Effect of Changing COPD Triple-Therapy Inhaler Combinations on COPD Symptoms

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ABSTRACT

OBJECTIVES: To determine if symptoms changed after changing chronic obstructive pulmonary disease (COPD) triple-therapy inhalers to a less expensive regimen.

STUDY DESIGN: Retrospective observational case-series analysis.

METHODS: A quality improvement program was instituted to reduce drug costs associated with COPD inhalers between fall 2016 and spring 2017. Patients identified as taking an inhaled corticosteroid (ICS)/long-acting β agonist (LABA) inhaler and a long-acting muscarinic agonist (LAMA) inhaler were changed to a LAMA/LABA inhaler and an ICS inhaler. Symptoms were assessed at baseline and subsequent follow-up using the COPD Assessment Test (CAT), with lower scores representing better symptom control. Then, a retrospective observational case-series analysis of 118 patient charts was completed. The primary outcome was mean difference in CAT score. Data were analyzed using a paired *t* test with an α value of 0.05.

RESULTS: Of 118 patients included in the quality improvement program, 19 met the inclusion and exclusion criteria. The mean (SD) CAT score prior to the change was 15.53 (5.36), and the mean (SD) CAT score after the change was 14.68 (6.98). Symptom scores improved after the change, with an average difference in postchange and prechange CAT scores of −0.84, although this difference was not statistically significant (95% CI, −3.57 to 1.89; *P* = .525).

CONCLUSIONS: Based on the results of this observational review, changing COPD triple-therapy inhalers did not result in a significant change in patient-reported symptom scores. Patients may use triple-therapy inhalers that are most affordable without a significant change in symptom control.

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Chronic obstructive pulmonary disease (COPD) triple therapy consists of treatment with an inhaled corticosteroid (ICS), a long-acting β agonist (LABA), and a long-acting muscarinic antagonist (LAMA). Studies comparing COPD triple therapy regimens are scarce despite the 2017 Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines recommending triple therapy as a step-up option in patients with severe symptoms and a history of multiple exacerbations.[1] Even with these guideline recommendations, there is no guidance for which specific inhalers to use.

Comparisons among triple-therapy combinations are limited. Recently, studies have shown the benefits of newer single-inhaler triple-therapy combinations compared with single or dual therapy.[2,3] Withdrawal of an ICS from triple therapy does not significantly affect exacerbation rates, although a decrease in forced expiratory volume in 1 second (FEV_1) was seen in one study.[4] A recent meta-analysis showed that the addition of a LAMA to a LABA improved FEV_1 compared with addition of an ICS to a LABA, but there was no significant impact on patient symptom scores.[5] In a randomized controlled trial comparing exacerbation rates in patients with COPD, LAMA/LABA inhalers were significantly better at reducing the risk of any exacerbation compared with ICS/LABA inhalers.[6]

The pharmacy department at Buffalo Medical Group, PC, in Buffalo, New York, is part of a large patient-centered medical home (PCMH) and works closely with a local insurance company for various population health initiatives. According to the insurer's 2016 formulary, single-agent ICS inhalers were in a lower tier than any other single or combination inhaler. According to 2015 gross cost data supplied by the insurer, the average cost per inhaler regimen consisting of an ICS/LABA inhaler ($298) and a LAMA inhaler ($310) was $608 compared with $493 for a LAMA/LABA inhaler ($300) and an ICS inhaler ($193), a difference of $115. These cost data led to the implementation of a quality improvement project to change patients from ICS/LABA and LAMA inhalers to LAMA/LABA and ICS inhalers. This study aims to describe the effect of these inhaler changes on symptom control and to review potential cost implications.

TAKEAWAY POINTS

A quality improvement program was implemented to change patients with chronic obstructive pulmonary disease (COPD) to a less expensive combination of inhalers. This retrospective study examined changes in patient-reported symptom scores after changing to a less expensive COPD triple-therapy inhaler regimen.

- Newly updated COPD guidelines offer recommendations on which agents to use based on patient presentation but do not recommend specific inhaler combinations.
- Prescription inhaler costs are high and can present significant barriers to maintaining COPD symptom control at a reasonable cost to the healthcare system.
- This study provides real-world data to support the use of the least expensive regimen without compromising patient care.

