*Full Length Research Paper*

# Patterns of behavior and adherence to inhalation therapy in patients with COPD

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## Abstract

**Background: COPD is a leading cause of chronic morbidity and mortality worldwide. For the treatment success it is also necessary to ensure long-term adherence to inhaled drug therapy, whose levels are generally around 50% due to a series of factors involving medication, characteristics of the device system, and patient's and healthcare professionals' behaviors. Today important gaps persist in the knowledge of behaviors, beliefs, preferences and self-perceived health status in patients with COPD, as well as in the social, economic or health contextual factors and their possible relationships with adherence to therapy as potential 'adherence determinants'. Objective: The present research aims to understand patterns of behaviour and type of routines related to the use of different kinds of device (spray or powder) and their possible relationships with the adherence to inhalation therapy in patients with COPD. Methods: CAWI-CATI-FtoF sociological survey with structured questionnaire with standardized scales of measurement of adherence to a specific therapy for COPD, symptoms management and self-perceived health status. Inclusion criteria: patients with medical diagnosis of COPD and currently under inhalation treatment. Percentage shares of prevalent users of MDI, DPI over the years and both such as to guarantee the sub-analysis of clusters. Results: COPD has a significant impact on life for most of the interviewees, in particular for 46% of them it has a high impact and for 15% a very high impact on their life and daily habits. A clear majority of interviewees reported partial (66%) or major (24%) limitations related to their physical health due to their disease, while almost half of the sample of respondents (44%) appears to be poorly adherent to treatment. Conclusions: impact of disease on the interviewee's activity is "high" or "very high" in the clear majority of patients with severe or moderate disease condition and the levels of adherence to therapies are very low. Improving patient adherence to inhalation therapy can lead to a better outcome for COPD treatment, with positive repercussions in terms of disease control, use of health services, positive impact on survival rate, patient's quality of life and health care costs.**

**Key words:** COPD, Patient-reported outcomes, inhalation treatment, chronic illness, self-perceived health.

## 1. INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a chronic progressive disease which causes both pulmonary and systemic consequences (Agustì et al., 2003; Barnes et al., 2009). COPD is one of the leading cause of chronic morbidity and mortality worldwide: it is currently the fourth leading cause of death globally (ALA, 2013; Lozano et al., 2012; Vos et al., 2010), accounting for 6% of all deaths. The overall prevalence in adults aged 40 years or over is estimated at 9-10% (Halbert, 2006). Prevalence is expected to increase due to high rates of tobacco use, population aging, and other environmental risk factors such as pollution (Feenstra et al., 2006; Murray et al., 1997). More than 3 million people died of COPD in 2012 and it is estimated that by 2060 there could be over 5.4 million deaths per year due to COPD and related conditions (Lopez et al., 2006; WHO, 2019).

The total direct costs of respiratory diseases in the European Union are estimated to be around 6% of the total annual health budget, with COPD accounting for 56% (€ 38.6 billion) of the cost of respiratory diseases (ERS, 2017). Also, in terms of health-related quality of life, several studies show that COPD causes a significant quality of life reduction in people who are affected (Kanervisto et al., 2010; Jones et al., 2011).

The use of inhaled drugs (long-acting bronchodilators, ICS, or a combination of both) is recommended by the international *guidelines Global Initiative for Chronic Obstructive Lung Disease* (GOLD) (2020) and is associated with a reduction in exacerbations for patients with moderate to severe COPD (Sin et al., 2003), hospital admissions (Simoni-Wastila et al., 2012; Vestbo et al., 2009), symptoms (Decramer et al, 2011), as well as improved disease control, survival (Mäkelä et al., 2013), exercise tolerance and quality of life.

For a successful treatment, it is necessary to ensure long-term adherence to inhalation drug therapy: in fact, in several studies on adults, adolescents and children, a positive correlation was highlighted between adherence to inhalation drug therapies and clinical efficacy, improving symptoms control and lung function (ivi).

Non-adherence leads to negative health outcomes, a reduction in quality of life and increased healthcare costs (Di Matteo, 2004; Corden et al., 1997)

As the LASSYC study shows, poor adherence was associated with more exacerbations. Vestbo et al., using data from the TORCH study, also found significant differences in survival rate and risk of severe exacerbations, based on patient's adherence level.

Drug adherence levels among COPD patients are generally low, around 50% due to a series of factors involving medication, characteristics of the inhalation device, and patient's and healthcare professionals' behaviors.

Non-adherence to inhaled medications is known to lead to poor disease control, increased use of healthcare services (ISTAT, 2016) and negative impact on survival, quality of life, and healthcare costs. Nevertheless, there is currently little evidence of this.

Data on adherence issues among asthma patients is useful for projecting potential problems for COPD patients. Like COPD, asthma is a chronic condition which is heavily reliant on inhaled medications. COPD patients, as well as those with asthma, can take up to 3-4 different types of inhalers that require high control. COPD patients have to face more challenges on correct inhaler use than asthma patients, because COPD patients are usually older people with multiple comorbidities, and they can experience impaired physical and cognitive function that can interfere with adherence to inhaler and its proper use (Lareaus et al., 2010).

For COPD patients, indeed, one of the elements to consider is the error in device use which can affect the effectiveness of treatment and therefore lead to suboptimal disease control.

