower adherence rate in for example the pharmacy.

Strengths

Strengths of the data of the COMIC cohort are the validated COPD diagnosis and the chance to assess the effect of inhaled medication in real life COPD outpatients and not a selected trial population. Next to the valid diagnosis, the available data on lung function, co morbidities, X-ray confirmed pneumonia, and HRQoL enabled us to study adherence to inhaled medication in a broad context. In addition, the use of pharmacy refill records for estimating adherence could be seen as strength. This method allowed us to obtain objective data and avoid recall and social desirability biases. In addition, computerized drug-dispensing histories from Dutch pharmacies are virtually complete because of a strong pharmacy-patient liaison for reimbursement of prescription drugs, a high degree of computerization, the use of standardized classification and coding systems, and a strong commitment of pharmacists to surveillance of medication. Next to this, the research period of three years is an asset because COPD is a chronic condition with long term medication use.

Limitations

Measuring adherence with pharmacy data: The problem with pharmacy data is they represent medication a patient collects and not the actual inhalation. Factors like dose dumping and dosage changes without a new prescription are not taken into account. Overall pharmacy data show the maximum potential levels of drug use and it is likely that the inhaled drug volumes are lower than the volumes dispensed by the pharmacy. (31,32)

Although the pharmacy data possibly do not completely reflect the actual ingestion of the medication, the three-year period of follow up increases validity of the registered adherence, especially for suboptimal use and underuse, because it is not possible for a patient to be classified as optimally adherent if not enough inhaled medication is collected. Therefore, the data enable us to distinguish different adherence categories and study the characteristics of these groups of patients. In future Dutch research the value of pharmacy data can be limited. In Dutch pharmacies, the last decade a new development called "Pro Active repeating prescriptions" has been introduced and has become very popular the past few years. Patients receive medication when the pharmacy-computer has calculated the medication at home is almost used up. The initiative of collecting medication is transferred to the computer of the pharmacy and not driven by the actual medication use of the patient. This reduces the value of pharmacy data as an indication tool for adherence for future research but did not affect the COMIC dataset.

Adverse effects

This thesis has not addressed the influence of adverse medication effects on therapy adherence. In the in-depth interviews adverse medication effects, although addressed specifically, were not reported to a great extent. The COMIC cohort consisted of long-term COPD patients that already used their inhaled medication over a prolonged period. It is feasible that some patients experienced adverse medication effects that were bothersome at the start of a therapy, which resulted in a change of therapy. These patients have subsequently received a therapy they were willing and able to use over a long period of time, which could explain the low number of reported adverse effects.

In-depth interviews: A weakness in *chapter 5* is that the interview data and pharmacy data were not collected in the same research period. Although this might be a weakness, given the stability of medication

intake in chronic disease and the three year follow up in the COMIC cohort, this limitation should not be overestimated. A missed opportunity is the omission of interview data on patients with optimal (and suboptimal) medication use. It would be interesting to investigate how patients with optimal adherence use their medication, and integrate their medication use in their daily life. It is likely that there are lessons to be learned from the substantial group of adherent patients that can be used in guiding non-adherent patients.

Definitions of non-adherence: Since there are no uniform definitions available on optimal adherence and non-adherence comparing research is difficult. In accordance with the introduction of the Ascertaining Barriers to Compliance (ABC) taxonomy, an initiative of the European Union to standardize adherence-related terminology for clinical and research use (33,34), the introduction of a standard for adherence levels could be very useful. Given the results with the four categories in this thesis we suggest the introduction of the differentiation of non-adherence in future research.

Recommendations and implications for future research and practice

In this thesis, we have shown that differentiating non-adherence in COPD into four categories is meaningful, because poor adherence including suboptimal use, underuse and overuse to ICS and tiotropium was related to higher mortality risk described in *chapter 6*. Next to this, non-adherence to tiotropium was related to higher morbidity. The patients that show under- and overuse have different disease specific factors such as lung function and HRQoL. This information can trigger health care providers to investigate the possibility of non-adherence. Especially the group of patients with suboptimal use should be subject for further study. The step these patients have to make to become optimal users with hopefully optimal effect of the medication is smaller than of those with underuse but research is needed to confirm that improving adherence reduces morbidity and mortality risks. The detection of this group of patients is a challenge. In the daily practice of a pharmacy, these suboptimal adherent patients are not extremely late for collecting their medication, which does not necessarily triggers a conversation on adherence and in contrast, physicians often do not have prescription data available. Patient-health care professional communication, especially between patient and physician or pharmacist, is central to optimizing patient adherence. (35)

