

New insights to improve treatment adherence in asthma and COPD

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Abstract: Chronic respiratory diseases such as asthma and COPD are typically managed by daily inhaled medication. However, the efficacy of an inhaled medication depends upon a patient's adherence to therapy, which refers to whether the medication is actually taken as prescribed. In patients with these diseases, higher adherence has been associated with better health outcomes, such as improved disease control and a reduction in severe and potentially costly exacerbations. Adherence is a multifaceted concept that includes medication-related, intentional, and unintentional reasons that patients may or may not take their medication as directed. The purpose of this integrative review is to present the individual patient factors that contribute to suboptimal adherence to inhaled therapies and the associated effects on health outcomes, while also highlighting evidence-based strategies for health care providers to improve adherence to such therapies in patients with asthma or COPD. Working closely with patients to establish a model of shared decision-making, which takes patient beliefs and preferences into account when choosing treatment options, has the potential to improve adherence and overall patient outcomes in the management of asthma and COPD.

Keywords: chronic disease, health behavior, evidence-based medicine, inhalers

Introduction

Recent advances in the understanding of the pathophysiology of asthma and COPD have led to the development of new therapies and combinations thereof to manage these chronic respiratory diseases. Health care providers who treat these patients generally follow international and national treatment guidelines as well as strategy reports that are updated more frequently to make recommendations based on the latest research.^{1,2} Nevertheless, the patient is responsible for following through with taking medication as prescribed.

Suboptimal adherence is defined as the failure of patients to take their medication as directed by their clinician.³ Higher adherence has been associated with positive health outcomes, including improved disease control and a reduction in mortality.⁴ General medicine reviews estimate that approximately 50% of medications for chronic disease are not taken as prescribed.⁵ Adherence rates tend to be even lower for patients with asthma or COPD,⁶ with estimates ranging widely from 22% to 78%.^{2,3,7,8} This may be due, in part, to the additional challenges of inhaled therapy, which has a central role in asthma and COPD disease management.

The terminology used in the ABC (3-step) adherence framework includes (A) initiation, (B) implementation, and (C) persistence or discontinuation.⁹ Initiation refers to whether or not the patient takes the first dose of medication. Implementation is related to the alignment between the patient's actual dosing

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and the prescribed regimen, which is a longitudinal measure of the patient's dosing history. Persistence is the time between initiation and treatment cessation, which may or may not be the intended end of the prescription.

Considerable variability exists in the measurement of adherence.³ Electronic monitoring via dispensing records can determine how often prescriptions are filled, or an electronic monitoring device attached to an inhaler can be used to record the number of times the inhaler was actuated¹⁰ and the medication inhaled.¹¹ Methods to evaluate adherence in clinical trials include patient behavioral questionnaires (eg, self-report measures like the validated Medication Adherence Report Scale for Asthma [MARS-A]^{12,13} and the Medication Intake Survey-Asthma [MIS-A]¹⁴), dispensing records, dose or pill counting/medication possession ratios (MPRs; number of days' supply/number of days in study), electronic inhaler monitoring, and drug assays. Adherence in asthma and COPD is most commonly measured by self-report (37.8%) and prescription refill data (32.8%), with electronic dose monitoring (19.3%) rising in popularity.³ However, self-report measures overall are notoriously unreliable, often overestimating adherence by as much as 50%.¹⁵

This integrative review encompasses discussion of both recent studies and other reviews that were published through 2018, providing a timely update of the adherence literature for these chronic diseases. We have chosen studies published in the past 10 years that investigated the relationship between adherence and outcomes in asthma and COPD. The purpose of this manuscript is to highlight the many factors that contribute to suboptimal adherence to inhaled medication in asthma and COPD, describe the consequences for health outcomes, and present strategies supported by the literature that clinicians can employ to improve adherence to inhaled therapies and, in turn, improve patient outcomes.

