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Clinical and economic impact of non-adherence in COPD: A systematic review

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Summary
Background: Medication for Chronic Obstructive Pulmonary Disease (COPD) has shown to substantially reduce symptoms and slow progression of disease. However, non-adherence to medication is common and associated with worsened clinical and economic outcomes.
Objective: The objective of this study was to perform a systematic review of published literature to assess the impact of non-adherence to COPD medication on clinical and economic outcomes.
Methods: A search in PubMed and Web of Science databases was conducted of original studies published from database inception to 2012. Studies must report on the association between adherence to COPD medication and outcomes, published in English in peer-reviewed journals and full texts needed to be available.
Results: Twelve full articles were included in the review. Most studies were retrospective database studies. Seven studies reported on the association between adherence and clinical outcomes, two on mortality, three on costs, four on quality of life and one on work productivity. Results indicated a clear association between adherence and both clinical and economic outcomes. Evidence from studies revealed increased hospitalizations, mortality, quality of life and loss of productivity among non-adherent patients.

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Conclusion: This review revealed a clear association between non-adherence to COPD medication and worsened clinical and economic outcomes making non-adherent patients a priority for cost-effective interventions.

Introduction

Medication for patients with Chronic Obstructive Pulmonary Disease (COPD) has demonstrated to improve disease symptoms and to avoid exacerbations [1,2]. However, efficacy reported in clinical trials may not reflect effectiveness in a real-world setting, and one of the major reasons is related to treatment adherence. Adherence (synonym: compliance) is defined as the extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen [3]. While therapy adherence in clinical trials is often relatively high, adherence to COPD medication in real world settings is far from optimal [4]. Factors associated with non-adherence to COPD medication include dosing regimen, comorbidity, age and cost [5—7].

Non-adherence in general has been linked to preventable morbidity and mortality and increased healthcare costs and productivity losses [8—10]. However, the clinical and economic consequences of non-adherence in COPD are not yet fully understood [11,12]. The objective of this study was to perform a systematic review of the literature assessing the clinical and economic impact of non-adherence in COPD.

Methods

Review strategy

Literature searches were performed in February 2013 in the PubMed and Web of Science (ISI) databases including studies from database inception to 2012. Studies needed to measure patients' adherence to COPD medication and its impact on clinical and/or economic outcomes. Search terms were combinations of disease-, medication-, adherence- and outcome terms. A specification of the review protocol is provided in Appendix 1.

Studies found were independently screened and underwent a quality assessment by two reviewers (JFMvB and SV). No major disagreement between the two reviewers occurred. A PRISMA flow diagram is provided in Fig. 1 [13].

Eligibility

To be included, studies needed to meet the following inclusion criteria:

(*i*) published in peer-reviewed journals, (*ii*) full text (i.e. no abstracts), (*iii*) in English (*iv*) and reflecting an original study. Non-English studies were not included as these tend to be smaller and of lower methodological quality [14].

Exclusion criteria

We excluded: (*i*) studies assessing physician or patient adherence to guidelines, programs or oxygen (*ii*) studies including primarily asthma patients (*iii*) reviews, comments, conference abstracts, case reports or editorials (*iv*) animal studies and (*v*) studies reporting no clinical or economic outcomes.

Data extraction

The following information was extracted for each study: (*i*) first author, country and year of publication, (*ii*) population characteristics (size, % male, mean age and FEV_1%pred), (*iii*) medication assessed, (*iv*) method of measuring and defining adherence, (*v*) an outcomes summary (vi) absolute and relative outcomes including *p*-values.

Quality assessment

The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist was used as the tool for quality assessment of the included observational studies [15]. This checklist, containing 22 items, was operationalized into a series of questions for each study design, answered by "yes", "partly", "no" or "not applicable". For each study, the proportion of adequately reported items ("yes") from all applicable items was analyzed (Appendix 2).

Results

Study selection

A search in PubMed and Web of Science yielded 3410 articles in total. Removing duplicates and screening of titles and abstracts identified 138 articles potentially relevant articles. After review of the full texts, twelve articles meeting the inclusion criteria remained. Results of the selection process are presented in Fig. 1. Details of search results are provided in Appendix 1. The quality assessment is presented in Appendix 2.