METHODS

Quality Improvement Program

The insurer created a list of patients with concurrent prescription fill claims for an ICS/LABA inhaler and a LAMA inhaler in May 2016. Members of the pharmacy team (eg, pharmacists and fourth-year pharmacy students) contacted these patients to offer them a therapy change to a less expensive inhaler regimen, after first considering the COPD regimen and self-reported adherence, as well as exacerbation history and baseline symptoms. Adherence was assessed by asking patients how many doses of their maintenance inhalers they missed, on average, during 1 week. Exacerbation history included any use of acute steroids or antibiotics (moderate exacerbation) or hospitalization for respiratory issues (severe exacerbation) in the last 12 months. Patient-reported symptoms that occurred in the previous 2 weeks were evaluated using the COPD Assessment Test (CAT), which is a validated tool for assessing COPD symptoms, with lower scores representing better symptom control.[7] Pulmonary function was not assessed because it is no longer used for classifying patients and determining therapy changes.[1] The refined ABCD assessment tool from the GOLD guidelines (**eAppendix A** [eAppendices available at **ajmc.com**]) was used to classify patients.[1]

A therapeutic interchange was developed with the help of board-certified pulmonologists at the PCMH, as this information is not published. The therapeutic interchanges are available in **eAppendices B** and **C**.

Patients categorized in group A were offered step-down to a LAMA/LABA inhaler alone. Patients categorized in groups B, C, or D were offered a change to a LAMA/LABA inhaler and an ICS inhaler to reduce costs as they continued triple therapy. Patients who accepted the recommended change were counseled on proper inhaler technique if the new inhaler device did not match one in their current regimen. These patients were called again to ensure adherence and reassess symptoms. Multiple attempts were made to reach each patient if they did not respond to the initial call. Baseline and follow-up calls took place during fall 2016 and spring 2017.

Retrospective Case-Series Analysis

A retrospective case-series analysis was performed after all patients had been reassessed. Patients were included if they were 18 years or older, were originally treated with an ICS/LABA inhaler and a LAMA inhaler and switched to a LAMA/LABA inhaler and an ICS inhaler, had a diagnosis of COPD in their electronic health record (EHR), had baseline CAT scores, and had follow-up CAT scores within 1 to 6 months of regimen change. Patients were excluded if they had an exacerbation within 6 weeks of reassessment, as this may have led to unreliable CAT scores during their recovery.[7]

Patient EHRs were reviewed for patient demographic information, insurance coverage, baseline and follow-up inhaler regimens, patient-reported CAT scores, and patient-reported number of moderate and severe exacerbations. Days between the original prescription date of the new regimen and the date of follow-up were also included in data collection.

The primary outcome was mean difference in CAT scores before and after the regimen change. The literature reports that a 2-point change in CAT score is considered clinically significant.[8-10] Microsoft Excel 2016 (Microsoft Corporation; Redmond, Washington) was used to collect and store data, and Minitab 17 (Minitab Inc; State College, Pennsylvania) was used to perform statistical analysis. Data were visually inspected for normal distribution and then analyzed using a paired *t* test with an α value of 0.05.

The University at Buffalo institutional review board approved this study, and the need for patient consent was waived. All patient data were deidentified and randomly assigned a patient number prior to data analysis.

RESULTS

Of the 118 patients identified by the insurer for the original quality improvement program, just 19 met the inclusion criteria. Baseline patient characteristics from the quality improvement project and the research study are presented in **Table 1**. Of the 118 initially eligible patients using triple therapy, 44 agreed to make a change, 11 were stepped down, and 63 had no change. Patient enrollment and outcomes are depicted in **eAppendix D**. A total of 22 patients failed to meet the inclusion criteria (no baseline CAT score [n = 1], physician denied change [n = 7], patient changed regimen [n = 7], changed insurers [n = 1], deceased [n = 2], unable to contact [n = 4]). Additionally, 2 patients were hospitalized for pneumonia and 1 for an upper respiratory infection; they were therefore excluded.

Patient CAT scores and inhaler regimens are presented in **Table 2**. The mean (SD) CAT score at baseline was 15.53 (5.36) and after the change in inhalers was 14.68 (6.98). The primary outcome of mean difference in CAT score was −0.84 (95% CI, −3.57 to 1.89; $P = .525$). The mean (SD) time between initial contact and reassessment was 136 (40) days.

DISCUSSION

In this study, patients who were changed from triple therapy with an ICS/LABA inhaler and a LAMA inhaler to a LAMA/LABA inhaler and an ICS inhaler showed a small improvement in symptoms as seen by the decreased CAT score (−0.84), although this difference was not statistically or clinically significant. The lack of change in CAT scores after changing COPD triple therapy supports the use of any combination of inhalers, particularly a regimen that is less expensive. Current guidelines do not support using 1 specific agent over others, so the uneven distribution of inhalers due to local prescribing practices would not limit the applicability of this study.[1]

With the increased prevalence of accountable care organizations, alternative payment models, and the Merit-based Incentive Payment System, healthcare providers need to provide quality care without incurring extra costs.[11,12] Identifying high-cost drugs and presenting less expensive options will be important for value-based contracting as fee-for-service is de-emphasized. Additionally, for conditions like COPD in which adherence to expensive drugs is essential for preventing complications, it is important to find regimens that patients can afford without compromising efficacy. Our pharmacy team is in a good position within the PCMH for identifying these trends and working with providers to address these issues, as seen with this quality improvement project.

