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Original Article

Personalized Medication Adherence Management in Asthma and Chronic Obstructive Pulmonary Disease: A Review of Effective Interventions and Development of a Practical Adherence Toolkit

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What is already known about this topic? Nonadherence management in asthma and chronic obstructive pulmonary disease remains challenging despite many existing interventions. The Test of Adherence to Inhalers (TAI) can identify reasons for nonadherence, but it does not provide health care professionals with practical advice regarding how to act.

What does this article add to our knowledge? This research reports on effective adherence-enhancing interventions and the development of the TAI Toolkit to select evidence-based interventions. The Toolkit was rated as useful by a multidisciplinary panel.

How does this study impact current management guidelines? This study provides an overview of effective interventions on medication adherence in asthma and chronic obstructive pulmonary disease. Furthermore, the created TAI toolkit provides practical guidance for health care professionals for how to act effectively upon identified barriers for nonadherence.

BACKGROUND: The management of medication nonadherence of patients with asthma or chronic obstructive pulmonary disease (COPD) remains challenging. Given the multitude of underlying causes, a personalized approach is required. The Test of Adherence to Inhalers (TAI) can identify reasons for nonadherence, but it does not provide guidance regarding how to act effectively after results.

OBJECTIVE: To develop a practical, evidence-based decision support toolkit for health care professionals managing adult patients with asthma and/or COPD, by matching TAI-identified adherence barriers to proven effective adherence-enhancing interventions.

METHODS: We performed a literature review in PubMed and Embase identifying interventions that enhanced medication adherence in adult patients with asthma and/or COPD. Randomized controlled trials published in English with full texts available were included. Effective interventions assessed by the Cochrane risk of bias tool were categorized, matched with specific TAI responses, and developed into a practical TAI Toolkit. The Toolkit was assessed for content and usability

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Abbreviations used
COPD- Chronic obstructive pulmonary disease
IRF- Inhaler reminders and feedback
PAD- Personalized adherence discussions
RCT- Randomized controlled trial
TAI- Test of Adherence to Inhalers
WHO- World Health Organization

(System Usability Scale) by a multidisciplinary group of health care professionals.
RESULTS: In total, 40 randomized controlled trials were included in the review. Seven effective interventions categories were identified, informing the TAI Toolkit: reminders, educational interventions, motivational strategies, feedback on medication use, shared decision-making, simplifying the medication regimen, and multiple component interventions. Health care professionals rated the TAI Toolkit with a mean System Usability Scale score of 71.4 (range, 57.5-80.0).
CONCLUSIONS: Adherence can be improved using the different interventions that the TAI Toolkit helps select. The TAI Toolkit was well-received by health care professionals. Further research is required to test its validity, practicality, and effectiveness in practice.
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Key words: *Asthma; Chronic obstructive pulmonary disease; Medication adherence; Inhaler; Compliance; Persistence*

INTRODUCTION

With adherence ranging from 22% to 78%, asthma and chronic obstructive pulmonary disease (COPD) medication adherence is the lowest for all medication groups.[1,2] Besides being related to poor symptom control and an increased number of exacerbations, poor adherence is associated with increased mortality, decreased quality of life, and increased direct and indirect costs.[1,3-7]

Medication adherence is defined by the World Health Organization (WHO) as "the degree to which use of medication by the patient corresponds with the prescribed regimen."[8] The WHO distinguishes three types of nonadherence: erratic, intelligent, and unwitting. Erratic (also called sporadic) nonadherence reflects forgetfulness, intelligent (or deliberate) nonadherence reflects a reasoned choice for not taking the medicine (eg, owing to fear of side effects), and unwitting (or unconscious) nonadherence reflects the failure to understand fully either the specifics of the regimen or the necessity for adherence.[8]

There is no typical nonadherent patient, because nonadherence is a complex and multifactorial problem.[9] Bourbeau and Bartlett[10] highlighted that medication, dosing regimen, patient factors, health care provider, and caregivers could all have a role. Most of these factors are modifiable and therefore can make the difference between adherence and nonadherence. Because there is so much diversity, there is no simple one-size-fits-all approach.

To manage nonadherence, the first step is to recognize and classify it. Yet for many years, no respiratory specific tool could easily identify the three WHO-defined phenotypes. In 2016, the Test of Adherence to Inhalers (TAI),[11] a questionnaire consisting of 10 patient-reported items and two health care professional reported items, was launched and validated. The TAI is increasingly translated in other languages and seems to be the first tool that can truly guide personalized adherence interventions. However, once completed, there is no guidance regarding how to act on each answer provided by the patient. To support health care professionals, there is the need for a toolkit that can efficiently match TAI-identified adherence barriers with effective interventions.

The objectives of this study were to identify effective medication adherence-enhancing interventions for adult patients with asthma or COPD and to use this information to develop a practical, evidence-based decision support toolkit for health care professionals to manage nonadherence.

METHODS

Study design

We searched the PubMed and Embase databases for articles published between 2003 and May 2020. We chose 2003 because the landmark WHO report about medication adherence,[8] which can be seen as the starting signal for the emergence of articles on the topic of adherence, was published that year. The current study is reported according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses reporting guidelines.[12]

Eligibility criteria

For inclusion, studies needed to meet the following criteria: (1) full text (ie, no abstracts), (2) English language, (3) randomized controlled trial (RCT), 4) adults with asthma and/or COPD, (5) medication adherence as the outcome (primary or secondary), (6) showing improvement in medication adherence, and 7) intervention led by health care professionals. No limits were set for sex or study setting (eg, clinical or community setting).

Search strategy

The search was performed with the use of key words and Medical Subject Headings of the National Library of Medicine. Search terms included "asthma," "chronic obstructive pulmonary disease/lung disease/COPD," "pulmonary/lung emphysema," "chronic bronchitis," "intervention," "strategy," "medication," "drug," "medicine," "medication adherence," "(non[-])adherence", "(non[-])compliance", "(non[-])concordance," and "(non[-])persistence." (The full PubMed and Embase search strategies are presented in Table E1 in this article's Online Repository at www.jaci-inpractice.org). The reference lists of all included articles, a previously published Cochrane review,[13] and the WHO report were manually searched to identify any additional relevant articles.[8]

Study selection

Articles identified by the search strategy were imported into Endnote X7 (Clarivate Analytic, Philadelphia, Pa). After duplicates were removed, all retrieved articles were assessed for relevance by J.E.P. Aarts using the Rayyan platform of the Qatar Computing Research Institute (QCRI, Qatar).[14] After screening on title and abstract, assessing full-text articles for eligibility, and adding articles identified from reference lists, two additional researchers (J.F.M. van Boven and S.J. van de Hei) checked the included articles for eligibility.