In fact, an inadequate technique can lead to insufficient drug administration and therefore to insufficient lung capacity. There are few updated systematic reviews (SRs) or meta-analyzes (MAs) on the subject of device errors in patients with asthma (Chrystyn et al., 2017; Mahon et al., 2017) and not many studies on COPD (Padmanabhan et al., 2019). Overall, it can be found that between 4% and 94% of patients, depending on the type of inhaler and evaluation methods, do not use their inhalers correctly (Lavorini et al., 2008). Instead, predictive elements of better inhalation methods are young age, well-controlled disease and patients who have learned the method from a medical staff (Padmanabhan et al., 2019). The most common mistakes include failing to exhale before activation, inability to hold breath after inhalation, incorrect positioning of the inhaler, incorrect rotation sequence and failure to perform a strong and deep inhalation.

A correct inhalation technique is therefore a key element for an effective treatment of the disease and not having detected any widespread improvement among patients in the last 40 years has shown the urgent need for new approaches to education and drug administration (Sanchis et al., 2016).

An important component of the aspect linked to errors in the use of the devices is the absence of patients' training on this topic: 25% of patients has never received instructions on inhalation technique through verbal counselling and, for those who receive them, the quality and the duration of the training are not adequate, nor reinforced by follow-up checks. In addition to the correct use of inhalation devices (Make, 2003; Usmani et al., 2018) and the impact of training on this, other factors in literature seem to have positive effects on adherence. These include disease-related knowledge, comfort and satisfaction of the inhaler device, age (adulthood), the absence of adverse effects (real or supposed by the patient,) low cost of drugs (Mäkelä, 2013; O'Toole et al., 2022), disease status (Bårnes et al., 2015) and therapeutic regimens or therapy that are not complex to follow (Bourbeau et al., 2007).

A systematic review (Dima et al., 2015) focused on qualifying and synthesizing observational evidence on the determinants of adherence to inhaled drugs in adults with asthma. This review reveals important knowledge gaps on this issue.

The 51 included studies show that there is more solid evidence in identifying a positive association between adherence (better implementaion of therapy) and stronger beliefs about the need for inhalers and, to a lesser extent, between adherence and patient's advanced age. Therefore, these findings suggest that patients better implement recommendations and use prescriptions if they believe more firmly in the need to use inhalers and if they have other positive beliefs (Bimbishar et al., 2020). Age is certainly a relevant aspect, considering on the one hand the low adherence rate in young people (Bårnes et al., 2015), and on the other the advanced age of COPD patients; this is often associated with cognitive decline, which in turn - particularly with memory problems - is associated with non-adherence (Incalzi et al., 1997).

Patients beliefs about their health status and the need to use inhalers are other relevant aspects related to adherence, especially the circumstance in which patients do not consider their condition serious enough to require long-term therapy (Krigsman et al, 2007; DiMatteo et al., 2007).

Patients are more likely to have better adherence to treatment when they believe it will improve disease management or control or if they suppose serious consequences of non-adherence (Bourbeau et al., 2007).

In some studies satisfaction with inhaler devices appears to be positively correlated with improved adherence, clinical outcomes, and reduced costs (Mäkelä et al., 2013).

A recent study on this topic (Aggarwal et al., 2018), where treatment satisfaction with inhaler medications using a spray inhaler (MDI) or a powder inhaler (DPI) was compared, demonstrates that the use of the spray inhaler (MDI) was associated with a better satisfaction, better disease control, and better adherence to treatment.

In a recent study on COPD, adherence was significantly related to the clinical and functional severity of disease (Duarte-de-Araújo et al., 2020). Patients who reported more symptoms or airflow limitation had better adherence to inhaler medications.

A previous study reported that patients are likely to change the recommended drug based on how they feel and therefore on self-perceived health status (George et al., 2005).

Adherence appears to decrease over time with chronic drug use and it is inversely proportional to the number of drugs taken by the patients (Claxton et al., 2001; Franssen et al., 2011). Finally, upon the issue of behaviors and the importance of a correct negotiation on therapy in doctor-patient relationship, it should be noted that systematic reviews have provided evidence that self-management interventions , including negotiated and written action plans to avoid the worsening of symptoms, lead to a lower probability of both respiratory and general hospital admissions (Lenferink et al., 2017).

## 1.1 Objective and Rationale of research

Gaps in the knowledge of COPD pateint's behaviors, beliefs, preferences and self-perceived health status as well as on social, economic or health contextual factors (Dima et al., 2015),show the need for observational studies on these topics that can demonstrate the possible relationship of these factors with adherence to therapy as potential 'adherence determinants',

Improving patient adherence to inhalation therapy could lead to better COPD treatment outcomes, greater disease control, less use of health services, positive impact on survival, COPD patients' quality of life and healthcare costs (Bryant et al., 2013).

The purpose of this study is to evaluate and understand behavioral patterns and types of routines on the use of devices (spray or powder) and their possible relationships to adherence to therapy. This study is part of a broader investigation aimed at exploring behaviors, digital experiences and self-perceived health status in disease management of patients with COPD.

The present study is part of an interdisciplinary line of research (*Outcome Research)* that explores the outcomes (not only clinical, but also subjectively perceived) of various types of interventions using consolidated experimental or observational methodological and technical approaches. The epistemological reflection from which these researches start, is that many "diseases or morbid conditions should not only be considered from a chronic point of view, but that the same context of the relationship between the patient-health professional-caregiver and the health system can't be reduced exclusively to the so-called *clinical setting* (Niero, 2008).

## 2. METHODS

This study was carried out in Italy between November and December 2019 and involved 424 patients with COPD.

