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RESEARCH ARTICLE

Exploring variables associated with medication non-adherence in patients with COPD

Anan S. Jarab[1] · **Tareq L. Mukattash**[1]

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Abstract

Background: Research has indicated that medication adherence is low and represents a barrier to achieve the desired health outcome in patients with Chronic Obstructive Pulmonary Disease (COPD). *Objective*: The aim of the study was to investigate the factors that are significantly associated with self-reported medication non-adherence in patients with COPD. *Setting*: Patients attending the outpatient respiratory clinic at the Royal Medical Services (RMS) Hospital in Amman. In addition to socio-demographics, validated measures including COPD knowledge questionnaire, the 4-item self-reported Morisky medication adherence scale, St George respiratory questionnaire and Health Anxiety and Depression scale were used in the present study. The stepwise logistic regression analysis was performed in order to identify variables that independently and significantly predicted medication non-adherence. *Main outcome measure*: Predictors of medication non-adherence. *Results*: A total of 133 patients participated in the study. Results indicated that majority of the patients (61.7%) were non-adherent. According to the model, patients were four times more likely to be non-adherent if they reported having depression (OR 0.251, CI 0.24–0.76) and approximately eight times to have medication non-adherence if they suffered from comorbid illness (OR 0.119, CI 0.11–0.80). Study participants were found to have a double risk of medication nonadherence if they received an increase in the frequency of administration of their COPD medication (OR 0.524, CI 0.08–0.69) and being concerned about side effects (OR 0.515, CI 0.36–0.92). *Conclusion*: Depression, dosage regimen complexity, the presence of co-morbidities and therapy side effects have significantly influenced adherence to COPD therapy in the present study. Clinical pharmacists should provide emotional support, simplify dosage regimen, use adherence aids, elicit patients' concerns about their illness comorbidities, select treatments with less side effect and help the patients coping with side effects in order to enhance adherence and health outcomes in patients with COPD.

Keywords COPD · Chronic obstructive pulmonary disease · Jordan · Medication adherence · Pharmaceutical care · Predictors

Impacts on practice

- Predictors of medication non-adherence for patients with COPD should guide the development of future clinical pharmacy service programs for patients with COPD.
- In addition to simplifying the dosage regimen and dispensing medications with lower risk of side effects for patients with COPD, clinical pharmacists should consider using adherence aids and providing advice on coping with potential medication side effects.
- Healthcare professionals need to elicit patients' concerns about their illness comorbidities along with periodic reinforcement in order to enhance adherence to the prescribed therapy. Healthcare professionals should also consider providing emotional support and involving the family members in the treatment of depressed patients with COPD.

✉ Anan S. Jarab
asjarab@just.edu.jo

[1] Department of Clinical Pharmacy, Faculty of Pharmacy, Jordan University of Science and Technology, P.O. Box 3030, Irbid 22110, Jordan

Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by progressive airflow limitation and inflammation that is usually associated with bronchitis or emphysema [1]. Currently, COPD is rated the fourth cause of death by disease globally, causing 2.7 million deaths per year and it is expected to be the third leading cause of death by 2030 due to the lack of interventions addressing COPD prevention and management [2].

Despite the development of effective treatment for COPD management, non-adherence to therapy recommendations represents a significant barrier to optimal outcomes and results in emergency hospitalization among patients with COPD. Research indicated that only 40% of COPD patients adhere to the prescribed therapy and only 15% of them use their inhaler effectively [3–5].

Adherence describes the extent to which taking medication and performing self-care activities matches with the recommendations from the healthcare team [6]. Management of COPD is complex and several factors could predispose COPD patients to non-adherence. The patients are required to make behavioral and lifestyle changes such as smoking cessation, wearing oxygen in addition to adherence to medications and exercise therapy [7]. Multiple comorbidities are common among patients with COPD who are often prescribed complex medication regimens to be administered by multiple routes up to six times daily for both respiratory and non-respiratory conditions [8]. While simplifying medication regimen via prescribing once-daily dosing may improve adherence via decreasing the number of doses missed due to simple forgetfulness, this is unlikely to promote adherence in patients who believe that medications are no longer needed [9] or because they are concerned about medication side effects [10]. Depression, a common comorbidity in patients with COPD, has also been recognized as risk factor for non-adherence [11, 12].

Identifying barriers to adherence and recognizing the type of non-adherence is essentially required to develop effective interventions to control COPD, which in turn could assist in improving health outcomes for patients with COPD. Several earlier studies have been implemented to explore variables associated with medication non-adherence in patients with COPD [13, 14]. Nevertheless, medication adherence is still suboptimal and further investigation for factors impacting medication adherence in patients with COPD is still needed.

