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Single-Inhaler Triple Therapy Is Just The Start

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New Era in Congestive Obstructive Pulmonary Disease (COPD)

The emergence of biologic therapies for reducing exacerbations of COPD heralds a new era in pharmacologic management and optimal patient care. Through pathophysiologic pathway and trajectory alterations, disease modification, and stability, biologic therapies in the setting of COPD raise the possibility of disease control. While asthma and COPD remain clinically distinct diseases, evolving insights into their underlying pathophysiology reveals areas of overlap and complexity.

In contemporary practice, key components of COPD management, including screening and case finding, diagnosis, clinical risk stratification, initial pharmacologic therapy, exacerbation management, action plan implementation, vaccination, pulmonary rehabilitation, and chronic

bronchitis management, largely fall within the domain of primary care. Although specialist respiratory consultation continues to support these fundamental aspects of COPD management, the advent of biologic therapies creates new possibilities for respiratory specialists to focus on therapies beyond single-inhaler triple therapy.

Current State of COPD Outcomes

Exacerbations of COPD remain disease-altering events in a patient's life course. Longitudinal cohort studies have demonstrated a 50% mortality within 5 years among patients experiencing one or two acute exacerbations requiring hospitalization per year, with mortality exceeding 50% within 3 years among those experiencing three or more exacerbations. Indeed, even exacerbations managed in the outpatient setting increase the risk of future hospitalization

by 21% following a single moderate exacerbation and the risk of death is 80% following two moderate exacerbations.^{1,2}

Severe exacerbations of COPD are associated with substantial mortality. Globally, 20% of patients will die within one year of their first hospitalization for a COPD exacerbation.²⁻⁴ In Ontario, the one-year mortality rate reaches 28% among those aged 65 years or older.⁵

Challenges related to healthcare system funding, resource availability, and workload remain persistent. Within these limitations, management of COPD in the modern era is more often task-based or event-driven by patients experiencing worsening respiratory symptoms, exacerbations, or a combination of worsening factors affecting respiratory status that prompt patients to seek care. Although targeted case finding of early and undiagnosed COPD using spirometry, supported by the Canadian Lung Health Test, is recommended, implementation remains challenging. Limited access to spirometry, difficulties with test interpretation among non-respiratory specialists, and barriers to adopting a preventive approach to case finding continue to hinder widespread uptake.⁶

Canadian Thoracic Society 2023 Guidelines for Pharmacotherapy in Stable COPD

In the modern era, the 2023 Canadian Thoracic Society (CTS) guidelines for pharmacotherapy in stable COPD place single-inhaler triple therapy as the preferred pharmacologic option, placing it in over 60% of the possible pharmacologic options within the framework.⁷ Given current healthcare system constraints and the challenges associated with proactive case finding and early diagnosis, it is reasonable to anticipate that single-inhaler triple therapy will serve as the initial and final pharmacologic therapy for many patients with COPD.

Dyspnea remains a prominent symptom burden in COPD, with modified MRC class 2 dyspnea remaining common. Across patient cohorts, 40 to 60% of patients exhibit a modified MRC dyspnea score of two or higher. Consequently, COPD patients often remain quite dyspneic on exertion.⁸

Spirometric severity distributions in real-world COPD patient cohorts are generally weighted toward more advanced disease. Indeed,

70 to 80% of patients often present with moderate, severe, or very severe COPD.^{9,10}

Exacerbations are common among patients with COPD, with up to 75% experiencing at least one moderate or severe exacerbation within a three-year period.¹¹ A substantial proportion of exacerbations go unreported, with studies from both local and international settings suggesting that 40 to 80% of exacerbations may be missed despite active monitoring.¹¹⁻¹³

The CTS 2023 pharmacologic framework for pharmacotherapy in patients with stable COPD places significant emphasis on high-risk symptoms, spirometric severity, and a high risk of acute exacerbation of COPD based on exacerbation history, all of which are associated with an increased risk of mortality. Given the high prevalence of significant symptoms, spirometric severity, and frequency of exacerbations, newly-diagnosed COPD patients will most likely be candidates for single-inhaler triple therapy as first-line pharmacotherapy.

