International Journal of Chronic Obstructive Pulmonary Disease Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Assessment of Medication Regimen Complexity of COPD Regimens in Individuals Visiting Community Pharmacies

Theresa R Prosser*, Suzanne G Bollmeier*

Department of Pharmacy Practice, St. Louis College of Pharmacy, University of Health Sciences & Pharmacy, St. Louis, MO, USA

*These authors contributed equally to this work

Correspondence: Theresa R Prosser, University of Health Sciences & Pharmacy, 4588, Parkview Place, St. Louis, MO, 63110, USA, Tel +1 314 446 8525, Fax +1 314 446 8500, Email Theresa.Prosser@uhsp.edu

Purpose: Non-adherence is common and linked to poor COPD outcomes. Medication Regimen Complexity Index (MRCI) scores affect other disease outcomes. Little is known about the implications of MRCI scores in COPD. Secondary analysis was done to calculate MRCI scores assessing relationship to symptoms, COPD severity and health literacy (HL) to identify potential interventions to optimize adherence.

Patients and Methods: Secondary analysis was conducted of cross-sectional, non-randomized survey data. Participants with self-reported COPD completed a survey of demographics, exacerbations, symptoms (COPD Assessment Test (CAT)), and self-reported COPD regimens. COPD severity was classified into Global Initiative for Chronic Obstructive Lung Disease (GOLD) ABCD categories using exacerbation history and CAT. CAT scores were categorized as low (<10), high (>10) and very high (>20). A 1-year proportion of days covered (PDC) was calculated. A MRCI calculator scored regimens (primary endpoint). Published cut-off points were used to categorize MRCIs as low (≤4), medium (5–8) and high (>8) and inhaled device polypharmacy (IDP) as ≥3 devices. Risk for low HL was assessed using a Single Item Literacy Screener. Descriptive and Chi-squared statistics were used.

Results: Participants' (N = 709) PDC for 1 maintenance medicine averaged 0.43 ± 0.37; 28.7% were adherent (PDC ≥ 80%). CAT scores were very high in 54.6% and high in 35.8%. Distribution of GOLD categories were A (6%), B (35%), C (4%) and D (55%). High, medium and low MRCI were 85%, 14% and 9%, respectively. Mean devices per regimen was 2.05 ± 0.8; IDP was 28%. MRCI and IDP increased with worsening CAT scores and COPD severity per GOLD category ($p<0.05$), but not low HL.

Conclusion: MRCI scores for COPD regimens increased with COPD severity and symptoms. Overall adherence was low despite high symptom scores; high MRCI scores could contribute. All COPD medication classes are available in multiple devices, combinations, and daily formulations; there is potential to simplify regimens. Prospective studies are needed to evaluate if interventions minimizing MRCI scores improve adherence and COPD outcomes.

Keywords: adherence, medication regimen complexity index, pharmacists, prescribing, pulmonary disease, chronic obstructive

Introduction

Chronic obstructive pulmonary disease (COPD) is in the top ten causes of death worldwide[1] and is an important source of disability, morbidity, and health-care costs from medications and urgent care.[2] Impact increases with age and prevalence of comorbidities including diabetes and cardiovascular disease.[2] Non-adherence in COPD is high and includes primary non-adherence, poor device technique and non-persistence.[3,4] Patients may be routinely prescribed complex medication regimens which can lower adherence.

The Medication Regimen Complexity Index (MRCI) is a validated tool to quantify the difficulty of correctly taking medications as prescribed.[5,6] It takes between 2–8 minutes to assess a regimen and has high inter-rater and test-retest reliability.[5] See Figure 1. The total of the three sub-scores can compare the regimen intricacy between individuals for the

Received: 18 April 2023
Accepted: 28 June 2023
Published: 19 July 2023

Subscale	Explanation
Subscale A: Dosage form/ route	Oral route is the least complicated to administer correctly. Inhaled medications can add 3-5 points depending on the complexity of device (e.g., metered-dose inhaler devices (+4), specific dry powdered inhalers (+3), and nebulizer (+5) have different device scores)
Subscale B: Dosage frequency	Additional points are added as the number of doses per day increases. A frequency of once daily (+1) scores fewer points than twice daily (+1), which is less than three times daily (+3). Specifically timed doses have a higher score. E.g., Every 8 hours is scored higher (+4) than three times daily (+3).
Subscale C: Additional Directions	Measuring adds complexity. E.g., multiple pills or inhalations, measuring specific amounts of liquids or nebulized solutions, or variable (1-2) inhalations are scored higher. Instructions for tapering or escalating doses or to take on an empty stomach or with food also increases the score.
Total score	The score for each medication is the sum of the subscales. (A + B+ C). The total score is the sum for all medications.