Aim of the study

The current research aimed to investigate variables influencing medication adherence in patients with COPD. Such variables need to be particularly targeted in future pharmaceutical care interventions designed to improve health outcomes for patients with COPD.

Ethics approval

The study received ethical approval from the Institutional Review Board at King Hussein Hospital in Amman.

Method

Study site and subjects

The present study used data which were collected from 133 outpatients with COPD at the RMS Hospital in Amman from September 2018 through January 2019. All participants in this study were diagnosed with COPD for at least one year, had a Forced Expiratory Volume in 1 s (FEV_1) of 30% or more of the predicted normal value, and were over 35 years old. Patients were excluded from the study if they had a congestive heart failure, learning difficulties or severe mobility problems. On the day of patients' clinic visit, the COPD nurse specialist provided a list of the attending patients for the researcher AJ, who used the medical files and hospital computers to check for patients' eligibility to participate in the study after they had their FEV1 measured. After meeting with the respiratory consultant, eligible patients were interviewed by the researcher AJ in a separate room at the COPD clinic and were asked to take their time to read the study information sheet carefully. The researcher confirmed to the patients that participation in this study is voluntary and they have the right to refuse the participation in the study. The patients were assured that even if they agreed to participate and signed a consent, they still have the right to withdraw from the study at any time, and signing a consent does not mean that participation is mandatory. Participants were also informed that their medical care and treatment will not be affected by their participation in or withdrawal from the present study, and that any information they provide through the study will be kept confidential. Patients who agreed to participate were asked to sign a consent form.

Study instruments

Data in this research were collected by the research pharmacist using medical files or via patients' interview using a custom-designed questionnaire. The collected data included socio-demographics in addition to disease and medication-related factors such as duration and severity of COPD, having comorbid conditions, total number of the prescribed medications, frequency of medication administration, using multiple inhalation technique, perceived

medication effectiveness and concerns about potential side effects. Validated questionnaires including COPD knowledge questionnaire [15], the 4-item Morisky self-reported medication adherence scale (MMAS) [16], hospital anxiety and depression scale (HAD) [17, 18] and the St. George respiratory questionnaire [19, 20] were completed by the study participants.

Knowledge about COPD questionnaire

This instrument consists of 16 items, in which correct responses are scored 1 and incorrect responses are scored 0, with unsure responses receiving no score. The instrument has been shown to be valid, with a Cronbach alpha of 0.89 for internal consistency [15].

The 4-item Morisky medication adherence scale (MMAS)

This survey measures the extent to which patients take their medications as prescribed. In the four questions with 'yes' or 'no' answer, each 'yes' response was given a score of 1 and each 'no' response was given a score of 0. According to the Morisky classification, adherence is divided into high for those scoring zero, medium for those scoring one or two, and low for those scoring three or four. For the purpose of the present analysis, patients scoring zero were considered adherent and those scoring 1–4 were deemed non-adherent. Morisky self-report adherence scale has been shown to have good validity, with a Cronbach α of 0.61 for internal consistency [16].

Hospital anxiety and depression scale (HAD)

The HAD scale is a 14-item questionnaire which contains a depression subscale and anxiety subscale scoring 0–21 each. Patients who scored 8 or less on the depression scale were not considered to have depression. Mild and moderate depression is represented by scores of (8 to10) and (11 to 14) respectively. Scores above 15 represent severe depression [17]. Bjelland et al. have reported that HAD scale is a valid measure with a Cronbach's alpha of 0.82 for depression and 0.83 for anxiety domains [18].

St George respiratory questionnaire (SGRQ)

Besides being specifically designed and validated to measure health impairment for patients with chronic airways disease, the SGRQ has been shown to be responsive to change as a result of therapy [19, 20]. It is a self-administered 76-item instrument which evaluates the patient's respiratory health via the domains of symptoms, activity, and impact. The scoring range for each component is from 0 to 100, with a score of 100 indicating the worst respiratory health [21].

