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To cite this article: Gerard Criner & Sean Duffy (2020): Reducing and managing chronic obstructive pulmonary disease exacerbations with tiotropium+olodaterol, Current Medical Research and Opinion, DOI: [10.1080/03007995.2020.1841615](https://doi.org/10.1080/03007995.2020.1841615)

To link to this article: <https://doi.org/10.1080/03007995.2020.1841615>



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Published online: 19 Nov 2020.



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Reducing and managing chronic obstructive pulmonary disease exacerbations with tiotropium + olodaterol

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ABSTRACT

Objective: The aim of this study was to review clinical evidence supporting the use of fixed-dose combination of tiotropium and olodaterol, a long-acting muscarinic antagonist (LAMA) and a long-acting β_2 -agonist (LABA), respectively, as the initial and follow-up treatment choice in patients with chronic obstructive pulmonary disease (COPD) as per Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2020 recommendations—the impact of this treatment strategy on the reduction in the risk of exacerbations—and the importance of early therapeutic interventions.

Methods: For this narrative review, the available literature was searched to identify studies including patients with COPD receiving tiotropium and olodaterol as either monotherapy or combination therapy and studies including patients with COPD receiving inhaled corticosteroids (ICS) in addition to long-acting bronchodilators. Relevant studies were included in the review.

Results: Patients with COPD are often prescribed ICS therapy, which, when used over a long term, can be associated with local and systemic adverse effects. The GOLD 2020 report recommends dual bronchodilator therapy as both an initial and follow-up treatment option. A LABA + LAMA combination is mechanistically synergistic, and cumulative evidence surrounding the efficacy and safety of fixed-dose combination of tiotropium and olodaterol supports therapeutic advantages over monotherapy in most patients with COPD.

Conclusions: The early stages of COPD may represent a “window of therapeutic opportunity” during which initiation of tiotropium and olodaterol dual bronchodilator therapy may improve lung function and quality of life and reduce exacerbations in patients with COPD.

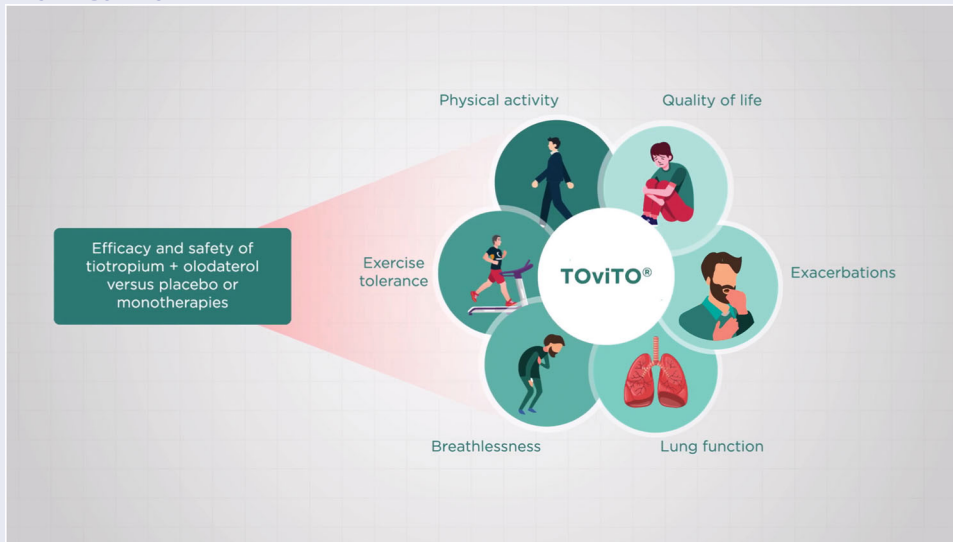
ARTICLE HISTORY

Received 5 December 2019
Revised 13 July 2020
Accepted 8 August 2020



KEYWORDS


Chronic obstructive pulmonary disease; long-acting β_2 -agonist; long-acting muscarinic antagonist; olodaterol; tiotropium

GRAPHICAL ABSTRACT



Impact of T+O therapy on COPD. Please see the online full text version to access Video 1, or the video can be accessed via the supplemental material tab [here](#).

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 Supplemental data for this article is available online at <https://doi.org/10.1080/03007995.2020.1841615>.

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Introduction

Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality, and is expected to rise from the fifth to the third leading cause of death globally by 2030¹. Furthermore, the management of COPD is a considerable health care liability—the total economic burden (direct and indirect costs) associated with COPD is projected to be \$49 billion in the United States by 2020².

Our understanding of COPD and the development of treatment strategies have progressed substantially, and the appreciation of differences in patient and disease characteristics has facilitated individualization of treatment³. Therapeutic options for COPD are varied and include mono-bronchodilation or dual bronchodilation (short- and long-acting β_2 -agonists [SABAs and LABAs, respectively] and long-acting muscarinic antagonists [LAMAs]), inhaled corticosteroids (ICS), phosphodiesterase-4 inhibitors, and antibiotics^{3–8}. Per the Global Initiative for Chronic Obstructive Lung Disease (GOLD), patients are categorized into one of four stages (stage 1 [mild] to stage 4 [very severe]), based on the degree of airway obstruction, and to one of the four groups (group A to group D), based on individualized assessment of symptoms and exacerbation risk³ (Figure 1). According to GOLD 2020 recommendations, initial treatment in patients with COPD should include a bronchodilator (SABA, LABA, or LAMA)³. Thereafter, patient response to treatment initiation should be reviewed and pharmacologic therapy adjusted regardless of the patient's GOLD group at diagnosis³.