Example:

Subscale	A	B	C	total
roflumilast 1 tablet daily	1	1		2
albuterol nebulizer 1 ampule 4 times daily	5	4		9
albuterol metered dose inhaler 2 puffs 4 times daily as needed	4	2	1	7
ipratropium Respimat® 2 inhalations daily	3	1	1	5
fluticasone/salmeterol dry powdered inhaler 1 puff 2 times daily	3	2		5
Medication Regimen Complexity Index total	16	10	2	28

Subscale	A	B	C	total
roflumilast 1 tablet daily	1	1		2
albuterol nebulizer 1 ampule 4 times daily	5	4		9
albuterol metered dose inhaler 2 puffs 4 times daily as needed	4	2	1	7
budesonide/glycopyronium/fluticasone furoate inhaler 2 puffs 2 times daily	0 [a]	2	1	3
Medication Regimen Complexity Index total	10	9	2	21

Figure 1 Calculation of the medication regimen complexity index.
Note: [a]As another medication is already in an inhaler, no additional device points are added for the second medication in an inhaler.

same or between conditions. A disease-specific score could be calculated (e.g., COPD regimen only) or the total regimen MRCI (i.e., all medications). An expert panel proposed using the MRCI to identify patients who would likely benefit from medication regimen review by pharmacists.[6]

Regimen complexity might lower adherence and worsen outcomes including mortality, exacerbation frequency and health-care use. An MRCI score over 8 was associated with 30-day hospital readmissions.[7] Other data associated higher MRCI scores with increased mortality, non-adherence and hospitalizations in the elderly.[8] Total MRCI score was related to 30-day readmissions and urgent care use for chronic diseases including COPD.[9] Those readmitted or using urgent care had a total MRCI score of 30.8 but this was only 26.3 in those not requiring such care ($p<0.01$). In another study of chronic conditions, the MRCI predicted the potential for adverse drug events and unplanned 20-day hospital readmissions.[10] Authors suggested that MRCI might identify those potentially benefiting from transitions of care interventions.

Data on MRCI COPD-specific regimens are very limited.[11,12] Complex medication regimens were shown to be associated with COPD severity and comorbid conditions.[11] An MRCI of 6 or more has been suggested as a screen for non-adherence.[12]

Objective

To perform a secondary analysis of previously collected data to calculate MRCI scores for COPD-specific regimens of participants from community pharmacies across Missouri and assess relationship to symptom and disease severity.

Materials and Methods

Study Design

For the initial study, inclusion criteria included participants over 40 years old with self-reported COPD, chronic bronchitis and emphysema who were recruited from 19 independent and 16 small-chain Missouri community pharmacies between October 10, 2016 and April 30, 2017. Dispensing records had screened for COPD medications in the previous 12 months including short-acting muscarinic antagonists (SAMA), long-acting muscarinic antagonists (LAMAs), long-acting beta agonists (LABAs), roflumilast and/or theophylline. Inclusion criteria also required that participants spoke English, were able to provide informed consent, complete a written questionnaire, and visit the community pharmacist investigator (CPI) within 30 days. The CPIs recruited 25 participants per pharmacy. Exclusion criteria were cognitive impairment limiting ability to participate in a face-to-face study visit, non-English speaking, and previously participating in this study at a different pharmacy site.

Participants were offered assistance with the questionnaire if the response to the Single-Item Literacy Screen (SILS) question[13] indicated a risk for low health literacy based on self-reported confidence in completing medical forms. Demographic information, COPD assessment test (CAT) symptom score, antibiotic and oral corticosteroid usage in the last year, selected co-morbidities, estimated out-of-pocket monthly expenses for COPD medicines and all medicines, and insurance type were collected.

Participants listed all breathing-related medications and current instructions after an open-ended prompt. The CPI further prompted for unmentioned COPD medicines on the dispensing record. If the medicine was still taken, it was added to the current COPD regimen. Additional prompts were given for samples and patient assistance medications. De-identified 12-month dispensing reports were used to calculate the individual proportions of days covered (PDCs). Detailed methodology for recruitment and data collection are reported with the initial study.[14] The St. Louis College of Pharmacy Institutional Review Board approved the protocol as consistent with the Nuremberg Code, Declaration of Helsinki, and Belmont Report. A waiver of consent for reviewing recruitment phase prescription data was also provided.

Data Analysis

Pharmacy prescription fill data were used to calculate the PDC for any one COPD maintenance medication rather than for each individual medication using previously described methods.[15] Adherence was defined as PDC ≥0.80. Symptoms of COPD were assessed using the COPD Assessment Test Score (CAT) and categorized as low symptoms (<10), medium symptoms (10–20), or very symptomatic (>20).[16,17]

The participant's Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2022 ABCD group was classified by primary investigators using CAT scores and risk for exacerbations[2] based on history of hospitalizations and oral corticosteroid and antibiotic use in the last year. Self-reported use of either an oral corticosteroid or antibiotic were considered "moderate" exacerbations. Use of an antibiotic and corticosteroid once each (or one of either) in the last 12 months was considered one exacerbation, use twice was counted as two exacerbations, and episodes associated with hospitalization or urgent care were classified as "severe".

