Barriers and Strategies for Improving Medication Adherence Among People Living With COPD: A Systematic Review

Bimbishar Bhattarai, Ramesh Walpola, Amary Mey, Shailendra Anoopkumar-Dukie, and Sohil Khan

BACKGROUND: While medication is an integral component of the effective management of COPD, contemporary studies report that more than half of all people who are prescribed medication for the management of their COPD do not adhere to therapy. Enhancing medication adherence and improving health outcomes for those living with COPD are among the key challenges for the global health community. This systematic review aims to identify the rate of nonadherence among people who are prescribed controller medication for the management of their COPD, and identifies the barriers and facilitators that influence their medication use behavior. METHODS: A systematic search of medical databases (ie, MEDLINE, CINHAL, and EMBASE) was conducted using key words to identify literature in the English language, published between January 2003 and December 2019. Included studies were assessed for quality using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist. RESULTS: A total of 1,474 studies were identified from the initial database search, of which 38 met the inclusion criteria. Of these 38 studies, 37 reported on rates of nonadherence (ranging from 22% to 93%), 30 reported on barriers to adherence, 24 reported on enablers to adherence, and 16 reported on both. The majority (33) of the studies were conducted in high-income nations. The quality of articles ranged from 47% to 90%. Medication-taking behavior was reported to be influenced by several factors such as subjects' beliefs about medication, their experiences of and satisfaction with medication effectiveness, their concerns regarding medication side effects, their personal circumstances, habits and health status, and their relationships with health care providers. CONCLUSIONS: Adherence to COPD medication was generally low, with the majority of studies identifying the presence of depression and subjects' concern about the harmful effects of the medicine as barriers to adherence. Variability exists on the reported rates of nonadherence, possibly due to different measures utilized to assess adherence. Future research in low-income nations is needed. *Key words: medication adherence; nonadherence; inhaler devices; chronic obstructive pulmonary disease; COPD*. [Respir Care 2020;65(11):1738–1750. © 2020 Daedalus Enterprises]

Introduction

Medication adherence is an integral part of chronic disease management, and it has been defined by the World Health Organization (WHO) as "the extent to which the person's behavior corresponds with the agreed recommendations from a health care provider."[1] Vrijens et al[2] divided adherence into 3 components: initiation, implementation, and discontinuation. Initiation is the first step, when patients take their first prescribed dose of medication, followed by implementation where patients take the actual dose, and finally discontinuation, where

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patients stop taking medication. In developed countries, almost half of the patients with long-term pharmacotherapy are not adherent.[1] Studies have suggested that around only half of the individuals with COPD are adherent to their prescribed therapy.[3-5]

COPD is a common disease that, if not managed appropriately, causes an enormous strain on health services. According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD), COPD is a common, preventable, and treatable disease that is characterized by persistent respiratory symptoms and airway limitation.[6] Common persistent symptoms include dyspnea, chronic cough, and sputum production. An update by the Global Burden of Disease in 2015 estimated that about 174 million people have COPD worldwide.[7] By 2030, COPD is projected to become the third leading cause of death globally.[8] In COPD patients, quality of life is impaired, leading to substantial limitations to their regular activity.[9] When not managed appropriately, COPD can result in complications that may lead to increased health care costs and a burden on the health care system.[10] For example, in 2004, a retrospective study conducted in the United States reported that patients with COPD utilized more health care services at a cost of $20,500 above a comparison cohort.[11] As such, appropriate disease management can lead to savings in health care and hospitalization costs, along with a reduction in the rate of hospitalization.[12]

Optimal medication adherence in patients with COPD assists in improving disease management and reducing health care costs.[13] Patients who adhere to treatment have a lower risk of exacerbating their medical condition as compared to those with poor adherence.[14] A study conducted by Vestbo et al[15] reported that those who did not adhere to their recommended treatment were twice as likely to be hospitalized when compared with adherent subjects. Medication adherence is a critical component for effective management of COPD and the key to tackling the ever-increasing burden of illness.[16] Conversely, poor adherence is wasteful in terms of resources and negatively affects health, resulting in higher health care costs.[17] Therefore, understanding what can help people adhere to their recommended medication regimen and what hinders them from taking their medications as prescribed is crucial to developing strategies that help people living with COPD adhere to their medications and subsequently optimize their health outcomes.

In the last decade, several systematic reviews have summarized findings from primary research that investigated the interplay between aspects of COPD management and outcomes.[12,18-22] For example, 3 reviews focused on economic and clinical outcomes of adherence[12,18,19]; 3 others respectively examined strategies to improve medication adherence,[20] factors related to the incorrect use of inhalers,[21] and outcomes of adherence for COPD medication,[22] while yet another review focused on the relationship between medication adherence and health-related quality of life.[23] Some of the reviews have established the relationship between adherence, cost, and quality of life. Challenges for appropriate use of medicine and approaches to enhance medication adherence were also analyzed. However, barriers to and enablers of medication adherence were not adequately reported. Additionally, unifying concepts regarding challenges to and facilitators of adherence and the prevalence of adherence in different countries and regions do not appear in these studies. Considering the various hindrances to medication adherence, identifying those factors and developing strategies to improve adherence appear worthwhile. Moreover, the interconnection of barriers to and facilitators of medication adherence necessitates a joint examination of both of these elements within the same review.

