Adherence to Therapy in Chronic Obstructive Pulmonary Disease: A Systematic Review

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Abstract

Adherence to therapy plays a key role in treatment optimization and clinical outcome in patients with chronic obstructive pulmonary disease (COPD). The adherence to inhaled medications is poor, ranging from 20% to 60%. In this study we searched Medline and PubMed literature regarding factors that could have an impact on therapy adherence in COPD patients, using the key words "COPD" or "chronic obstructive pulmonary disease" and "adherence". The search was limited to the English language article published between January 2013 and December 2019. Review papers, study protocols, and meta-analyses were excluded. The final material included 25 articles. The evaluation was performed using the Cochrane Review Manager guidelines. The 25 articles represented 29 countries from 5 continents. We assessed adherence to therapy and the impact of selected factors on the adherence in 27,660 COPD patients (60.9% of whom were male, mean age 64 years). The factors affecting adherence were broken down into three categories: sociodemographic, clinical, and psychological. There were two standardized instruments used in the analyzed studies: Test of Adherence to Inhalers (TAI) and self-reported Morisky Medication Adherence Scale (MMAS-8). We found that 46.3% of patients had a moderately good level of adherence to inhaled therapy (TAI range around 50 points), while 41.6% of patients had a high level of adherence to oral therapy. The nature of non-adherence was in most cases inadvertent rather than an erratic or deliberate demeanor (48.5% vs. 38.9% vs. 42.4%, respectively). We conclude that standardized instruments enable the prediction of adherence to therapy and should be used in clinical practice. The assessment of adherence is essential for undertaking interventions to counteract plausible non-adherence. Collaboration between an educator and a psychologist is required to evaluate the patient's motivation and to ensure his comprehension of treatment prescribed.

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1   Introduction

Adherence to treatment plays a key role in the course of chronic obstructive pulmonary disease (COPD). Non-adherence is rather common, as adherence ranges between 20% and 60% of COPD patients. Non-adherence results in symptom exacerbation, frequent hospitalizations, and poor quality of life. COPD was the fourth most common cause of death in 2000. It is estimated that 4.7 million people will die from COPD by 2020, making the disease the third most common cause of death worldwide. Human and economic losses due to non-adherence in COPD have been estimated at $300 billion per year (DiMatteo 2004).

The WHO has identified non-adherence to treatment as one of the most serious health problems. Non-adherence is a fundamental barrier to achieving the expected outcomes of evidence-based treatment. The consequences for non-adherent patients range from health deterioration to death. At the same time, non-adherence has serious health-related and economic ramifications for the entire society. To date, hundreds of factors that affect treatment adherence have been described. Their classification by the WHO comprises five broad categories: (1) socioeconomic factors, (2) healthcare system-related factors, (3) illness-related factors, (4) treatment-related factors, and (5) patient-dependent factors (WHO 2003).

Factors associated with satisfaction and technique of inhaled therapy have been identified as the most significant for COPD treatment adherence, while sociodemographic factors are considered the least significant. The main problem associated with inhaled therapy is a lack of the patients' savvy to use this treatment option. Other substantial predictors of adherence include psychological factors. Beliefs about medication and treatment satisfaction are the most common causes of treatment discontinuation. Chronically treated patients collect experiences and develop their own beliefs regarding the use of specific medications, sometimes also considering the experience of their friends or family members. Another major determinant of adherence is concern about the use of complex inhalers or other devices. In the literature, differences in adherence have been reported between inhaled and oral treatments. Thus, factors that would influence adherence should be considered when selecting specific treatment.

The available reports present contradictory findings regarding the impact of sociodemographic and clinical factors on adherence in COPD patients. In general, there are few studies that include the assessment of the impact of psychosocial factors on adherence to treatment in chronically ill patients. There is also an apparent shortage of the literature describing non-adherence risk factors in COPD patients. Therefore, this study was undertaken to present and evaluate the available literature findings on the influence of sociodemographic, clinical, and psychosocial factors on adherence to therapy in COPD patients.

