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Evidence-Based Recommendations, Real-World Utilization, and Considerations in the Total Cost of Care in COPD Treatment Strategies

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KEY TAKEAWAYS:

- Annual medical costs related to chronic obstructive pulmonary disease (COPD) increase with worsening disease severity, with the majority being attributable to inpatient costs.[1,2]
- Global Initiative for Chronic Obstructive Lung Disease (GOLD)-adherent prescribing practices to treat COPD have been associated with reductions in COPD-related symptoms, all-cause hospitalizations, and emergency department visits, compared with nonadherent practices.[1,3]

BACKGROUND

Chronic obstructive pulmonary disease (COPD) is an important public health challenge and continues to be a leading cause of mortality and morbidity in the United States.[1] As a chronic and progressive disease, a high correlation exists between disease severity and cost of care.[1,4] Because the management of the disease results in substantial healthcare resource utilization (HCRU) and high total cost of care, COPD is a key managed care concern.

Pharmacotherapy is the mainstay of COPD treatment, and the 2020 Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommendations for treatment provide the most up-to-date pharmacologic protocols.[1] However, despite consensus on appropriate treatments, adherence to guideline recommendations is suboptimal. This deviation from evidence-based guidelines has both clinical and cost implications.[5]

Here, we describe the latest (2020) GOLD recommendations, review recent research with real-world utilization data, and discuss the implications of prescription and utilization patterns on COPD HCRU and total cost of care.

PREVALENCE AND BURDEN OF COPD IN THE UNITED STATES

Prevalence

According to an analysis of the 2013 Behavioral Risk Factor Surveillance System by the CDC, an estimated 15.7 million Americans have been diagnosed with COPD. Although often perceived as a disease of the elderly, two-thirds (67%) of all patients diagnosed with COPD are 64 years or younger and still of working age.[6]

Pathophysiology

COPD is 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. Chronic airflow limitation

may be caused by a mixture of small airway disease and parenchymal destruction, which varies from patient to patient. Airflow limitation may change at different rates and at different times among patients.[1]

Economic Impact in the United States

Patients with COPD often experience exacerbations, or acute periods of symptom worsening, which can be associated with increased hospitalization and readmission rates, negative impacts to individual health status, and acceleration in disease progression overall.[1] These exacerbations and their associated hospitalizations account for the majority of COPD-related medical costs and show a distinct relationship between disease severity and total cost of care.[1,4]

Medical costs related to COPD were estimated to be more than $32.1 billion in 2010, and these costs are expected to increase to $49.0 billion by 2020. Approximately 700,000 patients were hospitalized for COPD in 2010, and it was the cause of 10.3 million recorded outpatient visits and 1.5 million emergency department (ED) visits. The data also reflect $3.9 billion (adjusted for 2012 US$) in national absenteeism costs attributed to COPD.[7]

DIAGNOSIS OF COPD

COPD should be considered in any patient who presents with dyspnea, chronic cough or sputum production, recurrent lower respiratory tract infections, and/or other known risk factors. Diagnosis of COPD requires the use of spirometry, which is a reliable measurement of airflow limitation. The presence of persistent airflow limitation is confirmed by a first second of forced expiration (FEV_1) to the full, forced vital capacity (FVC) ratio of less than 0.70 after administration of a short-acting bronchodilator. Because the physical signs of COPD are not typically present until significant lung impairment has occurred, the disease cannot be diagnosed by physical examination alone.[1]

Disease Classification

Once diagnosed, the impact of COPD on the patient is assessed according to the GOLD ABCD assessment tool, which incorporates both a spirometric grading system and patient-reported outcomes, such as symptom assessment. Higher spirometric severity is associated with increased risk of exacerbations, hospitalizations, and risk of death. However, FEV_1 alone is not sufficient to clinically predict exacerbation or mortality.[1]

The ABCD assessment scheme in the 2020 GOLD recommendations involves 3 components: (1) use of spirometry to diagnose airflow limitation and then determine its severity (grade 1-4); (2) use of the COPD Assessment Test (CAT) or modified Medical Research Council (mMRC) dyspnea scores for assessing symptomatic impact; and (3) use of medical history and prior hospitalizations to determine the number of previous moderate or severe exacerbations. The letter grade (A-D) is intended to indicate overall symptom burden and exacerbation risk (**Figure 1**).[1]

Spirometry remains the hallmark for diagnosis of COPD[1,8]; however, the revised GOLD assessment tool classifies patients with their severity grade from spirometry, followed by their letter group based on symptoms and exacerbation history leading to hospitalization.[1] As an example, consider a patient with an FEV_1 less than 30% predicted, who is labeled GOLD grade 4. If the patient had previously experienced 1 exacerbation that did not lead to a hospitalization, and had an mMRC score of 2 or higher, or CAT score of 10 or higher, they would be labeled GOLD grade 4, group B. If that same patient had experienced 1 or more exacerbation(s) that led to hospitalization, they would be labeled GOLD grade 4, group D.[1]

TREATMENT OF COPD: 2020 GOLD RECOMMENDATIONS

The GOLD recommendations for COPD management, including the escalation and de-escalation of treatment, focus on decreasing risk factor exposure, such as smoking cessation (in individuals who smoke), and reducing current symptom burden and the risk of future exacerbations. Treatment should be individualized for each patient based on exacerbation risk and level of symptoms.[1]

In 2019, GOLD updated the treatment algorithms to parse out both initial pharmacological treatment and follow-up management, and these remain in the 2020 guidelines (**Table 1**[1,9-12]).[13] Although the algorithm for treatment initiation is based on the patient's group letter (A-D), the follow-up treatment algorithm is not. The follow-up focuses on 1 of 2 predominant traits—dyspnea and exacerbations—which the patient may experience even after being on therapy for a significant amount of time.[1]

