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# Simplifying treatment from double-inhaler to single-inhaler triple therapy in patients with chronic obstructive pulmonary disease

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**ABSTRACT** A clinical decision report using:

Ferguson GT, Brown N, Compton C, et al. Once-daily single-inhaler versus twice-daily multiple-inhaler triple therapy in patients with COPD: lung function and health status results from two replicate randomized controlled trials. *Respir Res.* 2020;21(1):131.

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for a patient requesting a simplified therapeutic regimen with equal efficacy for chronic obstructive pulmonary disease (COPD) management.

**Keywords:** COPD, chronic obstructive pulmonary disease, triple therapy, inhaled corticosteroid (ICS), long-acting muscarinic antagonist (LAMA), long-acting  $\beta$ 2-agonist (LABA)

## Clinical-Social Context

Emily Harris (pseudonym) is a 59-year-old Black woman with a history of chronic obstructive pulmonary disease (COPD) who presented to the clinic to discuss medication management. She recently experienced two brief episodes of difficulty breathing while lying on her side watching TV. She used her albuterol which subsequently improved her symptoms. The past few weeks, she has also felt short of breath after walking two blocks or up a flight of stairs. She thinks her symptoms may be related to season changes as her previous exacerbations occurred in the fall when the air became cooler and drier. She denied any symptoms of obstructive sleep apnea. For management of her COPD symptoms, she uses Symbicort (budesonide/formoterol) and Spiriva (tiotropium bromide) with albuterol as her rescue inhaler. She showed us her inhalers and pointing at each one, she said she used two inhalations daily of Symbicort and one inhalation daily of Spiriva. She has approximately one hospitalization per year for COPD exacerbation. She has smoked 1-2 cigarettes daily for the past 25 years and denies alcohol or illicit substance use. Her highest level of education is high school, she is currently retired, and her insurance covers her current inhalers. Since her diagnosis of COPD, she notes not much has changed at home as she manages her medications, house chores, and errands on her own. She has adequate transportation and lives with her daughter who smokes hookah at home.

KELLY YANG and LEAH WARREN are medical students at Wayne State University School of Medicine. LEAH WARREN is a student editor of this journal.



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We first addressed smoking cessation and explained that living with someone who smokes can cause her symptoms to flare. We informed her that an hour hookah session can be equivalent to smoking 100 cigarettes and can affect others in the household. Next, we explained that she should take two puffs twice daily of the Symbicort instead of two puffs once daily. While reconciling her medications, Ms. Harris was surprised and said, "Wait, I need to take out the inhalers again because I can only remember them by their color. See, there's a blue one and a red one." We repeated how much of each inhaler she should use and marked the inhalers. When she repeated back the information, she confused the doses and took a paper out to write down the doses. She asked if there was a way to remember the doses as she felt she would forget. We offered her a sample of Trelegy (fluticasone furoate/umeclidinium/vilanterol), a triple therapy inhaler that only needs to be taken once daily. She was agreeable to trying it because she believed the current medication combination was working for her but admitted it was becoming cumbersome to remember the doses. She also asked if the inhaler would cost more. We informed her we would need to check if her insurance covers Trelegy. She inquired if the triple therapy using a single inhaler is just as effective in managing her COPD as her current two-inhaler therapy.

## Clinical Question

Is a triple therapy using a once-daily single-inhaler as effective as a twice-daily double-inhaler in managing COPD in patients struggling with adherence to their inhaler regimen?

## Research Article

Ferguson GT, Brown N, Compton C, et al. Once-daily single-inhaler versus twice-daily multiple-inhaler triple therapy in patients with COPD: lung function and health status results from two replicate randomized controlled trials. *Respir Res.* 2020;21(1):131.  
<https://doi.org/10.1186/s12931-020-01360-w><sup>1</sup>

## Description of Related Literature

A PubMed search was conducted using the following keyword terms: ((COPD) AND (inhaled corticosteroid) AND (Long-acting muscarinic antagonist) AND (Long-acting  $\beta$ 2-agonist)) OR ((COPD) AND (triple therapy)). This yielded 655 results. Filters were applied including clinical trials and randomized controlled trials within the past 10 years yielding 101 articles. Studies assessing the relevant triple therapy drugs of fluticasone furoate, umeclidinium, and vilanterol (FF/UMEC/VI) or budesonide/formoterol plus ipratropium (BUD/FOR+TIO) were selected. Relevant MeSH terms from this query include "Bronchodilator Agents / administration & dosage\*," "Pulmonary Disease, Chronic Obstructive / diagnosis," and "Pulmonary Disease, Chronic Obstructive / drug therapy\*."