Survey participants were recruited randomly, using internal databases held by Bhave, and a residual part (under 5% of the interviewees) with recruitment on the internet or general social networks, by following *snowball recruiting technique*. Measurement method is based on CATI(Computer Telephone Interviewing) (Di Gioia, 2010), CAWI (Computer Assist Web Interviewing) and FtoF (Face to Face) personal integrated interviews, so as to guarantee a representative and homogenous sample of the population questioned through this statistical survey. In this way it was also possible to ensure a widespread supply of contacts throughout the territory, while containing at the same time costs and data collection times.

The questionnaire was specifically developed and validated by a board of research methodologists and expert pulmonologists and it met the following methodological criteria:

- objectivity: administration, determination and evaluation of scores reported by individuals are independent from subjective judgment of the examiner or the individual;
- standardization: refers to the uniformity of the proofs repeated over time;
- sensitivity: relates to the identification of the most suitable evaluation scores range; semi-structured questions with multiple choice and / or Likert rating scales for attitudes measurement, specific standardized scales to measure adherence to asthma (TAI), symptoms control (ACT) and self-perceived physical health status (5 items of SF12 test).
- TAI (Test of Adherence for Inhalers) is a 12-item test (patient-related domain with 10 items and healthcare-related domain with 2 items) designed to measure adherence to inhalers in patients with COPD or asthma. The sensitivity, specificity, and positive and negative predictive values of the 10-item TAI scores help to identify patient groups which are adherent, intermediate adherent, and non-adherent with cut-off values, with the most favorable balance between the test sensitivity and specificity and by a score of 50 for adherent patients, 46 to 49 for intermediate adherent patients and under 45 for non-adherent patients. TAI test has demonstrated good psychometric properties and has proved to be suitable not only for classifying patients with asthma and COPD as adherent or non-adherent to inhalation therapy, but also to recognize the predominant behavioral pattern of non-adherence in individual patients. In addition, the questionnaires short and easy to use for patients with different ages and educational

levels, provide an inexpensive, quick and efficient way to obtain information on inhaler adherence and non-adherence patterns, that can be applied to daily practice.

- COPD Assessment Test (CAT) aims to assess the impact of COPD on patient's health status and consists of a one-dimensional 8-element scale of health impairment in COPD. It has been developed to be applied worldwide and validated translations are available in a wide range of languages. The score ranges from 0 to 40: a score between 0 and 10 indicates a low average impact on patient's life and daily activities, a score between 11 and 20 indicates a reduced impact, a score between 21 and 30 a high impact and a score between 31 and 40 a very high impact on patient's daily life and activity.

An Italian validated version of CAT questionnaire was studied with respect to the main personal and clinical variables of patients and to the spirometric indices of lung function.

Data from this study confirmed how CAT questionnaire is a sensitive, fast tool for assessing respiratory status of patients with COPD. CAT score was not affected by the patient's age, sex, build, geographical origin and educational level. It was related to spirometric values, although not uniquely related to them.

SF12 (Apolone et al., 2005) was used to detect physical health status as reported by the patient. Specifically, 5 of the items employed were obtained from standardized SF12 scale and they were extracted as the most representative of the detected variance with a factor analysis in principal components with Varimax rotation on a sample basis, on the Istat 2013 survey "Health conditions and use of health services". This way it was possible to guarantee the best balance among the highest level of variance and the minimum number of items with respect to physical limitation and self-perception of physical health. Internal reliability was measured with Cronbach's alpha coefficient.

Disease severity level was measured considering the interviewee's response to the question: "Which is your disease severity level as diagnosed by the doctor" with the following response options: "mild, moderate, severe, I don't know, not given".

- Reliability was assessed through test-retest verification (stability over time) and the intelligibility of the questionnaire, as well as its effectiveness in properly collecting useful information for achieving the objectives of the study and it was assessed through a pilot phase where a number of interviews (equal to 5% of the total sample) is carried out. Later, if the questionnaire has not gone through substantial changes, the interviews collected during the pilot phase are merged into the overall sample of the statistical survey. To ensure respondent's attention throughout the duration of the interview and to contain rejection and dropouts rate as much as possible, the questionnaire was designed in such a way that its compilation did not take more than 30 minutes.

The investigation tool as well as the execution of the entire research process is in full compliance with the Ephmra (European Pharmaceutical Market Research Association), ICC, ESOMAR, Farmindustria guidelines & deontological codes and according to the procedures of Bhave quality standards. Questionnaire administration was carried out in compliance with the regulations in force in Italy related to privacy, legislation on pharmaco vigilance and the Italian Communications Authority (AGCOM).

According with the objectives of this survey, the questionnaire was structured in the following sections:
- Section A – Respondent  profile
- Section B – Use and satisfaction of  inhaler
- Section C - Digital experience
- Section D Knowledge and use of medical Apps
- Section E – Health status

## 3. RESULTS

### 3.1 Statistical Analysis

This study was carried out in Italy between November and December 2019 and involved 424 patients with COPD.

A descriptive analysis of responses to the items of the questionnaire was performed in unvaried form and as for the bivariate analyses, statistical significance of the hypothesis of independence was detected through χ2 test with p = 0.05.

Stratified cluster analyses were performed as a comparison analysis of the cohort of respondents with severe COPD with the rest of the sample of respondents, while analyzing satisfaction on inhalers and perception about personal level of information on the disease.

