Predictors of patient adherence to COPD self-management exacerbation action plans

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ABSTRACT

Objective: Identifying patient characteristics predicting categories of patient adherence to Chronic Obstructive Pulmonary Disease (COPD) exacerbation action plans.
Methods: Data were obtained from self-treatment intervention groups of two COPD self-management trials. Patients with ≥1 exacerbation and/or ≥1 self-initiated prednisolone course during one-year follow-up were included. Optimal treatment was defined as 'self-initiating prednisolone treatment ≤2 days from the onset of a COPD exacerbation'. Predictors of adherence categories were identified by multinomial logistic regression analysis using patient characteristics.
Results: 145 COPD patients were included and allocated to four adherence categories: 'optimal treatment' (26.2 %), 'sub optimal treatment' (11.7 %), 'significant delay or no treatment' (31.7 %), or 'treatment outside the actual exacerbation period' (30.3 %). One unit increase in baseline dyspnoea score (mMRC scale 0–4) increased the risk of 'significant delay or no treatment' (OR 1.64 (95 % CI 1.07−2.50)). Cardiac comorbidity showed a borderline significant increased risk of 'treatment outside the actual exacerbation period' (OR 2.40 (95 % CI 0.98−5.85)).
Conclusion: More severe dyspnoea and cardiac comorbidity may lower adherence to COPD exacerbation action plans.
Practice implications: Tailored self-management support with more focus on dyspnoea and cardiac disease symptoms may help patients to better act upon increased exacerbation symptoms and improve adherence to COPD exacerbation action plans.

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1. Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a chronic progressive lung condition characterised by distressing exacerbations that cause impaired health-related quality of life (HRQoL), increased hospitalisations, mortality and healthcare costs [1]. COPD frequently occurs with comorbidities that further reduce HRQoL [2], such as ischemic heart diseases (IHD), chronic heart failure (CHF), anxiety, depression and diabetes mellitus (DM) [3–7].

Self-management is an essential part of the disease management of patients with COPD, e.g. by inhaler technique education [8]. A COPD self-management intervention is structured but personalised and often multi-component, with goals of motivating, engaging and supporting the patients to positively adapt their health behaviour(s) and develop skills to better manage their disease [9]. COPD exacerbation action plans that help patients to anticipate on and recognise early symptoms of a COPD exacerbation, are a key component of COPD self-management interventions [10–12]. Previous studies have shown that self-management interventions including COPD exacerbation action plans are cost-effective [13,14]. Moreover, COPD self-management interventions are associated with a lower probability of respiratory-related hospitalisations, improvement in HRQoL [15,16], and a reduction of COPD exacerbation duration [17].

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There is still limited evidence regarding patient characteristics and self-management intervention components that are associated with its effectiveness and safety [18,19]. One study showed that 42 % of intervention patients learnt to self-manage effectively and had a significantly reduced risk of hospital readmissions [11]. Another study demonstrated a similar result with 40 % of the included COPD patients being adherent to the written action plan during exacerbations [12]. Increasing the percentage of adherent self-managers is likely to increase patients' benefits of self-management interventions [11,20]. It is therefore important to explore underlying mechanisms or 'phenotypes of adherence' [21].

Adherence is generally defined as "the extent to which a person's behaviour – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a healthcare provider" [22]. Moreover, adherence is important for effective self-treatment of exacerbations [12,23,24]. Variations exist however in definitions (e.g. outcome or process oriented [25]), classifications, and cut-off values for optimal adherence or non-adherence in different disease management studies [26]. It is therefore no surprise that there is no consensus about a definition of adherence to COPD exacerbation action plans [27]. Previous COPD self-management studies have determined adherence in a binary way (i.e. adherent vs. non-adherent) [11,12] which could lead to loss of specific information about adherence (e.g. delay in proper treatment or starting treatment outside the actual exacerbation period). By using multiple adherence categories instead, unique patient characteristics could be found as predictors of different adherence categories. This information could then be used to further tailor action plans and self-management support to improve patient adherence. The aim of our study was therefore to evaluate what characteristics predict different categories of patient adherence to COPD exacerbation action plans.

