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Assessment of adherence to inhaled maintenance therapy and risk of exacerbations for COPD(Chronic Obstructive Pulmonary Disease) patients using the TAI questionnaire.

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ASSESSMENT OF ADHERENCE TO INHALED MAINTENANCE THERAPY AND RISK OF EXACERBATIONS FOR COPD (CHRONIC OBSTRUCTIVE PULMONARY DISEASE) PATIENTS USING THE TAI QUESTIONNAIRE.

Mémoire présenté pour l'obtention

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Assessment of adherence to inhaled maintenance therapy and risk of exacerbations for COPD (Chronic Obstructive Pulmonary Disease) patients using the TAI questionnaire.

LEYDER Thomas

Abstract

Background:

COPD is a common disease and the third leading cause of death worldwide. Major symptoms are dyspnea, cough and sputum production. COPD patients can suffer from exacerbations which are acute episodes during which the symptoms and airflow limitation increase. Inhaled bronchodilators and corticosteroids are the main drugs used for maintenance therapy. Adherence in the COPD population is low, which can have an impact on the control of the disease. The test of adherence to inhalers (TAI) questionnaire was recently developed to assess COPD patient's adherence to inhaled treatments. However, this questionnaire has not yet been rigorously validated in the COPD population.

Aims:

Our research project aims at determining the factors associated with poor/good adherence by comparing the adherence to various patient, disease and treatment characteristics. The second objective of our study is to assess/validate the TAI more rigorously by comparing the results obtained thanks to the TAI with the drug dispensing data obtained from the referring pharmacist of the patients.

Methods:

75 COPD patients were recruited. These patients responded to various questionnaires (including the TAI questionnaire) to enable us to collect data on patient, disease and treatment characteristics. Drug dispensing data were obtained from the referring pharmacists.

Analysis:
The adherence rate of this study population was high (69% according to the TAI-10 score and 77% according to the drug dispensing data score).
Patients were classified into the adherent group or the non-adherent group according to their TAI-10 score and their drug dispensing data score. The TAI classification showed very few significant differences. However, the classification according to the dispensing data showed significant differences that seem to be consistent such as differences concerning the disease severity (p-value = 0.035), FEV1 post-bronchodilator (p-value = 0.029), having inhaled corticosteroids (p-value = 0.020) and having rescue therapy ((p-value = 0.039), …
We did not find an association between adherence and exacerbations.
The concordance of the 2 adherence scores was evaluated by regression analysis, Kappa hypothesis test and ROC analysis. All analyses (Kappa: 0.0598, r^2: 0.0108, ROC AUC: 0.5437) pointed to a bad concordance between the 2 methods for assessing adherence.

Conclusion:
There was no concordance between the two measures of adherence. Our results suggested that the two tools did not assess the same thing. Classification according to dispensing data did, however, allow us to find consistent differences with the literature. In our analysis we did not find an association between adherence and exacerbations.

Key words: Chronic obstructive pulmonary disease, adherence, inhaled treatments, dispensing data, TAI questionnaire.

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List of abbreviations

CAT: COPD Assessment Test

COPD: Chronic Obstructive Pulmonary Disease

DPI: Dry powder inhalers

FEV1: Forced Expiratory Volume in 1 second

FVC: Forced Vital Capacity

H0: Null hypothesis

ICS: Inhaled corticosteroids

LABA: Long-acting β_2-agonists

LAMA: Long-acting antimuscarinics

MMAS-8: Morisky medication adherence scale

mMRC dyspnea scale: modified Medical Research Council dyspnea scale

NS: Non significant

PMDI: Pressurized metered-dose inhalers

SABA: Short-acting β_2-agonists

SAMA: Short-acting antimuscarinics

SMI: Soft mist inhalers

TAI: Test of adherence to inhalers

1. Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a common, progressive and not fully reversible lung disease that affects airways and pulmonary alveoli. This illness is preventable and treatable. COPD is characterized by progressive airflow limitation and respiratory symptoms such as dyspnea, cough and sputum production. The major cause is smoking that induces chronic inflammation in both the airways and the peripheral lung leading to structural abnormalities. These include airway lumen narrowing and a drop in lung elastic recoil that are responsible for progressive airflow limitation. The progressive airflow limitation is reflected by the worsening in the FEV1 (forced expiratory volume in one second) value measured in the pulmonary function lab.[1,2,3]
People who suffer from COPD can undergo exacerbations during which symptoms are increased and require treatment adaptation.[4]

1.1. Prevalence, mortality, morbidity and economic burden

1.1.1. Prevalence

The worldwide prevalence is between 7 and 12% with a slight preponderance of men over women.[3] Furthermore, the prevalence increases with age.[3]
The prevalence of COPD is increasing over time. Indeed, in 1990, 227 million people were affected whereas in 2010, the number of cases rose to 384 million. In percentage, this corresponds to 10.7% and 11.7% of the whole adult population (aged more than 30) in 1990 and 2010, respectively (figure 1).[5]
COPD affects certain regions of the world more than others, prevalence increased between 1990 and 2010 all around the world. Europe and the American region are more affected than Africa. People living in urban areas are more at risk than those living in rural areas. This can be explained by the fact that rates of pollution and irritant molecules which influences the development of the disease are higher in city centres than in the countryside. (figure 1).[5]

	1990		2010		% increase in COPD cases
	Cases (millions)	Prevalence (%)	Cases (millions)	Prevalence (%)	
World	227.3	10.7 (7.3–14.0)	384.0	11.7 (8.4–15.0)	68.9
AFRO	14.1	9.8 (8.9–10.7)	28.5	11.4 (10.5–12.3)	102.1
AMRO	41.6	13.3 (12.9–13.7)	72.0	15.2 (14.9–15.5)	73.1
EMRO	13.4	11.8 (10.1–13.5)	29.3	13.4 (11.8–15.1)	118.7
EURO	54.2	11.8 (11.6–12.0)	66.4	13.7 (13.5–13.9)	22.5
SEARO	44.5	7.9 (7.5–8.4)	75.1	9.7 (9.3–10.1)	68.8
WPRO	59.5	9.2 (9.0–9.4)	112.7	11.1 (10.9–11.3)	89.4
Urban	120.9	13.2 (10.0–16.4)	230.3	13.6 (11.2–16.9)	90.5
Rural	106.3	8.8 (6.5–11.1)	153.7	9.7 (7.6–11.8)	44.6

Figure 1: Prevalence of COPD and evolution of the prevalence between 1990 and 2010 in different parts of the world.
Legend: EURO: European regions; WPRO: Western Pacific region; AMRO: American region; EMRO: Eastern Mediterranean region; AFRO: African region; SEARO: South East Asia region.

1.1.2. Mortality

COPD is the third leading cause of death worldwide. In 2017, 3.2 million people died from this disease worldwide. In 2040, the number of deaths is expected to reach 4.4 million.[4]

1.1.3. Morbidity

In addition to its influence on mortality, the disease has a huge impact on the quality of life and day-to-day activities of people.[3,6]

Moreover, COPD also has a large impact on health-related costs that are mainly driven by hospitalizations and doctor visits.[1]

Comorbidities such as cardiovascular disease and diabetes mellitus can have an impact. These concomitant conditions are related to ageing and smoking and can affect the patient's health, the way COPD is managed, the number and the need for hospitalizations and finally health-related costs.[1]

1.1.4. Economic burden

In the European Union, 6% of the total healthcare budget is devoted to respiratory diseases. COPD represents 56% (38.6 billion euros) of the costs of respiratory disease.[1]

1.2. Risk factors

1.2.1. Smoking

Smoking is the most important risk factor. 80% to 90% of COPD patients are smokers or ex-smokers. Furthermore, smoking can increase the relative risk for COPD mortality by 2 to 32 depending on different factors such as age and sex.[7]

The tobacco smoke contains particles that increase lung and airway inflammation and thus cause chronic airflow limitation and increase disease symptoms.[1,8]

1.2.2. Age and gender

Regarding gender, men have a greater likelihood of developing this disease but the difference between men and women decreases over time because the proportion of women who currently smoke is higher than before.[1]

Over time, exposure to noxious particles increases. This may explain the increased likelihood of developing the disease with ageing. Other explanations such as the functioning of the lungs that normally decreases with age are at play.[1,9]

1.2.3. Other factors

Other factors increase the risk of developing COPD such as the genetic background or early life events.[1,9] A deficiency in of the serine protease α1-antitrypsin is the best known genetic factor. 1-3% of COPD patient suffers from this deficiency that increases the risk of developing emphysema.[9]

Suffering from asthma may be also a risk factor for chronic airflow limitation and for developing COPD. People who suffer from asthma are 12 times more likely to develop COPD.[1]

1.3. Diagnosis

Diagnosis requires pulmonary function tests which demonstrate an obstructive ventilatory disorder (lowered FEV1/ forced vital capacity ratio or Tiffeneau index) after bronchodilator administration in a patient with symptoms and exposure to risk factors.

Physicians use pulmonary function tests (spirometry) to measure FEV1 and forced vital capacity (FVC) during a forced expiration from total lung capacity (maximal inspiration). FEV1

is defined as the volume of air exhaled after one second and FVC is defined as the total volume of air exhaled from total lung capacity.[1] (Figure 2 and Figure 3)

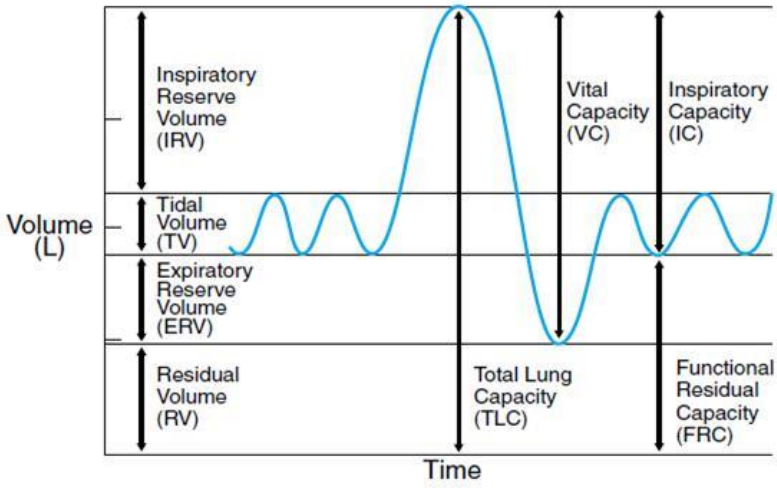

Figure 2: Illustration of the graph and the different volumes obtained from a spirometry test.

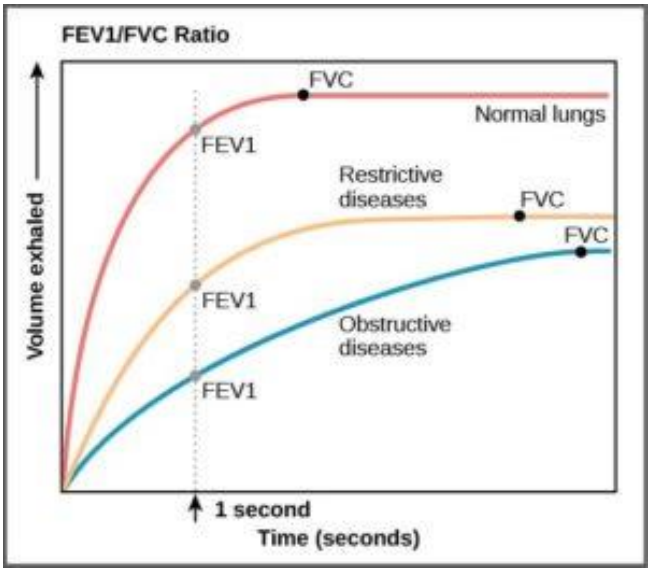

Figure 3: Illustration representing the FEV1 and FVC of a healthy subject (red line), a patient suffers from a restrictive disease (yellow line) and a patient suffer from an obstructive disease such as COPD (blue line). The vertical Y-axis shows the volume exhaled and the horizontal X-axis shows the time (in seconds).

An obstructive ventilatory disorder (airflow limitation) is deemed present if the post-bronchodilator FEV1/FVC ratio is less than or equal to 0.70.
Spirometry is used both for the diagnosis and the assessment of the severity of airflow limitation (according to FEV1 impairment) during the follow-up.[1,10]
The GOLD guidelines classify the severity of airflow limitation in 4 classes of severity (Table 1).[1]

Table 1: Classification of the severity of the airflow limitation based on the post-bronchodilators FEV1 value obtained thanks to the spirometry[1]

GOLD severity classes	**Post-bronchodilators FEV1 value**
Mild (GOLD 1)	FEV1 ≥ 80% predicted value
Moderate (GOLD 2)	50% ≤ FEV1 < 80% predicted value
Severe (GOLD 3)	30% ≤ FEV1 < 50% predicted value
Very severe (GOLD 4)	FEV1 < 30% predicted value

The post-bronchodilators FEV1 value is used to classify the airflow limitation severity.

