

# When is dual bronchodilation indicated in COPD?

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**Abstract:** Inhaled bronchodilator medications are central to the management of COPD and are frequently given on a regular basis to prevent or reduce symptoms. While short-acting bronchodilators are a treatment option for people with relatively few COPD symptoms and at low risk of exacerbations, for the majority of patients with significant breathlessness at the time of diagnosis, long-acting bronchodilators may be required. Dual bronchodilation with a long-acting  $\beta_2$ -agonist and long-acting muscarinic antagonist may be more effective treatment for some of these patients, with the aim of improving symptoms. This combination may also reduce the rate of exacerbations compared with a bronchodilator-inhaled corticosteroid combination in those with a history of exacerbations. However, there is currently a lack of guidance on clinical indicators suggesting which patients should step up from mono- to dual bronchodilation. In this article, we discuss a number of clinical indicators that could prompt a patient and physician to consider treatment escalation, while being mindful of the need to avoid unnecessary polypharmacy. These indicators include insufficient symptomatic response, a sustained increased requirement for rescue medication, suboptimal 24-hour symptom control, deteriorating symptoms, the occurrence of exacerbations, COPD-related hospitalization, and reductions in lung function. Future research is required to provide a better understanding of the optimal timing and benefits of treatment escalation and to identify the appropriate tools to inform this decision.

**Keywords:** COPD, dual bronchodilation, monobronchodilation, ICS, triple therapy

## Introduction

Bronchodilators are a cornerstone of COPD treatment, commonly provided on a regular basis to reduce or prevent symptoms.<sup>1</sup> While short-acting bronchodilators are an option for patients with occasional dyspnea at low risk of exacerbations, their use as regular treatment is not recommended.<sup>1</sup> The majority of patients have breathlessness leading to exercise limitation at the time of diagnosis, and may require more intensive treatment than short-acting bronchodilators alone. For these patients, whether or not they are also at higher risk of exacerbations, long-acting bronchodilators (as monotherapy or in combination) are recommended as a preferred treatment choice in current guidelines and treatment-strategy reports.<sup>1,2</sup> In some patients, particularly those at risk of exacerbation or with severe symptoms, dual bronchodilation can also be considered as initial therapy.<sup>1</sup>

Long-acting bronchodilator monotherapy has benefits across a range of parameters (airflow limitation,<sup>3-8</sup> dyspnea,<sup>3,4,8</sup> physical activity/exercise capacity,<sup>9-12</sup> health status,<sup>3,4,6-8</sup> and preventing exacerbations),<sup>4,8,13,14</sup> however, many patients remain symptomatic despite treatment.<sup>15</sup> When symptoms are uncontrolled or exacerbations occur, treatment should be adjusted with the aim of providing better symptom relief and reducing exacerbation risk. Identifying the need for treatment modification can be challenging, as patients with COPD often reduce physical activity levels in order to reduce symptom intensity, which complicates eliciting symptom burden.<sup>16</sup>

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Dual bronchodilation improves lung function compared with a single bronchodilator; however, when comparing active treatments for other outcomes (eg, Transition Dyspnea Index, St George's Respiratory Questionnaire) in clinical trials, the magnitude of effect is often not marked. For such outcomes, responder analyses (the proportion of patients achieving a specified treatment benefit) can indicate the likelihood of clinically important changes for an individual.<sup>17–26</sup> Currently, there are no clear recommendations on which clinical indicators would prompt a patient and physician to consider stepping up treatment from mono- to dual bronchodilation or whether some patients should be started on dual therapy earlier in an attempt to maintain exercise capacity. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) has issued some general criteria of escalating or de-escalating treatment, based on persistent symptoms and further exacerbations.<sup>1</sup> In this paper, we discuss what might trigger physicians to consider stepping up from mono- to dual therapy with long-acting bronchodilators and what further data are required to help physicians decide if step-up therapy is appropriate for their patient.

Relevant medical literature on long-acting bronchodilator monotherapy, dual bronchodilation, and/or inhaled corticosteroids (ICSs) plus long-acting  $\beta_2$ -agonists (LABAs) was identified by searching the PubMed (Medline) database for articles published in English since 2005. Search terms were “chronic obstructive pulmonary disease” OR “COPD” AND “long-acting  $\beta_2$ -agonist”, “long-acting muscarinic antagonist” OR “anti-cholinergic”, “LABA/LAMA” OR “dual bronchodilation”, “tiotropium”, “salmeterol”, “salmeterol/fluticasone propionate”, “IND/GLY”, “indacaterol”, “glycopyrronium”, “olodaterol”, “umeclidinium”, “vilanterol”, “UMEC/VI”, “formoterol”, “aclidinium”, and “arformoterol”. Results were filtered manually to identify studies of long-acting bronchodilation monotherapy reporting effects on lung function and/or patient reported outcomes in comparison with placebo and dual bronchodilation or ICS/LABA combinations in patients with COPD (Table 1). The authors have additionally selected papers that are relevant to clinical practice at the time of publication, and provide their opinions on the evolving therapy area of COPD management.

## What is the rationale for switching from mono- to dual bronchodilation?

LABAs and long-acting muscarinic antagonists (LAMAs) act via different mechanisms; when used together in patients with COPD, they exert additional bronchodilating effects.<sup>27,28</sup>