The self-reported list of current COPD medicines (including samples and patient assistance medicines) was used as the COPD regimen. Medicines self-discontinued (i.e., participant reported providers were unaware of discontinuation) were included in the current regimen, but not medicines reported as discontinued by providers. A medication count in the regimen consisted of the number of unique medications in the regimen (e.g., albuterol by inhaler and nebulizer are considered one medication); a combination product containing fluticasone and salmeterol were counted as two medications. The formulation count in the regimen consisted of the number of products (e.g., fluticasone plus salmeterol was counted as one formulation). However, albuterol inhaler and albuterol nebulizing solution were counted as two formulations. The number of maintenance medications included any regularly scheduled medication (including scheduled SABA and SAMA). The number of distinct devices was also calculated. Inhaled device polypharmacy (IDP) was identified as using three or more different respiratory devices.[18]

The MRCI for each COPD regimen was calculated using validated, previously published methods.[5] See Figure 1. The University of Colorado's electronic MRC Data Capture Tool and accompanying MRCI additional instructions[19] were

used to calculate MRCIs for the COPD regimen including as-needed medications. To update for newer respiratory devices, Respimat® was given a device weighting score of 3;[11] Neohaler® was weighted as 3 (consistent with Handihaler® capsule device). Pressair® and Ellipta® were weighted as "other dry powdered inhalers" (+3 weight). Ellipta® and Diskus® are not identical, so were counted as separate devices of equal complexity (+3 weight). MRCI regimen scores were categorized as low (≤4), medium (5–8) or high (>8).[18] Descriptive statistics were employed for demographic and regimen-related data. Chi-squared compared categorical data with significance defined as $p<0.05$.

Results

Baseline demographic data are summarized in Table 1. Most participants had a history of prior or current tobacco use, co-morbidities and some form of insurance. Self-reported spending on COPD and all medications was widely variable.

Table 1 Baseline Demographics and Clinical Characteristics of Participants

	N=709
Age, years, mean (SD)	63.0 (10.4)
Female, n (%)	400 (56.4)
Ethnicity: Hispanic or Latino, n (%)	26 (3.7)
Race: White, n (%)	603 (85)
Geographic designation of pharmacy	
Urban	27.6%
Rural	70.5%
Unknown	1.9%
Smoking status, n (%)[a]	
Current tobacco use	334 (47.4)
Former tobacco/nicotine use	182 (25.8)
Never smoked	88 (12.5)
Comorbidities, n (%)[b]	
Anxiety	384 (54.1)
Depression	369 (52.0)
Skeletal muscle weakness	326 (46.0)
Heart disease	248 (34.5)
Metabolic syndrome	214 (30.2)
Osteoporosis	136 (18.1)
Lung cancer	45 (6.3)
None	81 (11.4)
Insurance Type[b], n (%)	
Medicare	481 (67.8)
Medicaid	334 (47.1)

(*Continued*)

Table 1 (Continued).

	N=709
Private managed health insurance plan	208 (29.1)
None	24 (3.4)
Unknown	26 (3.7)
Self-reported Out-of-Pocket Medication Spending per Month, US dollars, range, interquartile range	
COPD (n = 668), median $10	0-$400, $84
All medications (n = 672) median $30	0-$465, $140
Body Mass Index, n (%)	
≥ 30 kg/m^2	321 (45.3)
Mean (SD)	30.4 (8.6)
Under care of pulmonologist, n (%)	250 (35.3)
Overall CAT score, mean (SD)	21.5 (8.4)
Overall CAT score, median (interquartile range)	21 (16–27)
GOLD Classification, n (%)	
Group A (CAT <10 and <2 exacerbations and without hospitalizations in last year)	42 (6)
Group B (CAT ≥10 and <2 exacerbations and without hospitalizations in last year)	270 (35)
Group C (CAT <10 and >2 exacerbations or 1 hospitalization in last year)	28 (4)
Group D (CAT ≥10 and >2 exacerbations or 1 hospitalization in last year)	369 (55)
Adherence	
PDC for any 1 COPD maintenance medication, mean (SD)	0.43 (0.37)
Participants with PDC >80%	28.7%
Health Literacy[c], n (%)	
At risk for low health literacy	233 (32.9)
Medications in COPD regimen[b], n (%)	
LABA	494 (69.7)
LAMA	302 (42.6)
ICS	479 (68.5)
Theophylline	9 (1.3%)
Roflumilast	31 (4.4)
SABA	178 (25.1)
SAMA	623 (87.9)
Number of maintenance medications per regimen, mean (SD)	1.85 (1.08)

Notes: [a]Remainder have no response or various nicotine replacement/smokeless tobacco use. [b]May include more than one response or medication. [c]Responded "Not at all", "a little bit" or "Somewhat confident" to completing medical forms by oneself.
Abbreviations: CAT, COPD assessment test; COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroid; LABA, long-acting beta agonist; LAMA, long-acting muscarinic antagonist; PDC, proportion of days covered; SABA, short-acting beta agonist; SAMA, short-acting muscarinic antagonist; SD, standard deviation.

The participant population was highly symptomatic (mean CAT 21.5 ± 8.4; 90% in GOLD categories B or D) and at high risk for exacerbations (59% GOLD categories C or D). Adherence to even one maintenance COPD medication was extremely low (average PDC 0.43 ± 0.37); PDC >80% for one medication (28.7%). Approximately one third of participants were at risk for low health literacy and under the care of a pulmonologist. The most common medications in regimens were LABA, ICS and SABA.

Data related to the MRCI are reported in Table 2. The average COPD MRCI score was 14.05 ± 5.4, with sub-score A (7.73 ± 3.2) and B (4.71 ± 2.2) contributing the majority. The COPD MRCI scores increased across the GOLD categories A to D. Over 90% reported an inhaler device with 30–40% using other devices as well. Close to 30% used three or more devices (i.e., inhaled device polypharmacy). The medication count averaged 3.79 ± 1.5 different medications with similar averages across CAT symptom and GOLD categories. Considering combination inhalers, the number of different formulations was 2.54 ± 1.1.