Pharmacists can play an important role in an integrated COPD patient care pathway because they are ideally placed to provide information on disease awareness and risk prevention. Pharmacists can assist patients by providing advice and education on dosage, inhaler technique, treatment expectations and the importance of adherence, and by supporting self-management. Next to this, pharmacists can play an important role in monitoring adherence and ongoing inhaler technique in patients with COPD. (36)

Risk reduction of morbidity and mortality are possibly not terms that have meaning for a patient and are not convincing enough for a patient to use inhaled medication optimally. There is limited published research into what really matters to people living with COPD. Most research in this area focuses on the impact of the symptoms of COPD, rather than on the issues defined as important by the patients themselves. (37) Williams et al. described that COPD patients considered engagement in specific activities like walking, household maintenance and driving, to be very important, even though these activities were mainly centered around the home environment, or within confined spaces, due to their physical limitations. (37) This restriction led to feelings of social isolation that these people tried to overcome through social participation. (37) This is supported by the interviewdata in *chapter 5* where overusers showed grief about losing participation in daily life. So maybe the focus in addressing adherence should be on improving everyday life activities. The question remains whether this approach also can be used to motivate suboptimal users and underusers to improve their adherence.

When we take into account, the fact that these patients have had substantial amounts of education on their disease and their medication by nurse practitioners, their physicians and their pharmacists, the question of “are we on the right track?” arises. It seems inhalation therapy in COPD is too complex. The Dutch association of pharmacists (KNMP) has recognized the problem of health literacy and launched in 2015 a campaign to address this issue, including the introduction of a series of pictograms explaining the mechanism of different medication categories. This line of thought could be extended to the use of color-coding for the inhalation devices. Whether pictograms and color-coding improves adherence, should be subject for further research.

Advise for healthcare providers in daily practice

Providing a profile or a tool for recognizing a non-adherent patient in daily practice is not an easy task. If non-adherence is detected several aspects have to be investigated.

1. Is the non-adherence intentional, driven by (lack of) disease severity? In the case of underuse does a patient choose to use less medication (because he feels well or claims he does not want to use too much). Or, in the case of overuse is the patient using more than prescribed due to (fear of) dyspnea?
2. Is the non-adherence device- or inhalation technique related?
3. Does the patient experience adverse effects? This can be a trigger for underuse but also have a negative effect on HRQoL.
4. What is the knowledge of a patient regarding the medication and the device?
5. If a patient uses different types of inhaled medication it should be taken into account that one patient can show different adherence patterns for different medication.

Treating a patient means cooperation between the patient and different health care providers. Each discipline should contribute their own expertise and the line of treatment should support the other disciplines. A patient should receive the same advice from every health care provider and it is very important that information is not contradictory. Health care structures around COPD patients can be different depending on the region and local relationships between health care providers. Contact between disciplines asks for teamwork and it should be easy for a physician to contact a pharmacist to inform about medication related issues and vice versa. In my opinion, the local pharmacist should be the leading health care provider with regard to patient adherence in COPD. Every patient should receive a tailored advice and interventions that are developed to improve adherence need to be adapted to incorporate different types of non-adherence for different types of medication. Since factors associated with long-term adherence to medications for the treatment of COPD likely differ by medication class, health care providers should inquire separately about the use of inhaled therapies and, in any case, potential interventions may need to be medication specific. (3,35)

The field needs pioneers who can bring different health care disciplines together and lift guidance to improve therapy adherence in COPD to the next level. However, in the end, after receiving optimal support from all health care providers, it is the patients who decide how to use their medication.

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Summary

8

Summary

Chronic obstructive pulmonary disease (COPD) is currently the fourth most common cause of death in the world and a major cause of chronic morbidity and mortality. Appropriate pharmacotherapy with inhaled medications can reduce mortality, symptoms, and the frequency and severity of exacerbations, and can improve health status and exercise tolerance. The effectiveness of inhaled medications is strongly influenced by the patient's therapy adherence. This thesis describes therapy adherence in COPD based on data of the "Cohort of Mortality and Inflammation in COPD" (COMIC) study, a single centre prospective cohort study in the Medisch Spectrum Twente hospital, Enschede, located in the Eastern part of the Netherlands. From December 2005 till April 2010, 795 patients were included with a follow-up period of three years.