Muscarinic receptors are expressed in the human lung, and are also localized in the smooth muscle of all airways, with a higher density of receptors in the larger airways.  $\beta_2$ -adrenoceptors are abundantly expressed on human airway smooth muscle. The density of the receptors is the same throughout the different airway levels, which is particularly important in COPD, as the small airways are affected. Bronchodilation can thus be achieved through stimulation of the  $\beta_2$ -adrenoceptors with BAs or by inhibiting the action of acetylcholine at muscarinic receptors with MAs, indirectly leading to smooth-muscle relaxation.<sup>29</sup> Multiple studies have assessed whether LABA/LAMA dual bronchodilation results in additional improvements in lung function, exacerbation rates, achievement of minimal clinically important differences in Transition Dyspnea Index and St George's Respiratory Questionnaire scores (Table 1), and other outcome measures when compared with monobronchodilation. In patients with moderate COPD who remained symptomatic despite LAMA monotherapy, the step-up to dual bronchodilation significantly improved lung function compared with continuation of previous treatment.<sup>30</sup> Another study by Donohue et al measured the efficacy of dual bronchodilation (umeclidinium/vilanterol 62.5/25  $\mu\text{g}$ ; GlaxoSmithKline, Brentford, Middlesex, UK) in patients identified as responsive or unresponsive to monobronchodilation (umeclidinium 62.5  $\mu\text{g}$ , vilanterol 25  $\mu\text{g}$ ).<sup>31</sup> Umeclidinium/vilanterol significantly increased lung function versus umeclidinium in umeclidinium responders and versus vilanterol in vilanterol responders. Notably in umeclidinium and vilanterol nonresponders, lung function was still significantly increased, but by a smaller amount.<sup>31</sup> The study did not assess the impact of mono- versus dual bronchodilation on exacerbations.<sup>32,33</sup> The CRYSTAL study examined directly switching from various treatments to glycopyrronium (GLY; Novartis, Basel, Switzerland) (50  $\mu\text{g}$ ) or indacaterol (IND)/GLY (110/50  $\mu\text{g}$ ; Novartis) in terms of lung function and symptoms in symptomatic patients with moderate COPD. IND/GLY significantly improved lung function and dyspnea after direct switch from LAMA, LABA, or ICS/LABA.<sup>34</sup>

Activity limitation is an important feature of COPD, with dyspnea, deteriorating physical conditioning, and avoidance of activity contributing to a vicious circle of decline.<sup>16</sup> Physical inactivity is associated with adverse clinical outcomes, including hospitalizations and mortality. Increasing activity is thus crucial for effective management strategies that could improve long-term outcomes in COPD.<sup>35</sup> Improving physical activity and exercise capacity are closely related clinical outcomes in COPD; however, it is important to make a

Table 1 Studies comparing the efficacy of dual bronchodilation with monobronchodilation

Study	Design and patients	Treatment	Lung-function response	Prevention of COPD exacerbations	MCID in TDI and SGRQ
Aaron et al <sup>12</sup>	1-year, randomized, double-blind, PBO-controlled trial; 449 patients with moderate or severe COPD	TIO 18 µg OD + PBO BID, TIO 18 µg OD + SAL 25 µg BID, or TIO 18 µg OD + SFC 250/25 µg BID	Lung function was not significantly better in the TIO + SAL group than in the TIO + PBO group	The proportion of patients who experienced an exacerbation did not differ between the TIO + SAL group (64.8%) and the TIO + PBO group (62.8%)	NR
Chapman et al <sup>17</sup>	26-week, randomized, double-blind, PBO- and active-controlled trial; 2,144 patients with moderate-severe COPD	IND/GLY 110/50 µg OD, IND 150 µg OD, GLY 50 µg OD, or open-label TIO 18 µg OD, or PBO OD	Trough FEV <sub>1</sub> at week 26 significantly improved ( $P < 0.001$ ) with IND/GLY vs IND and GLY (LSM differences 0.07 and 0.09 L, respectively), TIO and PBO (LSM differences 0.08 and 0.20 L, respectively)	Prevalence of exacerbations was 28.9% in the IND/GLY group, 32.1% with IND, 31.7% with GLY, 28.8% with TIO, and 39.2% with PBO (statistical comparisons NR)	A significantly greater proportion of patients achieved the MCID for TDI total score ( $\geq 1$ -point improvement) with IND/GLY vs TIO (68.1% vs 59.2%, $P = 0.016$ ) A significantly higher proportion of patients achieved the MCID for SGRQ total score ( $\geq 4$ -point reduction) with IND/GLY vs TIO (63.7% vs 56.4%, $P = 0.047$ )
Beeh et al <sup>20</sup>	Multicenter, randomized, double-blind, double-dummy, PBO-controlled, three-period, crossover study; 126 patients with moderate-severe COPD	IND/GLY 110/50 µg, PBO or TIO 18 µg OD	At day 21, mean treatment differences in trough IC, FEV <sub>1</sub> , and FVC were significantly higher for IND/GLY vs PBO (0.19, 0.2 and 0.28 L, respectively) and vs TIO (0.15, 0.1 and 0.11 L, respectively)	"COPD worsening" occurred in 9.1% of patients in the IND/GLY group, 3.9% of the PBO group, and 6% of the TIO group (statistical comparisons NR)	NR
Beier et al <sup>23</sup>	Incomplete-block, three-period, randomized, crossover design; 47 patients with a clinical history of COPD	Three of the following five treatments: GSK233705 (LAMA) 20 µg + SAL 50 µg BID, GSK233705 50 µg + SAL 50 µg BID; SAL 50 µg or PBO, each BID, and TIO 18 µg or PBO OD for 7 days	Compared with PBO, the adjusted mean change from baseline in trough FEV <sub>1</sub> on day 8 was 215 mL higher with GSK233705 20 µg + SAL and 203 mL higher with GSK233705 50 µg + SAL, whereas with SAL and TIO the changes were 101 and 118 mL higher, respectively	NR	NR
Buhl et al <sup>21</sup>	Two multinational, replicate, Phase III, multicenter, randomized, double-blind, active-controlled, five-arm, parallel-group studies (study 1,237.5 and study 1,237.6); 5,163 moderate-very severe COPD patients	TIO/OLO 5/5 µg FDC OD, TIO/OLO 2.5/5 µg FDC OD, OLO 5 µg OD, TIO 5 µg OD, TIO 2.5 µg OD	FEV <sub>1</sub> AUC <sub>0-3h</sub> responses for TIO/OLO FDC 2.5/5 µg, 5/5 µg, TIO 2.5 µg, 5 µg and OLO 5 µg were 241, 256, 148, 139, and 133 mL, respectively, in study 1,237.5, and 256, 268, 125, 165 and 136 mL, respectively, in study 1,237.6	There was a trend toward improvement in moderate/severe exacerbations with both fixed-dose combinations versus the monotherapy components (probability risk-ratio point estimates 0.69–0.92, $P < 0.05$ for all except TIO/OLO 5/5 µg vs TIO 5 µg)	NR