Considering this, chance favours the prepared mind. Prompt initiation of single-inhaler triple therapy in COPD following a severe exacerbation is associated with reductions in all-cause readmission and COPD-related readmission.¹⁴ Indeed, initiating therapy within 14 to 30 days of exacerbation appears to be superior compared to delaying treatment beyond 30 days.^{14,15} Each 30-day delay in initiation of single-inhaler triple therapy following a severe exacerbation is associated with a 10% risk of subsequent exacerbation.¹⁶

While once daily regimens are typically preferred over twice-daily regimens and are associated with improved patient adherence,¹⁷ overall adherence to COPD pharmacotherapy remains suboptimal.

Challenges related to inhaler devices persist, including correct dry powder inhaler technique, differences between metered dose inhaler devices, perceptions of treatment effectiveness of molecules with respect to longevity of symptom reduction and benefit, as well as regimen complexity and dosing frequency. Collectively, these factors contribute to the challenges associated with device-based therapy compared with oral pharmacotherapy.

Compounding these challenges is the reality that COPD therapies offer improvement of symptoms, quality of life, functional capacity, and exertional tolerance, yet even with optimal therapy, technique, and adherence, restoration

of normal respiratory function is not a reasonable objective. Consequently, long-term persistence with pharmacotherapy remains a challenge for many patients. Indeed, real-world evidence comparing once daily fluticasone furoate/umeclidinium/vilanterol (Trelegy 100) with twice-daily budesonide/glycopyrrolate/formoterol (Breztri) demonstrated a 43% increased likelihood of adherence with Trelegy 100. However, despite this advantage, overall adherence at 12 months remained low, reaching only 35% with Trelegy 100 and 25% with Breztri in a monitored real-world effectiveness study.¹⁸ This finding demonstrates an ongoing challenge of ensuring baseline foundational pharmacotherapy compliance and persistence in symptomatic patients with COPD. Although inhaled treatments are unable to eliminate symptoms completely, single-inhaler triple therapy remains central in COPD management, reducing exacerbation risk and serving as a therapeutic foundation upon which biologic therapies may be added for patients who continue to experience exacerbations.

Modelling studies demonstrate that the implementation of the 2023 CTS guideline for single-inhaler triple therapy could reduce exacerbation and mortality rates in Canada, increase life expectancy by 1.7 years, and over a 10 year period, reduce mortality rates by 22.2% while preventing up to 180,000 deaths. Taken together, these findings support the well-established benefits of single-inhaler triple therapy.¹⁹

Beyond Single-Inhaler Triple Therapy

While additional guideline-supported therapies toward exacerbation reduction are available for exacerbation prevention, including N-acetylcysteine, prophylactic macrolide, and Phosphodiesterase-4 (PDE4) inhibitor, challenges remain.

Daily azithromycin has demonstrated a relative risk reduction of exacerbation of 27% compared to placebo.²⁰ Unfortunately, cardiac concerns with respect to QTc prolongation, decreased auditory acuity, and tinnitus, in addition to gastrointestinal tolerability may limit its widespread use. Additionally, only 49% of patients in the seminal publication received triple therapy, which raises questions of real-world effectiveness in contemporary practice, where single-inhaler triple therapy is considered foundational therapy.²¹

PDE4 inhibition with roflumilast (Daxas) presents several challenges, including cost due to limited coverage across provincial and territorial formularies, variable access to private insurance coverage among older adults with COPD, and gastrointestinal tolerability. Similarly, real-world effectiveness in contemporary COPD practice remains a challenge. In the pivotal study, roflumilast reduced the annual exacerbation rate by 17% compared to placebo; however, inhaled corticosteroid therapy was discontinued at randomization, and only approximately half of the participants were receiving a long-acting beta agonist, which raises questions regarding the relevance of these efficacy findings to modern COPD care that includes single-inhaler triple therapy.²¹