2   Methods

2.1   Search Strategy

In this study, we searched Medline and PubMed databases for the articles addressing factors that could have an impact on therapy adherence in COPD patients, using the key words "COPD" or "chronic obstructive pulmonary disease" and "adherence" or "MMAS" or "TAI". The search was limited to the English language article published between January 2013 and December 2019. Review papers, study protocols, and meta-analyses were excluded. The final material included 25 articles comprising a total of 27,660 COPD patients. Of this cohort, 16,844 (60.9%) were men of the mean age of 64 years. The evaluation was performed using the Cochrane

Fig. 1 Study flow diagram
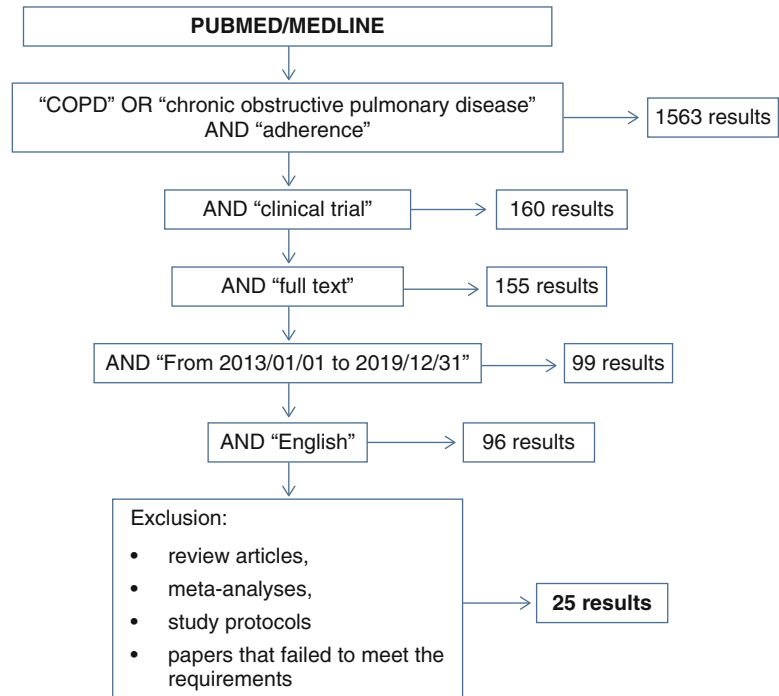
Review Manager guidelines. Subsequent analyses were performed using the Cochrane Review Manager guidelines (Lutje 2019). The search scheme is presented in detail in Fig. 1.

2.2 Statistical Elaboration

Statistical analysis was performed using a fixed effect or random effect model, depending on the heterogeneity of results. For the latter model, the DerSimonian–Laird estimator was used. A p-value <0.05 defined statistically significant associations. The analysis was performed using R software v3.6.1 (R Core Team 2019).

3 Results

There were two main standardized instruments used in the analyzed studies: Test of Adherence to Inhalers (TAI) and self-reported Morisky Medication Adherence Scale (MMAS-8). TAI

consists of 10 (short version) or 12 (full version) items. In the 10-item version of the test, each item was scored between 1 (worst) and 5 (best) possible score, yielding a total ranging from 10 to 50 points. The 12-item TAI includes additional two items addressing the healthcare professional, which are scored 1 (bad) and 2 (good), adding the maximum of 4 points. These two items were designed to unravel the inadvertent non-adherent pattern. This pattern was identified when the score for item 11 or 12 was 1. The erratic or deliberate non-adherent behavior pattern was identified when the score for items either 1–5 or 6–10 was ≤24, respectively (Plaza et al. 2016a).