COPD exacerbations are defined as episodic worsening of symptoms that require a modification of treatment strategy

or hospitalization, and reduction in the risk of exacerbations is a salient goal of COPD management³. Exacerbations severely impact the natural progression of COPD in many patients, and frequency of exacerbations correlates with a decline in lung function, an increase in mortality, and a reduction in quality of life (QoL)^{9–12}. An analysis of the Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points (ECLIPSE) trial data revealed that increased risk of exacerbations, including those leading to hospitalization, was associated with high St. George's Respiratory Questionnaire (SGRQ) scores (poor health status) in patients with COPD¹³. Additionally, evidence clearly indicates that exacerbations lead to increased health care resource utilization and are major contributors to costs associated with COPD management^{14,15}. Conventionally, exacerbation severity has been classified as mild, moderate, or severe based on the treatment needed to manage or control symptoms³. However, causes of exacerbations vary. In many patients, exacerbations may be inflammatory in nature and associated with high levels of T-helper cells¹⁶. Common treatment interventions, therefore, may not be effective in reducing exacerbations. Thus, identifying and carefully characterizing patients based on the underlying cause of exacerbations is crucial.

Here, we review clinical evidence supporting the use of LAMA + LABA combinations. Specifically, we focus on the fixed-dose combination (FDC) of tiotropium and olodaterol (T + O), a LAMA and a LABA, respectively, as the initial and follow-up treatment choice in patients with COPD as per GOLD 2020 recommendations³. We also review the impact of this treatment strategy on reducing exacerbations.

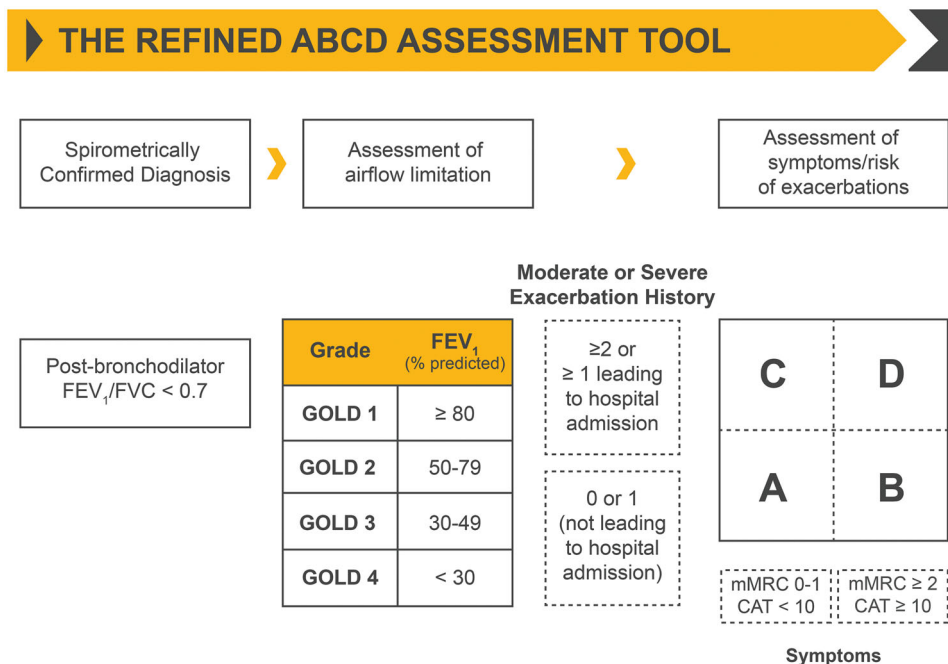


Figure 1. Classification of COPD based on spirometric determination of the severity of airway obstruction and the combination of symptomatic severity and history of exacerbations³. Abbreviations. CAT, COPD Assessment Test; COPD, chronic obstructive pulmonary disease; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; mMRC, modified British Medical Research Council. *Note:* Reused from Global Initiative for Chronic Obstructive Lung Disease 2020 report (Copyright © 2020 Global Initiative for Chronic Obstructive Lung Disease, Inc.).

Methods

A PubMed literature search was conducted from inception until July 31, 2018, using the following search string: (tiotropium AND olodaterol) AND (COPD OR chronic obstructive pulmonary disease). Additional searches were conducted for studies on tiotropium monotherapy and ICS. English-language articles reporting the efficacy and safety of the FDC of T + O in patients with COPD were included. The reference list of the articles was also scanned for relevant articles. Review articles, preclinical studies, congress reports, letters, commentaries, and other articles not meeting the inclusion criteria were excluded.

