Methods to assess COPD medications adherence in healthcare databases: a systematic review

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Shareable abstract (@ERSpublications)
Methods to assess adherence to COPD medication in healthcare databases are presented. More attention should be paid to the impact of inpatient stays, drug substitution, dose switching and early medication refills on adherence assessment. https://bit.ly/3q9b1VR

Cite this article as: Vauterin D, Van Vaerenbergh F, Vanoverschelde A, *et al*. Methods to assess COPD medications adherence in healthcare databases: a systematic review. *Eur Respir Rev* 2023; 32: 230103 [DOI: 10.1183/16000617.0103-2023].

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Received: 30 May 2023
Accepted: 20 July 2023

Abstract

Background: The Global Initiative for Chronic Obstructive Lung Disease 2023 report recommends medication adherence assessment in COPD as an action item. Healthcare databases provide opportunities for objective assessments; however, multiple methods exist. We aimed to systematically review the literature to describe existing methods to assess adherence in COPD in healthcare databases and to evaluate the reporting of influencing variables.

Method: We searched MEDLINE, Web of Science and Embase for peer-reviewed articles evaluating adherence to COPD medication in electronic databases, written in English, published up to 11 October 2022 (PROSPERO identifier CRD42022363449). Two reviewers independently conducted screening for inclusion and performed data extraction. Methods to assess initiation (dispensing of medication after prescribing), implementation (extent of use over a specific time period) and/or persistence (time from initiation to discontinuation) were listed descriptively. Each included study was evaluated for reporting variables with an impact on adherence assessment: inpatient stays, drug substitution, dose switching and early refills.

Results: 160 studies were included, of which four assessed initiation, 135 implementation and 45 persistence. Overall, one method was used to measure initiation, 43 methods for implementation and seven methods for persistence. Most of the included implementation studies reported medication possession ratio, proportion of days covered and/or an alteration of these methods. Only 11% of the included studies mentioned the potential impact of the evaluated variables.

Conclusion: Variations in adherence assessment methods are common. Attention to transparency, reporting of variables with an impact on adherence assessment and rationale for choosing an adherence cut-off or treatment gap is recommended.

Introduction

COPD is the third leading cause of death worldwide [1]. Pharmacological treatment is the cornerstone in COPD to reduce symptoms, exacerbation frequency and severity [2]. Nonadherence to maintenance treatment is associated with poor symptom control and an increased risk of exacerbations, healthcare costs and mortality [2]. The 2023 Global Initiative for Chronic Obstructive Lung Disease (GOLD) report highlights the importance of adherence as an essential aspect to optimise the benefits of drug therapy [2]. Electronic healthcare databases are a valuable resource to study adherence in a real-life setting, as they are easy to use, objective, inexpensive and relevant to evaluate clinical outcomes related to poor adherence [3–5].

To obtain a more complete picture of adherence, it is suggested to combine different measurement methods to assess adherence [6]. Transparency in the methods used to assess adherence is not only important for comparison of study results [4, 5], it is of the utmost importance, as small changes in the formula of the method can bias adherence assessment [7–10]. Furthermore, the need for standard definitions and attention to factors that may affect the calculation of adherence, such as inpatient stays and treatment adjustments, are advised by several standardisation initiatives, checklists and good practice recommendations for reporting of adherence research [4, 5, 7, 9, 11–13]. In the context of COPD, taking inpatient stays into account when assessing adherence is important as hospitalisations and readmissions are possible consequences of COPD exacerbations. COPD patients are hospitalised on average 0.09–2.4 times per year with 55% requiring readmission [14, 15]. In addition, therapeutic drug substitutions (medication switches such as augmentation (therapy escalation)) and dose switches are regular adjustments in the COPD management cycle [16, 17].

To the best of our knowledge, an overview of the methods applied to assess adherence to COPD medications in healthcare databases and an evaluation of reporting variables influencing adherence estimation are lacking. Therefore, we aimed to systematically review the literature to describe different methods used in these data sources. Secondly, we aimed to evaluate the reporting of inpatient stays, early refills, drug substitutions and dose switches.

Methods

This systematic review was reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 guidelines [18] and the Synthesis Without Meta-Analysis guideline [19]. The protocol of this study was registered on PROSPERO [20] (registration number CRD42022363449).

Definition of adherence concepts

The main intervention evaluated in this systematic review was the assessment of medication adherence in electronic healthcare databases (such as electronic healthcare records, pharmacy databases and claims databases). While undertaking this review, medication adherence was considered based on the Ascertaining Barriers to Compliance (ABC) taxonomy for medication adherence as presented by Vrijens and co-workers [21, 22]. To translate these adherence concepts into healthcare databases, initiation was defined as the dispensing of medication in a pre-defined period of time after prescribing. Implementation was defined as the extent to which a patient uses medication as recommended (taking into account the dosing regimen) over a specific period of time. Persistence was defined as the time from initiation to discontinuation of the therapy. The assessment of treatment discontinuation was integrated into the assessment of persistence.

Literature search and search strategy

An extensive search was conducted in three biomedical databases (MEDLINE using the PubMed interface, Web of Science and Embase using the Embase.com interface) with search terms that built on the following concepts: COPD, (medication) adherence and electronic healthcare database(s). A detailed description of the search strategy is available in the supplementary material, appendix 1. The search was performed on 10 October 2022. Reference lists and citations of the included studies and grey literature on adherence in COPD patients were searched manually to identify other relevant articles.

Study inclusion criteria

Studies were eligible for inclusion in the systematic review if they were written in English. No restriction on publication date was applied. Both observational studies and experimental studies were included. We selected studies on COPD and/or asthma–COPD overlap patients, with exclusion of study populations where only children were included. Inclusion of patients in the original studies might have been based on self-reported diagnosis, physician diagnosis, lung function testing (spirometry) or identification in an electronic healthcare database based on diagnosis codes (*e.g.* International Classification of Diseases codes) for COPD, medical records or the use of COPD-related medications. Only studies reporting the assessment of medication adherence (as initiation, implementation and/or persistence) of COPD maintenance medication (Anatomical Therapeutic Chemical (ATC) R03, exclusion of studies focusing on short-acting bronchodilators only) and specifying the evaluation method for assessment were included. Studies evaluating adherence to guidelines (*e.g.* agreement between prescription data and GOLD report) or to nonpharmacological interventions (*e.g.* pulmonary rehabilitation) were excluded. If the study did not determine medication adherence based on objective data from electronic healthcare databases, they were classified as ineligible (*e.g.* studies reporting the assessment of medication adherence based on patient-reported assessment (questionnaires) or based on the use of smart inhaler devices or smart nebulisers). Research reporting discontinuation only as a criterion to censor or to determine the end of

follow-up was judged to be outside the scope of this systematic review. A full overview of the inclusion and exclusion criteria can be found in the supplementary material, appendix 1.

Study selection

Two reviewers (D. Vauterin and F. Van Vaerenbergh) performed an independent screening of the title and abstract followed by full-text evaluation, using Rayyan software [23]. Disagreements in study selection were resolved by a consensus meeting with a senior researcher (L. Lahousse). Reviewers were blinded to each other's decisions, both for the first screening and the second screening. Cohen's κ coefficient [24] was calculated to determine the inter-rater reliability.

Quality assessment

The National Institutes of Health (NIH) quality assessment tool for observational cohort and cross-sectional studies [25] was used to evaluate the quality of the included studies. The quality assessment was completed independently by two reviewers (D. Vauterin and F. Van Vaerenbergh); discrepancies were resolved in a consensus meeting with the senior researcher (L. Lahousse). Poor quality was evaluated as a weakness of the respective study, but was not an exclusion criterion, as we aimed to review all methods to assess adherence currently used in the literature. More information about the quality assessment is added in supplementary material, appendix 1.