Non-adherence can present itself in different forms and can be unintentional as well as intentional. In order to differentiate adherence we introduced four adherence categories. We chose two lower cut-off points to distinguish suboptimal (50-<75%) and underuse (<50%) and an upper cut-off point for optimal adherence (75-125%) to identify overuse (>125%).

In *chapter 2* we described the differences in adherence to common inhaled medications including long acting muscarinic agonists (LAMA), inhaled corticosteroids (ICS), long acting beta agonists (LABA) and ICS/LABA combinations. The percentage of patients with optimal adherence described in *chapter 2* was high compared to literature, varying from 43.2 up to 75.8%, especially keeping in mind that the study was carried out in real life COPD patients who were not aware that the pharmacy data were going to be used to study adherence. In Twente, a region in the eastern part of the Netherlands, these results are in line with a national observational study that showed higher adherence levels in this region compared to other regions in the Netherlands.

While underuse was associated with a higher lung function at baseline compared to optimal adherence, overuse was associated with a lower lung function at baseline compared to optimal adherence. We observed that medications dosed once daily, tiotropium and ciclesonide, showed the highest percentage of patients with optimal adherence of respectively 75.8 and 68.2%. The idea of improving adherence by combining two medications (fluticasone/salmeterol, ICS /LAMA) in one device could not be confirmed in this thesis. This might be caused by a kind of selection

bias where a prescriber chooses a combination preparation for a patient with a problematic or suspected low adherence. In this way a combination preparation is introduced to a patient with a tendency for low adherence.

In *Chapter 3* the influence of type of inhalation device on medication adherence of the inhaled medication of patients with COPD studied in *chapter 2*, is described. Adherence to inhaled medication was device related. The highest percentage of optimal therapy adherence described in *chapter 3* was 78% for the Handihaler. However, this result cannot be seen as solely contributed by the device. One has to take into account the fact that the Handihaler is used for tiotropium, a medication with dyspnea relieving effect and once daily dosing. In addition, overuse was found most often in the Metered Dose Inhaler (MDI) (14%) and Turbuhaler (27%). Overuse can be due to both wasting of medication and overdosing. The ability of a device to release a dosage without actually inhaling increased the risk of overuse as registered in pharmacy records. In addition, most MDI's do not have a dose counter to indicate how many dosages are left, and perhaps patients perform "test puffs" to verify that there is still medication left in the MDI. And medication in the Turbuhaler has no taste, this can make a patient insecure about whether or not they have actually taken the medication, resulting in an extra inhalation. Therefore, the design of the device seemed to be related to underuse and overuse of inhaled medication.

In *chapter 4* we conducted a study to identify disease-specific and HRQoL factors that are associated with adherence to inhaled corticosteroids (ICS) and tiotropium in patients with COPD. Lung function showed to be an independent predictor for adherence to both ICS and Tiotropium. Patients with a higher lung function and ≥ 1 hospitalizations in the year prior to inclusion in this study had an increased risk of suboptimal adherence to ICS instead of optimal adherence. Next to this, an increased risk of underuse was predicted by a higher lung function. Predictors for the risk of overuse were a lower lung function, higher scores on Clinical COPD Questionnaire-question 3 (anxiety for dyspnea), and current smoking. Regarding tiotropium, predictors for suboptimal use were also a higher lung function and the inability to perform usual activities as asked by the EuroQol-5D questionnaire. A higher lung function was a predictor for the risk of underuse compared to optimal adherence. The risk of overuse increased again with higher scores on Clinical COPD Questionnaire-question 3 which asks about the concern for breathing

getting worse. Overall we observed that having more anxiety for dyspnea was a predictor for overuse. Since overuse was also more prevalent in patients with a worse lung function, it seemed that overuse was related to disease severity. Although several disease-specific and quality of life factors are related to ICS and tiotropium adherence, a clear profile of a non-adherent patient cannot yet be outlined.

In *chapter 5* the results of the previous chapters were completed with the COPD patients' point of view on adherence and the disease COPD, studied with in depth interviews.

