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# Clinical Evidence Supporting the Evolving COPD Treatment Paradigm: Considerations for Managed Care and Evidence-Based Recommendations for Appropriate Utilization of COPD Treatment Strategies

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In a key Academy of Managed Care Pharmacy (AMCP) Science and Innovation Theater Webinar, experts provided insights into the considerations for managed care in the evolving chronic obstructive pulmonary disease (COPD) treatment paradigm and the clinical evidence supporting the use of dual bronchodilation with long-acting muscarinic receptor antagonist (LAMA)/ long-acting beta<sub>2</sub> agonist (LABA) combination therapies compared with LABA/inhaled corticosteroid (ICS) therapies for the management of patients with COPD. A substantial change was introduced in the 2017 Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommendations, based on high-quality supporting evidence, which highlighted LABA/LAMA as the preferred combination treatment over LABA/ICS, and provided limitations to ICS-containing treatment use in the management of COPD.<sup>1</sup> The expert discussion highlighted managed care perspectives and clinical implications following the implementation of this substantial update in the 2018 GOLD report for the second year.<sup>2</sup>

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## PREVALENCE AND ECONOMIC BURDEN OF COPD IN THE UNITED STATES

### *The Growing Burden of COPD*

According to the CDC, an estimated 15.7 million Americans have been diagnosed with COPD.<sup>3</sup> Although COPD is often perceived as a disease of the elderly, more than half (67.0%) of all patients diagnosed with COPD are 64 years and younger.<sup>3</sup>

COPD is a treatable disease characterized by persistent respiratory symptoms that typically include breathlessness (dyspnea), chronic cough and/or sputum production, and airflow limitation due to airway and alveolar abnormalities attributed to toxic environmental gases and particles.<sup>2</sup> Patients with COPD are also subject to periods of symptom worsening, or exacerbations, which negatively impact health status, increase hospitalization rates and readmissions, and contribute to disease progression.<sup>2</sup> Chronic airflow limitations may be caused by a mixture of small airway disease and parenchymal destruction, which vary from patient to patient and may evolve at different rates and at different times.<sup>2</sup>

Co-leading the webinar discussion was Sanjay Sethi, MD, professor of medicine, chief in the Division of Pulmonary, Critical Care and Sleep Medicine, assistant vice president for Health Sciences, and medical director of the University of Buffalo Clinical Research Office. He addressed key challenges in diagnosing and treating patients with COPD, given its wide variability in presentation: "There is a substantial proportion of patients who have COPD in their so-called working years, and therefore that can have a substantial impact on their productivity."

**Table 1. Severity of Airflow Limitation Assessment in Patients With COPD<sup>2,a</sup>**

Classification	FEV <sub>1</sub> <sup>b</sup>
GOLD 1	≥80%
GOLD 2	50% - 79%
GOLD 3	30% - 49%
GOLD 4	<30%

<sup>a</sup>In patients with spirometrically confirmed diagnosis of COPD (postbronchodilator FEV<sub>1</sub>/FVC <0.70).

<sup>b</sup>FEV<sub>1</sub>, % predicted.

COPD indicates chronic obstructive pulmonary disease; FEV<sub>1</sub>, forced expiratory volume in 1 second; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease.

**Table 2. GOLD ABCD Symptom and Risk Assessment For Patients With COPD<sup>2</sup>**

Exacerbation history <sup>a</sup>	Group	
	0 or 1 exacerbation(s) (not leading to hospitalization)	A
≥2 exacerbations or ≥1 exacerbation(s) leading to hospitalization	C	D
	mMRC 0-1 CAT <10	mMRC ≥2 CAT ≥10
	<b>Symptom assessment<sup>a</sup></b>	

<sup>a</sup>Evaluated in patients with a spirometrically confirmed COPD diagnosis and assessment of airflow limitation by FEV<sub>1</sub> (GOLD 1-4).

CAT indicates COPD Assessment Test; COPD, chronic obstructive pulmonary disease; FEV<sub>1</sub>, forced expiratory volume in 1 second; GOLD, Global Initiative for Chronic Obstructive Lung Disease; mMRC, modified Medical Research Council dyspnea scale.

**Economic Impact of COPD**

COPD is responsible for substantial economic burdens on healthcare systems in the United States.<sup>4</sup> COPD exacerbations and associated hospitalizations account for the greatest proportion of the cost burden, with a clear relationship between disease severity and cost of care.<sup>4</sup> Total national medical costs attributable to COPD were estimated at \$32.1 billion in 2010 and are projected to reach \$49 billion in 2020.<sup>5</sup> In 2010, nearly 700,000 patients were hospitalized for COPD, while 10.3 million were treated as outpatients and 1.5 million visited an emergency department (ED).<sup>5</sup> The same data set from 2010 demonstrated that indirect COPD-attributable costs due to absenteeism were estimated at \$3.9 billion (in 2012 dollars).<sup>5</sup>

Chronic conditions associated with COPD may interfere with disease management and contribute to hospitalizations.<sup>2</sup> Factors driving the rising economic burden of COPD can be attributed to the aging US population coupled with the overall increase in healthcare utilization from COPD complicated by comorbidities and the growth of total medical costs.<sup>5</sup>

Andrew Cournoyer, RPh, MBA, vice president of formulary access solutions, Precision for Value, and former senior director of Formulary and Utilization Management, co-lead of the presentation, reemphasized the distribution of COPD patients by age and Medicare eligibility. Cournoyer noted that both age groups (ie, those younger than 65 years and the Medicare population) “should have equal weight across all lines of business [Medicare and commercial].” Although rising costs attributable to an aging population keep Medicare as a priority in COPD discussions, the total costs for both medical and pharmacy benefits need to be considered across age groups. Utilization management may offer opportunities to mitigate cost inflations due to rising medical and pharmacy costs.