Table 2 Medication Regimen Complexity Data

	N=709
COPD Total MRCI, average (SD)	14.05 (5.4)
Low (MRCI ≤4) n, (%)	9 (1.2)
Medium (MRCI 5–8) n, (%)	99 (14)
High (MRCI > 8) n, (%)	601 (84.8)
COPD MRCI Sub-scores average (SD)	
Sub-score A (route or device)	7.73 (3.2)
Sub-score B (frequency of administration)	4.71 (2.2)
Sub-score C (special instructions)	1.65 (0.8)
COPD MRCI by GOLD group, average (SD)	
GOLD A (CAT score <10 without exacerbations in last year)	9.9 (4.3)
GOLD B (CAT score ≥10 without exacerbations in last year)	12.6 (4.82)
GOLD C (CAT score <10 with exacerbations in last year)	14.4 (4.96)
GOLD D (CAT score ≥10 with exacerbations in last year)	15.5 (5.37)
Devices per regimen, mean (SD)	2.05 (0.8)
Devices[a], n (%)	
Inhalers	642 (90.5%)
Respimat® or Handihaler®/Neohaler®	246 (34.7)
Other Dry powdered inhalers[b]	300 (42.3)
Nebulizer	247 (34.8)
Inhaled device polypharmacy[c] (IDP), n (%)	198 (27.9)
COPD Medication count[d] per regimen, mean (SD)	3.79 (1.5)
Medication count, mean (SD)	
CAT <10,	3.5 (1.2)
CAT 10–20	3.7 (1.4)
CAT >20	3.9 (1.5)
COPD Medication count[d] per GOLD group, mean (SD)	
GOLD A CAT score <10 without exacerbations in last year	3.3 (1.1)
GOLD B CAT score >10 without exacerbations in last year	3.5 (1.42)
GOLD C CAT score <10 with exacerbations in last year	3.7 (1.31)
GOLD D CAT score >10 with exacerbations in last year	4.3 (1.51)
Number of inhaled formulations[e] per COPD regimen, mean (SD)	2.54 (1.1)

Notes: [a]Responses were not mutually exclusive. [b]Other Dry powdered inhalers included Diskus®, Ellipta® or Pressair®. [c]Three or more different inhalation devices.[11] [d]Medication count in the regimen: number of unique medications in the regimen e.g., Albuterol by inhaler and nebulizer are considered 1 medication; a combination product containing fluticasone and salmeterol are counted as 2 medications. [e]Combination products are counted as 1 formulation (e.g., fluticasone plus salmeterol combination would be counted as 1 formulation).
Abbreviations: CAT, COPD Assessment Score; MRCI, Medication Regimen Complexity Index; SD, standard deviation.

Statistical analysis of MRCI, inhaled device polypharmacy, and health literacy is reported by GOLD category and CAT scores in Table 3 and Table 4. High MRCI scores (>8) increased in GOLD Category C and D as did IDP ($p<0.05$). Similarly, MRCI increased and IDP increased with CAT score ($p<0.05$). No MRCI difference was detected based on risk for low health literacy for either GOLD category or CAT scores.

Discussion

In this analysis, scores for COPD MRCI appear high and regimens averaged almost four medications. This is consistent with a smaller COPD MRCI sampling previously reported.[11] See Table 5. The MRCI for COPD regimens also appears higher compared with other disease-specific MRCI reported. These participants' COPD MRCI averaged 14.05 ± 5.4 compared with congestive heart failure (7.2 ± 3.4)[20], HIV (4.93 ± 2.12)[19], geriatric depression (3.03 ± 1.1)[19] and hypertension (3.53 ± 1.47).[19]

Diabetes might be expected to have a higher MRCI than other chronic conditions due to regimens containing multiple oral and injectable medications. The diabetes MRCI in an Ethiopian study ranged from 2–10.[18] (See Table 5). The percentages in MRCI categories of low (≤4), medium (5–8) or high (> 8) complexity were 31.3%, 46.4 and 22.2% respectively. They reported 70% medication adherence using the 8-point Morisky Medication Adherence Scale (score >8) with 43% having good glycemic control (fasting blood glucose between 70–130 mg/dL). High MRCIs correlated to lower adherence and poorer control; low or medium MRCIs did not affect either. By comparison, close to 85% of

Table 3 Medication Regimen Complexity, Inhaled Device Polypharmacy and Health Literacy by GOLD Severity Classification[a] (N = 709)

	Group A 42 (6)	Group B 270 (35)	Group C 28 (4)	Group D 369 (55)	p values
MRCI scores[b], n (%)					
Low ≤4	3 (7)	4 (1)	1 (3.5)	1 (0.3)	< 0.05
Medium 5–8	13 (31)	53 (20)	1 (3.5)	32 (8.7)	
High >8	26 (62)	213 (79)	26 (93)	336 (91)	
Inhaled device polypharmacy[c], n (%)	5 (11.9)	56 (20.7)	9 (32.1)	128 (32.9)	<0.05
Health literacy[d] (at risk), n (%)	12 (28.6)	83 (30.7)	7 (25)	131 (35.5)	0.363

Notes: [a]GOLD classification based on COPD Assessment Test Score (CAT) and exacerbation history in the last year.[2] [b]MRCI categorized as low, medium and high regimen complexity.[18] [c]Inhaled device polypharmacy defined as 3 or more different respiratory devices (n=198).[11] [d]Per Single Item Literacy Screening question responses of "Not at all", "A little bit" or "Somewhat confident" completing medical forms[13] (n=233) at risk for low health literacy.
Abbreviation: MRCI, medication regimen complexity index.