Data extraction

A standardised data extraction form was developed to extract the study characteristics (supplementary material, appendix 1) of the included studies, pilot tested on 10% of the studies and refined by two reviewers (D. Vauterin and F. Van Vaerenbergh). Subsequently, one reviewer (D. Vauterin) performed the data extraction for all included studies; the other reviewer (F. Van Vaerenbergh) checked the extracted data. Any disagreements were resolved by consensus.

The data extraction focused on recommended key elements to report in adherence studies. Key elements were defined based on the Checklist for Assessing/Evaluating Medication Compliance and Persistence Studies Using Retrospective Databases of the International Society of Pharmacoeconomics and Outcomes Research (mainly the sections "Measurement of compliance" and "Standard methods for calculating persistence") [11] and on the "Issues to clearly disclose" section of the proposals for standardisation and the recommendations for good practices presented by members of the European Society for Patient Adherence, Compliance and Persistence [4]. The following variables were considered key: inpatient stays, early refills (causing stockpiling/oversupply), drug substitution (treatment change: drug switch, augmentation or de-escalation) or dose switches (change in frequency/strength of the same drug) and the reporting of a rationale/justification for the adherence threshold and/or treatment gap used. If there was inclusion of the variable in the adherence calculation (by adding it to the formula), if its impact was stated (*e.g.* how the adherence calculation was impacted by inhaler switch) or if there was an assumption about the variable (*e.g.* no medication switches were expected), then the influencing variable was considered reported. Furthermore, listing a lack of information about the element as a possible limitation (because information may be missing beyond the control of the researchers) was also considered reported.

Data analysis

A descriptive approach was used to present an overview of the selection process, the characteristics of the included studies and the methods used to assess adherence, categorised as initiation, implementation and persistence (definitions described earlier). Adherence thresholds used, treatment gaps and respective rationales were summarised. Additionally, we outlined the reporting of variables with an impact on the adherence assessment: inpatient stays, early refills, drug substitution and dose switches.

Results

Search results

We identified 9283 records, of which 7144 were screened on title and abstract after duplicates were removed (figure 1). Secondly, 399 articles were eligible for full-text review, of which 152 studies were selected for inclusion. The Cohen's κ coefficient [24] was 0.79 (substantial agreement) and 0.90 (almost perfect agreement) for the title/abstract screening and the full-text screening, respectively. An additional 33 records were identified from the manual search of the reference and citation lists, yielding eight additional studies for inclusion. In total, 160 studies were included in the systematic review.

Quality of the included studies

Most of the included studies (70.6%, 113 out of 160) were classified as good quality based on the NIH quality assessment tool for observational cohort and cross-sectional studies, with 46 studies rated as fair

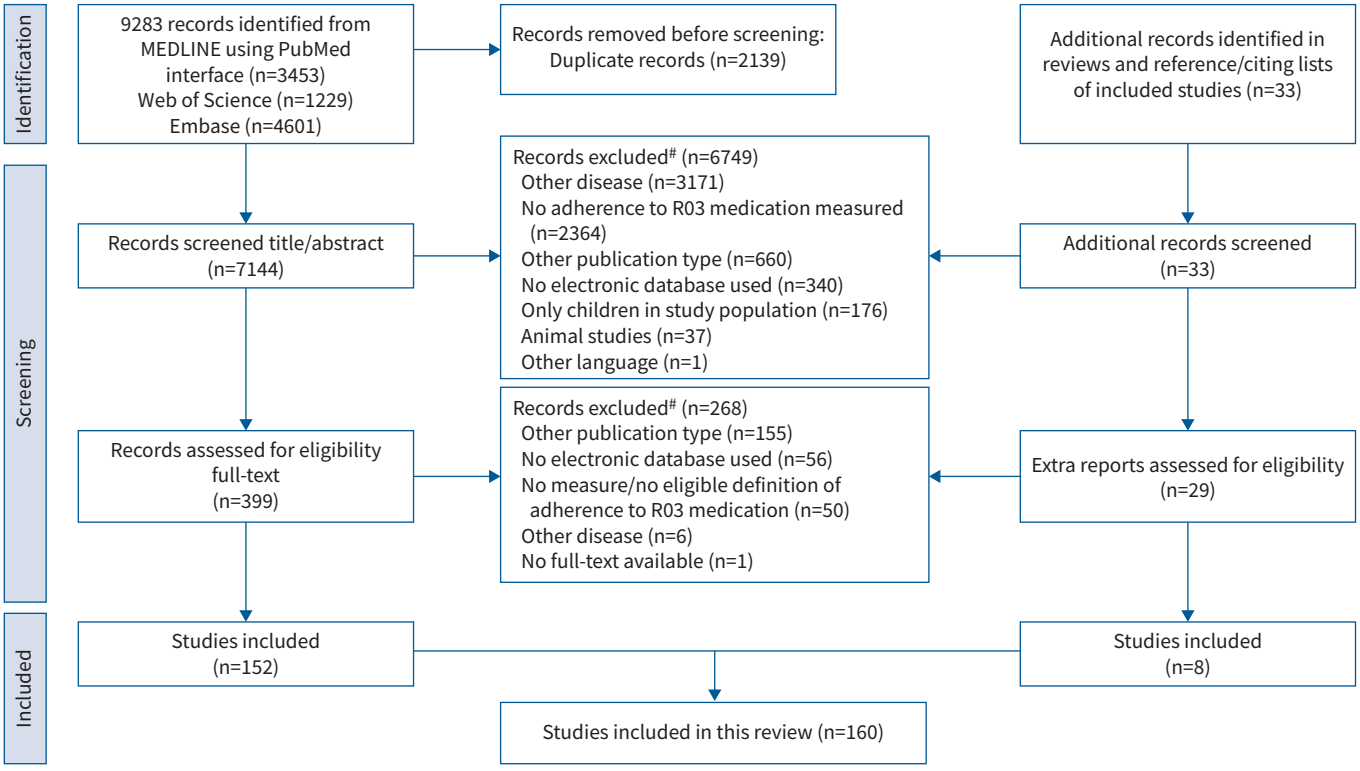

FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram. #: articles could be excluded based on more than one reason.

and one study as poor. More than half of the studies had no power description, or reporting of distinct adherence outcomes per medication class or specification of drugs evaluated (up to the fifth level of the ATC code). Attention to key variables is reported later (Reporting of variables with an impact on adherence assessment).

Study characteristics

The general characteristics of the studies reviewed are presented in table 1. The oldest studies dated from 1999 and the most recent were published in 2022. Both observational (88.8%, 142 out of 160) and interventional (11.3%, 18 out of 160) studies were included. The studied populations were located in North America (n=80), Europe (n=68), Asia (n=7) or Oceania (n=6). Adherence assessments were primarily based on outpatient (98.8%, 158 out of 160 studies) dispensing data (89.4%, 143 out of 160 studies, based on pharmacy and/or claims database). A limited number of studies combined outpatient and inpatient data (2.5%, four out of 160) or prescribing and dispensing data (5.0%, eight out of 160).

Initiation was assessed in only four studies (2.5%, four out of 160). The majority of the studies assessed implementation (84.4%, 135 out of 160) or persistence (28.1%, 45 out of 160). 24 studies (15.0%, 24 out of 160) evaluated both implementation and persistence. Long-acting β-agonists (LABA), long-acting muscarinic antagonists (LAMA) and inhaled corticosteroids (ICS) were the most investigated (91.3%, 146 out of 160), with 13 studies (8.1%) specifically focusing on triple therapy (LABA/LAMA/ICS in a single device or as a combination of multiple devices).

Adherence measurement methods

Tables 2–4 give an overview of the different definitions used, categorised by adherence phase. Overall, one method was used to measure initiation (table 2), 43 different methods were used for implementation (table 3) and seven methods were used for persistence (table 4).