Overview of included studies

After exclusion of non-relevant studies, twelve studies remained that focused on the impact of non-adherence with COPD medication on costs and clinical effects. The measured outcomes varied from clinical symptoms like cough and dyspnea to mortality and costs (Table 1). Most studies were retrospective database studies and had an average follow-up of one to two years. Two studies were cross-sectional analyses [16,17]. Population size varied between 24 [18] and 55,076 patients [19]. Most studies reported clinical outcomes; only three studies reported costs [17,19,20] and one study reported on the association between adherence and work productivity [16].

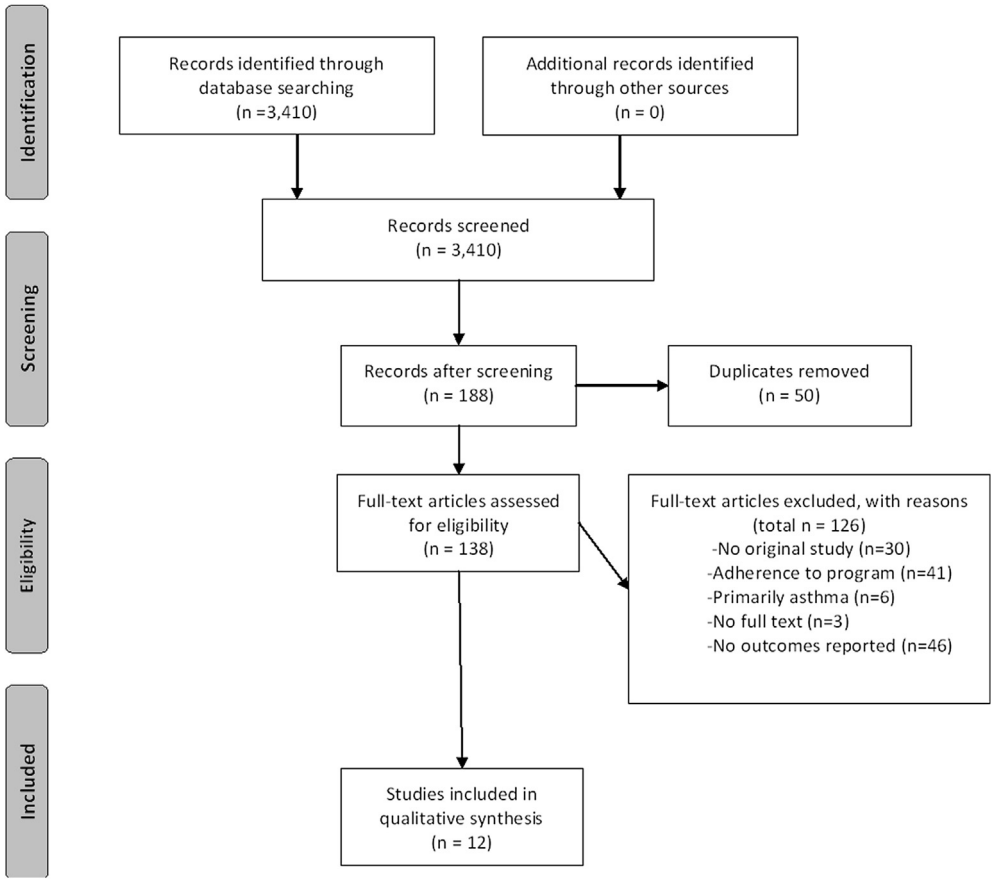

Figure 1 Selection process of the studies included in the review.

To measure adherence, most studies [16,17,19—21] used administrative or prescription databases. If a threshold was used to separate adherent patients from non-adherent patients, adherence was defined as 80% of the proportion of days covered (PDC) in the majority of studies [16,17,20,22].

Clinical outcomes

Seven studies explored the impact of non-adherence on clinical outcomes, with a primary focus on hospitalizations. Two studies reported significantly fewer hospitalizations in adherent patients [17,22].

The Simoni-Wastila et al. study was a retrospective cross-sectional study, included 33,816 COPD patients identified from an administrative database and had a maximum follow-up of 1.5 years. Both medication continuity (persistence) and proportion of days covered (PDC) was assessed and patients with a PDC $\geq$0.80 were considered adherent.

In adherent and continuing patients significant lower hospitalization rates were observed. The second study, by Vestbo et al., was a post-hoc analysis of the large multinational TORCH trial in which 6112 COPD patients were followed for 3 years [2]. Good adherence was defined as $>$80% use of study medication, counted by a dose counter on the inhaler device. Results showed that good adherence was significantly associated with a lower rate of severe exacerbations, independent of study treatment.