Initial Pharmacologic Treatment

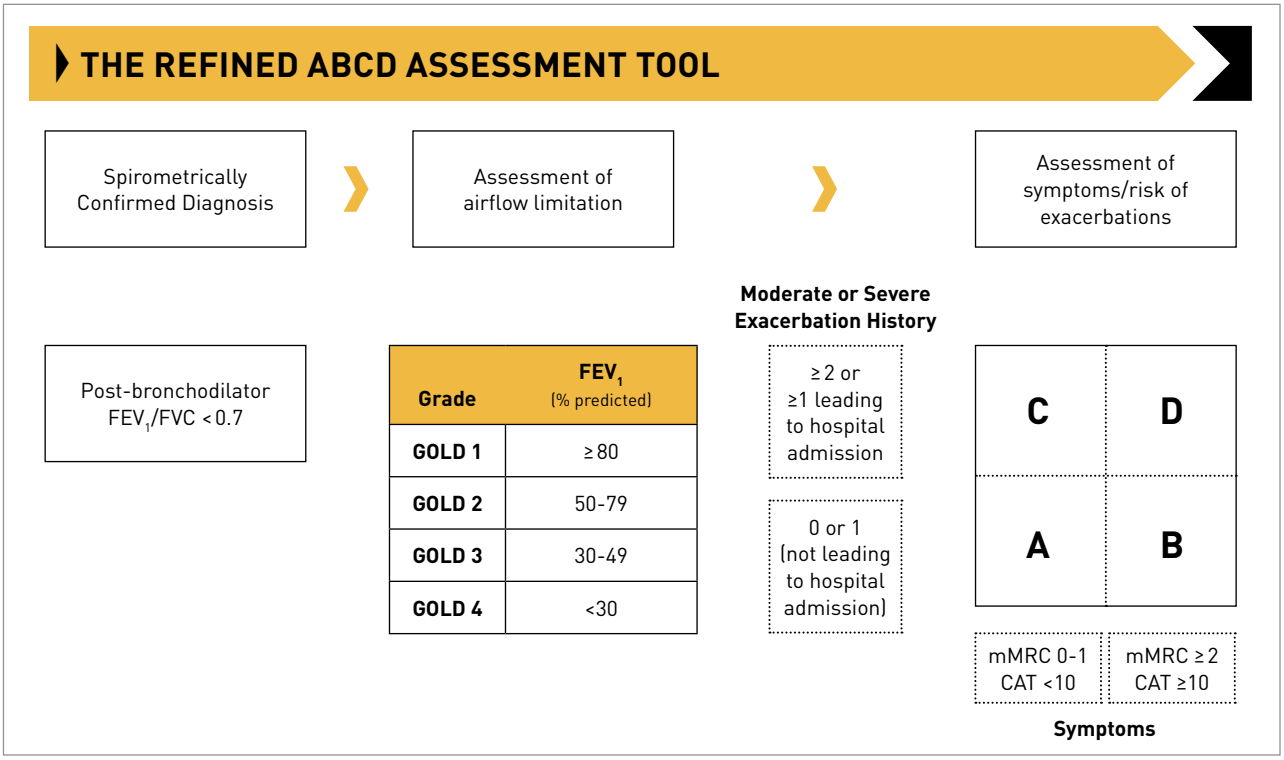
A model for the initiation of pharmacologic treatment for COPD, based on individualized symptom assessment and exacerbation risk, is described in **Table 2**.[1] Initial treatment for patients placed in group A at diagnosis is any bronchodilator (short- or long-acting). For group B patients, initial treatment at diagnosis consists of any long-acting bronchodilator. No evidence exists to support the superiority of a specific class of long-acting agent regarding initial relief of symptoms. Clinicians should base prescribing decisions on a patient's perception of symptom relief. If patients in group B have severe breathlessness, consideration may be given to initiation of 2 different bronchodilators. For group C patients, initial treatment with a long-acting muscarinic antagonist (LAMA) is recommended.[1]

For patients placed in group D, initial treatment recommended at diagnosis is a LAMA. In patients with greater symptom severity (CAT $\geq$ 20), a LAMA and long-acting beta-agonist (LABA) combination agent should be chosen. The decision to begin with a LABA/LAMA combination should be guided by symptom severity. LABA and inhaled corticosteroid (ICS) combinations should be considered for any group D patient with a blood eosinophil count of at least 300 cells/µL and in patients with a history of asthma, but the risk of pneumonia associated with ICS agents should be weighed against the anticipated benefits.[1]

Maintenance Treatment

The 2020 GOLD report recommendations include reassessing patients after treatment initiation to determine if treatment goals have been met. At follow-up, treatment changes should be guided by an

Figure 1. GOLD ABCD Symptom and Risk Assessment for Patients With COPD[1]



CAT indicates comparison between COPD assessment test; COPD, chronic obstructive pulmonary disease; FEV_1, first second of forced expiration; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; mMRC, modified Medical Research Council dyspnea score.

assessment of patient symptoms and/or exacerbations, regardless of the patient's ABCD classification at time of diagnosis. Treatment decisions should follow 1 of 2 pathways—dyspnea or exacerbation—with escalation or de-escalation of treatment according to the respective pathway algorithm. If both dyspnea and exacerbations are of equal concern, then the exacerbation pathway is recommended. A model for follow-up treatment based on dyspnea or exacerbation pathway is summarized in **Figure 2**.[1]

Follow-up Pharmacological Treatment: Dyspnea Pathway

The dyspnea pathway is recommended for patients with persistent breathlessness or exercise limitation at follow-up. If the patient has been on long-acting bronchodilator monotherapy (LABA or LAMA), escalation to dual therapy with 2 bronchodilators is recommended. If the patient has been on a LABA/ICS, escalation to triple therapy (TT; LABA/LAMA/ICS) is recommended. If the patient has been on a LABA/ICS and the indication for ICS was inappropriate (absence of previous exacerbations), or if the patient has experienced intolerable ICS adverse effects (AEs), then switching to a LABA/LAMA combination is recommended.[1]

Follow-up Pharmacological Treatment: Exacerbation Pathway

For patients who experience persistent exacerbations at time of follow-up, the exacerbations pathway should be followed. If the patient has been on long-acting bronchodilator monotherapy, escalation to LABA/LAMA or LABA/ICS combinations is recommended. LABA/ICS may be especially appropriate in patients who meet any of the following criteria[1]:

- Comorbid asthma (or history of asthma)
- Blood eosinophil count of at least 300 cells/µL with history of 1 exacerbation in the previous year
- Blood eosinophil count of at least 100 cells/µL with history of at least 2 moderate exacerbations in the previous year or at least 1 severe exacerbation requiring hospitalization in the previous year

For a patient who has been on LABA/LAMA dual therapy and has a blood eosinophil count of at least 100 cells/µL, escalation to LABA/LAMA/ICS TT is recommended. If the patient has been on LABA/LAMA dual therapy and has a blood eosinophil count of less than 100 cells/µL, adding roflumilast or azithromycin is recommended.[1]

Table 1. Initial Pharmacological Treatment and Follow-up Management of COPD: Highlights From the 2020 GOLD Recommendations[1,9-12]