Few studies (19 out of 135) assessed implementation using multiple methods.

TABLE 1 General characteristics of included studies (n=160)

First author, year [reference]	Study design	Country	Inpatient *versus* outpatient data	Prescribing *versus* dispensing data	Adherence phase[#]	Drug class(es)[¶]
Albrecht, 2016 [26]	Observational	USA	Outpatient	Dispensing	Implementation	LABA, LAMA, ICS
Albrecht, 2017 [27]	Observational	USA	Outpatient	Dispensing	Implementation	LABA, LAMA, ICS
Alcázar-Navarrete, 2022 [28]	Observational	Spain	Outpatient	Prescribing; dispensing	Persistence	TT
Anthonisen, 2005 [29]	Observational	Canada	Outpatient	Dispensing	Implementation	LABA, LAMA, ICS+other
Arfè, 2016 [30]	Observational	Italy	Outpatient	Dispensing	Persistence	LABA, LAMA, ICS
Balkrishnan, 2000 [31]	Observational	USA	Outpatient	Dispensing	Implementation	ICS
Balkrishnan, 2001 [32]	Observational	USA	Outpatient	Dispensing	Implementation	ICS
Barrecheguren, 2018 [33]	Observational	Spain	Outpatient	Dispensing	Implementation	LABA, LAMA
Belleudi, 2016 [34]	Observational	Italy	Outpatient	Dispensing	Implementation	LABA, LAMA, ICS+other
Beloin-Jubinville, 2013 [35]	Observational	Canada	Outpatient	Dispensing	Implementation	LABA, LAMA, ICS
Bender, 2006 [36]	Observational	USA	Outpatient	Dispensing	Implementation; persistence	LABA, ICS
Bender, 2016 [37]	Observational	Germany	Outpatient	Dispensing	Persistence	LABA, ICS
Bengtson, 2018 [38]	Observational	USA	Outpatient	Dispensing	Persistence	LABA, LAMA
Bengtson, 2021 [39]	Observational	USA	Outpatient	Dispensing	Implementation	LABA, LAMA
Bereznicki, 2015 [40]	Observational	Australia	Outpatient	Dispensing	Implementation	LAMA
Berg, 2015 [41]	Interventional	USA	Outpatient	Dispensing	Persistence	LABA, LAMA, ICS+other
Björnsdóttir, 2014 [42]	Observational	Iceland	Outpatient	Dispensing	Implementation	LABA, ICS
Blais, 2004 [43]	Observational	Canada	Outpatient	Dispensing	Persistence	ICS
Blais, 2010 [44]	Observational	Canada	Outpatient	Dispensing	Implementation	LABA, ICS
Blee, 2015 [45]	Interventional	USA	Outpatient	Prescribing; dispensing	Initiation	LABA, ICS
Bloom, 2019 [46]	Observational	UK	Outpatient	Prescribing	Implementation	LABA, LAMA, ICS
Bogart, 2019 [47]	Observational	USA	Outpatient	Dispensing	Implementation; persistence	MITT
Boland, 2016 [48]	Interventional	The Netherlands	Outpatient	Prescribing	Implementation	LABA, LAMA, ICS
Bollmeier, 2019 [49]	Observational	USA	Outpatient	Dispensing	Implementation	LABA, LAMA, ICS+other
Bollu, 2017 [50]	Observational	USA	Outpatient	Dispensing	Implementation	LABA+other
Breekveldt-Postma, 2004 [51]	Observational	The Netherlands	Outpatient	Dispensing	Persistence	ICS
Breekveldt-Postma, 2007 [52]	Observational	The Netherlands	Outpatient	Dispensing	Implementation	LABA, LAMA, ICS+other
Butler, 2011 [53]	Observational	USA	Outpatient	Dispensing	Implementation	Not specified
Carls, 2012 [54]	Observational	USA	Outpatient	Dispensing	Implementation	LABA, LAMA, ICS+other
Cecere, 2012 [55]	Interventional	USA	Outpatient	Dispensing	Implementation	LABA, ICS
Chen, 2020 [56]	Observational	China	Outpatient	Dispensing	Implementation	LABA, LAMA, ICS+other
Chen, 2018 [57]	Observational	Canada	Outpatient	Dispensing	Implementation	ICS
Chen, 2016 [58]	Observational	USA	Outpatient	Prescribing; dispensing	Implementation; persistence	LABA
Covvey, 2014 [59]	Observational	UK	Outpatient	Prescribing	Implementation; persistence	LABA, LAMA, ICS+other
Cramer, 2007 [60]	Observational	Canada	Outpatient	Dispensing	Implementation; persistence	LABA, LAMA, ICS+other
Dalal, 2010 [61]	Observational	USA	Outpatient	Dispensing	Implementation	LABA, LAMA, ICS

Continued

TABLE 1 Continued

First author, year [reference]	Study design	Country	Inpatient *versus* outpatient data	Prescribing *versus* dispensing data	Adherence phase[#]	Drug class(es)[¶]
Dalon, 2019 [62]	Observational	France	Outpatient	Dispensing	Persistence	LABA, LAMA, ICS
Dalon, 2019 [63]	Observational	France	Outpatient	Dispensing	Persistence	LABA, LAMA, ICS
Darbà, 2015 [64]	Observational	Spain	Outpatient	Dispensing	Implementation	LABA, ICS
Davis, 2016 [65]	Interventional	Canada	Outpatient	Dispensing	Implementation	Not specified
Davis, 2017 [66]	Observational	USA	Outpatient	Dispensing	Implementation	LABA, ICS
Delea, 2009 [67]	Observational	USA	Outpatient	Dispensing	Implementation	LABA, ICS +other
Dhamane, 2016 [68]	Observational	USA	Outpatient	Dispensing	Implementation	LABA, LAMA, ICS
Di Martino, 2014 [69]	Observational	Italy	Outpatient	Dispensing	Implementation	LABA, LAMA, ICS
Di Martino, 2017 [70]	Observational	Italy	Outpatient	Dispensing	Implementation	LABA, LAMA, ICS
Dormuth, 2006 [71]	Observational	Canada	Outpatient	Dispensing	Implementation	LABA, LAMA, ICS+other
Fan, 2003 [72]	Observational	USA	Outpatient	Dispensing	Implementation	LABA, ICS +other
Fathima, 2021 [73]	Interventional	Australia	Outpatient	Dispensing	Implementation	Not specified
Franchi, 2021 [74]	Observational	Italy	Outpatient	Dispensing	Implementation	ATC R03
Fronstin, 2013 [75]	Observational	USA	Outpatient	Dispensing	Implementation	LABA, LAMA, ICS+other
Gallefoss, 1999 [76]	Interventional	Norway	Outpatient	Dispensing	Implementation	LABA, ICS +other
Gauhar, 2009 [77]	Interventional	USA	Outpatient	Dispensing	Implementation	LAMA+other
Gilbert, 2021 [78]	Observational	USA	Outpatient	Dispensing	Implementation	LABA, ICS
Gillespie, 2020 [79]	Observational	USA	Outpatient; inpatient	Dispensing	Implementation; persistence	LABA, LAMA, ICS
Halpern, 2011 [80]	Observational	USA	Outpatient	Dispensing	Implementation; persistence	LABA, LAMA, ICS
Halpin, 2022 [81]	Observational	UK	Outpatient	Prescribing	Implementation; persistence	TT
Haupt, 2008 [82]	Observational	Sweden	Outpatient	Dispensing	Implementation	LABA, LAMA, ICS+other
Henriksen, 2018 [83]	Observational	Denmark	Outpatient	Dispensing	Implementation	Other
Hesso, 2020 [84]	Interventional	UK	Outpatient	Dispensing	Implementation	LABA, ICS
Hu, 2017 [85]	Observational	Denmark	Outpatient	Dispensing	Persistence	LABA, LAMA, ICS
Huetsch, 2012 [86]	Observational	USA	Outpatient	Dispensing	Implementation	LABA, ICS +other
Humenberger, 2018 [87]	Observational	Austria	Outpatient	Dispensing	Implementation	LABA, LAMA, ICS
Ingebrigtsen, 2015 [88]	Observational	Denmark	Outpatient	Dispensing	Implementation	LABA, LAMA, ICS
Ismaila, 2014 [89]	Observational	Canada	Outpatient	Dispensing	Implementation	LABA, LAMA, ICS
Izquierdo, 2016 [90]	Observational	Spain	Outpatient	Prescribing; dispensing	Implementation	LAMA
Jung, 2009 [91]	Observational	USA	Outpatient	Dispensing	Implementation; persistence	LABA, LAMA, ICS+other
Kardas, 2020 [92]	Observational	Poland	Outpatient	Prescribing; dispensing	Initiation	LABA, LAMA, ICS+other
Kim, 2018 [93]	Observational	South Korea	Outpatient; inpatient	Unclear	Implementation	LABA, LAMA, ICS
Koehorst-ter Huurne, 2018 [94]	Observational	The Netherlands	Outpatient	Dispensing	Implementation	LABA, LAMA, ICS
Koehorst-ter Huurne, 2016 [95]	Observational	The Netherlands	Outpatient	Dispensing	Implementation	LABA, LAMA, ICS