The interview data showed that the non-adherent patients had little knowledge of COPD and how to manage their COPD. In addition, there was a lack of knowledge about the mechanisms of action of medication, and when which medication should be used. Next to this, many patients stated that they did not accept their disease.

Underusers and overusers showed a different pattern in perceptions and beliefs on inhaled medication. For example, overusers reported more grief about decreased participation in daily life and were more frustrated in general. Main findings for beliefs and perceptions about the inhaled treatment were that underusers claimed using less medication because they felt well, did not want to use too much medication and used their inhalation devices too long after they were empty. Overusers reported medication "dependency" in the sense that they tend to catastrophize when being without medication and discarded inhalation devices too early because they feared to run out of medication. These differences and the above mentioned practical issues provide possible explanations for the registered under- and overuse. When under- or overuse is detected, for example in a pharmacy, it is important to investigate the underlying reasons. Is the under- or overuse related to practical issues regarding knowledge on the inhaled medication or device or is the adherence influenced by beliefs and/or anxiety concerning COPD or medication? These issues need to be addressed when we want to improve therapy adherence.

Chapter 6 describes the association between therapy adherence with ICS and tiotropium and morbidity and mortality. Regarding adherence and risk of having a severe COPD exacerbation that needs hospitalization (AECOPD), an independent association with adherence to ICS could not be demonstrated, whereas non-adherence to tiotropium was associated with an increased risk. Non-adherence to ICS was not related to time to first community

acquired pneumonia (CAP), whereas suboptimal and overuse of tiotropium were associated with an increased risk compared to optimal use. With regard to adherence and mortality, suboptimal use and underuse of ICS and tiotropium were associated with a substantially increased mortality risk compared to optimal use. The risk even seems to increase as adherence rates decrease, with even higher risks in underusers than suboptimal users. These effects could possibly be caused by the fact that the patient misses the protective effect of the medication. A reason for taking less medication could be that the patient is feeling well and does not see the need for using.

In addition to the adherence data, a lower lung function at baseline was associated with a higher risk of hospital admission for a severe AECOPD, CAP, and dying. Next to this, a higher mMRC score at baseline was associated with a higher risk of severe AECOPD and a higher risk of dying in both ICS and tiotropium users.

Whether the association between overuse of tiotropium and increased risk of severe AECOPD and CAP was caused by the medication or the underlying disease, although we corrected for lung function and mMRC, cannot be proven due to the observational nature of the data. Since overuse is associated with lower lung function and a higher mMRC score at baseline, it seems that overuse is related to COPD severity, and consequently could explain the increased risk. Overuse could be due to an overall poor health status, which results in feeling the urge to use more medication.

In *chapter 7*, the general discussion, we summarize our findings and provide a wider context. This chapter is concluded with the following recommendations for health care providers in daily practice and future research:

It seems inhalation therapy in COPD is too complex and information inserts with the dispensed medication do not guarantee adequate use of inhaled medication. Whether pictograms can improve adherence, should be subject for further research. At the introduction of different inhaled medication classes manufacturers chose color-coding for different therapy options to help the patient. Current generic manufacturers have introduced a wide range of new colors thus making it more difficult for patients with COPD to recognize their various medications. The use of color-coding for the inhalation devices could support patients in their medication use, remembering which medication does what. Also an inhalation device should be designed in such a way that patients should

be able to load a device only once prior to inhaling with as little handling steps as possible, the device should give feedback on inhaling, and it should be compulsory for manufacturers to put a dose counter on their device.

Providing a profile or a tool for recognizing a non-adherent patient in daily practice is not an easy task. If non-adherence is detected several aspects have to be investigated.

1. Is the non-adherence intentional, driven by (lack of) disease severity?
In the case of underuse does a patient choose to use less medication, because he feels well or claims he does not want to use too much.
Or, in the case of overuse is the patient using more than prescribed due to fear of dyspnea?
2. Is the non-adherence device- or inhalation technique related?
3. Does the patient experience adverse effects of the medication? This can be a trigger for underuse but also have a negative effect on HRQoL.
4. What is the knowledge of a patient regarding the medication and the device?
5. If a patient uses different types of inhaled medication it should be taken into account that one patient can show different adherence patterns for different medication.