2. Methods

2.1. Study design and population

This was a retrospective study that analysed patient adherence using pooled quantitative data of the self-treatment intervention groups of the COPE-II [13] and COPE-III study [17,28]. These COPE studies are two randomised controlled trials in which the effectiveness of self-management interventions including COPD exacerbation action plans in COPD patients were evaluated and compared with control groups (COPE-II: self-management programme without self-treatment; COPE-III: usual care). The COPE-III study [17,28] intervention was additionally modified to address frequently occurring comorbid conditions in COPD. In the COPE-II and COPE-III study, patients could be included if they were formally diagnosed with COPD [29], were ≥40 years, had ≥3 exacerbations or ≥1 COPD hospitalisation in the last two years preceding study entry, were stable at the time of inclusion, and were able to understand and read the English or Dutch language. In addition, COPE-III patients [17,28] had to have at least one comorbidity (CHF, IHD, DM, depression and/or anxiety) and were excluded when having a Mini-Mental State Examination (MMSE) score [30] <24.

In the current study, we selected only patients from the COPE-II [13] and COPE-III study [17,28] who were allocated to the self-treatment intervention groups and had experienced ≥1 exacerbation according to the symptoms reported in their diary and/or reported ≥1 self-initiated prednisolone course for the self-treatment of a COPD exacerbation during the first 12 months of follow-up. Detailed methodologies have previously been published [13,17,28].

Both COPE studies were approved by the Medical Ethical Committee Twente. The COPE-III study was in addition approved by the Southern Adelaide Clinical Human Research Ethics Committee. The COPE-II study was registered in the Netherlands Trial Registry (NTR325) and the COPE-III study in the public Australian New Zealand Clinical Trials Registry (ACTRN12612000514808). All patients gave written informed consent prior to study participation.

2.2. Self-treatment intervention

Patients in the COPE-II [13] and COPE-III study [17,28] self-treatment intervention groups received two group and two individual training sessions directed towards self-treatment of COPD exacerbations guided by a trained case-manager, who was an experienced respiratory nurse. Partners and carers were also invited to attend these sessions. It was up to the patient whether to include their carer in the disease management decision making. During the training sessions patients' individual symptom levels in a stable health state were defined and described on a personalised 'What are my "usual" symptoms' card (Appendix A, Fig. A.1) [17,28]. Patients also received their tailored written COPD exacerbation action plan from the case-manager and were trained in early recognition of COPD exacerbations using their 'What are my "usual" symptoms' card and their daily symptom diary (Appendix A, Fig. A.2) [17]. Subsequently, patients were taught when to start self-treatment of exacerbations according to their COPD exacerbation action plan (Appendix A, Fig. A.3) [17] that was linked to the symptom diary. The case-manager used 'self-management scenarios' to train the patients in completing the diaries and using the action plans. Moreover, the patients received individual feedback from the case-manager on their 'real-life' diary completion and action plan use.

When a patient experienced significantly increased COPD symptoms and ticked two red boxes in a row for at least two symptom diary questions, the action plan directed the patient to start a course of oral prednisolone (and when the sputum colour was different from normal a course of antibiotics as well). All patients had one course of oral prednisolone and antibiotics at home in addition to one repeat prescription. If a patient had no course left, they were asked to contact the case-manager, so another prescription could be arranged. The action plan instructed the patients to contact the case-manager or a healthcare provider for support if they did not feel better two days after the start of prednisolone or if the cause of symptom deterioration was unclear. Furthermore, the case-manager checked and consolidated specific behaviours by phone to reinforce self-management skills during the follow-up. Incomplete diary data were first compared with hospital admission data [17]. Subsequently, the patients were contacted by phone to fill gaps on missing diary days, to adjust symptom levels on the 'What are my "usual" symptoms' card, and were provided with feedback on proper use of the diary and action plan [17]. In addition to the COPD action plan, patients in the COPE-III study also received tailored action plans for comorbid conditions (e.g. CHF, IHD, DM, depression and/or anxiety) [17]. In the current adherence study, only the self-reported diary data and self-initiated self-treatment actions for COPD exacerbations were evaluated.

2.3. Outcomes

2.3.1. Patient adherence

In this patient adherence analysis, it was assessed whether a self-reported course of oral prednisolone was initiated for the self-treatment of a COPD exacerbation according to the COPD exacerbation action plan. A COPD exacerbation was determined, based on self-reported deterioration of COPD symptoms (i.e. not