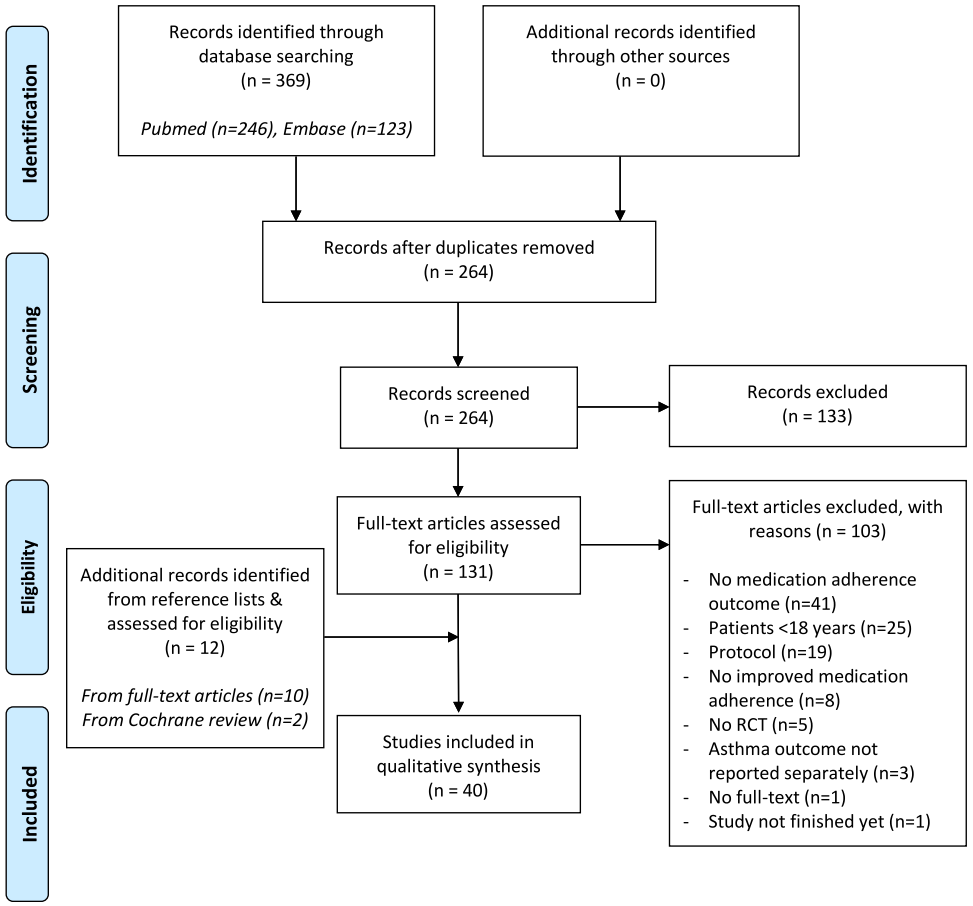

FIGURE 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram for study selection. *RCT,* randomized controlled trial.

Data extraction and quality assessment

The following data were extracted for each study: (1) first author, country, and year of publication; (2) sample size; (3) duration of the intervention and follow-up; (4) age of the study population; (5) setting; (6) intervention; (7) control; (8) method for measuring adherence; and (9) outcomes. The Cochrane Risk of Bias Tool was used as for quality assessment of the included studies.[15] The tool consists of six domains (selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias). For all included articles, the risk of bias was judged as low, unclear, or high risk (see Figure E1 and Table E2 in this article's Online Repository at www.jaci-inpractice.org). Finally, we assessed the overall level of evidence (high, medium, or low) based on the power of the study (powered on adherence or not) as well as the effect on adherence (between or within groups). Study data were first extracted and assessed by one researcher (J.E.P. Aarts) to maintain consistency throughout coding. Subsequently, data in included studies were validated by an independent second reviewer (S.J. van de Hei).

Development of adherence toolkit

All data were summarized and used to design a practical toolkit to support health care professionals selecting an effective adherence-enhancing intervention matching specific responses to the TAI (see Table E3 in this article's Online Repository at www.jaci-inpractice.org).

RESULTS

Study selection

The initial search yielded 369 studies, 105 of which were discarded as duplicates. After titles and abstracts were screened, 131 articles remained for full text review. Of these, 103 articles were excluded. Finally, 28 studies were included, with 12 additional studies identified through manual searching of reference lists, WHO reports, and Cochrane review (total n = 40). Two studies were identified as eligible from the reference lists, but were not included.[16,17] One study evaluated the same intervention in two separate studies; of those, we included one (the largest study with a longer follow-up).[16] Another study evaluated the same intervention: one study had a control group (which we included), and in the second study, the intensity of interventions was different between groups.[17] Figure 1 provides s Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of the process (Figure E1 and Table E2).

Overview of included studies

The 40 included articles (Tables I and II) all reported on intervention(s) that showed improvement in medication adherence in patients with asthma (n = 32) and/or COPD (n = 8). The sample size varied between 20 and 14,064 participants.[18,19] Medication adherence was the primary outcome in 16 studies[18,20-22,24,30,31,40,43,44,47-49,51,53,55] and the secondary