Factors that contribute to suboptimal adherence

To understand the reasons for suboptimal adherence, health care providers should elicit patients' beliefs and concerns about their disease and the medication(s) used to treat it.² Factors that contribute to suboptimal adherence fall into 3 main categories (Figure 1).² Medication factors include reasons that are directly related to the medication itself (eg, side effects, ease of inhaler use). For example, correct inhaler technique can be challenging for patients and is vital to optimal therapy delivery¹⁶ and thus a critical

component in adherence.^{17,18} Intentional factors contributing to suboptimal adherence are the result of the patient's choices (eg, perception that treatment is unnecessary), whereas unintentional factors are not conscious decisions made by the patient (eg, misunderstanding directions).²

Incorrect inhaler technique is 1 manifestation of unintentional suboptimal adherence. The use of inhalers adds to the complexity of the medication regimen. Patients may have difficulty using certain inhalers for a variety of reasons, including comorbidities such as arthritis or cognitive impairments.¹⁹ Other important aspects of the medication regimen include the use of multiple inhalers versus a single combined inhaler as well as the frequency of dose administration required each day, although available data have not shown meaningful changes in clinical outcomes with once-daily versus twice-daily dosing for inhaled therapies.²⁰ Furthermore, it may be difficult to establish and sustain the correct technique when inhalers require different administration techniques. For example, dry-powder inhalers (DPIs) require rapid and forceful inspiration to properly deliver the drug, whereas this type of inhalation is not recommended for metered-dose inhalers (MDIs) and nebulizers.²¹ Furthermore, in some cases, patients may have difficulty coordinating actuation and inspiration to correctly use a pressurized MDI, whereas other patients have difficulty inhaling forcefully enough to actuate a DPI.^{2,22} Cognitive impairment is especially an issue in elderly patients with COPD. For patients with reduced cognitive function, DPIs have been associated with better technique than MDIs.²³ In this context, it may be helpful for patients to have device types (ie, MDI vs DPI) that match for both controller and reliever therapy, avoiding complications that might arise from needing to distinguish and use more than 1 technique.²⁴ Critical errors in inhaler technique (eg, actuation against lips, teeth, or tongue) have been shown to increase risk of hospitalization, emergency department visits, and the use of antibiotics and oral corticosteroids (OCSs). The likelihood of these errors occurring can be reduced by proper instruction and checks on inhaler technique at follow-up appointments.²⁵

Asthma and COPD are generally accepted to be 2 distinct respiratory diseases that affect differing populations and take unique developmental courses. Each disease can present its own challenges to patient adherence; 1 such factor is the age of onset. Patients with COPD tend to be older and may have comorbidities as a result of smoking that require several medications, so it is important to