Treating a patient means cooperation between the patient and various health care providers. Every patient should receive a tailored advice and interventions that are developed to improve adherence. These need to be adapted to incorporate different types of non-adherence for different types of medication. Local pharmacists can play an important role in an integrated COPD patient care. Pharmacists can assist patients by providing advice and education on dosage, inhaler technique, treatment expectations, the importance of adherence, and by supporting self-management. Next to this, pharmacists can play an important role in monitoring adherence and ongoing inhaler technique in patients with COPD.

Samenvatting

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Samenvatting

Chronic obstructive pulmonary disease (COPD) is op dit moment de vierde meest voorkomende doodsoorzaak in de wereld en een grote bron van ziektelast en sterfte. Farmacotherapie met inhalatiemedicatie kan de kans op vroegtijdige sterfte, symptomen en de frequentie en zwaarte van exacerbaties verminderen. Het kan daarnaast de gezondheidstoestand en de inspanningscapaciteit verbeteren. De effectiviteit van inhalatiemedicatie wordt sterk beïnvloed door de therapietrouw van de patiënt. Dit proefschrift beschrijft de therapietrouw bij COPD en is gebaseerd op data van de "Cohort of Mortality and Inflammation in COPD" (COMIC) studie. De COMIC studie is een single centre prospectieve cohort studie in Medisch Spectrum Twente ziekenhuis te Enschede in het oosten van Nederland. Er werden 795 patiënten geïnccludeerd van december 2005 tot April 2010, met een follow-up periode van drie jaar. Therapieontrouw heeft verschillende verschijningsvormen en kan zowel bewust als onbewust optreden. Om differentiatie in therapietrouw aan te kunnen brengen hebben we in dit proefschrift vier therapietrouw-categorieën geïntroduceerd. We hebben gekozen voor twee afkapwaarden voor verminderde therapietrouw, 50- <75% voor suboptimaal en <50% voor ondergebruik en een maximum voor optimaal gebruik (75-125%) om tevens overgebruik (>125%) in kaart te brengen.

In *hoofdstuk 2* worden de therapietrouwverschillen beschreven van de gangbare inhalatiemedicatie bij COPD, waaronder langwerkende muscarine agonisten (LAMA), inhalatiecorticosteroiden (ICS), langwerkende beta-2-agonisten (LABA) en ICS/LABA combinatiepreparaten. Het percentage patiënten met optimale therapietrouw was hoog ten opzichte van de literatuur, variërend van 43,2 tot 75,8%. Het lijkt ook vooral hoog omdat in deze observationele studie de COPD patiënten zich niet bewust waren van het feit dat de apotheekgegevens gebruikt zouden worden voor het bepalen van therapietrouw. De beschreven resultaten komen overeen met een Nederlandse observationele studie waaruit bleek dat in de regio Twente, in het oosten van Nederland, sprake was van betere therapietrouw niveaus ten opzichte van andere regio's. Ondergebruik was geassocieerd met een betere longfunctie aan het begin van de studie vergeleken met patiënten met optimaal gebruik, terwijl overgebruik was geassocieerd met een lagere longfunctie aan het begin, ook weer vergeleken met patiënten met optimaal gebruik. We zagen het hoogste percentage

patiënten met optimale therapietrouw (75,8 en 68,2% respectievelijk) bij inhalatiemedicatie met een eenmaaldaagse dosering, tiotropium en ciclesonide. Het concept om therapietrouw te verbeteren door twee middelen in één inhalator te combineren (ICS/LABA combinatie fluticason/salmeterol) kon in dit proefschrift niet worden bevestigd. Dit kan mogelijk veroorzaakt worden door een vorm van selectiebias waarbij de voorschrijver kiest voor een combinatiepreparaat voor een patiënt bij wie een verminderde therapietrouw verwacht wordt.