**TREATMENT GOALS FOR COPD**

The GOLD report provides expert opinions and recommendations for clinicians on maintenance treatment for the short- and long-term impacts of COPD, with the goals of relieving and reducing symptom burdens and risk of future exacerbations, improving quality of life, and reducing the risk of adverse events (AEs) and disease progression.<sup>2</sup> GOLD recommendations emphasize individualized treatment for patients based on severity of symptoms, airflow limitation, and severity of exacerbations.<sup>2</sup>

Initial assessment and diagnosis requires spirometry to confirm the presence of persistent airflow limitation in patients with COPD symptoms, including dyspnea and chronic cough with or without sputum production.<sup>2</sup> Once diagnosis is confirmed, the severity of airflow limitation is assessed and classified as GOLD stage 1 to 4 (Table 1).<sup>2</sup> The GOLD recommendations include a COPD assessment tool which categorizes patients based on respiratory symptoms (severity of breathlessness, nature and magnitude of symptoms) and history of exacerbations to assign categories (ABCD) of disease (Table 2).<sup>2</sup> Pharmacologic treatment recommendations are stratified by GOLD ABCD scale classifications for each group of patients (Figure 1).<sup>2</sup>

**2018 GOLD Treatment Recommendations**

Pharmacologic therapy is the cornerstone of COPD management and it is used to reduce symptoms, reduce frequency and severity of exacerbations, and improve exercise tolerance and health status.<sup>2</sup> Many factors influence the choice of therapeutic agent, including cost, availability, and clinical response, balanced with the AE profile of the medication.<sup>2</sup>

**Combination Therapy With Long-Acting Bronchodilators**

Combination therapy with long-acting bronchodilators is central to the management of patients with COPD.<sup>2</sup> For patients with GOLD groups B, C, and D disease, LAMA/LABA combination therapies are the preferred treatment in the majority of patients with symptomatic COPD.<sup>2</sup> LAMAs bind to muscarinic receptors and block the bronchoconstrictive effects of acetylcholine binding. The cholinergic receptors are located on smooth muscle cells where activation by acetylcholine increases peripheral airway resistance.<sup>6</sup> LABAs bind to the beta<sub>2</sub> receptor to induce bronchodilation. Beta<sub>2</sub>-adrenergic receptors

also are located on smooth muscle cells where activation by beta<sub>2</sub> agonists results in relaxation of bronchial smooth muscle.<sup>6</sup> By combining therapies, different mechanisms of action target multiple receptor sites, which may have additive benefits for lung function and the reduction of both symptoms and the risk of exacerbations.<sup>2</sup> Combination LAMA/LABA bronchodilators may increase the degree of bronchodilation with a lower risk of AEs compared with increasing the dose of monotherapy.<sup>2</sup>

### Evolution of Changes in GOLD Recommendations for ICS Use

GOLD recommendations for the pharmacologic management of COPD no longer include ICS-containing regimens as the first-choice maintenance therapy in any GOLD group.<sup>2</sup> Current GOLD-recommended strategies include the use of LAMA, LABA, and combination LAMA/LABA as preferred treatments for symptomatic patients with COPD, regardless of exacerbation risk.<sup>2</sup> The GOLD report recommends LAMA/LABA bronchodilator combination therapy as a preferred treatment over LABA/ICS therapy due to an increased risk for developing pneumonia with ICS products.<sup>2</sup> Furthermore, this recommendation was implemented in the 2017 GOLD report and reinforced in the 2018 GOLD report based partially on evidence demonstrating that LAMA/LABA combinations are more effective at reducing the number of exacerbations compared with LABA/ICS combinations.<sup>2</sup>