1.4.Respiratory symptoms and its assessments

Dyspnea, cough and sputum secretion are the most common symptoms associated with COPD. These symptoms vary throughout the day, and daily, although the variability is lesser than in asthma. Most patients experience more symptoms in the morning.[11]
According to the American Thoracic Society, dyspnea is defined as "a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity".[12] This symptom is the most disabling for people suffering from COPD as it can severely impact on their quality of life. Indeed, dyspnea is strongly felt during daily activities.[11,13]
Scales such as the modified Medical Research Council (mMRC) dyspnea scale are used to assess dyspnea severity. (Table 2)

Table 2: The different severity levels of dyspnea according to the mMRC dyspnea scale[1]

Dyspnea grade	**Symptoms**
0	I only get breathless with strenuous exercise
1	I get short of breath when hurrying on level ground or walking up a slight hill
2	On level ground, I walk slower than people of the same age because of breathlessness or have to stop for breath when walking at my own pace
3	I stop for breath after walking about 100 metres or after a few minutes on level ground.
4	I am too breathless to leave the house or I am breathless when dressing

To evaluate the impacts of this pulmonary disease and its symptoms on the quality of life and the health status of COPD patients, other tools are used, such as the COPD assessment test (CAT; Annex 4). This questionnaire contains 8 items including cough, chest mucus, chest tightness, dyspnea, activity limitations, anxiety, sleep and energy. Each item is associated with a score ranging from 1 to 5, with a total score between 0 and 40. The higher the CAT score, the more COPD has an impact on the patients quality of life.[14]

1.5.Exacerbations

During COPD, patients can suffer from exacerbations which are acute episodes during which the symptoms and airflow limitation increase, leading to an adaptation in treatment. Accordingly, exacerbations impact exercise capacity and day-to-day activities. They are also a risk factor for hospitalisations, increased morbidity and they can lead to acute on chronic respiratory failure and death. Major causes of exacerbations are viruses, bacterial infections or environmental pollutants. [3,4,15,16]
The severity of exacerbations is usually graded as mild, moderate or severe, based on healthcare utilisation: mild exacerbations require an increase or a change in inhaled therapies, moderate exacerbations require systemic antibiotics and/or glucocorticoids, while severe exacerbation require hospitalization.[4]

1.6.Treatments

There are several ways to treat COPD patients such as pharmacological maintenance and rescue therapies, nonpharmacologic therapies and vaccines. In active smokers, the most important intervention is smoking cessation.

1.6.1. Maintenance therapy

The main goals of maintenance therapy are

- to improve the quality of life by reducing the symptoms and exercise intolerance.
- to reduce exacerbation frequency.[1]

This thesis will focus on adherence to maintenance therapy which includes inhaled bronchodilators and inhaled corticosteroids (ICS).

1.6.1.1. Bronchodilators

Bronchodilators are administered by inhalation and act by reducing the airway smooth muscle tone, which reduces airflow limitation and dyspnea.
β_2-agonists and antimuscarinics are the two major types of bronchodilators. Each type includes two subtypes according to the duration of activity: short-acting β_2-agonists (SABA), long-acting β_2-agonists (LABA) and short-acting antimuscarinics (SAMA), long-acting antimuscarinics (LAMA). SABAs and SAMAs have four to six hours of activity and are used as reliever or rescue medications to reduce symptoms quickly. LABAs and LAMAs work for 12 and up to 24 hours and are used for maintenance therapy.[1,17]
In addition to their effects on symptoms and quality of life, it has also been shown that bronchodilators reduce the number of hospitalizations and exacerbations, with a greater effect of LAMAs as compared to LABAs.[1,18]
Dual bronchodilation (LABA-LAMA) is often used because the effects of the two classes are additive on symptoms, respiratory function and also exacerbations.[16,17,19]

1.6.1.2. Inhaled corticosteroids

ICS are anti-inflammatory drugs. They are often added and combined to a LABA in a single inhaler which allows to have better effects on exacerbations, while the additive effects on symptoms and quality of life are limited.[1]
ICS are associated with several adverse effects such as pneumonia, thrush, and hoarseness.[1,20]
More recently, ICS have been combined with a LABA and a LAMA in a single inhaler, the so-called “triple therapy” that has several advantages. Compared to the association

LABA/LAMA[21,16] or a combination of LABA/ICS[22,16] this triple therapy has a greater impact on exacerbation rate reduction.
The effect on lung functions and quality of life are also superior with triple therapy as compared to LABA/LAMA[21,16] or LABA/ICS[22,16] combination.
The downside of this triple therapy is that it could increase the risk of developing pneumonia as compared to a LABA/LAMA combination.[23]

1.6.2. Nonpharmacological interventions

Nonpharmacological therapies include some types of smoking cessation such as nicotine replacement products, chest physiotherapy, oxygen therapy and pulmonary rehabilitation. Chest physiotherapy allows to relieve congestion in the lungs, pulmonary rehabilitation is used to improve physical capacities of the patients, oxygen therapy allows to decrease the mortality rate and smoking cessation is used to prevent COPD progression.[1,24]

1.6.3. Vaccines

Influenza and pneumococcal vaccines are recommended for COPD patients. Influenza vaccination allows to reduce the number of exacerbations.[1]

1.7. Adherence to therapy and its assessment in COPD

1.7.1. Adherence

"Medication adherence refers to the act of conforming to the recommendations made by the provider with respect to timing, dosage and frequency of medication taking"[25]
The meanings of the terms adherence, compliance and concordance are a little bit different. Adherence concerns the active role of patients concerning the approval and the follow-up of the prescription whereas compliance concerns the passive role of patients in regard to the prescription.
Concordance refers to the agreement between patients and physicians concerning the common decisions.[26]
In COPD, adherence has been shown to be low, which can decrease the effectiveness of treatments and the control of symptoms, worsen the patient quality of life, and increase exacerbation frequency. [26,27]
There is a marked difference between adherence measured in clinical trials and real-life because, in clinical trials, there is a follow-up and monitoring, which can result in a 70 to 90% adherence rate. In real life, it is estimated to be 20-60%.[26,28]
There are different types of non-adherence such as underuse, overuse and improper use.[26,29]
Underuse refers to a decrease in the number of times the drug is used as compared to what is written on the prescription or what is recommended by the physician. Overuse refers to the opposite.[29]

1.7.1.1. Factors influencing adherence

Adherence to treatment can be influenced by a lot of parameters such as patient characteristics, dosing regimen, the patient's confidence in the prescriber and the efficacy of the treatment as perceived by the patient.[26,30,31]
In one study[32], the most adherent patients have a significantly lower FEV1 but gender does not seem to be associated with adherence. The results with regard to age are contradictory.[26,33,34]
The degree of adherence is also influenced by the patient smoking status. Current smokers are less adherent to LABAs than former or never smokers.[31,34]

The severity of the disease can also influence treatment adherence. Patients with a mild form of the disease are less adherent than those with a severe form.[35,36,37] This can be explained by the fact that the higher the grade of the disease, the more severe and disabling the symptoms. The patient's perception of the disease can affect adherence. It is lower in people who find that their disease does not have a major impact on their lives and who have few or no symptoms.[27,34]
The major drugs used for COPD maintenance therapy are inhaled therapies. As compared to oral treatments, inhaled therapies require a good inhalation technique to be efficient. The technique for using inhaler devices also influences the level of adherence. If the technique is elaborated, it can prove to be an obstacle. That is why appropriate patient instruction and education is important.[26,27,29,35]
There are 4 types of inhaler devices:

- pressurized metered-dose inhalers (PMDI),
- dry powder inhalers (DPI),
- soft mist inhalers (SMI), and
- nebulizers.

Maintenance therapy is usually delivered using PMDI, DPI, and/or SMI. Each inhaler has its own inhalation technique. It has been demonstrated that if physicians take into account the patient preferences when they choose the inhaler device, the adherence is better. Patients who have been prescribed their preferred inhaler device will be more satisfied with their treatment and make fewer errors related to the use of the device. In general, patients prefer devices that are small, portable, with a dose counter and allow for a quick medication intake.[38]
Therapy-related side effects and treatment cost also affect adherence.[29,35,36,37]
Concerning the daily dosing frequency, the adherence will be higher if the treatment needs to be taken once a day than if it needs to be taken several times a day.[26,27,34,36,39,40] Adherence decreases as dosing frequency increases.
The number of medications that people have to take will also have an impact. Using the minimum number of drug types and inhalers can also help improve compliance.[27,33,34]
The perceived effectiveness of the treatment also influences the level of adherence. If the medication works quickly, patients will tend to be more adherent than if the effects of the treatment are felt after a long period.[26,34,37] The effects of bronchodilators are felt faster than those of ICS. Adherence to bronchodilators will, therefore, be better.[29]

1.7.1.2. Adherence and outcomes

Good adherence is generally associated with a drop in the number of emergency department visits and exacerbations. A reduction in the exacerbation rate allows to decrease the risk of death and hospital admission.[27,30,37,41,42]
In one study, a 44% lower rate of severe exacerbations was found in the adherent group.[41]
In a systematic review, only two studies looked at the association between adherence and mortality. The first showed no association and the second (a placebo-controlled study) showed an association between adherence and the reduction of mortality rate but there was no difference between the placebo and treatment groups. This means that the decrease in the mortality rate is not due to good adherence to treatment per se but rather by an adherence behaviour conferring an advantage. This is called “the healthy adherer effect”.[30]
According to other studies published after this systematic review, non-adherence is associated with a risk of increased mortality rate.[27,37,42]
A good adherence allows to have better control over symptoms and the disease.[26,27,42]

Most studies showed that adherence is associated with a better quality of life because, as mentioned above, it allows for better symptom control.[27,37,43]
However, others[30] found the quality of life to be lower in adherent patients. They argued that good adherence requires a certain rigour, discipline and adaptation in daily life. The benefits in terms of reducing the frequency of exacerbations would not counterbalance these requirements in some patients.[30] Furthermore, symptoms are more severe and the quality of life poorer as the disease worsens.[1] As said above, adherence increases the more severe the disease is. This could also explain that the quality of life is lower in adherent patients.
In general, treatment-related costs are higher for adherent patients than for non-adherent patients because of higher medication dispensation. However, as mentioned above, being adherent will reduce emergency room visits and hospitalizations due to exacerbations and thus reduce the associated costs. Accordingly, altogether, total health-related costs of adherent patients are lower as compared to non-adherent patients.[27,30,42]

1.7.1.3. How can we improve adherence? Moving towards more patient-centred medicine

Regarding the choice of inhaler devices, several parameters can be taken into account such as the access, cost, physician but also and above all the patient ability and preference. Unfortunately, studies have shown that physicians often do not take the patient preference into account when prescribing an inhaler device.[38] Patients should be more involved in the choice of treatment.[26]
Other methods can also be used to improve compliance. The relationship between doctors and patients must lead to trust and confidence.
Additional consultations for non-adherent patients can be set up and specialists could give patients information sheets on how to use inhaler devices.[26]
Doctors must clearly explain to patients the characteristics of the disease they are suffering from, how their treatments work, and the effects of their treatments.[26]
Pharmacists also have a role to play when patients come to collect their inhaled medications. Pharmacists could remind them of the method of use or at least make sure that patients know how to use their inhaler devices correctly. Pharmacists could also give out information sheets.
The explanations given by pharmacists added to those given by doctors could improve patients adherence.
In Belgium, a system has been set up to include pharmacists in patient education for the use of inhalator devices. This, however, is restricted to patients with asthma treated with ICS.[44]
This system consists of two meetings between the pharmacist and the patient to check whether the patient is taking its inhaled medications correctly. The first consultation will take place as soon as possible after the first delivery and the second will take place 3 to 6 weeks later. During these meetings, the pharmacist explains the method of use and motivate the patient to be adherent.[44] Doctors, pharmacists and patients themselves can apply to participate. However, if doctors or pharmacists request it, patients must give their consent.[44]

1.7.1.4. Adherence assessment methods

Assessing therapeutic adherence is complex and probably even more so for inhaled medications.
To assess adherence in general, several methods can be used such as healthcare provider estimation, patient self-reporting, pill count and electronic monitoring.[45]
In case of electronic monitoring, patients use an electronic device that allows to record the date and the time of each utilization. This method is reliable but expensive.[46]

Questionnaire-based scales such as the Morisky Medication Adherence Scale (MMAS-8), have been developed in an attempt to assess medication adherence based on self-reporting.
This and other questionnaires are not suitable for assessing adherence to inhaled therapies in COPD patients because they were not designed for inhaled therapies.
In order to overcome this problem, a new questionnaire has been developed: the Test of Adherence to Inhalers (TAI) questionnaire which is described in more detail below.[46]

Another way to measure adherence is to obtain dispensing data from the referring pharmacist. Again, this method may be subject to bias. Indeed, some patients may go to the pharmacist to get what their doctor prescribed for them but may throw them away or not take them properly. Using dispensing data to assess adherence can lead to an overestimation of drug consumption.[47]
One might hypothesize that as maintenance inhaled therapies for COPD have a good tolerability profile, they are less subject to this bias as compared to other types of treatment.
In our research project, we have used this method in addition to the TAI questionnaire.
It must be stressed that all evaluation methods are subject to different biases and that there is no golden standard for assessing adherence to therapy. This is probably even more true for inhaled therapies. For example, in the case of self-reporting, patients may not be honest and may pretend to be adherent when in fact they are not. The most reliable method is electronic monitoring, but it is expensive and does not exclude a bias, simply because a patient is susceptible to change his adherence behaviour when included in a prospective adherence study. Accordingly, we choose to use retrospective assessment of dispensing data in the present study to compare the TAI questionnaire with this second type of adherence assessment.