While single-inhaler triple therapy is firmly established as the foundation of treatment for patients with symptomatic, exacerbating COPD, exacerbation reduction remains incomplete. Nearly half of patients receiving single-inhaler triple therapy will experience another moderate or severe exacerbation in the 12 months following initiation of single-inhaler triple therapy.²² This risk is also observed in the Kaplan Meier curves in the IMPACT and ETHOS trials.^{23,24}

Although asthma and COPD are recognized as distinct clinical entities, the underlying pathophysiologic processes underlying the development of fixed airway obstruction may share areas of overlap. However, the extent of this overlap remains incompletely understood. Considering the spirometric pattern seen in both of these clinical entities, peripheral blood eosinophil count has emerged as an established biomarker of T2 inflammation and a predictor of the efficacy of T2 biologic therapy in COPD. Importantly, the prevalence of elevated peripheral blood eosinophil counts are common among patients with COPD.²⁵⁻²⁷

Eosinophilic inflammation of the airways is present in up to 40% of patients with COPD, with peripheral blood eosinophil levels serving as a biomarker of this inflammatory phenotype. Elevated blood eosinophil levels are associated with increased eosinophil counts in sputum, bronchoalveolar lavage fluid, and bronchial submucosa tissue, and are associated with a greater benefit from corticosteroid-containing regimens for exacerbation reduction.²⁵⁻²⁷ In a real-world Canadian cohort, 35% of patients treated for a severe acute exacerbation of COPD had a peak peripheral blood eosinophil count of 0.3 or higher in the previous 12 months.²⁸ Indeed, in a

prospective Canadian cohort, the presence of an elevated peripheral blood eosinophil count of 0.3 or higher identified patients set to experience an accelerated loss of lung function over time.

Dupilumab and mepolizumab are Health Canada-approved biologic therapies for patients with COPD who continue to experience exacerbations despite treatment with single-inhaler triple therapy. Eligibility includes those who have experienced two or more moderate or one severe exacerbation of COPD in the prior 12 months, together with evidence of type 2 inflammation, as indicated by one or more peripheral blood eosinophil counts measuring 0.3 or higher.

In the NOTUS and BOREAS phase 3 randomized controlled trials, dupilumab reduced the annual rate of moderate or severe COPD exacerbations by 34% and 30%, respectively, over 52 weeks. Similarly, in the MATINEE phase 3 randomized controlled trial involving mepolizumab, a 21% reduction in moderate or severe exacerbations was observed over a 104 week treatment period.^{29,30}

An indirect treatment comparison of mepolizumab and dupilumab in patients with exacerbation-prone COPD evaluated patients from the METREX, METREO, and MATINEE trials who met eligibility criteria for the NOTUS and BOREAS trials. This analysis demonstrated comparable efficacy between the two biologics, with similar effects on the annualized rate of moderate or severe exacerbations, time to first moderate or severe exacerbation, and the annualized rate of severe exacerbations.³¹ These findings further support the efficacy of T2 biologic therapy with dupilumab and mepolizumab in reducing exacerbations of COPD in symptomatic, exacerbation-prone patients on single-inhaler triple therapy, with an elevated peripheral blood eosinophil count of 0.3 or higher. Importantly, the analysis highlights the comparative efficacy of the two biologics with respect to exacerbation reduction.³¹

Future of COPD Care Begins Today

Advances in medical science drive innovation in pharmacotherapy and disease management. Accordingly, continued scientific progress can be expected to translate into meaningful changes in medical practice.

Single-inhaler triple therapy is firmly established as the foundation for

pharmacotherapy management of COPD in the modern era, recognizing system limitations, and the prevalence of symptomatic, non-mild, and exacerbation-prone COPD in real-world populations. The emergence of biologic therapy in COPD raises the prospect of a new era of disease modification that perhaps will parallel the transformative impact biologics have had in asthma.