The Morisky Medication Adherence Scale (MMAS-8) is a self-reported questionnaire to assess adherence to medication. The scale comprises eight items that assess behaviors and barriers related to the long-term adherence to medication. MMAS-8 score may range between 0 and 8, with the scores <6, 6–7, and 8 corresponding to low, medium, and high adherence, respectively (Morisky et al. 2008).
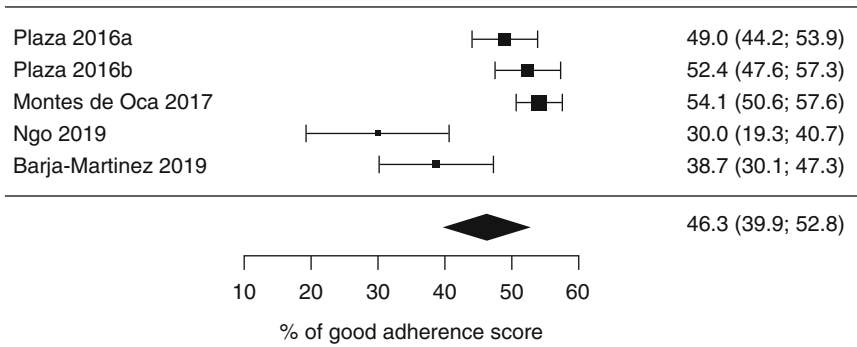
Fig. 2 Percentage of patients with good scores of adherence to therapy in COPD patients

3.1 Test of Adherence to Inhalers (TAI): Five Studies Included in the Analysis

3.1.1 TAI: % of Good Scores of Adherence to Therapy

The analysis shows that 46.3% of patients in the analyzed studies obtained good scores of adherence to therapy (95%CI; 39.9–52.8). The test for heterogeneity demonstrated a considerable heterogeneity of data, with the heterogeneity coefficient of $I^2 = 84.8\%$ ($p < 0.001$). The random effects model was applied in the data elaboration (Fig. 2).

3.1.2 TAI: % of Inadvertent Non-adherence to Therapy

The analysis shows that 48.5% of patients in the analyzed studies showed inadvertent non-adherence to therapy (95%CI: 21.3–75.7). The test for heterogeneity demonstrated considerable heterogeneity of data, with the heterogeneity coefficient of $I^2 = 99.4\%$ ($p < 0.001$). The random effects model was applied in the data elaboration (Fig. 3).

3.1.3 TAI: % of Erratic Non-adherence to Therapy

The analysis shows that 38.9% of patients in the analyzed studies showed erratic non-adherence to therapy (95%CI: 18.3–59.4). The test for heterogeneity demonstrated considerable heterogeneity of data, with the heterogeneity coefficient of

$I^2 = 98.9\%$ ($p < 0.001$). The random effects model was applied in the data elaboration (Fig. 4).

3.1.4 TAI: % of Deliberate Non-adherence to Therapy

The analysis shows that 42.5% of patients in the analyzed studies showed erratic non-adherence to therapy (95%CI: 12.0–72.9). The test for heterogeneity demonstrated considerable heterogeneity of data, with the heterogeneity coefficient of $I^2 = 99.6\%$ ($p < 0.001$). The random effects model was applied in the data elaboration (Fig. 5).

3.2 Morisky Medication Adherence Scale (MMAS-8): Six Studies Included in the Analysis

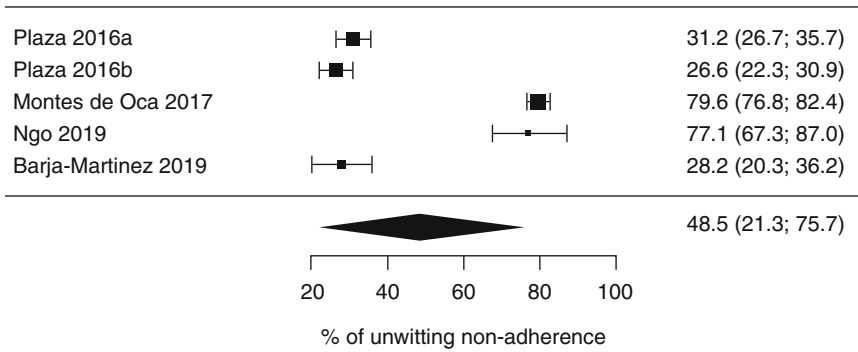#### 3.2.1 MMAS-8: % of High Scores of Adherence to Therapy