1.7.2. TAI questionnaire

The TAI questionnaire was recently developed to assess adherence to inhaled therapies in COPD and asthma patients. The developers of the questionnaire claim that it allows to determine the adherence or the non-adherence and identify the factors associated.[46]
Three phases were necessary to develop the TAI questionnaire. The first was based on a review of the literature and suggestions of the study scientific committee.192 investigators with different professions such as doctors and nurses participated in the second phase and worked together to find the items that should be included in the TAI. The final phase was a pilot study to develop the final version.[46]
There are two parts to the TAI questionnaire: TAI-10 with ten items; a second two-item section is part of the TAI-12 which also includes the ten-item TAI-10.
These two parts are complementary because the TAI-10 contains 10 items about the patient domain and the TAI-12 contains two more items about the health professional domain.[46]
Each of the first ten items is associated with a score ranging from 1 to 5 (1 being the worst score and 5 the best) (Table 3), with a total score between 10 and 50.
Concerning items 11 and 12, a score of 1 or 2 is associated with them (1 being a bad score and 2 a good score) (Table 3).[46]

The first five items assess erratic non-adherence. The next five items assess voluntary non-adherence. And finally, the last two items determine involuntary non-adherence (due to a lack of understanding)(Table 3).[46]
Erratic non-adherence is the when the patient forgets to take their medication, voluntary non-adherence is when the patient "deliberately" does not take their medication correctly and involuntary non-adherence is when there is a problem with the correct handling of the device (Technique of use).

The TAI questionnaire was validated more rigorously in the asthmatic population than in the COPD population. Indeed, some of the asthma participants in the seminal study were given an electronic inhaler device recording the date and time of each inhaler actuation. The results obtained with the TAI questionnaire were compared with those obtained with the electronic inhaler devices. The authors found a good correlation.[46]

In the COPD population, participants were not given an electronic inhaler device. To validate the TAI questionnaire in the COPD population, the results obtained with the TAI questionnaire were compared with those obtained with the Morisky Medication Adherence Scale.[46] This is a self-reported medication adherence scale (MMAS-8) that was developed to measure adherence in patients with chronic conditions such as hypertension[45] but was not designed for inhaled treatments.

Table 3: Description of the test of the adherence to inhalers (TAI) Questionnaire[46]

Patient domain	Scores* (1 to 5)
1. During the last 7 days, how many times did you forget to take your usual inhalers? 2. Do you forget to take inhalers? 3. When you feel good about your illness, do you stop taking your inhalers? 4. When you are on vacation or weekend, do you stop taking your inhalers? 5. When you are nervous or sad, do you stop taking your inhalers? 6. Do you stop taking your inhalers because of fear of side effects? 7. Do you stop taking your inhalers because of considering they are useless to treat your condition? 8. Do you take fewer inhalations than those prescribed by your doctor? 9. Do you stop taking your inhalers because you believe they interfere with your everyday or working life? 10. Do you stop taking your inhalers because you have difficulties to pay them?	
Health care professional domain	Score*[1] (1 to 2)
11. Does the patient remember the prescribed regimen (dose and frequency)? (checking the medical record) 12. The technique of using the evaluated inhaler device by the patient is* (checking the inhalation technique)	

*Items 1: All (1); More than half (2); Approximately a half (3); Less than half (4); None (5)
Items 2 to 10: Always (1); Mostly (2); Sometimes (3); Rarely (4); Never (5)
*[1]Items 11: No (1); Yes (2)
Items 12: With critical mistakes (1); Without critical mistakes (2)

2. Goals of the research project

Because of the scarcity of data on questionnaire-based adherence assessment for inhaled therapies in COPD in general and in Belgium in particular, this study aims to,

- assess adherence to inhaled maintenance therapy in COPD patients who are stable or hospitalized for exacerbations

- to compare adherence according to various patient characteristics (Annex 1) to determine factors and outcomes associated with poor adherence.

Therapeutic adherence to inhaled maintenance therapy was evaluated by

- the TAI-10 questionnaire and
- dispensing data obtained from the referring pharmacist providing patient gave its consent for the investigators to request these data.

On the other hand, as the TAI questionnaire has not yet been rigorously validated in the COPD population (cf. 1.7.2.), this study also aims to evaluate/validate the TAI questionnaire by measuring drug consumption based on drug dispensing data obtained from the shared pharmaceutical file of the patients included (giving their consent to the use of these data).
This study is an observational monocentric cross-sectional study.

3. Materials and methods

3.1. Literature review

The PubMed database has been used to make a state of the art on COPD and adherence. Keywords such as COPD, adherence, spirometry, inhaled therapies, bronchodilators, factors poor adherence, TAI questionnaire, dispensing data, pharmacy, ... were used.

3.2. Ethics committee approval

The research protocol was approved on 28 April 2020 by the Ethics Committee of the CHU UCL Namur site Godinne.

3.3. Privacy policy

The identity and participation of patients in this experiment is strictly confidential. They are not identified by name (pseudonymisation and access control to identification data) or in any other recognisable way in any of the files accessible to potential third parties (i.e. other than the investigators), results or publications related to the study.
The protection of personal data is ensured by the requirements of the General Data Protection Regulation (GDPR), the Belgian Law of 30 July 2018 and the Law on the Protection of Patients (2002).

3.4. Study population

3.4.1. Inclusion and exclusion criteria

The patients who took part in this study are among the patients followed at the COPD clinic at the CHU-UCL-Namur, site Mont-Godinne and were chosen because they met the inclusion criteria (Table 4).

Table 4: Inclusion and exclusion criteria

Inclusion criteria	**Exclusion criteria**
Female or male patient at least 40 years of age	Palliative care patients
Diagnosis of COPD confirmed by spirometry (FEV1/CVF post-bronchodilator < 0.70)	Patients deemed unable to read or understand the informed consent form and study questionnaires
Active or past smoking for at least 10 packs per year	Patients who underwent surgical lung resection in the 12 months before inclusion
Maintenance therapy with inhaled medication within the last 12 months	
Patient with a computerised medical record at the CHU-UCL-Namur site Godinne	
Patient able to read the informed consent form and answer the study questionnaires	
Signature of the informed consent form	

3.4.2. Recruitment

75 COPD patients were recruited at the pneumology consultation or among patients hospitalized in the pneumology department of the CHU-UCL-Namur, site Godinne.
The recruitment period began in June 2020 due to Covid-19, which prevented us from recruiting from March 2020 to June 2020, and ended in September 2020.
Every week, Professor Marchand identified potential participants in the study on the consultation agenda. Potential participants were first contacted by phone to explain the study and to find out if they would accept to take part in the study.
Patients were interviewed on the day of their consultation. During this interview, we started by explaining to the patients what the study consisted of, the goals, the benefits/risks, and answered questions ... In this research project, patients hospitalised in the pneumology department were also recruited.
Thereafter, the patients signed the two informed consent forms. The first consisted of describing the research project (Annex 2) and the second consisted of obtaining medication dispensing data from their referring pharmacist (Annex 3).

3.5.Data collection

After the patient had signed the informed consent forms, we collected data using a questionnaire (Annex 4). This allowed us to collect data concerning: the anthropometric characteristics of the patients (age, sex), smoking, dyspnea mMRC scale (table 2), CAT score, maintenance and rescue treatments, influenza and pneumococcal (conjugated and polysaccharide vaccines) vaccines, the patient perception of the effectiveness of maintenance therapy on breathlessness and the reduction in the number of exacerbations, ...

Data on treatment and dosage, smoking and disease characteristics such as FEV1 POST (in % and L), the GOLD classification based on FEV1 POST (Table 1), the number of exacerbations treated at home over the last 12 months and the number of exacerbations requiring hospitalisation over the last 12 months were retrieved from medical records.
Medical records were also consulted to verify the information provided by patients. In the event of a discrepancy, patients were called to verify the information they had provided.

Adherence to inhaled treatments was assessed based on the TAI questionnaire and based on the medication dispensing record for the past 12 months, obtained from the patient referring pharmacist, as mentioned by the patient. Initial contact was made with the pharmacist by phone to explain the study, the need for their collaboration and to ask for their email address for further contact. Subsequently, an email was sent to them to explain the study in more details, to provide them with the patient signed consent and to ask to provide us with the dispensing data.
This dispensing record was not used in case the patient received samples of maintenance COPD medications in the last 12 months nor for patients who have obtained medications from more than one pharmacist in the past 12 months without a shared medication record ("dossier pharmaceutique partagé").

3.6.Data analysis

Patients were classified according to their adherence to treatment based on the TAI score and drug dispensing data over the past 12 months.
We initially planned to define good adherence according to the TAI as a TAI-10 score = 50, intermediate adherence as a TAI-10 score between 46 and 49 and poor adherence as a TAI-10 score ≤ 45.[46] Since the majority of patients have a TAI-10 score of 50 (good adherence), we grouped patients with intermediate and poor adherence in a single group for the comparative analysis. In this study, we, therefore, have 2 groups: adherent (good adherence as defined above) and non-adherent (intermediate and poor adherence as defined above).
Concerning drug dispensing data over the past 12 months, the inhaled medication delivery score was calculated as the ratio of doses delivered in function of the doses prescribed according to the prescription schedule for each prescribed inhaled medication pertaining to maintenance therapy. This ratio is expressed in percent. If maintenance therapy comprised more than one medication, the average of the calculated ratios for each medication (weighted by the length of the prescription period if the latter was less than 12 months) was used for the analysis.
According to the literature[32], adherence is usually defined based on dispensing data as

- good: ≥ 80% of the prescribed doses dispensed;
- moderate: > 50%% and < 80% of the prescribed doses dispensed, and
- poor: ≤ 50% of the prescribed doses dispensed.

Once again, the majority of the patients in the present series had a good adherence (≥ 80%). We, therefore, choose to group patients who had < 80% of the prescribed doses dispensed to define 2 adherence groups:

- good adherence (adherent group): ≥ 80% of the prescribed doses dispensed;
- intermediate - poor adherence (non-adherent group): < 80% of the prescribed doses dispensed.

The 2 adherence groups assessed by drug delivery and TAI-10 were compared for various parameters including patient, treatment, and disease characteristics by student t-test analysis for continuous data and a chi-square or Fisher exact test when appropriate for parametric data.
Concordance between the two adherence scores was assessed by linear regression, ROC curve analysis and Kappa hypothesis tests.

In this research project, the statistical significance threshold was set at p-value < 0.05 (two-tailed test). If the p-value is greater than 0.05, the null hypothesis (H0: no differences between groups) is accepted and if the value is smaller than 0.05, the null hypothesis is rejected.

All data were analysed using the excel office 2019 statistical program or the NCSS 11 Statistical Software (2016). NCSS, LLC. Kaysville, Utah, USA.

4. Results

4.1. Description of the study population

The characteristics of the 75 patients recruited in this study, their disease and treatments are described in table 5. We obtained drug dispensing data for 53 patients.
The average age of the study population was 68 and most of the patients recruited were ex-smokers. The two genders were quite equally represented.
The average GOLD grade suffered by patients is grade 3, with an average FEV1 measured at 44% of the predicted value. 4/5 of patients recruited suffered from dyspnea grade of 2 or more.
Concerning therapies, 13/15 of the study population had 2 long-acting therapy, 3/4 had ICS, 7/10 had triple therapy and 4/5 had a rescue therapy. The majority of the study population had 2 or 3 devices (maintenance therapy and rescue therapy).
The averages of the patient perception of chronic treatment effectiveness on dyspnea and the reduction of exacerbation rate were 6.
The average number of moderate exacerbations treated at home in the last 12 months was 1.
4/5 of the study population was vaccinated against influenza and 3/4 received at least one of the two vaccines against pneumococcus.
Concerning patient adherence to their inhaled treatments, the average TAI-10 score was 49, the average TAI-12 score was 53 and the average drug dispensing data score was 94%.