One study found a non-significant association between adherence and fewer hospital days [23]. In this 1-year prospective cohort study (by Turner et al.) 985 COPD patients were stratified in two adherence groups based on average number of minutes using nebulizer therapy. The median observed time of 25 min was used as cut-off for being adherent or not. For this study, the lack of significance may be explained by the use of this nonconventional method of defining adherence.

In contrast, one study found no difference in non-adherence between hospitalized and non-hospitalized patients [24]. This study, by Matuszewski et al., used a case-control design. The population included 93 patients hospitalized for exacerbation of COPD and 93 control patients with COPD who were non-hospitalized. Non-compliance was calculated by dividing the number of days without medication by the total days of medication prescribed during the study (365 days). Results showed no significant difference in mean non-compliance ratio. However, results may be prone to bias as there was a significant difference in the number of medications used between cases and controls which is not only affecting adherence but is also a surrogate indicator of disease severity, implicating that if patients experience a hospitalization those are generally the more sicker group. Therefore, the value of using a case-control design for this purpose can be questioned.

Two studies found a significant association between adherence and emergency department (ED) visits [19,21].

Table 1 Characteristics of studies reporting outcomes associated with adherence to COPD therapy.

Study (1st author, country, year)	Study design (follow-up)	Population	Medication	Adherence definition	Reported outcomes associated with adherence					Study quality (STROBE)
					Clinical outcomes	Mortality	Costs	Quality of life	Productivity	
Dompeling	(Netherlands, 1992) [18]	Prospective intervention (1 year)	$N = 24$ Mean age: 55 Male: 58% FEV_1%pred: 63							
	Beclomethasone dipropionate 400 μg plus salbutamol or ipratropium	PDC 80—120	X					17/28		
Turner (US/ Canada, 1995) [23]	Prospective cohort (1 year)	$N = 985$ Mean age: 61 Male: 81% FEV_1%pred: 41	Metaproterenol or other bronchodilators [all by nebulizer]	>25 min per day use of nebulizer	X	X		X		18/26
Corden (UK, 1997) [26]	Prospective cohort (4 weeks)	$N = 82$ (74% COPD) Mean age: 65 Male: 54% FEV_1%pred: NA	SABA, LABA, SAAC or corticosteroids [all by nebulizer]	PDC, no threshold				X		20/29
Matuszewski (US, 1999) [24]	Retrospective case control (1 year)	$N = 186$ Mean age: 70 Male: 98% FEV_1%pred: NA	SAAC, LAAC, SABA, LABA, ICS, XAN	PDC, no threshold	X					19/28
Vestbo (Worldwide, 2009) [22]	Post-hoc analysis of RCT (3 years)	$N = 6112$ Mean age: 65 Male: 76% FEV_1%pred: 44	Placebo, SAL, FLU, Combination (SAL + FLU)	PDC > 80	X	X				28/32
Halpern (US, 2011) [20]	Retrospective database analysis (1.5 years)	$N = 4537$ Mean age: 61 Male: 53% FEV_1%pred: NA	TIO or SAL + FLU	MPR ≥ 80			X			26/30
Agh (Hungary, 2011) [28]	Observational cross sectional	$N = 170$ Mean age: 64 Male: 42% FEV_1%pred: NA	SABA, LABA, SAAC, LAAC, ICS, combinations	MMAS score ≥3				X		17/30
Butler (US, 2011) [21]	Retrospective longitudinal database (3 years)	$N = 24,138/3231$ Mean age: 66 Male: 35% FEV_1%pred:NA	Not specified	Non-adherent days/total days, no threshold	X					17/28

Takemura (Japan, 2011) [25]	Cross sectional questionnaire	$N = 55$ Mean age: 69 Male: 73% FEV_1%pred: 68	LAMA, LABA, SABA, ICS	Self-report					
questionnaire score >4				X		17/29			
Toy (US, 2011) [19]	Retrospective database (1 year)	$N = 55,076$ Mean age: 69 Male: 43−53% FEV_1%pred:NA	SAAC, LABA, LAAC	PDC, no threshold	X		X		21/28
Carls (US, 2012) [16]	Retrospective cross sectional (1 year)	$N = 20,985$ Mean age: 46−52 Male: 54% FEV_1%pred: NA	ICS, LEU, mast cell stabilizers, XAN, LAMA/SAMA, LABA, CORT	PDC >80				X	26/30
Simoni-Wastila (US, 2012) [17]	Retrospective cross sectional (1.5 year)	$N = 33,816$ Mean age: 71 Male: 35% FEV_1%pred: NA	ICS, ICS + LABA, SAAC, LAAC, XAN						
Continuation: No gap >3 months Adherent: PDC ≥ 80	X		X			26/30			

