Three-drug therapy versus two-drug therapy for management of patient-reported manifestations and quality of life in chronic obstructive pulmonary disease patients: A meta-analysis

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ARTICLE INFO
Received on: 17/03/2020
Accepted on: 30/08/2020
Available online: 05/10/2020

Key words: COPD assessment test (CAT), adverse events, St George Respiratory Questionnaire (SGRQ), meta-analysis, rescue medication use.

ABSTRACT
Patient-reported manifestations and quality of life (QoL) data for chronic obstructive pulmonary disease (COPD) drugs are sparse. This study compared three-drug therapy comprising inhaled corticosteroids (ICS), long-acting beta2 agonists (LABA), and long-acting muscarinic antagonists (LAMA) with two-drug therapy (ICS/LABA or LABA/LAMA) in terms of patient-reported manifestations and QoL. Randomized controlled trials (RCTs) comparing three-drug therapy with two-drug therapy in COPD patients were searched through PubMed and meta-analyzed. Efficacy endpoints included St George Respiratory Questionnaire (SGRQ) score, SGRQ responders, COPD assessment test (CAT) score, rescue drug use, rescue drug-free days, and adverse events resulting in drug cessation. Three-drug therapy showed improvement in SGRQ scores [mean difference (MD), −1.66; 95% confidence interval (CI), −2.09 to −1.23] and SGRQ responders [Odds Ratio (OR), 1.30; 95% CI, 1.18–1.44] compared to ICS/LABA dual therapy; and SGRQ scores (MD, −1.65; 95% CI, −2.31 to −0.99) and SGRQ responders (OR, 1.20; 95% CI, 1.08–1.34) compared to LABA/LAMA dual therapy. Similarly, results with CAT scores, rescue medication use, percentage of rescue medication-free days, and adverse events resulting in drug cessation favored the three-drug therapy compared to the two-drug therapy. Three-drug therapy had improved SGRQ scores, CAT scores, reduced rescue medication use, and better QoL.

INTRODUCTION
Chronic obstructive pulmonary disease (COPD) is a significant contributor to morbidity and mortality worldwide (Decramer et al., 2012; GBD 2016 Risk Factors Collaborators, 2017). The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines advocate a stepwise advancement from monotherapy to three-drug therapy comprising long-acting beta2 agonists (LABA), inhaled corticosteroids (ICS), and long-acting muscarinic antagonists (LAMA), as the management for severe symptoms and exacerbations (Global Initiative for Chronic Obstructive Lung Disease (GOLD), 2017). The supreme objective of COPD treatment is improving pulmonary health, quality of life (QoL), and eliminating exacerbations (Hutchinson et al., 2010). Weakened physical and mental health, dyspnea, and increased hospitalizations have been shown to be predictors of poor health-related quality of life (HRQoL) (Balcells et al., 2010; Carrasco et al., 2006; Cully et al., 2006; Hu and Meek, 2005). HRQoL can thus be viewed as an important marker for treatment efficacy providing a finishing touch to the existing efficacy parameters (Cazzola et al., 2008).

Recently, many multicenter randomized clinical trials have been performed to study three-drug therapy with two-drug therapy for pulmonary function, QoL, and exacerbations. All these trials proved three-drug therapy to be safer and efficacious than two-drug therapy in medium to serious COPD patients (Aaron et al., 2007; Ferguson et al., 2018; Lipson et al., 2018; Papi et al., 2018). Nevertheless, there are inconsistent results for patient-reported outcomes, like QoL, rescue drug use, and drug discontinuation, due to adverse events. Moreover, the previous meta-analysis did not document the effectiveness of three-drug therapy versus two-
drug therapy in context to the above-mentioned patient-reported outcomes (Calzetta et al., 2019; Zayed et al., 2019; Zheng et al., 2018).

In view of the increasing generalization of three-drug therapy in clinical application, this meta-analysis was conducted in order to study three-drug therapy (ICS/LABA/LAMA) with two-drug therapy (LABA/LAMA or LABA/ICS) for patient-reported outcomes and QoL, and to find out the effect of potential modifiers that may alter the effects of treatment regimens.