In *hoofdstuk 3* wordt de invloed van het type inhalator op therapietrouw van de medicatie, beschreven in *hoofdstuk 2*, bestudeerd. Therapietrouw van inhalatiemedicatie is gerelateerd aan de inhalator. Het hoogste percentage patiënten met optimale therapietrouw werd beschreven voor de Handihaler, namelijk 78%. Maar dit resultaat kan niet alleen worden toegeschreven aan de inhalator. Er dient rekening gehouden te worden met het feit dat de Handihaler gebruikt wordt voor het inhaleren van tiotropium, een geneesmiddel dat benauwdheidsklachten verminderd en slechts eenmaal daags gebruikt hoeft te worden. Overgebruik werd het meest geregistreerd voor de Turbuhaler (27%) en de dosisaerosol (14%). Overgebruik kan het gevolg zijn van zowel verspilling als overdoseren. De mogelijkheid van een inhalator om een dosis af te geven zonder daadwerkelijk te inhaleren, vergroot het risico op overgebruik, zoals geregistreerd met behulp van apotheekgegevens. Daarnaast hebben veel dosisaerosolen geen teller om aan te geven hoeveel doseringen het nog bevat; het is mogelijk dat patiënten een 'test puf' gebruiken om te kijken of er nog medicatie in de inhalator zit. Bovendien heeft de medicatie in de Turbuhaler geen smaak, wat een patiënt onzeker kan maken of de medicatie daadwerkelijk genomen is, resulterend in een extra inhalatie om zeker te zijn. Daarom lijkt het ontwerp van een inhalator gerelateerd aan onder- en overgebruik van inhalatiemedicatie.

In *hoofdstuk 4* is een studie uitgevoerd om ziekte-specifieke en kwaliteit van leven-specifieke factoren te identificeren die voorspellend zijn voor therapietrouw van ICS en tiotropium in COPD patiënten. Longfunctie bleek een onafhankelijke voorspeller te zijn voor therapietrouw met zowel ICS als tiotropium. Patiënten met een betere longfunctie en ≥ 1 ziekenhuisopname in het jaar vóór inclusie hadden een verhoogd risico op suboptimaal gebruik van ICS ten opzichte van patiënten met optimaal gebruik. Daarnaast voorspelde een betere longfunctie een verhoogd risico op ondergebruik. Voorspellers voor een verhoogde

kans op overgebruik waren een lagere longfunctie, hogere scores op de Clinical COPD Questionnaire-vraag 3 (angst voor toename benauwdheid) en roken.

Wat betreft de therapietrouw van tiotropium waren voorspellers voor suboptimaal gebruik eveneens een betere longfunctie en het onvermogen om dagelijkse activiteiten uit te voeren zoals uitgevraagd met de EuroQol-5D vragenlijst. Opnieuw was een betere longfunctie een voorspeller voor ondergebruik vergeleken met patiënten met optimaal gebruik. Ook nam hier het risico op overgebruik toe bij hogere scores op de Clinical COPD Questionnaire-vraag 3, (angst voor de toename van benauwdheidsklachten).

Hoewel meerdere ziektefactoren en kwaliteit van leven factoren samen hingen met therapietrouw van ICS en tiotropium is het nog niet mogelijk een duidelijk profiel van een patiënt met slechte therapietrouw op te stellen.

In *hoofdstuk 5* worden de resultaten uit de voorgaande hoofdstukken met behulp van diepte-interviews aangevuld vanuit de optiek van de COPD-patiënt. De interviews gingen over therapietrouw en percepties en overtuigingen betreffende de ziekte COPD en de gebruikte medicatie. De gegevens uit de interviews lieten zien dat de patiënten met therapieontrouw over weinig kennis van de ziekte COPD beschikten en over hoe ze hun ziekte in goede banen konden leiden. Daarnaast was er sprake van een gebrek aan kennis op het gebied van de werkingsmechanismen van de verschillende geneesmiddelen en wanneer welk specifiek geneesmiddel gebruikt zou moeten worden. Bovendien gaven veel patiënten aan dat ze niet konden accepteren dat ze de ziekte COPD hadden. Onder- en overgebruikers vertoonden een ander patroon wat betreft percepties en overtuigingen over inhalatiemedicatie. Overgebruikers rapporteerden bijvoorbeeld meer verdriet over het niet meer mee kunnen doen met dagelijkse activiteiten en waren in het algemeen meer gefrustreerd. De belangrijkste bevindingen over de percepties en overtuigingen rond inhalatiemedicatie waren dat ondergebruikers aangaven minder medicatie te gebruiken omdat ze zich goed voelden, omdat ze niet te veel medicatie wilden gebruiken en dat inhalatoren te lang werden doorgebruikt nadat de inhalator al leeg was. Overgebruikers rapporteerden meer "afhankelijkheid" van inhalatiemedicatie, spraken over "in paniek raken" als de medicatie niet voor handen was en over het vervroegd weggooien van inhalatoren omdat men bang was dat er geen medicatie meer vrij kwam bij

inhalatie.