Table 4 Medication Regimen Complexity, Inhaled Device Polypharmacy and Health Literacy by CAT Score (N= 709)

	CAT <10 68 (9.6)	CAT 10–20 254 (35.8)	CAT > 20 387 (54.6)	p values
MRCI scores[a], n (%)				
Low ≤4	3 (4.4)	4 (1.6)	1 (0.3)	0.001
Medium 5–8	14 (20.6)	46 (18.1)	40 (10.3)	
High > 8	51 (75)	204 (80.3)	346 (89.4)	
Inhaled device polypharmacy[b], n (%)	13 (19)	54 (21.2)	131 (33.9)	<0.05
Health literacy[c] (at risk), n (%)	20 (8.6)	77 (33)	136 (58.4)	0.415

Notes: [a]MRCI categorized as low, medium and high regimen complexity.[18] [b]Inhaled device polypharmacy defined as 3 or more different respiratory devices (n = 198).[11] [c]Per Single Item Literacy Screening question responses of "Not at all", "A little bit" or "Somewhat confident" completing medical forms[13] (n = 233) at risk for low health literacy.
Abbreviations: CAT, COPD Assessment Test; MRCI, medication regimen complexity index.

Table 5 Comparison of Reported MRCI for Chronic Disease Regimens

Disease	Sample Size	Number of Disease-Specific Medicines Mean (SD)	Range of Disease-Specific Medicines	Disease-Specific MRCI Mean (SD)	Range of Disease-Specific MRCI
Geriatric depression[19]	100	1.19 (0.42)	1–3	3.03 (1.12)	2–6.5
HIV[19]	100	2.33 (2.12)	1–6	4.92 (2.12)	2–12
Hypertension[19]	100	2.06 (1.03)	1–5	3.52 (1.47)	2–9
Diabetes[19]	100	1.93 (3.10)	1–4	6.28 (3.10)	1–15
Type 2 diabetes[18]	275	n/a	n/a	n/a	2–10
Heart failure[20]	145	3.2 (1.3)	0–7	7.2 (3.4)	0–15
COPD[11]	222	3 (3.4)[a]	n/a	14.5[a] (11.5, 17.5)	n/a
COPD (this analysis)	709	3.79 (1.5)	1–7	14.05 (5.4)14[a] (7, 17)	4–32

Note: [a]Median (quartile 1, quartile 3).
Abbreviations: n/a, not available; MRCI, medication regimen complexity index; SD, standard deviation.

participants in this study had a high MRCI (>8). This study lacked participant-specific PDC data, but adherence overall was very low (only about 29% adherent to even one maintenance medication). While possible, it is unknown whether higher MRCI COPD regimens in this study correlated to lower adherence.

In a US-based study,[19] diabetes regimens were reported to have a mean MRCI of 6.28 ± 3.4 (range 1–15) with a median of almost 2 medications. By comparison, in this COPD sampling the total and range of MRCI as well as number of disease-specific medications was much higher.

Data available on COPD-specific MRCI are limited.[11,12] For 222 Australians with COPD, the number of COPD-specific medications and MRCI are reported in Table 5.[11] Sub-scales A and B had more impact on the total COPD MRCI than sub-score C. The MRCI scores were significantly higher for participants in GOLD category D than A, B or C (15.5 vs 13.5, 12.5 and 13, respectively); the total medication number and devices were also higher in GOLD group D. Device polypharmacy was seen in 30.6%. The COPD MRCI scores, MRCI A and B sub-scores' relative contribution to the total MRCI, and incidence of IDP were similar to this analysis.

However, the Australian study[11] also looked at the participants' MRCI for all diseases and relationship to COPD outcomes. Participants with cardiovascular, gastrointestinal and neurologic comorbidities had a higher total MRCI with non-COPD MRCI making a greater contribution to total MRCI. Whereas both COPD and non-COPD medications contributed to higher MRCI scores in participants with metabolic or psychiatric comorbidities. COPD-specific MRCI and COPD-specific medication count were significantly correlated to COPD outcomes, such as CAT symptom scores, St. George Respiratory Questionnaire scores, 6-minute walk test, and prior year exacerbation and hospitalization history.

A US study assessed the association between total MRCI with adherence and COPD outcomes of 400 participants with COPD plus either hypertension or diabetes or both.[12] The total MRCI was calculated for all maintenance medications, but as-needed medications were not included. Adherence over 15 months was measured by self-report (Medication Adherence Rating Scale) and device dose counters. Severity was measured by COPD Severity score. The total MRCI was not significantly different between those with low and adequate adherence by self-report (33.5 ± 13.4 vs 32 ± 13.6) or by device dose counter (32.7 ± 13.6 vs 31.5 ± 13.6). There was a low correlation between COPD Severity scores and total MRCI score ($r = 0.26$, $p<0.0001$) and medication counts ($r = 0.19$; $p<0.0001$). Interestingly, there was no correlation between the total MRCI score and either blood pressure or diabetes control. Low COPD medication adherence (less than 80%) was 45% (self-report) and 52.6% (dose count); low adherence was less frequent for hypertension (28.9%) and diabetes (38.8%). Unfortunately, COPD-specific MRCI scores were not reported, but some associations between total MRCI scores and COPD severity and adherence were reported. In comparison, adherence by

self-report and dose counters were higher than in this analysis using PDC. Fewer participants (24%) were at risk of low health literacy (also assessed by the Single Item Literacy Screener) than in this analysis.