TABLE I. Study characteristics of included studies on patients with asthma*

Study (first author, country, year)	n (randomized)	Duration of study	Study population	Setting	Intervention	Control	Adherence measure	Outcomes (1: primary outcome; 2: secondary outcomes)	Level of evidence
Reminders									
Charles, New Zealand, 2007[18]	110	24 wk	Adolescents and adults, aged 12-65 y	Research clinical trials facility (recruited via research volunteer database, newspapers, and informal contacts)	Medication twice daily via a metered dose inhaler with covert adherence monitoring and audiovisual reminder function	No audiovisual reminder function	Electronic tracking device	1: Median adherence 93% vs 74% (difference 18%; $P < .0001$) 2: Ratio proportions adherent with >50%, 80%, or 90% of medication −1.33 (1.10-1.61) −2.27 (1.56-3.30) −3.25 (1.74-6.10) Proportion taking >80% at 24 wk: intervention 88.6% vs control 39.1%	High
Foster, Australia, 2014[19]	40 GPs, 143 patients	6 mo	Adolescents and adults, aged 14-65 y	General practice	Interventions (three times): 1. PAD led by a GP 2. IRF led by a GP 3. Both IRF and PAD	Usual care	Electronic tracking device plus self-reported Medication Adherence Report Scale	1: ACT: n.s. 2: Mean adherence: 46% (UC), 46% (PAD), 71% (IRF), 76% (IRF+PAD) ($P = .0003$). After 6 mo: 60% ± 38% (IRF and IRF+PAD) vs 29% ± 33% (UC and PAD). n severe exacerbations: n.s.	Medium
Strandbygaard, Denmark, 2010[20]	30	12 wk (start intervention at wk 4)	Adults, aged 18-45 y	Other (recruited by newspaper advertising)	Daily SMS reminder to take medication	No SMS reminder	Calculated from dose count on inhaler device and pharmacy data	1: Absolute difference in mean adherence rate 17.8% (3.2-32.3) ($P = .019$). Adherence rate at baseline: intervention 77.9% vs control 84.2%; at 12-wk follow-up: intervention 81.5% vs control 70.1%. 2: ACQ, mini-AQLQ, lung function: n.s.	Medium
Educational interventions									
Bender, United States, 2010[21]	50	10 wk	Adults aged 18-65 y	Tertiary care center/hospital	IVR telephone calls intervention	Usual care	Electronic tracking device or canister weight (when electronic tracking is unavailable)	1: Mean adherence: 64.5% IVR vs 49.1% control ($P = .0032$) 2: AQLQ n.s., ACT n.s.	High
Chatkin, Brazil, 2006[22]	271	3 mo	Adolescents and adults aged ≥12 y	Recruited by their own physician in their own clinical setting	Biweekly educational telephone calls led by specially trained nursing student	Usual care	Calculated from dose count on inhaler device	1: Proportion adherent patients (taking ≥85% of prescribed doses): intervention 74.3% vs control 51.9%; difference 43% ($P < .001$)	High
Côté, Canada, 1997[23]	188	12 mo	Adults aged ≥16 y	Tertiary care hospitals	Interventions: 1. Education with action plan based on peak-flow monitoring 2. Education with action plan based on monitoring of asthma symptoms	No formal education	Canister weight	†Asthma morbidity: n.s. Short-term adherence (1 mo): taking ≥60% of prescribed doses more in intervention than control ($P = .03$). Long-term adherence (3, 6, 9, and 12 mo): n.s.	Low
Ebrahimabadi, Iran, 2019[24]	85	1 mo	Adults aged 20-65 y	Hospital	Infographic: Education	Video education	Self-reported MMAS-8	1: Adherence score increased in both groups ($P < .05$). Difference in adherence score between intervention and control: n.s.	Low

Gallefoss, Norway, 1999[25]	140 (78 asthma, 62 COPD)	1 y	Asthma and COPD patients aged 18-70 y	Outpatient clinic at hospital	Educational intervention led by nurse and physiotherapist	Usual care by GP	Pharmacy data	†Proportion adherent asthma patients: intervention 57% vs control 32% ($P = .04$). Median adherence: intervention 82% vs control 55% (n.s.). COPD: n.s.	Medium
Goeman, Australia, 2013[26]	124	12 mo	Adults aged ≥55 y	Home or hospital	Face-to-face, person-centered education led by researcher	Brochure-only information	Electronic tracking device	1: Difference between groups in ACQ 0.3 ($P = .01$) 2: Change in adherence from baseline in intervention group: 19.3% (95% confidence interval, 6.9-31.6) Difference in adherence between groups n.s. AQOL ↑ Exacerbation: n.s.	Low
Poureslami, Canada, 2012[27]	92	9 mo	Adults aged ≥21 y	Pulmonary medicine clinic	Interventions: 1. Community educational video 2. Knowledge educational video 3. Both (community educational video and knowledge educational video)	Pictorial pamphlet	Self-reported adherence through questionnaire	†Adherence ("understanding physicians instructions on medication use") improved in all groups ($P < .01$), most in group 1 compared with other group ($P < .05$). Inhaler technique ↑	Low
Put, Belgium, 2003[28]	23	6 mo (last 3 mo follow-up)	Adults aged ≥18 and ≤65 y	Outpatient clinic at hospital	Individualized asthma program(psycho-education, behavioral and cognitive techniques)	Waiting list	Adherence scale	†Symptoms (ASC) ↓ McMaster AQLQ ↑ Adherence scale scores decreased significantly in intervention vs control ($P = .002$)	Medium
Schaffer, USA, 2004[29]	46	6 mo	Adults aged 18-65 y	Health science center campus	Interventions: 1. Audiotape alone: education 2. National Heart, Lung, and Blood Institute (NHLBI) booklet alone: Education 3. Audiotape and NHLBI booklet	Standard provider education	Self-reported plus pharmacy data	†Significant difference in pharmacy-verified adherence between group 2 and control ($P = .02$) and between group 3 and control ($P = .04$). Self-reported adherence: n.s., ACQ n.s., mini-AQLQ n.s.	Medium
Vollmer, United States, 2011[30]	14.064	18 mo	Adults aged ≥18 y	Home (contact by phone calls)	IVR; three types: refill reminder call, tardy refill call, and initiator/restart call	Usual care	Modified medication possession rate (based on pharmacy data)	1: Change in adherence 0.02 (95% confidence interval, 0.01-0.03; $P = .002$). Proportion of good adherers: n.s. 2: Asthma control n.s., mini-AQLQ n.s.	High
Windsor, United States, 1990[31]	267	12 mo	Adults aged ≥17 y	Pulmonary medicine clinic	Health education intervention led by health education specialist	Usual care	IAS plus MAS	1: Medication adherence from baseline to 6 mo: intervention 44% to 92% vs control 59% to 62% (95% confidence interval, 0.31-0.57) 2: Inhaler skills use ↑; inhaler adherence from baseline to 6 mo: intervention 20 to 58% vs control 28% to 29% (95% confidence interval, 0.24-0.50)	High

(continued)