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Table 1 (Continued)

Study	Design and patients	Treatment	Lung-function response	Prevention of COPD exacerbations	MCID in TDI and SGRQ
Celli et al <sup>94</sup>	24-week, double-blind, randomized, PBO-controlled, parallel-group study; 1,493 patients with COPD	UMEC/VI 125/25 µg OD, UMEC 125 µg OD, VI 25 µg OD, or PBO OD	All active treatments significantly improved trough FEV <sub>1</sub> vs PBO (0.124–0.238 L, all P<0.001). Improvements with UMEC/VI were significantly greater than for UMEC or VI (0.079 L and 0.114 L, both P≤0.001)	On-treatment exacerbations were reported more frequently in the PBO group (14%) compared with the three treatment groups (6%–8%, hazard ratios [95% CI] vs PBO: UMEC/VI 0.4 [0.2–0.6]; UMEC, 0.5 [0.3–0.8]; 0.5 [0.3–0.8]; all P≤0.006 vs PBO; statistical comparisons between active-comparator groups NR)	NR
Hanania et al <sup>95</sup>	6-week, randomized, double-blind, PBO-controlled, parallel-group study; 155 patients with COPD	TIO 18 µg OD + FOR <sup>b</sup> 20 µg BID or PBO BID	FEV <sub>1</sub> , AUC <sub>0–3 h</sub> at week 6 was significantly greater with FOR vs PBO (1.57 vs 1.38 L, P<0.0001)	Exacerbations occurred in 2.6% of patients receiving FOR and 7.8% of patients receiving PBO (statistical comparisons NR)	NR
Hoshino and Ohtawa <sup>96</sup>	Randomized, open-label, three-way clinical trial; 62 patients with moderate or severe COPD	TIO 18 µg OD, IND 150 µg OD, or TIO/OLO OD	Differences for FEV <sub>1</sub> and FVC between the improvements with TIO + IND and those with TIO alone and those with IND alone were significant (P<0.05)	NR	NR
Imran et al <sup>97</sup>	Randomized, double-blind, PBO-controlled, active drug-controlled parallel-design study; 42 moderate COPD patients without any other comorbidity	TIO (morning) and FOR <sup>b</sup> -matched PBO (evening), TIO/FOR (morning) and FOR-matched PBO (evening), and TIO/FOR (morning) and FOR (evening)	No lung-function advantage of adding FOR OD or BID to TIO	NR	NR
Jayaram et al <sup>98</sup>	Double-blind, randomized, crossover study; 38 patients with moderate-severe COPD	Patients on TIO were randomized to receive either FOR <sup>c</sup> or PBO for 6 weeks; following a 2-week washout period, participants crossed over to the alternate arm of therapy for a further 6 weeks	FEV <sub>1</sub> increased in both groups (160 mL combination therapy vs 30 mL TIO), with a mean difference of 110 mL (95% CI –100–320; P=0.07) between groups	NR	No significant differences between groups were shown for lung function, symptom scores, or quality of life
Mahler et al <sup>99</sup>	Two identically designed, randomized, double-blind, 12-week studies; 2,276 patients with moderate-severe COPD	IND 150 mg OD or matching PBO; all patients concurrently received open-label TIO 18 mg OD	Superiority of IND + TIO vs TIO + PBO demonstrated for FEV <sub>1</sub> , AUC <sub>5–480 min</sub> at week 12, with differences of 130 mL (95% CI 100–150) and 120 mL (95% CI 90–140) in studies 1 and 2, respectively (both P<0.001)	NR	NR
Maleki-Yazdi et al <sup>100</sup>	24-week, Phase III, multicenter, randomized, blinded, double-dummy, parallel-group study; 1,191 moderate-severe COPD patients	UMEC/VI 62.5/25 µg OD or TIO 18 µg OD	An improvement of 0.112 L (95% CI 0.081–0.144) in trough FEV <sub>1</sub> at day 169 was observed for UMEC/VI 62.5/25 µg vs TIO 18 µg	On-treatment exacerbations occurred in 4% of patients treated with UMEC/VI and 6% of those treated with TIO (hazard ratio [95% CI] 0.5 [0.3–1], P=0.044)	NR