Pearson's correlation coefficient was used to compare the cardinal variables, while for symmetric association of ordinal variable measurement, *Kendal's Tau*-coefficient was applied to rectangular tables (with ordinal variables with different number of modes) and *Kendal's Tau-b* for square tables (with ordinal variables with the same number of modes). *Eta2* (corresponding to Pearson's R2) was applied for a categorical with a cardinal, which is a coefficient indicating how much our ability to guess the scores of any case on the cardinal variable improves with respect to the condition in which we know only the general mean of the cardinal variable, when we know which modality that case belongs to. Coefficients with such an interpretation vary between zero and one and they are known with the acronym *pre* (proportional reduction in error). Finally, *Fisher-Snedecor F test* with a .10 threshold was used as a test of significance to consider the input of independent variables in the multiple linear regression model.

A multiple linear regression was performed with adherence as a dependent variable expressed in ordinal scores according to the TAI test, designed by specifying the model with recursive exclusion of the variables (*best sub-set regression* with selection by *Stepwise*) with low significance according to *Fisher-Snedecor F test* with a .10 threshold or low correlation coefficients. The excluded variables, based on relative importance criteria of the estimated effects to maximize the explained variance, and initially considered in the model were: gender, study level (dichotomized variable and treated in a complete disjunctive form; all modalities

were excluded from regression with the exception of the "degree" mode), the specific satisfaction (for each modality) with the inhaler used, geographical area, working condition, housing condition. The remaining independent variables are: age, information level about disease, comorbidities, disease severity level, overall satisfaction level, health-related restrictions, level of education (presence or absence of a degree).

Goodness of fit: the coefficient of determination R squared with 0.397 indicates that 39.7% of Y deviance is reproduced by the linear regression on predictors, not a very high value. Considering the significance levels, the analysis of residuals of regression and the form of relationship, it is likely that the relationship is not strictly linear.

However, it is good to specify that the model has no predictive but explorative and specifying functions in identifying, according to the cognitive needs of the survey, characteristics and trends in the structure of identified relationships as possible determining or predisposing factors for adherence.

Data analysis with SPSS version 18.0

### 3.2 Clinical features and sociodemographic data of the sample

Data were collected from a sample made by 424 patients with a medical diagnosis of COPD and currently under inhaled treatment (data reported by interviewees).

The average age of the respondents is 63 years (std. dev. 10.8) with 48% of women and 52% of men. A substantial part of the interviewees declared to be "sufficiently informed" (44%) while 13% declared to be "poorly informed" about the disease (Table 1). 55% of the respondents considered COPD a situation "which can be serious but not always serious".

**Table 1.** Sociodemographic features of respondents.

| | | Values % (*p.v.*) | CharacteristicValues |
|---|---|---|---|
| Sex | Men | 48 (*203*) | |
| | Women | 52 (*221*) | |
| Age | Up to 55 | 39 (165) | |
| | Between 56 and 70 | 45 (*191*) | Average: 63 |
| | Over 71 | 16 (*68*) | |
| Geographical area (Italy) | North West | 23 (*97*) | |
| | North East | 17 (*72*) | |
| | Center | 31 (*132*) | |
| | South | 29 (*123*) | |
| Degree | Elementary School Certificate | 7 (*29*) | |
| | Middle School Certificate | 20 (84) | |
| | High School Diploma | 42 (*179*) | |
| | University Degree | 26 (111) | |
| | Master Degree | 5 (*21*) | |
| Employment Status | Self-employed | 14 (59) | |
| | Employee | 51 (218) | |
| | Homemaker | 10 (*43*) | |
| | Student | 7 (*29*) | |
| | Retired | 12 (*50*) | |
| | Unemployed | 6 (*25*) | |
| DwellingConditions | Lives on his/herown | 9 (38) | |
| | Lives with his/her partner | 29 (*122*) | |

**Table 1 cont.**

| | | | |
|---|---|---|---|
| | Lives with his/her partner and children | 49 (*203*) | |
| | Lives with parents | 11 (*46*) | |
| | Lives with other people | 2 (*8*) | |
| Level of information on COPD* | Very well informed | 7 (*29*) | |
| | Wellinformed | 34 (*144*) | |
| | Sufficientlyinformed | 44 (*188*) | |
| | Poorlyinformed | 13 (*55*) | |
| | Not informed | 2 (*8*) | |

* Self-evaluation of interviewee

## 3.3 Self-perceived physical health status, disease management and severity level

46% of respondents report suffering from a "moderate" level of disease severity, while 18% from a "severe" level, 30% from a "mild" level and 6% declare that they "have not received any communication" by doctors about the severity level of diagnosed disease, or that he/she "does not remember" (Table 2).

By measuring adherence to therapy with the **TAI** test scale, it is highlighted that almost half of the sample of respondents (44%) appears to be poorly adherent to therapy while only 21% shows good adherence (Table 2).

The administration of CAT questionnaire has allowed to detect how COPD has a significant impact on their lives for 6most of the interviewees. In particular disease has a high impact for 46% of patients and for 15% of them it has a very high impact on their life and their daily habits.

Considering self-perceived physical health status with SF12 scale, it can be noticed how 66% of respondents perceives partial restrictions in terms of physical health status, and 24% important restrictions over their physical health due to their disease (Table 2). 57% of the sample report suffering from other disease in addition to COPD.