These data[11,12] along with this analysis support further investigation of the relationship between COPD MRCI scores and outcomes. For example, does an increasing MRCI score contribute to poor outcomes (e.g., lower adherence, more exacerbations)? Or does undetected non-adherence result in additional medication prescribing causing higher MRCI scores? Are increases in MRCI scores secondary to COPD progression over time? Additionally, COPD MRCI scores should be studied in the context of an individual's total medication regimen MRCI score. Those with COPD appear to have a high incidence of comorbidities, likely contributing to the total regimen MRCI scores.

An MRCI score has potential clinical applications for COPD patients. For example, prescribers and pharmacists can intervene when encountering patient regimens with high MRCI scores and low adherence based on PDC. An initial screen of COPD patient regimens can identify those with both a high total MRCI score (for all medications) and a high COPD MRCI score (>8). Patients with several medications (maintenance and as needed), various devices, and multiple daily dosing schedules may easily have a COPD MRCI score in the range of 15–20. Combining very high symptoms (e.g., CAT >20) with a high COPD MRCI score (e.g., >15) and a low PDC could provide a useful screen to target regimens for interventions. Health-care professionals have opportunities to intervene during medication reconciliation at transitions of care to lower regimen complexity, potentially improving adherence and hospital readmission rates.

As the largest portion of the MRCI score comes from A and B sub-scales, logical interventions would include decreasing the number of devices and formulations and by continuing a device the patient already knows and uses correctly (i.e., device continuity).[21] In considering how to simplify COPD regimens, Table 6 includes factors to consider and Figure 2 lists FDA-approved medications in available devices. For example, a patient has prescriptions for a SABA in a metered dose inhaler (MDI), and maintenance medicines an ICS/LABA, and a LAMA in two other devices. Device polypharmacy (i.e., three devices) exists. But all drug classes are available in MDIs. By recommending a switch to a combination ICS/LABA/LAMA MDI (budesonide/glycopyrronium/fluticasone furoate) only an MDI device is used for both maintenance and SABA and only one maintenance formulation. The device MRCI sub-score for maintenance medicines decreases from 10 to 4 and combined frequency and directions sub-scores decrease from 4 to 3 (decreasing the total COPD MRCI by 7). (See Figure 1.) It may be more commonplace to replace 3 or 4 devices with 2. For example, a regimen consists of LAMA twice daily and LABA once daily in different dry powdered formulations plus albuterol MDI as needed. A once daily combination LABA/LAMA dry powdered product (and continuing albuterol MDI as needed) could decrease both the number of devices and doses. Both examples lowered the MRCI score, however the total MRCI score would still be "high" at >8. On the other hand, providers and pharmacists may identify highly symptomatic individuals despite adherence to therapy. In such cases it would be useful to consider "stepping up" therapy with minimal MRCI score increases (e.g., adding a combination formulation or an additional medication in the same device vs another

Table 6 Factors to Consider Before Recommending Device Regimen Changes

Cost	• Will new device(s) be covered on patient's insurance formulary? • Are programs available to decrease cost? (E.g., patient assistance programs, coupons) • Are generic medications available in this device?
Device-related	• Does patient have co-morbid condition(s) making a specific device not preferred (e.g., manual dexterity or vision problems) • Has patient mastered the device technique? • Can patient mount the inspiratory effort needed to properly utilize the device? (Dry powdered inhalers.) • Does patient prefer one type of device over another?
Regimen-related	• Will this regimen decrease frequency of dosing? • Will this regimen decrease overall number of respiratory devices?
Patient-related	• Use shared decision making to ensure patient preference plays a role. • Can patient buy-in be obtained related to new device regimen?

Device available & Drug classes	MDI	Digihaler	Respiclick	Ellipta	Diskus	Respimat	Twisthaler	Flexhaler	Redihaler	Inhub	Handihaler	Pressair
SABA	LEV ALB	ALB	ALB									
SAMA	IPRA											
SABA/SAMA						ALB/IPR						
LABA					SAL	OLO						
LAMA				UM		TIO					TIO	ACL
LABA/LAMA	GLY/FF			UM/VIL		TIO/OLO						ACL/ FF
LABA/LAMA/ICS	BUD/GLY/FF			FF/UM/ VIL								
ICS	CIC MOM FP	FP	FP	FF	FP		MOM	BUD	BEC			
ICS/LABA	FP/SAL MOM/FF BUD/FF	FP/SAL	FP/SAL	FF/VIL	FP/SAL					FF/SAL		
Is generic available?	ALB BUD/FF	No	No	No	FP/SAL	No	No	No	No	FP/SAL	No	No
Typical dosing frequency for maintenance medications:	variable	Twice daily	Twice daily	Once daily	Twice daily	Once daily	Twice daily	Twice daily	Twice daily	Twice daily	Once daily	Twice daily