Changing patients who require triple therapy to a regimen containing a LAMA/LABA inhaler and an ICS inhaler would show drug cost savings to the patient, as well as the healthcare system. Using our insurer's formulary as an example, a Medicare patient would pay 2 co-pays of $45 each for an ICS/LABA inhaler and a LAMA inhaler. If changed to a LAMA/LABA inhaler and an ICS inhaler, the patient would pay a $45 co-pay and a $15 co-pay, respectively. Medicare patients would take longer to meet the threshold for the coverage gap and would have lower monthly costs during that time because ICS inhalers have a lower average wholesale price.[13] The LAMA/LABA inhaler and ICS inhaler combination would also simplify future step-down to dual therapy with a LAMA/LABA inhaler in patients whose COPD remains well controlled and no longer requires triple therapy.

In our patient population, 77% in the quality improvement project and 79% in the research group had Medicare plans through the insurer. According to cost data provided by the insurer, Medicare patients saved $30 per month out of pocket and $115 in total drug costs. Commercially insured patients would also have received cost savings in the form of reduced monthly co-payments. Based on the 19 patients who changed regimen and using a cost difference between regimens of $115 per month, the insurer would save $26,220 annually. Extrapolating these savings to the other 99 potential patients from the original population would yield an additional $136,620 in savings for the insurer annually. This highlights the importance of finding less expensive regimens while maintaining adequate efficacy, as seen in our study population.

TABLE 1. Patient Characteristics at Baseline

Variable	Quality Improvement Program Group (n = 118)	Research Group (n = 19)
Age in years, mean (SD)	71 (10.5)	71 (8.6)
Female, n (%)	69 (58)	11 (58)
Insurance, n (%)		
Commercial	14 (12)	2 (11)
Medicare	91 (77)	15 (79)
Medicaid	10 (8)	2 (11)
Medicare and Medicaid	3 (3)	0 (0)
Race/ethnicity, n (%)		
White	106 (90)	16 (84)
Black	7 (6)	3 (16)
Prefer not to answer	5 (4)	0 (0)

Limitations

A small sample size limited this study. Common barriers were that patients refused the recommended change (n = 27), the physicians denied the change (n = 7), or the patients changed the regimen by stopping one inhaler or returning to their previous regimen (n = 7). Reasons for returning to the previous regimen were not recorded but could have been due to unfamiliarity with a newly prescribed device or worsening symptoms. The sample mostly accounts for Medicare patients living in the northeastern United States, which may limit the widespread applicability.

COPD exacerbations have been shown to be more frequent during winter months.[14] As the quality improvement project took place over a period of time between fall 2016 and spring 2017, seasonality may have affected patients' symptom scores.

Patient-reported symptom scores are a subjective measure. Although the CAT is a validated test, there may be variability in the perceived severity of symptoms among patients. The same person made all the calls to patients, which eliminated interrater variability. Additionally, patients were asked to think about symptoms over a 2-week period, which may have led to recall bias. We attempted to avoid interpatient variability by evaluating the mean difference in CAT scores instead of individual scores.

Lastly, this project focused on COPD symptoms and treatment assessed with scripted phone calls. Adherence was not a major focus of the quality improvement project, so nonvalidated methods were used. We could not assess the accuracy of each patient's inhalation technique, although patients were asked if they had issues with their devices. We did not include questions about events or interventions related to comorbid conditions. Data from patients with exacerbations were excluded from analysis because we attempted to assess stable patients. Three patients had acute respiratory issues during the review period. The hospital notes and costs associated with these exacerbations were unavailable for review. Although drug costs were decreased, as noted previously, the total cost of COPD care may have been negatively affected without our knowledge.