Blood eosinophil count is recommended as a biomarker for identifying patients most likely to benefit from ICS in addition to long-acting bronchodilator therapy. A blood eosinophil count > 300 cells/μL, or a blood eosinophil count <100 cells/μL, combined with an exacerbation history, can be used to estimate the treatment benefits of using an ICS-containing regimen.[1]
LABA plus ICS dual therapy is recommended for consideration at treatment initiation only in those group D patients whose blood eosinophil count is ≥ 300 cells/μL. Treatment recommendations for all other groups (A, B, and C) do not include an ICS at initiation.[1]
LABA plus LAMA dual therapy is recommended at treatment initiation for highly symptomatic group D patients (eg, CAT > 20).[1]
Escalation to LABA plus LAMA dual therapy is recommended for most patients who are still experiencing symptoms or exacerbations while on monotherapy. Escalation to triple therapy (LABA/LAMA/ICS) is recommended only for those patients who fail after attempting dual therapy with either a LABA plus LAMA or LABA plus ICS regimen.[1a]
ACO is no longer used; rather asthma and COPD should be recognized as distinct disorders. Pharmacotherapy should follow asthma guidelines for those patients who are diagnosed with asthma and COPD; however, additional pharmacological and nonpharmacological treatment may be needed for COPD.[1]

ACO indicates asthma & COPD overlap; CAT, COPD Assessment Test; COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICS, inhaled corticosteroids; LABA, long-acting beta-agonist; LAMA, long-acting muscarinic antagonist.

[a]LAMA/LABA combinations are associated with airway adverse effects, such as pharyngitis and nasopharyngitis.[9-11] ICS-containing products used for COPD are associated with adverse events such as oropharyngeal candidiasis, skin bruising, and increased risk of cataracts, diabetes, and pneumonia.[12]

Table 2. Initial Pharmacological Treatment Summary[1]

GOLD Grade	Therapy	
Group A	A bronchodilator	
Group B	A long-acting bronchodilator (LAMA or LABA)	
Group C	LAMA	
Group D	LAMA or LAMA + LABA[a] or ICS + LABA[b]	[a]Consider if highly symptomatic (eg, CAT > 20). [b]Consider if eos ≥ 300, or patient has a history of asthma.

CAT indicates COPD assessment test; COPD, chronic obstructive pulmonary disease; eos, blood eosinophil count; ICS, inhaled corticosteroids; LABA, long-acting beta-agonist; LAMA, long-acting muscarinic antagonist.

For patients on LABA/ICS who develop further exacerbations, GOLD recommends escalation to LABA/LAMA/ICS TT. However, if there was a lack of response to ICS treatment or if the patient has experienced intolerable ICS AEs, then switching to a LABA/LAMA is recommended. For patients on LABA/LAMA/ICS TT who continue to experience exacerbations, adding roflumilast or a macrolide antibiotic such as azithromycin may be considered. De-escalation to LABA/LAMA dual therapy can be considered if AEs such as pneumonia occur with the ICS or if the ICS has not been efficacious.[1]

Treatment With Long-Acting Bronchodilators: Mechanisms of LAMA/LABA

Inhaled bronchodilators are central to COPD symptom management. 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 prolongs bronchodilation. LABAs are beta$_2$ agonists. Beta$_2$ agonists stimulate beta$_2$ adrenergic receptors to relax smooth muscle.[1]

The combination of a LAMA with a LABA allows for the targeting of different receptor types that influence bronchodilation. Combination LAMA/LABA therapy has been shown to increase FEV$_1$ and reduce symptoms and exacerbations compared with monotherapy. Additive effects and further improve bronchodilation may be improved with combining bronchodilators that have different mechanisms of action. This strategy also may lower the risk of adverse effects compared with increasing the dose of a single LAMA or LABA.[1]

Treatment With Inhaled Corticosteroids

The 2020 GOLD report affirms that regular treatment with ICS escalates the chance of pneumonia and is associated with oral candidiasis, hoarse voice, and skin bruising.[1] However, GOLD includes ICS therapy as an appropriate therapy for certain patients.

Peripheral blood eosinophil count should be used as a biomarker for identifying patients most likely to benefit from ICS therapy as an addition to bronchodilator therapy. A patient's symptoms and severity of disease, based on recommended cut points, can help guide clinician decisions regarding the use of ICS therapies. Patients with a high risk of exacerbations (≥ 2 exacerbations and/or ≥ 1 hospitalization in the previous year) may benefit most from an ICS-containing regimen. In these patients, an ICS combined with a LABA has been effective at reducing exacerbations in clinical trials.[1]