TABLE I. *(Continued)*

Study (first author, country, year)	n (randomized)	Duration of study	Study population	Setting	Intervention	Control	Adherence measure	Outcomes (1: primary outcome; 2: secondary outcomes)	Level of evidence
Multiple component interventions									
Armour, Australia, 2007[32]	57 pharmacies/396 patients	6 mo	Adults aged 18-75 y	Pharmacies	Pharmacist asthma care program led by pharmacist	Usual care	Self-reported Brief Medication Questionnaire	1: Asthma control (change from severe to not severe): ↑ 2: Proportion adherent to preventer medication: odds ratio = 1.89 (95% confidence interval, 1.08-3.30). Improvement in risk of nonadherence ($P = .04$). Decrease in reliever medication use ($P = .03$). AQOL ↑, inhaler technique ↑	Medium
Garcia-Cárdenas, Spain, 2013[33]	65 pharmacies/373 patients	6 mo	Adults aged ≥18 y	Community pharmacies	Protocol-based pharmacist intervention led by pharmacist	Usual care	Self-reported four-item MMAS	1: Proportion controlled asthma patients: ↑ 2: Proportion adherent patients at baseline: intervention 38.2% vs control 39.3%; at 6 mo: intervention 78.5% vs control 52.0% ($P < .001$) Correct inhaler technique ↑	Medium
Manfrin, Italy, 2017[34]	283 pharmacies/ 1263 patients	9 mo	Adults aged ≥18 y	Community pharmacies	Medicines use review led by pharmacist. Interventions: 1. Intervention at baseline 2. Intervention at 3 mo	-	Self-reported using two questions from MMAS-8	1: ACT ↑ 2: Adherence improved by 35.4% 3 mo after intervention and 40.0% at 6 mo ($P < .01$)	Low
Mehuys, Belgium, 2008[35]	66 pharmacies/201 patients	6 mo	Adults aged 18-50 y	Community pharmacies	Protocol-defined pharmacist intervention led by pharmacist	Usual pharmacist care	Pharmacy data plus self-reported	1: ACT: n.s. (improvement in subgroup with insufficiently controlled asthma) 2: Adherence by prescription refill rates: intervention 90.3% vs control 74.6% ($P = .016$). Self-reported adherence n.s., AQLQ n.s., inhalation technique ↑	Medium
Wong, Malaysia, 2017[36]	171	6 mo	Adults aged ≥21 y	Government health hospitals and clinics	Pharmacy management service led by pharmacist	Usual pharmacy service	MAS	1: Proportion patients with well-controlled asthma ↑ 2: Proportion patients adherent at baseline: intervention 76.3% vs control 67.5%; at mo 6: intervention 92.5% vs control 45.5% ($P < .001$). Correct inhaler technique ↑	Medium
Bailey, United States, 1990[37]	267	1 y	Adults aged ≥18 y	Pulmonary medicine clinic/ hospital	Self-management program led by health educator	Usual care; only educational pamphlet	IAS plus MAS plus rating by project staff	1: Health use (emergency department visit or hospitalization): n.s. 2: Change in adherence between groups according to IAS ($P = .0001$) and MAS ($P = .0001$). Proportion adherent (IAS adherent on all six items, MAS adherent on all 6 items) at baseline: intervention 20.4%, 43.6% vs control 28.0%, 59.3%; at 12 mo: intervention 58.3%, 91.9% vs control 29.0%, 61.7%	Medium

Berg, United States, 1997[38]	55	8 wk (1 wk run-in, 6 wk intervention, 1 wk run-out)	Adults aged ≥18 y	Community	Self-management program led by registered nurses	Usual care	Self-reported plus electronic tracking device	†Change in adherence between groups according to electronic monitoring ($P < .05$). Self-reported adherence n.s. Total daily symptoms n.s.	Medium
Farag, Egypt, 2018[39]	20 pulmonologists/ 400 patients	6 mo	Adults aged >18 y	Hospital	Asthma action plan with peak flow meter and usual care led by pulmonologist	Usual care	Self-reported MMAS	1: Asthma attacks: mild n.s, severe higher in control group ($P < .05$) 2: Proportion of patients with high and medium adherence was higher in intervention than control ($P < .05$), low adherence was higher in control ($P < .05$)	Medium
Janson, United States, 2009[40]	84	24 wk (4 wk run-in, 4 wk intervention, 14 wk observation)	Adults aged 18-55 y	Private and public community clinics	Individualized self-management educational intervention led by trained advanced practice nurse and respiratory therapist	Usual care with self-monitoring alone	Electronic tracking device	1: Mean and median adherence: n.s. 2: Maintaining >60% adherence odds ratio = 9.2 intervention vs 0.4 control ($P = .02$). Perceived control of asthma ↑, quality of life n,s	Medium
Olivera, Brazil, 2016[41]	119	4 mo	Adults aged 18-73 y	Outpatient clinic at hospital	Self-management model/ meetings led by pharmacist	Usual care	Self-reported MGLS plus pharmacy data	1: Knowledge ↑ 2: Dispensed medication increased in intervention group over time ($P = .0113$), no comparison between groups. Proportion adherent patients increased within both groups ($P = .0244$), between-group difference unclear. Inhaler technique ↑, quality of life ↑	Low
Young, United States, 2012[42]	98	6 mo (intervention in first 3 mo)	Adults aged ≥19 y	Health center	Telephone consultations by pharmacist	Usual care (mail receipt of prescription refill)	Eight-item MMAS	Pilot study †Asthma control n.s. Proportion patients with low adherence: n.s. ($P = .07$). Within group-analyses: Asthma control intervention group ↑. Proportion patients with low adherence intervention group (26% follow-up vs 58% baseline; $P < .01$)	Low
Motivational strategies									
Gamble, Ireland, 2011[43]	20	12 mo (intervention in first 12 wk)	Adults aged ≥18 y	Specialist difficult asthma service	Individualized psycho-educational intervention led by experienced respiratory nurse	Usual care	Refill records (GP prescription records)	1: % inhaled combination therapy inhalers filled: intervention 37.6% to 61.9% vs control 31.7% to 28.8% ($P < .01$). 2: Asthma control score n.s. AQLQ n.s.	Medium
Petrie, New Zealand, 2012[44]	147	9 mo (intervention in first 18 wk)	Adolescents and adults, aged 16-45 y	Home (contact by phone calls)	Text message program; individually tailored text messages based on illness and medication beliefs	No text messages	Self-reported	1: Group effect ($P = .003$) and group by time effect ($P < .05$). Average adherence 43.2% control vs 57.8% intervention ($P = .003$). Proportions participants with average adherence of ≥80% 10.6% control vs 25.9% intervention ($P = .034$)	High

(continued)

TABLE I. *(Continued)*

Study (first author, country, year)	n (randomized)	Duration of study	Study population	Setting	Intervention	Control	Adherence measure	Outcomes (1: primary outcome; 2: secondary outcomes)	Level of evidence
Schmaling, United States, 2001[45]	27	2 wk	Adults aged 18-60 y	Chest clinics at hospital	Education intervention and motivational interviewing	Educational intervention	Decisional Balance Questionnaire	†Level of readiness to adhere to medication as prescribed higher intervention compared with control ($P < .05$). Inhaler technique n.s. between groups	Low
Shared decision-making									
Wilson, United States, 2010[46]	612	12 mo	Adults aged 18-70 y	Center for health research	Intervention (two times): 1. Shared decision-making (SDM) 2. Clinician decision-making (CDM)	Usual care	Pharmacy data	†SDM vs UC, 1-y follow-up: Controller adherence 0.67 vs 0.46 ($P < .0001$) LABA adherence 0.51 vs 0.40 ($P = .0225$) Canister equivalent 10.9 vs 5.2 ($P < .0001$) Mini-AQLQ ↑, asthma control ↑ SDM vs CDM, 1-y follow-up: Controller adherence 0.67 vs 0.59 ($P = .029$) LABA adherence 0.51 vs 0.41 ($P = .0143$) Canister equivalent 10.9 vs 9.1 ($P = .005$) Mini-AQLQ n.s., asthma control n.s.	Medium
Simplifying medication regimen									
Price, United Kingdom, 2010[47]	1233	12 wk	Adolescents and adults aged ≥12 y	Clinic center	Interventions: 1. Medication once daily in evening 2. Medication twice daily	—	Electronic tracking device plus self-reported	1: Mean adherence group 1 93.3% vs group 2 89.5% ($P < .001$). Self-reported mean adherence group 1 97.2% vs group 2 95.3% ($P < .001$). 2: Health-related quality of life, n.s.	High
Feedback on medication use									
Onyirimba, United States, 2003[48]	30	10 wk (intervention in first 3 wk)	No age in/exclusion criteria	Hospital and medical center	Direct clinician-to-patient feedback discussion on medication use from clinician	Standard asthma care	Electronic tracking device	1: Adherence rates at baseline: intervention 61% vs control 51%. Significant difference in adherence between groups starting at wk 2 until end (10 wk) ($P < .0001$); 2: AQLQ n.s.	Medium
Sulaiman, Ireland, 2018[49]	218	3 mo	Adults aged ≥18 y	Specialist asthma clinics	Intensive education plus (bio)feedback-guided training led by nurse	Intensive education	Electronic tracking device	1: Adherence rate at baseline: intervention 63% vs control 67%; in third mo: intervention 73% vs 63% in control ($P < .01$). Significant change in adherence from mo 1 to mo 3 ($P = .02$)	High