TABLE 2. Patient CAT Scores

Patient Number	Inhaler Regimen (prechange)	CAT Score (prechange)	Inhaler Regimen (post change)	CAT Score (post change)	Difference in CAT Score (post change minus prechange)
1	BUD/FOR + TIO-R	13	TIO/OLO + BUD	24	11
2	FPr/SAL + TIO-H	12	TIO/OLO + FPr	20	8
3	FPr/SAL + TIO-R	21	TIO/OLO + FPr	26	5
4	FPr/SAL + TIO-H	13	TIO/OLO + FPr	10	–3
5	FPr/SAL + TIO-H	17	TIO/OLO + FPr	6	–11
6	FPr/SAL + TIO-R	19	TIO/OLO + FPr	10	–9
7	FPr/SAL + TIO-H	15	TIO/OLO + FPr	15	0
8	FPr/SAL + TIO-R	10	TIO/OLO + FPr	7	–3
9	FPr/SAL + TIO-H	20	TIO/OLO + FPr	24	4
10	FPr/SAL + TIO-R	11	TIO/OLO + FPr	6	–5
11	FPr/SAL + TIO-H	20	TIO/OLO + FPr	17	–3
12	FPr/SAL + TIO-R	19	TIO/OLO + FPr	15	–4
13	BUD/FOR + TIO-H	8	TIO/OLO + BUD	5	–3
14	FPr/SAL + TIO-H	25	TIO/OLO + FPr	17	–8
15	FPr/SAL + TIO-H	23	TIO/OLO + FPr	25	2
16	FPr/SAL + TIO-H	15	TIO/OLO + FPr	17	2
17	FPr/SAL + TIO-H	13	TIO/OLO + FPr	11	–2
18	FFu/VIL + TIO-H	17	TIO/OLO + FFu	17	0
19	FPr/SAL + TIO-H	4	TIO/OLO + FPr	7	3
Mean (SD)		15.53 (5.36)		14.68 (6.98)	–0.84 (95% CI, –3.57 to 1.89)

BUD indicates budesonide; CAT, COPD (chronic obstructive pulmonary disease) Assessment Test; FFu, fluticasone furoate; FOR, formoterol; FPr, fluticasone propionate; H, HandiHaler device; OLO, olodaterol; R, Respimat device; SAL, salmeterol; TIO, tiotropium; VIL, vilanterol.

CONCLUSIONS

This study did not show any significant change in COPD symptoms when inhalers were changed to a less expensive combination in a small sample of patients. Given the limitations noted, this would need to be confirmed with randomized controlled studies with a greater focus on total cost of care. ■

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eAppendix A. The Refined ABCD Assessment Tool

≥2 moderate exacerbations OR ≥1 hospitalization	C	D
0-1 moderate exacerbations	A	B
	CAT <10	CAT ≥10

CAT indicates COPD Assessment Test score.

eAppendix B. Therapeutic Interchange for Determining ICS Inhaler

Original ICS/LABA inhalers and doses	**Subsequent ICS inhalers and doses**
Budesonide-formoterol 80-4.5 mcg 1 – 2 puffs twice daily	Budesonide 90 mcg 1 puff twice daily
Budesonide-formoterol 160-4.5 mcg 1 – 2 puffs twice daily	Budesonide 180 mcg 1 puff twice daily
Fluticasone furoate-vilanterol 100-25 mcg 1 puff daily	Fluticasone furoate 100 mcg 1 puff daily
Fluticasone furoate-vilanterol 200-25 mcg 1 puff daily	Fluticasone furoate 200 mcg 1 puff daily
Fluticasone propionate-salmeterol 100-50 mcg 1 puff twice daily	Fluticasone propionate 44 mcg 2 puffs twice daily
Fluticasone propionate-salmeterol 250-50 mcg 1 puff twice daily	Fluticasone propionate 110 mcg 2 puffs twice daily
Fluticasone propionate-salmeterol 500-50 mcg 1 puff twice daily	Fluticasone propionate 220 mcg 2 puffs twice daily
Mometasone-formoterol 100-5 mcg 1 puff twice daily	Mometasone 110 mcg 2 puffs twice daily
Mometasone-formoterol 200-5 mcg 1 puff twice daily	Mometasone 220 mcg 2 puffs twice daily

ICS = inhaled corticosteroid, LABA = long-acting beta-agonist

eAppendix C. Therapeutic Interchange for Determining LAMA/LABA Inhaler

Original LAMA inhalers and doses	**Subsequent LAMA/LABA inhalers and doses**
Aclindinium 400 mcg 1 puff daily	Umeclindinium-vilanterol 62.5-25 mcg 1 puff daily
Tiotropium 2.5 mcg 2 puffs daily	Tiotropium-olodaterol 2.5-2.5 mcg 2 puffs daily
Tiotropium 18 mcg 1 capsule inhaled daily	Tiotropium-olodaterol 2.5-2.5 mcg 2 puffs daily
Umeclindinium 62.5 mcg 1 puff daily	Umeclindinium-vilanterol 62.5-25 mcg 1 puff daily

LAMA = long-acting muscarinic agent, LABA = long-acting beta-agonist

eAppendix D. Patient Enrolment and Outcomes