A Network Meta-Analysis of Triple Therapy Inhalers Used in Moderate to Severe Chronic Obstructive Pulmonary Disease

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Introduction

- Triple therapies are more effective than dual therapies in treating patients with moderate to severe chronic obstructive pulmonary disease (COPD).
- However, it remains uncertain whether all triple therapy combinations have similar efficacy.
- Published network meta-analyses (NMAs) have inconsistent conclusions, likely due to methodological differences.

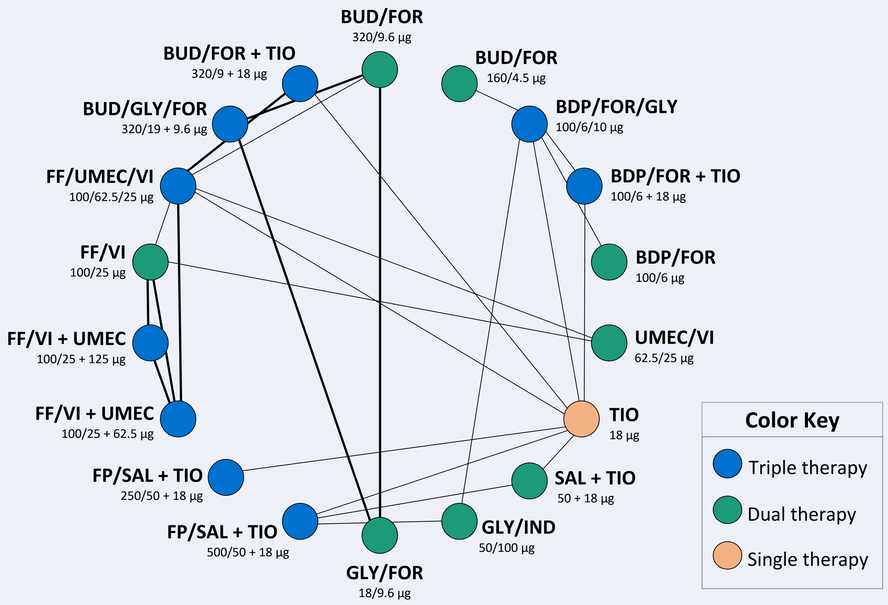
Objective

- To evaluate the comparative clinical effectiveness of triple therapy inhalers for COPD using the most recent evidence and methodological guidance.

Methods

- Our NMA included randomized controlled trials (RCTs) comparing triple therapies in adults with at least moderate COPD for 12 or more weeks designed using placebo inhalers to ensure all arms had identical inhaler regimens.
- RCTs were identified from prior NMAs comparing triple therapy regimens and a systematic search for new RCTs published since the most recent NMA's last search year (2020).
- We performed random-effects Bayesian NMAs for patient-important outcomes:
  - Moderate to severe exacerbation rate
  - St. George's Respiratory Questionnaire (SGRQ) total score
  - Discontinuations due to adverse events
  - All-cause mortality

Figure 1. Network Diagram: Moderate to Severe Exacerbations



Legend: A thicker line signifies more than one trial contributed to the comparison. The network diagram for SGRQ Total Score shares a similar structure with the addition of FP/SAL + GLY in place of lower dose FP/SAL + TIO. Both diagrams include data from 18 RCTs on 9 triple therapies.

Results

- We identified 17 publications meeting our criteria, two of which were new evidence from 2020 to 2025.
  - The publications covered 19 RCTs evaluating 10 unique triple therapies.
- The NMA results showed no statistically significant differences between any single- or multi-inhaler triple therapies on moderate to severe exacerbation rates (Table 1), SGRQ total score (Table 2), or discontinuation due to adverse events.
- No conclusions could be made about all-cause mortality due to data limitations.

Table 1. League Table of NMA Results: Moderate to Severe Exacerbations

BUD/FOR+TIO									
0.93 (0.54, 1.59)	FF/UMEC/VI								
0.89 (0.40, 2.18)	0.96 (0.53, 1.94)	FF/VI+UMEC^{LD}							
0.75 (0.27, 2.25)	0.81 (0.33, 2.10)	0.84 (0.37, 1.91)	FF/VI+UMEC^{HD}						
0.72 (0.23, 2.21)	0.78 (0.29, 2.08)	0.82 (0.23, 2.48)	0.97 (0.24, 3.57)	BUD/GLY/FOR					
0.57 (0.22, 1.47)	0.61 (0.24, 1.59)	0.64 (0.19, 1.91)	0.76 (0.2, 2.74)	0.78 (0.2, 3.12)	BDP/FOR/GLY				
0.57 (0.21, 1.58)	0.62 (0.23, 1.71)	0.65 (0.18, 2.04)	0.77 (0.19, 2.88)	0.79 (0.2, 3.28)	1.01 (0.47, 2.16)	BDP/FOR+ TIO			
0.53 (0.20, 1.38)	0.57 (0.22, 1.49)	0.60 (0.18, 1.79)	0.70 (0.18, 2.56)	0.73 (0.19, 2.91)	0.93 (0.42, 2.06)	0.92 (0.35, 2.38)	FP/SAL+TIO^{HD}		
0.53 (0.16, 1.72)	0.57 (0.17, 1.86)	0.59 (0.15, 2.18)	0.70 (0.15, 3.06)	0.73 (0.16, 3.42)	0.93 (0.28, 3.04)	0.92 (0.27, 3.16)	1.0 (0.3, 3.31)	FP/SAL+TIO^{LD}