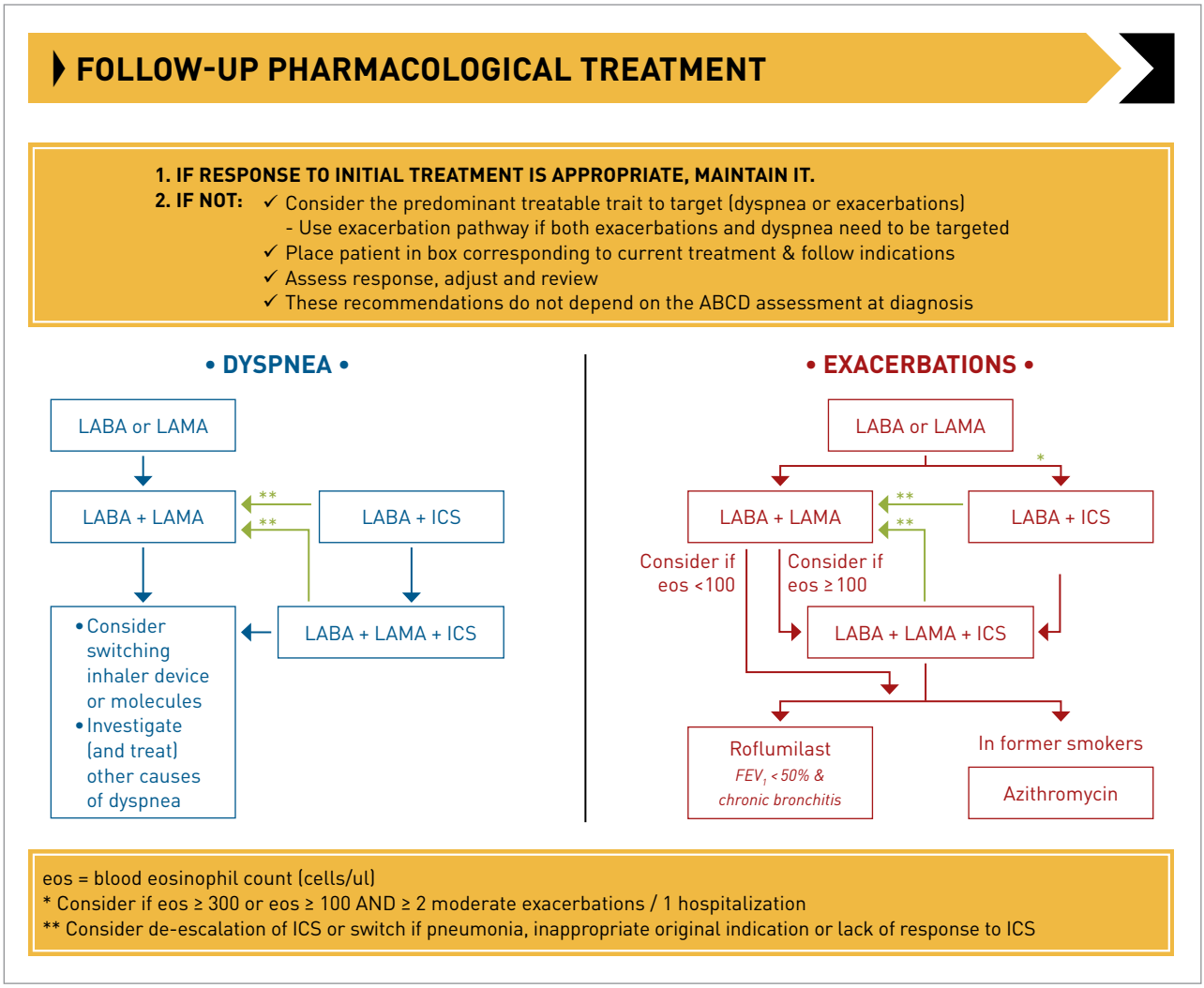
ICS Use at Treatment Initiation

GOLD does not recommend ICS use at treatment initiation for mild or moderate disease. LABA/ICS dual therapy is recommended for consideration at treatment initiation in only those group D patients whose blood eosinophil count is at least 300 cells/μL. Treatment recommendations for all other groups (A, B, and C) do not include an ICS at initiation.[1]

ICS Use at Treatment Follow-up

Escalation to LABA/ICS dual therapy is recommended in patients whose predominant trait is exacerbations despite treatment with a LABA or LAMA monotherapy, and who meet 1 of 3 blood eosinophil count cut-point criteria (≥ 300 cells/μL; ≥ 100 cells/μL with ≥ 2 moderate exacerbations; or ≥ 100 cells/μL with ≥ 1 hospitalization). Escalation to LABA/LAMA/ICS TT can be considered in patients whose predominant trait is exacerbations despite treatment with LABA/ICS dual therapy or LABA/LAMA dual therapy and whose blood eosinophil count is at least 100 cells/μL. Escalation to LABA/LAMA/ICS TT also may be considered in patients whose predominant trait is dyspnea despite

Figure 2. Follow-up Pharmacologic Treatment[1]



CAT indicates COPD assessment test; FEV_1, first second of forced expiration; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICS, inhaled corticosteroids; LABA, long-acting beta-agonist; LAMA, long-acting muscarinic antagonist.

treatment with LABA/ICS dual therapy. De-escalation from an ICS regimen to a non–ICS-containing regimen is recommended for any patient who experiences pneumonia or lack of response to the ICS.[1]

CONSEQUENCES OF REAL-WORLD NON-ADHERENCE TO GOLD RECOMMENDATIONS

Despite GOLD recommendations, recent data suggest that inappropriate initiation of TT is prevalent. The results of an analysis on prescription data completed in 2018 indicated that 43% of patients with COPD who were initiating closed TT were not previously on a long-acting maintenance therapy in the prior 12 months; 22% were on LABA/ICS therapy; 15% were on open TT; 10% were on LAMA/LABA combination, and just 8% were on LAMA monotherapy.[14] (Percentages do not add up to 100% due to rounding.) Further analyses on claims-based data indicated that 55% of patients in a Medicare population who initiated TT (n = 3232) were maintenance-naïve, while 23% were on LAMA monotherapy, and 23% were on LABA/ICS therapy.[15] (Percentages do not add up to 100% because some patients may have been receiving multiple medications.)

Earlier studies have shown that overuse of TT is common as well. The proportion of overuse or early use of ICS/TT in the United States was analyzed in a retrospective claims analysis (January 1, 2009–December 31, 2013) of 2 patient cohorts. Data for cohort 1 was analyzed

Table 3. COPD-Related Costs by GOLD Stage, From Index Date to 24 Months Post Index (in 2015 US$)[2]

	GOLD I	GOLD II	GOLD III	GOLD IV	Overall
Mean annual COPD-related total medical costs[a,b]	$5945	$6978	$10,751	$18,070	$7780
COPD-related inpatient costs (percentage of mean annual COPD-related total medical costs)[b]	$3853 (65%)	$4449 (64%)	$6277 (58%)	$12,139 (67%)	$4865
COPD-related pharmacy costs (percentage of mean annual COPD-related total medical costs)[b,c]	$592 (10%)	$1101 (16%)	$2000 (19%)	$2479 (14%)	$1207
COPD-related medical costs (multivariate analysis)[b,d]	$5855 (95% CI, $4506-$7227)	$6923 (95% CI, $6066-$7781)	$11,119 (95% CI, $9398-$12,841)	N/A[e]	—

COPD indicates chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease; N/A, not applicable.

[a]Includes inpatient visits, emergency department visits, office visits, outpatient visits, and pharmacy claims.

[b]Costs are adjusted to 2015 US dollars using the medical care component of the Consumer Price Index available from the Bureau of Labor Statistics.

[c]Includes COPD rescue and maintenance medications.

[d]Multivariate analysis covariates include age on COPD diagnosis index date (continuous and categorical), sex, race, geographic region, health insurance type (commercial or Medicare), setting of index COPD diagnosis (inpatient or outpatient), Elixhauser Comorbidity Index, smoking status, and any hospitalization during the pre-COPD diagnosis period. Analyses were calculated from index date to 24 months after the index date and categorized by GOLD stage adjusted for covariates (n = 1471).

[e]GOLD IV was excluded due to small sample size (<100).