more than usual, slightly more than usual, or significantly more than usual). The onset of a COPD exacerbation was defined as a significant negative change in two major symptoms (dyspnoea, sputum purulence, sputum volume) or one major and one minor (coughing, wheezing, fever) from the 'usual' baseline health state for at least two consecutive days, according to the criteria of Anthonisen et al. [31] and Rodriquez-Roisin et al. [32]. Exacerbation recovery was pre-defined as the first day of: 1) at least three consecutive days that the patient returned to the 'usual' baseline health state; or 2) at least seven consecutive days on which patients reported no or only a slightly increase of COPD symptoms compared to the 'usual' baseline health state [13,28]. Together with the exacerbation data, all self-reported initiated self-treatment actions (i.e. actual start (date) of a prednisolone course) were retrospectively evaluated, even when no actual COPD exacerbation was reported during the follow-up. In this study, four categories of patient adherence to COPD exacerbation action plans were defined using expert opinion, literature [33], and taking into account all possible combinations of having or not having a symptom-based exacerbation linked to starting (i.e. date) or not starting a prednisolone course: optimal treatment, sub optimal treatment, significant delay or no treatment, and treatment outside the actual exacerbation period (Table 1 and Fig. 1).

The classification to the adherence categories was done in several steps for each patient: 1) classification of the initiated self-treatment actions into adherence categories as described in Table 1; 2) determining the number of self-treatment actions within each of the four adherence categories; and 3) allocation of patients to one of the four adherence categories based on the highest number of initiated self-treatment actions in a certain category. When a patient had an equal number of individual self-treatment actions in two or more categories, the last initiated action defined the allocation to one of the adherence categories, as we assumed a learning effect over time. For example, when the first two self-treatment actions were classified as 'sub optimal treatment' and the third and fourth self-treatment action as 'optimal treatment', the patient was allocated to the 'optimal treatment' category.

2.3.2. Predictors of patient adherence

The set of potential predictors of patient adherence to COPD exacerbation action plans that could be taken into account for this study was restricted by the measured baseline patient characteristics in both the COPE-II and COPE-III study (Table 2). Only those variables that were assessed in both studies were included in the analyses.

2.4. Statistical analysis

2.4.1. Missing diary data

When COPD symptom diary data showed less than four consecutive days of missing data, a predefined algorithm was used that combined the last observation carried forward and next observation carried backward to the missing value (see Appendix A, Table A.1 [17]). Respiratory-related hospitalisation days were scored as COPD exacerbation days with maximum symptom scores (i.e. significantly more than usual). Missing data for the self-reported starting dates of prednisolone courses were not imputed and prednisolone courses initiated by the pulmonary physician during hospitalisation were deliberately not included.

2.4.2. Development of the prediction model

Potential predictors of patient adherence to COPD exacerbation action plans were identified by checking crude associations between the four adherence categories and each patient characteristic (Table 2) using univariate analyses. These associations were tested with ANOVA or Kruskal-Wallis tests for continuous variables and by means of Chi-square tests or Fisher exact tests for categorical variables, as appropriate. Variables associated ($p < 0.10$) with the adherence categories were subsequently included in a multinomial logistic regression analysis with a backward elimination procedure based on the -2loglikelihood ($p < 0.05$). Finally, Nagelkerke's R-square was calculated as a pseudo measure of the model's predictive performance. All data were analysed using SPSS Statistic software version 24.0.

3. Results

Of the total 343 patients included in both COPE studies, 145 (42.3 %) were included in the current study (Fig. 2). Of these patients, 60.7 % were male, the mean age was 66.3 (SD 8.8) years, 26.9 % were current smokers, 90 % of the patients had GOLD stage II (51.7 %) or III (38.6 %) and half of the patients (50.3 %) had a low education level (Table 2). Patients with 'treatment outside the actual exacerbation period' predominantly had a cardiac comorbidity (61.4 %). Baseline characteristics of each separate COPE-

Table 1
Classification of self-treatment actions into patient adherence to COPD exacerbation action plans based on the time difference between the self-initiation of the prednisolone course and the onset of the COPD exacerbation.

Optimal treatment	Prednisolone course initiated at the day of exacerbation onset
	Prednisolone course initiated 1 day prior to onset of exacerbation
	Prednisolone course initiated 1 day after onset of exacerbation
Sub optimal treatment	Prednisolone course initiated 2 days prior to onset of exacerbation
	Prednisolone course initiated 2 days after onset of exacerbation
	No prednisolone course initiated, exacerbation duration ≥1 and ≤3 days
Significant delay or no treatment	No prednisolone course initiated, exacerbation duration ≥4 days
	Prednisolone course initiated ≥3 days after onset of exacerbation, but before exacerbation recovery
Treatment outside the actual exacerbation period	Prednisolone course initiated, but no actual exacerbation
	Prednisolone course initiated ≥3 days prior to onset of exacerbation
	Prednisolone course initiated after exacerbation recovery