FLU: fluticasone, ICS: inhaled corticosteroids, LABA: long-acting beta agonists, LAAC: long acting anticholinergics, LEU: leukotrienes, MMAS: Morisky Medication Adherence Scale, MPR: medication possession ratio, NA: not available, PDC: proportion of days covered, RCT: Randomized Clinical Trial, SAAC: short acting anticholinergics, SABA: short acting beta agonists, SAL: salmeterol, TIO: tiotropium, XAN: xanthines.

Toy et al. analyzed the relationship between adherence, daily dosing regimen, healthcare resource utilization (inpatient, outpatient and ED visits) and costs. A large administrative claims database was used to identify COPD patients ($N = 55,076$). Adherence was measured as proportion of days covered (PDC) over a 1-year period after initiation of treatment. Results of a multivariate regression model showed that a 5% increase in adherence would lead to a 2.6% reduction in hospital visits and a 1.8% reduction in ED visits.

The other study, from Butler et al. aimed, using a retrospective longitudinal design, to determine the association between adherence to medication and total (non-disease specific) emergency department visits. They especially focused on long-term benefits of adherence. Data on the use of prescription drugs were obtained from a national Medical Expenditure Panel Survey (MEPS), but specific medication was not specified. The non-adherence ratio was calculated by dividing the number of non-adherent days by the total days in a year.

While no significant short-term effects of adherence on number of ED visits were observed, long-term effects of non-adherence were detected.

Other clinical outcomes that were associated with adherence included pulmonary symptoms (cough, phlegm and dyspnea), decrease in lung function and provocative concentration causing a 20% fall in FEV_1 (PC_{20}) during steroid treatment [18,23]. However, these results were based on studies with either a small population (Dompeling et al.) or were measured in patients using nebulized therapy only (Turner et al.) making results less generalizable.

Mortality

Only two studies investigated the association between adherence and mortality. The study by Vestbo et al. [22] showed that good adherence was not only associated with decreased risk of severe exacerbations but also with a decreased risk of death. Using different threshold levels to define adherence, revealed a hierarchic association between rate of adherence and mortality: the lower the adherence, the higher the mortality. However, authors noted that patients with poor adherence may have had more comorbidities with multiple medications affecting adherence and prognosis, which may have biased the results. Remarkable was that the effect of adherence was as strong in the placebo group as in the group treated with medication, which is referred to as the 'healthy adherer effect': adherence to therapy is an indicator for an overall healthier lifestyle. In contrast, the other study, by Turner et al. [23] found no significant differences in mortality between adherent and non-adherent patients. However, the lack of significance may be, just as for the other clinical outcomes, due to the use of a nonconventional threshold for adherence.

Costs

Three studies were identified describing the association between adherence and costs [17,19,20].

The Simoni-Wastila et al. study showed that adherent patients had higher costs for prescription medication compared with non-adherent patients. However, these costs were offset by lower inpatient- and outpatient costs resulting in lower total spending for adherent compared to non-adherent patients.

The second study was the administrative database analysis of Toy et al. In addition to the influence of a 5% increase of adherence on healthcare utilization they also calculated related costs. To obtain a cost estimate reflecting the national population, patient data were weighted. Increasing PDC with 5% resulted in lower expenditures for inpatient- and ER visits. In contrast, costs for outpatient visits would slightly increase, resulting in an overall net cost reduction.

The retrospective claims analysis from Halpern et al. compared adherence and outcomes between COPD patients initiating tiotropium ($n = 1561$) or salmeterol/fluticasone ($n = 2976$) therapy using claims data from a large national US health plan. Follow-up was at least one year with a maximum follow-up of 1.5 years.

Adherence was defined as a medication possession ratio (MPR) $\geq$0.80. Pharmacy costs were higher in adherent patients compared with non-adherent patients. In contrast, in inpatient stay costs were lower in adherent patients as compared with non-adherent patients.