Tiotropium monotherapy in the treatment of COPD

Tiotropium is a United States Food and Drug Administration–approved LAMA for long-term, once-daily maintenance treatment of bronchospasms associated with COPD and for the reduction of COPD exacerbations^{17,18}. Tiotropium is available as a dry powder formulation, delivered *via* HandiHaler (Spiriva HandiHalerⁱ; 18 µg once daily)¹⁷, and as an aqueous solution, delivered *via* Respimat Soft Mist Inhaler (Spiriva Respimatⁱⁱ; 5 µg once daily)¹⁸. Tiotropium delivered *via* HandiHaler or Respimat improved lung function^{19,20} and QoL^{19–21} and reduced exacerbations^{19–22} compared with placebo or other active comparators in patients with COPD.

The effect of tiotropium on exacerbations was evaluated in a number of studies^{19,21,23–28}. Findings from two separate reviews (a Cochrane review of 22 studies [$N = 23,309$] of tiotropium HandiHaler 18 µg or tiotropium Respimat 5 or 10 µg²⁰ and a pooled analysis of nine studies with tiotropium HandiHaler 18 µg [$N = 6171$])²⁹ showed that tiotropium significantly reduced the risk of exacerbations and exacerbation-associated hospitalizations. For example, tiotropium HandiHaler 18 µg significantly delayed the median time to first exacerbation (16.7 vs 12.5 months vs placebo [14% risk reduction]¹⁹; 187 vs 145 days vs salmeterol [17% risk reduction])²³ and reduced the mean number of exacerbations vs placebo (by 14%)¹⁹, annual rate of exacerbations (by 11% [moderate and severe by 7% and 27%, respectively])²³, and risk of moderate and severe exacerbations vs salmeterol (by 14% and 28%, respectively)²³ in the Understanding Potential Long-Term Impacts on Function with Tiotropium (UPLIFT; $N = 5993$)¹⁹ and 1-year Prevention Of Exacerbations with Tiotropium in COPD (POET-COPD; $N = 7376$)²³ trials. Of note, in UPLIFT, patients in the placebo group received usual treatment for COPD, which included ICS and/or LABA in up to 62% of patients at baseline and up to 74% of patients at any time during follow-up. Further, in several 1-year trials, tiotropium Respimat 5 µg^{21,24} significantly delayed the time to first exacerbation (160 vs 86 days²¹; 169 vs 119 days)²⁴ and reduced the proportion of patients with ≥ 1 exacerbation (37.2% vs 44.1% [25% risk reduction]²¹; 35.3% vs 43.1% [31% risk reduction])²⁴, exacerbation rates (per patient-year: 0.93 vs 1.91²¹; 0.69 vs 0.87)²⁴, and exacerbations requiring

hospitalization (0.12 vs 0.15 [19% risk reduction])²⁴ compared with placebo.

Olodaterol monotherapy in the treatment of COPD

β_2 -agonists have been used for COPD treatment for over 50 years; however, initial formulations had short durations of action³⁰. Over the years, twice-daily (e.g. salmeterol and formoterol) and eventually once-daily (e.g. indacaterol, vilanterol, and olodaterol) β_2 -agonists became available. Olodaterol is a highly selective LABA that provides bronchodilation for more than 24 h^{31,32}. The short- and long-term efficacy (improvements in lung function, QoL, and exercise tolerance) and safety of olodaterol were demonstrated in patients with moderate-to-very severe COPD^{33–35}. In two replicate, placebo-controlled, phase 3 trials, both olodaterol and formoterol monotherapies were significantly superior to placebo in improving lung function, but only olodaterol significantly improved QoL³⁴. In an indirect treatment comparison, the impact of olodaterol on lung function, QoL, and exacerbations was similar to that of indacaterol³⁶. In a study by Maltais et al.³⁷, fewer patients experienced exacerbations with olodaterol 10 µg (2.7%–4.9%) compared with olodaterol 5 µg (6.0%–7.5%) and placebo (6.7%–7.0%).

LAMA + LABA combinations in the treatment of symptomatic COPD

LAMA and LABA monotherapies have been compared in several studies, and, in general, LABAs are more efficacious in improving lung function and health status^{38–40}, whereas LAMAs are more efficacious in reducing the risk of exacerbations^{23,41–43}. Differences in efficacies coupled with nonoverlapping, synergistic mechanisms of action provided a compelling rationale for combination treatment with a LABA and a LAMA⁴⁴. In fact, LAMA + LABA combinations have become the mainstay of COPD treatment, offering beneficial effects on lung function, health status, and exacerbations compared with respective monotherapies or LABA + ICS combinations^{45,46}. In addition, LAMA + LABA improved cardiac function by increasing left-ventricular end-diastolic volume⁴⁷. The GOLD 2020 report provides different recommendations for initial treatment (based on symptom and exacerbation risk) and a follow-up algorithm (based on most treatable trait and current medications), and LAMA + LABA combination therapy is recommended as a part of both algorithms³.