Undoubtedly, the vast majority of those with COPD are managed in primary care settings. The central role of single-inhaler triple therapy in the pharmacotherapy armamentarium for COPD is supported by the 2023 CTS guidelines, real-world patient characteristics, widespread adoption by respiratory specialists, and modelling studies showing favourable outcomes with broader implementation. Importantly, respiratory specialists are not required for single-inhaler triple therapy. For most patients, evidence-based COPD care can be delivered by primary care until consideration of biologic therapy arises.

Respiratory specialists are the gatekeepers for biologic therapy in COPD. Recognizing that pharmacologic and non-pharmacologic management of COPD short of biologic therapies can and should occur within primary care, specialists can focus on evaluating patients for disease-modifying injectable therapies and advocating their potential benefits among referring clinicians. For patients who continue to exacerbate despite optimized treatment, these therapies offer an important opportunity to further improve outcomes.

Given that even a single moderate or severe exacerbation places a patient in a high risk category according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD),³² and recognizing the likelihood of exacerbation risk despite single-inhaler triple therapy, treatment goals should extend beyond acceptance of recurrent events. For patients who exacerbate on single-inhaler triple therapy, pursuing additional therapies is essential to improving outcomes.

Nothing changes if nothing changes. The emergence of biologic therapies in COPD presents an opportunity to advance pharmacologic management and to drive change in respiratory clinical practice toward the broader integration of biologic therapy.

Our foremost responsibility is to the patient before us. The emergence of biologic therapies represents a call to action to prevent the exacerbations that continue to drive morbidity and

mortality in COPD. By acting today, we have the opportunity to improve outcomes and provide our patients with more tomorrows.