Continued

TABLE 1 Continued

First author, year [reference]	Study design	Country	Inpatient *versus* outpatient data	Prescribing *versus* dispensing data	Adherence phase[#]	Drug class(es)[¶]
Koehorst-ter Huurne, 2015 [96]	Observational	The Netherlands	Outpatient	Dispensing	Implementation	LABA, LAMA, ICS
Koehorst-ter Huurne, 2016 [97]	Observational	The Netherlands	Outpatient	Dispensing	Implementation	LABA, LAMA, ICS
Krack, 2021 [98]	Observational	Germany	Outpatient	Dispensing	Implementation; persistence	LABA, LAMA
Krigsman, 2007 [99]	Observational	Sweden	Outpatient	Dispensing	Implementation	LABA, LAMA, ICS+other
Krigsman, 2007 [100]	Observational	Sweden	Outpatient	Dispensing	Implementation	LABA, LAMA, ICS+other
Krigsman, 2007 [101]	Observational	Sweden	Outpatient	Dispensing	Implementation	LABA, LAMA, ICS+other
Laforest, 2013 [102]	Observational	France	Outpatient	Dispensing	Implementation; persistence	LAMA
Lane, 2018 [16]	Observational	USA	Outpatient	Dispensing	Persistence	LABA, LAMA, ICS
Le, 2022 [103]	Observational	USA	Outpatient	Dispensing	Implementation	LABA, LAMA, ICS
Lee, 2022 [104]	Observational	South Korea	Outpatient	Dispensing	Implementation	MITT
Liao, 2019 [105]	Observational	Taiwan	Outpatient	Dispensing	Implementation	LABA, LAMA, ICS+other
Lonigro, 2022 [106]	Observational	Italy	Outpatient	Dispensing	Implementation	LABA, LAMA, ICS+other
López-Pintor, 2021 [107]	Observational	Spain	Outpatient	Dispensing	Persistence	LABA, LAMA, ICS
Magnussen, 2021 [108]	Observational	UK	Outpatient	Prescribing	Implementation	ICS
Mannino, 2022 [109]	Observational	USA	Outpatient	Dispensing	Implementation; persistence	TT
Matuszewski, 1999 [110]	Observational	USA	Outpatient; inpatient	Dispensing	Implementation	LABA, ICS +other
Meeraus, 2018 [17]	Observational	France	Outpatient	Prescribing	Persistence	LABA, LAMA, ICS
Mehuys, 2010 [111]	Observational	Belgium	Outpatient	Dispensing	Implementation	ATC R03
Milea, 2021 [112]	Observational	New Zealand	Outpatient	Prescribing	Persistence	LABA, LAMA, ICS
Monteagudo, 2017 [113]	Observational	Spain	Outpatient	Dispensing	Implementation	LAMA
Monteagudo, 2021 [114]	Observational	Spain	Outpatient	Prescribing	Persistence	TT
Moran, 2017 [115]	Interventional	Ireland	Outpatient	Dispensing	Implementation	LABA, ICS
Moretz, 2019 [116]	Observational	USA	Outpatient	Dispensing	Implementation	LABA, LAMA
Moretz, 2020 [117]	Observational	USA	Outpatient	Dispensing	Implementation	LABA, LAMA, ICS
Moretz, 2019 [118]	Observational	USA	Outpatient	Dispensing	Implementation	LABA, LAMA, ICS
Mueller, 2017 [119]	Observational	Germany	Outpatient	Dispensing	Implementation; persistence	LABA, LAMA, ICS
Neugaard, 2011 [120]	Observational	USA	Outpatient; inpatient	Dispensing	Implementation	LABA, LAMA, ICS+other
Ng, 2020 [121]	Observational	Canada	Outpatient	Dispensing	Implementation	ICS
Nili, 2021 [122]	Observational	USA	Outpatient	Dispensing	Implementation	LABA, ICS
Nishi, 2018 [123]	Observational	USA	Outpatient	Dispensing	Implementation	LABA, LAMA, ICS
Ottenbros, 2014 [124]	Interventional	The Netherlands	Outpatient	Dispensing	Implementation	LABA, ICS
Parimon, 2007 [125]	Observational	USA	Outpatient	Dispensing	Implementation	ICS
Parkin, 2018 [126]	Observational	New Zealand	Outpatient	Dispensing	Persistence	LABA, LAMA, ICS
Paske, 2022 [127]	Interventional	The Netherlands	Outpatient	Dispensing	Implementation	Not specified