↑/↓, significant improved/deteriorated; *ACQ*, Asthma Control Questionnaire; *ACT*, Asthma Control Test; *AQLQ*, Asthma Quality of Life Questionnaire; *AQOL*, Asthma Quality of Life; *ASC*, Asthma Symptom Checklist; *COPD*, Chronic Obstructive Pulmonary Disease; *GP*, general practitioner; *IAS*, Inhaler Adherence Scale; *IRF*, inhaler reminders and feedback; *IVR*, automatic interactive voice response; *LABA*, long-acting β-agonist; *MAS*, Medication Adherence Scale; *MGLS*, Morisky Green Levine Medication Adherence Scale; *MMAS*, Morisky Medication Adherence Scale; *n.s.*, not significant; *PAD*, personalized adherence discussion; *SMS*, short message service.

*All primary outcomes are described. Secondary outcomes described are quality of life, disease control, exacerbations, and inhaler technique.

†No sample size calculation was available, or the primary and secondary outcomes were not described.

TABLE II. Study characteristics of included studies in patients with chronic obstructive pulmonary disease (COPD)*

Study (first author, country, year)	n (randomized)	Duration of study	Study population	Setting	Intervention	Control	Adherence measure	Outcomes (1: primary outcome; 2: secondary outcomes)	Level of evidence
Reminders									
Gregoriano, Switzerland, 2019[50]	169	6 mo	Asthma and COPD. No age inclusion or exclusion-criteria	Home	Audio reminder or daily alarm clock and support phone calls led by pharmacist or nurse	Usual care	Electronic tracking device	1: Time to first exacerbation: n.s. 2: Frequency of exacerbation: n.s. Days with 80% to 100% taking adherence: −Puff inhalers: intervention 81.6% vs control 60.1% ($P <$ .001) −Dry powder: intervention 89.6% vs control 80.2% ($P =$ .01) Timing adherence (% days with correct dosing interval) in participants using puff inhalers: intervention 68.9% vs control 50.6% ($P <$ .001) and in participants using dry powder capsules: intervention 79.6% vs control 71.7% ($P =$ .052). Quality of life: n.s	Medium
Educational interventions									
Abdulsalim, India, 2018[51]	260	24 mo	Adults	Hospital	Pharmacist-led educational intervention program led by clinical pharmacist	Usual care	Self-reported MAQ	1: Proportions of patients with high, moderate, and low adherence at 6, 12, 18, and 24 mo between groups ($P <$ .001). Proportion high adherent (MAQ score 3-4) at baseline: intervention 48.5% vs control 47.7%; at 24 mo: intervention 80.8% vs control 49.0%	High
Multiple component interventions									
Jarab, Jordan, 2012[52]	133	6 mo	Adults aged >35 y	Outpatient clinic at hospital	Pharmaceutical care program led by clinical pharmacist	Usual care	Self-reported MMAS	1: Health-related quality of life: n.s. 2: Proportion nonadherent patients at baseline: intervention 63.6% vs control 59.7%; at 6 mo: intervention 28.6% vs. control 48.8% ($P <$ .05). Hospital admission for exacerbation ↓	Medium
Tommelein, Belgium, 2014[53]	170 pharmacies/734 patients	3 mo	Adults aged ≥50 y	Community pharmacies	Protocol-defined pharmaceutical care program led by pharmacist	Usual pharmacist care	Pharmacy data	1: Difference in medication adherence 8.51% (95% confidence interval, 4.63-12.4; $P <$ .0001). Inhalation technique ↑ 2: Hospitalization rate ↓ CAT n.s.	High

(continued)

TABLE II. *(Continued)*

Study (first author, country, year)	n (randomized)	Duration of study	Study population	Setting	Intervention	Control	Adherence measure	Outcomes (1: primary outcome; 2: secondary outcomes)	Level of evidence
Khdour, Northern Ireland, 2009[54]	173	12 mo	Adults aged >45 y	Outpatient clinic at hospital	Clinical pharmacy-led disease and medicine (self) management program led by clinical pharmacist	Usual care	Self-reported MMAS	1: Hospital admission ↓, emergency department visits ↓, SGRQ: symptom ↓, impact ↓, physical activity n.s. 2: Adherence: intervention 77.8% vs control 60.0% ($P = .019$)	Medium
Leiva-Fernández, Spain, 2014[55]	146	12 mo	No age inclusion/exclusion criteria	Primary care center	Multifactorial intervention; motivational and cognitive aspects, and skills development led by two professionals	Usual care	Dose or pill count	1: Adherence at baseline: intervention 40.3% vs control 41.9%; at 12 mo: intervention 48.6% vs control 32.4% ($P = .046$)	High
Song, Korea, 2014[56]	46	2 mo	Adults aged 65-75 y	Hospital	Self-care support intervention using motivational interviewing by two nurse interventionists	Usual care	Self-reported through structured questionnaire	†Self-care adherence scores of medication difference after 2 mo between groups ($t = -2.946$; $P = .047$) SGRQ scores for symptom, activity, impact and total ↓	Medium
Feedback on medication use									
Nides, United States, 1993[57]	251	4 mo	Adults, aged 35-60 y	University centers	Detailed feedback on metered-dose inhaler use patterns using electronic medication monitor (Nebulizer Chronolog)	No specific feedback	Self-reported plus canister weight or electronic tracking device	†Mean sets per day (three prescribed): 1.95 ± 0.68 vs 1.63 ± 0.82 ($P = .003$) Mean percent adherent days 60.2% vs 40.4% ($P < .0001$) Mean percent total actuations taken as prescribed 88.8% vs 68.8% ($P < .0001$)	Medium

↑/↓, significant improved/deteriorated; *CAT*, COPD Assessment Test; *MAQ*, Medication Adherence Questionnaire; *MMAS*, Morisky Medication Adherence Scale; *n.s.*, not significant; *SGRQ*, Saint George's Respiratory Questionnaire.
*All primary outcomes are described. Secondary outcomes described are quality of life, disease control, exacerbations, and inhaler technique.
†No sample size calculation was available or primary and secondary outcomes are not described.