Table 5: Study population characteristics

Criteria	**Sub-criteria**	**Mean ± SD; Median**	**Proportions (percentage)**
Age (years)		68 ± 8; 68	
Sex (n (%))	Men/Women		39/36 (52%/48%)
Setting (n (%))	Non-hospitalized/ Hospitalized		71/4 (95%/5%)
Smokers (n (%))	Active/Ex-smokers		12/63 (16%/84%)
Smoking history (packs year)		40 ± 20; 40	
Illness duration (y)[*1]		10 ± 7; 9	

GOLD classification (grade)		2,9 ± 0,9; 3	
FEV1 post-bronchodilator (%)		44 ± 18; 42	
FEV1 post-bronchodilator (L)		0.93 ± 0.31; 0,95	
mMRC dyspnea scale (grade) (n (%))	Grade 0 or 1		16/75 (21%)
	Grade 2, 3 or 4		59/75 (79%)
Patient education level (n (%))	No diploma		1/75 (1%)
	First 3 years of primary school		1/75 (1%)
	Primary school completed		14/75 (19%)
	First three years of secondary school		23/75 (31%)
	Secondary school completed		24/75 (32%)
	Bachelor		12/75 (16%)
Maintenance therapy (n (%))	Number of long-acting bronchodilator: 1/2		10/65 (13%/87%)
	ICS: Yes/No		55/20 (73%/27%)
	Number of device: 1/2		42/33 (56%/44%)
Classification according to their maintenance therapy (n (%))	LABA or LAMA		6/75 (8%)
	LABA and LAMA (1 or 2 devices)		14/75 (19%)
	LABA and ICS (1 or 2 devices)		4/75 (5%)
	LABA and LAMA and ICS (1 or 2 devices)		51/75 (68%)
Number of treatment time/day (maintenance therapy) (n (%))	1 treatment time/day		31/75 (41%)
	2 treatment times/day		44/75 (59%)
Number of inhalations/day (maintenance therapy) (n (%))	1 inhalation/day		19/75 (25%)
	2 inhalations/day		11/75 (15%)
	3 inhalations/day		9/75 (12%)
	4 inhalations/day		24/75 (32%)
	5 inhalations/day		7/75 (9%)
	6 inhalations/day		5/75 (7%)
Rescue therapy (n (%))	Yes/No		60/15 (80%/20%)
Number of devices (Maintenance therapy + Rescue therapy) (n (%))	1 device		12/75 (16%)
	2 devices		33/75 (44%)
	3 devices		29/75 (39%)
	4 devices		1/75 (1%)
Patient perception of chronic treatment effectiveness (10-point visual scale)	On dyspnea[*2]	6.1 ± 2.5	
	On the reduction of exacerbation rate[*3]	5.6 ± 2.9	

Influenza vaccination (n (%))	Yes/No		59/16 (79%/21%)
Pneumococcal vaccination (n (%))	Conjugate vaccine*[4]: Yes/No		45/27 (62%/38%)
	Polysaccharide vaccine*[5]: Yes/No		47/26 (64%/36%)
	At least one pneumococcal vaccine*[6]: Yes/No		55/18 (75%/25%)
CAT score		19 ± 7	
Number of moderate exacerbations in the last 12 months		0.95 ± 1.53; 1	
Number of exacerbations requiring hospitalization in the last 12 months		0.33 ± 0.62; 0	
TAI-10 score (/50)		49 ± 3; 50	
TAI-12 score (/54)		53 ± 3; 53	
Drug dispensing data score (%)*[7]		93.6 ± 23.6	

The median was calculated for continuous variables that did not follow a normal distribution.

*[1]: 2 of the 75 patients recruited could not answer this question. The medical records of these patients did not provide this information either.

*[2:] 10 of the 75 patients recruited could not answer this question.

*[3]: 26 of the 75 patients recruited could not answer this question.

*[4]: Information on the vaccination status of three patients could not be found. These three patients could not remember if they had been vaccinated. The medical records of these patients did not provide this information either.

*[5]: Information on the vaccination status of two patients could not be found. These two patients could not remember if they had been vaccinated. The medical records of these patients did not provide this information either.

*[6]: Information on the vaccination status of two patients could not be found. These two patients could not remember if they had been vaccinated. The medical records of these patients did not provide this information either.

*[7]: Of the 75 patients recruited, we received dispensing data from referring pharmacists for only 53 patients.

4.2. Patient adherence

4.2.1. Adherence assessed by the TAI-10 score

Based on the TAI-10 score, 52 patients (69%) were in the adherent group while the other 23 patients were in the non-adherent group. Of the 75 patients recruited, 4 patients were recruited when they were hospitalised. 3 patients were non-adherent and 1 patient was adherent.

4.2.2. Adherence assessed by the drug dispensing data score

Of the 75 patients recruited, we received dispensing data from the referring pharmacists for 53 patients only. Based on the drug dispensing data score, 41 patients (77%) were in the adherent group while the other 12 patients were in the non-adherent group.

Concerning hospitalized patients, 3 were adherents (We did not receive dispensing data of the fourth patient).

4.3. Comparison between the 2 classes of adherence and the patient, disease and treatment characteristics

4.3.1. Based on the TAI-10 score

The characteristics of the 2 adherence groups according to the TAI-10 score were compared (Tables 6 and 7).

Table 6: Comparison of the patient, disease and treatment characteristics between the 2 adherence groups according to the TAI-10 score (continuous data)

Criteria	**Mean ± SD; Median**	**Mean ± SD; Median**	**p-value**
	Adherent group	**Non-adherent group**	
Number of patients (n)	52	23	/
Age (years)	69 ± 8; 69	67 ± 9; 65	NS
Smoking history (pack years)	38 ± 19; 35	45 ± 22; 40	NS
Illness duration (y)	10 ± 7[*1]; 8,5	11 ± 6[*2]; 10,5	NS
GOLD classification (grade)	2,9 ± 0,9; 3	2,9 ± 0,9; 3	NS
FEV1 post-bronchodilator (%)	44 ± 19; 38	45 ± 17; 45	NS
Patient perception of chronic treatment effectiveness on dyspnea (10-point visual scale)	6,0 ± 2,4[*3]	6,3 ± 2,6[*4]	NS
Patient perception of chronic treatment effectiveness on the reduction of exacerbation rate (10-point visual scale)	5,6 ± 3,0[*5]	5,7 ± 2,8[*6]	NS
CAT score	20 ± 7	18 ± 5	NS
Number of moderate exacerbations treated at home in the last 12 months	0,98 ± 1,72; 0,5	0,86 ± 1,01; 1	NS
Number of exacerbations requiring hospitalization in the last 12 months	0,33 ± 0,65; 0	0,35 ± 0,57; 0	NS
TAI-10 score (/50)	50,0 ± 0,0; 50	46,8 ± 4,5; 48	/
TAI-12 score (/54)	53,6 ± 0,5; 54	50,3 ± 4,6; 52	/
Dispensing data (%)	96,5 ± 24,2[*7]	91,0 ± 33,5[*8]	NS

The median was calculated for continuous variables that did not follow a normal distribution.

[*1]: 1 of the 52 adherent patients could not answer this question. The medical records of this patient did not provide this information either.

[*2]: 1 of the 23 non-adherent patients could not answer this question. The medical records of this patient did not provide this information either.
[*3]: 8 of the 52 adherent patients could not answer this question.
[*4]: 2 of the 23 non-adherent patients could not answer this question.
[*5]: 18 of the 52 adherent patients could not answer this question.
[*6]: 8 of the 23 non-adherent patients could not answer this question.
[*7]: Of the 52 adherent patients, we did not receive dispensing data from the referring pharmacist for 14 patients.
[*8]: Of the 23 non-adherent patients, we did not receive dispensing data from the referring pharmacist for 8 patients.

For all characteristics (in table 6), the differences between the averages of the 2 groups were non-significant.
It should be noted that there was no significant difference in the number of moderate or severe exacerbations in the last 12 months between the 2 groups.

Table 7: Comparison of the patient, disease and treatment characteristics between the 2 classes of adherence groups according to the TAI-10 score (parametric data)

Criteria	**Sub-criteria**	**Proportions (percentage)**		**p-value**
		Adherent group	**Non-adherent group**	
Number of patients		52	23	/
Sex (n; %)	Men/Women	25/27;48%/52%	14/9; 61%/39%	NS
Smokers (n; %)	Active/Ex-smokers	8/44; 15%/85%	4/19; 17%/83%	NS
Patient education level	No diploma	0/52 = 0%	1/23 = 4%	NS
	First 3 years of primary school	0/52 = 0%	1/23 = 4%	
	Primary school completed	10/52 = 19%	4/23 = 17%	
	First three years of secondary school	14/52 = 27%	9/23 = 39%	
	Secondary school completed	21/52 = 40%	3/23 = 13%	
	Bachelor	7/52 = 13%	5/23 = 22%	
mMRC dyspnea scale	Grade 0 or 1	11/52 = 21%	5/23 = 22%	NS
	Grade 2, 3 or 4	41/52 = 79%	18/23 = 78%	
Maintenance therapy (n; %)	Number of long-acting bronchodilator: One/Two	6/46; 12%/88%	4/19; 17%/83%	NS
	ICS: Yes/No	39/13;75%/25%	16/7; 70%/30%	NS
	Number of device: 1/2	32/20;62%/38%	10/13;43%/56%	NS
Classification according to their maintenance therapy	LABA or LAMA	5/52 = 10%	1/23 = 4%	NS
	LABA and LAMA (1 or 2 devices)	8/52 = 15%	6/23 = 26%	

	LABA and ICS (1 or 2 devices)	1/52 = 2%	3/23 = 13%	
	LABA and LAMA and ICS (1 or 2 devices)	38/52 = 73%	13/23 = 57%	
Number of treatment time/day (maintenance therapy)	1 treatment time/day	22/52 = 42%	9/23 = 39%	NS
	2 treatment times/day	30/52 = 58%	14/23 = 61%	
Number of inhalations/day (maintenance therapy)	1 inhalation/day	15/52 = 29%	4/23 = 17%	NS
	2 inhalations/day	6/52 = 12%	5/23 = 22%	
	3 inhalations/day	5/52 = 10%	4/23 = 17%	
	4 inhalations/day	18/52 = 35%	6/23 = 26%	
	5 inhalations/day	4/52 = 8%	3/23 = 13%	
	6 inhalations/day	4/52 = 8%	1/23 = 4%	
Rescue therapy (n; %)	Yes/No	41/11; 79%/21%	19/4; 83%/17%	NS
Number of devices (Maintenance therapy + Rescue therapy)	1 device	9/52 = 17%	3/23 = 13%	NS
	2 devices	25/52 = 48%	8/23 = 35%	
	3 devices	18/52 = 35%	11/23 = 48%	
	4 devices	0/52 = 0%	1/23 = 4%	
Influenza vaccination (n; %)	Yes/No	44/8; 85%/15%	15/8; 65%/35%	NS
Pneumococcal vaccination (n; %)	Conjugate vaccine: Yes/No	35/15[*1]; 70%/30%	10/12[*2]; 45%/55%	0,047
	Polysaccharide vaccine: Yes/No	36/15[*3]; 71%/29%	11/11[*4]; 50%/50%	NS
	At least one pneumococcal vaccine: Yes/No	42/9[*5]; 82%/18%	9/13[*6]; 41%/59%	0,034

[*1]: Information on the vaccination status of two patients could not be found. These two patients could not remember if they had been vaccinated. The medical records of these patients did not provide this information either.

[*2]: Information on the vaccination status of one patient could not be found. This patient could not remember if they had been vaccinated. The medical records of this patient did not provide this information either.

[*3]: Information on the vaccination status of one patient could not be found. This patient could not remember if they had been vaccinated. The medical records of this patient did not provide this information either.

[*4]: Information on the vaccination status of one patient could not be found. This patient could not remember if they had been vaccinated. The medical records of this patient did not provide this information either.

[*5]: Information on the vaccination status of one patient could not be found. This patient could not remember if they had been vaccinated. The medical records of this patient did not provide this information either.

[*6]: Information on the vaccination status of one patient could not be found. This patient could not remember if they had been vaccinated. The medical records of this patient did not provide this information either.

For all characteristics (in table 7), the differences between the proportions of the 2 groups were non-significant except for the pneumococcal vaccination (conjugate vaccine or at least one pneumococcal vaccine).

Adherent patients were more likely to have received at least one of the two pneumococcal vaccines.

4.3.2. Based on the drug dispensing data score

The different characteristics of the 2 adherence groups according to the dispensing data score were compared (Tables 8 and 9).

Table 8: Comparison of the patient, disease and treatment characteristics between the 2 adherence groups according to the drug dispensing data score (continuous data)

Criteria	**Mean ± SD; Median**	**Mean ± SD; Median**	**P-value**
	Adherent group	**Non-adherent group**	
Number of patients	41	12	/
Age (years)	68 ± 8; 70	66 ± 8; 65	NS
Smoking history (pack years)	40 ± 18; 40	50 ± 30; 40	NS
Illness duration (y)	11 ± 7[*1]; 9	8 ± 6; 7	NS
GOLD classification (grade)	3,2 ± 0,7; 3	2,6 ± 1,0; 2	0,035
FEV1 post-bronchodilator (%)	37 ± 14; 34	52 ± 21; 51	0,029
Patient perception of chronic treatment effectiveness on dyspnea (10-point visual scale)	6,2 ± 2,6[*2]	5,4 ± 2,8[*3]	NS
Patient perception of chronic treatment effectiveness on exacerbation rate (10-point visual scale)	5,5 ± 3,2[*4]	6,5 ± 3,2[*5]	NS
CAT score	19 ± 7	19 ± 6	NS
Number of exacerbations treated at home in the last 12 months	0,95 ± 1,70; 1	0,83 ± 1,40; 0	NS
Number of exacerbations requiring hospitalization in the last 12 months	0,34 ± 0,66; 0	0,67 ± 0,78; 0,5	NS
TAI-10 score (/50)	48,9 ± 3,6; 50	49,1 ± 1,6; 50	NS
TAI-12 score (/54)	52,5 ± 3,7; 53	52,7 ± 1,6; 53	NS
Dispensing data (%)	104,9 ± 16,4	55,1 ± 16,8	/

The median was calculated for continuous variables that did not follow a normal distribution.

[*1]: 1 of the 41 adherent patients could not answer this question. The medical records of this patient did not provide this information either.

[*2]: 4 of the 41 adherent patients could not answer this question.

[*3]: 1 of the 12 non-adherent patients could not answer this question.

[*4]: 12 of the 41 adherent patients could not answer this question.

[*5]: 4 of the 12 non-adherent patients could not answer this question.