**Table 2**. Health status, Adherence, Disease Management and Severity Level*

| | | |
|---|---|---|
| Disease severity level | MILD | 30 (*128*) |
| | MODERATE | 46 (*196*) |
| | SEVERE | 18 (*76*) |
| | NOT COMMUNICATED | 2 (*8*) |
| | DOES NOT REMEMBER | 4 (*16*) |
| Adherence level (TAI) | Good adherence | 21 (*89*) |
| | Intermediate Adherence | 35 (*148*) |
| | Pooradherence | 44 (*187*) |
| Disease Management Level (ACT) | Low impact | 6 (*25*) |
| | Reduced impact | 33 (*140*) |
| | High impact | 46 (*196*) |

**Table 2 cont.**

|  |  |  |
|---|---|---|
|  | Very high impact | 15 (63) |
| Health status_Restrictionslevel (SF12) | No restrictions | 10 (*42*) |
|  | Partialrestrictions | 66 (*280*) |
|  | Importantrestrictions | 24 (*102*) |
| Suffering from other disease | Otherdisease | 57 (*242*) |
|  | Only COPD | 56 (*182*) |

*Self-evaluation of interviewee

Considering self-perceived physical health status in patients with COPD in relation with disease severity, it is possible to detect that the majority of patients with severe illness lives with important physical health restrictions.