Salvi et al <sup>99</sup>	Randomized, double-blind, multicenter, crossover study; 44 COPD patients	Single dose of 18 µg of TIO vs a single dose of a combination of TIO/FOR 18/12 µg	Combination of TIO/FOR showed faster onset of bronchodilator response ( $P < 0.01$ for $FEV_1$ and FVC), a greater mean maximum change in $FEV_1$ ( $P = 0.01$ ) and FVC ( $P = 0.008$ ), and greater $AUC_{0-24h}$ values for $FEV_1$ . At week 24, ACL/FOR led to significant improvements from baseline in 1-hour postdose $FEV_1$ vs ACL ( $P < 0.001$ for both doses) and trough $FEV_1$ vs FOR ( $P < 0.01$ for both doses); coprimary end points	NR	NR	There was a nonsignificant trend toward an increase in the proportion of patients achieving the MCID in TDI with ACL/FOR 400/12 µg and 400/6 µg versus the monocomponents Corresponding proportions for SGRQ were NR, but all active treatments were associated with improvements in mean SGRQ total score $> 4$ units (MCID $\geq 4$ units)
Singh et al <sup>23</sup>	24-week, double-blind, randomized, parallel-group, active- and PBO-controlled, multicenter study; 1,729 patients with COPD	ACL/FOR 400/12 µg BID, 400/6 µg BID, ACL 400 µg BID, FOR: 12 µg BID or PBO BID		ACL/FOR 400/12 µg and 400/6 µg reduced the HCRU rate of exacerbations of any severity by 11% and 2%, respectively, compared with ACL (not significant), and by 36% and 30%, respectively, compared with FOR (borderline significance for 400/12 µg, not significant for 400/6 µg) ACL/FOR 400/12 µg and 400/6 µg reduced the EXACT rate of exacerbations of any severity by 22% and 9%, respectively, compared with ACL (borderline significance for 400/12 µg, not significant for 400/6 µg); this rate changed by -14% and +1%, respectively, compared with FOR (not significant)	NR	
Tashkin et al <sup>100</sup>	6-week, randomized, double-blind, PBO-controlled, parallel-group study; 130 current or former smokers with COPD	FOR <sup>b</sup> 20 µg BID + TIO 18 µg OD or PBO + TIO 18 µg OD	$FEV_1$ , $AUC_{0-3h}$ at week 6 was significantly greater with FOR + TIO vs PBO + TIO (1.52 L vs 1.34 L, $P < 0.0001$ )	Fewer patients treated with FOR + TIO experienced exacerbations vs those treated with PBO + TIO (4.5% vs 7.9%, statistical comparisons NR)	NR	
Tashkin et al <sup>101</sup>	12-week, active-controlled, randomized, double-blind, multicenter trial; 255 patients with COPD	FOR <sup>d</sup> 12 µg BID + TIO 18 µg OD or TIO 18 µg OD	Greater improvements in $FEV_1$ , $AUC_{0-4h}$ were seen with FOR + TIO vs TIO at all time points ( $P < 0.01$ )	Exacerbations occurred in 17% of patients in the FOR + TIO group and 11% of the TIO group ( $P = 0.149$ )	NR	
Tashkin et al <sup>102</sup>	2-week, randomized, modified-blind, parallel-group study; 235 patients with COPD	ARF 15 µg BID, TIO 18 µg BID, or combined therapy (sequential dosing of ARF 15 µg BID and TIO 18 µg OD)	Mean $FEV_1$ , $AUC_{0-24h}$ improved similarly from baseline for ARF (0.1 L) and TIO (0.08 L) treatment groups and greater for the combined therapy group (0.22 L, all $P < 0.005$ )	Exacerbations occurred in 3.9% of patients in the ARF group; no exacerbations were reported in the TIO or ARF + TIO groups (statistical comparisons NR)	NR	A greater proportion of patients in the combined-therapy group had $\geq 1$ -unit improvement in TDI (77.9% vs ARF (66.7%) or TIO (57.1%) monotherapies; this difference was statistically significant for combined therapy vs TIO (95% CI 0.06-0.35) SGRQ NR

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Table 1 (Continued)

Study	Design and patients	Treatment	Lung-function response	Prevention of COPD exacerbations	MCID in TDI and SGRQ
Terzano et al <sup>103</sup>	Randomized, blind, crossover study; 80 patients with COPD	Five different bronchodilator 30-day treatments in random order; treatments were: TIO 18 µg OD (8 am), TIO 18 µg (8 am) + FOR <sup>a</sup> 12 µg (8 pm), FOR 12 µg BID (8 am and 8 pm), TIO 18 µg BID (8 am and 8 pm), TIO 18 µg (8 am) + FOR 12 µg BID (8 am and 8 pm), FOR 12 µg BID (8 am and 8 pm) + TIO 18 µg OD (8 pm)	TIO 18 µg (8 am) + FOR 12 µg BID (8 am and 8 pm) was associated with larger daily changes in FEV <sub>1</sub> at day 30 compared with the monotherapy treatments	NR	NR
van Noord et al <sup>104</sup>	Randomized, open-label, PBO-controlled, three-way crossover study; 95 patients with COPD	TIO 18 µg OD, TIO 18 µg OD + FOR 12 µg OD, TIO 18 µg OD + FOR <sup>a</sup> 12 µg BID	Average FEV <sub>1</sub> AUC <sub>0-24 h</sub> improved by 0.08 L with TIO, by 0.16 L with TIO + FOR OD, and by 0.2 L with TIO + FOR BID (all P<0.01)	NR	NR
van Noord et al <sup>105</sup>	Randomized, double-blind, three-way, crossover study; 71 patients with COPD	TIO 18 µg OD, FOR 12 µg BID, or both combined OD for three 6-week periods	Combination therapy provided greater improvement in FEV <sub>1</sub> than monotherapies (P<0.05)	Exacerbations occurred in 14.1% of patients in the FOR + TIO group, 20.3% in the FOR group and 5.7% in the TIO group (statistical comparisons NR)	NR
van Noord et al <sup>106</sup>	6-week, randomized, double-blind, four-way crossover study of 6-week treatment periods; 95 patients with COPD	TIO 18 µg OD + SAL 50 µg (OD or BID) vs respective monotherapies	TIO + SAL provided greater improvements vs respective monotherapies in FEV <sub>1</sub> AUC <sub>0-24 h</sub> (P<0.0001)	Exacerbations occurred in 5.4% of patients in the TIO + SAL OD group, 7.6% of the TIO + SAL BID group, 16.1% of the SAL BID group and 10.8% of the TIO group (statistical comparisons NR)	NR
Vincken et al <sup>107</sup>	12-week, randomized, double-blind, parallel-group study; 449 patients with moderate-severe COPD	IND 150 µg OD + GLY 50 µg OD, or IND 150 µg OD + PBO	IND + GLY significantly improved trough FEV <sub>1</sub> versus IND + PBO, with treatment differences of 74 mL on day 1 and 64 mL at week 12 (both P<0.001)	"COPD worsening" <sup>**</sup> : occurred in 0.4% of patients receiving GLY and 0.9% of patients receiving PBO (statistical comparisons NR)	Patients receiving GLY were significantly more likely to achieve an MCID (≥1-unit improvement) in dyspnea than those receiving PBO (76.6% vs 62.2%, odds ratio [95% CI] 1.97 [1.24–3.11]; P=0.004) A higher percentage of patients receiving GLY achieved an MCID in SGRQ score (≥4-point reduction) vs patients receiving PBO, but the difference was not statistically significant (56.5% vs 46.8%, OR [95% CI] 1.43 [0.95–2.17], P=0.089)