The analysis shows that 41.6% of patients in the analyzed studies obtained high adherence scores (95%CI: 26.7–56.4). The test for heterogeneity demonstrated considerable heterogeneity of data, with the heterogeneity coefficient of $I^2 = 99.3\%$ ($p < 0.001$). The random effects model was applied in the data elaboration (Fig. 6).
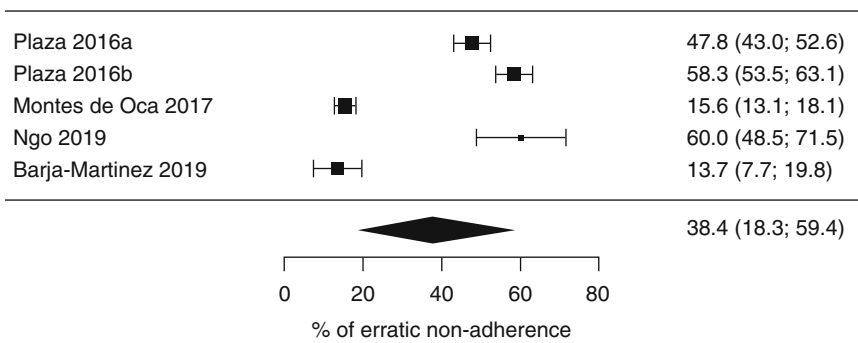
3.3 Factors Affecting Adherence to Therapy in COPD Patients

Table 1 shows sociodemographic, clinical, and psychological factors contributing to

Plaza 2016a		31.2 (26.7; 35.7)
Plaza 2016b		26.6 (22.3; 30.9)
Montes de Oca 2017		79.6 (76.8; 82.4)
Ngo 2019		77.1 (67.3; 87.0)
Barja-Martinez 2019		28.2 (20.3; 36.2)
		48.5 (21.3; 75.7)

20   40   60   80   100

% of unwitting non-adherence

Fig. 3 Percentage of patients with inadvertent non-adherence to therapy in COPD patients

Plaza 2016a		47.8 (43.0; 52.6)
Plaza 2016b		58.3 (53.5; 63.1)
Montes de Oca 2017		15.6 (13.1; 18.1)
Ngo 2019		60.0 (48.5; 71.5)
Barja-Martinez 2019		13.7 (7.7; 19.8)
		38.4 (18.3; 59.4)

0   20   40   60   80

% of erratic non-adherence

Fig. 4 Percentage of patients with erratic non-adherence to therapy in COPD patients

Plaza 2016a		34.2 (29.6; 38.7)
Plaza 2016b		41.2 (36.5; 46.0)
Montes de Oca 2017		78.0 (75.1; 80.9)
Ngo 2019		54.3 (42.6; 66.0)
Barja-Martinez 2019		4.8 (1.1; 8.6)
		42.5 (12.0; 8.6)

0   20   40   60   80   100

% of deliberate non-adherence
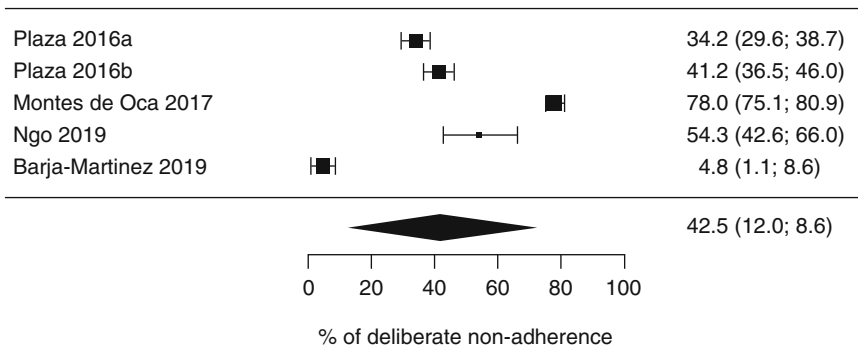
Fig. 5 Percentage of patients with deliberate non-adherence to therapy in COPD patients

non-adherence to therapy in COPD patients. The most commonly reported factors having a negative connotation were those of sociodemographic (low income), clinical (disease duration, severity, and medication), and psychological nature (coping with disease stress, depression, or negative beliefs concerning curability).