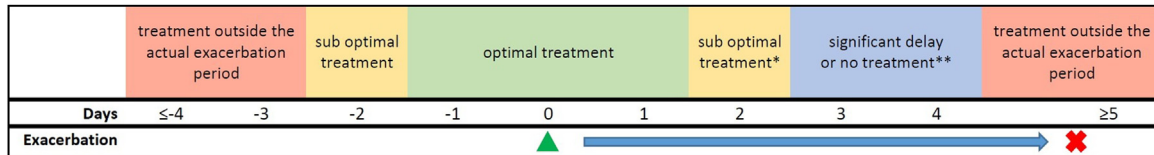**Fig. 1.** Schematic description of the patient adherence categories in relation to the onset the COPD exacerbation.
Note: ▲ = onset of exacerbation, ✖ = exacerbation recovery.
*Patients who did not act while having an exacerbation duration between ≥1 and ≤3 days, were assigned to the 'sub optimal treatment' category.
**Patients who did not act while having an exacerbation duration of ≥4 days, were assigned to the 'significant delay or no treatment' category.

Table 2
Baseline characteristics of the study subjects according to different patient adherence categories of COPD exacerbation action plans.

	Total (n = 145)	Optimal treatment (n = 38)	Sub optimal treatment (n = 17)	Significant delay or no treatment (n = 46)	Treatment outside the actual exacerbation period (n = 44)	P-value
Age (years) (mean (SD))	66.3 (8.8)	65.1 (9.6)	66.5 (8.2)	65.5 (9.8)	68.1 (7.1)	0.407
Male (n (%))	88 (60.7)	23 (60.5)	11 (64.7)	22 (47.8)	32 (72.7)	0.113
BMI (median (IQR))	27.4 (24.0–27.0)	25.9 (23.5–30.8)	29.3 (26.6–32.5)	27.5 (23.7–31.8)	27.8 (23.6–31.9)	0.347
Post-bronchodilator spirometry (mean (SD))						
FEV1 (l)	1.4 (0.5)	1.5 (0.5)	1.4 (0.5)	1.4 (0.6)	1.3 (0.5)	0.606
FEV1/FVC	46.5 (13.5)	48.1 (15.4)	47.5 (13.3)	47.9 (13.0)	43.3 (12.1)	0.302
FEV1 % predicted	51.1 (16.0)	51.9 (16.6)	51.7 (14.9)	52.4 (17.2)	48.8 (15.0)	0.729
GOLD stage [29] (n (%))						
II	75 (51.7)	22 (57.9)	9 (52.9)	25 (54.3)	19 (43.2)	0.595
III	56 (38.6)	11 (28.9)	7 (41.2)	16 (34.8)	22 (50.0)	
IV	14 (9.7)	5 (13.2)	1 (5.9)	5 (10.9)	3 (6.8)	
Current smoker (n (%))	39 (26.9)	11 (28.9)	3 (17.6)	15 (32.6)	10 (22.7)	0.578
Education level (n (%))						
Low	73 (50.3)	19 (50.0)	8 (47.1)	24 (52.2)	22 (50.0)	0.997
Middle	58 (40.0)	16 (42.1)	7 (41.2)	7 (37.0)	18 (40.9)	
High	14 (9.7)	3 (7.9)	2 (11.8)	5 (10.9)	4 (9.1)	
General health status* (EQ VAS score [47,48]) (mean (SD))	63.7 (15.2)	67.2 (12.3)	66.1 (14.3)	63.8 (11.7)	59.7 (19.9)	0.142
Quality of life domains (CRQ [49]) (mean (SD))						
Dyspnoea	4.3 (1.4)	4.4 (1.6)	4.8 (1.2)	4.2 (1.2)	4.3 (1.4)	0.507
Fatigue	3.9 (1.2)	4.0 (1.3)	4.4 (0.9)	3.8 (1.1)	3.9 (1.2)	0.369
Emotional	4.7 (1.2)	4.9 (1.0)	4.8 (1.1)	4.4 (1.2)	4.9 (1.2)	0.199
Mastery	5.0 (1.1)	5.2 (1.1)	5.2 (1.1)	4.8 (1.1)	5.1 (1.0)	0.206
Dyspnoea score (mMRC [50]) (mean (SD))	1.9 (1.1)	1.7 (1.1)	1.7 (1.2)	2.2 (1.1)	1.8 (0.9)	0.083[a]
Exacerbations two years prior to study entry* (median (IQR))	3.0 (2.0–4.8)	3.5 (3.0–5.0)	4.0 (2.0–5.0)	3.0 (2.0–4.0)	3.0 (2.0–4.0)	0.468
Hospitalisations one-year prior to study entry (median (IQR))	0.0 (0.0–1.0)	1.0 (0.0–1.0)	0.0 (0.0–1.0)	0.0 (0.0–1.0)	0.0 (0.0–1.0)	0.474
Employment* (n (%))	32 (22.2)	7 (18.9)	5 (29.4)	12 (26.1)	8 (18.2)	0.691
Cardiac comorbidity (n (%))	62 (42.8)	15 (39.5)	7 (41.2)	13 (28.3)	27 (61.4)	0.016[a]
Living together (n (%))	94 (64.8)	23 (60.5)	12 (70.6)	30 (65.2)	29 (65.9)	0.887