Figure 2 FDA approved COPD medications and available devices[a].
Note: [a]When making product switches, consider if a similar dose (e.g., low, medium, high) is available in new device.
Abbreviations: ACL, aclidinium; ALB, albuterol; BEC, beclomethasone; BUD, budesonide; CIC, ciclesonide; FF, formoterol furoate; FP, fluticasone propionate; GLY, glycopyrrolate; IPRA, ipratropium; LABA, long-acting beta agonist; LAMA, long-acting muscarinic antagonist; LEV, levalbuterol; MDI, metered-dose inhaler; MOM, mometasone; OLO, olodaterol; SABA, short-acting beta agonist; SAL, salmeterol; SAMA, short-acting muscarinic antagonist; TIO, tiotropium; UM, umeclidinium; VIL, vilanterol.

drug in a different device). When brainstorming, simplification strategies such as co-pays, formulary status, patient device preferences and ability to use devices correctly are also important to consider (Table 6).

In designing interventions, not all factors affecting adherence, adverse events or poor health outcomes are included in the MRCI score. For example, warfarin orally once daily may have a low MRCI score, but the underlying condition and bleeding may result in adverse outcomes despite good adherence. Current data do not indicate a relationship between MRCI and low health literacy. However, in individuals with low health literacy, high total or COPD MRCI may require more caregiver home support including use of medication organizational tools such as pill boxes, medication alarms, phone apps, etc.

Strengths

Our secondary analysis of previously collected data had a larger participant size than other MRCI reports for COPD or other chronic diseases. Including both rural and urban participants with COPD from across the state lends some external validity. A uniform method of collecting medication histories was used. The COPD regimen was collected from the participant perspective likely reflecting the participants' "real world" perception of their regimen complexity. The MRCI was calculated using validated methods and an automated program for uniformity and accuracy. This report adds to the limited data available on the MRCI in COPD and matches MRCI scores to COPD symptoms and GOLD severity categories (A, B, C, D). The risk for low health literacy was evaluated in relation to COPD MRCI scores.

Limitations

This secondary analysis does have drawbacks. First, participants' self-reported COPD without spirometric confirmation; however, these data could apply to those with respiratory diseases. Second, MRCI was not matched to patient-specific PDCs; adherence was calculated for the entire cohort. However, overall adherence was extremely poor for even one maintenance medication. Future studies would benefit from calculating the total MRCI. As co-morbidities were common, other medications (e.g., metformin, insulin, lisinopril, atorvastatin) could add substantially to the MRCI total score, adversely affecting adherence and outcomes. Participants' self-reported medication costs were collected and risk for low health literacy was assessed. However, it would be useful in future studies to attempt to capture actual and perceived burden of medication costs. It would be important to consider health literacy and medication costs when interpreting the impact of lowering MRCI scores on adherence and COPD outcomes.

Future Research

There is a need for further investigation of MRCI scores in COPD. Prospective studies are needed to assess if decreasing COPD-specific or total MRCI scores improves adherence or COPD outcomes (e.g., lowers symptoms, exacerbation frequency, urgent care use, hospital admissions or readmissions) or decreases health-care and medication costs. Nothing has been reported about the effect of MRCI score on patients' experience. E.g., what is the patient's perception of the burdensomeness of taking medications? Do patients feel more empowered if included in shared decision-making regarding device selection?

Another avenue to explore would be comparing patient-specific PDC to MRCI scores. This would help assess the individual impact of COPD as well as the entire medication regimen on individual adherence. Including non-prescription medications in the calculation of total MRCI score has been suggested as these can add to the overall score.[22] An integrated assessment of MRCI score into the electronic record or prescription dispensing systems could also help identify high MRCI[23] scores making it easier for prescribers and pharmacists to identify and simplify complex regimens. Prescription dispensing systems that calculate MRCI scores (both total and COPD specific) could help pharmacists identify patients for therapeutic and transition of care interventions.

Of note GOLD 2023 recommendations[24] adjusted the ABCD categories. Categories C and D were collapsed into a single category of those at high risk for exacerbations (category E). Due to the small number of our participants in the C category, this would not be expected to alter our overall results. However, the new categories (A, B, E) should be used in future studies.

Conclusion

COPD MRCI scores are higher than for other chronic diseases; COPD MRCI scores increase with symptom scores and GOLD severity categories. The MRCI could be used to identify complex regimens and patients who may benefit from prescriber and pharmacist interventions. More research is needed to assess whether prospectively lowering MRCI scores could improve adherence and COPD outcomes.