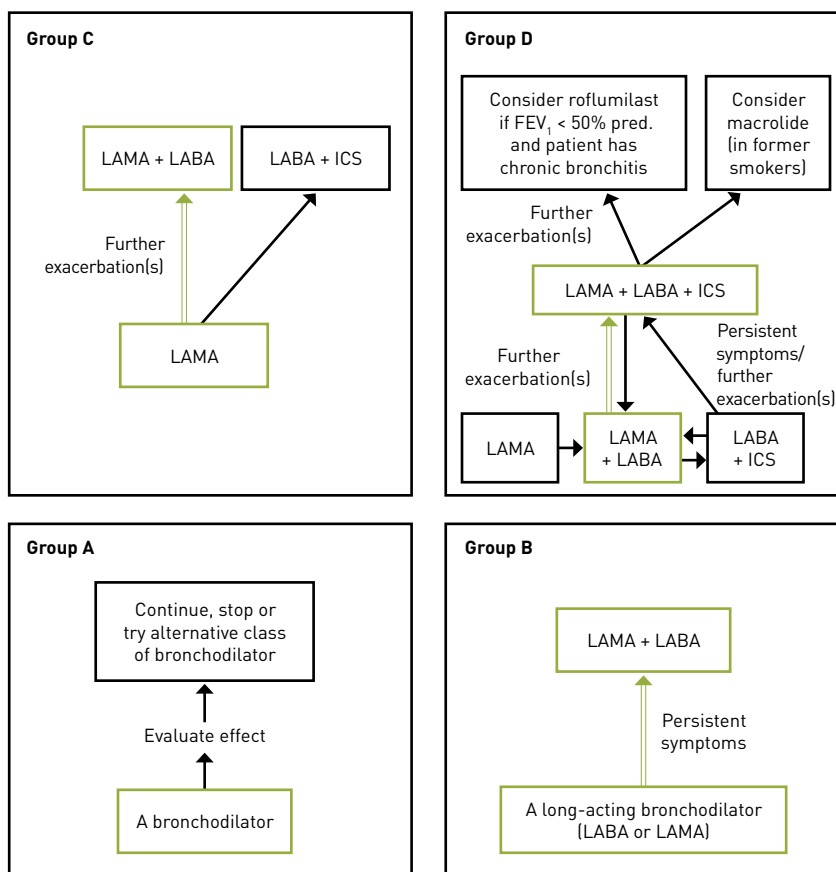
LAMA/LABA/ICS triple therapy is recommended only for those patients who develop further exacerbations while on LAMA/LABA combination therapy.<sup>2</sup> Dr Sethi emphasized the importance of adherence with recommendations: "ICS-containing regimens have a role, not as first-line therapy, but as add-ons, and triple therapy is also only recommended if you have further exacerbations beyond the use of the LAMA/LABA."

## CLINICAL EVIDENCE SUPPORTING A SHIFT IN THE PHARMACOLOGIC MANAGEMENT OF COPD

### Adverse Events With ICS Versus LAMA/LABA Therapies

AEs are to be expected with any pharmacologic treatment for COPD. However, the relative impact and/or seriousness of the AEs should be considered and weighed in the balance of treatment response. LAMA/LABA combinations are often associated with airway AEs, such

**Figure 1. Summary of Treatment Recommendations by GOLD Grade<sup>2,a,b</sup>**



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<sup>a</sup>Green arrows and box outlines represent preferred treatment. In patients with a major discrepancy between the perceived level of symptoms and severity of airflow limitation, further evaluation is warranted.

<sup>b</sup>In Group A, a bronchodilator can be short-acting (SABA or SAMA) or long-acting (LAMA or LABA), based on its effect on breathlessness.

COPD indicates chronic obstructive pulmonary disease; FEV<sub>1</sub>, forced expiratory volume in 1 second; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICS, inhaled corticosteroid; LABA, long-acting beta<sub>2</sub> agonist; LAMA, long-acting muscarinic receptor antagonist; SABA, short-acting beta<sub>2</sub> antagonist; SAMA, short-acting muscarinic antagonist.

as pharyngitis and nasopharyngitis.<sup>7-9</sup> For ICS-containing products, Dr Sethi noted a range in impact from "nuisance" AEs, such as oropharyngeal candidiasis and skin bruising, to increased risk of cataracts, diabetes, and fractures.<sup>10</sup>

The most concerning AE discussed in terms of clinical and economic impact was pneumonia. Studies have demonstrated that ICS use is associated with an increased risk of pneumonia in patients with COPD. A 2016 meta-analysis of data from 29 randomized controlled trials (RCTs) and 9 observational studies assessed the risk of pneumonia in patients taking ICS-containing therapy. The analysis showed a significantly increased risk of pneumonia among ICS users in the RCTs

(relative risk [RR], 1.61; 95% CI, 1.35-1.93;  $P < .001$ ) and in the observational studies (odds ratio [OR], 1.89; 95% CI, 1.39-2.58;  $P < .001$ ).<sup>11</sup>

In a case-control analysis of 175,906 patients with COPD, culled from health databases in Quebec, Canada, from January 1, 1988, to December 31, 2001, a dose-related increase in the risk of hospitalization for pneumonia and of hospitalization for pneumonia leading to death was shown among patients with COPD who were using ICS-containing products.<sup>12</sup> There was a dose-response relationship, with the rate of pneumonia greatest with the highest doses of ICSs (RR, 2.25; 95% CI, 2.07-2.44).<sup>12</sup>

Conversely, the discontinuation of ICS-containing products was also discussed. Using Quebec health insurance databases, investigators formed a cohort of 103,386 new users of ICSs and followed them for approximately 5 years. A total of 14,020 serious pneumonia events occurred during this time. Discontinuation of ICSs resulted in a 37% decrease in the rate of serious pneumonia (rate ratio, 0.63; 95% CI, 0.60-0.66). Moreover, the investigators concluded that ICSs were overused in COPD, counter to treatment recommendations.<sup>13</sup>

Managing severe COPD brings increasing challenges and awareness of the impact of ICS use. Even though the GOLD report recommends ICS-containing regimens for more severe cases of COPD when LAMA/LABA therapy does not control symptoms or exacerbations continue, group D patients are at a higher risk of developing pneumonia when treated with ICS-containing products.<sup>2</sup> The GOLD report also notes that more evidence supports the use of LAMA/LABA combinations over LABA/ICS combinations in preventing exacerbations in group D patients.<sup>2</sup>