Abbreviations; SD: Standard Deviation; IQR: interquartile range; FEV$_1$: Forced Expiratory Volume in 1 s; FVC: Forced (expiratory) Vital Capacity; GOLD: Global Initiative for Chronic Obstructive Lung Disease; EQ VAS: EuroQol Visual Analogue Scale; CRQ: Chronic Respiratory Disease Questionnaire; mMRC: modified Medical Research Council.
[a] Significantly different between patient adherence categories at a p < 0.10 level.
* Number of subjects differs due to missing variables for EQ VAS score (n = 1), Exacerbations 2 years prior to study entry (n = 13) and Employment (n = 1).

population are detailed in Appendix A, Table A.2.) A total of 438 COPD exacerbations were extracted from the self-reported diary data (median per patient 2.0 (IQR 1.0–4.0)); 127 (87.6 %) patients had at least one exacerbation during 12 months follow-up. A median number of 8.0 (IQR 5.0–13.5) exacerbation days/patient/ year was observed. COPE-II and COPE-III patients from the self-treatment intervention groups completed 85.0 % and 81.3 % of the symptom diary data, respectively [13,17].

Based on the self-reported treatment actions of the COPE-II and COPE-III data, the included patients initiated 591 (median per patient 3.0 (IQR 1.5–6.0)) COPD exacerbation self-treatment

actions (Table 3). Most of these actions were classified as 'significant delay or no treatment' (32.0 %) and 'optimal treatment' (27.6 %). A detailed specification including the number of self-treatment actions classified into different categories of adherence to COPD exacerbation action plans are provided in Appendix A (Table A.3). Within the 'significant delay or no treatment' category, 102 (54.0 %) actions were initiated ≥3 days after the onset of an exacerbation, but before the exacerbation recovery. In 87 (46.0 %) cases, no actions were initiated, whereas the exacerbation duration was ≥4 days (Appendix A, Table A.3). Within the 'treatment outside the actual exacerbation period' category, 70 (47.9 %) actions
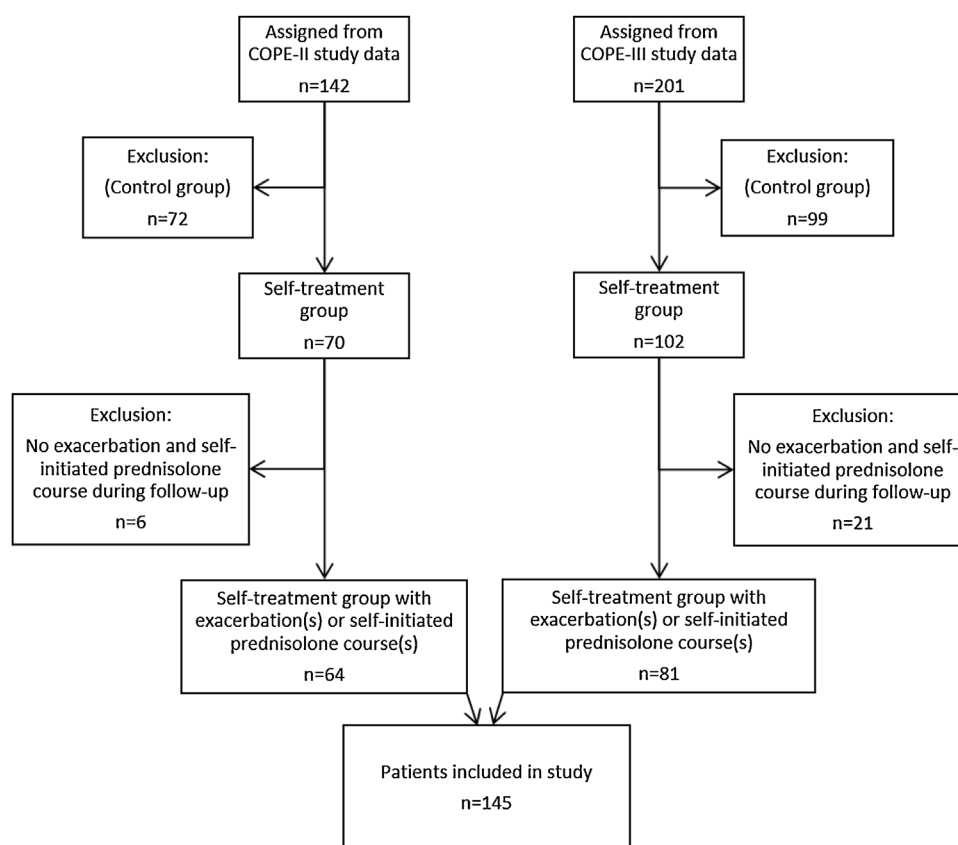
Fig. 2. Study flow diagram including patients of the COPE-II [13] and COPE-III [17] study.