Thus, this review aims to evaluate the barriers to and facilitators of medication adherence in subjects with COPD, and specifically to identify the knowledge gaps from the literature. Considering the prevalence of medication nonadherence worldwide, this review also aims to identify the rates of nonadherence to COPD controller medication.

Methods

Search Strategy

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement was followed in conducting this systematic review.[24] The electronic databases MEDLINE, CINAHL, and EMBASE were used to conduct searches. Due to the extensive coverage of journal articles in the fields of nursing, health, and medical sciences, these 3 databases were chosen. Articles published in the English language and human studies from January 2003 to December 2019 were retrieved for analysis. In the first GOLD report, published in 2001, it was anticipated that it could take up to 2 y for the initial recommendations to be implemented. Therefore, in accordance with the GOLD guideline of commencing a review 2 y after publication of the initial report, we conducted this

Supplementary material related to this paper is available at http://www.rcjournal.com.

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review with articles published from 2003, collecting the best evidence from extensive literature over the past 16 y.

The search was performed using key words and proximity search: (medicat* OR drug*) N3 ("chronic obstructive pulmonary disease" OR "chronic obstructive airway disease" OR "emphysema" OR "chronic bronchitis" OR "COPD") AND (adhere* OR compliance OR persist* OR nonadhere* OR noncompli* OR nonpersist* OR nonadhere* OR noncompli* OR nonpersist*). "N3" is the proximity term for the EBSCOhost searches (ie, MEDLINE and CINAHL), and "NEAR/3" was used for the Embase search. Truncation (*) was used to search for a term and several spellings of that term.

Study Selection

Primary observational studies conducted on subjects with COPD or health care professionals with a focus on barriers to or facilitators of medication adherence were included. Studies that identified health care professionals' perspectives on medication adherence on subjects with COPD were also included. Here, medication adherence refers to "the extent to which the person's behavior corresponds with the agreed recommendations from a health care provider." Papers without a focus on medication adherence and only examining adherence to pulmonary rehabilitation, oxygen therapy, exercise, and self-management programs were excluded. Studies that did not differentiate between asthma and COPD in their results were also excluded.

Eligible studies included participants of any age or sex with a diagnosis of COPD (regardless of other comorbid conditions) or health care professionals involved in the management of COPD. Initially, titles and abstracts were screened by a single investigator (BB) based on the inclusion criteria. Studies that did not meet the inclusion criteria were excluded by verifying titles and abstracts. Remaining studies that met the inclusion criteria were verified by 2 authors (BB, SK). Any discrepancies were reviewed by other authors (AM, RW). To identify additional relevant literature, a manual search was conducted.

Data Items

Details retrieved from the articles included study design, population characteristics (eg, sample size, age), the classification of nations based on economy, method to assess adherence, definition of nonadherence, rates of nonadherence, type of therapies used, time since therapy initiation, method to assess barriers and facilitators, barriers to medication adherence, facilitators of medication adherence, and study findings.

Quality Assessment of Included Studies

The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist for cohort, case-control, and cross-sectional studies was used for assessing the quality of the included studies.[25] The 22-point STROBE checklist was used to score these studies by calculating "yes" answers compared to the result of "yes + no" answers, whereas "not applicable" had no relation with the results. Therefore, the percentage score was calculated as: {[yes/(yes + no)] × 100}. The result of each study was summarized as a percentage and ranked. Quality assessment was independently evaluated by 2 authors (BB, SK), and any disagreements were resolved by the third author (RW). Details about quality assessment are reported in the supplementary materials (see the supplementary materials at http://www.rcjournal.com).

Results

Search Results

The initial database and manual search identified 996 results after removing duplicates. Excluding records by title and abstract and assessing for eligibility criteria yielded 38 relevant papers to be included in this study. Further details about the results included in this review are shown in Figure 1.

Study Characteristics

Details about the study features are reported in Table 1 and the supplementary materials (see the supplementary materials at http://www.rcjournal.com). The articles in this systematic review include studies from 24 countries. The majority of the studies were conducted in Europe (no. = 17),[3,26-41] followed by North America (no. = 13),[13,29,42-51] Asia (no. = 8),[29,52-58] Australia (no. = 2),[59,60] Africa (no. = 1),[61] and South America (no. = 1).[29] Among the 38 studies reviewed, 2 were conducted in multiple countries,[29,37] and 1 study was conducted in 2 countries of Asia.[54] The total of the study populations was 343,689, and the mean age of the participants was 66.94 y. Thirty-seven studies were conducted with patients, whereas one of the studies assessed perspectives of both patients and health care professionals.[49] The majority of the studies had a cross-sectional design (no. = 20), and the remainder were cohort studies (no. = 18). Of the 38 articles reviewed, 37 studies were conducted using quantitative methods, whereas 1 study applied both quantitative and qualitative methodologies. Thirty-one studies in this review were conducted in high-income nations; 4 studies were conducted in high/upper-middle-income nations, 2 studies in lower-middle-income nations, and 1 study in a low-income nation.