De hierboven beschreven verschillen zowel in instelling als in praktisch gebruik, geven mogelijke verklaringen voor het geregistreerde over- en ondergebruik in de apotheekdata. Wanneer over- en/of ondergebruik worden gesignaleerd, bijvoorbeeld in de apotheek, is het belangrijk om op zoek te gaan naar de onderliggende redenen. Wordt het onder- of overgebruik veroorzaakt door (gebrekkige) kennis over de inhalatiemedicatie en/of de inhalator of is er sprake van overtuigingen en/of angst betreffende de ziekte COPD of de medicatie. Als we therapietrouw willen verbeteren is het van belang om aan alle hierboven benoemde zaken aandacht te besteden.

Hoofdstuk 6 beschrijft de associatie tussen therapietrouw met ICS en tiotropium en morbiditeit en mortaliteit. Er kon geen associatie worden aangetoond tussen therapietrouw met ICS en het risico op een COPD exacerbatie waarvoor een ziekenhuisopname noodzakelijk was. Een therapieontrouw met tiotropium was wel geassocieerd met een verhoogd risico hierop. Therapietrouw met ICS was niet geassocieerd met tijd tot eerste pneumonie, terwijl supoptimaal en overgebruik van tiotropium wel geassocieerd waren met een verhoogd risico ten opzichte van optimaal gebruik.

Suboptimaal en ondergebruik van zowel ICS als tiotropium waren geassocieerd met een substantieel verhoogd sterfterisico vergeleken met optimaal gebruik. Dit risico lijkt zelfs toe te nemen als de therapietrouw afneemt, met hogere risico's bij ondergebruik dan suboptimaal gebruik. Het is mogelijk dat dit veroorzaakt wordt doordat de patiënt het beschermende effect van de medicatie mist. Als een patiënt zich goed voelt kan dat een reden zijn minder medicatie te gebruiken omdat de patiënt geen behoefte voelt en/of het nut van de medicatie niet inziet. Een lagere longfunctie op aan het begin van de studie hing samen met een hoger risico op een ziekenhuisopname voor een ernstige exacerbatie, een hoger risico op een pneumonie en een hoger sterfterisico. Bovendien was een hogere dyspneu mMRC score (dit betekent dat een patiënt meer beperkt wordt door zijn kortademigheid) aan het begin van de studie geassocieerd met een hoger risico op een ziekenhuisopname voor een ernstige exacerbatie en met een hoger sterfterisico voor zowel ICS als tiotropiumgebruikers.

Of de associatie tussen het overgebruik van tiotropium en het verhoogde risico op een exacerbatie met ziekenhuisopname en pneumonie veroorzaakt werd door de medicatie of de onderliggende ziekte kan niet aangetoond worden door het observationele karakter van de data,

hoewel er wel gecorrigeerd werd voor longfunctie en mMRC. Overgebruik lijkt samen te hangen met de ernst van COPD aangezien overgebruik was geassocieerd met een lagere longfunctie en een hogere mMRC-score op baseline. Dit kan een verklaring zijn voor het verhoogde risico. Overgebruik kan het gevolg zijn van een slechte gezondheidstoestand die resulteert in een drang om meer medicatie te gebruiken.

In hoofdstuk 7 worden de bevindingen samengevat en in een ruimere context geplaatst. Dit hoofdstuk wordt afgesloten met aanbevelingen voor zorgverleners in de dagelijkse praktijk en voor toekomstig onderzoek.