Table 3
Data of initiated self-treatment actions and classification of patients to categories of adherence to COPD exacerbation action plans.

	Self-treatment actions (n = 591)	Classification of patients (n = 145)
Optimal treatment	163 (27.6)	38 (26.2)
Sub optimal treatment	93 (15.7)	17 (11.7)
Significant delay or no treatment	189 (32.0)	46 (31.7)
Treatment outside the actual exacerbation period	146 (24.7)	44 (30.3)

Data of actions and patients are presented as n (%).

Table 4
Results of the multinomial logistic regression model of patient characteristics vs. adherence to COPD exacerbation action plans.

	Predictor	OR (95 % CI)	P-value
Sub optimal treatment (n = 17)	mMRC score	0.99 (0.57–1.71)	0.965
	Cardiac comorbidity	1.08 (0.34–3.46)	0.903
Significant delay or no treatment (n = 46)	mMRC score	1.64 (1.07–2.50)	0.023*
	Cardiac comorbidity	0.58 (0.23–1.48)	0.256
Treatment outside the actual exacerbation period (n = 44)	mMRC score	1.13 (0.74–1.73)	0.570
	Cardiac comorbidity	2.40 (0.98–5.85)	0.055

Note: Optimal treatment was set as reference.
Abbreviations: CI: Confidence Interval; OR: Odds Ratio; mMRC: modified Medical Research Council.
* Significant at a p < 0.05 level.

were initiated ≥3 days prior to the onset of an exacerbation, and 58 (39.7 %) actions were initiated after the exacerbation recovery (Appendix A, Table A.3).

The adherence category 'optimal treatment' included 38 patients (26.2 %), 'sub optimal treatment' category 17 patients (11.7 %), 'significant delay or no treatment' 46 patients (31.7 %), and 'treatment outside the actual exacerbation period' 44 patients (30.3 %). The baseline dyspnoea score (modified Medical Research

Council (mMRC) score, p = 0.083) and baseline cardiac comorbidity (p = 0.016) differed significantly between the adherence categories (Table 2). Table 4 shows the final multinomial logistic regression prediction model of patient characteristics vs. adherence to COPD exacerbation action plans. One unit increase in baseline dyspnoea score (mMRC scale 0–4) showed a 1.64 (95 % CI 1.07–2.50) fold increased risk of 'significant delay or no treatment' compared to 'optimal treatment' (Table 4). Cardiac comorbidity showed a

borderline significant 2.40 (95 % CI 0.98–5.85) fold increased risk of 'treatment outside the actual exacerbation period' compared to 'optimal treatment'.

We indicated a significant better model fit including both baseline dyspnoea score and cardiac comorbidity as predictors compared to a model including only baseline dyspnoea score as a predictor (based on -2log likelihood value). Nagelkerke's R-square was 0.121.

4. Discussion and conclusion

4.1. Discussion

To our knowledge, this is the first study that evaluates patient adherence to COPD exacerbation action plans in more detail, by using multiple adherence categories. A more severe baseline dyspnoea score and cardiac comorbidity were identified as potential predictors of patients treating their exacerbation with significant delay or outside the actual exacerbation period, or starting no treatment at all.