Impact of T + O on lung function, QoL, and physical activity in patients with COPD

Tiotropium was considered a promising LAMA for dual bronchodilator (LAMA + LABA) therapy because of its favorable efficacy. Further, tiotropium may also improve left ventricular function in patients with COPD and chronic heart failure and may have anti-inflammatory effects^{48,49}. Additionally, with a similar duration of action and complementary mechanism of action, olodaterol was considered a viable LABA to pair with tiotropium in an FDC. Results of the ANHELTO and ToViTO

ANHELTO 1 + 2	TONADO 1 + 2	OTEMTO 1 + 2
<ul style="list-style-type: none"> N=2267 12-week study T^a + O^b (18 + 5 µg); T^a (18 µg) + placebo^b T + O significantly improved <ul style="list-style-type: none"> FEV_{1AUC0-3} Trough FEV₁ SGRQ scores <p>^adelivered <i>via</i> HandiHaler ^bdelivered <i>via</i> Respimat</p>	<ul style="list-style-type: none"> N=5162 52-week study T + O FDC (2.5 + 5 µg or 5 + 5 µg); T (2.5 µg or 5 µg); O (5 µg) <i>via</i> Respimat T + O FDC significantly improved <ul style="list-style-type: none"> FEV_{1AUC0-3} Trough FEV₁ SGRQ scores^a <p>^avs monocomponents for 5 + 5 µg only</p>	<ul style="list-style-type: none"> N=1621 12-week study T + O (2.5 + 5 µg or 5 + 5 µg); T (5 µg); placebo <i>via</i> Respimat T + O significantly improved <ul style="list-style-type: none"> FEV_{1AUC0-3} Trough FEV₁^a SGRQ scores^a <p>^avs placebo</p>
ENERGITO	MORACTO 1 + 2	VIVACITO
<ul style="list-style-type: none"> N=229 6-week study Complete crossover study T + O (5 + 5 µg or 2.5 + 5 µg) <i>via</i> Respimat; salmeterol + fluticasone propionate (50 + 250 µg or 50 + 500 µg) <i>via</i> Accuhaler T + O significantly improved <ul style="list-style-type: none"> FEV_{1AUC0-12} FEV_{1AUC0-24} 	<ul style="list-style-type: none"> N=586 6-week study T + O (2.5 + 5 µg or 5 + 5 µg); T (5 µg); O (5 µg); placebo <i>via</i> Respimat T + O significantly improved <ul style="list-style-type: none"> IC Exercise endurance time^a Lung hyperinflation <p>^avs placebo</p>	<ul style="list-style-type: none"> N=219 6-week study T + O FDC (2.5 + 5 µg or 5 + 5 µg); T (2.5 µg or 5 µg); O (5 µg); placebo <i>via</i> Respimat T + O significantly improved FEV_{1AUC0-24}
PHYSACTO	TORRACTO	DYNAGITO
<ul style="list-style-type: none"> N=303 12-week study All patients participated in SMBM program T (5 µg); T + O (5 + 5 µg); T + O (5 + 5 µg) + ExT; placebo <i>via</i> Respimat T + O with or without ExT significantly improved <ul style="list-style-type: none"> EET^a Activity-related dyspnea^a <p>^avs placebo</p>	<ul style="list-style-type: none"> N=404 12-week study T + O (2.5 + 5 µg or 5 + 5 µg); placebo <i>via</i> Respimat T + O (5 + 5 µg) significantly improved endurance time during CWRCE T + O improved endurance time during <ul style="list-style-type: none"> ESWT (n=165; p=.055, 5 + 5 µg; p=.056, 2.5 + 5 µg) 	<ul style="list-style-type: none"> N=7880 52-week study T + O (5 + 5 µg); T (5 µg); <i>via</i> Respimat T + O <ul style="list-style-type: none"> Reduced rates of moderate and severe exacerbations Improved change from baseline in CAT score

Figure 2. Clinical trials assessing the efficacy of T + O in patients with COPD^{51-53,55,59,60,63,76,77}. Abbreviations. CAT, COPD Assessment Test; COPD, chronic obstructive pulmonary disease; CWRCE, constant work-rate cycle ergometry; EET, exercise endurance time; ESWT, endurance shuttle walk test; ExT, exercise training; FDC, fixed-dose combination; FEV₁, forced expiratory volume in 1 second; FEV_{1AUC0-3}, area under the curve for FEV₁ within 3 hours of dosing; FEV_{1AUC0-12}, area under the curve for FEV₁ within 12 hours of dosing; FEV_{1AUC0-24}, area under the curve for FEV₁ within 24 hours of dosing; IC, inspiratory capacity; O, olodaterol; SGRQ, St. George's Respiratory Questionnaire; SMBM, self-management behavior-modification; T, tiotropium.

trials demonstrated the clinical efficacy of this combination in managing COPD symptoms^{50,51} (Figure 2).

Results of two short-term phase 3 ANHELTO trials showed that once-daily tiotropium 18 µg (delivered *via* HandiHaler) and olodaterol 5 µg (delivered *via* Respimat) significantly improved lung function and QoL vs tiotropium 18 µg alone⁵¹. In the two replicate, 52-week, phase 3 Tiotropium + Olodaterol Fixed Dose Combination (FDC) Versus Tiotropium and Olodaterol in COPD (TONADO) trials, the once-daily FDC T + O 2.5 + 5 µg or T + O 5 + 5 µg delivered *via* Respimat led to significant improvements in lung function vs tiotropium (2.5 and 5 µg, and 5 µg, respectively) or olodaterol (5 µg) monotherapy. However, significant improvement

in QoL was observed only with T + O (5 + 5 µg)⁵². In the two replicate, 12-week, phase 3 Tiotropium + Olodaterol Fixed Dose Combination (FDC) in Chronic Obstructive Pulmonary Disease (OTEMTO) trials, FDC T + O (5 + 5 µg and 2.5 + 5 µg) delivered *via* Respimat resulted in improved lung function and QoL vs placebo and tiotropium monotherapy⁵³. Further, pooled analyses of TONADO and OTEMTO data showed that FDC T + O significantly improved QoL and breathlessness vs placebo or either monocomponent⁵⁴. Finally, once-daily FDC T + O (5 + 5 µg and 2.5 + 5 µg) was superior to twice-daily salmeterol + fluticasone (50 + 500 µg and 50 + 250 µg) in improving lung function in patients with moderate-to-severe COPD in the 6-week ENERGITO study⁵⁵.