Vogelmeier et al <sup>108</sup>	6-month, partially blinded, randomized study; 847 patients with COPD	FOR: 10 µg BID + TIO 18 µg OD, FOR 10 µg BID, TIO 18 µg OD, or PBO	At 24 weeks, FEV <sub>1</sub> 2 hours postdose was not significantly different with combination therapy vs monotherapy; all three treatments were superior to PBO ( $P<0.001$ )	Exacerbations requiring additional therapy were observed in 6.3% of the FOR + TIO group, 8.1% of the FOR group, 10.4% of the TIO group, and 14.4% of those receiving PBO Corresponding proportions for exacerbations requiring hospitalization were 1.4%, 0.5%, 2.3%, and 1.4%, respectively (statistical comparisons between active-comparator groups NR)	NR
Wedzicha et al <sup>45</sup>	64-week, randomized, double-blind, parallel-group study; 2,224 patients with COPD	IND/GLY 110/50 µg OD, GLY 50 µg OD, or TIO 18 µg OD	Trough FEV <sub>1</sub> was significantly higher with IND/GLY at all assessments compared with GLY (differences 70–80 mL, $P<0.0001$ ) and TIO (differences 60–80 mL, $P<0.0001$ )	IND/GLY significantly reduced the rate of total exacerbations by 15% (rate ratio [95% CI] 0.85 [0.77–0.94], $P=0.0012$ ) vs GLY and by 14% vs TIO (0.86 [0.78–0.94], $P=0.0017$ )	NR
ZuWallack et al <sup>109</sup>	Two replicate, double-blind, randomized, 12-week studies; 1,134 patients with moderate–severe COPD	OLO 5 µg OD + TIO 18 µg OD vs TIO 18 µg OD + PBO	OLO + TIO was associated with improvements vs TIO + PBO in FEV <sub>1</sub> AUC <sub>0–3 h</sub> ( $P<0.001$ in both studies)	The incidence of exacerbations was similar between treatment arms	NR

**Notes:** \*COPD exacerbations were combined with adverse-event data and reported using the term “COPD worsening”; an MCID  $\geq$  l-unit improvement in TDI was only validated for comparisons against placebo. Manufacturers details: ACL, AstraZeneca, Luton, UK; ACL/FOR, Almirall SA; FOR, <sup>a</sup>Novartis; Basel, Switzerland, <sup>b</sup>Dey LP, Napa, USA, <sup>c</sup>Almirall SA; Barcelona, Spain, <sup>d</sup>Schering Corporation; Kenilworth, USA; GLY, IND and IND/GLY, Novartis, Basel, Switzerland; SFC, SAL and GSK233705, GlaxoSmithKline; Middlesex, UK; TIO/FOR, Cipla Ltd; Mumbai, India; Barcelona, Spain; TIO/OLO, Boehringer Ingelheim International GmbH, Ingelheim am Rhein, Germany; UMEC/VI, GlaxoSmithKline, Brentford, Middlesex, UK.

**Abbreviations:** ACL, acclidinium; AUC, area under the curve; BID, bis in die (twice daily); EXACT, Exacerbations of Chronic Pulmonary Disease Tool; FDC, fixed-dose combination; FEV<sub>1</sub>, forced expiratory volume in 1 second; FOR, formoterol; FVC, forced vital capacity; GLY, glycopyrronium; HCRU, health-care resource utilization; IC, inspiratory capacity; IND, indacaterol; LAMA, long-acting muscarinic antagonists; LSM, least squares mean; MCID, minimal clinically important difference; NR, not reported; OD, once daily; OLO, olodaterol; PBO, placebo; SAL, salmeterol; SFC, salmeterol fluticasone propionate; SGRQ, St George's Respiratory Questionnaire; TDI, Transition Dyspnea Index; TIO, tiotropium; UMEC, umeclidinium; VI, vilanterol; 95% CI, 95% confidence intervals.

distinction between the two. Physical activity reflects what someone actually does that results in energy expenditure, whereas exercise capacity indicates what a person is physically capable of doing.<sup>36</sup> Clinical trials are yet to find a clear association between physical activity and exercise capacity. This may be because physical activity is hard to assess, as it is measured by direct observation, such as questionnaires or patient diaries, which can be subjective and a time-consuming method to assess in large populations.<sup>35</sup> This may explain why studies focus more on exercise capacity in clinical trials and a clear association is yet to be found.

Monobronchodilators have been shown to improve exercise tolerance in COPD patients,<sup>9,12</sup> and while some early exercise studies of dual bronchodilators demonstrated benefit versus placebo, benefit versus monobronchodilators was not seen,<sup>37,38</sup> perhaps due to the absence of a training or rehabilitation component within the older study designs.

The more recent PHYSACTO study was designed to evaluate the effects of bronchodilation alone or in combination with 8 weeks of additional exercise training on exercise capacity, and level of physical activity in patients with moderate–severe COPD. All patients were enrolled in a 12-week self-management behavior-modification program, focused on improving patient engagement in, and maintenance of, physical activity.<sup>39</sup> PHYSACTO found that tiotropium (TIO)/olodaterol (Boehringer Ingelheim International GmbH, Ingelheim am Rhein, Germany), either alone or in combination with exercise training, did not significantly improve physical activity compared with placebo, although a significant reduction in symptom burden was observed. It is interesting to note that self-managed behavior modification alone significantly improved physical activity compared with baseline; this may have made any detectable differences in treatment benefit difficult. Furthermore, there was no correlation between exercise tolerance and change in physical activity.<sup>36</sup>

Recently, the dual bronchodilator IND/GLY was shown to reduce hyperinflation and improve daily physical activity levels compared with placebo, despite no patient education or lifestyle advice, suggesting a potential role in major clinical concerns in COPD.<sup>40</sup> Therefore, a picture of the potential benefit of dual bronchodilation on activity is emerging; however, as lung-function decline in COPD is progressive, it is unknown whether earlier intervention with these treatments may be more beneficial in preserving physical ability. The impact of delaying step-up therapies on clinical parameters, such as activity levels, has yet to be established.