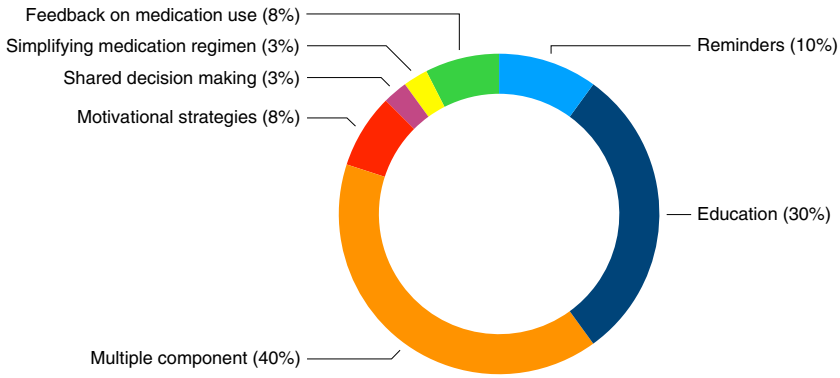

FIGURE 2. Type of adherence enhancing interventions identified (total n = 40).

outcome in 12 studies.[19,26,32-37,39,50,52,54] In 12 studies, there was no specified outcome.[23,25,27-29,38,41,42,45,46,56,57] Follow-up varied from 1 to 24 months,[24,51] in which 6 months was the most common.

Medication adherence was measured by self-report,[29,35,38,44,47,57] validated questionnaires or scales,[19,24,27,28,31-34,36,37,39,41,42,45,51,52,54,56] pharmacy or prescription data,[20,25,29,30,35,41,43,46,53] dose or pill counts,[20,22,55] electronic monitoring,[18,19,21,26,38,40,47-50,57] canister weighing,[21,23,57] and staff ratings.[37] Some studies had more than one medication adherence measure.

Interventions could be classified into seven categories (Figure 2): (1) reminders,[19,20,50,53] (2) educational interventions,[21-31,55] (3) multiple component intervention (eg, pharmacy care and self-management),[32-42,45,52,53,55,56] (4) motivational strategies,[43,45,47] (5) shared decision-making,[46] (6) simplifying the medication regimen,[47] and (7) feedback on medication use.[48,49,57]

Reminders

Four studies examined the impact of reminders on medication adherence.[18-20,50] Three studies were conducted on patients with asthma, and one was on patients with COPD and/or asthma. Charles et al[18] evaluated the effectiveness of a metered dose inhaler with an audiovisual reminder function in asthma patients. The audiovisual reminder device, which is attached to the inhaler, has the ability to emit both audio and visual reminders at predesigned times. In total, 110 patients with asthma were randomized to either the intervention or control group for 24 weeks. The proportion of medication taken in the last 12 weeks of the study was higher in the intervention group (93%) compared with the control group (74%), with a significant difference of 18% ($P < .0001$). Furthermore, the proportion of patients who were taking greater than 50%, greater than 80%, or greater than 90% of the medication was significantly higher in the reminder group. The second study, by Foster et al,[19] examined the effectiveness of two interventions (inhaler reminders and feedback [IRF] and/or personalized adherence discussions [PADs] about barrier[s], goal setting, and goal achievement strategies) compared with usual care. The 143 patients were divided into four groups: IRF, PAD, IRF and PAD and usual care for 6 months. At 6 months, medication adherence was significantly higher in the IRF groups compared with the non-IRF groups (73% vs 43%; $P < .0001$). Strandbygaard et al[20] examined the effectiveness of daily text reminders for medication adherence. In total, 26 adult patients were randomized to an intervention period of 8 weeks. After 12 weeks, the absolute difference in mean adherence rate between groups was 17.8% ($P = .019$). The 6-month study of Gregoriano et al[50] randomized 169 asthma or COPD patients to either acoustic smartphone reminders and support phone calls or usual care. The reminder was always used, whereas support phone calls were employed only when medication was used incorrectly for more than 2 consecutive days. The intervention group had significantly more days, in which 80% to 100% of patients were adherent (pressurized metered dose inhaler: 82% vs 60%, $P < .001$; dry powder inhaler: 90% vs 80%, $P = .01$) and had better timing adherence (ie, correct dosing intervals).

Education

Eleven studies evaluated the impact of education on medication adherence in asthma; one study focused on COPD.[21-31,51] Educational interventions were frequently described, but often in insufficient detail and combined with other types of interventions (ie, multiple component intervention). Therefore, we chose to describe the effects of successful education in general rather than at the study level. Education was given by telephone calls,[21,22,30,31] face-to-face sessions,[23,25,26,28,31,51] written information (book, brochure, or infographic),[23-25,29] audiotape,[29] and video.[24,27] Some studies combined these formats. Educational subjects were pathophysiology, triggers and symptoms, the role of medication, importance of adherence, side effects, and rescue medication instructions. Details regarding exact content were frequently missing. The duration of education ranged from 30 minutes to 24 months.

Multiple component intervention

Multiple component interventions were examined in 16 studies (asthma: n = 11; COPD: n = 5).[19,32-40,42,46,52-56] There were two subtypes of multiple component interventions: (1) pharmacy care interventions, which were led by pharmacists and focus on medication (eg, education and counseling, review and correct inhaler technique including physical demonstration, motivational interviewing on drug-related problems, attitudes regarding medication and adherence, and shared decision-making); and (2) self-management interventions, which were led by different types of health care professionals educators and researchers, and focus on self-management (eg, education and counseling, review and correct inhaler technique, motivational

interviewing (exercise and smoking), and self-management of stress, triggers, and attacks). These interventions consisted of multiple components, which makes it difficult to determine which component had most impact on medication adherence.