Funding

No grant or other funding was received to support the secondary data analysis or publication of this work.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Centers for Disease Control. Leading causes of death. Available from: https://www.cdc.gov/nchs/fastats/leading-causes-of-death.htm. Accessed April 10, 2023.
2. Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease, 2022 report. Available from: https://goldcopd.org/wp-content/uploads/2021/12/GOLD-REPORT-2022-v1.1-22Nov2021_WMV.pdf. Accessed April 10, 2023.
3. van de Hei SJ, Dierick BJH, Aarts JEP, Kocks JWH, van Boven JFM. Personalized medication adherence management in asthma and chronic obstructive pulmonary disease: a review of effective interventions and development of a practical adherence toolkit. *J Allergy Clin Immunol Pract*. 2021;9(11):3979–3994. doi:10.1016/j.jaip.2021.05.025
4. Jansen EM, van de Hei SJ, Dierick BJ, Kerstjens HA, Kocks JW, van Boven JF. Global burden of medication non-adherence in chronic obstructive pulmonary disease (COPD) and asthma: a narrative review of the clinical and economic case for smart inhalers. *J Thorac Dis*. 2021;13(6):3846–3864. doi:10.21037/jtd-20-2360
5. George J, Phun YT, Bailey MJ, et al. Development and validation of the medication regimen complexity index. *Ann Pharmacother*. 2004;38(9):1369–1376. doi:10.1345/aph.1D479
6. Hirsch JD, Metz KR, Hosokawa PW, et al. Validation of a patient-level medication regimen complexity index as a possible tool to identify patients for medication therapy management interventions. *Pharmacotherapy*. 2014;34(8):826–835. doi:10.1002/phar.1452
7. Wilson MN, Breer CL, Weeks DL. Medication regimen complexity and hospital readmission for an adverse event. *Ann Pharmacother*. 2014;48(1):26–32. doi:10.1177/1060028013510898
8. Brysch EG, Couthon KA, Kalich BA, Sarbacker GB. Medication regimen complexity index in the elderly in an outpatient setting: a literature review. *Consult Pharm*. 2018;33(9):484–496. doi:10.4140/TCP.n.2018.484
9. Abu-Karam N, Bradford C, Lor KB, et al. Medication regimen complexity and readmissions after hospitalization for heart failure, acute myocardial infarction, pneumonia, and chronic obstructive pulmonary disease. *Sage Open Med*. 2016;4:1–9. doi:10.1177/2050312116632426

10. Schoonover H, Corbett CF, Weeks DL, Willson MN, Setter SM. Predicting potential post-discharge adverse drug events and 30-day unplanned hospital readmissions from medication regimen complexity. *J Patient Saf*. 2014;10(4):186–191. doi:10.1097/PTS.0000000000000067
11. Negewo N, Gibson PG, Wark PAB, et al. Treatment burden, clinical outcomes, and comorbidities in COPD: an examination of the utility of medication regimen complexity index in COPD. *Int J Chron Obstruct Pulmon Dis*. 2017;12:2929–2942. doi:10.2147/COPD.S136256.
12. Federman AD, O'Conor R, Wolf M, Wisnivesky JP. Associations of medication regimen complexity with COPD medication adherence and control. *Int J Chron Obstruct Pulm Dis*. 2021;16:2385–2392. doi:10.2147/COPD.S310630
13. Chew LD, Griffin JM, Partin MR, et al. Validation of Screening Questions for Limited Health literacy in a large VA outpatient population. *J Gen Intern Med*. 2008;23(5):561–566. doi:10.1007/s11606-008-0520-5
14. Bollmeier SG, Seaton TL, Prosser TR, et al. Assessment of chronic obstructive pulmonary disease symptom burden and medication adherence within a community pharmacy setting. *JAPhA*. 2019;59(4):479–488. doi:10.1016/j.japh.2019.04.017
15. Peterson AM, Nau DP, Cramer JA, Benner J, Gwadry-Sridhar F, Nichol M. A checklist for medication compliance and persistence studies using retrospective databases. *Value Health*. 2007;10(1):3–12. doi:10.1111/j.1524-4733.2006.00139.x
16. The COPD Assessment Test (CAT). Available from: https://www.catestonline.org/hcp-homepage.html. Accessed April 10, 2023.
17. Jones PW, Harding G, Berry P, Wiklund I, Chen WH, Kline Leidy N. Development and first validation of the COPD Assessment Test. *Eur Resp J*. 2009;3(3):648–654. doi:10.1183/09031936.00102509
18. Ayele AA, Tegegn HG, Ayele TA, Ayalew MB. Medication regimen complexity and its impact on medication adherence and glycemic control among patients with type 2 diabetes in an Ethiopian general hospital. *BMJ Open Diab Res Care*. 2019;7(1):e000685. doi:10.1136/bmjdrc-2019-000685
19. Libby AM, Fish DN, Hosokawa PW, et al. Patient-level medication regimen complexity across populations with chronic disease. *Clin Ther*. 2013;35(4):385–398. doi:10.1016/j.clinthera.2013.02.019
20. Corbetti MR, Page RL, Linnebur SA, et al. Medication regimen complexity in ambulatory older adults with heart failure. *Clin Interv Aging*. 2017;12:679–686. doi:10.2147/CIA.S130832
21. Halpin DMG, Mahler DA. A systematic review of published algorithms for selecting an inhaled delivery system in chronic obstructive pulmonary disease. *Ann Am Thoracic Soc*. 2022;19(7):1213–1220. doi:10.1513/AnnalsATS.202108-930OC
22. Lenz M, Clark JA, Gates BJ. Medication regimen complexity in patients receiving consultant pharmacy services in home health care. *Sr Care Pharm*. 2020;35(2):81–84. doi:10.4140/TCP.n.2020.81
23. Chang WT. Medication regimen complexity index. (editorial). *Sr Care Pharm*. 2020;35(2):50–51. doi:10.4140/TCP.n.2020.50
24. Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease, 2023 GOLD Report. Available from: https://goldcopd.org/2023-gold-report-2. Accessed April 10, 2023.