In symptomatic patients, the recently updated GOLD strategy document recommends that patients at lower risk of

exacerbations (GOLD group B) should be treated with a long-acting bronchodilator, escalating to dual bronchodilation if symptoms persist.<sup>1</sup> The LABA/LAMA IND/GLY has been shown to reduce dyspnea significantly compared with placebo and TIO monotherapy in dyspneic patients (modified Medical Research Council (mMRC) dyspnea scale score >2).<sup>41</sup> This finding is supported by another post hoc analysis indicating that IND/GLY significantly reduced dyspnea compared with TIO in patients with a baseline dyspnea index score  $\leq 7$ .<sup>42</sup> Similarly, for the nonexacerbator phenotype, GesEPOC (Guía Española de la Enfermedad Pulmonar Obstructiva Crónica) recommends initial therapy with LAMA or LABA monotherapy escalating to second-line therapy with a LABA/LAMA combination.<sup>2</sup> GesEPOC cites evidence from replicate studies demonstrating IND plus TIO to be superior to TIO alone,<sup>43</sup> and another demonstrating IND/GLY to be superior to the ICS/LABA combination salmeterol/fluticasone (SFC; GlaxoSmithKline) on lung-function parameters in nonexacerbating patients to support the recommendation.<sup>2,44</sup> In high-risk symptomatic patients (GOLD D), GOLD recommends LABA/LAMA as the preferred choice.<sup>1</sup> If a single bronchodilator is chosen as initial treatment, LAMA is recommended, escalating to LABA/LAMA if exacerbations persist.<sup>1</sup> SPARK and FLAME demonstrated that IND/GLY significantly reduced COPD exacerbations versus the LAMA GLY and SFC in patients with severe–very severe COPD.<sup>45,46</sup> Additionally, both studies found a significant reduction in rescue-medication use versus the active comparators.<sup>45,46</sup> Notably, the safety profile of dual bronchodilators is similar to that observed with placebo and individual monocomponents, with a comparable incidence of adverse events and serious adverse events.<sup>17,19,23</sup> Furthermore, dual bronchodilators are associated with a lower incidence of pneumonia and oral candidiasis than ICS/LABA (SFC).<sup>46–49</sup>

## Role of ICS

According to GOLD and GesEPOC, initial therapy with ICS/LABA may be first choice in those with suggestions of a steroid-responsive component to their airway disease, eg, those with a confirmed comorbid diagnosis of asthma, or those with a biomarker signature of  $T_H2$  disease.<sup>1,2,50</sup> If exacerbations persist despite therapy with LABA/LAMA or ICS/LABA, treatment can be escalated to triple therapy (ICS/LABA/LAMA).<sup>1,2</sup> Trial evidence showing a reduction in exacerbations with ICS/LABA compared with one or both components alone forms the basis for such recommendations; in the majority of these trials, patients had a history of one or more exacerbations in the year prior to the study.<sup>5,51–54</sup> The addition of an ICS to a LABA/LAMA has not been studied specifically

to date in any completed trials. Findings from the ongoing IMPACT and TRIBUTE are eagerly anticipated; both studies will investigate the efficacy of triple therapy vs LABA/LAMA in GOLD D patients.<sup>55,56</sup> Post hoc analyses have suggested greater efficacy of ICS vs LABA monotherapy in patients with a blood eosinophil count  $\geq 2\%$  or  $\geq 297.8$  cells/ $\mu\text{L}$ .<sup>57,58</sup> However, recently published data from FLAME demonstrated that a blood eosinophil count  $\geq 2\%$  was not a useful clinical biomarker in identifying patients who are likely to have a response to an ICS/LABA regimen when compared with a LABA/LAMA.<sup>46,59</sup> Following ICS withdrawal, one analysis found an increased exacerbation rate in patients with higher eosinophil counts,<sup>60</sup> and when stratified by exacerbation history, high eosinophils ( $\geq 400$  cells/ $\mu\text{L}$ ) were only associated with increased exacerbations in patients with two or more exacerbations in the previous year.<sup>61</sup> Most studies showing an effect of an ICS have included participants with an FEV<sub>1</sub>  $< 50\%$  predicted.<sup>62</sup>

Among patients at low risk of future exacerbation, a considerable proportion of patients inappropriately receive ICS/LABA, either alone or as part of triple therapy.<sup>63,64</sup> Management of exacerbating patients has largely focused on maximizing bronchodilation, rather than prescribing an ICS-containing regimen.<sup>1,65</sup> Due to the increased risk of pneumonia with an ICS,<sup>66</sup> GOLD 2017 recommends that ICS withdrawal be considered if no benefit is seen.<sup>1</sup> This recommendation is based on findings from WISDOM, which demonstrated that ICSs can be withdrawn in COPD patients without increased risk of exacerbation, provided adequate bronchodilator therapy is in place.<sup>67</sup> If patients develop further exacerbations despite treatment with ICS/LABA/LAMA, the addition of a macrolide, roflumilast, carbocysteine, or theophylline should be considered, depending on patient phenotype.<sup>1,2,68</sup>

## Which criteria might be most useful to guide treatment step-up from mono- to dual bronchodilation?

While different guidelines and strategy documents provide advice on the parameters to monitor routinely, namely lung-function measurements, symptoms, exacerbations, imaging, and smoking status,<sup>1,2</sup> guidance related to the criteria that warrant step-up from mono- to dual bronchodilation are generally unclear, due to a lack of specific evidence.

The GesEPOC guidelines<sup>2</sup> state that dual bronchodilation “should be tried” in symptomatic patients or those with evident exercise limitations following bronchodilator monotherapy. The National Institute for Health and Care Excellence guidelines provided more detailed recommendations

compared with other guidance at the time of their publication; however, it is generally recognized that these have not been updated since 2010, and more evidence has become available since their publication.<sup>69</sup> Recently, the GOLD recommendations have provided more specific guidance for stepping up from mono- to dual bronchodilation, ie, in group B patients with “persistent symptoms” and in group C patients with “persistent exacerbations”.<sup>1</sup>

Although a lack of evidence makes any particular recommendations speculative, several factors offer potential in aiding decisions on whether patients should change treatments, as shown in Table 2 and described in the following sections.