METHODS

Search strategy

Medline and Cochrane databases were manually explored to find the relevant randomized controlled trials (RCTs) contrasting three-drug therapy (ICS/LABA/LAMA) with two-drug therapy [(ICS/LABA) or (LABA/LAMA)]. The following search strategies were used to find the relevant RCTs in the pubmed database.

#1 (COPD OR "Chronic obstructive pulmonary disease")
#2 (Beta agonist OR LABAOR salmeterol OR indacaterol OR formoterol OR vilanterol OR olodaterol)
#3 (muscarinic OR LAMA OR tiotropium OR glycopyrroium OR umeclidinium OR aclidinium OR ipratropium)
#4 (ICS OR fluticasone OR budesonide OR beclomethasone OR ciclesonide OR flunisolide OR mometasone OR tramcinolone)
#5 #1 AND #2 AND (#3 OR #4)

The filters used were clinical study, clinical trial, and comparative study. The search was conducted for the period of January 2006 to July 2019.

Inclusion criteria

1) RCTs with duration no less than 12 weeks.
2) Studies contrasting three-drug therapy (ICS/LABA/LAMA) with two-drug therapy [(ICS/LABA) or (LABA/LAMA)].
3) Patients with medium to serious COPD.
4) Outcomes included were rescue drug use, St George Respiratory Questionnaire (SGRQ) score, COPD assessment test (CAT) score, and adverse events resulting in drug cessation.

Quality assessment

The present study confirms the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines (Moher et al., 2015). The data were drawn out by two reviewers and the differences were settled by a third reviewer. The extricated data are shown in Table 1 and 2. Cochrane manual of systematic review was used to examine the likelihood of bias of included studies. The following items were taken into consideration: random sequence generation, allotment concealment, blinding of patients and trial staff; blinding of result evaluation, incomplete result reporting, selective reporting, and other bias (Higgins et al., 2011). The Consolidated Standards of Reporting Trials (CONSORT) guidelines were used for checking the completeness of clinical trials (Moher, 1998). Only those trials which matched the completeness criteria of CONSORT guidelines were incorporated in the meta-analysis. The grading of recommendations assessment, development, and evaluation (GRADE) approach was utilized for categorizing the standard of evidence and produced absolute effect estimates for the outcomes (Guyatt et al., 2011).

Statistical analysis

For dichotomous outcomes, an effect measure was presented as odds ratio (OR) accompanied by their related 95% confidence interval employing the Mantel–Haenszel method. Similarly, parametric data effect measures were presented as average differences, with their corresponding 95% confidence intervals employing the inverse variance method. Heterogeneity between trials was examined employing chi-square tests and F statistics and F values more than 50% representing significant heterogeneity. The fixed-effects model was employed where heterogeneity was less than 50%; in all other cases, the random-effects model was utilized. Publication bias was examined employing funnel plots in the case where 10 or more trials were involved in meta-analysis. Meta-regression analysis assessed the possible causes of heterogeneity. Data were analyzed employing RevMan v5.3 software as well as Comprehensive Meta-analysis v3 software.

RESULTS

An exhaustive literature search yielded 584 research articles contrasting three-drug therapy with two-drug therapy in COPD patients. After careful evaluation by the reviewers, 12 publications (14 RCTs), published between 2007 and 2018, were found to be eligible as per the inclusion/exclusion criteria and incorporated in this meta-analysis (Aaron et al., 2007; Cazzola et al., 2007; Ferguson et al., 2018; Frith et al., 2015; Hoshino et al., 2011; Lipson et al., 2017; Lipson et al., 2018; Papi et al., 2018; Siler et al., 2015, 2016; Singh et al., 2016; Sousa et al., 2016). A summary of study sorting process is shown in Figure 1. The study baseline characteristics are presented in Table 1 and 2. The duration of study varied between 12 and 52 weeks. Five trials (Ferguson et al., 2018; Lipson et al., 2017; Lipson et al., 2018; Papi et al., 2018; Singh et al., 2016) used single inhaler triple therapy, while the remaining included trials used separate inhalers for triple therapy. Two publications (Siler et al., 2015, 2016) presented a pair of RCTs as a joint result. The possibility of bias in incorporated studies was categorized into low, high, and unclear based on Cochrane’s risk of bias instrument (Figs. 2 and 3).