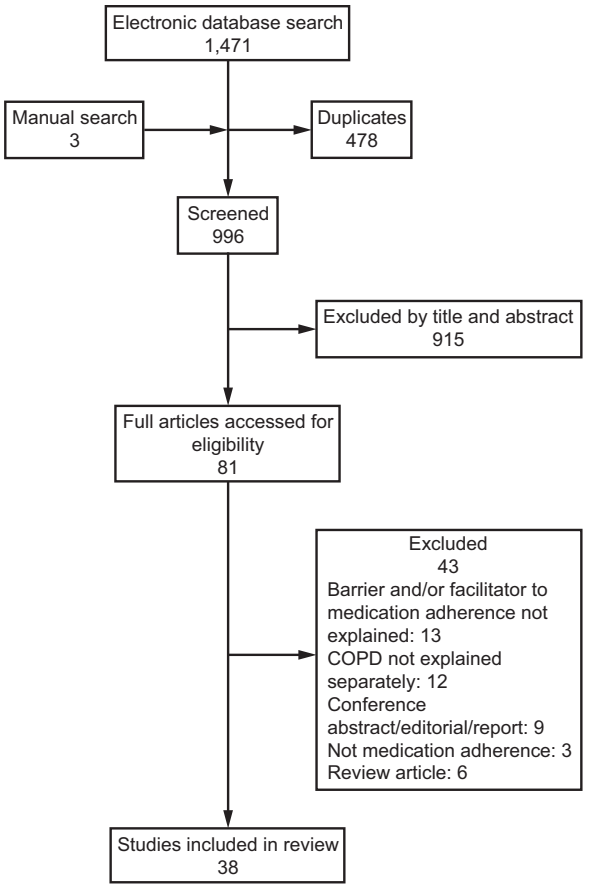

Fig. 1. Flow chart.

Methodological Quality

The STROBE checklist for the quality of articles ranged from 46.67%[61] to 90%.[46] All the studies met the criteria for describing the abstract, background, objectives, and setting. Seven studies performed sensitivity analyses to measure the robustness of the statistical methods used.[28,38,40,41,43,45,57] Furthermore, only 6 studies clarified the results of included subjects with a flow diagram.[31,33,38,40-42] Among the included studies, 8 studies noted potential sources of bias.[28,35,42,47,52,55,59,60] The majority of the studies used self-reporting assessment measures, while the reporting bias of the subjects was presented in 5 studies.[28,47,55,59,60] One of the studies reported both selection bias and recall bias among subjects,[55] and another study considered the selection bias in the use of the periodic instrument for the subject.[52]

Prevalence of Nonadherence and Type of Therapies

Thirty-seven studies reported rates of nonadherence. The reported rates and the definition of nonadherence in subjects with COPD are shown in Table 1. Nonadherence rates ranged from 22%[27] to 93%.[61] More than half of the studies stated nonadherence in $>$ 50% of the subjects. Thirty-seven of the 38 studies assessed the rates of nonadherence at one time only due to the study design. However, in 1 longitudinal study, nonadherence was measured at baseline, after 3 months, and after 12 months.[28] In this study, although the number of subjects decreased at each time point after the baseline measurement, the subjects adherent to their medication was increased at 3 months and at 12 months. There was little difference between the rates of nonadherence between the economic levels of the countries. For example, studies conducted in low-income (Nepal) and lower-middle-income (Vietnam) countries have nonadherence rates of 65% and 70%, respectively, which is similar to the findings from high-income countries like Australia (63%) and Germany (66.2%).[28,53,55,59] Self-report (no. = 18) and pharmacy claims data (no. = 18) were equally used to assess adherence, followed by electronic monitoring (no. = 1); one study did not assess adherence.[57] Several scales without specific names (no. = 6)[36,37,49,54,56,61] were the most frequently used self-report measure followed by the Medication Adherence Report Scale (no. = 4),[28,47,59,60] the 8-item Morisky Medication Adherence Scale (no. = 3),[49,54,61] the 4-item Morisky Medication Adherence Scale (no. = 2),[3,58] the Morisky Scale (no. = 1),[26] the Measure of Treatment Adherence Scale (no. = 1),[30] and the Test of Adherence to Inhaler Scale (no. = 1).[55]

In 12 studies,[13,27,32,34,36,38,39,41-43,51,60] subjects were using either monotherapy (long-acting β_2 agonist [LABA], long-acting muscarinic antagonist [LAMA], or inhaled corticosteroid [ICS]) or dual therapy (ICS/LABA or LABA/LAMA); in 3 studies, subjects were using either monotherapy, dual therapy, or triple therapy (ie, ICS/LABA/LAMA),[31,45,54] and in 1 study subjects were using only triple therapy.[50] Two studies reported that subjects were using only monotherapy (ie, LABA or LAMA[35,57] and another study reported that subjects were using only dual therapy (ie, ICS/LABA).[33] The other 19 studies did not mention the types of therapies that subjects were using. Among the 19 studies that reported the type of inhaled therapy (ie, monotherapy, dual therapy, or triple therapy) used by subjects, 7 studies examined the difference in the rates of nonadherence based on the therapies used.[27,32,38,39,43-45] Four studies noted that subjects had higher adherence to LAMA (tiotropium) than LABA, ICS, or ICS/LABA,[27,32,38,39] and 2 studies reported that subjects had higher adherence to LABA than LAMA or ICS.[43,44] Subjects from 12 of the 38 studies were using their COPD medication for $\geq$ 12 months[29,31,33,34,36,41,43,44,49,50,52,60]; in 3 studies subjects were using their COPD medication for $<$ 12 months,[35,48,51] and 2 studies had both newly prescribed (ie, medicine users for $<$ 12 months) and prevalent users as subjects (medicine user for $\geq$ 12 months).[32,57]