## Inadequate response to initial treatment

In clinical practice, response to COPD pharmacotherapy and other medical treatment is often judged on the patient’s symptomatic response, eg, reduced breathlessness, increased exercise capacity, or reduced need for rescue medication.<sup>1</sup> In the absence of other evidence, this may provide an indication to the physician as to whether a response is sufficient. This is inevitably subjective, as it is rare to abolish symptoms completely in COPD patients, and clinicians and patients must justify whether the treatment response is sufficiently large to make symptoms bearable and whether the change in functional capacity is adequate for the patient’s needs. An objective measure, such as the COPD Assessment Test (CAT), may be useful in assessing patient response to treatment and can be used routinely every 2–3 months.<sup>70</sup> Research is ongoing to understand the minimal clinically relevant change in CAT score from one visit to the next, but a development steering group suggests a score difference of  $\geq 2$  suggests a clinically significant change in health status.<sup>70,71</sup> Such a change or lack thereof could inform evaluation of treatment response after a suitable trial period. Adherence to treatment and inhalation technique should be assessed,<sup>1</sup> and suboptimal adherence and inhalation technique should be addressed before concluding that current therapy is insufficient. If the patient or physician perceives inadequate symptomatic relief, assuming adherence to therapy and inhalation technique are acceptable, a change in treatment regimen should be considered.

## Increased use of rescue medication

In our clinical experience, patients with a sustained daily requirement for short-acting bronchodilators may benefit from treatment intensification with long-acting bronchodilators. A retrospective analysis of clinical trial data (810 patients with moderate–very severe COPD) showed that short-acting BA reliever use is a predictor of short- and long-term (3-week and 10-month) exacerbation risk in patients with a history of

**Table 2** Clinical events or parameters that may indicate a requirement for modifying COPD treatment

Clinical event or parameter	Measure
Inadequate response to initial treatment	CAT score improvement $<2$ following intervention <sup>70,71</sup> Insufficient symptomatic relief perceived by patient or physician <sup>1</sup> <ul style="list-style-type: none"> <li>• Changes in breathlessness</li> <li>• Changes in ability to carry out activities</li> <li>• Sleep quality</li> <li>• Are improvements worthwhile to patient?</li> </ul>
Increased use of rescue medication	Sustained, increased requirement for short-acting bronchodilators <ul style="list-style-type: none"> <li>• Eg, <math>\geq 6</math> inhalations/day of salbutamol<sup>72</sup></li> </ul>
Hospitalization	Any single hospitalization related to COPD or its complications
Worsening of symptoms	Worsening of COPD symptoms on clinical evaluation; deterioration in symptom or health-status assessment scores over time
Suboptimal symptom control across the whole day	Problematic nighttime, early morning, and/or daytime COPD symptoms
Suboptimal COPD control	Patient not achieving individualized treatment objectives in areas relating to COPD impact and stability: <ul style="list-style-type: none"> <li>• CAT/CCQ scores</li> <li>• Degree of dyspnea</li> <li>• Use of rescue medication</li> <li>• Level of physical activity</li> <li>• Sputum color over time</li> </ul>
Exacerbation events	Occurrence of an exacerbation (or hospitalization) after maintenance-treatment initiation
Reduction in lung function (in combination with other measures of clinical worsening)	Reduced FEV <sub>1</sub> accompanied by an increase in disease severity, symptoms, or exacerbation rate, a decrease in exercise tolerance, or COPD comorbidities

**Abbreviations:** CAT, COPD Assessment Test; CCQ, Clinical COPD Questionnaire; FEV<sub>1</sub>, forced expiratory volume in 1 second.

exacerbations receiving budesonide/formoterol (AstraZeneca, Luton, UK) or formoterol.<sup>72</sup> Exacerbation rate increased substantially with increasing reliever-medication use. Compared with patients who used a mean of fewer than two inhalations/day of reliever medication over a 2-month period, those who used a mean of 2–5, 6–9, and  $\geq 10$  inhalations/day (over the same time period) experienced 21% ( $P=0.22$ ), 67% ( $P=0.0016$ ), and 135% ( $P<0.001$ ) higher exacerbation rates, respectively, over the following 10 months.<sup>72</sup>

## Worsening of symptoms

Worsening of COPD symptoms on clinical evaluation may lead patients and physicians to consider stepping up treatment. Symptom or health-status assessment scores (eg, using the CAT or the Clinical COPD Questionnaire) may also inform patient–physician discussions on this topic, but trends and changes are more valuable than single measurements.<sup>1</sup> As both questionnaires are short and easy to administer,<sup>71,73,74</sup> these tools could be used at follow-up visits to provide additional confirmation of disease progression. The mMRC may not have sufficient sensitivity for this purpose.<sup>75</sup>

## Suboptimal symptom control across the whole day

Although COPD symptoms can vary throughout the day, they are known to be problematic during both the day and

night.<sup>76,77</sup> An observational study of patients with stable COPD ( $n=727$ ) reported a significant relationship between nighttime, early morning, and daytime symptoms.<sup>78</sup> In each period, symptoms were associated with worse patient-reported outcomes (dyspnea, health status, sleep quality, and elevated anxiety and depression levels; all  $P<0.001$  versus patients without symptoms in each corresponding period), suggesting that improving 24-hour symptom control should be an important consideration in the management of COPD. Most newer long-acting bronchodilators are effective for the full 24 hours after once-daily administration, and may be useful in improving overnight symptom control.<sup>79</sup>

## Suboptimal COPD control

The concept of disease control considers the variable nature of the disease within the broader context of disease phenotype and severity. The two components of the “COPD control” concept are impact and stability.<sup>80</sup> Impact refers to the clinical situation of a patient at a given moment in time, and can be measured by such instruments as the CAT, or by the degree of dyspnea, the use of rescue medication, the level of physical activity, and sputum color.<sup>80</sup> Stability refers to the temporal evolution of impact over time (ie, by assessing impact at more than one time point and determining how this has changed or remained the same).<sup>80</sup> The concept of COPD control has implications for treatment decisions, such

that treatment may need to be stepped up if control is poor or maintained in the same way if there is disease stability. The ultimate goal of COPD treatment is optimal COPD control, as evidenced by the achievement of individualized treatment objectives. The proposal of the concept of control in COPD has yet to be validated.