Triple therapy versus ICS/LABA dual therapy

Ten publications (Cazzola et al., 2007; Ferguson et al., 2018; Frith et al., 2015; Hoshino et al., 2011; Lipson et al., 2017; Lipson et al., 2018; Siler et al., 2015, 2016; Singh et al., 2016; Sousa et al., 2016) used three-drug therapy versus ICS/LABA therapy in comparison with moderate to severe COPD patients. Three-drug therapy showed improvement in terms of
Table 1. Characteristics of incorporated trials (three-drug therapy vs. ICS/LABA and LABA/LAMA).

| Study          | Intervention | Total patients | Average age (years) | Male (%) | SGRQ score (Average difference from baseline) | CAT score (Average difference from baseline) | Rescue medication use (puffs/day) | Follow up (weeks) |
|----------------|--------------|----------------|---------------------|----------|-----------------------------------------------|---------------------------------------------|----------------------------------|-------------------|
| Cazzola, 2007  | FCP/STL/TTM  | 29             | 66.9                | 86.7     | NA                                            | NA                                          | 5.20                             | 12                |
|                | FCP/STL      | 26             | 64.4                | 86.7     | NA                                            | NA                                          | 5.13                             |                   |
|                | FCP/STL/GPM  | 257            | 68.2                | 63.4     | −2.81                                         | NA                                          | 2.19                             |                   |
| Frith, 2015 (GLISTEN) | FCP/STL/TTM | 258            | 68.0                | 62.0     | −3.90                                         | NA                                          | 2.09                             | 12                |
|                | FCP/STL      | 257            | 67.8                | 67.7     | −0.65                                         | NA                                          | 2.91                             |                   |
| Lipson, 2017 (FULFILL) | FTF/ULM/VTL | 911            | 64.2                | 74       | −6.6                                          | −2.5                                         | −1.8                              | 24                |
| Lipson, 2018 (IMPACT) | FCP/STL/TTM | 258            | 68.0                | 62.0     | −3.90                                         | NA                                          | 2.09                             |                   |
|                | FCP/STL      | 257            | 67.8                | 67.7     | −0.65                                         | NA                                          | 2.91                             |                   |
| Lipson, 2017 (FULFILL) | FTF/ULM/VTL | 4151           | 65.3                | 67       | −5.5                                          | NA                                          | NA                               | 52                |
|                | FTF/VTL     | 4134           | 65.3                | 66       | −3.7                                          | NA                                          | NA                               |                   |
| Siler, 2016 A  | FCP/STL/ULM | 205            | 63.2                | 69       | −2.77                                         | −0.92                                        | NA                               |                   |
|                | FCP/STL      | 204            | 62.7                | 65       | −3.57                                         | −0.81                                        | NA                               | 12                |
|                | FCP/STL      | 205            | 63.4                | 64       | −2.26                                         | −0.77                                        | NA                               |                   |
| Siler, 2016 B  | FCP/STL/ULM | 203            | 64.5                | 69       | −3.50                                         | −1.31                                        | NA                               | 12                |
|                | FCP/STL      | 201            | 65.7                | 61       | −1.50                                         | 0.41                                         | NA                               |                   |
|                | FTF/VTL/ULM | 207            | 63.8                | 61       | −1.77                                         | −0.1                                         | −0.6                             |                   |
| Siler, 2015 C  | FCF/VTL/VTL | 206            | 64.9                | 67       | −3.05                                         | −1.1                                         | −0.7                             | 12                |
|                | FCF/VTL     | 206            | 64.7                | 68       | −2.23                                         | 0.3                                          | −0.3                             |                   |
|                | FCF/VTL/ULM | 207            | 63.6                | 63       | −1.04                                         | −0.5                                         | −0.3                             |                   |
| Siler, 2015 D  | FCF/VTL/ULM | 206            | 62.6                | 66       | −1.56                                         | −0.6                                         | −0.4                             | 12                |
|                | FCF/VTL     | 206            | 62.6                | 61       | 0.1                                           | 0.59                                         | 0.1                              |                   |
| Singh, 2016 (TRILOGY) | FTF/STL/ULM | 687            | 63.3                | 74       | −5.13                                         | NA                                          | NA                               | 52                |
|                | FCD/FTF     | 680            | 63.8                | 77       | −3.45                                         | NA                                          | NA                               |                   |
| Sousa, 2016    | ICS/LABA/ULM | 119           | 65.2                | 83       | −2.26                                         | −0.37                                        | −0.53                            | 12                |
|                | ICS/LABA    | 117            | 63.1                | 75       | −0.00                                         | 0.94                                         | −0.15                            |                   |
|                | BSD/FO/GPM  | 639            | 64.9                | 72.0     | −7.5                                          | NA                                          | −1.3                             |                   |
| Ferguson, 2018 (KRONOS) | BSD/FO | 314            | 65.2                | 71.3     | −7.1                                          | NA                                          | −1.1                             | 24                |
|                | BSD/FO (open label) | 318      | 65.9                | 74.2     | −6.3                                          | NA                                          | −1.6                             |                   |
| Hoshino 2013   | FCP/STL     | 16             | 67                  | 81.3     | −4.73                                         | NA                                          | NA                               | 16                |