In our study, the percentage of patients who showed 'optimal treatment' and 'sub optimal treatment' (38 %) was comparable to literature [11,12]. Previous studies reported that 42 % of patients learnt to self-manage effectively [11] and that in 40 % of the exacerbations patients were adherent to the action plan [12]. Lack of standardisation of action plan components and the use of different definitions of COPD exacerbations and patient adherence however complicate comparisons between studies. Patients were only included in our study if they have had ≥3 exacerbations or ≥1 COPD hospitalisation in the last two years preceding study entry. They may therefore have had more opportunities to use their action plan and receive feedback which may have positively affected patient adherence rates. However, whereas we do not consider having exacerbations per definition as a sign of not coping, having included patients with exacerbation rates (and multiple comorbidities), may have led to higher disease burden and may have negatively influenced patient adherence compared to literature [11,12]. Previous studies showed the following variables as predictors of effective self-management: younger age [11,12], sex (female) [34], uptake of influenza vaccination [12], higher education level [34], living with others [11], more severe airflow obstruction [12], and increased walking capacity [34]. Apart from cardiac comorbidity, these were not detected as potential predictors of patient adherence to COPD exacerbation action plans in our study. The wide variety in detected predictors in studies is also most likely a result of heterogeneity in definitions of adherence and exacerbations, measured baseline characteristics, patient populations, and study interventions.

We found that 32 % of the patients showed 'significant delay in treatment or no treatment'. The severity of dyspnoea was identified as a potential predictor of lower patient adherence to COPD exacerbation action plans, with every one unit increase in dyspnoea score at baseline increasing the risk of delay in or no proper treatment. Previous studies have highlighted that COPD patients experience fluctuating symptoms prior, during and after the COPD exacerbation [32,35,36]. Our study results suggest that those patients who already had a relatively high dyspnoea score at baseline might not have considered the change in COPD exacerbation symptoms – particularly breathlessness – severe enough to follow the action plan and start treatment. As our study did not evaluate motivation of patients for their (lack of) actions, we should be cautious with the interpretation of these findings.

Our results also show that 30 % of the patients started their treatment outside the actual exacerbation period; i.e. almost half of the self-treatment actions in this adherence category were initiated ≥3 days prior to the onset of the COPD exacerbation, 40 % after the exacerbation recovery, and 12 % without an actual exacerbation. Patients who started a prednisolone course earlier compared to the pre-defined exacerbation action plan, may well have recognised early signs of an exacerbation to prevent or reduce the impact of an impending COPD exacerbation. This is in line with results from a qualitative study showing that patients identified exacerbations by both objective visible (e.g. sputum colour) and subjective invisible symptoms (e.g. heaviness, tightness, and soreness of the chest), in which the body 'told' the patient that an exacerbation was developing [37]. Patients who started treatment after the exacerbation recovery or without an actual COPD exacerbation period, may have been treating overlapping symptoms from a comorbid exacerbation instead. This is supported by our study finding that cardiac comorbidity was found as a borderline significant risk factor for 'treatment outside the actual exacerbation period'; 61 % of the patients in this adherence category had a cardiac comorbidity at baseline. Whereas in the COPE-III study the patients were specifically trained to differentiate between COPD and CHF, this could still have posed a challenge to patients due to symptom overlap (e.g. breathlessness) [7,38–40].

As a result of different inclusion criteria with regard to comorbidities, patient characteristics of the COPE study populations were slightly different. Whereas in the COPE-II study patients with severe comorbidities were excluded from study participation, COPE-III patients had to have at least one comorbidity to be eligible for inclusion (see Appendix A, Table A.2). This may have resulted in frailer patients in the COPE-III compared to the COPE-II population. Cardiac comorbidity has been found as one of the predictors that increased the likelihood of adhering to the action plan in a previous study [12]. Although this contradicts our findings, it strengthens the importance of cardiac comorbidity in relation to patient adherence.

We made the assumption that there may be a learning effect of patients using the COPD exacerbation action plan over time by manually allocating patients with an equal number of individual self-treatment actions to the adherence category of the last initiated action. This assumption in line with previous research findings suggesting that patients use their experiential knowledge of individual symptoms to identify and manage COPD exacerbations [37]. In future studies, this potential learning effect could be evaluated using dynamic pattern recognition of symptoms and self-treatment actions. Machine learning techniques could for example be used to develop algorithms based on a large dataset to make predictions on patient adherence at the individual level over different points in time [41].

The main strength of this study was that we evaluated multiple patient adherence categories which provided detailed insight about the patient's use of a COPD exacerbation action plan. The detected specific predictors of patient adherence to COPD exacerbation action plans may help to identify patients who will benefit from self-management interventions including COPD exacerbation action plans. Moreover, combining data of two COPE populations resulted in addition in a relatively large sample size and a real-world population consisting of COPD patients with and without comorbidities. The latter increases the generalisability of the prediction model.