Motivational strategies

Three studies evaluated the impact of motivational strategies on medication adherence in asthma patients.[43-45] Gamble et al[43] investigated psycho-education (based on motivational interviewing) covering self-motivation and resolving ambivalence toward taking medication. In total, 20 adults were randomized to either the intervention (eight visits in 12 weeks) or the control group (usual care). At 6 months, medication adherence improved (intervention: 37.6% to 61.9% vs control: 31.7% to 28.8%; $P <$ .01). In the second study, 27 adults were randomized to either motivational interviewing and education or education only. The study examined the effectiveness of motivational interviewing on attitudes about medication adherence.[45] Motivational interviewing consisted of one 30- to 60-minute session and covered an assessment of the patient's readiness to use medication, personalized feedback about current pulmonary function, a discussion about the patient's thoughts about received feedback, and specific intervention strategies matched to the patient's readiness to change. One week after the intervention, the level of readiness to adhere over time was stable or increased in the intervention group and the attitude toward taking medication over time was higher. One study used a text message program that sent predefined tailored text messages to counteract illness and medication beliefs supporting nonadherence. In that study, Petrie et al[44] randomized 147 patients to either intervention or control (no tailored text messages). At 6, 12, and 18 weeks, and at 6 and 9 months, medication adherence was significantly higher in the intervention group compared with the control group, with a relative average increase in adherence of 10% ($P <$ .001).

Shared decision-making

One study examined the effectiveness of shared and clinician decision-making on medication adherence and clinical outcomes in patients with asthma.[46] In shared decision-making, the beliefs and preferences of the patient are considered when making a treatment decision, whereas in clinician decision-making those beliefs and preferences are not taken into account. Patients (n = 612) were randomized into three groups: shared decision-making, clinical decision-making, and usual care. After 12 months, medication adherence was significantly higher in the shared decision-making group compared with the clinical decision-making group (67% vs 59%; $P = .03$) and the control group (67% vs 46%, $P = .0001$).

Simplifying medication regimen

A study[47] evaluated the impact of medication administration once daily instead of twice daily on medication adherence in patients with asthma. For 12 weeks, 1233 patients were randomized to receive mometasone furoate 400 μg once daily or mometasone furoate 200 μg twice daily. The mean adherence rate was significantly higher in the once-daily group compared with the twice-daily group (93.3% vs 89.5%; $P <$ .001).

Feedback on medication use

Three studies evaluated feedback on medication use (asthma: n = 2; COPD: n = 1).[48,49,57] Nides et al[57] used the Nebulizer Chronolog, a microprocessor device that records the exact date and time of each inhalation, to monitor metered-dose inhaler use electronically for 4 months in 251 COPD patients. The intervention group received detailed feedback at the end of weeks 1 and 7 to discuss inhaler use, whereas the control group did not receive feedback. After 4 months, adherence was higher in the intervention group compared with the control group (mean puffs per day: 1.95 vs 1.63; $P = .003$). The second study, by Onyirimba et al,[48] randomized 30 asthma patients to the intervention group (direct clinician-to-patient feedback discussion) or the control group (usual care) for 3 weeks. Between-treatment adherence rates were comparable at week 1 but were significantly higher in the intervention group compared with the control group starting at week 2 (81% vs. 47%; $P = .003$). A significant group difference (favoring the intervention group) existed in adherence rates over the course of the study period of 10 weeks ($P < .0001$). Finally, Sulaiman et al[49] examined the effectiveness of feedback on inhaler technique and medication adherence. The feedback consisted of visual feedback training based on records on the electronic monitor. In total, 218 patients were randomized to the intervention (with feedback) or control group (without feedback) for a study period of 3 months. Mean adherence in the last month was significantly higher in the intervention group compared with the control group (73% vs 63%; $P = .02$).

Test of Adherence to Inhalers Toolkit

We integrated all effective adherence-enhancing strategies as identified in this review into a toolkit that provides recommendations for each TAI answer (Figure 3). The toolkit can guide health care professionals to effective interventions based on the main behavioral phenotype level (sporadic, deliberate, and unconscious nonadherence) and the individual question level (TAI questions 1-12) (see Table E3 in this article's Online Repository at www.jaci-inpractice.org for a description of the development of the TAI Toolkit). The Toolkit consists of a wheel that can be used digitally or printed on paper. The wheel is accompanied by a user guide with further elaboration on the practical application of the interventions and the strength of underlying evidence (see Table E4 in this article's Online Repository at www.jaci-inpractice.org). The first prototype of the Toolkit was assessed by a panel of eight health care professionals (physicians, nurses, and pharmacists) on usability (System Usability Scale),[58,59] feasibility, and practical implications. The median System Usability Scale score was 71.4 (range, 57.5-80.0) (see Figures E2 and E3 and Table E5 in this article's Online Repository at www.jaci-inpractice.org). Their feedback was integrated into the final version (Figure 3).

DISCUSSION

Main findings

In this review, we identified multiple medication adherence-enhancing interventions for adults with asthma and/or COPD. The studies included seven different types of interventions; the most commonly reported ones were educational and multiple component interventions. Other effective intervention types were reminders, motivational strategies, shared decision-making, simplifying the medication regimen, and feedback on medication use. The effective adherence-enhancing interventions were integrated into a practical, evidence-based toolkit.