Table 1. Study Characteristics and Nonadherence Rates

Study	Country	Study Design	Sample, *n*	Age, y	World Bank Economic Classification of Nations	Adherence Measurement	Definition	Nonadherence Rate, %	Types of Therapy	Time Since Therapy Initiation
George et al, 2005[59]	Australia	Cross-sectional	276	71.25 ± 7.81 71.10 ± 9.12	High-income	Self-report (MARS)	Higher score on MARS indicated good adherence	63	ND	ND
Laforest et al, 2010[36]	France	Cross-sectional	177	63 ± 8.4	High-income	Self-report	ND	45	LABA, LAMA, ICS, ICS/LABA, LABA/LAMA	≥ 12 mo
Mehuys et al, 2010[34]	Belgium	Cross-sectional	555	68.6 ± 9.6	High-income	Pharmacy claims data	Receiving < 80% or > 125% of the prescribed dose	48.2	LABA, LAMA, ICS, ICS/LABA	≥ 12 mo
Agh et al, 2011[3]	Hungary	Cross-sectional	170	63.83 ± 11.24	High-income	Self-report (MMAS-4)	Score of ≥ 3 indicated adherence	41.8	ND	ND
Takemura et al, 2011[52]	Japan	Cross-sectional	55	69 ± 8	High-income	Self-report	Score of < 4 indicated nonadherence	45	ND	≥ 12 mo
Toy et al, 2011[13]	United States	Cohort study	55,076	69 ± 11.01	High-income	Pharmacy claims data (PDC)	ND	56.7–77	LABA, LAMA, ICS/LABA	ND
Yu et al, 2011[42]	United States	Cohort study	11,747	66 ± 9.8	High-income	Pharmacy claims data (PDC)	Receiving ≤ 80% of the prescribed dose	61.1–67.7	LAMA, LABA, ICS/LABA	ND
Cecere et al, 2012[43]	United States	Cohort study	376	ND	High-income	Pharmacy claims data (ReComp)	ReComp score of ≥ 0.8 was classified as adherence	46–60	LABA, ICS, ICS/LABA	ND
Huetsch et al, 2012[44]	United States	Cross-sectional	2,730	66.1 ± 1.8	High-income	Pharmacy claims data (ReComp)	ReComp score of < 0.8 was classified as nonadherence	69.4–80.2	ND	≥ 12 mo
Khdour et al, 2012[26]	Ireland	Cross-sectional	173	66.6 ± 9.7	High-income	Self-report (Morisky scale)	Scores of 2–4 indicated nonadherence	29.5	ND	≥ 12 mo
Laforest et al, 2012[35]	France	Cohort study	1,147	68 (ND)	High-income	Pharmacy claims data	ND	36	LAMA	<12 mo
Chrystyn et al, 2014[37]	France, Germany, Italy, Spain, United Kingdom	Cross-sectional	1,443	65.2 (ND)	High-income	Self-report	Scores of 5 indicate fully adherent	66.4	ND	ND
Ismaila et al, 2014[45]	Canada	Cohort study	23,707	73.17 ± 10.34	High-income	Pharmacy claims data (MPR)	Receiving < 80% of the prescribed dose	38.9–64.6	LAMA, ICS/LABA LAMA+LABA/ICS	ND
Qian et al, 2014[46]	United States	Cohort study	74,863	72.2 ± 12	High-income	Pharmacy claims data (PDC)	Receiving < 80% of the prescribed dose	38.2	ND	ND
Turan et al, 2014[56]	Turkey	Cross-sectional	78	64.9 ± 9.9	Upper-middle-income	Self-report	Scores of ≥ 9 indicated adherence	46.8	ND	ND
Ingebrigtsen et al, 2014[38]	Denmark	Cohort study	5,812	66 ± 12	High-income	Pharmacy claims data (MPR)	Receiving ≤ 80% of the prescribed dose	67–84	LABA or LAMA, ICS/LABA	ND
Koehorst-ter et al, 2015[39]	The Netherlands	Cohort study	795	67.8 ± 9.9	High-income	Pharmacy claims data	Receiving < 75% or >125 % of the prescribed dose	18.2–56.8	LABA or LAMA or ICS, ICS/LABA	ND
Krauskopf et al, 2015[47]	United States	Cross-sectional	188	67 (ND)	High-income	Self-report (MARS)	Scores of ≤ 4.5 was classified nonadherence	58	ND	ND
Shrestha et al, 2015[53]	Nepal	Cross-sectional	100	68.41 ± 9.64	Low-income	Self-report	ND	65	ND	ND
Tanaka et al, 2015[57]	Japan	Cohort study	644	69 (ND)	High-income	ND	ND	ND	LAMA	< 12 mo, ≥ 12 mo

(Continued)