Regular physical activity is associated with reduction in lung function decline and in the risk of COPD among smokers⁵⁶ and of readmission to hospital with COPD⁵⁷. Therefore, improvement in exercise tolerance is another goal of COPD management³. Improved physical activity is an indicator of better QoL⁵⁸, and FDC T+O Respimat had favorable effects on physical activity in multiple trials. In the 12-week TORRACTO trial, in which exercise endurance was evaluated, FDC T+O 5+5 µg, but not 2.5+5 µg, significantly improved endurance time during constant work-rate cycle ergometry⁵⁹. A strong tendency toward improved walking endurance time was also demonstrated with both doses. FDC T+O (5+5 µg) improved exercise endurance time and reduced physical activity-related dyspnea with or without exercise training in patients with COPD participating in a self-management behavior-modification program in the PHYSACTO trial⁶⁰.

Of note, the benefits of the T+O combination are not at the expense of an increased risk of adverse events. Robust evidence from about 10,000 patients suggests that the T+O combination is a suitable treatment option for patients with COPD, including those with a history of cardiovascular risk factors^{61,62}.

Impact of T+O on exacerbation control in patients with COPD

As described previously, exacerbations are substantial determinants of disease prognosis in COPD. Of interest, studies evaluating the impact of FDC T+O Respimat on exacerbation control have yielded encouraging results (Table 1 and Video 1).

In the TONADO trials, FDC T+O significantly reduced exacerbations in patients with moderate or very severe COPD compared with olodaterol alone⁵². The effect of FDC T+O and tiotropium monotherapy on the annual rate of exacerbations was also evaluated in the large-scale, 52-week, phase 3 DYNAGITO trial⁶³. FDC T+O reduced the rate of moderate and severe exacerbations by 7% compared with tiotropium alone; however, the predefined significance level of 0.01 was not met. Moreover, a post hoc analysis using multiple covariate models similar to those used in the SPARK and FLAME trials showed a 11% reduction in moderate-to-severe

exacerbations. Furthermore, FDC T+O significantly reduced exacerbations treated with corticosteroids and those treated with corticosteroids+antibiotics vs tiotropium monotherapy (Figure 3).

Interestingly, in a prespecified subgroup analysis of Japanese patients in the DYNAGITO trial, FDC T+O reduced moderate-to-severe COPD exacerbations by 29% vs tiotropium monotherapy⁶⁴.

Appropriate use of ICS in COPD

The therapeutic benefits of ICS in asthma prompted the investigation of the efficacy of ICS, such as fluticasone and budesonide, in the management of symptomatic COPD; monotherapy with ICS is indeed associated with modest improvements in COPD. In the Inhaled Steroids in Obstructive Lung Disease in Europe (ISOLDE) trial, fluticasone twice daily produced an increase in the forced expiratory volume in 1 s (FEV₁) levels after bronchodilator use and resulted in fewer exacerbations and a slower decline in health status compared with placebo⁶⁵. In the TOWARDS a Revolution in COPD Health (TORCH) trial, the combination of salmeterol and fluticasone improved lung function and health status and reduced exacerbations⁶⁶.

The use of ICS is associated with adverse events, including a slight increase in risk of pneumonia, reduced bone mineral density, and cataract⁶⁷. Although the GOLD 2020 report recommends considering ICS use in the patient population at risk for exacerbations with elevated eosinophil counts³, LABA+ICS continues to be more widely prescribed^{3,68}. Thus, it is important to ascertain the feasibility and impact of switching patients already on LABA+ICS to LAMA+LABA treatment regimens. In an effort to highlight the efficacy and safety of treatment de-escalation, the CRYSTAL trial showed that a switch from LABA or LAMA monotherapy or LABA+ICS to LAMA+LABA was associated with superior improvements in lung function with comparable safety⁶⁹. Such findings necessitate careful selection and identification of patient populations in whom the use of ICS can be limited to prevent adverse effects, and recommendations on effective ways to wean off ICS in patients with COPD have been proposed⁷⁰. Emerging data, although only suggestive,

Table 1. Summary of clinical trials assessing the impact of FDC T+O on exacerbations in patients with COPD^{52,63,64}.