SGRQ = St Georges respiratory questionnaire; CAT = COPD assessment test; LAMA = long acting muscarinic receptor antagonist; LABA = long acting β2 adrenoreceptor agonist; FCP = fluticasone propionate; STL = salmeterol; TTM = tiotropium; BCD = beclometasone dipropionate; FTF = formoterol fumarate; GPM = glycopyrronium; ULM = umeclidinium; VTL = vilanterol; BSD = budesonide; FOR = formoterol; IDL = indacaterol; NA = not available.

Table 2. Characteristics of included studies (Triple therapy vs. LAMA/LABA).

| Study          | Intervention | Total patients | Average age (years) | Male (%) | SGRQ (Average difference from baseline) | CAT (Average difference from baseline) | Rescue medication use (puffs/day) | Follow up (weeks) |
|----------------|--------------|----------------|---------------------|----------|----------------------------------------|----------------------------------------|----------------------------------|-------------------|
| Lipson, 2018   | FTF/ULM/VTL | 4151           | 65.3                | 67       | −5.5                                    | NA                                     | NA                               | 52                |
|                | ULM/VTL     | 2070           | 65.2                | 66       | −3.7                                    | NA                                     | NA                               |                   |
| Ferguson, 2018 (KRONOS) | BSD/FO/GPM | 639            | 64.9                | 72.0     | −7.5                                    | NA                                     | −1.3                             | 24                |
|                | FOR/GPM     | 625            | 65.1                | 68.8     | −6.3                                    | NA                                     | −1.1                             |                   |
| Papi, 2018 (TRIBUTE) | BCD/FTF/GPM | 764            | 64.4                | 72       | −3.51                                   | −0.8                                   | NA                               | 52                |
|                | IDL/GPM     | 768            | 64.5                | 72       | −1.86                                   | −0.6                                   | NA                               |                   |
| Aaron 2007     | FCP/STL/TTM | 145            | 67.5                | 57.9     | −8.6                                    | NA                                     | NA                               | 52                |
|                | STL/TTM     | 148            | 67.6                | 57.4     | −6.3                                    | NA                                     | NA                               |                   |