Table 1. Continued

Study	Country	Study Design	Sample, *n*	Age, y	World Bank Economic Classification of Nations	Adherence Measurement	Definition	Nonadherence Rate, %	Types of Therapy	Time Since Therapy Initiation
Albrecht et al, 2016[48]	United States	Cohort study	31,033	68.4 ± 12.2	High-income	Pharmacy claims data (PDC)	Receiving ≤ 80% of the prescribed dose	78	ND	< 12 mo
Koehorst-ter Huurne et al, 2016[27]	The Netherlands	Cohort study	635	67.1 ± 9.7	High-income	Pharmacy claims data	Receiving < 75% or > 125% of the prescribed dose	22–43	LAMA, ICS, ICS/LABA	ND
Mueller et al, 2016[32]	Germany	Cohort study	52,585	71.6 ± 11.4	High-income	Pharmacy claims data (MPR)	Receiving < 80% of the prescribed dose	70	LABA, LAMA, ICS, ICS/LABA	< 12 mo, ≥ 12 mo
Sriram et al, 2016[60]	Australia	Cross-sectional	150	70.3 ± 8.9	High-income	Self-report (MARS)	Score of 25 was measured as optimal adherence	58	LABA, LAMA, ICS, ICS/LABA	≥ 12 mo
Tottenborg et al, 2016[40]	Denmark	Cohort study	13,369	ND (not reported as mean)	High-income	Pharmacy claims data (PDC)	Receiving < 80% of the prescribed dose	37	ND	ND
Sulaiman et al, 2017[33]	Ireland	Cross-sectional	244	70.6 ± 9.7	High-income	Electronic monitoring	Error in the inhaler technique and dose not taken correctly on time indicate nonadherence	77.4	ICS/LABA	≥ 12 mo
Amin et al, 2017[49]	United States	Cross-sectional	373	67 (ND)	High-income	Self-report (MMAS-8)	Score of < 6 was classified low adherence	44.5	ND	≥ 12 mo
Vetrano et al, 2017[41]	Italy	Cohort study	22,505	67.3 ± 13.2	High-income	Pharmacy claims data (PDC)	Receiving < 80% of the prescribed dose	22.3	LABA, ICS/LABA	≥ 12 mo
Galal et al, 2018[61]	Egypt	Cross-sectional	509	60.39 ± 9.22	Lower-middle-income	Self-report (MMAS-8)	Score of < 8 was classified nonadherence	93	ND	ND
Fischer et al, 2018[28]	Germany	Cohort study	206	65.3 ± 8.85	High-income	Self-report (MARS)	Score of < 25 was considered nonadherence	66.2	ND	ND
Kokturk et al, 2018[54]	Turkey, Saudi Arabia	Cross-sectional	405	ND	Upper-middle-income and high-income	Self-report (MMAS-8)	Score of < 6 indicated nonadherence	49.2	LABA, LAMA, ICS/LABA, ICS/LAMA, ICS/LABA/LAMA	ND
Wei et al, 2018[51]	United States	Cohort study	25,458	ND (not reported as mean)	High-income	Pharmacy claims data (PDC)	Receiving < 80% of the prescribed dose	61	LABA, LAMA, ICS, LABA/LAMA, ICS/SABA	< 12 mo
Price et al, 2018[29]	Brazil, Canada, France, Italy, Germany, Japan, The Netherlands, United Kingdom, United States	Cross-sectional	764	56 ± 9.8	Upper-middle-income and high-income	Self-report	ND	48–52	ND	≥ 12 mo
Duarte-de-Araújo et al, 2018[30]	Portugal	Cross-sectional	319	ND	High-income	Self-report (MTA)	Score of ≤ 6 was poor adherence	48	ND	ND
Humenberger et al, 2018[31]	Austria	Cohort study	357	66.5 ± 10.6	High-income	Pharmacy claims data (MPR)	Receiving ≤ 80% of the prescribed dose	66.4	LABA, LAMA, LABA/LAMA, ICS/LABA, ICS/LABA/LAMA	≥ 12 mo

(Continued)

Table 1. Continued

Study	Country	Study Design	Sample, n	Age, y	World Bank Economic Classification of Nations	Adherence Measurement	Definition	Nonadherence Rate, %	Types of Therapy	Time Since Therapy Initiation
Bogart et al, 2019[50]	United States	Cohort study	14,635	61.9 ± 8.5	High-income	Pharmacy claims data (PDC)	Receiving < 80% of the prescribed dose	86.2	ICS/LABA/LAMA, ICS/LABA +LAMA, LABA/LAMA+ICS	≥ 12 mo
Ngo et al, 2019[55]	Vietnam	Cross-sectional	70	68.6 ± 8.7	Lower-middle-income	Self-report (TAI)	Score of < 50 on 10-item TAI	70	ND	ND
Jarab et al, 2019[58]	Jordan	Cross-sectional	133	63 (ND)	Upper-middle-income	Self-report (MMAS-4)	Score of 1–4 indicated nonadherence	61.7	ND	ND

Age is presented as mean ± SD.
MARS = medication adherence report scale
MMAS-8 = 8-item Morisky medication adherence scale
MMAS-4 = 4-item Morisky medication adherence scale
MTA = measure of treatment adherence
TAI = test of adherence to inhaler
MPR = medication possession ratio
PDC = proportion of days covered
LABA = long-acting β_2 agonist
LAMA = long-acting muscarinic antagonist
ICS = inhaled corticosteroid
ND = no data or not reported

Barriers to Medication Adherence

Of the 38 included studies, 30 listed issues that hindered medication adherence.[3,26-34,36,38-41,43,44,46-49,53-61] Different methods were used to assess barriers to and facilitators of medication adherence. For example, 23 studies used regression analyses,[13,27,28,31,32,35,37-41,43-49,51,54,55,57,58] 6 studies used both regression analyses and questionnaires,[3,26,36,52,59,61] 3 studies used questionnaires only[29,53,56]; separate studies used inhaler technique evaluation and regression analyses,[34] assessment of acoustic recordings and regression analyses,[33] inhaler technique evaluation,[60] and interviews and regression analyses.[30] Additionally, 2 studies compared the differences between adherence rates of different drugs.[42,50]