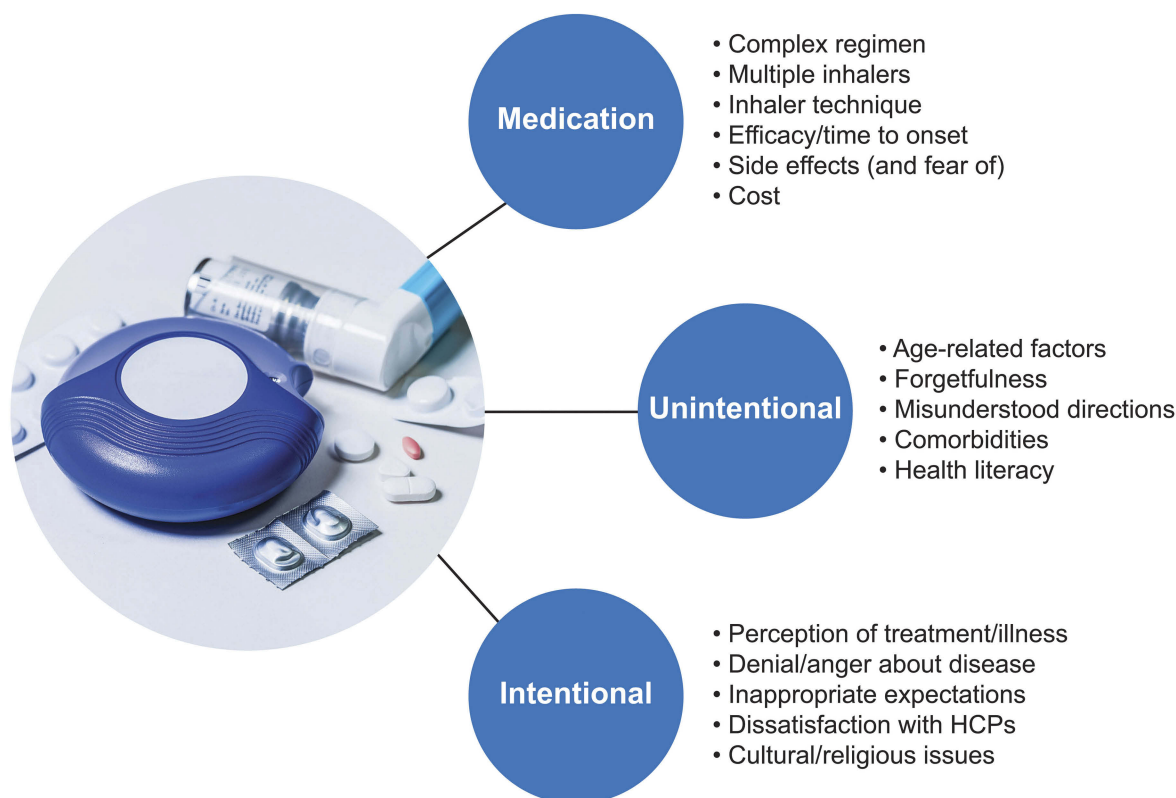


Figure 1 Factors contributing to suboptimal adherence in asthma and COPD. The factors that contribute to suboptimal adherence in asthma and COPD are grouped into 3 major categories.

Notes: Image: iStock.com/Alessandro2802. Data from Global initiative for asthma <http://www.ginasthma.org>²; Makela et al³; Bryant et al⁷ and van Boven.¹⁸

Abbreviations: COPD, chronic obstructive pulmonary disease; HCP, health care provider.

consider all medications the patient is taking and any potential contraindications or potential cognitive changes that may cause difficulty with correct inhaler usage.⁹ In contrast, asthma can present at any age,²⁶ and younger children with asthma may also have difficulty using inhalers correctly, especially in terms of inhalation technique.²⁷ Concerns about adverse effects, such as growth suppression and osteoporosis,^{28,29} and particularly about the necessity of steroid treatment (inhaled or oral),³⁰ may cause parents of children with asthma to be less likely to enforce adherence to prescribed therapy.³¹ Some clinicians may also be hesitant to prescribe inhaled corticosteroids (ICSs) to children for these same reasons.³² However, the 2018 Global Initiative for Asthma (GINA) report does recommend daily ICS therapy in children,² and this course of therapy has not been shown to significantly impact final adult height when used at lower doses compared with higher doses.³³

Additional difficulties with adherence to inhalation therapy may occur as children with asthma age and become more independent. Adolescents with asthma have reported forgetfulness, lack of routine, social stigma

around using inhalers, and lack of family support (eg, parents not accepting their asthma diagnosis) as reasons for suboptimal adherence.³⁴ However, overall, increasing age has been associated with higher adherence to asthma therapy.³⁵ Another important factor that distinguishes asthma from COPD is the course of the disease itself. The airflow obstruction that occurs in asthma is variable and can be reversed with medication, whereas COPD is a progressive and irreversible deterioration of lung function.⁹ Additionally, depression is a common comorbidity in asthma and COPD that undermines adherence; as a result, treatment for depression in patients with asthma or COPD is generally associated with improved adherence.^{36,37}

Effects of suboptimal adherence on patient outcomes

Asthma

Studies have shown that higher adherence is associated with better symptom control in patients with asthma, whereas suboptimal adherence is a modifiable independent risk

factor for asthma exacerbations (Table 1).^{2,3} Specifically, high adherence (eg, MPR $\geq 80\%$) to asthma controller therapy, such as ICS, has been associated with significantly reduced risk of exacerbation, reduced OCS use, and positive impacts on asthma-related mortality.^{3,8,38,39} A study in pediatric patients with moderate persistent asthma showed that medication adherence was also a strong determinant of asthma control (as defined by the 2018 GINA report).^{2,30}