## Exacerbation events

The occurrence of exacerbations despite initial therapy may also be an indicator of the need for treatment escalation, such as switching to dual bronchodilation. Whether a single exacerbation is sufficient to merit escalation, or whether two exacerbations in a 12-month period or a single hospitalization should be the trigger, will be a matter of clinical judgment and depend to some extent on the severity of the COPD.

## Reduction in lung function

Deterioration in lung function alone may not be an appropriate reason for switching therapy, as it does not capture the complexity of COPD: at a given level of airflow limitation, there is large variability in disease severity, symptoms, exercise tolerance, exacerbation rate, and the prevalence of comorbidities.<sup>81</sup> However, a reduction in lung function considered alongside these factors may be a trigger for escalating COPD treatment.

## Where are the evidence gaps?

Further work is needed to provide clear guidance for physicians regarding which tools and biomarkers can be used to assess patients and to guide decisions on which patients may need to progress from mono- to dual bronchodilation. Similarly, of all patients requiring an increase in medication from monotherapy with a long-acting bronchodilator, there is a need to clarify between those who would be more likely to benefit from a second long-acting bronchodilator and those more likely to benefit from an ICS and the effective dose.<sup>57,82,83</sup> Investigations into the potential use of blood eosinophil counts as a predictive biomarker of ICS response are ongoing.

There is limited but increasing evidence directly assessing the proportion of patients who respond to dual bronchodilation who were uncontrolled with monotherapy. The benefits of directly switching from previous COPD treatment to dual bronchodilation on lung function and symptoms have been demonstrated in both CRYSTAL and a study by Kerwin et al.<sup>30,34</sup> Donohue et al showed that nonresponders to LAMA or LABA monotherapy can experience significant and clinically meaningful improvements in lung function when treated with a LABA/LAMA combination,<sup>31</sup> although other clinical outcomes were not evaluated.<sup>31</sup> Nonetheless,

this study supports the findings from many of the studies outlined in Table 1 in showing greater improvements in lung function with dual bronchodilation versus monotherapy. A subgroup analysis of data from SHINE and ILLUMINATE (n=2,667), showed that IND/GLY improved lung function in patients with moderate–severe COPD who had been previously treated with LAMA or LABA monotherapy. Improvements in dyspnea and health status with IND/GLY were also observed in participants previously receiving LAMA.<sup>84</sup> However, several of the subgroups analyzed in this study were small, notably the prior-LABA-treatment group. Furthermore, all patients receiving medications during the prescreening of SHINE underwent extensive drug washout, except for those receiving short-acting BAs.<sup>84</sup>

As well as studies examining the magnitude of benefits of switching from mono- to dual-bronchodilator therapy, studies are required to look at the optimal timing of this escalation. It is not known whether greater benefits can be achieved if treatment is intensified early in the course of the disease or whether delaying the introduction of maximal bronchodilator therapy has any impact on overall disease progression.

Various applications of telemedicine and smartphone interventions are being investigated in COPD, and reports indicate some benefit in terms of reducing exacerbations, hospitalizations, and emergency-room visits.<sup>85,86</sup> The use of smartphones requires effective synergistic strategies to improve outcomes,<sup>85,87</sup> and a well-designed application could facilitate patient monitoring and alert physicians to the need to review treatment. With estimates of 2.6 billion smartphone owners by the end of 2017,<sup>88</sup> the potential benefit of this direct interface with the patient should be assessed.

## Avoiding unnecessary polypharmacy

In addition to the potential requirement for increasing treatment, physicians should be aware of the need to avoid unnecessary polypharmacy,<sup>1</sup> eg, in patients in whom triple therapy, dual-, or monobronchodilation plus ICS therapy has been initiated, but who have not responded with perceived benefit (eg, symptom improvement) compared with previous dual therapy or monotherapy, respectively. “Perceived benefit” can be challenging to evaluate in clinical practice, particularly where the aim of therapy is to reduce exacerbations. For example, it can be difficult to discern whether an individual who continues to experience exacerbations following the addition of an ICS would have experienced a similar number or more of these events without this addition.

There is very little evidence to guide the stepping down of treatment between dual and monobronchodilation.

There is evidence to support the withdrawal of ICSs in some patients receiving triple therapy. In addition to WISDOM<sup>67</sup> (as mentioned earlier), OPTIMO also assessed the withdrawal of ICS therapy in patients at low risk of exacerbation receiving maintenance therapy with long-acting bronchodilators and ICSs. OPTIMO did not find any deterioration in lung function or exacerbation rate when ICS was withdrawn compared with continued ICS therapy, providing regular treatment with long-acting bronchodilators was maintained.<sup>89</sup>

Despite limited evidence related to stepping down from triple or dual therapy, there is general consensus that a large number of COPD patients are overtreated, particularly at the milder end of the spectrum.<sup>64,90,91</sup> Ultimately, the decision to continue or withdraw stepped up therapy must be made on a patient-to-patient basis and must balance the risk of adverse events with any potential impact on lung function, symptoms, and exacerbation risk.

## Summary

Bronchodilators are central to COPD treatment. Long-acting bronchodilators are recommended as initial therapy in symptomatic patients, whether or not the patient has a high risk of exacerbations. Dual bronchodilation may be suitable as a step-up approach in those with persistent symptoms or exacerbations. Initial therapy with dual bronchodilation could be appropriate for some patients, particularly those at risk of exacerbation or with severe symptoms at diagnosis. New evidence shows that LABA/LAMA combinations may reduce the rate of exacerbations compared with ICS/LABA, even in patients with a history of exacerbations. However, COPD is a heterogeneous condition, and an individualized treatment approach is required. Currently, it is not clear at which stage patients should progress from mono- to dual bronchodilation. We have identified and discussed a number of factors that may help physicians to identify the point at which patients should change treatment, although further work is required to clarify specific thresholds (Table 2). This may encompass the use of indicators such as symptomatic response, use of rescue medication, hospitalizations, disease control, and the occurrence of exacerbations. Future research should aim to provide a better understanding of when a patient should progress treatment, and identify the appropriate tools to inform this decision.

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