Trial	Treatment	Comparator	Outcome, RR (95% CI)	p-Value
TONADO				
Probability of moderate-to-severe COPD exacerbations	T+O 5+5 µg	O 5 µg	0.83 (0.71–0.99)	.0332
		T 5 µg	0.92 (0.78–1.09)	NS
	T+O 2.5+5 µg	O 5 µg	0.69 (0.58–0.82)	<.0001
		T 2.5 µg	0.76 (0.64–0.91)	.0021
		T 5 µg	0.76 (0.64–0.91)	.0021
DYNAGITO				
Rate of moderate and severe COPD exacerbations	T+O 5+5 µg	T 5 µg	0.93 (0.85–1.02)	.0498
Rate of moderate-to-severe COPD exacerbations**	T+O 5+5 µg	T 5 µg	0.71 (0.46–1.10)	.0434
Time to first moderate-to-severe COPD exacerbation**	T+O 5+5 µg	T 5 µg	0.81* (0.57–1.17)	NS

Abbreviations. CI, confidence interval; COPD, chronic obstructive pulmonary disease; FDC, fixed-dose combination; HR, hazard ratio; NS, not significant; O, olodaterol; RR, rate ratio; T, tiotropium.

*Value reported as HR (99% CI).

**In a prespecified subgroup analysis of Japanese patients in the DYNAGITO study.

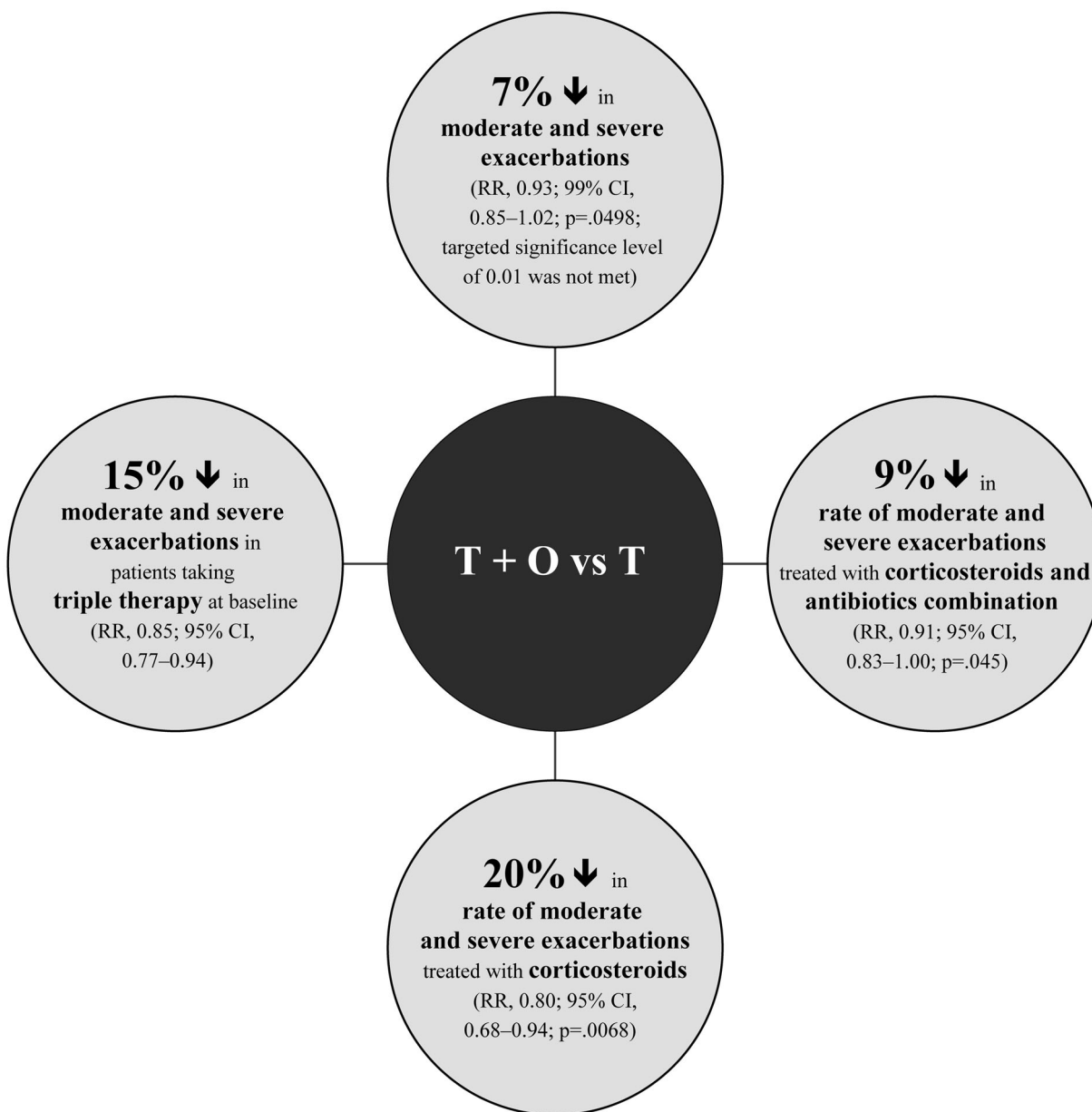


Figure 3. Benefits of FDC T+O treatment in exacerbation management compared with tiotropium monotherapy⁶³. Abbreviations. CI, confidence interval; FDC, fixed-dose combination; O, olodaterol; RR, rate ratio; T, tiotropium.