Given that poor asthma control can be a result of suboptimal adherence, it is important to distinguish between a patient with asthma who is not adhering to his or her current therapy and a patient with asthma who requires progression to a higher GINA treatment step to control his or her symptoms. For these reasons, it is important to assess both adherence and inhaler technique before stepping up asthma therapy so as to avoid unnecessary medications.² The use of electronic monitoring devices has been proposed to better identify pediatric patients with severe disease who require step-up therapy despite reportedly high adherence.⁴⁰

COPD

Exacerbations resulting in hospitalization are thought to account for approximately 45% of direct medical costs associated with COPD and therefore can be expensive for the health care system.⁴¹ In fact, complex admissions requiring intensive care, intubation, or both, accounted for only 5.8% of hospital-based COPD care but 20.9% of costs in 2008.⁴² Higher adherence has been shown to significantly reduce moderate and severe exacerbations in COPD and also to lower mortality rates (Table 2).^{38,43} In contrast, suboptimal adherence has been associated with increased hospitalization and mortality, reduced quality of life, and loss of productivity.^{38,44} For patients with severe COPD, adherence to treatment is associated with lower health care costs and a lower risk of an intensive care unit stay.⁴⁵ Adherence in combination with persistence of treatment is necessary to achieve improved clinical outcomes.⁴⁴

Improving adherence to inhaled therapies in clinical practice

According to international guidelines for both asthma and COPD, it is important for clinicians to have empathetic discussions with patients to assess adherence, along with symptom control and inhaler technique, at every office visit. Suggested topics^{1,2} for discussions with patients who have asthma or COPD include: 1) the number of

days per week the patient takes his or her inhaled medication; 2) the patient's beliefs about his or her medication (including the perceived necessity), the cost of medications, and how often they are refilled; and 3) the importance of adherence with daily controller medications even when symptoms are infrequent. Although forgetfulness is the most often-cited reason for suboptimal adherence,⁴⁶ patients may claim that they forgot in order to avoid further discussion of the true reason(s) for not taking their medication as prescribed.

Good communication by health care providers helps with increased satisfaction and better adherence, in turn improving health outcomes and reducing the use of health care resources.^{2,47} Assessing patients' beliefs about their preferred treatment strategies and their prescribed medications is critical.⁴⁸ For example, a recent German study showed that patients with asthma or COPD who believed their specific medications were necessary were more likely to be adherent, whereas patients with asthma who were concerned about overprescription of medication by doctors were less likely to adhere to their prescribed treatment.⁴⁹

Training patients on correct inhaler technique is crucial and should be conducted routinely.²⁵ When providing patient education about inhalers, providers should do the following: 1) know how each device works and how to optimize delivery to the lungs; 2) be able to effectively demonstrate for the patient how the device works; 3) teach the patient how to use the device with the correct technique; and 4) regularly review the patient's technique and provide additional training as necessary.⁵⁰ Educational interventions on inhaler technique are effective, and predictors of success of the intervention include low baseline performance, outpatient setting, and short follow-up time.⁵¹ A number of studies have shown that 1-on-1 educational counseling by pharmacists about correct inhaler technique, as well as the importance of adherence, smoking cessation, exercise, and follow-up, not only increases adherence in patients with COPD⁵² but can also reduce severe exacerbations and hospitalization rates.⁵³ One study also showed that home visits by trained asthma educators increased adherence and decreased emergency department visits, but the improvements in outcomes were inconsistent and not long-lasting.⁵⁴ In contrast, a school nurse-supervised asthma program, in which pediatric patients with persistent asthma and suboptimal adherence received nurse-supervised daily ICS therapy at school, decreased asthma-related emergency department visits, reduced asthma-related hospital admissions, and lowered asthma reliever medication refills over 1 year.⁵⁵

Table I Summary of study results linking inhaled medication adherence to patient outcomes in asthma