SGRQ = St Georges respiratory questionnaire; CAT = COPD assessment test; LAMA = long acting muscarinic receptor antagonist; LABA = long acting β2 adrenoreceptor agonist; FCP = fluticasone propionate; STL = salmeterol; TTM = tiotropium; BCD = beclometasone dipropionate; FTF = formoterol fumarate; GPM = glycopyrronium; ULM = umeclidinium; VTL = vilanterol; BSD = budesonide; FOR = formoterol; IDL = indacaterol; NA = not available.
SGRQ scores [MD, −1.66; 95% Confidence interval (CI), −2.09 to −1.23] (Fig. 4) and SGRQ responders [OR, 1.30; 95% CI, 1.18–1.44] (Fig. 5) compared to ICS/LABA therapy. Similarly, triple therapy showed improvements in CAT scores (MD, −0.86; 95% CI, −1.29 to −0.43) (Fig. 6) compared to ICS/LABA therapy. Three-drug therapy resulted in reduced use of rescue medication use (MD, −0.30; 95% CI, −0.40 to −0.20) (Fig. 7), puffs/day and enhancement in percentage of rescue medication-free days (MD, 6.42; 95% CI, 3.51–9.33) (Fig. 8). Three-drug therapy resulted in reduced adverse events relating to medication discontinuation (OR, 0.96; 95% CI, 0.74–1.25) (Fig. 9), albeit this association was far from statistical significance.

**Triple therapy versus LABA/LAMA dual therapy**

Four trials (Aaron et al., 2007; Ferguson et al., 2018; Lipson et al., 2018; Papi et al., 2018) used three-drug therapy versus LABA/LAMA therapy in comparison with moderate to severe COPD patients. Three-drug therapy showed improvement in SGRQ scores (MD, −1.65; 95% CI, −2.31 to −0.99) (Fig. 10) as well as SGRQ responders (OR, 1.00; 95% CI, 1.08–1.34) (Fig. 11) compared to LABA/LAMA therapy. Triple therapy showed a statistically insignificant reduction in adverse events (OD, 0.89; 95% CI, 0.65–1.23) (Fig. 12).

**Bias, quality of evidence, and meta-regression analysis**

The use of funnel plots demonstrated the largely symmetrical distribution of studies for the outcome SGRQ scores’ average difference from baseline (Fig. 13). Nevertheless, the chance of evident publication bias has to be ruled in for other outcomes like SGRQ responders, CAT scores, rescue drug use, and adverse events, leading to drug discontinuation due to a lesser amount of available trials included in the meta-analysis.
The GRADE approach revealed a medium quality of evidence for efficacy of three-drug therapy versus ICS/LABA and LABA/LAMA therapy on the SGRQ scores average difference from baseline and SGRQ responders, with no less than a 4-unit drop in the SGRQ score. Likewise, the medium standard of evidence was found for three-drug therapy versus LABA/LAMA therapy in terms of adverse events resulting in drug cessation. On the other hand, a very low quality of evidence was available for CAT scores’ average difference from baseline and rescue medication use when three-drug therapy was compared with ICS/LABA therapy. Similarly, adverse events resulting in drug cessation produced low quality of evidence when three-drug therapy was compared with ICS/LABA therapy (Table 3).

Meta-regression analysis revealed the impact of several variables that may act as potential effect modifiers for the effect of three-drug therapy compared to ICS/LABA and LABA/LAMA therapy. These variables included age, percentage of men, fixed combination (single inhaler) versus open combination (separate inhaler), consistent versus inconsistent drug combination, study duration, and FEV1 (%pred). An inconsistent drug combination compared ICS/LABA/LAMA therapy with a non-identical ICS/LABA or LABA/LAMA drug therapy that was different from the three-drug therapy. None of the variables was found to significantly affect the SGRQ scores (Table 4). The graphical representation of the impact of different variables on SGRQ scores is shown in Figures 14–19. The condensed results table along with the standard of evidence is given in Table 5.