Data analysis

Data were analyzed by the researcher TM using SPSS® software version 21. Although double data entry procedure was not undertaken, visual checking was performed for preventing and catching data entry errors. Descriptive statistics were performed to describe the sociodemographic, disease and therapy factors in the study population. Independent t-test and the Mann–Whitney U-test were used to describe the association of continuous variables including age, number of prescribed medications, duration of COPD, disease and medication knowledge score, HAD scores and number of patients who scored 11 or more on both depression and anxiety scales with medication adherence. Associations between categorical variables including gender, marital status, educational and occupational levels, smoking status, using multiple inhalation technique, frequency of COPD medication, having concern about side effects, perceiving medication as effective, perceiving disease as severe, COPD severity and the presence of comorbid disease with medication adherence was assessed using Chi-squared test with Fisher's Exact test used when $> 20\%$ of the expected frequency was < 5 or any expected frequency was < 1. Binary stepwise logistic regression was performed on factors which had a P value < 0.05 at the univariate analysis using stepwise logistic regression. The analysis was performed with variable entry at a P value of < 0.05 and removal at a P value of > 0.1 [22] using the odds ratio to assess the impact of each predictor on medication adherence.

Results

Baseline measurements and assessments

Out of the 188 patients who were eligible to participate in the study, a total of 133 patients decided to take part and were asked to sign a consent form. Table 1 shows demographics in addition to medical and disease characteristics of the study participants. The majority of the recruited patients were female (59.4%), married (83.5%), and with low educational level (90.2%). More than half of the patients were current smokers (55.6%). The mean number of prescribed medications per patient was 8.1 (±3.3). Most of the patients (80.5%) were found to have moderate to severe disease as per the National Institute for Health and Care Excellence (NICE) guideline [23]. Of the 133 participants, 61.7% (n = 82) were found non-adherent. Missing doses due to forgetfulness, which is referred to item-1 of the MMAS, was the most common form of non-adherence and was represented by 71% of the non-adherent patients.

Table 1 Characteristics of study patients

Gender [n (%)]	
Male	54 (40.6)
Female	79 (59.4)
Age (median, IQR)	63 (15)
Education [n (%)]	
High (University)	13 (9.8)
Low	120 (90.2)
Occupation level [n (%)]	
Low	80 (60.2)
Moderate	45 (33.8)
High	8.0 (6.0)
Marital Status [n (%)]	
Married	111 (83.5)
Other	22 (16.5)
Current smoker [n (%) yes]	74 (55.6)
Living arrangements [n (%)]	
Alone	16 (12.0)
Not alone	117 (88.0)
Disease severity* [n (%)]	
Mild	26 (19.5)
Moderate	67 (50.4)
Severe	40 (30.1)
FEV_1 (mean, SD)	
Liters	1.1 (0.52)
% predicted	53.5 (16.8)
FEV_1/ FVC	51.3 (11)
Duration of COPD (median, IQR)	10 (8.0)
Number of medications (median, IQR)	0 (5.0)
Patient's own rating of medication effectiveness (little/ not effective) [n (%)]	32 (24.1)
Co-morbid conditions present [n (%) yes]	72 (54.1)
Medications use [n (%)]	
Short-acting β2-agonist	122 (91.7)
Long-acting β2-agonist	111 (83.5)
Long acting anticholinergic	90 (67.7)
Inhaled steroids	93 (69.9)
Oral steroids	14 (10.5)
Antibiotics	73 (54.9)

IQR interquartile range, *SD* standard deviation, *FEV_1* forced expiratory volume in one second, *FVC* forced vital capacity, *COPD* chronic obstructive pulmonary disease, *ED* emergency department

*Adapted from National Institute for Health and Care Excellence (NICE) guideline

Univariate analysis of predictors of medication non-adherence

The following variables were identified as significant predictors of medication non-adherence: smoking($P<0.05$), frequency of administration of COPD medication ($P<0.01$), having concerns about side effects ($P<0.05$), presence of comorbid disease ($P<0.01$) and depression ($P<0.05$) as shown in Table 2.

Multivariate analysis of predictors of medication non-adherence

According to the final logistic model shown in Table 3, the odds of a patient being adherent to medications was inversely associated with the presence of depression or comorbid illness ($P<0.05$) and frequency of administration of COPD medication or being concerned about medication side effects ($P<0.01$). The odds ratio values indicate that patients were four times less adherent if they reported having depression (OR 0.251, CI 0.24–0.76) and approximately eight times less adherent if they had comorbid illness (OR 0.119, CI 0.11–0.80). Study participants were found twice less likely to be adherent with each unit increase in the frequency of administration of COPD medication (OR 0.524, CI 0.08–0.69) and if they had concerns about side effects (OR 0.515, CI 0.36–0.92).