Study	Population	Study design	Measure(s) of adherence	Outcomes
Bender 2010 ⁵⁶	US patients aged 18–65 years	Randomized clinical trial	<ul style="list-style-type: none"> Electronic dose counter Changes in canister weight (budesonide/formoterol only) 	<ul style="list-style-type: none"> IVR significantly improved adherence by 32% ($P=0.003$) BMQ showed a greater upward shift in medication beliefs for the IVR group ($P=0.007$) No difference observed in AQLQ or ACT between groups
Melani 2011 ²⁵	Italian patients aged ≥ 14 years	Cross-sectional, observational study of patients using an inhaler regularly at home	Investigator-observed placebo inhaler use	<ul style="list-style-type: none"> Suboptimal inhaler technique increased risk of hospitalization (47%, $P=0.001$) and the use of the ER (62%, $P=0.0006$), antibiotics (50%, $P=0.00004$), and OCSs (54%, $P=0.00003$)
Petrie 2012 ³⁵	New Zealander patients aged 16–45 years	Randomized clinical trial	Patient-reported	<ul style="list-style-type: none"> Average adherence over time was significantly higher in the intervention group (57.8%) than the control group (43.2%, $P=0.003$) Patients with an average adherence $\geq 80\%$ included significantly more patients from the intervention group (25.9%) compared with the control group (10.6%, $P=0.034$) Perceptions of controller medication necessity, long-term nature of asthma, and asthma control were all positively increased in the intervention group relative to the control group (all $P<0.05$)
Vollmer 2013 ⁵⁷	US patients aged ≥ 18 years	Pragmatic clinical trial	mMPR ≥ 0.8	<ul style="list-style-type: none"> Primary analysis: IVR significantly increased adherence by 0.02 ($P=0.002$) compared with usual care Post hoc analysis (receiving ≥ 2 IVR contacts): adherence increased by 0.06 ($P<0.001$) No difference observed in asthma morbidity (SABA use or urgent asthma health care use)
Ismaila 2014 ³⁸	Canadian patients aged ≥ 12 years	Observational study of patients taking FSC	<ul style="list-style-type: none"> MPR $\geq 80\%$ Persistence: ≤ 30-day treatment gap 	<ul style="list-style-type: none"> MPR $\geq 80\%$ reduced exacerbation risk by 52% ($P<0.001$) Persistence reduced exacerbation risk by 58% ($P<0.001$)
Makhinova 2015 ³⁹	US patients aged 5–63 years	Retrospective claims database study of patients taking any asthma controller medication	PDC $\geq 50\%$	<ul style="list-style-type: none"> Adherent patients were 96.7% more likely to have ≥ 6 SABA prescription claims ($P<0.001$) Adherent patients had 0.11 fewer OCS prescription claims ($P<0.001$)
Jentsch 2017 ³⁰	Brazilian patients aged 5–16 years	Prospective, observational study of patients with uncontrolled moderate, persistent asthma despite high adherence	Electronic dose counter	<ul style="list-style-type: none"> Patients with controlled asthma had significantly higher adherence rates at 2, 4, and 6 months (87.8%, 74.9%, and 62.1%, respectively) compared with uncontrolled patients (71.7%, 56.0%, and 47.6%; $P=0.000$, $P=0.000$, $P=0.002$, respectively)
Trivedi 2017 ⁵⁵	US patients in grades 1–12; mean age of 10.5 years	Retrospective study of children with persistent asthma	Daily school nurse-supervised ICS therapy	<ul style="list-style-type: none"> Asthma-related ER visits decreased 37.5% ($P<0.001$), asthma-related hospital admissions decreased from a mean of 0.3 to 0 ($P<0.001$), and the number of reliever medication refills decreased by 46.3% ($P<0.001$) compared with pre-intervention

(Continued)

Table 1 (Continued).

Study	Population	Study design	Measure(s) of adherence	Outcomes
Jochmann 2017 ⁴⁰	UK patients aged 5–17 years	Prospective, observational study to distinguish between severe disease and suboptimal adherence	Electronic dose counter	<ul style="list-style-type: none"> 4 groups were identified based on adherence and asthma control; 24% had high adherence and improved control, 18% had suboptimal control despite high adherence, 26% had good control despite suboptimal adherence, and 32% had suboptimal control and suboptimal adherence

Abbreviations: AQLQ, asthma quality of life questionnaire; ACT, asthma control test; BMQ, belief in medications questionnaire; ER, emergency room; FSC, fluticasone propionate/salmeterol combination; ICS, inhaled corticosteroid; IVR, interactive voice recognition; mMPR, modified medication possession ratio; MPR, medication possession ratio; OCS, oral corticosteroid; PDC, proportion of days covered; SABA, short-acting beta-agonist.