Among the factors contributing to better adherence to COPD therapy, age $\geq$ 60 years and male gender are the most commonly reported sociodemographic factors (Table 2). On the clinical side, frequency of hospitalization and the knowledge about the number and type of medications and the use of inhalers also had a
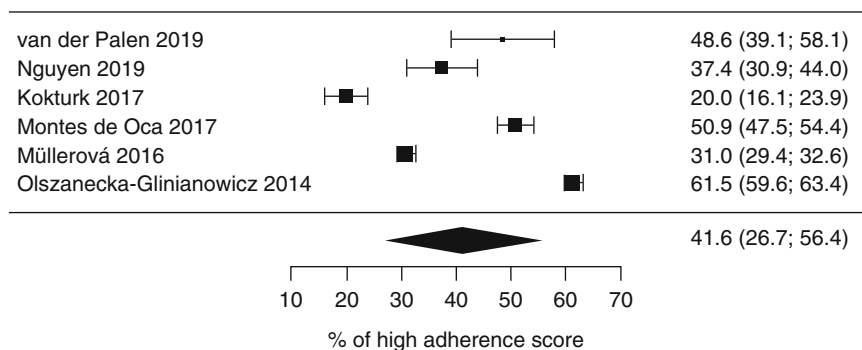
Fig. 6 Percentage of patients with high scores of adherence to therapy in COPD patients

Table 1 Factors decreasing adherence to therapy in COPD patients

Group of factors	Factor	First author and year
Sociodemographic	Income	Liao and Chen (2019)
Clinical	Comorbidities (diabetes, hyperlipidemia)	Liao and Chen (2019)
	Decreasing FEV1	Jouleh (2018)
	Gold stage 2	Jouleh (2018)
		Ivanov (2018)
	Alcohol	Toyama (2019)
	Drugs (bronchodilators, beta-2 adrenergic agonists, xanthines)	Tran (2016)
		Leiva-Fernández (2014)
	Duration of hospitalization	Ngo (2019)
	Duration of COPD	Ngo (2019)
		Olszanecka-Glinianowicz and Almgren-Rachtan (2014)
	Dyspnea (mRC)	Ngo (2019)
	Smoking (number of packs per year)	Ngo (2019)
Psychological	HADS depression 8–10 or > 10	Kokturk (2018)
	Emotional impact of disease	Olszanecka-Glinianowicz and Almgren-Rachtan (2014)
	Negative beliefs about treatment	Toyama (2019)

FEV1 forced expiratory volume in 1 s, *GOLD* Global Initiative for Lung Disease staging, *mRC* Modified Medical Research Council dyspnea scale, *HADS* Hospital Anxiety and Depression Scale

positive influence on adherence to therapy. Satisfaction with inhalation treatment was commonly reported as a strong predictor of better adherence as well.

4   Discussion

This article is a review of recent studies on factors affecting adherence to COPD treatment. Most of the analyzed studies used self-reported measures.

The findings demonstrate that COPD patients have lower adherence to therapy than those with other chronic diseases, such as cardiovascular disorders, hypercholesterolemia, osteoporosis, or diabetes. In COPD, adherence rates ranged between 20% and 60%. George et al. (2005), using a patient-reported medication adherence scale, have found a good adherence in 37% of patients. Ágh et al. (2011) have reported that 58.2% of patients had optimum adherence, based on MMAS-8 scores. Plaza et al. (2016b)