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References

1. Soler-Cataluña JJ, Martínez-García MA, Román Sánchez P, Salcedo E, Navarro M, Ochando R. Severe acute exacerbations and mortality in patients with chronic obstructive pulmonary disease. *Thorax*. 2005;60(11):925-931. doi:10.1136/thx.2005.040527
2. Rothnie KJ, Müllerová H, Smeeth L, Quint JK. Natural history of chronic obstructive pulmonary disease exacerbations in a general practice-based population with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2018;198(4):464-471. doi:10.1164/rccm.201710-2029OC
3. Ho TW, Tsai YJ, Ruan SY, Huang CT, Lai F, Yu CJ. In-hospital and one-year mortality and their predictors in patients hospitalized for first-ever chronic obstructive pulmonary disease exacerbations: a nationwide population-based study. *PLoS One*. 2014;9(12):e114866. doi:10.1371/journal.pone.0114866
4. García-Sanz MT, Cánive-Gómez JC, Senín-Rial L, Aboal-Viñas J, Barreiro-García A, López-Val E, et al. One-year and long-term mortality in patients hospitalized for chronic obstructive pulmonary disease. *J Thorac Dis*. 2017;9(3):636-645. doi:10.21037/jtd.2017.03.34
5. Nie JX, Wang L, Upshur RE. Mortality of elderly patients in Ontario after hospital admission for chronic obstructive pulmonary disease. *Can Respir J*. 2007;14(8):485-489. doi:10.1155/2007/425248
6. O'Donnell DE, Hernandez P, Kaplan A, Aaron S, Bourbeau J, Marciniuk D, et al. Canadian Thoracic Society recommendations for management of chronic obstructive pulmonary disease - 2008 update - highlights for primary care. *Can Respir J*. 2008;15 Suppl A(Suppl A):1a-8a. doi:10.1155/2008/641965
7. Bourbeau J, Bhutani M, Hernandez P, Aaron SD, Beaulieu M-F, B. Kermelley S, et al. 2023 Canadian Thoracic Society Guideline on pharmacotherapy in patients with stable COPD. *Canadian Journal of Respiratory, Critical Care, and Sleep Medicine*. 2023;7(4):173-191. doi:10.1080/24745332.2023.2231451
8. Punekar YS, Mullerova H, Small M, Holbrook T, Wood R, Naya I, et al. Prevalence and burden of dyspnoea among patients with chronic obstructive pulmonary disease in five European countries. *Pulmonary Therapy*. 2016;2(1):59-72. doi:10.1007/s41030-016-0011-5
9. Bednarek M, Maciejewski J, Wozniak M, Kuca P, Zielinski J. Prevalence, severity and underdiagnosis of COPD in the primary care setting. *Thorax*. 2008;63(5):402-407. doi:10.1136/thx.2007.085456
10. Haughney J, Gruffydd-Jones K, Roberts J, Lee AJ, Hardwell A, McGarvey L. The distribution of COPD in UK general practice using the new GOLD classification. *Eur Respir J*. 2014;43(4):993-1002. doi:10.1183/09031936.00065013
11. Hurst JR, Vestbo J, Anzueto A, Locantore N, Müllerova H, Tal-Singer R, et al. Susceptibility to exacerbation in chronic obstructive pulmonary disease. *N Engl J Med*. 2010;363(12):1128-1138. doi:10.1056/NEJMoa0909883
12. Han MK, Quibrera PM, Carretta EE, Barr RG, Bleecker ER, Bowler RP, et al. Frequency of exacerbations in patients with chronic obstructive pulmonary disease: an analysis of the SPIROMICS cohort. *Lancet Respir Med*. 2017;5(8):619-626. doi:10.1016/s2213-2600(17)30207-2
13. Tashkin DP, Celli B, Senn S, Burkhart D, Kesten S, Menjoge S, et al. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. *N Engl J Med*. 2008;359(15):1543-1554. doi:10.1056/NEJMoa0805800
14. Ismaila AS, Haeussler K, Czira A, Youn J-H, Malmenäs M, Risebrough N, et al. Network meta-analysis of the efficacy of fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) Versus other triple therapies for the treatment of chronic obstructive pulmonary disease (COPD): a comparison of annual moderate and severe exacerbations. *American Journal of Respiratory and Critical Care Medicine*. 2022;205(Supplement_1):A1454-A1454. doi:10.1164/ajrccm-conference.2022.205.1_MeetingAbstracts.A1454
15. Bogart M, Germain G, Huang S, Ismaila AS, Jung Y, Laliberté F, et al. Benefit of prompt versus delayed initiation of single inhaler triple therapy on exacerbations and healthcare costs among patients with chronic obstructive pulmonary disease in the United States. *American Journal of Respiratory and Critical Care Medicine*. 2021;203(Supplement_1):A2252-A2252. doi:10.1164/ajrccm-conference.2021.203.1_MeetingAbstracts.A2252
16. Tkacz J, Evans KA, Touchette DR, Portillo E, Strange C, Staresinic A, et al. PRIMUS - Prompt Initiation of Maintenance Therapy in the US: a real-world analysis of clinical and economic outcomes among patients initiating triple therapy following a COPD exacerbation. *Int J Chron Obstruct Pulmon Dis*.