Table 2 Summary of study results linking inhaled medication adherence to patient outcomes in COPD

Study	Population	Study design	Measure of adherence	Outcome(s)
Vestbo 2009 ⁴³	TORCH cohort, aged 40–80 years	Subanalysis of TORCH patient database	Electronic dose counter	<ul style="list-style-type: none"> High adherence was associated with 60% decreased risk of death ($P<0.001$) over the 3-year study period High adherence was associated with a 44% lower rate of severe exacerbations ($P<0.001$)
Ismaila 2014 ³⁸	Canadian patients aged ≥ 40 years	Observational claims database study	<ul style="list-style-type: none"> MPR $\geq 80\%$ Persistence: ≤ 30-day treatment gap 	<ul style="list-style-type: none"> Tiotropium MPR $\geq 80\%$ decreased the rate of both moderate (-0.65^*) and severe (-0.2^*) exacerbations ($P<0.001$ for both) Tiotropium persistence decreased the rate of moderate exacerbations (-0.14^*) Tiotropium+FSC MPR $\geq 80\%$ decreased the rate of both moderate (-0.72^*) and severe (-0.33^*) exacerbations ($P<0.001$ for both) Tiotropium+FSC persistence decreased the rate of both moderate (-0.38^*) and severe (-0.19^*) exacerbations ($P<0.001$ for both)
Tommelein 2014 ⁵³	PHARMACOP cohort, aged ≥ 50 years	Randomized, controlled, parallel-group trial	MRA $\geq 80\%$	<ul style="list-style-type: none"> Severe exacerbation rate decreased by 55% ($P<0.007$) after medication counseling by a pharmacist Hospitalization rate decreased by 72% ($P=0.003$) after medication counseling by a pharmacist
Kim 2017 ⁴⁵	South Korean high-grade COPD patients aged ≥ 40 years	Observational claims database study	MPR $\geq 80\%$	<ul style="list-style-type: none"> Adherent patients had 10.4% lower all-cause health care costs ($P=0.0003$), 11.7% lower COPD-related health care costs ($P<0.0001$), and were less likely to require ICU treatment (OR 0.74, [95% CI 0.60–0.91])

Note: *Mean number of events/patient/100 days during the follow-up period.

Abbreviations: CI, confidence interval; FSC, fluticasone propionate/salmeterol combination; ICU, intensive care unit; MPR, medication possession ratio; MRA, medication refill adherence; OR, odds ratio.

A multidisciplinary approach to patient care supports the patient in the management of both mental and physical aspects of their disease. The inclusion of psychologists on such teams can, therefore, improve self-management by eliciting changes in behavior.⁵⁸ Adherence can also be improved by implementing a shared decision-making process regarding medication and dose regimen choices

between health care provider and patient.⁵⁹ Shared decision-making is an approach whereby patients and health care providers make joint health care decisions based upon the best available evidence regarding possible risks and benefits associated with viable options yet still anchored to patient preferences and values.⁶⁰ It is also important to consider the health literacy of the patient when developing

education and treatment action plans, so these plans can be delivered at the appropriate level to support adherence to therapy.²