Bremner et al. conducted a randomized controlled trial among 1,055 patients with COPD with 527 patients receiving FF/UMEC/VI and 528 receiving FF/VI+UMEC for 24 weeks. The single-inhaler was found to be similar to the dual-inhaler in efficacy, safety, and change in baseline forced expiratory volume (FEV1). However, this study was not included because it did not offer a comparison to BUD/FOR+TIO dual-inhaler therapy.<sup>2</sup>

Lipson et al. conducted the FULFIL (Lung Function and Quality of Life Assessment in Chronic Obstructive Pulmonary Disease with Closed Triple Therapy) trial, a randomized controlled 24-week trial comparing once-daily FF/UMEC/VI with twice-daily BUD/FOR in 1,810 patients with COPD. The study found single-inhaler triple therapy to be more beneficial than double therapy in reducing moderate/severe COPD exacerbation rates and improving quality of life. A subset of 430 patients remained in the study for up to 52 weeks and the benefits of single-inhaler triple therapy on lung function, quality of life, and exacerbation remained. The study was not included because it did not compare triple therapy regimens.<sup>3</sup>

Tabberer et al. analyzed co-primary outcomes and secondary endpoints from the FULFIL trial using patient-reported assessments, such as Evaluating Respiratory Symptoms in COPD (E-RS: COPD), St. George's Respiratory Questionnaire (SGRQ), and COPD Assessment Test (CAT), to compare the effects of FF/UMEC/VI and BUD/FOR on patients' respiratory symptoms based on Patient Reported Outcomes. The study found that once-daily triple therapy improved patient perceptions of respiratory symptom severity



compared to BUD/FOR. While the study emphasized the importance of incorporating patients' perspective of symptom severity and its impact on the treatment course, it did not analyze the effects of different triple therapy regimens on respiratory symptoms.<sup>4</sup>

Mehta et al. conducted a pharmacokinetic analysis on 74 patients with symptomatic COPD who received the single-inhaler FF/UMEC/VI from the FULFIL trial. The study found systemic drug concentrations of FF/UMEC/VI were within range when the drugs were administered in their individual monotherapy forms. While this study demonstrated that a single-inhaler triple therapy has no pharmacokinetic interactions, it did not compare different triple therapies.<sup>5</sup>

Panettieri et al. conducted a post hoc analysis on 1,810 patients from the FULFIL trial. Patients were categorized as having one or more moderate to severe exacerbations the year prior to the study or having no exacerbations. The study found that FF/UMEC/VI reduced the number of exacerbations per year and improved lung function compared to BUD/FOR, but was excluded as it did not include a BUD/FOR plus ipratropium comparison group.<sup>6</sup>

To answer whether a triple therapy using a once-daily single-inhaler or twice-daily double-inhaler is more beneficial for Ms. Harris, the study by Ferguson et al. was selected for critical appraisal. This was a 12-week randomized, double-blind, parallel-group, multicenter replicate trial study comparing once-daily FF/UMEC/VI with twice-daily BUD/FOR+TIO. The study found that FF/UMEC/VI was not inferior to BUD/FOR+TIO with similar health status improvements and safety outcomes. This study was selected because it compared two triple therapies (FF/UMEC/VI and BUD/FOR+TIO) and was well-randomized with an appropriate sample size.<sup>1</sup>

The Strength of Recommendation is grade B given the single study publication.<sup>2</sup>

## Critical Appraisal

In this study, two replicate prospectively registered trials were performed comparing once-daily FF/UMEC/VI with twice-daily BUD/FOR plus once-daily TIO in patients with COPD. Using the SORT criteria, the level of evidence is 2 for this study.<sup>7</sup> Because dummy inhalers were used to ensure blinding, the authors noted the study was not designed to assess adherence to inhaler therapies. Thus, the study may only offer insight into the different therapies' effects on lung function, safety profile, and health outcomes.

2,064 patients were screened and the following inclusion criteria were used: (1) outpatient, (2)  $\geq 40$  years old, (3) current or former smokers with  $\geq 10$  pack-year history, (4) diagnosed with COPD,<sup>8</sup> (5) receiving daily maintenance therapy for  $\geq 3$  months, (6) a postbronchodilator FEV1  $< 50\%$  predicted (or a post-bronchodilator FEV1  $< 80\%$  and  $\geq 2$  moderate exacerbations or 1 severe exacerbation in the last year), (7) a post-bronchodilator FEV1/forced vital capacity ratio  $< 0.70$ , (8) and a CAT score  $\geq 10$ .<sup>9</sup> Excluded patients were those with another clinically significant respiratory disorder, and those at risk of non-compliance.

After screening, 1,637 patients entered a 4-week run-in period during which they discontinued all COPD medications and received BUD/FOR+TIO plus placebo once daily. 177 patients who failed the run-in period were not selected for the study with reasons being investigator discretion, adverse event, withdrew consent, or lost to follow-up, which may contribute to selection bias. Patients also needed to demonstrate 80–120% compliance with the run-in medication. This may not reflect the real-world COPD population's adherence, as demonstrated by Ms. Harris's difficulty adhering to the dosage frequency recommendations. Otherwise, Ms. Harris fits into the inclusion criteria.