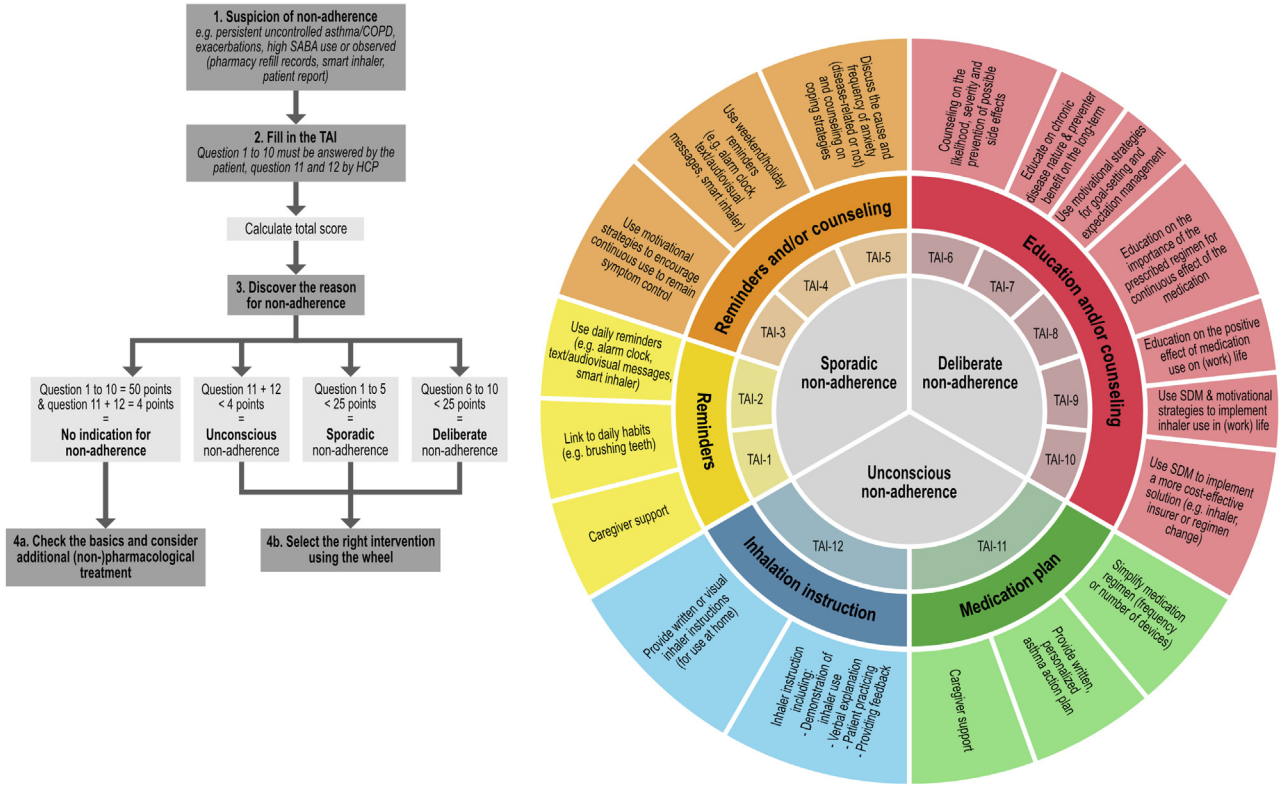

FIGURE 3. The Test of Adherence to Inhalers (TAI) toolkit. A full description of how to use the TAI toolkit can be found in Table E4. *HCP,* health care professional; *SDM*, shared decision-making.

Interpretation

We identified 40 RCTs evaluating interventions that could enhance medication adherence; of those, seven different types of interventions could be distinguished that allow further personalization of adherence management. However, their content, relationship to clinical outcomes, and methodologic quality were all variable. Power calculations and randomization methods were often not reported. Furthermore, it was difficult to compare studies because of the heterogeneity in settings and adherence measures applied. These findings regarding effectiveness and shortcomings were also identified in most previous reviews on adherence interventions in adults and children with asthma/COPD.[13,60-62] Indeed, a Cochrane review also pointed out inconsistent effects on clinical outcomes of adherence-enhancing interventions.[13] Potential reasons for this discrepancy may be the short follow-up of interventions (median, 6 months), the lack of selection of patients with room for clinical improvement, and the inaccurate adherence measures that were used. Especially in asthma, owing to its variable nature and the adaptation of medication use to symptom frequency, it has been difficult to show the direct relation of adherence to outcomes.[63]

Because we aimed to inform the Toolkit with effective interventions regarding adherence, studies that showed no improvement in medication adherence were excluded from this review. During study selection, eight studies were excluded for this reason. This is a small part of all studies in our literature search, which could be a consequence of publication bias. Another explanation could be the small number of patients included in some of these studies.

Although it was difficult to compare studies directly, a general observation was that medication adherence in these RCTs was often much higher than in real-world settings.[7] For example, the study by Price et al[47] indicated an adherence rate of 89.5% in the control group at 12 weeks' follow-up. This is higher than adherence rates found in many observational studies using pharmacy refills.[64] Several factors could explain this, such as information bias (blinding was often not possible) and selection bias (motivated patients are willing to take part in studies). Moreover, not every patient has to be fully adherent (100%) for optimal clinical outcomes. For some patients, lower adherence may result in appropriate disease control. Further optimization of adherence is required only in case of disease deterioration.

Regarding the use of toolkits to manage adherence, we could identify no toolkit specifically designed to personalize nonadherence management in adults with asthma and/or COPD. In other fields such as diabetes, however, toolkits have been developed and studies evaluating those seem to be effective.[65] Regarding the TAI specifically, most previous studies using the TAI were observational.[11,66] We chose the TAI as the adherence measure tool for this study because it is the only respiratory-specific tool that identifies reasons for nonadherence, which can be linked to the three WHO-defined phenotypes. The TAI is a validated tool with a Cronbach α of 0.860 and a test-retest reliability of 0.883. Furthermore, the TAI scores correlated

with electronically monitored adherence ($\rho = 0.293$; $p = .01$).[11] The first evidence regarding the use of the TAI to guide interventions seems promising, highlighting the practical value of an evidence-based toolkit.[67]

Strengths and limitations

This review provides an overview of all effective interventions on medication adherence in adults with asthma and COPD and summarize them into a practical, evidence-based toolkit, thus fulfilling a long-standing need as identified by the WHO.[8] Several tools exist to identify nonadherence or reasons for nonadherence in patients with asthma or COPD,[11,68-71] yet none of those provide advice regarding interventions a health care provider could actually apply to enhance medication adherence. To our knowledge, this is the first evidence-based toolkit that can provide tailored interventions to nonadherent patients with asthma and COPD. The Toolkit allows health care professionals to manage nonadherence in an efficient, personalized, yet protocol-based manner.

Some limitations should also be noted. Our review of effective interventions was limited to RCTs. As such, other useful interventions, not yet tested in RCTs, or not possible to test in RCTs, may have been excluded. Examples of such potentially effective interventions are caregiver support and removing financial barriers.[72,73] Another limitation was the partial description of most educational and multiple component interventions. This made it difficult to describe the exact content of those interventions and which parts were effective.

Implications and recommendations

Assessment and management of medication adherence are advised in many national and international asthma and COPD guidelines.[74,75] However, health care professionals generally have little time to identify nonadherence, discover the reasons for it, and provide the right interventions all in one consultation. The TAI Toolkit may help health care professionals to select the right evidence-based intervention efficiently for the right patient. The Toolkit could create more awareness about the topic of nonadherence, and could potentially be time-saving; yet optimal implementation of the TAI Toolkit in practice, including its usability, feasibility, and validity, needs to be assessed in future studies. Moreover, practical barriers, such as integration into current clinical workflows and consultations, need to be evaluated. The Toolkit is designed to be a dynamic tool that can be periodically updated when novel evidence emerges. Also, specific training and/or tools may be required to deliver each recommended intervention properly. Finally, further personalization of the TAI Toolkit will be required for populations with poorer healthy literacy, because this has been shown to be an important driver of suboptimal medication adherence.[76] This may include the use of intuitive graphical information.[77]

Regarding novel evidence on adherence management, we recommend future studies to employ objective and uniform adherence measures, to allow better comparison of study outcomes. Also, because little is known about the long-term effects of adherence interventions, longer follow-up is recommended.

CONCLUSION

This review provides an overview of interventions that can enhance medication adherence in adult patients with asthma and/or COPD. Effective interventions were integrated into the practical TAI Toolkit, which can help health care professionals personalize adherence management by efficiently selecting the right adherence enhancing invention for the right patient.

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