**DISCUSSION**

The findings of our meta-analysis demonstrated superior benefits of three-drug therapy in contrast to both ICS/LABA and LABA/LAMA combinations in various efficacy parameters. These efficacy parameters included improvement in SGRQ scores, more number of SGRQ responders (patients who gained a 4 or more units decrease in SGRQ scores), improvement in CAT scores, rescue drug use decrease, increase in rescue drug use free days, and decrease in drug discontinuation due to adverse events. Thus, the ICS/LABA/LAMA based three-drug therapy was able to improve HRQoL and dyspnea with the adverse events profile that was not significantly distinct from the two-drug therapy.
Our results are similar with the most recent meta-analysis that demonstrated the dominance of three-drug therapy over two-drug therapy in improving SGRQ scores and reduction in drug discontinuation attrition rates due to adverse events (Calzetta et al., 2019; Zayed et al., 2019; Zheng et al., 2018). Many of the patient-oriented efficacy parameters, like CAT scores and rescue drug use, which were neglected in the above-mentioned meta-analysis were the center of interest of our meta-analysis. Patient-oriented perspectives capture additional insights into efficacy parameters that are of particular interest for the practicing pulmonologist in the choice and monitoring of therapies at the individual patient level (Tabberer et al., 2018).
Figure 7. Average difference from baseline in rescue drug use (puffs/day) for triple therapy versus LABA/ICS dual therapy.

Figure 8. Average difference from baseline in percentage of rescue drug-free days for triple therapy versus LABA/ICS dual therapy.

Figure 9. Adverse events resulting in drug cessation for triple therapy versus LABA/ICS dual therapy.

Figure 10. Average difference from baseline in SGRQ scores for triple therapy versus LABA/LAMA dual therapy.
Moreover, this study analyzed the modifier impact of various variables on the SGRQ score which was not done in the previous meta-analysis.

Meta-regression analysis failed to show any significant confounding effect of the variables on the SGRQ average difference of three-drug therapy versus two-drug therapy. SGRQ scores have been shown to predict exacerbations, hospitalizations, and death due to COPD making SGRQ scores a valid tool to evaluate drug efficacy (Mullerova et al., 2017). Thus, factors affecting SGRQ scores will add additional insights into drug efficacy. Previous studies have shown significant correlations of SGRQ scores with age, frequency of exacerbations per year, comorbidities, and modified Medical Council Research Dyspnea scale (Farag et al., 2018; Lee et al., 2017). In the present study, covariates, consistent versus inconsistent drug combination, and fixed versus open combination were found to have the maximum influence on the SGRQ mean difference (MD), although this influence was ruled out due to statistically insignificant results. Unfortunately, the lesser number of available RCTs included can be one of the reasons behind the statistical insignificant covariates in the meta-regression analysis.
Table 3. Condensed results.

| No of patients/ study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Triple therapy | Dual therapy | Absolute benefit with Triple therapy over dual therapy |
|-----------------------------|-------------|---------------|--------------|-------------|----------------------|----------------|--------------|------------------------------------------------------|
| Mean change from baseline in SGRQ scores (Triple therapy vs. ICS/LABA dual therapy) | Not serious | Not serious | Not serious | Serious<sup>a</sup> | None | 7,661 | 5,925 | MD 1.66 lower (2.09 lower to 1.23 lower) |
| Mean change from baseline in SGRQ scores (Triple therapy vs. LABA/LAMA dual therapy) | Serious<sup>b</sup> | Not serious | Not serious | Not serious | None | 4,866 | 3,609 | MD 1.65 lower (2.31 lower to 0.99 lower) |
| SGRQ responders with at least 4 unit decrease in SGRQ score (Triple vs. ICS/LABA dual therapy) | Not serious | Not serious | Not serious | Serious<sup>c</sup> | None | 2,794/5,818 (48.0%) | 2,275/5,475 (41.6%) | OR 1.30 (1.18–1.44) |
| SGRQ responders with at least 4 unit decrease in SGRQ score (Triple vs. LABA/LAMA dual therapy) | Not serious | Not serious | Not serious | Not serious | None | 2,034/4,082 (49.8%) | 975/2,238 (43.6%) | OR 1.20 (1.08–1.34) |
| Mean change from baseline in CAT scores (Triple vs. ICS/LABA dual therapy) | Very serious<sup>e</sup> | Not serious | Serious<sup>f</sup> | Serious<sup>c</sup> | None | 1,632 | 1,562 | MD 0.86 lower (1.29 lower to 0.43 lower) |
| Mean change from baseline in rescue medication use (Triple therapy vs. ICS/LABA dual therapy) | Serious<sup>d</sup> | Serious<sup>e</sup> | Serious<sup>c</sup> | Serious<sup>f</sup> | None | 1,237 | 1,054 | MD 0.3 lower (0.4 lower to 0.2 lower) |
| Adverse events leading to medication discontinuation (Triple therapy vs. ICS/LABA dual therapy) | Not serious | Not serious | Not serious | Not serious | None | 145/5,552 (4.1%) | 123/2,899 (4.2%) | OR 0.96 (0.74–1.25) |
| Adverse events leading to medication discontinuation (Triple therapy vs. LABA/LAMA dual therapy) | Not serious | Not serious | Not serious | Not serious | None | 75/1,548 (4.8%) | 83/1,541 (5.4%) | OR 0.89 (0.65–1.23) |