Legend: The interventions are SUCRA-ranked, arranged from most effective (top left) to least effective (bottom right). Each box represents the relative risk and 95% credible interval for the combined direct and indirect comparisons between two drugs. All estimates' 95% credible intervals contain 1, indicating no statistically significant differences.

Table 2. League Table of NMA Results: St. George Respiratory Questionnaire (SGRQ) Total Score

BDP/FOR+TIO								
-0.24 (-2.54, 2.14)	FP/SAL+TIO^{HD}							
-0.76 (-3.00, 1.52)	-0.52 (-2.72, 1.67)	FF/UMEC/VI						
-0.96 (-3.78, 1.97)	-0.71 (-3.56, 2.12)	-0.19 (-1.96, 1.59)	FF/VI+UMEC^{HD}					
-1.03 (-3.09, 1.09)	-0.79 (-2.78, 1.22)	-0.26 (-1.39, 0.89)	-0.07 (-2.19, 2.05)	BUD/FOR+TIO				
-1.21 (-3.13, 0.71)	-0.97 (-2.89, 0.85)	-0.43 (-2.55, 1.57)	-0.25 (-3.03, 2.43)	-0.17 (-2.13, 1.64)	BDP/FOR/GLY			
-1.34 (-4.53, 1.91)	-1.10 (-3.27, 1.09)	-0.55 (-3.68, 2.53)	-0.37 (-3.96, 3.18)	-0.29 (-3.27, 2.64)	-0.12 (-2.95, 2.77)	FP/SAL + GLY		
-1.77 (-4.41, 0.92)	-1.54 (-4.16, 1.08)	-1.02 (-2.41, 0.4)	-0.82 (-2.41, 0.74)	-0.74 (-2.57, 1.07)	-0.57 (-3.02, 1.99)	-0.46 (-3.84, 2.99)	FF/VI+UMEC^{LD}	
-1.93 (-5.03, 1.08)	-1.70 (-4.75, 1.25)	-1.16 (-3.28, 0.83)	-0.97 (-3.74, 1.65)	-0.90 (-3.33, 1.4)	-0.73 (-3.65, 2.19)	-0.61 (-4.35, 3.08)	-0.15(-2.71, 2.28)	BUD/GLY/FOR

Legend: The interventions are SUCRA-ranked, arranged from most effective (top left) to least effective (bottom right). Each box represents the relative mean difference and 95% credible interval for the combined direct and indirect comparisons between two drugs. All estimates' 95% credible intervals contain 0, indicating no statistically significant differences.

Key Takeaways

- There were no differences in efficacy among the triple therapies for key patient-important outcomes when used as prescribed.
  - There were some variances in the SUCRA rank order of the triple therapies across outcomes.
- Our NMA is the first to control for adherence by including only blinded RCTs comparing arms with the same number of inhalers & dosing schedule.
  - In real-world settings, single inhalers may result in better adherence and thus reduced risk of exacerbations as compared to multiple inhalers.
- The comparable efficacy of triple therapies may allow clinicians to prescribe based on affordability or accessibility to an individual patient.
- In comparison to previous NMAs, the results of this NMA highlight that conclusions likely depend on the following:
  - Study selection (e.g., open-label vs. blinded)
  - Controlling for the number of inhalers across treatment arms
  - Statistical model used (e.g., fixed vs. random effects, Frequentist vs. Bayesian)
  - Merging of dual therapy arms into one node (e.g., combining all ICS/LABA or all LAMA/LABA)
- Full reporting of results, including discontinuation due to adverse events and all-cause mortality, can be found by scanning the QR code →

ABBREVIATIONS | BDP: beclomethasone dipropionate, BUD: budesonide, COPD: chronic obstructive pulmonary disease, FF: fluticasone furoate, FOR: formoterol fumarate, FP: fluticasone propionate, GLY: glycopyrronium, HD: high dose, ICS: inhaled corticosteroid, LABA: long-acting beta-agonist, LAMA: long-acting muscarinic agonist, LD: low dose, NMA: network meta-analysis, SAL: salmeterol, SGRQ: St. George's Respiratory Questionnaire, SUCRA: Surface Under the Cumulative Ranking curve, RCT: randomized controlled trial, TIO: tiotropium, UMEC: umeclidinium, VI: vilanterol, µg: microgram

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