For all characteristics (in table 8), the differences between the averages of the 2 groups were non-significant except for the FEV1 post-bronchodilator (%) and the GOLD classification. Patients who were in the adherent group had a significantly lower FEV1 post-bronchodilator than the non-adherent group.
Concerning the COPD grade, adherents suffered from more severe grades of COPD than non-adherents.
As for the TAI-10 score classification, it should be noted that there was no significant difference in the number of moderate exacerbations treated at home in the last 12 months and in the number of exacerbations requiring hospitalization in the last 12 months between the 2 groups.

Table 9: Comparison of the patient, disease and treatment characteristics between the 2 adherence groups according to the drug dispensing data score (parametric data)

Criteria	**Sub-criteria**	**Proportions (percentage)**		**P-value**
		Adherent group	**Non-adherent group**	
Number of patients		41	12	/
Sex (n; %)	Men/Women	22/19; 54%/46%	7/5; 58%/42%	NS
Smokers (n; %)	Active/Ex-smokers	6/35; 15%/85%	1/11; 8%/92%	NS
Patient education level	No diploma	1/41 = 2%	0/12 = 0%	NS
	First 3 years of primary school	1/41 = 2%	0/12 = 0%	
	Primary school completed	5/41 = 12%	4/12 = 33%	
	First three years of secondary school	17/41 = 41%	3/12 = 25%	
	Secondary school completed	13/41 = 32%	1/12 = 8%	
	Bachelor	4/41 = 10%	4/12 = 33%	
mMRC dyspnea scale	Grade 0 or 1	5/41 = 12%	5/12 = 42	0,017
	Grade 2, 3 or 4	36/41 = 88%	7/12 = 58	
Maintenance therapy (n; %)	Number of long-acting bronchodilator: One/Two	2/39; 5%/95%	2/10; 17%/83%	NS
	ICS: Yes/No	34/7; 83%/17%	6/6; 50%/50%	0,020
	Number of device: 1/2	19/22; 46%/54%	8/4; 67%/33%	NS
Classification according to their maintenance therapy	LABA or LAMA	2/41 = 5%	2/12 = 17%	NS
	LABA and LAMA (1 or 2 devices)	5/41 = 12%	4/12 = 33%	
	LABA and ICS (1 or 2 devices)	0/41 = 0%	0/12 = 0%	
	LABA and LAMA and ICS (1 or 2 devices)	34/41 = 83%	6/12 = 50%	0,020

Number of treatment time/day (maintenance therapy)	1 treatment time/day	16/41 = 39%	7/12 = 58%	NS
	2 treatment times/day	25/41 = 61%	5/12 = 42%	
Number of inhalations/day (maintenance therapy)	1 inhalation/day	9/41 = 22%	4/12 = 33%	NS
	2 inhalations/day	3/41 = 7%	3/12 = 25%	
	3 inhalations/day	7/41 = 17%	0/12 = 0%	
	4 inhalations/day	16/41 = 39%	2/12 = 17%	
	5 inhalations/day	3/41 = 7%	2/12 = 17%	
	6 inhalations/day	3/41 = 7%	1/12 = 8%	
Rescue therapy (n; %)	Yes/No	38/3; 93%/7%	8/4; 67%/33%	0,039
Number of devices (Maintenance therapy + Rescue therapy)	1 device	3/41 = 7%	4/12 = 33%	NS
	2 devices	16/41 = 39%	4/12 = 33%	
	3 devices	21/41 = 51%	4/12 = 33%	
	4 devices	1/41 = 2%	0/12 = 0%	
Influenza vaccination (n; %)	Yes/No	34/7; 83%/17%	10/2;83%/17%	NS
Pneumococcal vaccination (n; %)	Conjugate vaccine: Yes/No	25/14[*1];64%/36 %	6/6; 50%/50%	NS
	Polysaccharide vaccine: Yes/No	29/10[*2];74%/26 %	6/6; 50%/50%	NS
	At least one pneumococcal vaccine: Yes/No	33/6[*3];85%/15%	6/6; 50%/50%	0,013

[*1]: Information on the vaccination status of two patients could not be found. These two patients could not remember if they had been vaccinated. The medical records of these patients did not provide this information either.

[*2]: Information on the vaccination status of two patients could not be found. These two patients could not remember if they had been vaccinated. The medical records of these patients did not provide this information either.

[*3]: Information on the vaccination status of two patients could not be found. These two patients could not remember if they had been vaccinated. The medical records of these patients did not provide this information either.

For all characteristics in table 9, the differences between the 2 groups were not significant except for having dyspnea grade of 2 or more (mMRC dyspnea scale), being treated with an ICS, having a rescue therapy, having a triple therapy and having received at least one pneumococcal vaccine.
Adherent patients were more likely to present with a dyspnea level of 2 or more on the mMRC scale.
Adherents were more likely to be treated with triple therapy or with an ICS, to be treated with rescue therapy, and a triple therapy.
Adherent patients were more likely to have received at least one of the two pneumococcal vaccines.

The TAI-10 score and the drug dispensing data score were correlated to various patient, treatment and disease characteristics by correlating Spearman or Pearson's r ranks. The analysis of the results did not provide any additional information compared to the information described above.

4.4. Concordance of the two adherence scores

Concordance of the two adherence scores was assessed by Kappa hypothesis test, linear regression and ROC curve analysis.

To assess the concordance of the 2 scores, patients were classified according to their TAI-10 and drug dispensing data scores (Table 10).
30 patients were adherent according to their TAI-10 score and drug dispensing data score, 4 patients were non-adherent based on their two scores, 11 patients were non-adherent according to their TAI-10 score but adherent according to their drug dispensing data score and 8 patients were adherent based on their TAI-10 score but non-adherent based on their drug dispensing data score (Table 10).

Table 10: Patient classification according to their TAI-10 score and drug dispensing data score[*1]

		Number of patients (according to the drug dispensing data)	
		Adherent group (n)	**Non-adherent group (n)**
Number of patients (according to the TAI)	**Adherent group (n)**	30	8
	Non-adherent group (n)	11	4

[*1]: Of the 75 patients recruited, we received dispensing data from referring pharmacists for only 53 patients.

4.4.1. Kappa hypothesis test

The Cohen's Kappa coefficient was calculated (based on table 10) to assess the concordance of the 2 adherence categories according to the 2 definition criteria (TAI-10 score or drug dispensing data score).
The Kappa coefficient was 0.0598, meaning that the 2 methods to classify patients according to their adherence did not allow for concordant classification.[48]
Considering the TAI-10 as the tested score, the drug dispensing data as the reference score and being adherent as a positive test, we had 30 true positives, 4 true negatives, 8 false positives and 11 false negatives (Table 10). Accordingly, 19 patients (36%) were not classified in a concordant manner with the 2 adherence scores.

4.4.2. Regression analysis

A large proportion of patients had a TAI-10 score equal to 50 and a wide range of drug dispensing data score (Figure 4).

The coefficient of determination (r^2) was 0.0108 (Figure 4) which means that 1 score explained 1% of the variability of the other. According to the linear regression, the relationship between the 2 scores was therefore non-significant.

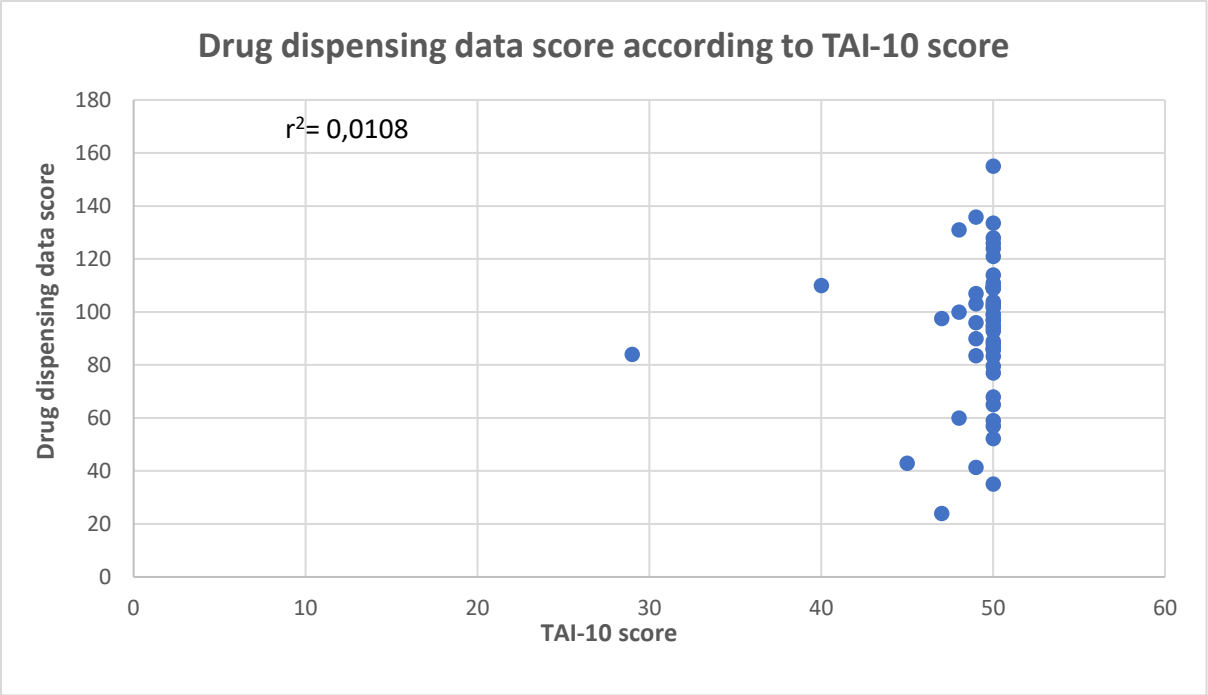

Figure 4: Linear regression of the drug dispensing data score according to the TAI-10 score.

4.4.3. ROC analysis

The hypothesis that the TAI score would predict good adherence defined by dispensing data score ≥ 80% was tested with a receiver operating characteristic (ROC) curve.
The area under the curve (AUC) was equal to 0.5437.
The ROC curve (Figure 5) was very bad which means that the concordance of the 2 scores was also very bad.

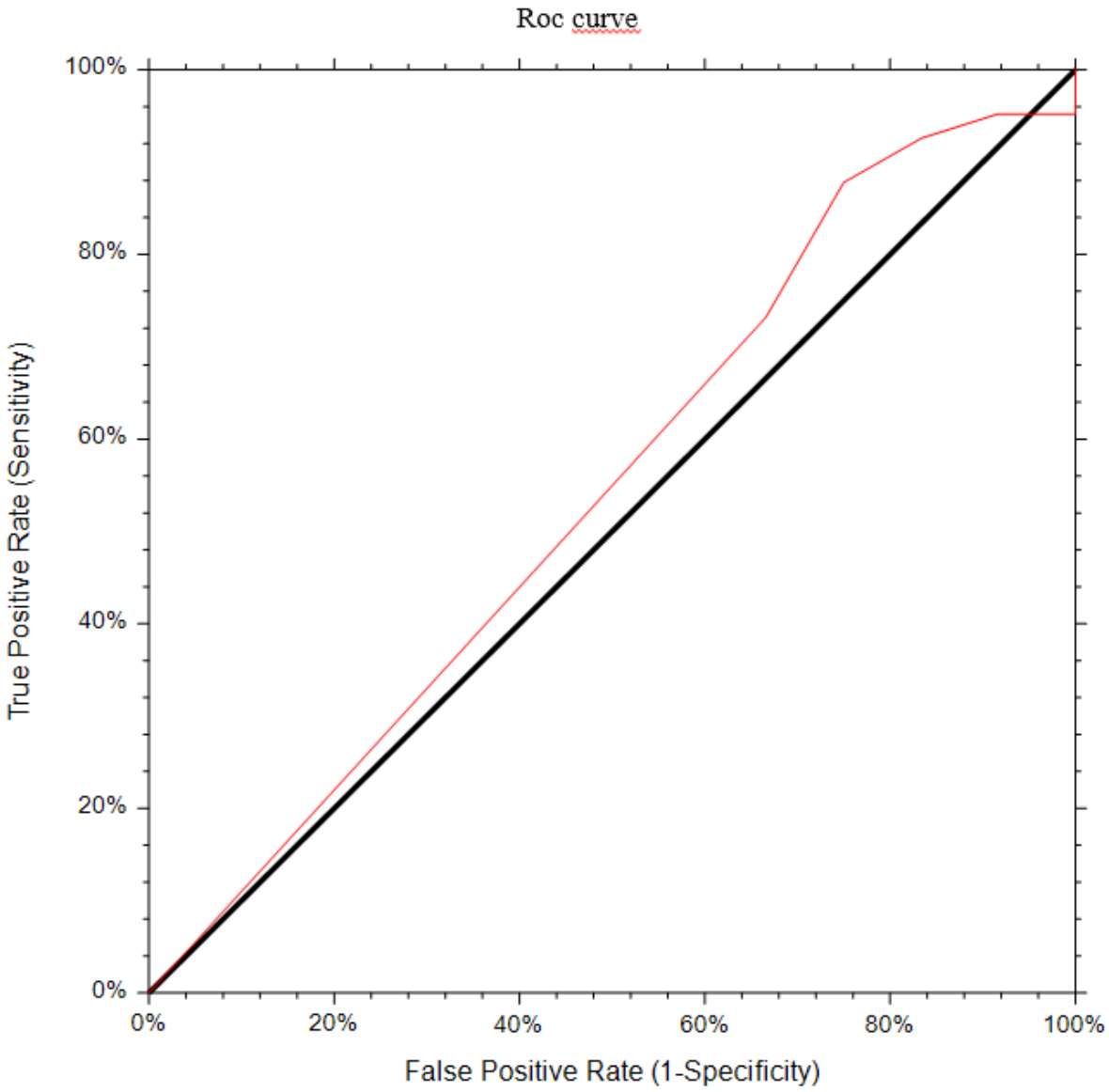

Figure 5: ROC curve for the TAI score as a predictor of good adherence according to the drug dispensing data score.