<sup>a</sup>Two studies had insufficient sample size to produce precise results.

<sup>b</sup>Incomplete outcome data from one study.

<sup>c</sup>One study had sample size less than 300.

<sup>d</sup>Results obtained by meta-analysing only two studies.

<sup>e</sup>Allocation concealment not done. Blinding of result examination not done. Blinding of patients and trial staff not done.

<sup>f</sup>Smaller sample size makes generalizability difficult.

<sup>g</sup>Smaller sample size and wider confidence intervals.

<sup>h</sup>Wider confidence intervals. Results inconsistent across studies.

Table 4. Meta-regression analysis for variables influencing SGRQ scores.

| Covariates | Coefficient | Std Error | 95% CI lower | 95% CI higher | Z-value | 2 sided P-value |
|------------|-------------|-----------|--------------|---------------|---------|----------------|
| Intercept  | 7.6238      | 19.392    | -30.7759     | 46.0234       | 0.39    | 0.6972         |
| Age        | -0.0558     | 0.3637    | -0.7687      | 0.6571        | -0.15   | 0.8781         |
| % Men      | -0.0111     | 0.1099    | -0.2264      | 0.2042        | -0.1    | 0.9194         |
| Fixed versus open combination | -0.7616 | 1.316 | -3.3409 | 1.8177 | -0.58 | 0.5628 |
| Inconsistent versus consistent combination | -0.7783 | 1.2345 | -3.1978 | 1.6413 | -0.63 | 0.5284 |
| Study duration | -0.0285 | 0.0419 | -0.1106 | 0.0535 | -0.68 | 0.4957 |
| FEV1 %predicted | -0.0795 | 0.1316 | -0.3373 | 0.1784 | -0.6 | 0.5464 |
Triple therapy excelled in terms of SGRQ scores, indicating better patient QoL and additional number of patients gaining a 4 or more units improvement in SGRQ score compared to both ICS/LABA and LABA/LAMA therapies. Surprisingly, the advantage of triple therapy over both the dual therapies was almost similar when the SGRQ score and the number of SGRQ responders were taken into account. Nevertheless, two of the included studies (Siler et al., 2015; Sousa et al., 2016) did not show significant improvement in the SGRQ scores.

The patient’s viewpoint is an inseparable part of clinical studies when it comes to the clinical application of drugs. Patient perspectives can be easily measured using CAT scores,

Figure 14. Variation in SGRQ MD scores based on percentage of men.

Figure 15. Variation in SGRQ MD scores based on age.
rescue medication use, and safety parameters like medication discontinuation due to adverse events (Lipson et al., 2017; Perfetto et al., 2015). This study reported moderate improvements in CAT scores for triple therapy versus ICS/LABA dual therapy, indicating moderate patient satisfaction as CAT scores are a reflection of patients’ health status from the patient’s perspective. Dismally, CAT scores did not reach minimally, clinically important differences (MCID) of ≥2-unit change, which is the minimum
difference in score that patients confirm as advantageous or
harmful and is helpful in clinical interpretation of results (Jones et al., 2012;
Kon et al., 2014). On similar lines, none of the included
studies (Siler et al., 2015, 2016; Sousa et al., 2016) reached MCID,
indicating the inability of triple therapy toward complete patient
satisfaction against ICS/LABA dual therapy.