Inhalatietherapie voor de behandeling van COPD lijkt te complex en de bijsluiters die bij de geneesmiddelen meegeleverd worden bieden geen garantie voor een adequaat gebruik van de inhalatiemedicatie. Toekomstig onderzoek is nodig om te bepalen of bijvoorbeeld het gebruik van pictogrammen therapietrouw bij COPD kan verbeteren. Toen de verschillende klassen inhalatiemedicatie op de markt gebracht werden, gebruikten de fabrikanten een kleurcodering voor de verschillende therapieopties om de patiënt te ondersteunen. De huidige generieke fabrikanten hebben echter een hele range van nieuwe kleuren geïntroduceerd die het herkennen van de verschillende middelen bemoeilijkt. Het gebruik van een kleurcodering zou een patiënt kunnen ondersteunen bij het onthouden welke medicatie wat doet. Daarnaast zou een inhalator zo ontworpen moeten worden dat een patiënt de inhalator kan laden met een zo beperkt mogelijk aantal handelingen, de inhalator zou feedback op een inhalatie moeten geven en fabrikanten moeten verplicht worden om een teller in de inhalator op te nemen. Het maken van een profiel of instrument voor het herkennen van een patiënt met therapieontrouw is geen gemakkelijke taak. Wanneer therapieontrouw opgemerkt wordt is het van belang om naar verschillende aspecten te kijken.

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1. Is er sprake van bewuste therapieontrouw, ingegeven door de ernst van de ziekte? Bij ondergebruik; kiest de patiënt er voor om minder medicatie te gebruiken omdat hij zich goed voelt of omdat hij niet te veel medicatie wil gebruiken? Of in het geval van overgebruik; gebruikt de patiënt meer medicatie dan voorgeschreven omdat er sprake is van angst voor benauwdheid?
 2. Wordt de therapieontrouw veroorzaakt door problemen met de inhalator of de inhalatie techniek?
 3. Heeft de patiënt last van bijwerkingen van de inhalatiemedicatie? Dit kan een trigger zijn voor ondergebruik maar kan daarnaast ook een negatief effect hebben op kwaliteit van leven.
 4. Hoe is het gesteld met de kennis van de patiënt op het gebied van de medicatie en de inhalator?
 5. Wanneer een patiënt verschillende types inhalatiemedicatie gebruikt moet er rekening gehouden worden met het feit dat er sprake kan zijn van verschillende therapietrouw patronen voor de verschillende middelen.

Bij de behandeling van een patiënt is er sprake van een samenwerking tussen de patiënt en verschillende zorgverleners. Iedere patiënt zou advies en interventies op maat moeten ontvangen die ontworpen zijn om therapietrouw te verbeteren. Lokale apothekers kunnen een belangrijke rol spelen bij geïntegreerde COPD zorg. Apothekers kunnen een patiënt begeleiden met advies en scholing op het gebied van dosering, inhalatietechniek, verwachtingen omtrent de therapie, het belang van therapietrouw en daarnaast ondersteunen bij zelfmanagement. Bovendien kan de apotheker een belangrijke rol spelen bij het volgen van therapietrouw en inhalatietechniek van COPD patiënten.

Dankwoord

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Dankwoord

Het is klaar! De wens om onderzoek te doen is vervuld met de hulp van heel veel mensen. Ik wil dan ook iedereen, die op welke wijze dan ook bij dit promotietraject betrokken is geweest, heel hartelijk bedanken. Zonder iemand te kort te willen doen, wil ik toch graag een aantal mensen in het bijzonder bedanken. Te beginnen met mijn promotor Job van der Palen. Beste Job, jouw vraag of ik iets zou kunnen met de medicatiegegevens van 800 COPD patiënten zette een trein in beweging die resulteerde in een heel interessante reis. Hartelijk dank! Gaandeweg het traject verschoof de directe begeleiding steeds meer naar Marjolein maar je bleef altijd makkelijk bereikbaar, een must voor iedere promovendus.

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Curriculum Vitae

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Curriculum Vitae

Kirsten Koehorst-ter Huurne was born on March 9th 1977 in Haaksbergen. After graduating from secondary school (Scholengemeenschap Het Assink in Haaksbergen) in 1995, she studied pharmacy at the Rijksuniversiteit Groningen. In 2002 she received her Master of Science degree in Pharmacy. After her graduation she started working as a pharmacist at Apotheek Stoop in Borne. In 2010 and 2011 she worked in Kringapotheek Lichtenvoorde in Lichtenvoorde and in November 2011 she started to work in Haaksbergen for "Maatschap Apotheken Haaksbergen" with quality management system as special interest.

In 2012 she started her PhD project at the department of Pulmonary Medicine of Medisch Spectrum Twente, Enschede. Her research was on therapy adherence to inhaled medication in COPD patients.

After her PhD defence, she will continue to work as a pharmacist in Maatschap Apotheken Haaksbergen, Haaksbergen.