Following the run-in period, 1,460 participants were randomized with 729 patients receiving FF/UMEC/VI in the morning plus placebo twice in the morning and once at night, and 731 patients receiving BUD/FOR in the morning and evening plus TIO once in the morning plus placebo in the morning for 84 days. The trial was well randomized with overall patient baseline characteristics similar in both treatment arms. Rescue albuterol was available throughout the study but was withheld at least 4 hours prior to spirometry assessments. However, albuterol can have a half-life of 4 to 6 hours and its use by participants was not specifically reported.<sup>10</sup>

Data was analyzed in the intention-to-treat and the modified per protocol population, which was determined by excluding data involving discontinuation of treatment, noncompliance, or COPD exacerbation. The statistical method used to analyze non-inferiority was a mixed model repeated measure analysis. 620 patients would have 90% power to determine non-inferiority. In total, 36

withdrew from the BUD/FOR+TIO arm and 34 withdrew from the FF/UMEC/VI arm with adverse events or patient choice being the most common reasons for withdrawal.

The primary outcome of this study was a change from baseline in mean FEV1 over 0–24 hours at Week 12. Secondary outcomes included change from baseline in trough FEV1 on Days 2, 28, 84, 85, St. SGRQ total score,<sup>11</sup> and CAT score. Both trials demonstrated the mean treatment difference of FEV1 in FF/UMEC/VI was not inferior to BUD/FOR+TIO on day 84. Both treatment combinations were well tolerated. No statistically significant differences between treatments were seen in the SGRQ total score or CAT score at Week 12.

A limitation of the study was the short 12-week study period which limits analysis of long-term treatment and safety outcomes. As this was a multi-center study with up to 59 centers from four countries involved, variability in data collection quality should be considered. The time that patients self-administered the second daily dose at home may reduce the optimal treatment effect. Moreover, this study was funded by the pharmaceutical company GSK the owner of the Ellipta inhalers used in this study.<sup>1</sup>

## Clinical Application

Ms. Harris expressed the current regimen has been working for her but desired a more streamlined and equally effective inhaler therapy. When offered Trelegy, Ms. Harris asked me if this therapy was equally effective and if there were any side effects. In Ferguson's study, FF/UMEC/VI provides similar overall improvements in weighted mean FEV1, health status, and safety profile, as twice-daily multiple-inhaler BUD/FOR+TIO. This suggests that the single-inhaler Trelegy would be an acceptable treatment alternative. Ms. Harris's main goal was to simplify her medication regimen while attaining similar therapeutic efficacy as her current regimen.

Cardiovascular and respiratory tract infection adverse events have been associated with the medications studied. However, both treatment combinations were well tolerated with low percentages of patients experiencing cardiovascular adverse events (FF/UMEC/VI: 1.4%, BUD/FOR+TIO: 1.1%) or respiratory tract infections (FF/UMEC/VI: 1.2%, BUD/FOR+TIO: 0.8%). Simplifying treatment regimens with once-daily therapy has been suggested to improve adherence to therapy, which may lead to improved clinical outcomes. After considering the potential adverse events, Ms. Harris was still agreeable to trying the sample inhaler because it would help reach her main goal of simplifying her daily regimen.

The main barrier to switching to a single inhaler such as Trelegy is insurance. If Trelegy is covered by insurance, using a single inhaler can help decrease co-pay costs. If the medication is not covered, Ms. Harris will need regular medication counseling at her pulmonology and primary care visits to ensure that she is adhering to the doses of her current dual inhaler therapy. Regardless of the inhaler regimen she uses, living with someone who smokes can cause COPD exacerbation. This can be overcome by educating Ms. Harris on the effects of hookah on her daughter as well as herself.

While we did not use a standardized questionnaire, we asked the patient basic history of present illness questions similar to the CAT. The CAT is an eight-item questionnaire used to assess the impact of COPD on a patient's health status and daily life to improve management.<sup>9</sup> The questionnaire has been found to be valid and responsive to interventions, but the minimum clinically important difference is still being studied.<sup>12</sup> SGRQ is a weighted-response 50-item questionnaire used to assess the health status of patients with COPD in clinical trial studies, however the tool is found to be time-consuming.<sup>12</sup> Nevertheless, the CAT may be of value to numerically monitor the patient's response to interventions between clinic visits.

Ms. Harris was a real-world example of a patient not taking her inhalers correctly, which could be due to a busy schedule, complicated daily dosing regimen, or improper medication counseling at the time of prescription and follow-up visits. This research is applicable after the patient is informed about proper inhaler use and continued adherence.

## New Knowledge Related to Clinical Decision Science

Clinical Decision Science attempts to understand patients in their social setting. Inhaled medications for COPD are prohibitively expensive, for instance with one generic Symbicort or Spiriva Handihaler costing approximately \$160 plus each month on GoodRx, and Health Insurance coverage is frequently frustrating to the point of discouraging adherence to inhaler regimens.

Doctors often think in terms of patient education, but Clinical Decision Science asks us to consider social prescribing. Examples include the Medicare Drug Price Negotiation Program. Another example of social prescribing is advocacy while interacting with for-profit corporations.<sup>13</sup>

Because medications can be regulated by the government, doctors should lobby legislatures to create mandatory color-coded labeling for inhaled medication indicating the four major categories of medication and clear labeling on inhaler devices indicating the frequency of use. In other words, shift the burden of adherence to the manufacturers who are profiting to help the patient.

## Conflict Of Interest Statement

The authors declare no conflicts of interest.

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