In addition to the clinical impact of these data, Cournoyer discussed the substantial economic burden of pneumonia, particularly when hospitalization is needed. Data on community-acquired pneumonia were quantified in both inpatient and outpatient settings in a retrospective study of claims from a large US health plan from July 1, 2006, to December 31, 2007.<sup>14</sup> Of the 28,575 pneumonia episodes examined, 28% were treated in an inpatient setting and 72% were treated in an outpatient setting.<sup>14</sup> Overall cost per episode reached \$2212 for outpatient management and \$27,661 for hospitalized patients, with an average cost per episode of more than \$9000.<sup>14</sup>

Cournoyer remarked, "When we look at the overall population utilizing ICS regimens, this number [ $> \$9000$ ] might not be so insignificant. It prompts the payer to look at their data and not just look at the ICS utilization but also the medical impact that might be happening."

### Exacerbation Risk and Control: ICS Versus LAMA/LABA Combination Therapies

Dr Sethi noted that clinicians historically relied on ICS products for reducing exacerbations, until data emerged, somewhat surprisingly, showing that LAMA/LABA combinations were superior to ICS products for exacerbation control.<sup>15-17</sup> Multiple studies have shown reduced frequency of exacerbations and delays in time to first exacerbation with LAMA/LABA combinations compared with ICS-containing regimens (Table 3).<sup>15-17</sup>

The results of the Informing the Pathway of COPD Treatment (IMPACT) trial were released after the webinar, which investigated the safety and efficacy of single-inhaler triple therapy compared with

LAMA/LABA and LABA/ICS treatment once daily over 52 weeks to reduce the annual rate of moderate or severe exacerbations in patients with moderate-to-very-severe symptomatic COPD ( $N = 10,355$ ).<sup>18</sup> Patients in the triple therapy group experienced a significantly lower rate of moderate or severe exacerbations compared with combination LABA/ICS therapy (RR, 0.85; 95% CI, 0.80-0.90;  $P < .001$ ) and combination LAMA/LABA therapy (RR, 0.75; 95% CI, 0.70-0.81;  $P < .001$ ).<sup>18</sup> Additionally, there was a higher incidence of pneumonia in the groups treated with ICS-containing regimens; the risk of pneumonia was significantly higher with triple therapy compared with LAMA/LABA combination (hazard ratio [HR], 1.53; 95% CI, 1.22-1.92;  $P < .001$ ).<sup>18</sup>

In response to the published results of the IMPACT trial, an editorial by Suissa and Drazen in the *New England Journal of Medicine* identified several key issues in the trial design and interpretation of results.<sup>19</sup> This editorial response added merit to questioning the benefits of stepping up to triple therapy over dual bronchodilation.

Of the 10,355 patients enrolled in the IMPACT trial, the majority of the population was receiving treatment with ICS-containing regimens; 38% of patients were receiving treatment with triple therapy and 29% were receiving treatment with LABA/ICS.<sup>18</sup> Upon randomization to the LAMA/LABA treatment arm, patients previously treated with an ICS-containing regimen were abruptly withdrawn from treatment and inadvertently stepped down in therapy.<sup>19</sup> This discontinuation of the ICS component of treatment may have contributed to the increased exacerbation rate within 1 month of randomization reported in the LAMA/LABA treatment arm compared with the triple therapy and LABA/ICS treatment arms.<sup>19</sup> Additionally, Suissa and Drazen noted that during the subsequent 11 months of follow-up, the incidence of exacerbation in the LAMA/LABA treatment arm was nearly the same as reported in the triple therapy arm.<sup>19</sup>

Suissa and Drazen concluded that the results of the IMPACT trial do not support stepping up to triple therapy in clinical practice and recommended that until high-quality evidence supports the addition of ICS to LAMA/LABA therapy, escalation to triple therapy should be reserved for symptomatic patients in GOLD group D, as supported by the GOLD 2017 and 2018 reports.<sup>2,19</sup>

Figure 2 shows the larger body of evidence supporting LAMA/LABA combinations versus LABA/ICS combinations with comparison of impact on lung function.<sup>16,17,20-24</sup>

### ICS Withdrawal

Multiple studies have shown that withdrawing ICS from treatment showed no change in risk of exacerbations. Three trials—WISDOM, OPTIMO, and INSTEAD—demonstrated that patients maintained on bronchodilator therapy did not experience an increased risk of exacerbations after withdrawal of ICSs.<sup>25-27</sup>

In the largest of the 3 trials, the 52-week WISDOM trial enrolled 2485 patients with a history of exacerbations to receive triple combination therapy twice daily or be treated with triple therapy initially with a systematic dosage reduction of the ICS every 6 weeks. There were no statistically significant differences in the risk of moderate to severe exacerbations (HR, 1.06; 95% CI, 0.94-1.19) or frequency of exacerbations (HR, 1.20; 95% CI, 0.98-1.48) between patients who