Adapted from Wallace AE, Kaila S, Bayer V, et al. *J Manag Care Spec Pharm*. 2019;25(2):205-217. doi: 10.18553/jmcp.2019.25.2.205.

to determine the proportion of patients with COPD who received maintenance TT, while cohort 2 was analyzed to determine patient characteristics and GOLD stage prior to maintenance TT regimen. Approximately 75% of all patients with COPD in the study had mild or moderate COPD (GOLD Grade 1 or 2), despite GOLD recommendations to reserve TT for severe or very severe airflow limitation (GOLD Grade 3 or 4). Spirometry was absent in over half of all patients; therefore, airflow limitation and corresponding GOLD grade could not be assessed. These data further suggest overuse of maintenance TT therapy in patients with COPD.[5]

More research has been conducted outside of the United States, with results showing ICS use in mild or moderate GOLD stages. Database analysis of patients with COPD who were newly diagnosed (n = 41,592) from 2007 to 2012 in Catalonia, Spain, revealed the proportion of patients treated with ICS combination therapies across GOLD stages were 28.3%, 37.3%, 51.3%, 59.3% for stages 1 through 4, respectively. Diagnoses were made in 56.3% of patients in the absence of spirometry.[16]

Similarly, in a historical analysis of 11,858 patients who received a diagnosis of COPD from a UK primary care practice database (n = 318 practices) from 2002 to 2010, data showed that overuse of ICS-containing regimens was common in primary care practices and led to overuse of TT. Thirty-two percent (n = 3755) of all patients in the analysis received TT during the study period. By GOLD (2013) stage, TT was received by 19%, 28%, 37%, and 46% of patients classified as GOLD A, B, C, and D, respectively, (P <.001). One-quarter (25%) of patients who progressed to TT did so within 1 year of diagnosis (P = .065).[17]

These results are aligned with a 2017 point prevalence study of a group of patients (n = 500) recruited from an Ontario academic center, where a high level of TT use was observed throughout all GOLD categories, including 26.8% of patients in GOLD category A and 42.6% in Group B.[18]

And, finally, the results of a study by Casas et al, from 2018 in which the investigators analyzed use and adherence to different inhaled therapies in 7 Latin American countries, indicated that according to the GOLD 2013 COPD categories, TT was used frequently in mild and moderate COPD (GOLD A: 17.3%; GOLD B: 30.2%).[19]

Costs of Care and ICS Use by GOLD Severity Grade

In a study by Wallace and colleagues, HCRU and costs were analyzed using an administrative claims database for commercially insured and Medicare Advantage plan enrollees. The sample for this retrospective observational cohort study included COPD patients aged at least 40 years who had at least 12 months of continuous enrollment prior to the index date and at least 1 inpatient or outpatient claim associated with a COPD diagnosis according to *International Classification of Diseases, Ninth Revision, Clinical Modification* code between January 1, 2012, and November 30, 2013. The index date was the earliest service date with a COPD diagnostic code.[2] HCRU, costs, and treatment patterns were calculated using data from at least 24 months prior to the index date.

Among the 1505 patients with confirmed COPD, costs related to COPD increased with worsening disease severity (**Table 3**), with patients classified as GOLD grade I and IV having mean annual COPD-related costs of $5945 and $18,070, respectively. Univariate and multivariate analyses were similar. Correlations among HCRU and costs with exacerbation and disease severity shown in this study align with those of other claims data studies.[2]

ICS use was high (67% of patients) across all groups. On average, more than 40% of patients (43.3%) were prescribed a LABA/ICS combination agent at some point during the 24-month follow-up period; nearly 12% (11.6%) were prescribed a LAMA/LABA/ICS combination agent; and fewer than 1% were prescribed a LAMA/LABA combination agent. ICS was prescribed as monotherapy in nearly 9.5% of patients in the study population (**Table 4**).[2]

Limitations

The investigators acknowledged some limitations to this study. Because the study was observational, certain descriptive statistical analyses were not performed. This may have limited the potential for drawing conclusions among GOLD-stratified groups. In addition, the data analyzed in this study are from 2012 and 2013 and results may differ with more recent data. Furthermore, the use of Medicare Advantage members only may not be representative of the full Medicare population. Coding errors may have occurred, or spirometry tests may not have been coded by providers. Although prescription claims were captured in claims data, most drugs administered during inpatient visits were not. Furthermore, the beginning of treatment may not be accurately reflected. Because primary reasons for outpatient visits were undetermined, and may not have been due to a COPD exacerbation, an overestimation of these data is possible. The study investigators also acknowledged a potential channeling bias from the study design in that some providers had office spirometry, and some did not.[2]

Effects of Nonadherence on Cost of Care

Nonadherence to GOLD-recommended treatment strategies leads to a measurable impact on COPD-related symptoms and all-cause HCRU. In a retrospective study of electronic health records (EHRs) from January 1, 2007, to December 31, 2012 (n = 4234 treated patients; 1521 untreated patients), Mannino and colleagues assessed the effect of adherence and nonadherence to GOLD 2011–defined prescribing guidelines. Study assessments included COPD symptom burden, exacerbations, and all-cause HCRU during the 180 days following index treatment start.[3]

Patients were classified according to GOLD 2011 letter grades, except 1678 treated patients who were subsequently assigned to group C, determined by absence of shortness of breath. Of the 4234 patients who were treated, 1531 patients received treatments according to GOLD prescribing recommendations, while 2703 patients did not. Of those patients who did not receive appropriate treatment, 1158 patients were undertreated and 1545 patients were overtreated.[3]

The study results indicated that during the 180 days after index treatment start, a significantly fewer proportion of patients who were prescribed treatment according to GOLD-adherent prescribing experienced COPD-related symptoms, such as shortness of breath, cough, and wheezing (all odds ratios [OR]; 0.46-0.55; $P < .0001$) compared with patients who were undertreated, whereas a significantly higher proportion of patients in the GOLD-adherent prescribing group experienced shortness of breath compared with patients who were overtreated (OR, 1.29; $P = .0005$). Although the incidence and frequency of exacerbations were not statistically different between GOLD-adherent and GOLD-nonadherent groups, those patients who received GOLD-adherent treatment had significantly less oral or intravenous steroid and antibiotic use compared with patients who were undertreated (OR, 0.78; $P = .0338$), and significantly more use compared with those patients who were overtreated (OR, 1.32; $P = .0256$).[3]

GOLD-adherent prescribing practices also were associated with reductions in all-cause hospitalizations and ED visits compared with nonadherent practices (OR, 0.69 and 0.63, respectively). Patients in the nonadherent prescribing group were divided into 2 subgroups: undertreated and overtreated, as defined by GOLD 2011 guidelines. Analyses of these subgroups showed that a significant decrease in all-cause ED visits was associated with GOLD-adherent prescribing compared with overtreatment (OR, 0.61; $P = .0042$) (**Figure 3**).[3]

Table 4. Prescription by GOLD Stage During 24-Month Follow-up Period[2]

	GOLD I	GOLD II	GOLD III	GOLD IV
LABA/ICS	47.6%	45.3%	36.8%	41.7%
LAMA/LABA/ICS	4.9%	9.2%	19.9%	16.7%
LAMA/LABA	0%	0%	0.4%	0%
ICS Monotherapy	16.1%	9.4%	5.6%	8.3%

GOLD indicates Global Initiative for Chronic Obstructive Lung Disease; ICS, inhaled corticosteroids; LABA, long-acting beta-agonist; LAMA, long-acting muscarinic antagonist.