Continued

TABLE 1 Continued

First author, year [reference]	Study design	Country	Inpatient *versus* outpatient data	Prescribing *versus* dispensing data	Adherence phase[#]	Drug class(es)[¶]
Penning-van Beest, 2011 [128]	Observational	The Netherlands	Outpatient	Dispensing	Persistence	LABA, LAMA, ICS
Plaza, 2021 [129]	Observational	Spain	Outpatient	Dispensing	Implementation	Not specified
Pottegård, 2014 [130]	Observational	Denmark	Outpatient	Prescribing; dispensing	Initiation	LABA, ICS
Price, 2021 [131]	Interventional	UK	Outpatient	Prescribing	Implementation	LABA, LAMA
Priest, 2011 [132]	Observational	USA	Outpatient	Dispensing	Implementation	LABA, LAMA, ICS+other
Priest, 2012 [133]	Observational	USA	Outpatient	Dispensing	Implementation	LABA, LAMA +other
Prosser, 2022 [134]	Observational	USA	Outpatient	Dispensing	Implementation	LABA, LAMA, ICS+other
Punekar, 2015 [135]	Observational	UK	Outpatient	Prescribing	Implementation	LABA, LAMA, ICS
Qian, 2014 [136]	Observational	USA	Outpatient	Dispensing	Implementation	LABA, LAMA, ICS+other
Quint, 2020 [137]	Observational	UK+France+Germany+ Australia+Italy	Outpatient	Prescribing	Implementation; persistence	TT
Quint, 2020 [138]	Observational	UK	Outpatient	Prescribing	Implementation; persistence	TT
Requena, 2021 [139]	Observational	UK	Outpatient	Prescribing	Implementation; persistence	LABA, LAMA, ICS
Roberts, 2011 [140]	Observational	USA	Outpatient	Dispensing	Implementation	LABA, ICS
Roebuck, 2018 [141]	Observational	USA	Outpatient	Dispensing	Implementation	LABA, LAMA, ICS+other
Rolnick, 2013 [142]	Observational	USA	Outpatient	Dispensing	Implementation	Not specified
Rolnick, 2013 [143]	Observational	USA	Outpatient	Dispensing	Implementation	LABA, LAMA, ICS+other
Romagnoli, 2020 [144]	Observational	Italy	Inpatient	Dispensing	Implementation; persistence	LABA, LAMA, ICS+other
Sá-Sousa, 2019 [145]	Observational	Portugal	Outpatient	Prescribing; dispensing	Implementation	LABA, LAMA, ICS+other
Salvesen, 2018 [146]	Observational	Denmark	Outpatient	Dispensing	Implementation	Other
Sansbury, 2021 [147]	Observational	UK	Outpatient	Prescribing	Persistence	MITT
Savaria, 2017 [148]	Observational	Canada	Outpatient	Dispensing	Implementation; persistence	LAMA
Schabert, 2021 [149]	Observational	USA	Inpatient	Dispensing	Persistence	MITT
Schnoor, 2022 [150]	Interventional	The Netherlands	Outpatient	Dispensing	Implementation	ATC R03
Shenolikar, 2016 [151]	Observational	USA	Outpatient	Dispensing	Implementation; persistence	Not specified
Shlomi, 2022 [152]	Observational	Israel	Outpatient	Dispensing	Implementation	LABA, LAMA
Simon-Tuval, 2015 [153]	Observational	Israel	Outpatient	Dispensing	Implementation	LABA, LAMA, ICS
Simoni-Wastila, 2012 [154]	Observational	USA	Outpatient	Dispensing	Implementation; persistence	LABA, LAMA, ICS+other
Simoni-Wastila, 2012 [155]	Observational	USA	Outpatient	Dispensing	Implementation; persistence	LABA, LAMA, ICS+other
Singer, 2021 [156]	Observational	Canada	Outpatient	Prescribing; dispensing	Initiation	ATC R03
Slade, 2021 [157]	Observational	USA	Outpatient	Dispensing	Implementation	LABA, LAMA
Spain, 2022 [158]	Observational	USA	Outpatient	Dispensing	Persistence	LAMA+other
Stanford, 2019 [159]	Observational	USA	Outpatient	Dispensing	Implementation	LABA, ICS
Strange, 2019 [160]	Observational	USA	Outpatient	Dispensing	Implementation	LABA, LAMA
Stuart, 2013 [161]	Observational	USA	Outpatient	Dispensing	Implementation	LABA, LAMA, ICS+other
Stuart, 2014 [162]	Observational	USA	Outpatient	Dispensing	Implementation	LABA, LAMA, ICS+other
Suissa, 2015 [163]	Observational	Canada	Outpatient	Dispensing	Implementation	ICS

Continued

TABLE 1 Continued

First author, year [reference]	Study design	Country	Inpatient *versus* outpatient data	Prescribing *versus* dispensing data	Adherence phase[#]	Drug class(es)[¶]
Suzuki, 2020 [164]	Observational	Japan	Outpatient	Dispensing	Implementation	MITT
Tommelein, 2014 [165]	Interventional	Belgium	Outpatient	Dispensing	Implementation	LABA, LAMA, ICS+other
Tommelein, 2014 [166]	Interventional	Belgium	Outpatient	Dispensing	Implementation	LABA, LAMA, ICS+other
Tøttenborg, 2016 [167]	Observational	Denmark	Outpatient	Dispensing	Implementation	LABA, LAMA, ICS
Toy, 2011 [168]	Observational	USA	Outpatient	Dispensing	Implementation	LABA, LAMA, ICS+other
Tran, 2016 [169]	Observational	USA	Outpatient	Dispensing	Implementation	LABA, LAMA, ICS
Tran, 2019 [170]	Observational	Canada	Outpatient	Dispensing	Implementation	LABA, LAMA, ICS+other
Trivedi, 2012 [171]	Interventional	USA	Outpatient	Dispensing	Implementation	LABA
Van Boven, 2016 [172]	Interventional	The Netherlands	Outpatient	Dispensing	Implementation	LABA, LAMA, ICS
Van Boven, 2014 [173]	Observational	The Netherlands	Outpatient	Dispensing	Persistence	LABA
Vetrano, 2017 [174]	Observational	Italy	Outpatient	Dispensing	Implementation	LABA, LAMA, ICS
Voorham, 2017 [175]	Observational	UK	Outpatient	Prescribing	Implementation	LABA, ICS
Wallace, 2019 [176]	Observational	USA	Outpatient	Dispensing	Implementation; persistence	LABA, LAMA, ICS+other
Wei, 2018 [177]	Observational	USA	Outpatient	Dispensing	Implementation	LABA, LAMA, ICS+other
Wurst, 2014 [178]	Observational	USA	Outpatient	Dispensing	Implementation	LABA, LAMA
Xu, 2021 [179]	Observational	New Zealand	Outpatient	Dispensing	Implementation; persistence	MITT
Yousif, 2020 [180]	Observational	Canada	Outpatient	Dispensing	Implementation	Not specified
Yu, 2011 [181]	Observational	USA	Outpatient	Dispensing	Implementation; persistence	LABA, LAMA, ICS+other
Yu, 2016 [182]	Observational	USA	Outpatient	Dispensing	Implementation	LABA, LAMA
Zucchelli, 2020 [183]	Observational	Italy	Outpatient	Prescribing	Implementation	MITT

LABA: long-acting β-agonist; LAMA: long-acting muscarinic antagonist; ICS: inhaled corticosteroid; TT: triple therapy; MITT: multi-inhaler triple therapy; ATC: Anatomical Therapeutic Chemical. [#]: initiation: the dispensing of medication in a pre-defined period of time after prescribing; implementation: the extent to which a patient uses medication as recommended (taking into account the dosing regimen) over a specific period of time; persistence: the time from initiation to discontinuation of the therapy; [¶]: TT includes the combination of LABA/LAMA/ICS in a single device or as MITT; the category "other" includes at least one of following drug classes: short-acting β-agonists, short-acting muscarinic antagonists, (methyl) xanthines, leukotriene receptor antagonists and/or phosphodiesterase type 4 inhibitors.

Most of the included implementation studies calculated adherence based on the medication possession ratio (MPR) (40 out of 135) and/or the proportion of days covered (PDC) (58 out of 135) and/or based on an alteration of the MPR/PDC (30 out of 135). Variations were observed in both the numerator and denominator of the formulas. Modifications of the numerator were generally introduced to better define the days supplied or the days covered or to adjust for fills before the assessment period and/or leftovers at the end of the observation period. Similarly, adjustments for inpatient stays or for calendar days after death during a fixed time period were included. The fixed time period used for implementation assessment in the included studies ranged from 30 days [26, 27] to 4 years [93].