5. Discussion

In this study, the patients adherence rate for their inhaled treatments was high as compared to the literature.[28,33,49–52]

When looking at the association with various parameters and adherence assessed by the TAI-10, we only found adherent patients to be more likely to be vaccinated against the pneumococcus. There were otherwise no significant differences between adherent and non-adherent patients classified according to the TAI questionnaire.
When classified according to the drug dispensing data score, adherent patients had more severe disease (higher GOLD grade and lower post-bronchodilator FEV1), more severe dyspnea and were more likely to be treated with an ICS, a triple therapy, or to use rescue therapy. Adherent patients were also more likely to have been vaccinated with at least one pneumococcal vaccine.

According to the Kappa hypothesis test, regression analysis and ROC curve, the TAI-10 score and the drug dispensing data score did not allow for a concordant classification of the patients.

In the following discussion, we will discuss the results of the present study.
First of all, we will discuss the adherence rate of patients in our study.

Then we will discuss the factors that could be associated with good or poor adherence by comparing the two classes of adherence and the patient, disease and treatment characteristics. This part will be divided into two. Firstly, patients are adherent or non-adherent according to their TAI-10 score and secondly, patients are adherent or non-adherent according to their drug dispensing data score.

Finally, the last part of the discussion will deal with the level of concordance between the two adherence scores (TAI-10 score and drug dispensing data score) and the potential validation of the TAI questionnaire for assessing the adherence of COPD patients.

We will also discuss the study limitations and potential perspectives.

5.1. Adherence rate

Somewhat surprisingly, the adherence rate in our study was high. 69% and 77% of the study population had a good adherence to inhaled therapies according to the TAI-10 score and the drug dispensing data score, respectively.
These adherence rates were higher than described in the literature as being between 20 and 60% in real life although adherence rates between 70 and 90% have been reported in clinical trials because of a closer follow-up and monitoring during in those trials.[28,33,49–52]
The high adherence rate observed in the present study was despite an average duration of the disease of 10 years whereas according to the literature[36], the duration of treatment and illness are factors associated with reduced adherence.
This high adherence rate may be due to the choice of our study population. Most patients were followed in ambulatory tertiary care (university hospital). So, there were check-ups at regular intervals and the follow-up was very meticulous. The selected patients were therefore likely to be well disciplined. Moreover, regular visits in tertiary care are an opportunity for a reminder of the importance of treatment that may play a role in the adherence process.
Looking at the few studies having assessed the recently developed TAI questionnaire, the study by Plaza et al.[46] recruited patients in primary to tertiary care. Although patients included were similar to ours regarding age or disease duration, they had a higher mean FEV1. The mean TAI-10 score was 46,1 ± 5,2 (median: 48) as compared to 49 ± 2,8 (median: 50) in our study.
In the LASSYC study[49], a much larger population was recruited (795 patients) in tertiary care centres from 7 different Latin American countries. The mean TAI-10 score (47 ± 5) was significantly lower while the FEV1 (50 ± 18.6% predicted) was significantly higher than in our cohort.
In another study conducted in primary care in Greece[50], only 26% of the 257 participants had good adherence according to the TAI-10 questionnaire, as compared to 69% in our population. Our patients were also more symptomatic when assessed by the proportion of patients having

an mMRC dyspnea score ≥ 2 (79% versus 61%) or by the mean CAT score (19.2 ± 6.5 versus 17.2 ± 6.7).
Cultural differences might also influence the observed differences between the TAI score in our study as compared to those mentioned above.[49,50]
The literature dealing with dispensing data to assess adherence in COPD is also scarce. In one study performed in Flanders, Belgium,[51] a self-reported measure of adherence was compared with the medication refill or dispensing data. 63% of the study population was adherent according to the medication refill data as compared to 77% in our population. The patients they include had a similar average age and COPD duration to our patients but had a lower CAT score (16.6 ± 7.6 versus 19.2 ± 6.5). Based on the mMRC dyspnea score ≥ 2 (67% versus 79%), their patients were also less symptomatic.[51]
In another cross-sectional study conducted by the same group in 93 Belgian pharmacies[52], 52% of the recruited patients were adherent as assessed by prescription refill rates. The average age and dyspnea score were similar to those of our population but as for the previous study [51], a large proportion of the patients (near 40%) were followed exclusively by their general practitioner.[52]
In a large population database from the Copenhagen General Population Study, the adherence assessed by the dispensing data was much lower, depending on the type of inhaled medications, the highest (only 33%) being observed for ICS-LABA associations (triple therapy was unavailable at the time this study was conducted).[53]

Another factor that may have influenced our high adherence rate is pharmacists. Patients received explanations about their treatment during consultations by their pulmonologist but also when they went to the pharmacy to pick up their inhaled treatments. 98% of the referring pharmacists of patients in this study explained and gave instructions and advice on the method of inhalation and reminded them of the frequency of administration at the time of the first delivery. 62% of referring pharmacists did this at each delivery. Some pharmacists used videos and gave explanatory sheets that patients can take home with them.
This may therefore be an assumption that the adherence rate in our study was high.
A study conducted in 2015 assessed the impact that pharmacists could have on patient adherence. They assessed adherence by medication refill adherence scores. They divided their study population into 2 groups. The first group was coached by a pharmacist and the second group was not coached. They found that the adherence rate was higher in the group being coached by a pharmacist.[54]

5.2.Factors and outcomes associated with good/poor adherence

5.2.1. According to the TAI-10 score classification

5.2.1.1. Factors associated with adherence

The differences between the adherent group and the non-adherent group according to the TAI-10 questionnaire were few and small (Table 6 and table 7). Indeed, the only significant difference that could be found was the one concerning the pneumococcal vaccination. Adherent patients were more likely to be vaccinated against pneumococcus (having received at least one of the 2 vaccines; p=0.034). When looking at individual vaccines, there was only a significant difference between the 2 groups for the conjugate vaccine. Of note, the p-value (0.047) was very close to the significance threshold.

5.2.1.2. Adherence and exacerbations

According to our study, there was no association between adherence defined by the TAI score and the frequency or the number of exacerbations, contrary to what was described in the literature according to which being adherent makes it possible to reduce the frequency of exacerbations and therefore of morbidity and hospitalisation.[49,50] Quite unexpectedly, patients in the LASSYC study with a poor adherence according to the TAI (TAI-10 < 45) had a higher exacerbation frequency while having a higher FEV1 despite the fact that a reduced FEV1 is associated with a higher exacerbation risk.[49] Only 3 patients in our series had a TAI-10 < 45. The data from the study by Ierodiakonou et al. are even more difficult to interpret since patients with good adherence according to the TAI had a lower exacerbation rate in this study but a higher frequency of hospitalisation.[50]

5.2.1.3. Adherence and quality of life

Being adherent according to the TAI score was not associated with a lower CAT score, with a better quality of life while in the literature, several articles mentioned the fact that being adherent is associated with a better quality of life because being adherent was associated with better disease and symptoms control.[27,37,43,49] Only two studies using the TAI-score are available and reported contradictory results. The LASSYC study found patients with a higher TAI-10 score to have a better quality of life as reflected by a lower CAT score [49]. Another study did not find any significant difference in the mean CAT score between adherent and non-adherent patients as assessed by the TAI-10 score, though the proportion of patients with a CAT score ≥ 10 was higher in patients with poor adherence.[50]

In our study, there were no significant differences between the two group of adherences concerning the patient perception of chronic treatment effectiveness on exacerbation rate and dyspnea. It could explain why there was no association between adherence and quality of life.

5.2.2. According to the drug dispensing data score classification

5.2.2.1. Factors associated with adherence

When defined according to drug dispensing data, the 2 groups differed on their post-bronchodilator FEV1, their grade of severity according to the GOLD classification, having or not an ICS or a rescue therapy, having a triple therapy or not, presenting with a dyspnea level of 2 or more on the mMRC scale and having been vaccinated with at least one pneumococcal vaccine (Table 8 and table 9).

All differences point to an association between higher adherence and a more severe disease. Indeed, adherent patients had a lower post-bronchodilator FEV1, were more likely to be affected by a more severe grade of the disease (grade 3 and 4 according to the GOLD classification), and to suffer from a dyspnea level of 2 or more on the mMRC scale. They were also more likely to be treated with an ICS, a rescue therapy or a triple therapy (LABA + LAMA + ICS).

Moreover, adherent patients were more likely and to have been vaccinated with one of the two vaccines against pneumococcus.

The severity of the disease and the symptoms increase in parallel, and since one of the main goals of maintenance therapy is to improve the symptoms, it is logical to hypothesize that more severe patients are more adherent, such as observed in the present study. Since COPD is a disease where the symptoms are not completely alleviated, and even less so when the disease

is severe, maintenance therapies can, therefore, be perceived as more necessary by the patient with severe COPD.[32,49,53]

An association between adherence and more severe disease was also shown in a large population based study assessing adherence with dispensing data.[53] This is also in line with a Belgian study conducted in pharmacies where adherence was higher in patients being treated with a greater number of inhaled therapies[52], as well as a study conducted in the US.[55]

The association between treatment and adherence follows the same lines. Patients affected by the most severe forms of the disease are more likely to be treated by two long-acting bronchodilators and an ICS (triple therapy as maintenance therapy) and to use rescue therapy to relieve dyspnea as quickly as possible. Indeed, a double long-acting bronchodilator (LABA-LAMA) is recommended fort more severely dyspneic patients while ICS are recommended in case of frequent exacerbations, the severity of the disease being one of the main risk factors for exacerbations.[1]

As being vaccinated pertains to the adherence process, it is quite logical to find a higher proportion of adherent patients being vaccinated against pneumococcus in the present study. Of note, there was no difference for the influenza vaccine.

5.2.2.2. Adherence and exacerbations

As for the TAI-10 score classification, we did not found an association between adherence and the rate of exacerbation which is in discordance with the literature according to which the susceptibility of adherent patients to exacerbations was lower than for non-adherent patients.[37] There are very few data however looking at the association between exacerbation rate and adherence assessed by drug dispensing data. As in the present study, Ingebrigtsen et al. did not find any association between exacerbation rate and dispensing data.[53] In another study conducted in the US, Huetsch et al found few associations between adherence to several individual inhaled medications and exacerbation rate. The exacerbation rate was higher in patients with good adherence to a SAMA.[55]
One can hypothesize that since the severity of the disease is associated both with higher adherence and higher risk of exacerbations[1], it is difficult to show an association between adherence and a reduction in exacerbation rate in a cross-sectional study such as the present one.

5.2.2.3. Adherence and quality of life

Unlike literature[27,37,43,49], in our study, there was no association between adherence and the quality of life (cf. 5.2.1.3). We are however unaware of any study addressing the association between quality of life in COPD with the adherence rate assessed by drug dispensing data.

5.2.3. Other associations discussed in the literature

According to our study, whether the classification of patients (in the adherent or non-adherent group) was based on the TAI-10 score or the drug dispensing data score, there was no association between adherence and the smoking status (and smoking history), the education level, the daily dosing frequency, the number of inhalers and the effectiveness of the treatments perceived by the patients. These results were not in accordance with what was described in the literature. Indeed, current smokers were less adherent than ex-smokers[31,34] and adherence increased as dosing frequency and the number of inhalers decreased.[27,34] If the patient's

perception of the effectiveness of their treatments was good, he will tend to be more adherent.[26,34]

We also found no association between adherence-age and adherence-gender.
There are few data regarding the association of these patient and treatment characteristics with adherence assessed by the TAI questionnaire or dispensing data. The LASSYC study found patients with a higher TAI-10 score to have a lower smoking history and a lower education level.[49]
Ingebrigtsen et al. found an association between low adherence (assessed by dispensing data) and higher education level.[53] In another study in which adherence was assessed by dispensing data, Huetsch et al. found that adherence is not associated with the gender or with the smoking status.[55]

5.3. Concordance between the two adherent scores

Concordance of the two adherence scores was assessed by Kappa hypothesis test, linear regression and ROC curve analysis.

Since the Kappa (0.0598), the r^2 (0.0108) and the ROC curve AUC (0.5437) were very low, we can conclude that there was no significant relationship between the two scores and that the TAI-10 score cannot be relied upon to predict the dispensing of medicines.

According to these 3 methods, the TAI-10 score and the drug dispensing data score did not make it possible to classify adherent patients and non-adherent patients concordantly. Two-thirds of the patients classified as non-adherent according to the drug dispensing data were classified as adherent with the TAI questionnaire, while about one-fourth of the patients classified as adherent according to the drug dispensing data were classified as non-adherent with the TAI questionnaire.

The hypothesis that the TAI score would predict good adherence defined by delivery greater than or equal to 80% can be rejected.