Adherence to evidence-based guidelines could have a positive impact not just on patient outcomes, but also on healthcare costs. The data in this study suggest that guideline-adherent prescribing may reduce COPD-related healthcare costs in 2 domains relevant to managed care decision makers: reduction in the proportions of patients with all-cause hospitalizations and ED visits, along with reductions in per-patient frequencies of these end points.[3]

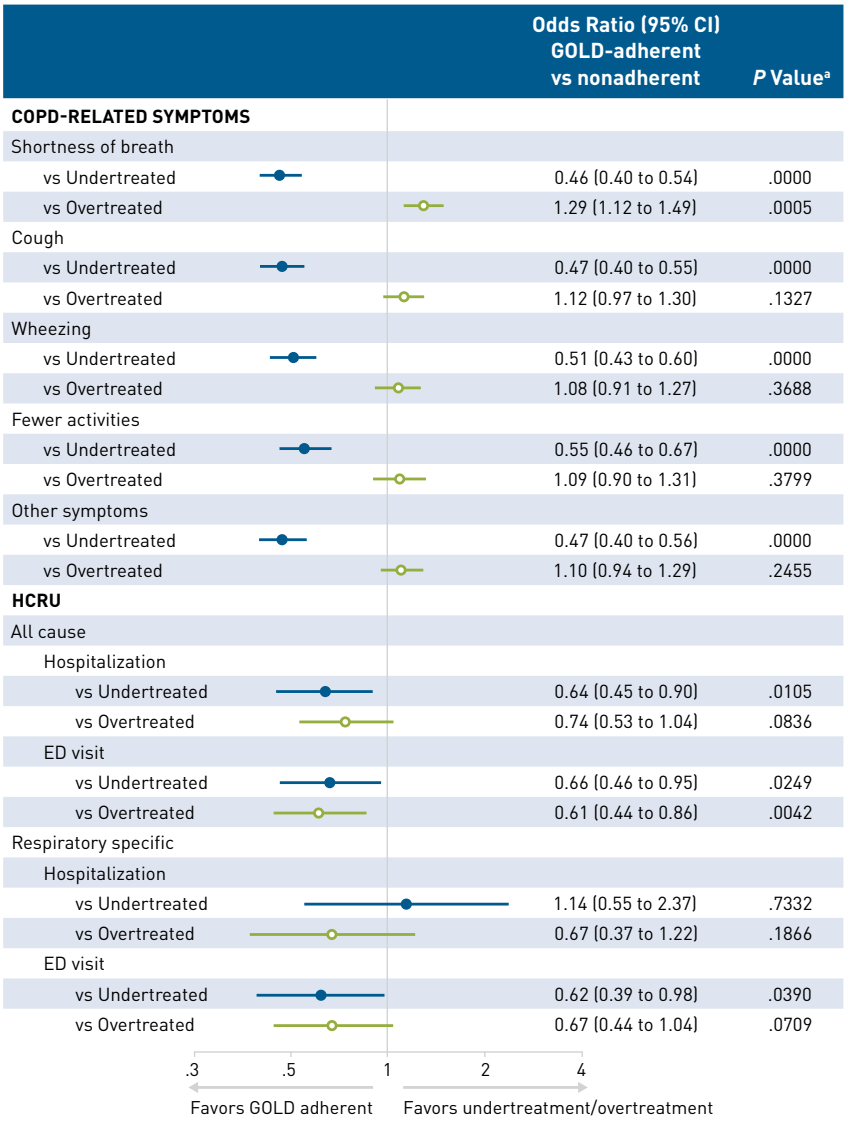
In alignment with GOLD recommendations, risks for prescribing ICS-containing therapies should be weighed against disease severity. Payers may choose to analyze safety profiles and risks of ICS-containing therapies when considering utilization management. These data present an opportunity to improve not only patient outcomes, but also the downstream impact on medical cost offsets and possibly even drug savings.

Limitations

The investigators acknowledged that data on GOLD-adherent prescribing practices was collected between 2007 and 2012 and then compared against GOLD 2011 guidelines, which would not have been available to physicians during a large section of their study period. In addition, patients with index dates closer to the end of 2012 may not have been included in the analysis because of condensed healthcare activity and look-forward adherence periods. This also likely resulted in a larger portion of patients with index dates that were earlier in the study period.[3]

Furthermore, because patients often initially present with symptoms of COPD to their primary care physician and spirometry is not often used in primary care setting, most patients included in the analysis (98%) were not classified to a GOLD stage prior to the start of treatment. Patients may have been prescribed nonadherent treatments prior to receiving a diagnosis of COPD. In addition, the analysis of HCRU end points may have been strengthened by the inclusion of patients who did not receive COPD treatment in the undertreated group. The investigators also acknowledged that the use of EHR data in the analysis may have underestimated HCRU

Figure 3. Effect of GOLD-Adherent Prescribing Versus Undertreatment or Overtreatment During 180 Days Following Index Treatment Start[3]



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

[a]Chi-square test (Fisher exact test is employed when ≥ 20% of the cells have an expected value < 5).