TABLE 2 Method to measure initiation

Definition to measure initiation	Original studies
Filling the prescription within a pre-defined time period following prescribing	[45, 92, 130, 156]

https://doi.org/10.1183/16000617.0103-2023

TABLE 3 Methods to measure implementation

	Methods to measure implementation	Original studies
MPR: the ratio of the sum of the days supplied for a medication during a pre-defined refill interval (numerator) to the number of days in the refill interval (denominator, *e.g.* days between first and last dispensing [4, 11, 13] or to the number of days in the study period [4, 13])		
Denominator: days between first and last dispensing	(1) $\frac{\sum^{days\ supplied}}{days\ between\ first\ and\ last\ dispensing}$	[59, 94, 99–101, 119]
	(2) $\frac{\sum^{days\ supplied}\ (excluding\ the\ final\ refill)}{days\ between\ first\ and\ last\ dispensing}$	[60, 120, 132, 133, 135, 139, 160, 178]
Denominator: days in study period	(3) $\frac{\sum^{days\ supplied}}{study\ period}$ (this method is sometimes called the medication refill adherence)	[57, 84, 89, 120, 131–133, 148, 165, 166, 174, 180, 183]
	(4) $\frac{\sum^{days\ supplied}}{study\ period\ -\ inpatient\ days}$	[80]
	(5) $\frac{\sum^{days\ supplied}\ -\ inpatient\ days}{study\ period\ -\ inpatient\ days}$	[80]
mMPR: in this case, the denominator of the MPR is modified from days between first and last prescription to days between first and last dispensing+duration of last prescription	(6) $\frac{\sum^{days\ supplied}}{days\ between\ first\ and\ last\ dispensing\ +\ duration\ of\ last\ prescription\ in\ days}$	[29, 46, 82, 94–97]
	(7) $\frac{(\sum^{days\ supplied\ of\ each\ inhaler\ device})/number\ of\ inhalers}{duration\ of\ therapy}$	[179]
Unclear MPR calculation		[87, 113, 142, 143, 164, 175]
PDC: the proportion of days covered is the ratio of the sum of the days covered by a medication (numerator) to a fixed time period (denominator, *e.g.* 365 days) [4, 11] or to the study period [4, 13]		
Denominator: fixed time period	(8) $\frac{\sum^{days\ covered\ with\ all\ drugs\ available}}{fixed\ time\ period}$	[39, 47, 81, 104, 109, 179]
	(9) $\frac{\sum^{days\ covered\ with\ \geqslant 1\ drug\ available}}{fixed\ time\ period}$	[48–50, 52, 56, 66, 68, 75, 78, 79, 103, 106, 115, 121, 123, 134, 139, 141, 150, 151, 157, 172, 178, 179, 181]
	(10) $\frac{\sum^{days\ covered\ with\ \geqslant 1\ drug\ available}\ +\ inpatient\ days}{fixed\ time\ period}$	[54, 93, 98]
	(11) $\frac{\sum^{days\ covered\ with\ \geqslant 1\ drug\ available}}{fixed\ time\ period\ -\ inpatient\ days}$	[177]

Continued

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TABLE 3 Continued

	Methods to measure implementation	Original studies
Denominator: days in study period	(12) $\frac{\sum^{\text{days covered with } \geqslant 1 \text{ drug available}}}{\text{study period}}$	[61, 84, 105, 137, 138, 140, 155, 159, 160, 163, 167, 170, 176, 182]
	(13) $\frac{\sum^{\text{days covered with } \geqslant 1 \text{ drug available}} + \text{inpatient days}}{\text{study period}}$	[116–118]
Other definitions of PDC	(14) The relationship between the proportion of the billed doses of pharmacy and the number of days covered according to the labelling of the product	[33, 90]
	(15) $\frac{\text{Quantity dispensed (unclear whether in days or canisters)}}{\text{fixed time period}}$	[153]
No definition available		[58, 164, 169]
Unclear definition		[34]
A combination of PDC and MPR: the numerator is a variant of the days supplied or the days covered and/or the denominator is a fixed time period or a variant of the study period	(16) $\frac{\sum^{\text{defined daily doses supplied}}}{\text{study period}}$	[70]
	(17) $\frac{\sum^{\text{defined daily doses supplied}}}{\text{study period} - \text{inpatient days}}$	[69]
	(18) $\frac{\sum^{\text{defined daily doses supplied}}}{\text{fixed time period}}$	[42, 71, 74, 88]
	(19) $\frac{\sum^{\text{defined daily doses supplied}}}{\text{fixed time period} - \text{inpatient days}}$	[69]
	(20) $\frac{\left(\sum^{\text{defined daily doses supplied}}\right) \times 1.25}{\text{fixed time period}}$	[83, 146]
	(21) $\frac{\sum^{\text{days supplied}}}{\text{fixed time period}}$ (sometimes called medication refill adherence)	[26, 27, 35, 36, 64, 65, 67, 73, 102, 108, 115, 165, 168]
	(22) $\frac{\sum^{\text{days supplied}}}{\text{fixed time period} - \text{inpatient days} - \text{days after death during fixed time period}}$	[119]
	(23) $\frac{\sum^{\text{days supplied}} - \text{excess days of last prescription at end of study period}}{\text{fixed time period}}$	[44]
	(24) $\frac{\sum^{\text{days supplied}} - \text{excess days of last prescription at end of study period}}{\text{fixed time period} - \text{inpatient days}}$	[91]
	(25) $\frac{\sum^{\text{days supplied}} + \text{excess days of previous prescription extended into fixed time period}}{\text{fixed time period}}$	[72]
	(26) $\frac{\sum^{\text{days supplied}} + \text{excess days of previous prescription extended into fixed time period}}{\text{fixed time period} - \text{inpatient days}}$	[161]

Continued

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TABLE 3 Continued

	Methods to measure implementation	Original studies
	(27) $\frac{\sum^{days\ supplied} + excess\ days\ of\ previous\ prescription\ extended\ into\ fixed\ time\ period}{fixed\ time\ period - inpatient\ days - days\ after\ death\ during\ fixed\ time\ period}$	[162]
	(28) $\frac{\sum^{days\ supplied} + excess\ days\ of\ previous\ prescription\ extended\ into\ fixed\ time\ period}{study\ period + excess\ days\ of\ last\ prescription\ at\ end\ of\ study\ period}$	[165]
	(29) $\frac{\sum^{days\ covered\ with\ \geqslant 1\ drug\ available}}{days\ between\ first\ and\ last\ dispensing}$	[124, 136]
	(30) $\frac{\sum^{days\ covered\ with\ \geqslant 1\ drug\ available}}{days\ between\ first\ and\ last\ dispensing + duration\ of\ last\ prescription}$	[154]
	(31) $\frac{\sum^{days\ in\ study\ period} - days\ without\ available\ medication}{study\ period}$ (~ CMA7 method) [185]	[127]
Other methods	(32) $\frac{\sum^{refills}}{fixed\ time\ period}$ (~ refill rate)	[40, 67, 77, 87, 111, 121, 129, 152]
	(33) ReComp algorithm [186]	[55, 86, 171]
	(34) Profile score method [187]	[32]
	(39) $\frac{\sum^{daily\ doses\ supplied}}{\sum^{prescribed\ daily\ doses}}$	[144]
	(40) $\frac{\sum^{defined\ daily\ doses\ supplied}}{\sum^{prescribed\ daily\ doses}}$	[76]
	(41) $\frac{\sum^{refills\ dispensed}}{\sum^{fills\ prescribed}}$	[145]
	(42) $\frac{\sum^{nonadherence\ days}}{fixed\ time\ period}$ with a nonadherence day=Σ days of which time between end of prescription and refill >7 (~ nonadherence ratio)	[53]
	(43) Trajectory of binary variable (yes/no) for different fixed time periods with yes=days supplied/fixed time period ⩾1 and with days supplied corrected for previous refills	[122]
Modifications of methods proposed by Steiner *et al.* [184]	(35) Med-total: $\frac{\sum^{days\ supplied}}{days\ between\ first\ and\ last\ prescription\ refill - inpatient\ days}$	[31]
	(36) Med-total: $\frac{\sum^{days\ supplied}}{fixed\ time\ period - inpatient\ days}$	[32]
	(37) Med-out: $\frac{\sum^{days\ withoutmedication\ in\ the\ fixed\ time\ period}}{fixed\ time\ period - inpatient\ days}$	[32]
	(38) Noncompliance ratio: $\frac{\sum^{days\ without\ medication\ in\ fixed\ time\ period}}{\sum^{days\ covered\ in\ fixed\ time\ period}}$	[110]
	Unclear which modification was used	[125]

MPR: medication possession ratio; mMPR: modified MPR; PDC: proportion of days covered; CMA7: continuous multiple-interval measures of medication availability/gaps.