**Table 3.** LAMA/LABA Clinical Efficacy Reducing Exacerbation Risk in Patients With COPD<sup>15-17</sup>

Trial	Population	Treatment <sup>a</sup>	Efficacy Outcomes			
			Rate of Exacerbation	RR (95% CI) P value	Time to First Exacerbation	HR (95% CI) P value
FLAME	Enrolled patients with COPD and a history of at least 1 exacerbation during the previous year (N = 3362)	Randomized (1:1) to receive either treatment for 52 weeks:	11% reduction in annual rate of all COPD exacerbations with LAMA/LABA vs LABA/ICS	RR, 0.89 (95% CI, 0.83-0.96) P = .003	22% longer time to first exacerbation with LAMA/LABA vs LABA/ICS	51 days vs 71 days
		LAMA/LABA (n = 1680) > 50/110 µg once daily LABA/ICS (n = 1682) > 50/500 µg twice daily	17% reduction in annual rate of moderate or severe COPD exacerbations with LAMA/LABA vs LABA/ICS	RR, 0.83 (95% CI, 0.75-0.91) P < .001	16% reduced risk of exacerbation with LAMA/LABA vs LABA/ICS	HR, 0.84 (95% CI, 0.78-0.91) P < .001
ILLUMINATE	Enrolled patients with moderate-to-severe COPD without a history of exacerbations in the previous year (N = 523)	Randomized (1:1) to receive either treatment for 26 weeks: LAMA/LABA (n = 258) > 50/110 µg once daily LABA/ICS (n = 264) > 50/500 µg twice daily	Comparable results in terms of frequency of COPD worsening, including exacerbation, in patients treated with LAMA/LABA vs LABA/ICS (17.1% vs 23.5%)			
LANTERN	Enrolled patients with moderate-to-severe COPD with a history of no more than 1 exacerbation in the previous year (N = 744); 50% of patients classified as GOLD group D	Randomized (1:1) to receive either treatment for 26 weeks: LAMA/LABA (n = 372): > 50/110 µg once daily LABA/ICS (n = 372): > 50/500 µg twice daily	31% reduction in annual rate of moderate or severe exacerbations with LAMA/LABA vs LABA/ICS	RR, 0.69 (95% CI, 0.48-1.00) P = .048	35% reduced risk of moderate or severe exacerbation with LAMA/LABA vs LABA/ICS treatment	HR, 0.65 (95% CI, 0.44-0.95) P = .028

COPD indicates chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HR, hazard ratio; ICS, inhaled corticosteroid; LABA, long-acting beta<sub>2</sub> agonist; LAMA, long-acting muscarinic receptor antagonist; RR, rate ratio.

<sup>a</sup>Across all studies, LAMA/LABA treatment was glycopyrronium (LAMA) and indacaterol (LABA); LABA/ICS treatment was salmeterol (LABA) and fluticasone (ICS).

continued with the ICS compared with those withdrawn from ICS.<sup>25</sup> Additionally, patients withdrawn from ICS experienced a statistically significant decrease in lung function compared with patients who continued triple therapy (P = .001) by the 52-week mark of the study.<sup>25</sup>

In the OPTIMO study, patients at low risk of exacerbation receiving ICS plus bronchodilator maintenance experienced no deterioration of lung function symptoms, and exacerbation rate was similar 6 months after ICS withdrawal when appropriate maintenance therapy with bronchodilators was maintained compared with patients who continued ICS treatment (26% vs 29%, respectively).<sup>26</sup>

Results from the INSTEAD study demonstrated that patients at low risk of exacerbations who were switched from a LABA/ICS combination to a LABA monotherapy (n = 293) had no evidence of an increased rate of exacerbations compared with patients who continued to receive the LABA/ICS treatment (n = 288) over the 26-week study period (exacerbation rate of 0.57 and 0.67 per year, respectively).<sup>27</sup> As noted previously, data have shown that discontinuation of ICS also resulted in reduced risk of pneumonia.<sup>13</sup>

The clinical benefit of bronchodilation for improved lung function, as well as withdrawal of ICSs with no increase in exacerbation

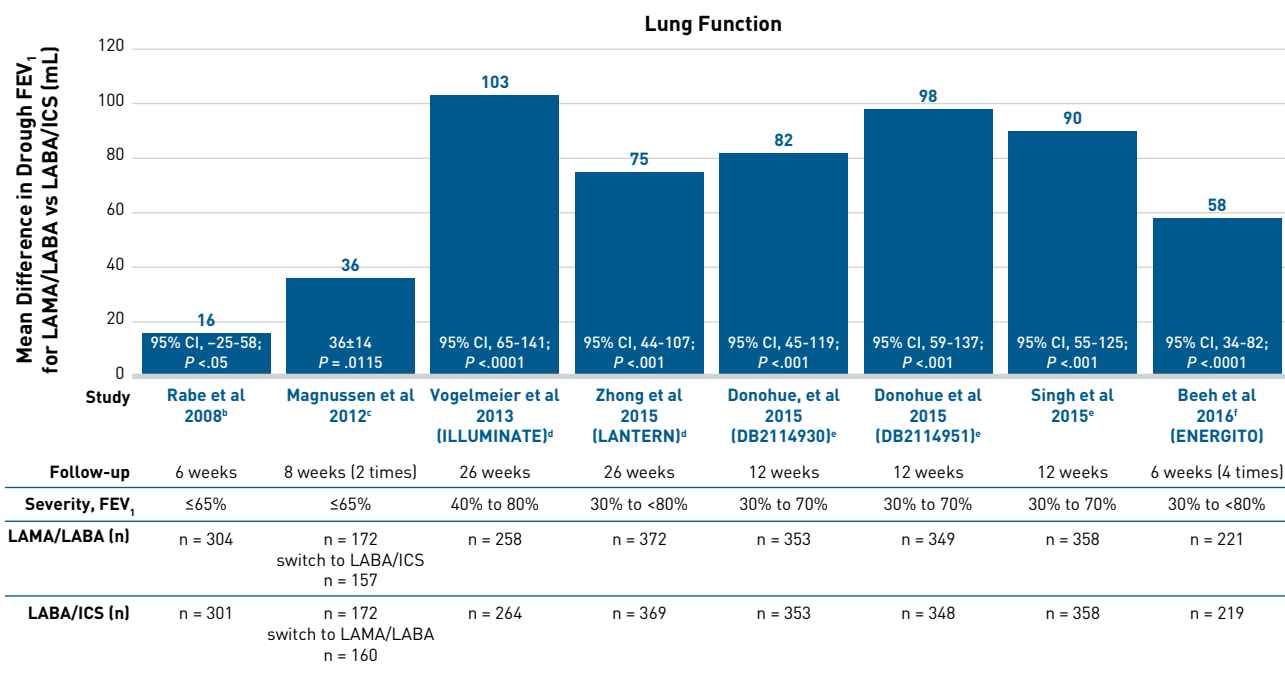
risk, are considerations for payers during their review of the full body of clinical evidence surrounding pharmacologic therapy for COPD to make informed decisions. Cournoyer noted, "These are the outcomes that we as payers like to see when considering total medical cost reduction. This evidence supports clinical policy, [and] considering management initiatives, it gives us basis or footing to stand on that we are basing [our decision] upon a scientific, peer-reviewed, evidence-based guideline to support the premise of that particular policy. Ultimately, if payers are going to look at utilization management programs, it's this type of evidence that they really look for to help create that policy and defend that policy."