Reprinted with permission from *Chronic Obstructive Pulmonary Diseases: Journal of the COPD Foundation*.[3]

and may not have captured patients' entire medical history as they may have been seen at a facility which does not participate in EHRs, the record may have been missing, or the patient may not have had disease. In addition, the EHR database used did not include data on prescription medication fills or patient compliance to prescriptions, although, it did include drug prescription information. Finally, the authors' assignments of patients to their respective GOLD letter grade (A-D) pharmacotherapy groups were based on physician notes that implied the patient was suffering from shortness of breath, instead of mMRC scores, which were not included in the dataset. Comparisons seen in the incidence and frequency of COPD-specific and respiratory-specific ED visits and hospitalizations may have been weakened by the use of a small number of events; the accuracy of the effect of GOLD-adherent prescribing on these outcomes may be improved with longer follow-up. Larger patient groups and fewer endpoints would have allowed for adjusting the multiple comparisons of HCRU between GOLD-adherent and -nonadherent groups in the analyses. Finally, the assignment of 40% of patients to group C in the analysis of adherent versus nonadherent treatment introduced a degree of uncertainty.[3]

Cost of Care With Combination Tiotropium Bromide Olodaterol Versus TT

In a retrospective, observational study by Palli and colleagues, health plan–paid costs, exacerbations, and pneumonia outcomes for COPD were compared between patients identified from a managed care Medicare database who were initiating tiotropium bromide and olodaterol (TIO+OLO, STIOLTO® RESPIMAT®) versus those initiating TT in a real-world setting.[20] Eligible patients had

an *International Classification of Diseases, Ninth Revision, Clinical Modification* or *International Classification of Diseases, Tenth Revision, Clinical Modification* diagnosis code related to COPD recorded for 2 or more medical claims during the study period (January 1, 2013-June 30, 2017). The date that the patient initiated TIO+OLO or TT was defined as the index date. Compared with the TT group (n = 347), a significantly lower proportion of patients in the TIO+OLO group (n = 3232) had at least 1 COPD-related acute inpatient stay (16.8% vs 28.7%, *P* <.001), ED visit (22.0% vs 30.0%, *P* = .045) and/or outpatient visit (36.1% vs 54.0%, *P* <.001). The TIO+OLO cohort also had shorter mean COPD-related acute inpatient stays (1.9 days vs 3.2 days, *P* = .018), fewer mean acute inpatient stays (0.3 vs 0.5, *P* = .006), ED visits (0.3 vs 0.6, *P* = .002), and outpatient visits (1.7 vs 2.6; *P* = .008), compared with patients taking triple therapy. There was no significant difference in the average number of office visits (4.1 in the TIO+OLO group vs 3.9 in the TT group, *P* = .440) (**Table 5**).[20]

Pre-adjustment total mean weighted COPD-related costs were almost $4834 lower for the TIO+OLO group vs TT ($7076 vs $11,910, *P* <.001). The largest contributor (43.5% to 45.6%) to the total costs in both cohorts was acute inpatient costs. After adjustment for baseline characteristics, mean COPD-related costs remained $4118 lower for TIO+OLO versus TT ($7794 vs $11,912, *P* <.001). Pre-adjustment annual all-cause total costs (weighted) were $6274 lower for TIO+OLO versus TT ($15,758 vs $22,031, *P* <.001). Adjusted mean all-cause costs (weighted) were 23% lower ($5384) for TIO+OLO versus TT ($17,504 vs $22,887; CR = 0.77, 95% CI = 0.65-0.90) (**Table 6**).[20]

COPD Exacerbations

In the 12-month post-index (follow-up) period, severe exacerbations were significantly less common in patients in the TIO+OLO group. Data showed that 8.3% experienced severe exacerbations compared with 15.5% of patients in the TT group (*P* = .014). There was no significant difference between groups in the number of patients with a COPD exacerbation of any severity.[20]

Pneumonia and Acute Bronchitis/Bronchiolitis

Pneumonia and acute bronchitis/bronchiolitis also were reported during follow-up, with significantly lower incidence in patients in the TIO+OLO group versus the TT group (18.9% vs 30.9%; *P* <.001).[20]

The differences in occurrence of pneumonia or acute bronchitis/bronchiolitis aligned with lower total annual pneumonia-related medical costs for TIO+OLO, averaging $1566 versus $2897 for patients taking TT (*P* = .045). Acute inpatient costs accounted for more than

Table 5. Annual Weighted Medical Resource Use Post Initiation of TIO+OLO Versus TT[20]

COPD-Related	TIO+OLO (n = 347)	TT (n = 3232)	*P*
Acute inpatient stays % (n)	16.8% (58)	28.7% (927)	<.001
Acute inpatient length of stay, days, mean (SD)	1.9 (6.7)	3.2 (8.8)	.018
Acute inpatient stay count, mean (SD)	0.3 (0.8)	0.5 (0.9)	.006
ED visits % (n)	22.0% (76)	30.0% (968)	.045
ED visit count, mean (SD)	0.3 (0.7)	0.6 (1.3)	.002
Outpatient visits % (n)	36.1% (125)	54.0% (1746)	<.001
Outpatient visit count, mean (SD)	1.7 (3.7)	2.6 (4.6)	.008
Office visits % (n)	89.4% (310)	83.3% (2692)	.052
Office visits, mean (SD)	4.1 (3.2)	3.9 (3.9)	.440

COPD, chronic obstructive pulmonary disease; ED, emergency department; SD, standard deviation; TIO+OLO, tiotropium olodaterol; TT, triple therapy.

Table 6. Pre-Adjusted Total Annual Costs[20]

Pre-Adjustment Total Annual Costs				
	TIO+OLO	TT	*P*	Cost Difference
COPD-related	$7076	$11,910	<.001	$4834
All-cause	$15,758	$22,031	<.001	$6274[a]
Adjusted Total Annual Costs				
	TIO+OLO	TT	CR	Cost Difference
COPD-related	$7794	$11,912	0.65; 95% CI = 0.54–0.80	$4118
All-cause	$17,504	$22,887	0.77; 95% CI: 0.65–0.90	$5384[a]

COPD, chronic obstructive pulmonary disorder; CR, cost ratio; TIO+OLO, tiotropium olodaterol; TT, triple therapy.

[a]Cost difference due to rounding.

IMPORTANT SAFETY INFORMATION for STIOLTO RESPIMAT (tiotropium bromide and olodaterol)

CONTRAINDICATION

Use of a LABA, including STIOLTO RESPIMAT, without an inhaled corticosteroid (ICS) is contraindicated in patients with asthma.

STIOLTO is contraindicated in patients with hypersensitivity to tiotropium, ipratropium (atropine derivatives), olodaterol, or any component of this product.

In clinical trials and postmarketing experience with tiotropium, immediate hypersensitivity reactions, including angioedema (including swelling of the lips, tongue, or throat), itching, or rash have been reported. Hypersensitivity reactions were also reported in clinical trials with STIOLTO.

Table 7. Total Average Annual Pneumonia-Related Medical Costs[20]

	TIO+OLO	TT	*P*
COPD-related	$1566	$2897	.045
Non–COPD-related	$1223	$2058	NS

COPD indicates chronic obstructive pulmonary disease; NS, not significant; TIO+OLO, tiotropium olodaterol; TT, triple therapy.