All studies found, not surprisingly, that medication costs were higher in adherent patients compared with non-adherent patients. In contrast, inpatient stay (hospitalization) costs were lower in adherent patients compared to non-adherent patients in all studies. In the study of Halpern et al. [20] adherence was associated with lower respiratory related medical costs but overall healthcare costs in adherent patients where higher compared with non-adherent patients, which may be explained by a possible 'healthcare seeking behavior' of adherent patients. The two remaining studies found lower total healthcare costs in adherent patients [17,19]. Regarding all costs, standard deviations were considerable, indicating large between patient variation.

Quality of life

Four studies assessed the impact of non-adherence on health related quality of life (HRQoL). The instruments used to measure HRQoL differed between studies. Two studies [25,26] used the St. George's Respiratory Questionnaire (SGRQ), which is COPD specific, widely applied in the field of COPD and is considered a suitable tool to assess quality of life. [27] The Corden et al. study was a small ($n = 82$) 4-week prospective cohort study in patients using nebulized therapy. 74% were COPD patients and most patients were using bronchodilators. Patients' adherence was measured using data loggers attached to the nebulizer. Poor compliance was defined as taking less than 70% of the prescribed treatment. The second study, from Takemura et al. was a cross-sectional analysis of 88 COPD patients and assessed factors related to inhalation therapy adherence and its correlation with quality of life. Adherence was measured using a self-reported questionnaire where patients with a score of $\geq$4 (on a 5-point Likert scale) were considered adherent.

Both studies showed that the SGRQ total, symptoms and impact scores were negatively correlated with adherence,

although the association with symptoms and impact scores did not achieve statistical significance in the Corden et al. study, which may be due to the relatively small study population [26]. On the other hand, note that the Takemura et al. study applied a method of self-reported adherence that may have biased patient adherence in a positive direction and thereby have resulted in an overestimation [25].

In contrast, another study found an association between adherence and lower HRQoL as measured with the EQ-5D [28].

The Agh et al. study was an observational cross sectional study in 170 COPD outpatients from Hungary. Adherence was measured with the Morisky Medication Adherence Scale (MMAS) and patients scoring $\geq$3 (out of 4) were considered adherent.

The EQ-5D is a general instrument and therefore may not be sensitive to COPD specific HRQoL; furthermore better quality of life may be considered a trigger for non-adherence. In addition, patient's decision regarding adherence was suggested a personal trade-off between benefits of treatment and the associated negative effects (lifestyle changes, side effects).

Other HRQoL-tools used included the Sickness Impact Profile (SIP), the Profile of Mood States (POMS), and the Recent Life Changes Questionnaire (RLCQ); for the latter a significant association was found between non-adherence and a more disrupted home and family life [23]. This prospective cohort study in patient using nebulized therapy (by Turner et al.) demonstrated that an unstable environment may have a negative effect on treatment adherence, especially when the medication regimen requires adjustments in daily living.

Productivity

Regarding the association between adherence and productivity only one study was identified [16]. This 1-year retrospective cross sectional analysis of administrative healthcare claims by Carls et al. aimed to estimate the impact of medication adherence on absenteeism and short-term disability. A population of 5417 (absenteeism) respectively 20,985 (short-term disability) patients with asthma/COPD was assessed. Employees were classified adherent as the proportion of days covered was $\geq$80% and during hospital days patients were assumed to be adherent. Results were corrected for switching between medication and relevant confounders. However, no clear distinction was made between asthma and COPD patients in particular. Adherent patients were significantly fewer days absent from work and had fewer days of short-term disability. In their discussion the authors estimated the potential annual savings of adherent employees compared with non-adherent employees around $1714 per employee. Short-term absenteeism accounted for $178 to $833 per employee per year (Table 2).

Discussion

Main findings

This review revealed a clear association between adherence to COPD medication and both clinical and economic outcomes. Evidence from the twelve studies included, showed increased hospitalizations, mortality, quality of life and loss of productivity among non-adherent patients. Several key elements were uncovered regarding the direction of this association reported in adherence studies measuring clinical symptoms. Adherence alone is not always sufficient to obtain improved clinical outcomes, but rather the combination of continuous use (persistence) in combination with high adherence [17]. Furthermore, the omission to include long-term effects of non-adherence may cause an underestimation of the actual costs and effects of non-adherence [21].