There is no data in the literature regarding the concordance between the 2 scores we used in the present study although the association between dispensing data and another questionnaire regarding adherence (the Medication Adherence Report Scale (MARS-5)) was reported in a study by a Belgian group.[51] The MARS-5 is a self-reported adherence questionnaire that was not specifically designed for inhaled therapies as opposed to the TAI questionnaire. In that study, there was also no concordance between the 2 ways of assessing adherence, with the self-reported adherence questionnaire being inaccurate to identify non-adherence in patients with COPD.
Another study conducted in Quebec evaluates the level of concordance concerning the adherence assessed by a 4-item self-reported questionnaire and by the pharmacy records for each prescribed drug that had been filled at least four times. During this study, they recruited patients aged 65 or older. They found a poor concordance between the 2 adherence assessment tools.[56]
Shalansky et al. conducted a study in which they assess the ability of the self-reported questionnaire (Morisky medication adherence scale) to determine non-adherents. They

recruited patients having cardio-vascular medications. They compared the scores obtained with this questionnaire with the prescription refill data. They found that, in settings where the non-adherence rate is low, the ability of the MMAS-8 questionnaire to identify non-adherents is limited.[57]

5.4.TAI-10 score or drug dispensing data score?

Based on these analyses, it was not possible to say which was the best method. There is no golden standard for measuring adherence because all the methods were subject to bias and were not appropriated for all conditions.
If we accept that the TAI-10 and dispensing data are reliable instruments to assess adherence, we have to conclude from the present data that they did not evaluate the same characteristics of adherence.
However, our data did not allow us to say whether one of the methods is more reliable for assessing adherence in COPD. However, indications were pointing to weaknesses in the TAI, in particular, the distribution of scores within the population and the almost total lack of association between TAI score and parameters described as usually associated with adherence in a COPD population, whereas we were able to show an association between dispensing and some parameters already described as associated with adherence in the COPD population.

When patients were classified according to their drug dispensing data score, we found an association between good adherence and severity of the disease. This association is in accordance with what is described in the literature. This tends to favour this method, although drug dispensing data also has some limitations. The major limitation of using dispensing data to assess adherence is the overestimation of drug consumption.[47,58] Buying medications at a pharmacy does not mean consuming these medications. Patients could receive drugs from friends, family or private provider. In this case, these drugs will not be on the dispensing record. Similarly, when patients are hospitalised, the medications they will receive will not be in the drug dispensing record of the pharmacies.[47]

5.5.Study limitations

Firstly, as mentioned above, 67 patients out of 75 have a TAI-10 score greater than or equal to 48, which means that the dispersion of the TAI-10 score in the present study population is low. This is line with the literature showing that adherence scores from questionnaire are highly skewed towards high scores.[51,59]
This, therefore, represents an obstacle for comparing the adherent group with the non-adherent group when patients were classified according to their TAI-10 score and for analysing the concordance between the TAI-10 score and the drug dispensing data score.

Secondly, the TAI questionnaire is subject to bias like other questionnaires. Patients may not be honest in claiming to be adherent when they are not. Besides, answering a questionnaire is subjective, as not all patients have the same meaning of the words "Always; Mostly; Sometimes; Rarely; Never". The subjectivity can lead to an overestimation, as suggested in the literature.[60]

The different items of the TAI questionnaire ask patients about a more or less long period. It is therefore possible that patients may have forgotten certain things about taking or forgetting their treatment.
In addition, although participation in this study was voluntary, as our interviews lasted between 20 and 30 minutes, some patients might have lost patience and not answered all the questions and questionnaires correctly.

Thirdly, the method of analysing dispensing data to assess adherence may also be subject to bias (cf 5.4.). Just because patients pick up the exact number of drugs from their referring pharmacist does not mean that once they return home, they will take their medication properly. They may also throw it away once they get home.

Finally, the population we have chosen to study may induce limitations to our study. Indeed, we have recruited patients who are followed in a university hospital with consultations every few months. There is also follow-up and monitoring. This may have influenced the adherence rate, which in this study is very high.

5.6. Perspectives

This study is the first to compare the TAI questionnaire as a tool to assess COPD patients adherence to inhaled therapies with drug dispensing data. Our results point towards the limitations of the TAI questionnaire.

Future studies should include a larger and more varied population, with patients from the primary care setting, and general hospitals.

They could also use a different adherence assessment method than the one used in this study to reduce bias. The best would be to use electronic monitoring, although this technique is also subject to bias.

6. Conclusion

This study aimed to evaluate the TAI questionnaire by comparing it with drug dispensing data for assessing adherence to inhaled maintenance therapy in COPD patients.

The adherence rate of our study population was high. This can be related to the characteristics of our study population that was recruited in tertiary care.

According to the TAI-10 classification, we did not find any significative differences between the adherent and non-adherent group except concerning the pneumococcal vaccination. We did not find any association with other parameters that are usually reported to be associated with adherence in the literature.

On the other side, according to the drug dispensing data score, adherence was associated with a severe grade of the disease, a higher chance of suffering from grade 2 or higher dyspnea, a

lower post-bronchodilator FEV1, having ICS, having a rescue therapy and having a triple therapy which were in accordance with what is described in the literature.

We did not find any association between adherence and the rate of exacerbation according to the 2 classifications.

We found no concordance between the two assessment measures. This suggests that the two tools do not assess the same thing.
The association of various patient characteristics with adherence however tend to favour the use of the drug dispensing data since the findings were in line with the published literature.

In the future, the TAI questionnaire may also need to be evaluated and compared to dispensing data in a less selected population.

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Figure 3: https://prohealthinsight.com/diseases-and-conditions/respiratory-disease/restrictive-lung-disease-smoking-cause-outside-box/

ANNEX 1

- Anthropometric characteristics of the patient: age, sex.
- Smoking characteristics: active or ex-smoker, cumulative smoking (CP) and the number of cigarettes/day or gram of tobacco/day if active smoker.
- Characteristics of COPD treatment:
    - Maintenance therapy:
        - Current treatment:
            - Inhaled medications: Names, prescribed dosages
        - Other treatments in the last 12 months:
            - Inhaled medications: Names, prescribed dosages
    - Current rescue treatment (short-acting bronchodilators)
- Characteristics of chronic drug therapy (prescribed before hospitalization for hospitalized patients): number of different drugs at assessment
- Characteristics of COPD:
    - GOLD classification according to the A, B, C, D scale requiring a reading
        - Of symptoms assessed by
            - The CAT score (questionnaire)
            - The mMRC dyspnea scale (questionnaire)
        - Of the number of exacerbations treated at home with antibiotics and/or corticosteroids by systemic route in the last 12 months (questionnaire and file review)
        - Of the number of exacerbations requiring hospitalization (questionnaire and file review)
    - GOLD classification according to the severity of the obstructive ventilatory disorder assessed by spirometry (post-bronchodilation FEV1-IV) evaluated during consultation or hospitalisation for patients in stable condition, based on spirometry performed at least 4 weeks after an exacerbation if available or if this is not available based on the last post-bronchodilation FEV1 value available in the file if this value is less than one year old.
    - Duration of the disease based on the start date of a background treatment for COPD
- Vaccination status
    - Influenza vaccination in the last 12 months;
    - Pneumococcal vaccination according to recommendations for
        - The conjugate vaccine
        - The polysaccharide vaccine
- Patient perception of the effectiveness of background treatments for COPD
    - On dyspnea
    - On reducing exacerbations
- Influence of patient education level on COPD background adherence.

ANNEX 2

CHU UCL NAMUR	**Modèle d'information aux patients pour les études réalisées par les étudiants et paramédicaux**
Référence du document: modèle info patient mémoire/Vers2	**Date d'application:** 31.01.2019
Rédigé par: Monsieur Etienne GOURDIN Mademoiselle Cécile PHILIPPIN Docteur Marie de SAINT-HUBERT	**Vérifié par:** Professeur Patrick EVRARD

INFORMATION AU PATIENT

Evaluation du questionnaire TAI comme outil de mesure de l'observance thérapeutiques aux traitements de fond inhalés dans une population de patients BPCO

Vous êtes invité(e) à participer de façon volontaire à une expérimentation. Avant d'accepter d'y participer, il est important de lire ce formulaire qui en décrit l'objectif et les modalités pratiques. Vous avez le droit de poser à tout moment des questions en rapport avec cette expérimentation.

Objectif et description de l'expérimentation

Il s'agit d'une expérimentation qui devrait inclure environ 50 à 150 patients.

L'objectif de cette expérimentation consiste à évaluer l'observance aux traitements de fond inhalés chez des patients BPCO en état stable ou hospitalisés pour exacerbation via le questionnaire TAI et via les données de délivrance obtenues auprès du pharmacien référent.

Plus précisément, l'étude vise à valider le questionnaire TAI en comparant le score qu'il permet de calculer à votre observance aux traitements inhalés évaluée par les données de délivrance de médicaments par votre pharmacien sur la dernière année.

Par ailleurs l'étude vise également à mettre en relation votre observance aux traitements inhalés avec certaines de vos caractéristiques et des caractéristiques de votre maladie respiratoire.

Si vous acceptez de participer à cette expérimentation, il vous sera demandé de remplir plusieurs questionnaires lors de votre visite à l'hôpital ou au cours de votre hospitalisation si vous êtes hospitalisé.

Il vous sera demandé de participer à l'expérimentation au cours de votre passage en consultation ou si vous êtes hospitalisé, au cours de cette hospitalisation. Cette participation suppose un petit supplément de temps lors de votre passage en consultation. Au besoin, si la réponse à certaines questions posées

nécessitait une précision, nous pourrions vous proposer de l'obtenir en vous recontactant par téléphone à une date postérieure à votre consultation ou hospitalisation.

L'ensemble des frais relatifs à cette participation seront pris en charge par l'institution responsable.

Données collectées : Vos données concernant votre observance (la prise correcte, comme il l'est mentionné sur votre prescription de vos traitements) aux traitements, en particulier les traitements inhalés, seront recueillies via un questionnaire (questionnaire TAI) ainsi que, si vous y consentez via les données de délivrance obtenues par nos soins auprès de votre pharmacien référent. D'autres données seront également collectées afin de les mettre en relation avec les résultats obtenus concernant votre observance aux traitements. En effet, vous serez mesuré et pesé et questionné sur vos habitudes tabagiques, sur les répercussions de votre (symptômes, phases d'exacerbation, …) et des traitements que vous prenez (traitements actuels et autres traitements dans les 12 derniers mois) ainsi que votre perception de l'efficacité de ces derniers (sur la réduction des phases d'exacerbations et sur vos difficultés respiratoires). Et finalement, vous serez questionné concernant les vaccinations contre les maladies respiratoires dont vous avez pu bénéficier.

Responsable des traitements et promoteur de l'expérimentation

L'expérimentation étant faite dans le cadre d'un mémoire nécessaire à l'obtention d'un diplôme, c'est l'institution qui délivre celui-ci qui est au sens du RGPD responsable, à savoir l'Université de Namur.

Par ailleurs, l'institution désigne le Prof. Eric MARCHAND, professionnel de santé, tenu au secret médical comme expérimentateur responsable. Ce professionnel de santé est tenu de surveiller l'expérimentation qui, dans le cadre de son mémoire de fin d'étude, est confiée à l'étudiant(e): Leyder Thomas, leyderthomas081098@gmail.com, qui a pris connaissance de ces devoirs légaux et s'est engagé à les respecter, en particulier il sera tenu dans le cadre de son mémoire à la plus stricte confidentialité des données qu'il reçoit.

Participation volontaire

Votre participation à cette expérimentation est entièrement volontaire et vous avez le droit de refuser d'y participer. Vous avez également le droit de vous retirer de l'expérimentation à tout moment, sans en préciser la raison, même après avoir signé le formulaire de consentement. Vous n'aurez pas à fournir de raison au retrait de votre consentement à participer ; toutefois, les données collectées jusqu'à l'arrêt de la participation à l'expérimentation font partie intégrante de celle-ci. Votre refus de participer à cette expérimentation n'entraînera pour vous aucune pénalité ni perte d'avantages. Votre traitement médical ne sera pas affecté par votre décision.

Votre médecin traitant sera averti de votre participation à l'expérimentation si vous le désirez (voir choix dans le formulaire de consentement).

Bénéfices et risques potentiels

Ni le traitement qui vous a été proposé, ni les procédures de diagnostic et de surveillance de votre situation clinique ne sortent de la bonne pratique médicale.

Compte tenu de la nature de cette étude, elle ne comporte pas de risque pour votre santé.

Nous ne pouvons vous assurer que si vous acceptez de participer à cette expérimentation vous tirerez personnellement un quelconque bénéfice direct de votre participation.

Votre observance et l'utilisation correcte que vous faites de vos traitements inhalés étant évaluée dans cette étude, votre participation pourrait cependant amener à vous faire des recommandations utiles pour votre santé.

Assurance

Si vous ou vos ayants droit (famille) subissez un dommage lié à cette expérimentation, ce dommage sera indemnisé par l'assurance de l'institution d'enseignement responsable du mémoire de l'étude conformément aux textes réglementaires signalés dans le cadre de ce document et en particulier à la loi relative aux expérimentations sur la personne humaine du 7 mai 2004. Vous ne devrez prouver la faute de quiconque.