**Fig. 1:** Disease severity and restrictions in daily life.
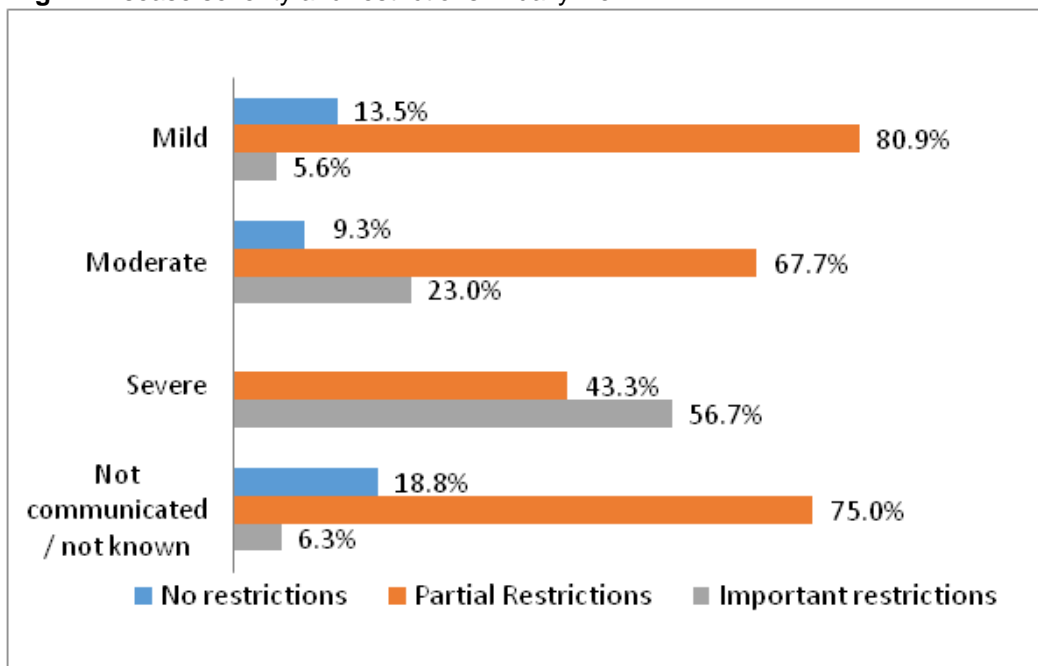


$p<0,05$

On the basis of the CAT scale, we can notice that the impact of disease on daily activities is "high" or "very high" for the clear majority of patients with severe illness and that even in case of moderate severity level of disease the impact stands at a "high" level for the majority of them.
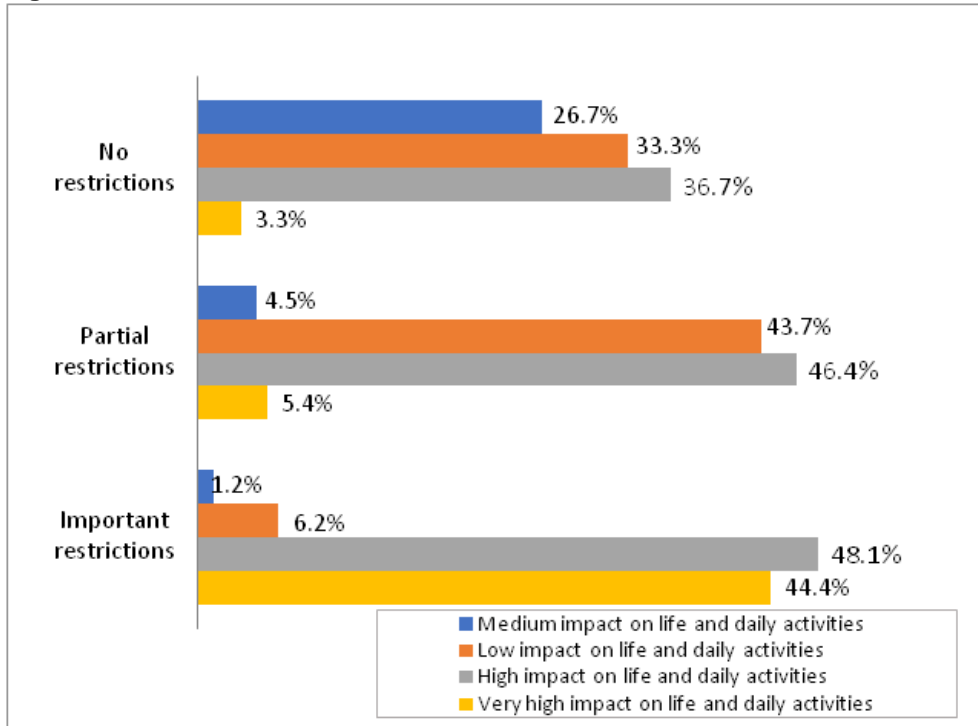
**Fig. 2**: Disease severity level and CAT.
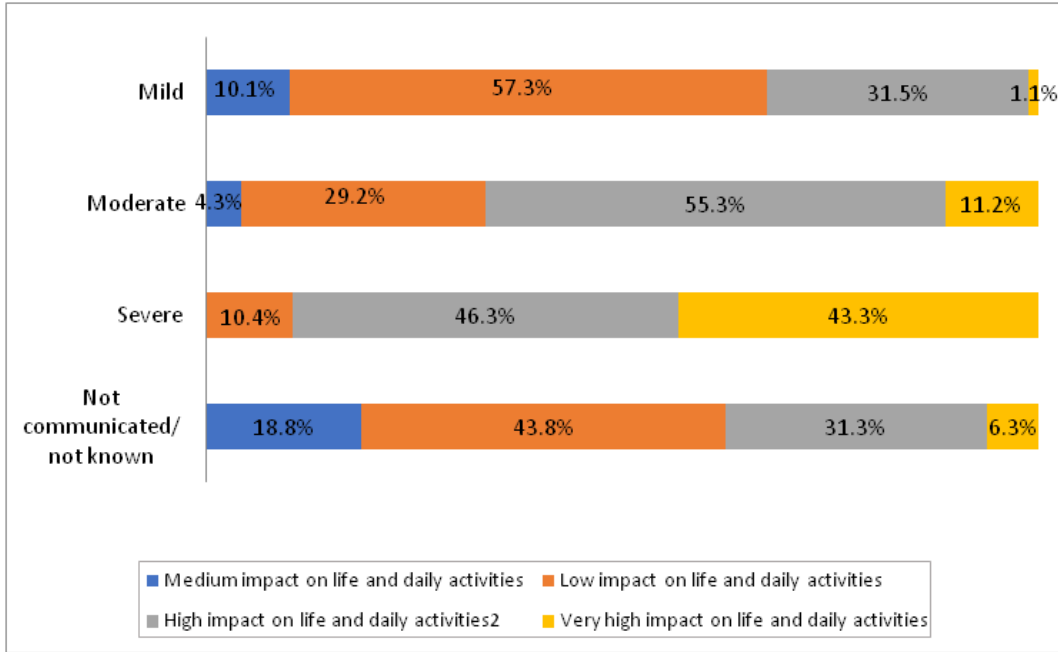


*p<0,05*

Comparing SF12 scale values with CAT, we notice that even in cases where respondents believe that their physical health status has "partial restrictions", disease still has a "high" impact on their daily life.
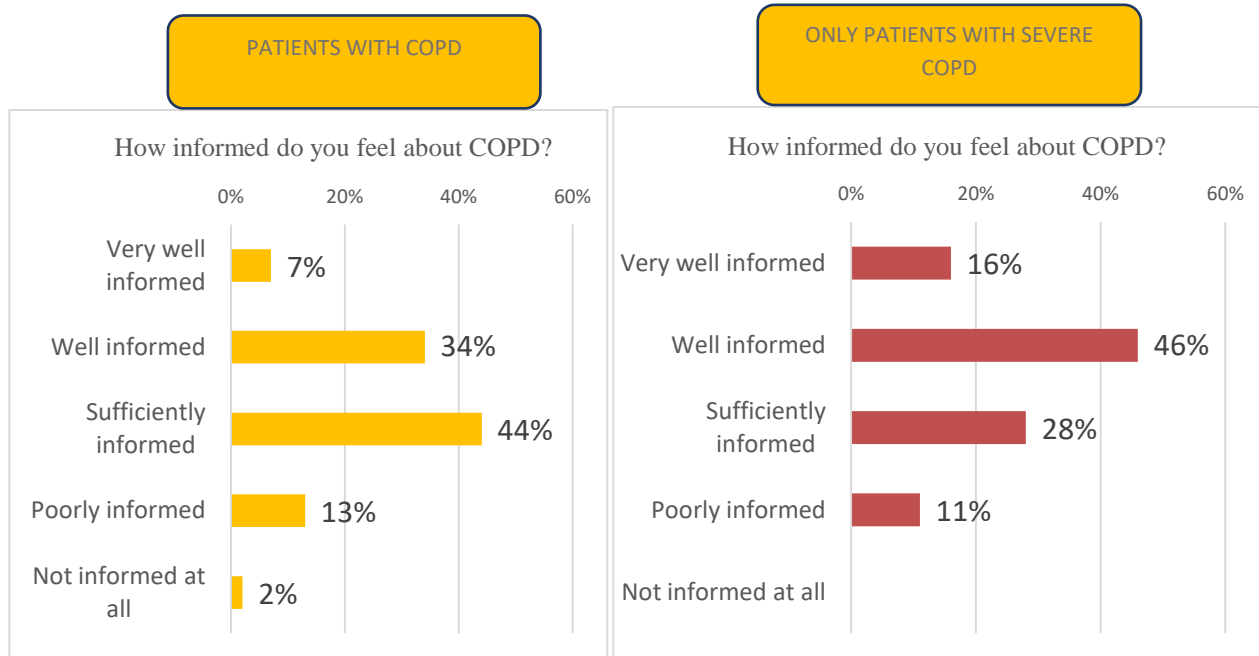
**Fig. 3:** Questionnaire SF12 vs CAT.



*p<0,05*

Relating to information about their condition, people with severe COPD feel more informed than other respondents.