Figure 18. Variation in SGRQ MD scores based on study duration.

Figure 19. Variation in SGRQ MD scores based on FEV1 (%pred).
Table 5. Standard of evidence.

| Outcomes                                                                 | No of trials | Effect size(95% CI) | I² | p-value | GRADE evidence |
|--------------------------------------------------------------------------|--------------|---------------------|----|---------|----------------|
| Average difference from baseline in SGRQ scores (4 trials)              | 4            | -1.65 (-2.31 to -0.99) | 0  | 0.87    | Moderate       |
| SGRQ responders                                                           | 2            | 1.20 (1.08 to 1.34)   | 0  | 0.99    | Moderate       |
| Average difference from baseline in drug cessation                        | 3            | 0.89 (0.65 to 1.23)   | 0  | 0.58    | Moderate       |
| Triple therapy versus LABA and LAMA (12 trials)                          |              |                      |    |         |                |
| Average difference from baseline in SGRQ scores                           | 9            | -1.66 (-1.09 to -1.23) | 0  | 0.44    | Moderate       |
| SGRQ responders                                                           | 6            | 1.30 (1.18–1.44)      | 18 | 0.29    | Moderate       |
| Average difference from baseline in CAT scores                            | 3            | -0.86 (-1.29 to -0.43) | 20 | 0.27    | Very low       |
| Average difference from baseline in rescue medication use                 | 5            | -0.30 (-0.40 to -0.20) | 0  | 0.92    | Very low       |
| Average difference from baseline in percentage of rescue drug free days   | 2            | 6.42 (3.51 to 9.33)   | 62 | 0.010   | Very low       |
| Adverse events resulting in drug cessation                                 | 5            | 0.96(0.74 to 1.25)    | 0  | 0.46    | Low            |

LIMITATIONS

Several limitations can be attributed to this meta-analysis. Most of the trials did not include a run-in period and patients were given triple or dual therapies at baseline, making it difficult to judge whether the efficacy outcomes were due to baseline therapy or previous therapies. Head-to-head analysis was not performed in any of the trials and comparison was made between different medications with distinct devices and frequency schedules. Trials lacked real-world data and all the studies were designed as RCTs. Cost-effectiveness was not performed in any of the trials which could change the overall results. This meta-analysis was focused on patient-reported outcomes and QoL. Hence, other efficacy parameters, like FEV1 change, exacerbations, and incidence of adverse events, were not taken into consideration.

CONCLUSION

Triple therapy improved the QoL and patient-described outcomes compared to ICS/LABA and LAMA/LABA dual therapies in medium to serious COPD patients. Future trials should focus on other efficacy parameters like cost-effectiveness, cost–utility analysis, and stratification of results based on eosinophil levels, phenotypes, age, exacerbation history, etc.

ACKNOWLEDGMENTS

We express our profound gratitude to Dr. Syed Abdul Azeez Basha, the Honorable Principal of Deccan School of Pharmacy, Hyderabad, and Dr. Birendra Shrivastav, Honorable Director of School of Pharmaceutical Sciences, Jaipur National University, Jaipur, Rajasthan, for providing necessary facilities, valuable guidance, and continuous encouragement.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

FUNDING

None.

AUTHOR’S CONTRIBUTION

Syed Aamir Ali: concept, data acquisition, data analysis, statistical analysis, manuscript preparation, manuscript editing, and manuscript review. Dr. Ganesh Narayan Sharma: concept, design, and definition of intellectual content. Dr. Birendra Shrivastav and Dr. Mohd Aleemuddin Naveed: literature search, data acquisition, and data analysis.

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How to cite this article:
Sharma GN, Ali SA, Shrivastav B, Mohd AN. Three-drug therapy versus two-drug therapy for management of patient-reported manifestations and quality of life in chronic obstructive pulmonary disease patients: A meta-analysis. J Appl Pharm Sci, 2020; 10(10):036–049.