### Consequences of Real-World Nonadherence to GOLD Recommendations

Despite GOLD recommendations for LAMA/LABA combination therapy as the preferred treatment in the majority of patients, the most common medications used to treat COPD are LABA/ICS combinations, followed by LAMA monotherapy and triple therapy.<sup>28</sup> The most common combinations used to treat patients with COPD were demonstrated in a real-world analysis of claims from patients with COPD (N = 358,199).<sup>28</sup>



**Figure 2.** The Clinical Evidence Supporting Improvements in Lung Function With a LAMA/LABA Versus LABA/ICS<sup>16,17,20-24,a</sup>



COPD indicates chronic obstructive pulmonary disease; FEV<sub>1</sub>, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; LABA, long-acting beta<sub>2</sub> agonist; LAMA, long-acting muscarinic receptor antagonist; ±, standard deviation.

<sup>a</sup>LABA/ICS treatment with salmeterol/fluticasone (50/500 µg or 50/250 µg).

<sup>b</sup>LAMA/LABA treatment with tiotropium (18 µg) plus formoterol (12 µg).

<sup>c</sup>LAMA/LABA treatment with tiotropium (18 µg) plus salmeterol (50 µg).

<sup>d</sup>LAMA/LABA treatment with glycopyrronium/indacaterol (50/110 µg).

<sup>e</sup>LAMA/LABA treatment with umeclidinium/vilanterol (62.5/25 µg).

<sup>f</sup>LAMA/LABA treatment with tiotropium/olodaterol (5/5 µg). Data not shown for treatment arms of alternative doses.

Overtreatment with ICS-containing regimens was observed, as the majority of patients with COPD were treated with an ICS-containing regimen (72%); 26.1% were prescribed triple therapy, and 45.6% were treated with an LABA/ICS combination (Figure 3).<sup>28</sup>

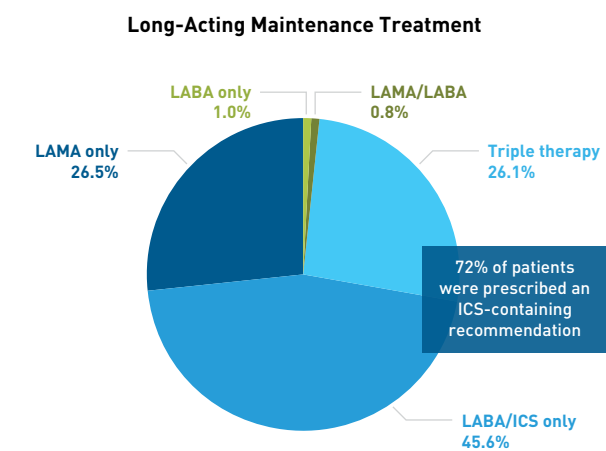
Of the patients receiving triple therapy, more than half of the population (52.6%) did not have a history of exacerbations (Figure 4).<sup>28</sup> Triple therapy is recommended for patients with severe symptoms and a high risk of exacerbations after persistent COPD symptoms and exacerbations with LAMA/LABA treatment. Despite this recommendation, only 8.6% of the population treated with triple therapy had a history of severe exacerbations.<sup>2,28</sup>

Cournoyer highlighted the impact of nonadherence to GOLD recommendations and payer concerns with elevated healthcare resource utilization. He stated that “the 72% of patients receiving an ICS-containing regimen and the 26% of patients receiving the most aggressive form of therapy, triple therapy, are the areas I would look at.” The safety component is another area that payers may scrutinize when considering utilization management. Cournoyer added, “We highlighted pneumonia and what that cost of the added risk

might look like. It’s these types of factors that make me want to think about my utilization and my particular plan.” He added that these data present an opportunity to improve not only patient outcomes, but also the downstream impact on medical cost offsets and possibly even drug savings.