**Fig. 4.** Disease information.



**3.4 Adherence to therapy and its determinants**

On the basis of TAI test, we can observe that greater problems in terms of adherence to therapy can be found in case of respondents who claim to suffer from moderate COPD. It is interesting to point out the high percentage of interviewees with low level of adherence within the category of those who are not aware of the disease severity (Fig. 5)

**Fig. 5** Comparison between adherence and severity level.
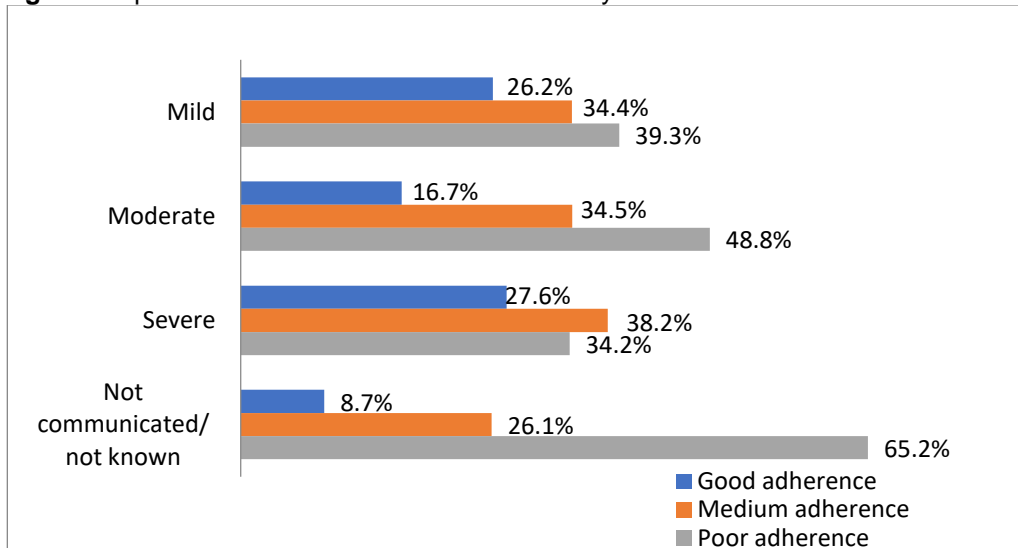


$p<0,05$

Finally, from multiple linear regression (Table 3) it is possible to measure that adherence increases in the following conditions:
• As the age decreases
• In patients with high educational degrees, especially university degrees
•  Higher level of information about disease
• In absence of comorbidities

• In case of high disease severity
• Greater overall   satisfaction with the inhaler
• Higher limitations related to patients health status

**Table 3.** Multiple linear regression.

| R | R-squared | Std. Error of estimate | Amendment F | gl1 | gl2 | Amendment Sign. F | Durbin-Watson |
|---|---|---|---|---|---|---|---|
| ,63[a] | ,397 | 4,056 | 2,84 | 8 | 85 | ,91 | 1,154 |

**Table 4.** Adherence coefficients related to models.

| Model | Unstandarized coefficients | Standarized coefficients | |
|---|---|---|---|
| | B | Beta | *Sign. -di T* |
| (Constant) | 29,56 | | ,012 |
| Age | -4,921 | -,437 | ,027 |
| Degree (presence/absenceuniversity degree) | -,494 | -,178 | ,042 |
| Information levelabout COPD | 2,78 | ,387 | ,027 |
| Comorbidities (presence/absence) | ,816 | ,542 | ,032 |
| Disease severity level (presence/absence of high severitylevel) | -3,67 | ,498 | ,021 |
| Overall satisfaction level | 3,76 | ,276 | ,039 |
| Daily activities restrictions | ,456 | ,354 | ,014 |

## 4. DISCUSSION

COPD is a leading cause of chronic morbidity and mortality worldwide: it is currently the fourth leading cause of death globally (ALA, 2013; Lozano et al., 2012; Vos et al., 2010), accounting for 6% of all deaths.
For treatment to be successful, it is necessary to ensure long-term adherence to inhaled drug therapy: a positive connection has been highlighted in several studies between adherence to inhalation drug therapies and clinical efficacy, improving symptom control and lung function (Mäkelä et al., 2013).
Adherence levels in patients with COPD are generally low, around 50% (Bourbeau et al., 2008) due to a series of factors involving medication, characteristics of the delivery device, patient's and healthcare professionals' behaviors (
Improving the patient adherence to inhalation therapy could lead to a better COPD treatment outcome, greater disease control, less use of health services, positive impact on survival, COPD patients' quality of life, and healthcare costs (Lareau et al., 2010; Restrepo et al., 2008; Iuga et al., 2014)
From this perspective, this study aimed to evaluate and understand behavioral patterns and types of routines on the use of devices (spray or powder) and their possible relationships to the adherence to therapy.
It also focused on measuring patients 'Quality of Life, evaluating outcomes as referred by the same patient (PRO: Patient-Reported-Outcomes)
This reflection leads to the need to consider a broader health-disease context, which requires tools for measuring and evaluating outcomes that are not just strictly clinical in nature. Here, of course, reference is made to social and psychological dimensions and to what in the literature can be considered as *surrogate outcomes* and outcome based on patient's subjectivity, thus considering outcomes as a continuum between "simple pathophysiological values to real evaluations of quality of life" (Apolone in Niero,

2008). In this context, those measures defined as out-of-skin are particularly relevant as they do not belong to health care internal domain, but to external aspects such as satisfaction with therapy (Kaplan et al., 1989).