Electronic devices that track adherence have been available for over 3 decades,¹⁰ but new adherence-intervention smart technology includes a growing number of potential uses for asthma patients, such as feedback on inhaler technique, portable fractional exhaled nitric oxide measurement devices, and GPS devices with alerts about environmental contaminants that could worsen symptoms.⁶¹ Such technology has the potential to remotely track disease variables and remind patients to take their medication, avoid triggers, or contact their physician when symptoms worsen. A review of patient-reminder systems that are meant to combat forgetfulness in taking medications found an increase in adherence of up to 22% but no effect on outcomes or quality of life,⁶² whereas education tailored to patients' illness and medication beliefs significantly improved adherence in adolescents and adults.³⁵ A study investigating the use of a monitor attached to patients' inhalers showed that patients with asthma who received medication reminders and feedback from such a device had significantly higher adherence than the control group who did not receive feedback or reminders.⁶³ Another study used an electronic monitoring device in patients with COPD to track the quality and timing of inhaler use to improve adherence in distinct clusters of patients (regular use, frequent technique errors; irregular use, good technique; and irregular use, frequent technique errors).⁶⁴ One recently completed trial (NCT02864342) showed that electronic medication reminders improved adherence to inhaled medication in patients with COPD. The majority of patients indicated that they found the device with accompanying smartphone application easy to use and the reminders helped to ensure their medication was taken as prescribed.⁶⁵ Additional studies in progress are investigating electronic means of increasing adherence to inhalation therapies, but electronic interventions also raise a number of potential ethical questions related to patient privacy.⁶⁶ Furthermore, the real-world feasibility of shared decision-making, in which providers deliver a brief, 7-minute intervention during 1 regular office visit, is currently being explored. An assessment of the effects of this decision process on patient adherence to ICS therapy is one of the secondary outcomes being measured in this study.⁶⁷

In COPD, multifaceted interventions have been shown to have the greatest impact on improved medication adherence, although not all studies have shown a positive



Figure 2 Strategies for improving adherence to inhaled medications for asthma and COPD. A multifaceted care plan tailored to an individual patient can improve adherence and, ultimately, health outcomes.

Notes: Upper left image: iStock.com/Vesnaandjic. Upper right image reprinted from *The Lancet*, Vol. 3, No. 3, Chan AH, Stewart AV, Harrison J, Camargo CA, Black PN, Mitchell EA, The effect of an electronic monitoring device with audiovisual reminder function on adherence to inhaled corticosteroids and school attendance in children with asthma: a randomised controlled trial, p210-219, Copyright 2015, with permission from Elsevier.⁷⁰ Bottom left image: iStock.com/Steve Debenport. Bottom right image: iStock.com/DragonImages. Data from Tommelein et al⁵³ Wilson et al⁵⁹ and Chan et al.⁷⁰

Abbreviations: COPD, chronic obstructive pulmonary disease; HCP, health care provider.

effect.⁷ For example, pulmonary rehabilitation is a comprehensive intervention to promote long-term adherence to health-enhancing behaviors in patients with COPD, but the specific effects on medication adherence are not well studied.^{1,68} However, individually tailored care plans, educational sessions about the illness and inhaler technique, health care provider visits, and/or weekly phone calls do improve adherence.^{7,53,69} Figure 2 illustrates how these different types of interventions can fit together in a patient's overall care plan to improve medication adherence.

Conclusions

Although inhaled maintenance therapy is vital for many patients with asthma or COPD, suboptimal adherence is frequently an issue, and the underlying causes of it are multifactorial and complex. Suboptimal adherence is associated with negative consequences related to disease control, mortality, and health care resource use; it is, therefore, important to optimize each patient's therapy to improve adherence and maximize the therapeutic effects of prescribed medications. Therapy optimizations may include routine inhaler technique training or changing to a different type of inhaler that is easier for the patient to use

correctly. Shared decision-making allows for collaboration between patient and physician to develop a treatment plan that addresses barriers to adherence and fosters an environment that is favorable to patient education, communication, and counseling.

Abbreviation list

COPD, chronic obstructive pulmonary disease; GINA, Global Initiative for Asthma; GPS, global positioning system; ICS, inhaled corticosteroid; MARS-A, Medication Adherence Report Scale for Asthma; MIS-A, Medication Intake Survey-Asthma; MPR, medication possession ratio; OCS, oral corticosteroid.

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Author contributions

Both authors were involved in the analysis and interpretation of the literature search results. Both authors participated in the development and critical review of the manuscript, provided final approval to submit for publication, and agree to be accountable for all aspects of the work.

Disclosure

MG has served as a consultant for AstraZeneca and Teva. MG also reports personal fees from Teva and AstraZeneca, outside the submitted work. The authors report no other conflicts of interest in this work.

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