Chi-squared value of 28.45 with degrees of freedom = 4 and $P<0.001$ indicated that the final model was reliable and the probability of the independent variables taken together, have no effect on the outcome variable was < 0.001. Hosmer and Lemeshow goodness-of-fit [24] gave a chi-squared value of 6.137 (8 degrees of freedom; $P=0.656$) i.e. not significant; therefore, the predictors, as a set, reliably distinguished between adherent and non-adherent patients and the model was statistically reliable and had acceptable fit to the data used. The Nagelkerke R^2 value was 0.247, indicating that 24.7% of the variance in medication adherence was accounted for by the predictors in the model. When the cut value for risk assessment was set at 0.5 i.e. below this point, the patient is considered to be at high risk of non-adherence; the specificity of this model was 74% and the sensitivity was 52%, indicating that 74% of non-adherence cases and 52% of adherence cases were correctly classified. The overall accuracy was 65.6% indicating that approximately two-third of the cases were correctly predicted by the model.

Discussion

Poor adherence to medication therapy has been identified as a major barrier for optimal health outcomes and resulting in emergency hospitalization among patients with COPD [25]. Although several studies have been conducted to explore variables associated with medication adherence in patients with COPD [26–33], adherence is still suboptimal and a better understanding of medication adherence and its associated factors among patients with COPD is still needed [14]. The current study was conducted to further investigate the

Table 2 Univariate analysis of predictors of medication non-adherence

Predictor variable	Adherence		
	Adherent (n = 51)	Non-adherent (n = 82)	*P* value
Sociodemographic variables			
Age [median (IQR)]	61 (14)	64 (11)	NS
Gender [n (%) female]	27 (52.9%)	52 (63.4%)	NS
Marital status [n (%) not-married]	8 (15.7%)	14 (17.1%)	NS
Education [n (%) high] #	8 (15.7%)	5 (6.1%)	NS
Occupation [n (%) low]	30 (58.5%)	50 (61.0%)	NS
Smoking [n (%) yes]	21 (41.2%)	53 (64.6%)	0.021*
Disease and treatment			
Total number of medications [median (IQR)]	7 (3)	8 (5)	NS
Using multiple inhalation technique [n (%) yes]	36 (70.1%)	61 (74.4%)	NS
Frequency of COPD medication [n (%) more than twice daily]	21 (41.1%)	64 (79.3%)	0.009*
Having concerns about side effects [n (%) yes]	18 (35.3%)	53 (64.6%)	0.011*
Perceiving medication as effective [n (%) yes]	11 (21.6%)	21 (25.6%)	NS
Perceiving disease as severe [n (%) yes]	12 (23.5%)	26 (31.7%)	NS
Duration of disease [median (IQR)]b	9 (7)	10 (9)	NS
Severity of disease[n (%) severe]	13 (25.5%)	27 (32.9%)	NS
Comorbid disease[n (%) yes]	14 (27.5%)	58 (70.7%)	0.005**
Other variables			
Disease and medication knowledge [median (IQR)]	44.8 (22)	43.9 (25)	NS
Health-related quality of life score(mean, SD)	47.6 ± 17.3	43.2 ± 18.8	NS
HAD depression [mean, 95%CI]	7.02 (6.5–7.7)	8.93 (8.2–9.7)	0.031*
HAD anxiety [mean, 95%CI]	8.32 (7.5–8.8)	8.74 (8.1–9.4)	NS
Number of patients who scored 11 or more (depression scale)	15 (29.4%)	40 (48.7%)	0.028*
Number of patients who scored 11 or more (anxiety scale)	16 (31.4%)	32 (39.0%)	NS

*Significant at 0.05 level, **significant at 0.01 level, *NS* non-significant ($P > 0.05$)

Table 3 Variables associated with self-reported medication non-adherence

Variables	B	OR	Sig	95% CI
Depression	− 1.715	0.251	0.032*	0.24–0.76
Co-morbidity	− 0.873	0.119	0.016*	0.11–0.80
Frequency of administration of COPD medication	− 0.594	0.524	0.008**	0.08–0.69
Having concerns about side effects	− 0.053	0.515	0.005**	0.36–0.92

*Significant at 0.05 level, **significant at 0.01 level

obstacles to medication adherence in patients with COPD. Findings from the present study could be fed in future pharmaceutical care intervention programs aim at improving health outcomes for patients with COPD. Evidence from the literature shows that clinical pharmacists-led intervention programs demonstrated improvement in medication adherence in patients with COPD. In a randomised -controlled clinical trial implemented on patients with COPD in Jordan, an integrated pharmaceutical care program which included educational intervention about COPD and the prescribed inhalers demonstrated a significant improvement in medication adherence and hospital admissions reduction [34]. Another patient's tailored pharmacist-led intervention involving an education on COPD and its management had significantly improved self-reported medication adherence at 6 and12 months follow-up periods in Northern Ireland [35]. In the latter study, emergency department visits and hospital admissions were also significantly reduced. The PHARMACOP trial conducted by the community pharmacists on COPD patients in Belgium revealed a significant improvement in medication adherence and hospitalization rate after 3 months follow-up [36]. Based on these findings, it is clear that medication adherence in patients with COPD represents an area for improvement that should be targeted by future pharmacists' intervention programs, and since recognizing obstacles to medication adherence represents the cornerstone for developing effective interventions aim at improving[e] medication adherence in patients with COPD, the current research should provide useful insight on the factors that should be specifically targeted in future pharmaceutical care programs designed for improving health outcomes in patients with COPD.