Protection des données

Votre identité et votre participation à cette expérimentation demeureront strictement confidentielles. Vous ne serez pas identifié(e) par votre nom (pseudonymisation[1] et contrôle d'accès aux données d'identification) ni d'aucune autre manière reconnaissable dans aucun des dossiers accessibles à des tiers (c'est-à-dire autres que l'étudiant et l'expérimentateur responsable de l'investigation), résultats ou publications en rapport avec l'étude.

La protection de vos données à caractère personnel est assurée conformément aux exigences du règlement général de protection des données (RGPD), de la loi belge du 30 juillet 2018 et de la loi sur la protection des patients (2002).

Droit d'accès et de rectification

Conformément au RGPD vous avez le droit d'accéder à vos données sous les réserves prévues par le texte du règlement. Ce droit s'exerce auprès du DPO (Délégué à la Protection des Données) du

[1] *La pseudonymisation permet de séparer les données identifiant directement les personnes des autres données non pertinentes. Le mécanisme de pseudonymisation génère une clé d'identification qui permet d'établir le lien entre les différentes informations des personnes. Ces clés d'identification doivent être stockées de manière sécurisée avec un contrôle d'accès robuste. Ainsi, les données ne sont pas anonymes sans être identifiables pour autant.*

promoteur de l'expérimentation (Mme Caroline SCOUBEAU) via courrier électronique (caroline.scoubeau@uclouvain.be) ou par tout autre moyen.

Comité d'éthique

Cette expérimentation est évaluée par un comité d'éthique indépendant, à savoir le comité d'Ethique Médicale du CHU-UCL-Namur (site Godinne), qui a émis un avis favorable le 01 mai 2020. Cet avis est légal et ne doit pas influencer votre décision de participer à cette étude.

Personnes à contacter si vous avez des questions à propos de l'expérimentation

Si vous avez des questions, voulez donner un avis ou exprimer des craintes à propos de l'expérimentation ou à propos de vos droits en tant que patient participant à une étude clinique, maintenant, durant ou après votre participation, vous pouvez contacter:

Personne préposée par le responsable: Prof Eric MARCHAND

Téléphone ou e-mail: eric.marchand@uclouvain.be

FORMULAIRE DE CONSENTEMENT ECLAIRE

1. Je soussigné(e),

   ……
   ……

   déclare avoir lu l'information qui précède et accepter de participer à …. (Exemple: l'enquête)

   ……
   …….

2. Une copie de ce formulaire de consentement éclairé signé et daté par le responsable du traitement, ainsi que la note d'information destinée au patient m'ont été remises. J'ai reçu une explication concernant la nature, le but, la durée de l'enquête, de même que des mesures de sécurité qui seront prises pour veiller à la confidentialité de mes données durant et au-delà de l'expérimentation. J'ai été informé(e) de ce qu'on attend de ma part. J'ai eu le temps et l'occasion de poser des questions sur l'enquête; toutes mes questions ont reçu une réponse satisfaisante.

3. J'ai été informé(e) de l'existence d'une assurance et de mes droits d'accès aux données me concernant.

4. Je sais que cette enquête a été soumise et approuvée par le Comité d'Ethique du CHU UCL Namur, site Godinne

5. Je suis libre de participer ou non, de même que d'arrêter l'enquête à tout moment sans qu'il soit nécessaire de justifier ma décision et sans que cela n'entraîne le moindre désavantage.

6. En signant ce document, j'autorise l'utilisation des données me concernant dans le strict respect du Règlement général européen de protection des données à caractère personnel, des lois du 30 juillet 2018 relative à la protection des données et du 22 août 2002 relative aux droits du patient et du 7 mai 2004 relative à l'expérimentation humaine.

7. J’ai compris que des données me concernant seront récoltées pendant toute ma participation à cette étude et que le responsable du traitement et le promoteur de l’étude se portent garant de la confidentialité de ces données et de leur destruction en principe, un an après la défense du mémoire.

8. Je souhaite/Je ne souhaite pas que mon médecin traitant soit averti de ma participation à cette expérimentation.

9. En conséquence, je consens de mon plein gré à participer à cette expérimentation.

_____ _____

Signature du patient(e) *Date(jour/mois/année)*

Je, soussigné, Mme/Mlle/Mr …….. confirme que j'ai expliqué la nature, le but et la durée de l’expérimentation au patient(e) mentionné(e) ci-dessus.

_____ _____

Signature de la personne qui procure *Date (jour/mois/année)*

l'information et habilitée à le faire

ANNEX 3

Consentement à l'obtention des données de délivrance des médications

Je soussigné Mr/Mme ……..……. accepte que les investigateurs (Leyder Thomas, Marchand Eric, Boulanger Sarah) de l'étude intitulée « Evaluation du questionnaire TAI comme outil de mesure de l'observance thérapeutique aux traitement de fond inhalés dans une population de patients BPCO » approuvé par le Comité d'Ethique médicale du CHU-UCL-Namur (numéro unique belge : B0392020000012) en date du 28/04/2020 obtiennent les données de délivrance des médicaments sur les 12 derniers mois auprès de mon pharmacien référent (données récoltées par mon pharmacien et sur mon dossier pharmaceutique partagé si celui-ci existe).

Date et signature :

ANNEX 4

Questionnaire

Observance du traitement par inhalateur chez le patient atteint de BPCO

ANNEE ACADEMIQUE 2019-2020

Professeur E. Marchand

Thomas Leyder

1. *Données personnelles :*

- ✓ Date de naissance : / /
- ✓ Age : _____
- ✓ Sexe : *Homme - Femme*

2. *Données anthropomorphiques :*

- ✓ Poids : _____
- ✓ Taille : _____
- ✓ IMC *:* _____

3. *Autres données à cocher :*

- o Le patient a un dossier médical informatisé au CHU-UCL-Namur site Godinne.
- o Le patient est capable de lire le formulaire de consentement éclairé et l'a signé.
- o Le patient est capable de répondre aux questionnaires relatifs à l'étude.

4. *Examen (spirométrie 4 semaine après exacerbation ou, à défaut, dernière mesure de VEMS post-broncho disponible datant de moins d'un an) :*

- ✓ Date de la dernière Epreuve Fonctionnelle Respiratoire : / / 20
- ✓ Valeur du VEMS post bronchodilatation : L ou %
- ✓ Classification de Gold : Grade ____

Echelle de dyspnée MRC

Pas de dyspnée, sauf en cas d'effort physique important	0
Dyspnée lors de la marche rapide à plat ou en légère pente	1
A plat, dyspnée à l'origine d'une cadence plus lente par rapport aux personnes du même âge ou obligeant à faire des pauses plus fréquentes	2
Dyspnée après 100 mètres à plat ou après quelques minutes	3
Dyspnée lors de l'habillage et du déshabillage; dyspnée ne permettant plus de quitter le domicile	4

Nom et Prénom : _____

Date et heure : _____

Nom:

Date:

COPD Assessment Test

Quel est l'état de votre BPCO? Répondez au questionnaire CAT (COPD Assessment Test™) pour évaluer votre BPCO

Ce questionnaire vous aidera, ainsi que votre médecin, à mesurer l'impact de la BPCO (BronchoPneumopathie Chronique Obstructive) sur votre bien-être et votre vie au quotidien. Vous pourrez, ainsi que votre médecin, utiliser les réponses et les scores du questionnaire pour mieux prendre en charge votre BPCO et obtenir le meilleur bénéfice de votre traitement.

Pour chaque élément ci-dessous, veuillez indiquer d'une croix (x) la case qui correspond le mieux à votre état actuel. Prenez soin de ne sélectionner qu'une seule réponse par question.

Exemple: Je suis très heureux (heureuse) 0 X 2 3 4 5 Je suis très triste

			POINTS
Je ne tousse jamais	0 1 2 3 4 5	**Je tousse tout le temps**	
Je n'ai pas du tout de glaires (mucus) dans les poumons	0 1 2 3 4 5	**J'ai les poumons entièrement encombrés de glaires (mucus)**	
Je n'ai pas du tout la poitrine oppressée	0 1 2 3 4 5	**J'ai la poitrine très oppressée**	
Quand je monte une côte ou une volée de marches, je ne suis pas essoufflé(e)	0 1 2 3 4 5	**Quand je monte une côte ou une volée de marches, je suis très essoufflé(e)**	
Je ne suis pas limité(e) dans mes activités chez moi	0 1 2 3 4 5	**Je suis très limité(e) dans mes activités chez moi**	
Je ne suis pas inquièt(e) quand je quitte la maison, en dépit de mes problèmes pulmonaires	0 1 2 3 4 5	**Je suis très inquièt(e) quand je quitte la maison, en raison de mes problèmes pulmonaires**	
Je dors bien	0 1 2 3 4 5	**Je dors mal à cause de mes problèmes pulmonaires**	
Je suis plein(e) d'énergie	0 1 2 3 4 5	**Je n'ai pas d'énergie du tout**	

SCORE TOTAL

TAI Test d'Adhésion aux Inhalateurs

Score

1. Au cours des 7 derniers jours, combien de fois avez-vous oublié d'utiliser vos inhalateurs habituels ?
   ☐1. Toujours ☐2. Plus de la fois ☐3. Environ la moitié des moitié des fois ☐4. Moins de la moitié des fois ☐5. Jamais

2. Vous oubliez d'utiliser vos inhalateurs :
   ☐1. Toujours ☐2. Presque toujours ☐3. Parfois ☐4. Rarement ☐5. Jamais

3. Lorsque vous vous sentez bien, vous arrêtez d'utiliser vos inhalateurs :
   ☐1. Toujours ☐2. Presque toujours ☐3. Parfois ☐4. Rarement ☐5. Jamais

4. Pendant les week-ends ou lorsque vous partez en vacances, vous arrêtez d'utiliser vos inhalateurs :
   ☐1. Toujours ☐2. Presque toujours ☐3. Parfois ☐4. Rarement ☐5. Jamais

5. Lorsque vous êtes nerveux ou triste, vous arrêtez d'utiliser vos inhalateurs :
   ☐1. Toujours ☐2. Presque toujours ☐3. Parfois ☐4. Rarement ☐5. Jamais

6. Vous arrêtez d'utiliser vos inhalateurs par peur d'éventuels effets secondaires :
   ☐1. Toujours ☐2. Presque toujours ☐3. Parfois ☐4. Rarement ☐5. Jamais

7. Vous arrêtez d'utiliser vos inhalateurs, car vous considérez qu'ils sont peu efficaces pour traiter votre maladie :
   ☐1. Toujours ☐2. Presque toujours ☐3. Parfois ☐4. Rarement ☐5. Jamais

8. Vous prenez moins d'inhalations que le nombre prescrit par votre médecin :
   ☐1. Toujours ☐2. Presque toujours ☐3. Parfois ☐4. Rarement ☐5. Jamais

9. Vous arrêtez d'utiliser vos inhalateurs parce que vous considérez qu'ils vous gênent dans votre vie quotidienne ou professionnelle :

☐1. Toujours ☐2. Presque toujours ☐3. Parfois ☐4. Rarement ☐5. Jamais

10. Vous arrêtez d'utiliser vos inhalateurs, car vous avez des difficultés à les payer :

☐1. Toujours ☐2. Presque toujours ☐3. Parfois ☐4. Rarement ☐5. Jamais

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Le professionnel de santé responsable du patient doit répondre aux deux questions suivantes, d'après les données qui figurent dans son dossier médical (question 11) et après avoir contrôlé sa technique d'inhalation (question 12).

11. Le patient connaît-il ou se souvient-il de la posologie (dose et fréquence) qui lui a été prescrite ?

☐1. Non ☐2. Oui

12. Pour le dispositif, la technique d'inhalation du patient :

☐1. Comporte des erreurs critiques ☐2. Ne pas d'erreurs critiques ou est correcte

SCORE TOTAL

5. *<u>Données médicales :</u>*

a) Depuis quand êtes-vous soigné pour votre bronchopneumopathie chronique obstructive (bronchite chronique-emphysème) ; depuis quand avez-vous des traitements en inhalation ?

- Avez-vous présenté une dégradation de votre état respiratoire ayant nécessité la prise d'antibiotiques ou de corticostéroïdes (Medrol) au cours des 12 derniers mois ? Quand (date), combien d'épisodes ?

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- Exacerbations ayant nécessité une hospitalisation ?

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6. *Traitement :*

a) Quels médicaments prenez-vous actuellement ?

Nom	Posologie

b) Médicaments inhalés ?

Nom	Posologie

c) Autres médicaments pris dans les 12 mois ?

Médicament	Posologie
Inhalateur	Posologie

d) Traitement de secours (bronchodilatateur à courte durée d'action) :

Nom	Posologie

e) Statut vaccinal :

- Vaccination grippe (12 derniers mois) : OUI - NON

- Vaccination pneumocoque : conjugué – polysaccharidique – NON

f) Perception du patient par rapport à l'efficacité de son traitement de fond sur :

✓ Sur la dyspnée :

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✓ Sur la réduction des exacerbations :

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g) Niveau d'instruction :

- ✓ Dernier diplôme obtenu :
  _____
- ✓ Profession exercée :
  _____

h) Tabagisme

- ✓ Tabagisme : *Oui* - *Jamais* - *Ancien(ne) fumeur-se*
- ✓ Nombre de cigarettes par jour : _____
- ✓ Nombre de paquet par année : _____