There is a measurable impact of nonadherence to GOLD-recommended treatment strategies on patient outcomes and associated healthcare utilization. In a study of electronic health records from January 1, 2007, to December 31, 2012 (N = 4234 treated patients), investigators assessed the effect of adherence and nonadherence to GOLD 2011 prescribing recommendations on COPD symptom burden, exacerbations, and healthcare resource utilization during the 180 days following index treatment start.<sup>29</sup> GOLD-adherent prescribing practices were associated with significant reductions in all-cause hospitalizations and ED visits compared with nonadherent practices (OR, 0.69 and 0.63, respectively) (Figure 5).<sup>29</sup> GOLD-adherent prescribing was accompanied by a significant decrease in all-cause ED visits compared with overtreatment (OR, 0.61; P = .0042).<sup>29</sup> Cournoyer noted that in these data, “we can potentially see medical cost offsets

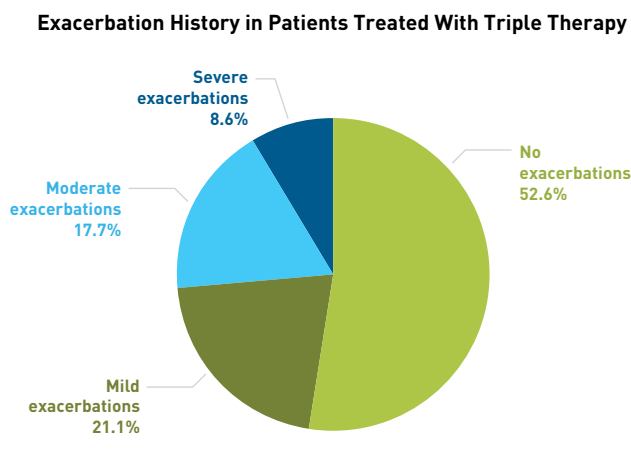
**Figure 3.** Real-World Prescribing Practices Nonadherent With GOLD-Recommended Long-Acting Maintenance Treatment<sup>28</sup>



GOLD indicates Global Initiative for Chronic Obstructive Lung Disease; ICS, inhaled corticosteroid; LABA, long-acting beta<sub>2</sub> agonist; LAMA, long-acting muscarinic receptor antagonist.

<sup>a</sup>Based on claims data from January 1, 2010, to June 30, 2015, for patients with COPD (N = 358,199).

**Figure 4.** Real-World Triple Therapy Prescribing Practices Nonadherent with GOLD-Recommended COPD Treatment Strategies<sup>28</sup>



COPD indicates chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease.

<sup>a</sup>Based on claims data from January 1, 2010, to June 30, 2015, for patients with COPD receiving triple therapy (N = 31,660).

<sup>b</sup>Exacerbations were physician defined and occurred 12 months prior to index date.

when we are GOLD-adherent and steering patients to be adherent with [the] GOLD. That [informs] the medical piece.”

Drug costs for COPD have not historically held much concern for payers, largely overshadowed by medical costs from hospitalizations and ED visits as a result of exacerbations. However, triple therapy entered the market at a higher price point.<sup>30</sup> The pharmacy spend on triple therapy (\$530) is 50% more expensive than LAMA monotherapy (\$324-\$398) or LAMA/LABA combination therapy (\$355-\$398) for a 30-day supply.<sup>30</sup> Coupled with the risks of AEs with ICS use, specifically pneumonia, the utility of triple therapy will likely initiate further discussion among payers to consider utilization management strategies.<sup>11</sup>

## APPROPRIATE ICS USE: CONSIDERATIONS FOR MANAGED CARE

Treatment with ICS-containing therapies for patients with COPD is the most aggressive form of maintenance medication and is associated with increased healthcare resource utilization. Payers will consider nonadherence to recommendations, increased pharmaceutical costs, and added healthcare costs due to AEs as a result of aggressive therapy. Cournoyer discussed that the real-world data showing a 72% rate of utilization of ICS-containing treatment regimens add to concerns about nonadherence to the GOLD recommendations: “The ICS component is not a primary treatment option in most groups, and is second-line in group D, which doesn’t promote ICSs as frontline treatment.” Payers are concerned with this high rate of utilization, coupled with AEs from ICS usage. According to Cournoyer, “Pneumonia comes with a cost. Payers are concerned