Consistent with the earlier research findings [3–5], medication non-adherence was represented by 61.7% of the participants in the present study. Dose missing was represented by 71% of the non-adherent patients, which is similar to an earlier research finding [26, 37, 38].

Variables including frequency of administration of COPD medication, being concerned about medication side effects, presence of co-morbid disease and having depression were identified by the multiple logistic regression as determinants of medication non-adherence in the present study.

The finding that depression is associated with poor adherence to treatment recommendations in different disease states is supported by numerous studies [39–41]. Although few studies have examined the relationship between depression and medication non-adherence in patients with COPD, these studies have shown significant association between the two variables [35, 42]. Depression may influence the subjective experience of the medication and could make the patient neglect themselves and their prescribed treatment [43]. A recent study showed that higher perceived emotional support by family and friends led to better outcome manifested by recovery from major depression of the study participants [44]. Therefore, pharmacy educators should provide emotional support and appropriate coping strategies for patients with COPD who are suffering from depression.

Results identified dosage regimen frequency as a significant predictor of medication non-adherence in the present study. Toy et al. [45] revealed that the risk of non-adherence was higher in patients with four times daily dosing (77%) compared with three times daily dosing (69.8%), twice $^{\text{daily}}_{\text{dosing}}$ (63%) and once daily dosing (56.7%). A cross-sectional study was conducted in the outpatient department of Dhulikhel Hospital in Nepal, indicated significantly higher rates of non-adherence in patients who were prescribed more than twice daily regimen when compared with those who were prescribed twice or once daily dosing (27.3% vs. 8.9%) [46]. In a cross-sectional study conducted on COPD outpatients, Agh et al. found higher risk of medication non-adherence with more frequent daily dosing and therefore, less frequent dosing regimens could help enhancing medication adherence [36].

Consistent with Khdour et al. findings [35], patients with comorbid illness were more likely to be non-adherent. The presence of comorbidities makes patients with COPD more likely to be on complex medication regimen, a variable that was found to increase the risk of medication non-adherence in the present research. On the other hand, patients in the present study who had a comorbid illness were found to have significantly higher mean HAD score than those who did not have any comorbidity. Accordingly, comorbidity influence on therapy adherence might have been mediated by depression which also was found a significant predictor of medication non-adherence in the present study. Healthcare professionals and clinical pharmacists should elicit patients' concerns about their illness comorbidities, along with periodic monitoring and reinforcement in order to enhance adherence to the prescribed therapy.

Results in the present research indicated a significant association between medication non-adherence and the presence of concerns about side effects. The presence of concerns about side effects of the medications can have a devastating effect on adherence [47]. Selecting treatments with less side effects, informing the patients about the potential side effects, and providing advice on coping with such side effects would form a guide for clinical pharmacists to improve medication adherence in patients with COPD.

Study limitations

The number of participants in this study was reasonably small, which may impede the output of strong conclusions from the current research. The self-report method to assess medications adherence could have overestimated adherence due to social desirability bias. Furthermore, the study questionnaire was not piloted in order to make adjustments as appropriate before moving to the main study.

Conclusions

The present study revealed low adherence rates among patients with COPD in Jordan. All the barriers to medication adherence identified in the present study should guide the development of future COPD management programs implemented to improve health outcomes in patients with COPD. Variables such as depression, dosage regimen complexity, presence of co-morbidities and the concerns about medication side effects have significantly influenced adherence to COPD therapy in the present study. Providing emotional support for patients with COPD and involving the family members in the treatment of depressed COPD patients may reduce the likelihood of isolation and help overcoming depression barrier. Clinical pharmacists should consider less frequent dosing regimens in addition to the use of adherence aids and to elicit patients' concerns about their illness comorbidities, along with periodic reinforcement in order to enhance adherence to the prescribed therapy. Finally, dispensing medications with fewer side effects and providing advice on or coping with such side effects is necessary to attain optimal health outcomes for patients with COPD.

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Conflicts of interests None to declare.

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