indicate that patients with COPD in whom the eosinophil count is 300 cells/ μL or higher are more likely to benefit from continued treatment with ICS⁷¹. Hence, the GOLD 2020 report recommends that the use of ICS should be guided by a biomarker assessment³. For example, LABA + ICS could be considered for initial treatment in subpopulations of Group D patients with eosinophil counts ≥ 300 cells/ μL ³. LABA + ICS can also be considered as a follow-up pharmacological option for patients with exacerbations despite LAMA or LABA therapy if eosinophil counts are ≥ 300 cells/ μL or are ≥ 100 cells/ μL with ≥ 2 moderate or ≥ 1 severe (requiring hospitalization) exacerbation in the previous year³. Similarly, use of triple therapy is recommended only as a follow-up pharmacological option if patients who have eosinophil counts ≥ 100 cells/ μL do not respond to LAMA + LABA

therapy or in patients who fail to respond to LABA + ICS³. Importantly, patients can be switched from LABA + ICS to LAMA + LABA when they fail to respond to ICS, the safety associated with ICS use is a concern, or resolution of symptoms requires less therapy³.

Early intervention in COPD

The progressive nature of COPD is well appreciated, and lung function in patients with COPD deteriorates over time⁷². In this regard, underdiagnosed, early-stage COPD is likely to progress to more severe disease and lead to a greater impact on exacerbations and QoL. However, the conventional opinion is that early therapeutic interventions are futile and

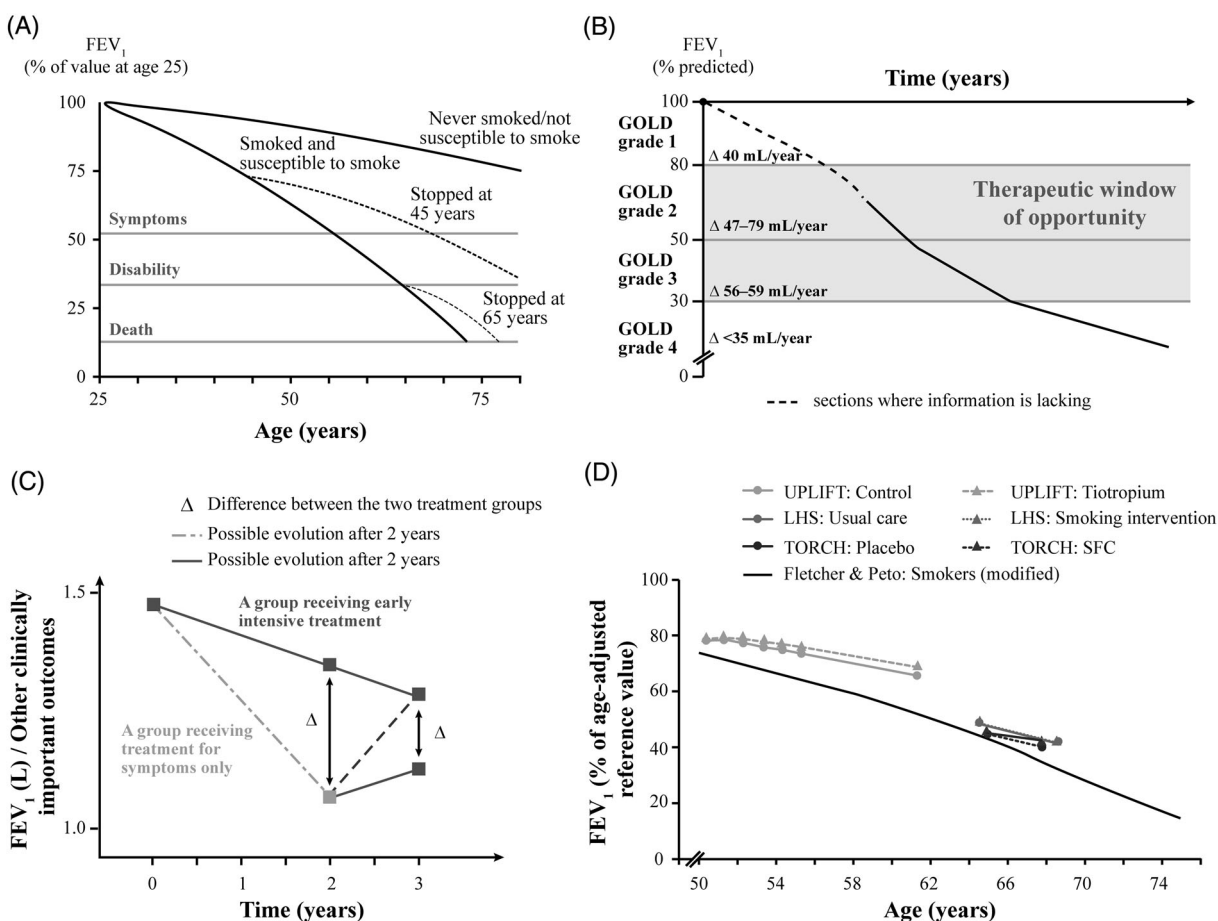


Figure 4. Therapeutic benefits of early intervention in the management of patients with COPD^{72–74}. Abbreviations. COPD, chronic obstructive pulmonary disease; FEV₁, forced expiratory volume in 1 second; GOLD, Global Initiative for Chronic Obstructive Lung Disease; LHS, Lung Health Study; SFC, salmeterol-fluticasone combination; TORCH, Towards a Revolution in COPD Health trial; UPLIFT, Understanding Potential Long-Term Impacts on Function with Tiotropium trial. *Note:* Panel A has been adapted with permission from Fletcher and Peto, *British Medical Journal*, 1977 (Copyright © 2020 BMJ Publishing Group Ltd); panel B has been adapted with permission from Tantucci and Modina, *International Journal of Chronic Obstructive Pulmonary Disease*, 2012 (Copyright © 2012 Tantucci and Modina, publisher and licensee Dove Medical Press Ltd.); panels C and D are adapted with permission from Decramer and Cooper, *Thorax*, 2010 (Copyright © 2010 Decramer and Cooper, publisher and licensee BMJ Publishing Group Ltd & British Thoracic Society).

smoking cessation is the only intervention capable of improving disease progression in early stages of COPD⁷³.