Regarding barriers to adherence, the presence of depression was identified as one of the potential barriers to adherence.[26,36,44,46,48,54,56,58] Concern about the side effects or harmful effects of medicines was reported in 7 studies associated with lower treatment adherence,[3,28,47,53,57,58,61] followed by smoking (no. = 5),[3,30,43,56,57] forgetfulness (no. = 4),[3,26,36,53] presence of comorbid conditions (no. = 4),[26,32,41,58] and polypharmacy (no. = 3).[36,41,53] Poor inhaler technique was stated as the cause of suboptimal adherence in 2 of the studies.[34,60] Amin and colleagues[49] reported poor adherence among subjects who had a low level of confidence in using their inhaler devices. One study associated reduced quality of life with nonadherence,[54] whereas another study reported that a better quality of life was linked with nonadherence.[3]

One of the included studies identified dissatisfaction with the treating physician and limited interaction between clinician and patient as the cause of nonadherence.[59] Several studies reported that severity of the disease was the barrier to medication adherence.[29,31,33,55] For example, Price and colleagues[29] reported that younger subjects with less disease severity were less likely to take medicine. Similarly, Humenberger et al[31] stated that subjects with mild disease severity were less likely to adhere to their recommended therapy, whereas a study conducted in Vietnam reported that subjects with frequent exacerbations and greater disease severity had suboptimal adherence.[55] Sulaiman and colleagues[33] reported that damage in lung function and decline in cognitive status were barriers to adherence. Koehorst-ter Huurne and colleagues[27,39] concluded that underuse and overuse of inhaler device were associated with higher FEV_1 and lower FEV_1 at baseline, respectively.

Facilitators of Medication Adherence

Among the 38 included studies, 24 studies reported enablers to medication adherence among subjects with COPD.[3,13,26,28-31,34-39,41-45,50-52,54,57,59] Four of these studies highlighted that the patient's belief in the medication is an

essential factor to enhance medication adherence.[26,28,30,59] Subjects had greater adherence when they had a better understanding of their disease and drug therapy.[36,59] Two studies reported that subjects' confidence in health care professionals' expertise was a facilitator to medication adherence.[43,59] In addition, several studies concluded that using fewer inhaler devices and reducing the dosing regimen was associated with higher adherence.[13,39,42,50] Five studies identified that adherence was enhanced in subjects with greater disease severity.[30,31,38,41,44] One study independently identified repeated instruction in the use of inhaler devices as reducing nonadherence,[52] while another study noted that training for inhaler use and inhaler technique checks were responsible for overcoming nonadherence.[29] Two studies reported that elderly subjects had higher adherence,[3,34] while another study reported that higher education and older age ($\geq$ 60 y) were linked with better treatment adherence.[54] Chrystyn et al[37] revealed that better quality of life, less frequent exacerbations, and patient satisfaction with their inhaler device are linked with better adherence. Fourteen studies did not discuss enablers to adherence.[27,32,33,40,46-49,53,55,56,58,60,61]

Discussion

This review has provided insight into barriers to medication adherence and strategies to improve adherence among subjects with COPD through peer-reviewed studies. Variations in the rates of medication nonadherence (22–93%) were identified in subjects from 24 countries. Although only 3 studies from low-income and lower-middle-income countries were included, there was not a significant difference between nonadherence rates from these countries and nonadherence rates in studies conducted in high-income countries.[28,31,53,55,59] This review has identified a number of factors that result in nonadherence: depression, comorbid conditions, concerns about medication, forgetfulness, reduced as well as better quality of life, smoking, choice of medicines, limited patient-clinician interaction, and incorrect use of inhaler devices. Another review reported that the cost of medicines was also a factor for nonadherence among COPD subjects.[62] Although cost may be a barrier to adherence, none of the studies included in this review considered cost as a major barrier. Cost-related nonadherence is one of the major problems in both high-income and low-income countries.[63,64] A multi-country study conducted in high-income nations revealed that cost-related nonadherence is higher in low-income subjects.[63] Even in low-income nations, cost-related nonadherence among individuals with chronic disease is higher in low-income subjects than high-income subjects.[64] Cost as a barrier to medication adherence may vary depending upon the income level of the subjects and the country's universal drug coverage policy.[63-65] In particular, low-income subjects have poor adherence.

Several methods were used to assess nonadherence in the included studies. This could be due to the unavailability of accepted measures to assess rates of nonadherence. Among the instruments used, there were discrepancies in the definition and measurement criteria of nonadherence, which may influence the rate reported. Moreover, other measures that were used, such as pharmacy claims data and electronic measures, have different measurement criteria of nonadherence than self-reported measures. This may also lead to variances in the rates of nonadherence. Even if studies used the same method to assess adherence (eg, pharmacy claims data,[27,32] the 8-item Morisky Medication Adherence Scale,[54,61] and the 4-item Morisky Medication Adherence Scale,[3,58] we noted variations in cutoff values to define nonadherence. The use of different measures to evaluate adherence could yield varying results. Another reason for the variance in rates of nonadherence may be differences in patients' beliefs regarding effectiveness of or concern about their medication.[26,28,30,47,53] In chronic illness, the patient's belief is one of the important predictors for differences in adherence.[66] In this review, individual belief may have varied among the included studies and may have resulted in a difference in rates of nonadherence.