Table 2 Factors increasing adherence to therapy in COPD patients

Group of factors	Factor	First author and year
Sociodemographic	Age $\geq$ 60 years	Barja-Martínez (2019)
		Liao and Chen (2019)
		Kokturk (2018)
		Müllerová (2016)
	Male gender	Liao and Chen (2019)
		Chrystyn (2014)
		Müllerová (2016)
		Kokturk (2018)
	Country	Kokturk (2018)
	Higher educational level (high school or college graduate)	Kokturk (2018)
		Montes de Oca (2017)
	Lower educational level (primary school)	Barja-Martínez (2019)
	Being unemployed	Plaza (2016b)
Clinical	Type of inhaler (soft mist)	Ngo (2019)
	Low % post-BD FEV1	Montes de Oca (2017)
	Low % post-BD FEV1/FVC	Montes de Oca (2017)
	Telemonitoring	Moy (2016)
		Broadbent (2018)
		Pinnock (2013)
	Increasing number of prescribed drugs	Jouleh (2018)
	GOLD-stage 3–4	Jouleh (2018)
		Mısırlıgil et al. (2017)
		Ivanov (2018)
		Olszanecka-Glinianowicz and Almgren-Rachtan (2014)
	Fewer comorbidities	Müllerová (2016)
	Fewer exacerbations	Leiva-Fernández (2014)
		Ngo (2019)
		Montes de Oca (2017)
	Fewer health center visits	Leiva-Fernández (2014)
		Olszanecka-Glinianowicz and Almgren-Rachtan (2014)
		Jouleh (2018)
	Lower CAT	Müllerová (2016)
		Ngo (2019)
		Montes de Oca (2017)
	Fewer devices	Leiva-Fernández (2014)
	Self-reported history of past spirometry	Müllerová (2016)
	No emergency visits due to COPD in past 12 months	Müllerová (2016)
Psychological	Inhaler satisfaction	van der Palen (2019)
		Chrystyn (2014)
	Sense of disease control	Olszanecka-Glinianowicz and Almgren-Rachtan (2014)
	Satisfaction with doctor's management of COPD	Müllerová (2016)
	Fewer maintenance drugs	Chrystyn (2014)
	Positive beliefs about treatment	Olszanecka-Glinianowicz and Almgren-Rachtan (2014)

Table 2 (continued)

Group of factors	Factor	First author and year
	Knowledge about treatment and inhalers	Tommelein (2014)
		Poureslami (2016)
		Barja-Martínez (2019)
		Moy (2016)
		Broadbent (2018)
		Dudvarski Ilic (2016)
		Nguyen (2019)

FEV1 forced expiratory volume in 1 s, *FVC* forced vital capacity, *GOLD* Global Initiative for Lung Disease staging, *Post-BD* post bronchodilator test, *CAT* COPD Assessment Test

have found that adherence to inhaled therapy was present in 49% of COPD patients. Referring to the causes of non-adherence, authors report a variety of factors, and the issue is yet debatable in the literature. In the present review, we broke down the factors associated with adherence to COPD therapy into the sociodemographical, clinical, and psychological category, akin to the classification used by WHO (2003).

In screening tests performed in daily clinical practice, the level of adherence in patients treated for asthma and COPD rarely exceeds 50%. In a study by Wiśniewski et al. (2014), only 67% of patients adhered to treatment 30 days after discharge from the hospital. COPD treatment is primarily based on inhalation therapy, although most patients prefer oral medications. In the studies included in this review, the rate of satisfactory adherence ranged between 46.3% for inhalation and 41.6% for oral therapy. This may be exemplified by the findings of Montes de Oca et al. (2017) who reported the scores for 10-item TAI and MMAS-8 questionnaires of 47.4 ± 4.9 vs. 6.8 ± 1.6, i.e., high vs. medium adherence, respectively. In that study, however, the incorrect use of inhalers could influence the adherence level. Patients who adhere better to inhalation than oral therapy usually have a better savvy in using inhalers, and use a variety of inhaler devices and inhaled drugs. Among factors contributing to better adherence, the ones associated with taking medication using an inhaler have been assessed most frequently. In a GAPP study, 23% of patients reported that no time was devoted to discuss with them the use

of proper treatment techniques for successful asthma management (Canonica et al. 2007). The literature demonstrates that as many as 90% of patients may inhale medication incorrectly, although the estimate varies depending on the selection of a study sample and on the type of inhaler used. Multiple studies clearly demonstrate the efficacy of education performed by a pharmacist, nurse, or physician in increasing the adherence rate (Broadbent et al. 2018; Dudvarski Ilic et al. 2016; Moy et al. 2016; Poureslami et al. 2016; Tommelein et al. 2014). Broadbent et al. (2018) have shown that patients who receive training from a pharmacist perform a greater number of puffs *per* day compared to the non-trained subjects; mean 48.5% vs. 29.5%, respectively; $p = 0.03$.