Initial research indicated that the rate of decline in lung function increased with disease progression⁷² (Figure 4(A)). However, findings from other investigations suggested that decline in lung function, as assessed by the decline in FEV₁, is most rapid in the early stages of COPD and slows down in the advanced stages of COPD⁷⁴ (Figure 4(B)). Further, as shown in Figure 4(C), intensive treatment could be more beneficial at an early stage rather than at a later stage in patients receiving symptomatic treatment⁷³. In Figure 4(D), data from published studies (Lung Health Study, TORCH, and UPLIFT) have been compared with the overall clinical course of COPD⁷³. These findings suggest that a “window of therapeutic opportunity” might exist in the early stages of COPD, during which appropriate treatment interventions may be most effective in arresting disease progression and considerably improving prognosis. Of note, subgroup analyses of data from UPLIFT showed that, compared with placebo, tiotropium reduced the rate of decline in mean postbronchodilator FEV₁ in patients with

GOLD stage 2 COPD. Further, both median time to first exacerbation and median time to first exacerbation resulting in hospitalization were longer with tiotropium. Tiotropium also significantly reduced the number of exacerbations in patients in the early stages of COPD⁷⁵. The potential symptomatic and exacerbation benefits associated with FDC T+O suggest that this dual bronchodilator therapy might be a promising intervention to prevent disease progression in the early stages of COPD. The enhanced efficacy of the combination and comparable safety with monotherapies provide physicians a steroid-free treatment option which is suitable for early initiation.

Conclusions

COPD is the most common chronic lung disease worldwide and results in considerable morbidity, mortality, and health care burden. COPD exacerbations are critical drivers of disease prognosis in COPD—they diminish QoL and increase mortality and exacerbation management is associated with considerable costs. Much progress has been made in our

understanding of the etiology of COPD, which has resulted in the development of a number of pharmacological strategies for the management of COPD throughout its natural history—from early to advanced stages of the disease. Although bronchodilators are the recommended initial treatment for COPD, evidence indicates that patients with COPD are often prescribed ICS therapy, which, when used over a long term, is associated with local and systemic adverse effects. A LABA + LAMA combination is mechanistically synergistic, and cumulative evidence supports the therapeutic advantage of such a combination over individual monotherapies in most patients with COPD. The dual bronchodilator combination of T+O improves lung function and QoL in patients with COPD and may reduce exacerbations. The early stages of COPD may represent a “window of therapeutic opportunity” during which initiation of T+O may reduce the rate of lung function decline and improve QoL and disease control.

Notes

- i. Boehringer Ingelheim Pharmaceuticals, Inc; Ridgefield, CT, USA.
- ii. Boehringer Ingelheim Pharmaceuticals, Inc; Ridgefield, CT, USA.

Transparency

Declaration of funding

This work was supported by Boehringer Ingelheim Pharmaceuticals, Inc.

Declaration of financial/other relationships

GC has received grants from NIH-NHLBI, PA DOH, GSK, Boehringer Ingelheim, Novartis, AstraZeneca, Respironics, MedImmune, Actelion, Forest, Pharmaxis, Pulmonx, Aeris, PneumRx, Pearl, Spiration, Broncus, and Genentech; has pending grants from NIH-NHLBI, GSK, AstraZeneca, Boehringer Ingelheim, Nuvaair, Genentech, Patara, and Galapagos; provides consultation for MedImmune, Bayer, GSK, Amgen, Chiesi, Respironics, Nuvaair, CSA, Boehringer Ingelheim, AstraZeneca, Novartis, Verona, Free Flow Medical, EOLO, Celerion, PneumRx, Olympus, Broncus, Patara, and Prometics; and has equity interest in HGE Health Care Solutions. SD has nothing to disclose. Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Author contributions

Both authors, GC and SD, contributed equally towards development of this manuscript. Both authors agree to be accountable for all aspects of the work.

Acknowledgements

The authors meet the criteria for authorship as recommended by the International Committee of Medical Journal Editors (ICMJE). The authors received no direct compensation related to the development of the manuscript. Writing, editorial support, and formatting assistance was provided by Kushal Banerjee, PhD, Saurabh Gagangras, PhD, Suchita Nath-Sain, PhD, and Maribeth Bogush, PhD, of Cactus Life Sciences (part of Cactus Communications), which was contracted and compensated by Boehringer Ingelheim Pharmaceuticals, Inc. (BIPI). BIPI was given the

opportunity to review the manuscript for medical and scientific accuracy as well as intellectual property considerations.

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