PROs detection takes place with a standardized questionnaire with measures able to quantify patients' point of view on their health and life as main or complementary end-points.

The value of these findings lies in the reduction of the distance between medical and humanistic disciplines and in an outcome evaluation process more patient-centered. Focusing on perceived health status is crucial in COPD for determining disease severity, impact on daily life and effect of treatment on patients (Ekström et al., 2016).

It should be noted that the perceived measurements (PRO) do not always correlate with physiological ones. For example, the achievement of clinical results and physiological healing does not mechanically correspond to a positive patient's perceived health index (Kunz et al., 2008).

From this point of view it is certainly important to comment the relationships found between the different variables as well as the inconsistencies between self-perceived health status and more standardized measures, as in our case happens with condition control and adherence.

**The investigation revealed that:**

1. 44% of interviewees declares to be "sufficiently informed" while 13% declare to be "poorly informed" about his/her disease. People with severe COPD report being more knowledgeable than other respondents.
2. 55% of respondents consider COPD a situation "which may be serious but not always serious".
3. Almost half of the sample of respondents, 44%, appears to be poorly adherent to therapies despite the fact that a significant part of the sample claims to suffer from moderate (46%) or severe (18%) COPD.
4. For most of the interviewees disease has a significantly negative impact on their life, in particular for 46% of the interviewees a high impact and for 15% a very high impact on their life and daily habits.
5. A clear majority of respondents report experiencing partial (66%) or major (24%) limitations related to their physical health due to COPD.
6. The negative impact of COPD on interviewee's daily activities is "high" or "very high" in the clear majority of cases of severe patients and patients with moderate COPD who also report that their physical health is severely limited.
7. Greater problems with adherence to therapy are found in the case of respondents who claim to suffer from moderate COPD.
8. Adherence is positively correlated to
a) degree (increasing with university degree),
b) the level of disease knowledge
c) the level of disease severity (increasing in cases of severe COPD),
d) the level of general satisfaction with the inhaler used
e) the level of limitations in daily life related to health status COPD patient
9. Adherence, on the other hand, is negatively correlated with
a) age
b) comorbidities.

Our investigation has some limitations:
- difficulty in identifying stable questions, due to the instability in defining some concepts over time;
- cultural process of validation of the survey instrument, above all, its effective standardization.
- The goodness of fit (greater ability to adapt) of the model to data as well as the strength of the detected associations have relatively low values, as they allow to identify characteristics or trends in the structure of the identified relationships as possible determinants or predisposing factors for adherence, but a forecast on major outcomes is not possible for residuals or high gaps. (they do not enable).

## 5. CONCLUSIONS

Important gaps in the knowledge of adherence determinants, specially linked to patient behaviors, conditions or therapies as well as to social, economic or health contextual factors (Dima et al., 2014), show the need for observational studies on these topics.

Improving patient adherence to inhalation therapy can lead to a better outcome for COPD treatment (López-Campos et al., 2008), with positive repercussions in terms of disease control, use of health services, positive impact on survival rate, patient's quality of life and health care costs (Iuga et al., 2014). Important gaps in the knowledge of adherence determinants, especially linked to patient behaviors, conditions or therapies as well as to social, economic or health contextual factors (Dima et al., 2014) show the need for observational studies on these topic.

The investigation revealed that the impact of disease on the interviewee's activities is "high" or "very high" in the clear majority of patients suffering of severe or moderate COPD, who also report that their physical health is severely limited. The study also found that adherence is positively correlated to the type of academic degree (increasing with university degree), the level of disease knowledge, the level of disease severity (increasing in cases of severe COPD), the level of general satisfaction with the inhaler used and the level of limitations in daily life related to health status COPD patient, while it is negatively correlated

to age and to comorbidities.

Future studies could benefit from adopting broader theoretical approaches which may also explore factors that go beyond the individual patient level, to facilitate the designing of effective interventions to improve drug adherence and inhalation technique (Bryant et al., 2013). An example of this, could be models of short-term counseling, health coaching (Willard-Grace et al., 2020), or effective forms of health education (Lopez-Campos, 2019). Finally, future studies could support the planning of structured and multidisciplinary COPD self-management interventions such as personalized integrated care (Global Initiative for Chronic Obstructive Lung Disease, 2020) with the goal of motivating, engaging and supporting patients to positively adjust their health behaviors and develop skills for a better disease management (Effing et al., 2016).

## Availabiliy of data and material

The datasets generated and analysed during the current study are not publicly available due but are available from the corresponding author on reasonable request.

## Additional File

Additional File 1: Appendix S1. Questionnaire.

## Abbreviations

ICS Inhaled corticosteroids
Evaluated devices were metered dose inhalers (MDI), and dry powder inhalers (DPI)

## Consent to participate

Informed consent was obtained from all individual participants included in the study.

## Ethical approval

This observational study was a non-interventional and non-experimental sociological research on health behaviour. No drug has been involved in the conducting of this study, which makes the present not subject to Ethical Committee Approval according to Italian law (in particular, legislative decree n.211 24 June 2003, published in Ordinary Supplement n.130, page 35, to the Official Journal of 9 August 2003 n.184 and AIFA (Italian Medicines Agency) resolution of 20 March 2008 and official memorandum n.6, 2 September 2002). This study was performed in line with the principles of the Declaration of Helsinki and its later amendments and according to the laws relating to the prevention of corruption. Due to the nature of this observational research, no insurance policies were needed.

## Author contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by all authors as well as the first draft of the manuscript. All authors read and approved the final manuscript.

**Consent to publication** All authors provided consent for publications

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