TABLE 4 Methods to measure persistence

Persistence: time from the index date/initiation to treatment discontinuation with treatment discontinuation defined as…	Original studies
Time between end of one prescription and the start of a subsequent one	
Treatment gap of >X days between the end of one prescription and the start of the subsequent one	[16, 30, 37, 41, 43, 51, 58, 59, 62, 63, 79, 81, 109, 112, 126, 128, 147, 149, 151, 158, 173, 176]
Treatment gap of >X days between the end of one prescription (prescription end corrected for early refills) and the start of the subsequent one	[47, 60, 80]
Treatment gap of >X days between the end of one prescription (prescription end corrected for inpatient stays) and the start of the subsequent one	[38, 91]
Treatment gap of >X days between the end of one prescription (prescription end corrected for early refills and inpatient stays) and the start of the subsequent one	[98, 119]
Treatment gap of >X days (value of X adapted for inpatient stays) between the end of one prescription and the start of the subsequent one	[85]
Treatment gap of >X days between the end of one prescription and the start of the subsequent one and no re-initiation during the subsequent period	[154, 155]
Time between prescription refill dates	
Exceeding a pre-defined period between prescribing or dispensing dates (~ >X days without a prescription refill)	[17, 28, 114, 137–139, 148]
No description to define discontinuation or last dispensing	[102]
Unclear definition although specification of treatment gap (not possible to distinguish if discontinuation was based on time between prescription refill dates or between the end of one prescription and the start of the subsequent one)	[36, 107, 144, 179, 181]

In general, two approaches were distinguished to define discontinuation in order to calculate persistence: one based on the time between the end of a prescription and the start of the next prescription (incorporation of days supplied) and one based on the time between prescribing/dispensing dates (no integration of days supplied). The end of the last prescription was occasionally adjusted for early refills and inpatient stays.

Adherence thresholds and treatment gap

Implementation was assessed both as a continuous variable and as a categorical variable based on a threshold to distinguish between good adherence and moderate or poor adherence. A cut-off point of 0.80 was mostly used (91 out of 109). Less than half of the included studies that used an adherence threshold provided a rationale for their choice (48 out of 109; supplementary material, appendix 2).

The treatment gap between the end of one prescription and the start of the subsequent one or the pre-defined period of time between the prescription refill dates varied between 1 day [47] and 180 days [98, 119]. One study corrected their treatment gap for inpatient stays [85]. Analogously, the gap for filling a prescription to assess initiation varied between 3 days [45] and 4 months [130]. ~25% of the initiation or persistence studies (12 out of 49) (supplementary material, appendix 2) cited a rationale for the chosen treatment gap (*e.g.* sensitivity analysis [51], previous research [98, 112, 128, 173] or duration of a prescription [62, 63, 81, 85, 92, 119, 148]).

Reporting of variables with an impact on adherence assessment

~11% of the included studies (18 out of 160) reported the possible impact of the evaluated variables on treatment adherence (supplementary material, appendix 2). These variables were inpatient stays, drug substitutions, dose switches and early refills. The influence of medication substitutions was estimable in four out of five included studies (127 out of 160), as some studies limited their assessment to only one specific drug (class)/therapy (*e.g.* triple therapy/primary inhaler/index medication) (51 out of 127) or, in contrast, took all medication together (41 out of 127). In addition, several authors clearly described the impact of medication switch/augmentation/de-escalation (35 out of 127). However, in >40% of the studies (65 out of 150, initiation studies and refill rate studies excluded) it was less clear whether dose switching affected adherence assessment. Regarding inpatient stays, one-third (55 out of 160) reported this variable by including it in the calculation formula (tables 2–4), by adjusting the study design (exclusion or end of follow-up in case of hospitalisation) or by acknowledging it as a limitation. Finally, the impact of early refills was assessed in 46 out of 116 studies (exclusion of initiation studies and implementation methods based on all days supplied as oversupply is automatically included). In general, for patients who refilled

early before running out of drug supply (stockpiling), the start of the subsequent prescription was shifted to the end of the previous prescription. Other authors mentioned this factor as a possible influencing factor or made assumptions about not retrieving medication before stock ran out.

Discussion

As demonstrated in this systematic review, numerous studies reported an adherence measure for COPD medication in electronic healthcare databases; however, to date, to the best of our knowledge, an overview of the different methods was lacking. A total of 160 studies were included in this systematic review, yielding one method for initiation, 43 methods for implementation and seven methods for persistence. Key variables (inpatient stays, drug substitutions, dose switching and early refills) were reported in only 11% of the included studies.

Adherence research today seems to be based mainly on outpatient dispensing data. Assessment can be difficult when only prescribing or only dispensing data is available. When only prescribing data is available, adherence is likely to be overestimated because not all patients collect their medication from the pharmacy. In contrast, when only dispensing data is available, nonadherent patients who do not collect their medication will not be detected. In practice, it can be complex to link prescribing and dispensing data, as mentioned by Hutchins *et al.* [12]. This complexity may also be a possible explanation for the low number of initiation studies included in our systematic review, compared with the large number of studies that focused on implementation and persistence. Analogous trends are seen in asthma research [188].

Different methods to assess implementation and persistence were observed, with complex methods in some studies. No method was specifically developed for COPD or respiratory medication in general. We did not observe different equations for inhaled and nebulised medication, nor did the methods differ between observational and experimental studies using electronic healthcare databases for adherence assessment. The described methods are in line with previous research in asthma patients [189] and with reviews focusing on oral dosages [3] or on polypharmacy [190]. Similarly, the medication possession ratio and the proportion of days covered were the most commonly reported methods for implementation [3, 189, 190]. Data availability may have influenced the choice of adherence measure [190]. A combination of different methods has been proposed to provide a broader picture of the adherence process [6]. However, we observed that this seems limited in COPD research. Contrary to the review of Asamoah-Boaheng *et al.* [189], we did not consider the ratio of units of controller medication to the sum of units of controller medication and rescue medication (known as the asthma medication ratio or the COPD treatment ratio [191]) as a measure of implementation. While it can be a valuable parameter in assessing disease control by treatment, it is not designed to optimally measure adherence.

The reporting of variables with an impact on adherence assessment was low. First, a possible reason for under-reporting could be the lack of awareness of these variables. We observed that reporting has not substantially improved since the publication of reporting guidelines [4, 11]. Therefore, we request more attention to the use of these guidelines in COPD adherence research. Where there is a lack of information about an influencing variable beyond the researchers' control (for example, when information about inpatient stays is missing in the database), authors should acknowledge this limitation. In this way, other researchers are informed that the reported adherence values may over- or underestimate true adherence values, depending on the information missing. Second, hospitalisations may impact adherence outcomes in COPD and only one-third of the included studies reported this influencing factor. As indicated in the introduction, each COPD patient is admitted to a hospital on average 0.09–2.4 times per year and readmissions are frequent [14, 15]. Although inpatient stays are in general short [192, 193], the cumulative duration of inpatient stays per year may be substantial. To the best of our knowledge, it is unknown which minimum duration of inpatient stays significantly impacts on COPD adherence assessment. Dong *et al.* [194] concluded that for β-blocker initiators (after myocardial infarction) and for statin initiators, adherence outcomes varied >15% when hospitalisations of >28 days were taken into account *versus* not [194]. Further research in COPD patients should confirm this finding. Moreover, it is currently unclear on how to best incorporate inpatient days [4, 194]. Inhaler devices during inpatient stays can be dispensed by the hospital pharmacy or taken from home [195, 196]. It could be suggested that drug adherence is underestimated during the length of inpatient stays if medication is dispensed by the hospital pharmacy and if inpatient days are not a correction factor. Further research on how to correctly estimate the impact of hospitalisations on adherence assessments in COPD is desirable. Third, the inclusion of dose switching in the adherence assessment is mainly dependent on the availability of data concerning the dosing regimen. The number of days supplied is available in some databases. In other cases, researchers consider the used dose equal to the defined daily doses [4]. Nevertheless, reporting of dose switching is important, as the defined daily dose does not always reflect how the physician (initially) prescribed treatment and treatment

changes are to be expected in longitudinal research [2, 22]. Similarly, assumptions of no treatment switch or lack of reporting of the impact of dose switching may be inappropriate and lead to over- and/or underestimation [197]. Even when only one specific medication is studied, treatment switches can be important to consider. Moreover, when only prescribing data is used to assess adherence, it is difficult to determine whether, and to what extent, inhaler switching by pharmacists within the same drug class affects adherence outcomes. Fourth, attention to early refills (stockpiling) should be supported, as only 40% of the included studies reported this. Especially when prevalent users (non-naïve patients) are included in the study, it is possible that prescriptions are prescribed before study start [198]. In addition, early refills can impact the amount of days covered and/or persistence calculations [4].