- 2022;17:329–342. doi:10.2147/copd.S347735
17. De Keyser H, Vuong V, Kaye L, Anderson WC, 3rd, Szefer S, Stempel DA. Is once versus twice daily dosing better for adherence in asthma and chronic obstructive pulmonary disease? *J Allergy Clin Immunol Pract.* 2023;11(7):2087–2093.e2083. doi:10.1016/j.jaip.2023.03.053
18. Noorduyn S, Young C, Lee L, Germain G, Laliberté F, Lejeune D, et al. Adherence and persistence with fluticasone furoate/umeclidinium/vilanterol and budesonide/glycopyrrolate/formoterol fumarate among patients with chronic obstructive pulmonary disease: a real-world United States study. *American Journal of Respiratory and Critical Care Medicine.* 2024;209(Supplement_1):A3301–A3301. doi:10.1164/ajrccm-conference.2024.209.1_MeetingAbstracts.A3301
19. Bhutani M, Kaplan A, Kayaniyil S, Jamieson K, Ormsby R, Bell J, et al. Implementation of 2023 Canadian Thoracic Society Guidelines for Single-Inhaler Triple Therapy could reduce exacerbation and mortality rates in COPD: PROMETHEUS Canada. *Chronic Obstr Pulm Dis.* 2026;13(3):184–194. doi:10.15326/jcopdf.2025.0687
20. Albert RK, Connett J, Bailey WC, Casaburi R, Cooper JA, Jr., Criner GJ, et al. Azithromycin for prevention of exacerbations of COPD. *N Engl J Med.* 2011;365(8):689–698. doi:10.1056/NEJMoa1104623
21. Calverley PM, Rabe KF, Goehring UM, Kristiansen S, Fabbri LM, Martinez FJ. Roflumilast in symptomatic chronic obstructive pulmonary disease: two randomised clinical trials. *Lancet.* 2009;374(9691):685–694. doi:10.1016/s0140-6736(09)61255-1
22. Vogelmeier CF, Worth H, Buhl R, Crie CP, Gückel E, Kardos P. Impact of switching from triple therapy to dual bronchodilation in COPD: the DACCORD 'real world' study. *Respir Res.* 2022;23(1):109. doi:10.1186/s12931-022-02037-2
23. Lipson DA, Barnhart F, Brealey N, Brooks J, Criner GJ, Day NC, et al. Once-daily single-inhaler triple versus dual therapy in patients with COPD. *N Engl J Med.* 2018;378(18):1671–1680. doi:10.1056/NEJMoa1713901
24. Rabe KF, Martinez FJ, Ferguson GT, Wang C, Singh D, Wedzicha JA, et al. Triple inhaled therapy at two glucocorticoid doses in moderate-to-very-severe COPD. *N Engl J Med.* 2020;383(1):35–48. doi:10.1056/NEJMoa1916046
25. Tworek D, Antczak A. Eosinophilic COPD - a distinct phenotype of the disease. *Adv Respir Med.* 2017;85(5):271–276. doi:10.5603/ARM.a2017.0045
26. Vedel-Krogh S, Nielsen SF, Lange P, Vestbo J, Nordestgaard BG. Blood eosinophils and exacerbations in chronic obstructive pulmonary disease. The Copenhagen general population study. *Am J Respir Crit Care Med.* 2016;193(9):965–974. doi:10.1164/rccm.201509-1869OC
27. Ko FWS, Xu X, Hon P, Ratnasingham P, Milea D, Hui DSC. Clinical characteristics of patients with COPD in Hong Kong. *European Respiratory Journal.* 62(suppl 67):PA1316. doi:10.1183/13993003.congress-2023.PA1316
28. Saint-Pierre MD, Abdounour J. Oral add-on therapies and blood eosinophils in severe acute exacerbations of chronic obstructive pulmonary disease: A real-world hospital chart review. *Canadian Journal of Respiratory, Critical Care, and Sleep Medicine.* 2024;8(6):254–259. doi:10.1080/24745332.2024.2396463
29. Bhatt SP, Rabe KF, Hanania NA, Vogelmeier CF, Bafadhel M, Christenson SA, et al. Dupilumab for COPD with blood eosinophil evidence of type 2 inflammation. *N Engl J Med.* 2024;390(24):2274–2283. doi:10.1056/NEJMoa2401304
30. Bhatt SP, Rabe KF, Hanania NA, Vogelmeier CF, Cole J, Bafadhel M, et al. Dupilumab for COPD with type 2 inflammation indicated by eosinophil counts. *N Engl J Med.* 2023;389(3):205–214. doi:10.1056/NEJMoa2303951
31. Bourbeau J, Min J, Kolterer S, Yang S, Hunger M, Wang X, et al. Indirect treatment comparison (ITC) of mepolizumab and dupilumab in treating COPD. *European Respiratory Journal.* 66(suppl 69):PA488. doi:10.1183/13993003.congress-2025.PA488
32. Cazzola M, Bajpai J, Calzetta L, Matera MG, Rogliani P. GOLD 2026: Transforming COPD management with early intervention, multi-dimensional assessment, and personalized care. *Drugs.* 2026;86(5):581–597. doi:10.1007/s40265-026-02303-3