Vestbo et al. [22] provides evidence for an association between high adherence and significantly decreased mortality in patients with moderate to severe COPD. Note that this evidence is based on a selective trial population, so generalizing these results towards the complete COPD population may be tendentious [29]. Three recent studies described the association between adherence and costs and showed some clear patterns. Not surprisingly, costs of medication will increase when adherence is increased. However, both medical (inpatient) and total costs are likely to decrease in adherent patients as reported by Toy et al. and Simoni-Wastila et al. [17,19] Halpern et al. did not observe effects on total costs, which was explained by a higher healthcare seeking behavior of adherent patients [20].

Regarding quality of life, studies showed contrasting effects by reporting either small positive or small negative effects of improved adherence [23,25,26,28]. It was suggested that better quality of life may be considered a trigger for non-adherence [23,28]. Good adherence requires some rigorous adjustments in patients' daily life and this may have a negative reflection on their perceived quality of life, outweighing for instance the benefits of somewhat less frequent exacerbations [28].

The association between adherence and work productivity was least described, but evidence indicated that adherence was significantly associated with reduced days off work, putting a high burden on societal expenses [16]. Further research on work productivity is recommended, as better understanding of this topic would be of great value in order to reduce non-adherence related costs in the working age population [30].

An overall interesting theory some studies refer to is the so called 'healthy adherer effect' [17,22]. The healthy adherer effect assumes that therapy adherence is a surrogate marker for an overall healthy behavior [22]. This raises the question whether better clinical and economic outcomes can be solely explained and established by the improvement of patients' medication adherence, or rather by an extensive change in patients' behavior (lifestyle, adherence to co-medication).

Limitations and considerations

Though the association between adherence and outcomes is rather clear, evidence is mainly based on observational studies not well-suited to measure any causal effect of non-adherence. On the other hand, compared to clinical trials, observational studies provide long-term 'real world' evidence as seen in daily practice, thereby providing

Table 2 Outcomes associated with adherence to COPD therapy.

Study	Outcome specification	Absolute outcomes		Relative outcomes	Significance
		Non-adherent	Adherent		*p*-value
Clinical outcomes					
Dompeling [18]				***r***	
	Pulmonary symptoms	NR		0.57	0.036
	Change in FEV_1	NR		0.6	n.s.
	Change in PC20	NR		0.72	0.031
Turner [23]					
	Change in FEV_1	−0.034	−0.04	NR	n.s.
	Days hospitalized	4.2	3.8	NR	n.s.
Matuszewski [24]					
	Hospitalizations	NR			n.s.
Vestbo [22]				**Rate ratio**	
	Hospitalizations	0.27	0.15	0.58 (0.44–0.73)	<0.001
Butler [21]				**Hazard rate**	
	ED visits	NR		1011	n.s.
Toy [19]				**Difference (%)**	
	ED visits	802	817	−15 (−1.8%)	NR
	Hospitalizations	1275	1243	−33 (−2.6%)	NR
	Hospital days	5906	5720	−186 (−3.1%)	NR
	Outpatient visits	16,981	17,010	29 (+0.2%)	NR
Simoni-Wastila [17]				**Adjusted RR**	
	Hospitalizations	1.13	0.88	0.90 (0.87–0.93)	<0.05
Mortality					
Turner [23]					
	Percentage died	22.6%	23.7%	NR	n.s.
Vestbo [22]				**Hazard rate**	
	Percentage died	26.4%	11.3%	0.40 (0.35–0.46)	<0.001
Economic outcomes					
Halpern [20]				**Cost ratio**	
	Healthcare costs	NR		1.469 (1.13–1.91)	<0.01
	Medical costs	NR		0.629 (0.43–0.91)	<0.05
	Inpatient costs	NR		0.466 (0.30–0.72)	<0.01
Toy [19]				**Difference (%)**	
	ED costs	$412.658	$405.248	−$7.410 (−1.8%)	NR
	Hospital costs	$11.635.099	$11.338.501	−$296.598 (−2.6%)	NR
	Outpatient costs	$1.867.863	$1.871.082	$3.219 (+0.2%)	NR
Simoni-Wastila [17]				**Marginal effects**	
	Inpatient costs	$19.594	$14.061	−$4.609	<0.001
	Outpatient costs	$12.664	$11.450	−$606	<0.001
	Drug costs	$7.546	$9.190	$1.654	<0.001
Quality of life					
Turner [23]					
	POMS total score	26.3	27.7	NR	n.s.
	SIP total score	16.3	16.5	NR	n.s.
	RLCQ home score	1.22	1.04	NR	0.04
Corden [26]				***r***	
	SGRQ symptoms	NR		−2201	0.054
	SGRQ impact	NR		−2213	0.053
	SGRQ total	NR		−2477	0.03
Agh [28]					
	EQ-5D	0.62	0.50	NR	0.001
Takemura [25]				***r***	
	SGRQ symptoms	NR		−0.43	0.002
	SGRQ impact	NR		−0.35	0.011
	SGRQ activities	NR		−0.17	n.s.
	SGRQ total	NR		−0.35	0.023