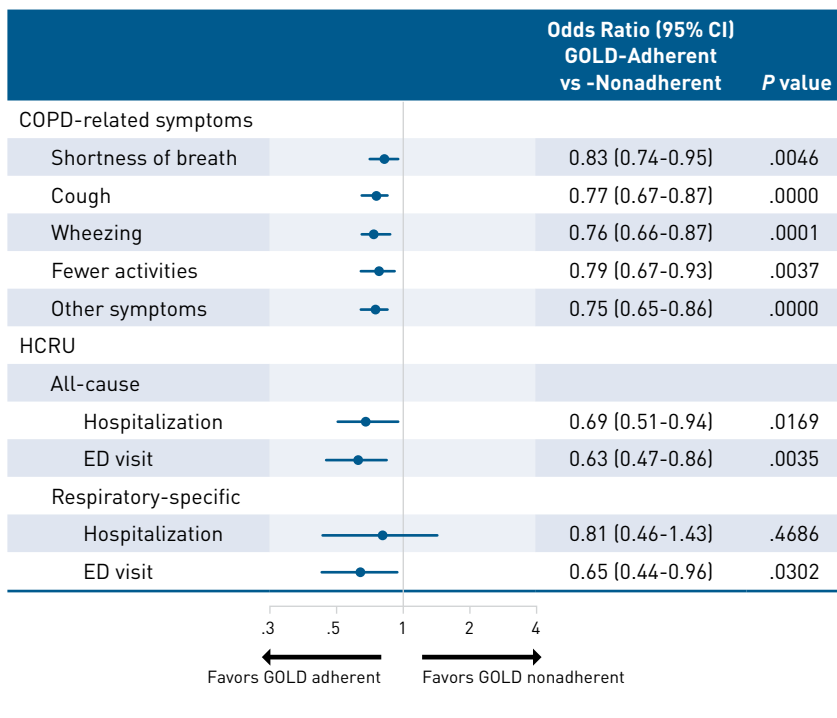
with healthcare resource utilization and minimizing [the] cost of AEs tied to pneumonia, as well as associated outpatient and inpatient costs.” He emphasized the importance of payers reviewing the data on utilization of these ICS-containing regimens in their populations and seeing if this population was associated with hospitalizations for pneumonia. These analyses would support decision making and step edits around the usage of ICSs to minimize inappropriate use.

Cournoyer discussed how these intersecting factors could spur interest in payer management of triple therapy. “There’s the guidelines [component]. Secondly, there are the inappropriate utilization trends that ultimately are components of the total medical cost spend. There’s the cost saving opportunity from both the medical and pharmacy points of view. Based on these issues, payers should probably take a step back, look at their data, and initiate a dialogue to determine if these pertain to their plan,” he said. If so, Cournoyer posed questions for payers to consider: “Do the guidelines give us clinical justification to manage this? Does this drive improved patient outcomes such as care management programs and case management interventions?”

ICS-containing regimens are not beneficial for all patients with COPD and the GOLD recommends limiting the use of ICSs to that of add-on therapy.<sup>2</sup> Considering the GOLD ABCD treatment model, payers may find opportunity by including step therapy that is guided by the GOLD algorithm.<sup>2</sup>

Cournoyer summarized a potential decision process for COPD management: “The type of utilization management strategy would be a step therapy because of its point-of-sale operations. Overall, the class....contains highly utilized drugs, and I think putting something

**Figure 5.** Effect of GOLD-Adherent and -Nonadherent Prescribing Practices During 180 Days Following Start of Index Treatment<sup>29</sup>



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\*Defined using the GOLD 2011 recommendations for pharmacologic therapy.

COPD indicates chronic obstructive pulmonary disease; ED, emergency department; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HCRU, healthcare resource utilization.

like a prior authorization out there—that’s a hard stop at the point of sale—would put a lot of burden on the precertification departments.” He noted that prior authorization would be especially burdensome in the precertification department in a Medicare setting.

As providers and payers continue to look for solutions in the new COPD treatment paradigm, Cournoyer noted that payers “do have some basis to create such a policy and gain support through pharmacy and therapeutics committees because we have the appropriate scientific evidence. So the question is, ‘is your COPD population GOLD-adherent?’”

### Addressing the Challenges and Unmet Needs in GOLD Adherence for COPD

There is an opportunity for managed care to improve outcomes by analyzing current utilization trends and comparing them with GOLD recommendations. Given that nonadherence to GOLD recommendations is associated with high resource utilization, decision makers can reevaluate the appropriateness of strategies in their population of patients with COPD.<sup>29</sup>

Decision makers are uniquely positioned to analyze the data which highlight the challenges and unmet needs in the current state of

COPD management for evidence-based decision making. Despite mounting evidence, real world data show frequent use and overtreatment with ICS-containing regimens, including the higher-cost triple therapy.<sup>28</sup>

LAMA/LABA therapy improves lung function and reduces exacerbation risk compared with LABA/ICS combinations.<sup>20</sup> Additionally, patients maintained on bronchodilator therapy did not experience an increased risk of exacerbations after withdrawal of ICSs.<sup>25-27</sup> ICS-containing therapies have a role in the management of COPD, but they are not recommended as the preferred initial treatment in the majority of patients with COPD.<sup>2</sup> ICS use is associated with an increased risk of pneumonia, an often serious and costly AE.<sup>11</sup> GOLD recommendations note that ICS-containing therapies should be used when the preferred medication does not offer symptom control.<sup>2</sup>

Formulary decision makers may want to consider the growing body of evidence that supports a more limited role for ICS-containing regimens than what is currently in use. Understanding the role of ICS-containing therapy and its place within the treatment algorithm for patients with COPD in groups B, C, and D could help decision makers implement appropriate strategies to improve patient outcomes, which may include care management programs or case management interventions.<sup>2</sup>

## CONCLUSIONS

To conclude the AMCP Science and Innovation Theater Webinar, Cournoyer reiterated, “Payers understand the guidelines and look at their data. If they haven’t reviewed the new GOLD [recommendations], then maybe it’s time to take a look and understand the appropriate roles and places of therapy for the various drugs and when to use them for maintenance.” ●

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