Referring to non-adherence, the present review shows that a substantial number of patients (42.5%) purposely chose not to take their medication, which was deliberate non-adherence. On the other side, 48.5% of patients failed to follow the instructions received from medical personnel, which demonstrated inadvertent non-adherence, and 38.9% of patients failed to adhere to treatment due to their lifestyle, which was erratic non-adherence. We also found that psychological factors, such as a belief in the effectiveness of treatment, satisfaction with one's physician, and the ease and training in the inhaler use, count significant for having good adherence. In a study by Olszanecka-Glinianowicz and Almgren-Rachtan (2014), non-adherence is inversely proportional to the sense of control over one's disease and the opinion on the effectiveness of treatment.

In another study, a strong correlation has been reported between adherence to pharmaceutical treatment and patient's perceived health (Wiśniewski et al. 2014). According to Sanduzzi et al. (2014), adverse consequences of non-adherence include a gradual deterioration of quality of life, a sense of the disease being out of control, a greater number of exacerbations, and a higher mortality. Observations from a 3-year-long TORCH study demonstrate a greater than twofold increase in the risk of death and a nearly twofold increase in the risk of rehospitalization in non-adherent patients (Vestibo et al. 2009). These findings were confirmed in the present review, where the number of hospitalizations was a predictor of lower adherence.

The studies reviewed in this article differed in terms of COPD severity. The effect of disease severity on adherence to therapy is a contentious issue. Most studies show a better adherence with increasing severity of disease. Some other studies, however, show the opposite trend, a better adherence when the disease runs a mild course (Liao and Chen 2019; Leiva-Fernández et al. 2014). The discrepancy might be explained by the strength of motivation to continue treatment, associated with persistent symptoms that interfere with the patient's daily functioning. Another consideration concerns the adverse effects of medications, which may affect the patient's willingness to take them. In the GAPP study, patients who categorized their asthma as severe, and those who were treated by specialists, were most likely to discuss the knowledgeable aspects of their condition (Canonica et al. 2007).

The influence of sociodemographical factors on adherence to therapy in COPD patients is yet another debatable issue. In this review, we show that better adherence associates with older age, male gender, and daily functioning. The reason could be that pensioners have more time for regular living, exercising, and following dietary guidelines. On the other side, older patients may have a difficulty to adhere to treatment due to the presence of comorbidities. In contrast, younger patients are more likely to oppose medical advice and tend not to accept their illness, which may lead to non-adherence (Świątoniowska et al. 2018). In the studies reviewed herein male gender predominated among patients. That is in line with a study by Liao and Chen (2019) who have shown that adherence is outstandingly greater in men than women (87.3% vs. 12.7%, respectively). Other studies also show that men are more likely to adhere to therapy than women (Vestibo et al. 2009). The issue is somehow contentious as in a study by Dhamane et al. (2017), 59% of COPD patients are women, but the authors do not show any influence of gender on adherence. Other authors point out that low income and a lack of professional activity undermine adherence to COPD treatment (Liao and Chen 2019; Plaza et al. 2016b), although the underlying reasons for that are not full well clear. In patients experiencing economic difficulties, adherence to disease monitoring may be improved by addressing modifiable barriers such as cost and access (Campbell et al. 2014). There are, however, studies that put into question the association between sociodemographical factors and adherence to therapy (Khadour et al. 2012; Bourbeau and Bartlett (2008).

In conclusion, standardized questionnaire tools enable the prediction of adherence to therapy in COPD patients and should be used in clinical practice. The assessment of adherence is essential for undertaking interventions to counteract plausible non-adherence. Collaboration between an educator and a psychologist is needed to evaluate the patient's motivation and to ensure he comprehends the treatment prescribed.

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