Table 2 (*continued*)

Study	Outcome specification	Absolute outcomes		Relative outcomes	Significance
		Non-adherent	Adherent		*p*-value
Productivity					
Carls [16]				**Difference**	
	Absent days	NR		−7.1 (−3.0 − −11.7)	<0.05
	Short-term disability days	NR		−3.7 (−1.7 − −5.8)	<0.05

NR: not reported; n.s.: not significant.

important added value regarding the generalizability of results among the overall COPD population.

To include all the evidence, no stringent inclusion criteria related to the design of the studies were applied. As a result a wide variety of studies was included, making it difficult to combine quantitative results and synthesize evidence through a meta-analysis. In this review, unpublished and non-English studies were excluded; although non-English works have been shown to result in limited added value [14] this may be considered a limitation of our literature search.

Regarding measurement of adherence, most studies used prescription refill data from pharmacy or administrative databases. Although prescription records provide a relatively cheap and fast platform to obtain adherence data, a prescription may not guarantee patients have actually taken their medication, or when taken, used their inhalers correctly. Mishandling of inhalers is common and also associated with reduced disease control [31]. Some studies used self-reported adherence but these were considered to be prone to patient information bias in a positive direction [32].

Furthermore, although well accepted in current literature, the most often used threshold of 80% of the proportion of days covered remains rather arbitrary. Electronic pills count or measuring blood serum levels may provide a more accurate way of measuring adherence but are expensive and invasive. Database studies often lacked information on disease severity. To overcome this limitation, two studies recommend to use proxies for disease severity such as use of oxygen or the number of prior hospitalizations [17,19].

It is recommended to assess the effect of different levels of adherence on medication efficacy in prospective clinical trials. It would be of great value to report the effect of non-adherence on the effectiveness of the therapy, as in 'real life' adherence is much lower than in trials performed in a highly controlled setting [4,33]. These measurements would also provide some evidence on the minimum effective dosing regimen needed to still obtain a high benefit from COPD medication. To fully understand the long-term clinical and economic effects of non-adherence, the time patients are followed should be extended to a period more than one year. Longitudinal disease control should be measured using validated questionnaires like the SGRQ [27], Clinical COPD Questionnaire (CCQ) [34] or COPD Assessment Test (CAT) [35]. One of the problems may be the difficulty of avoiding that patients are aware that their adherence behavior is being monitored.

Implications for future research, policy and practice

Interventions that improve adherence (behavior) are recommended, focusing not only on adherence to medication but on the total 'package' of modifying patients' adherence behavior as a whole.

Adherence is dependent on the patient, treatment and societal factors [5–7]. Strategies to improve adherence have been described [36] and include increasing patients' knowledge about self-management, enhancing healthcare providers' communication skills and counseling.

There is some evidence that interventions can increase patients' adherence to COPD medication [25], but in general studies assessing both the effect on adherence and the effect on outcomes are limited [37]. Further studies are recommended to identify the most (cost)effective interventions to improve medication adherence in patients with COPD. Latest studies show that interventions need to focus on both adherence as well as continued use (persistence) to fulfill the maximal potential of improved health and economic outcomes [17].

Regarding the association between non-adherence and overall worsened outcomes, targeting on specific patients in need of interventions will be facilitated by actively searching for patients with suboptimal adherence to COPD therapy. These 'targeted' interventions are expected to be highly cost-effective compared with interventions using a 'one-size-fits-all' principle.

Conclusions

This review showed a clear association between adherence to COPD medication and clinical and economic outcomes, making non-adherent patients a priority for cost-effective interventions.

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Conflicts of interest

The authors declare that they have no conflicts of interest in relation to this article.

Author contributorship

JvB takes responsibility for the content of the manuscript, including the data and analysis. All authors made substantial contributions to conception and design of the study. JvB and SV collected the data. All authors interpreted

the data, revised the draft critically and approved the submitted manuscript.

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Appendix A. Supplementary data

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