This study has some limitations. We were not able to use a valid adherence classification method from literature as no consensus has been reached regarding adherence definitions (e.g. outcome or process oriented), classifications, and cut-off values. Action plan adherence is currently most frequently reported as a binary variable [11,12], whereas we explored the use of multiple adherence categories in this study. Because we allocated patients to four adherence categories, the number of patients per adherence category were limited. A larger sample size is warranted in future research when evaluating multiple adherence categories. In our model, Nagelkerke's R-square was 0.121, indicating that the predictive performance in terms of pseudo-explained variance

was 12 %. This suggests that the model is currently not complete and must therefore be interpreted carefully. Furthermore, some baseline characteristics were only assessed in the COPE-III study or were assessed by using different measurements (see Appendix A, Table A.2). As a result, COPD patient characteristics such as influenza vaccination, motivation, disease perception, patient self-management knowledge and behaviour, self-efficacy, and common comorbidities could not be included in our prediction model. Whereas we aimed to find predictors of different patient adherence categories, we only found potential predictors of two of the four adherence categories 'sub optimal treatment' and 'optimal treatment'. The limited number of patients and patient characteristics that could be included in the prediction model may have influenced this.

Before statements can be made regarding factors that will actually drive effective COPD self-management, associations between adherence categories and health outcomes (e.g. HRQoL, COPD exacerbations, hospitalisations, emergency department visits, self-efficacy, mortality) of COPD exacerbation action plans and experiences from patients and healthcare professionals should also be explored. In addition, clinical consequences of non-adherence need to be defined and further tailoring of patient support using known predictors of non-adherence are necessary to improve patient adherence to COPD exacerbation action plans. Whereas cognitive decline [42] and inadequate health literacy [43–45] are in generally recognised as factors that can influence adherence to exacerbation action plans [46], clear evidence about the association and distinct information about what test to use, cut-off points, and alternative approaches are lacking. This is certainly an important point for future research. Finally, qualitative research (e.g. observations, in-depth interviews, focus groups) can provide information about barriers and facilitators (e.g. support from partners and carers) that may influence the uptake and initiation of COPD exacerbation action plans. Gaining more knowledge and insights in this area is crucial to overcome barriers for adherence and to ultimately improve individual patient health outcomes of COPD self-management interventions. This contributes to further patient-tailored COPD self-management interventions.

4.2. Conclusions

Allocating patients to multiple adherence categories based on the initiation of their self-treatment compared to the onset of the exacerbation revealed detailed information about predictors of adherence to COPD exacerbation action plans. A more severe baseline dyspnoea score was found to be a potential predictor for 'significant delay or no treatment' and the prevalence of cardiac comorbidity increased the risk of 'treatment outside the actual exacerbation period'.

4.3. Practice implications

To improve patient adherence to COPD exacerbation action plans we recommend using a patient-tailored approach by providing additional support (e.g. by case-managers), especially for those patients with more severe dyspnoea and cardiac comorbidity. Discussing and defining patients' dyspnoea symptoms in detail at baseline, possible fluctuations in symptoms around exacerbations (e.g. using individual assessments or real-time symptom monitoring) and experiences with previous exacerbations, and including cardiac biomarkers in multi-morbidity action plans might help patients to better distinguish between (COPD and comorbid) exacerbation symptoms and to proper act upon it. This approach is likely to improve patient adherence to COPD exacerbation action plans, and also may improve health outcomes of COPD self-management interventions.

Contributors

Authors JS, TE, MB and AL contributed to the conception, design, data analysis, data interpretation, initial outline and draft of the manuscript. All authors (JS, TE, MB, JP, PV and AL) reviewed the draft manuscript providing critical intellectual contributions, and all authors approved the final version before submission.

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Jade Schrijver: Conceptualisation, Methodology, Formal analysis, Writing - original draft, Writing - review & editing, Visualization, Project administration. **Tanja W. Effing:** Conceptualisation, Methodology, Investigation, Supervision, Writing - original draft, Writing - review & editing, Funding acquisition. **Marjolein Brusse-Keizer:** Conceptualisation, Methodology, Writing - original draft, Writing - review & editing. **Job van der Palen:** Conceptualisation, Methodology, Supervision, Writing - review & editing. **Paul van der Valk:** Conceptualisation, Resources, Writing - review & editing. **Anke Lenferink:** Conceptualisation, Methodology, Investigation, Supervision, Writing - original draft, Writing - review & editing, Funding acquisition.

Declaration of Competing Interest

The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.pec.2020.06.015.

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