85% of total pneumonia-related medical costs in the TIO+OLO group and the TT group. The between-group difference ($1138) may account for the observed difference in medical costs. Non-COPD pneumonia-related medical costs (ie, pneumonia-related claims without a concurrent COPD diagnosis on the same claim) for the TIO+OLO group were $1223 on average (78.1% of pneumonia-related medical costs) versus $2058 for the TT cohort (71.0% of pneumonia-related medical costs; *P* = .104)(**Table 7**).[20]

Treatment with ICS-containing therapies for patients with COPD is the most aggressive form of maintenance therapy and is associated with increased HCRU. In alignment with GOLD-recommended use of ICS-containing regimens, lower costs of care may be achieved when TT is reserved for patients with more severe COPD.[20]

Limitations

The use of claims data is associated with certain limitations. For example, it is possible for a patient without COPD to have a medical claim that includes a diagnosis code for COPD, as the coding may not be correct or the diagnosis code may have been included because the clinician was ruling out COPD. Also, pharmacy claims data indicate that prescriptions were filled, but not whether patients take their medications. Furthermore, there may have been differences in COPD severity between groups that were not captured, as certain data related to disease severity were not available via the administrative claims database (eg, symptom burden as assessed by the COPD assessment test or modified British Medical Research Council questionnaire, use of tobacco, spirometry results).[20]

An intent-to-treat analysis was performed and outcomes were tied to the index treatment; however, patients may have switched or discontinued therapy. Also, TIO+OLO was administered via 1 inhaler, while TT was administered via multiple inhalers, which may have affected medication adherence. In addition, TT was administered via various combinations of medications, compared with a single combination of medications for TIO+OLO; the impact of the composition of the medication regimen on the outcome is unknown.[20]

The 12-month follow-up requirement may have resulted in the selection of healthier patients. Furthermore, the study evaluated a population of patients who were enrolled in Medicare, and the results may not be generalizable to other populations of patients.[20]

Pharmacy Costs: LAMA Monotherapies, LAMA/LABA Combinations, and TT

A comparison of the most commonly prescribed maintenance treatments for COPD reveals that pharmacy costs for TT are substantially higher than for other therapeutic categories. As of January 2020, average wholesale price for a 30-day supply of closed TT of umeclidinium/vilanterol/fluticasone ($687.84) is, on average, 46% higher than some branded LAMA/LABA combination therapies ($472.78) and 32% higher than some LAMA monotherapy brands ($520.43).[21] Pharmacy costs may become increasingly important to payers, given that COPD is a chronic disease requiring long-term maintenance therapy.

CONCLUSIONS

Addressing the Challenges of COPD Management and Cost of Care

Data from real-world analyses highlight the challenges and unmet needs in the management of COPD. Despite guideline recommendations and a growing body of evidence that describes optimal treatment across all GOLD stages, gaps in real-world utilization remain. Nonadherence to GOLD recommendations is associated with high HCRU and high total cost of COPD care. The disconnect between optimal care and real-world utilization may provide an opportunity for managed care decision makers to improve outcomes and reduce cost of care by evaluating utilization trends within their member populations and reevaluating the appropriateness of current strategies.

As guidelines continue to evolve and as evidence for optimal use of pharmacological therapies for COPD grows, managed care organizations should consider how best to align utilization strategies with guidelines-driven data. •

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IMPORTANT SAFETY INFORMATION for STIOLTO RESPIMAT (tiotropium bromide and olodaterol)

WARNINGS AND PRECAUTIONS (*continued*)

If immediate hypersensitivity reactions occur, such as urticaria, angioedema, rash, bronchospasm, anaphylaxis, or itching, discontinue STIOLTO at once and consider alternative treatment. Patients with a history of hypersensitivity reactions to atropine or its derivatives should be closely monitored for similar hypersensitivity reactions to STIOLTO.

If paradoxical bronchospasm occurs, discontinue STIOLTO immediately and institute alternative therapy.

STIOLTO can produce a clinically significant cardiovascular effect in some patients, as measured by increases in pulse rate, systolic or diastolic blood pressure, and/or symptoms. If such effects occur, STIOLTO may need to be discontinued.

Use caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, ketoacidosis, in patients with known or suspected prolongation of the QT interval, and in patients who are unusually responsive to sympathomimetic amines.

Use with caution in patients with narrow-angle glaucoma. Instruct patients to contact a physician immediately if signs or symptoms of acute narrow-angle glaucoma develop.

Use with caution in patients with urinary retention especially in patients with prostatic hyperplasia or bladder-neck obstruction. Instruct patients to consult a physician immediately should any of these signs or symptoms develop.

Patients with moderate to severe renal impairment (creatinine clearance of <60 mL/min) should be monitored closely for anticholinergic side effects.

Be alert to hypokalemia and hyperglycemia.

ADVERSE REACTIONS

The most common adverse reactions with STIOLTO (>3% incidence and higher than an active control) were: nasopharyngitis, 12.4% (11.7%/12.6%), cough, 3.9% (4.4%/3.0%), and back pain, 3.6% (1.8%/3.4%).

DRUG INTERACTIONS

- Use caution if administering adrenergic drugs because sympathetic effects of olodaterol may be potentiated.
- Concomitant treatment with xanthine derivatives, steroids, or diuretics may potentiate any hypokalemic effect of olodaterol.
- Use with caution in patients taking non–potassium-sparing diuretics, as the ECG changes and/or hypokalemia may worsen with concomitant beta-agonists.

IMPORTANT SAFETY INFORMATION for STIOLTO RESPIMAT (tiotropium bromide and olodaterol)

DRUG INTERACTIONS (*continued*)

- The action of adrenergic agents on the cardiovascular system may be potentiated by monoamine oxidase inhibitors or tricyclic antidepressants or other drugs known to prolong the QTc interval. Therefore, STIOLTO should be used with extreme caution in patients being treated with these drugs. Use beta-blockers with caution as they not only block the therapeutic effects of beta-agonists, but may produce severe bronchospasm in patients with COPD.
- Avoid co-administration of STIOLTO with other anticholinergic-containing drugs as this may lead to an increase in anticholinergic adverse effects.

STIOLTO is for oral inhalation only.

The STIOLTO cartridge is only intended for use with the STIOLTO RESPIMAT inhaler.

Inform patients not to spray STIOLTO into the eyes as this may cause blurring of vision and pupil dilation.

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Please see accompanying full Prescribing Information, Patient Information, and Instructions for Use for STIOLTO RESPIMAT.

NOTES