Optimal medication adherence can be attained when subjects have positive beliefs about their medication; conversely, adherence is reduced when subjects have concerns about their medication.[26,28,30,47,53,57,58,61] This review revealed that subjects were more likely to be adherent if they had greater belief about the medication's effectiveness.[26,28,59] On the one hand, when thoughts about a medication are dominated by side effects and fear of unusual side effects, subjects are more likely to discontinue their medication.[67,68] For example, due to the side effects of ICS, almost half of the Americans low-income minority patients were nonadherent.[69] On the other hand, optimal adherence is related to patients' perceived treatment benefits and confidence in their treatment management.[70,71] Medication adherence is increased in patients who have a specific belief about the necessity of COPD medicines and their feeling toward medication effectiveness.[28,72] If the subjects felt their medicine was effective, then they were more likely to adhere to it.[26,30,59] This finding is consistent with a study conducted in different European countries where subjects' satisfaction with the use of their inhaler devices was one of the key attributes for treatment adherence.[37,73] In fact, subjects observed both benefits and ill effects of medicines depending on whether they accepted and understood the necessity of their medicines.[69] These beliefs, which subjects experience in their everyday life regarding medicine, are complex and crucial determinants of self-management behaviors. Therefore, it may be essential to focus on these underlying beliefs to

improve medication adherence. Although patients' beliefs about their medication is an important factor of adherence, none of the studies from low-income or lower-middle-income nations have reported evaluating subjects' beliefs as a factor of their adherence. This may be an issue in low-income and lower-middle-income nations, and this knowledge gap about patients' beliefs and the association with medication adherence in literature should be addressed.

Studies revealed that the use of multiple respiratory inhalers is more strongly associated with suboptimal adherence than treatment with a single inhaler device, which may be due to challenges related to having multiple inhaler devices.[42,74] In this review, use of a single inhaler device was associated with better adherence.[42,50] Notably, the majority of the studies did not report a correlation between nonadherence and therapies used by subjects.[3,26,28-30,35-37,40,41,44,46-51,55-59] Studies indicated that subjects on monotherapy with LAMA had better adherence than those treated with LABA, ICS, or ICS/LABA.[27,32,38,39] In subjects with asthma, better adherence was observed in those who were using dual therapy (ie, ICS/LABA) than in those using ICS alone, which may be due to the increased benefit of the medicine and better symptom control with combination therapy.[75] This review could not establish any relationship between treatment adherence and subjects initiating therapy because more than half of the included studies did not report the time since therapy was initiated. A limitation among the reviewed articles is that, even though the majority of subjects in half of the studies were using their medication for $>$ 12 months, the data were still inadequate to compare adherence of newly prescribed medicine users with the adherence of prevalent users. However, a recent study conducted among statin users reported that subjects adherent to statin medicine dropped from 54% at 6 months to 30.7% at 9 y.[76] The lack of studies reporting on the differences between adherence to treatment among monotherapy, dual therapy, and triple therapy in newly prescribed and long-time COPD medicine users might be an important opportunity for researchers and health care professionals to consider in the near future.

This review has identified a number of factors that have reduced treatment adherence in subjects with COPD. The finding of one previous study suggested that subjects with a better quality of life were associated with poor treatment adherence.[5] Another review noted that when the quality of life is enhanced, it may result in nonadherence[18]; however, good adherence is associated with improved quality of life.[19] Our results indicate that the correlation between medication adherence and quality of life may be ambivalent. Our review supports that a better quality of life is not only related to optimal adherence, but poor adherence also leads to reduced quality of life. Conversely, better adherence might result in an improved quality of life.[23,52] Quality of life and adherence may have a dual relationship, and both of these elements may affect each other. Furthermore, the presence of comorbidities such as cardiovascular disease, depression, anxiety, and musculoskeletal disease in patients with COPD reduce the quality of life.[77] Depression also reduces the quality of life, and medication adherence and quality of life can be linked because $>$ 40% of patients with COPD have depression.[78,79] This review supports the finding of a previous review that depression results in lower health status and is connected with reduced adherence among subjects with COPD.[80] Cognitive function in subjects with COPD could be affected by depressive and anxiety symptoms, which may, in due course, affect treatment adherence.[56] A study conducted by Bosley et al[81] observed a relationship between adherence and psychological factors associated with nebulized therapy. The authors identified that depressed people negatively observe their condition and report that an increased disability causes a depressed mood.[81] Both respiratory disability and depression may interact and exacerbate each other leading to increased patient discomfort.

Although studies have reported that greater disease severity is associated with suboptimal adherence, this was not established in all studies.[33,55] In some of the studies, there was an inverse association between treatment adherence and higher disease severities.[38,41,44] This inverse association might be explained by the fact that continuous medication is required for patients to treat their disease severity. Furthermore, in one of the former studies, subjects had impaired cognitive status resulting in poor adherence, and the relatively small sample size ($N = 70$) of another study means that the results might not be generalizable.