The aim of this systematic review was to summarise the methods used to assess initiation, implementation and persistence for COPD medications in electronic healthcare databases. For this reason, no statements have been made about population sizes, definitions to assess COPD diagnosis or mean/median age of the population studied. Additionally, both observational cohort studies and interventional studies were included. It is important to highlight that these characteristics are important when comparing adherence rates between different study cohorts; however, no impact on the adherence assessment method or the reporting of variables with an impact on the adherence assessment was expected. Particularly in the case of randomised controlled trials (RCTs), adherence rates can be biased and provide a more positive illustration than real life, as RCT participants tend to be more adherent due to the study setting [22]. Nevertheless, and independently of the stated adherence rates in these studies, the methods used to study initiation, implementation or persistence may inspire further research.

Our review focused on published research rather than on clinical practice directly. Hence, to move towards more high-quality adherence assessments in clinical practice, quality improvement research using data from electronic healthcare databases may be important. Electronic healthcare databases are an objective resource and can be useful in clinical practice to quickly identify nonadherent patients, patients who can be selected for adherence interventions. However, due to limitations of these data sources (*i.e.* lack of information on actual clinical use and inhaler/nebuliser technique), present and future interventions may combine the use of electronic healthcare databases for screening followed by an in-depth assessment of real-life clinical use (*e.g.* inhaler technique and patient user data).

The ABC taxonomy was selected as reference for adherence definitions, as, to our knowledge, it is the only terminology that has been translated to respiratory diseases [22]. While the authors of the studies screened in this systematic review may not have followed this taxonomy, nor distinguished between the different stages of adherence, we did not make our judgement for inclusion, data extraction or analysis dependent on the used terms. Nevertheless, we encourage the use of an international taxonomy that promotes transparency and uniformity, as we observed many different terminologies [5, 13, 21, 199].

This systematic review offers multiple strengths. While other reviews listed an overview of methods to measure adherence in general [7] or in specific diseases [189, 200], to the best of our knowledge, this study is the first to provide an overview of medication adherence measurements methods for COPD in electronic healthcare databases specifying the methods used and categorised by adherence phase. The use of different data sources (PubMed, Embase and Web of Science) in combination with broad COPD inclusion criteria, adherence to treatment and electronic healthcare databases shows our intention to provide a good synopsis of literature. The selection of variables with an impact on adherence assessment was based on recommendations for reporting of adherence studies by researchers with considerable expertise in medication adherence. However, our systematic review is also characterised by several limitations. Other variables may influence adherence assessment such as free samples provided by the physician or patients' awareness of extra doses in the inhaler device, although the reporting of these parameters has not been assessed in this review. Second, only studies written in English were included and our definitions for translating initiation, implementation and persistence into electronic healthcare databases were based on our own expertise. Third, studies published after 11 October 2022 (*i.e.* the date on which we conducted our literature search) may provide interesting information, but were not included in this review. No methods specifically designed for COPD medication have been detected. Further research could focus on the need of a specific method for inhaled respiratory medication, taking into account the complexity of combining different inhaler devices, extra doses available in the inhaler, difficulties in determining the prescribed dose (the defined daily dose does not always reflect how the physician (initially) prescribed treatment) and the use of maintenance medication in case of deterioration as influencing variables specifically related to respiratory diseases. In-depth research on methodological choices and the impact of key variables in COPD adherence assessment in electronic healthcare databases is recommended.

Points for clinical practice

- Adherence assessment is recommended in clinical practice.
- To move towards more high-quality adherence assessments in clinical practice, quality improvement research using data from electronic healthcare databases (*e.g.* electronic healthcare records, pharmacy dispensing data) may play an important role.
- Electronic databases are useful to quickly identify nonadherent patients, despite their limitations such as a lack of information on actual clinical use and inhaler/nebuliser technique.
- This systematic literature review provides an overview of methods used to assess adherence in electronic healthcare databases and describes the reporting of several influencing variables which may impact adherence.
- Future interventions may use adherence assessment in these databases for screening followed by in-depth assessment of real-life clinical use.

Questions for future research

Adherence assessment can be complex for COPD, due to the combination of different inhaler devices, extra doses available in the inhaler, difficulties in determining the prescribed dose (the defined daily dose does not always reflect how the physician (initially) prescribed treatment) and the use of maintenance medication in the case of deterioration. Further research should focus on the need of a specific adherence assessment method for inhaled respiratory medication, taking into account these complexities. This method should preferably combine different general methods to form the best possible reflection on actual clinical use. In-depth research on methodological choices and the influence of key variables which impact COPD adherence evaluation in electronic healthcare databases is suggested.

Conclusions

This systematic review provides the first overview of methods to measure adherence in terms of initiation, implementation and persistence of COPD medication in electronic healthcare databases. The reporting of variables with an impact on adherence assessment, such as inpatient stays, drug substitutions, dose switches and early refills, is low. More attention to the reporting of the adherence method and influencing variables is desirable. Where there is lack of information about an influencing variable, authors should acknowledge this limitation.

Provenance: Submitted article, peer reviewed.

Acknowledgements: The authors want to thank Nele Pauwels (Knowledge Center for Health Ghent, Ghent University, Belgium), for her advice concerning the methodology of this systematic review.

Data availability: The data that support the findings of this study are available upon request from the corresponding author.

Author contributions: D. Vauterin was responsible for the study concept, design and data analyses. F. Van Vaerenbergh, A. Vanoverschelde and L. Lahousse provided feedback to D. Vauterin to optimise the methodology of this systematic review. D. Vauterin and F. Van Vaerenbergh performed the study selection, the quality assessment and the data extraction. D. Vauterin drafted the manuscript and F. Van Vaerenbergh, A. Vanoverschelde, J.K. Quint, K. Verhamme and L. Lahousse critically reviewed the manuscript. All authors read and approved the final manuscript.

Conflict of interest: Outside this manuscript, J.K. Quint received grants paid to her institution from the Medical Research Council, Health Data Research UK, GlaxoSmithKline, Boehringer Ingelheim, Asthma + Lung UK and AstraZeneca, and consulting fees from GlaxoSmithKline, Evidera, AstraZeneca and Insmed. None of which are related to the content of this work. Outside this manuscript, K. Verhamme received unconditional research grants paid to her institution from Chiesi, Amgen, Union Chimique Belge (UCB), Johnson & Johnson (J&J) and the European Medicines Agency (EMA). None of which are related to the content of this work. Outside this manuscript, L. Lahousse received a consulting fee paid to her institution from AstraZeneca and honoraria for lectures paid to her institution from Chiesi and IPSA vzw, a non-profit organisation facilitating lifelong learning for healthcare providers. L. Lahousse is an unpaid member of European Respiratory Society and Belgian Respiratory Society, member of Faculty board of Ghent University – Faculty of Pharmaceutical Sciences and faculty committees. None of which are related to the content of this work. All other authors declare no competing interests.

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