In this review, smokers were less likely to adhere to their medication than nonsmokers.[3,30,43,56,57] This finding supports previous research which suggests that smoking results in suboptimal use of medication among subjects with COPD.[82,83] Inhaled corticosteroids which are one of the most commonly prescribed medicines for patients with COPD, are less effective in smokers, leading to a reduced therapeutic effect.[82,84] This may be one of the reasons why smokers may not refill their prescriptions, thus leading to suboptimal medication adherence. Another reason may be that smokers spend more on tobacco products, which may be the cause of a cash deficit to buy their medication.[82] Although smoking results in suboptimal adherence, only 5 of the studies in this review highlighted the effect of smoking on adherence. Smoking is also one of the leading causes of COPD, yet the role of health care professionals to raise awareness in COPD subjects to cease smoking was not a focus in the reviewed articles. This represents another area that needs further study.

In other chronic diseases, optimal adherence to the therapeutic regimen was enhanced with successful patient-clinician interaction.[85,86] However, in this review, subjects were nonadherent when their physicians provided less time and limited information about the illness.[59] Subjects who have less understanding of their disease management exhibited suboptimal adherence as well as low satisfaction and belief in their treating physician. In contrast, subjects with a better understanding of their disease and drug therapy and greater confidence in their treating physician demonstrated better adherence.[36,43,59] The literature suggests that education can provide various benefits and ameliorate the health trajectory of patients.[87] Educating subjects is crucial because it helps them understand their disease and the benefits and proper use of medication.

Appropriate use of the inhaler devices by patients is an essential predictor of medication adherence and is the cornerstone of COPD therapy. Previous studies have reported that 4–94% of subjects demonstrate incorrect use of inhaler devices,[21,62,88] depending upon the method of assessment and type of inhaler device used. To minimize the suboptimal use of inhaler devices, device use education is an influential factor in enhancing adherence. A review by Lareau and Hodder[89] highlighting the use of inhaler devices explained that patients should be informed about an inhaler's indication and frequency of use, should be asked to demonstrate the use of the device, and should be made aware of the importance of training in inhaler techniques. Interestingly, our results indicate that greater confidence in subjects' ability to use inhaler devices helps improve medication adherence.[49] It is important to consider that the inhaler devices should be easy to use, have minimal steps to operate, and have a breath-actuated mechanism.[90] Despite the ease of use of the inhaler devices, 2 articles in this review highlighted that adherence to inhaled medication also depends upon the specific class of medication, because subjects use the medication class that provides them better relief.[27,44] Therefore, it is critical to contemplate that adherence to one type of medication class does not necessarily mean subjects may be adherent to another type of medication. Further studies are required to fully understand the connection between the class of medication and adherence.

This review has identified several knowledge gaps among the articles reviewed. The majority of the studies were conducted in high-income countries; only 3 studies were from lower-middle-income and low-income countries. This is paradoxical because $> 90\%$ of COPD deaths occur in low-income and middle-income countries.[91] Unfortunately, there are limited studies to understand factors associated with medication adherence in these countries. This shows a geographical knowledge gap among the included studies with a scarcity of literature from low-income countries. Further research from these countries is warranted.

Health care professionals are key players in the management of disease, and their understanding of patients' medication-taking is crucial. However, there are limited studies in understanding the health care professionals' perspectives of their patients' medication adherence. Of the 38 articles included in this review, only 1 study highlighted health care professionals' perspectives regarding patients' medication adherence.[49] This is an important issue, and consideration should be given to future research among health care professionals because they are the ones who provide health- and medication-related services to patients with COPD. Moreover, conducting research among these groups of the population will help rectify the dearth of information.

All of the included studies identified rates of nonadherence and, with the inclusion of mostly structured questionnaires and with regression analyses, they examined factors associated with medication adherence. One study included a structured questionnaire followed by semistructured interviews to justify participants' opinions.[30] A limitation among the reviewed studies was the fact that 37 articles did not delve into the subjects' opinions and behaviors to explain precisely why subjects were not taking their medicines as prescribed. Reasons for medication nonadherence and facilitators to medication adherence were based on the answers from closed-ended questions and regression analyses. Due to this style of questionnaire and analyses, the responses from patients, including their thoughts and feelings, were missing. Thus, this review highlights the lack of qualitative studies in assessing barriers to and facilitators of medication adherence. Future research should evaluate the patients' lived experience and medication use behavior through qualitative studies.

A limitation of our review was that we examined 3 databases with peer-reviewed literature published in the English language, which may have led to the exclusion of some articles such as gray literature. However, we included the most relevant and recent articles that met the review criteria. Although the findings from this study are clear with regard to medication adherence, the evidence is mainly generated from observational studies without the inclusion of randomized controlled trials.

Conclusions

This review highlights factors associated with challenges to and facilitators of medication adherence. Adherence to COPD medication was low with nonadherence rates $> 50\%$ in more than half of the studies. The presence of comorbid conditions such as depression and concern about the harmful effects of the medicine were considered barriers to adherence in the majority of the studies, whereas patients' positive beliefs in the medication were considered

a facilitator to adherence. Variability exists in the reported rates of nonadherence, which may be a result of the type of measures that the studies utilized. This review reveals a lack of qualitative studies to identify factors associated with medication adherence. Currently, there are few studies that discuss health care professionals' perspectives of their patients' medication adherence, thus careful assessment of their views is warranted. Future research design requires evaluation of the patients' lived experiences and medication use behavior through qualitative studies, as well as more focus on low-income nations.

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