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Inhaled therapies for chronic obstructive pulmonary disease: a systematic review and meta-analysis

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ABSTRACT

Objectives To integrate evidence from randomised controlled trials (RCTs) and observational studies on the efficacy of inhaled treatments for chronic obstructive pulmonary disease using network meta-analyses.

Methods Systematic searches MEDLINE and Embase based on predetermined criteria. Network meta-analyses of RCTs investigated efficacy on exacerbations (long-term: ≥20 weeks of treatment; short-term: <20 weeks), lung function (≥12 weeks), health-related quality of life, mortality and adverse events. Qualitative comparisons of efficacies between RCTs and observational studies.

Results 212 RCTs and 19 observational studies were included. Compared with combined long-acting beta-adrenoceptor agonists and long-acting muscarinic antagonists (LABA+LAMA), triple therapy (LABA+LAMA+inhaled corticosteroid) was significantly more effective at reducing exacerbations (long-term 0.85 (95% CI: 0.78 to 0.94; short-term 0.67 (95% CI: 0.49 to 0.92)) and mortality (0.72 (95% CI: 0.59 to 0.89)) but was also associated with increased pneumonia (1.35 (95% CI: 1.10 to 1.67)). No differences in lung function (0.02 (95% CI: −0.10 to 0.14)), health-related quality of life (−1.12 (95% CI: −3.83 to 1.59)) or other adverse events (1.02 (95% CI: 0.96 to 1.08)) were found. Most of the observational evidence trended in the same direction as pooled RCT data.

Conclusion Further evidence, especially pragmatic trials, are needed to fully understand the characteristics of patient subgroups who may benefit from triple therapy and for those whom the extra risk of adverse events, such as pneumonia, may outweigh any benefits.

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Strengths and limitations of this study

- ► Expands on previous research by examining evidence from both randomised controlled trials (RCTs) and real-world data from observational studies.
- ► Distinguishes between short-term and long-term treatment efficacies in terms of exacerbations in order to minimise study selection bias for the length of study.
- ► Subgroup analyses based on patient characteristics were not possible due to inconsistent reporting of these measures and various methods of reporting.
- ► Limited by bias due to systematically differing entry criteria in RCTs or observational studies.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is characterised by respiratory symptoms (cough, dyspnoea, sputum production), structural abnormalities (emphysema, bronchitis) and airflow limitation that is not fully reversible.[1] COPD affects 174 million people worldwide, causing an estimated 3.2 million deaths in 2015.[2] Patients with COPD often experience acute exacerbations, worsening of symptoms leading to a change in COPD management, hospitalisation or death.[3]

Smoking is the most common cause of COPD and smoking cessation is the most effective intervention; however, pharmacotherapy may be used to reduce symptoms and exacerbation risk.[3]

Three main classes of drugs are commonly used alone and in combination to manage COPD: long-acting beta-adrenoceptor agonists (LABA), long-acting muscarinic antagonists (LAMA) and inhaled corticosteroids (ICS). The new National Institute for Health and Care Excellence (NICE) guidance suggests ICS is reserved for people who have one severe or two moderate exacerbations, those people with asthma or features suggesting steroid responsiveness, or in those who remain symptomatic on LAMA+LABA as a trial to see if symptoms improve.[4] The Global Initiative for Chronic Lung Disease strategy (GOLD) now suggests using ICS+LABA or LAMA or LAMA+LABA for patients in group D with ICS particularly for people with blood eosinophil counts ≥300 cells/µL.[5] While treatments should be prescribed in accordance with guidelines, we know this is not always the case.[6 7]

Effectiveness of therapeutic interventions in COPD is primarily determined through randomised controlled trials (RCTs); however,

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RCTs provide little insight into real-world application and effects of therapies that can be gained through observational research.[8] Additionally, a number of systematic reviews and meta-analyses pertaining to inhaled therapies for COPD have been published recently; however, these did not review observational research.[9–11] In this systematic review and network meta-analysis (NMA), we investigate which inhaled therapy strategy is most effective at reducing exacerbation risk, improving lung function, improving health-related quality of life and minimising adverse events in patients with COPD. Here we examine the risk benefit of inhaled therapies, with particular emphasis on triple therapy (LAMA+LABA+ICS) versus LAMA+LABA. We examine evidence from published RCTs and observational studies to provide the largest examination of inhaled COPD therapy effectiveness to date.

METHODS

Our systematic review protocol was drafted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses for Protocols guidelines.[12 13] The protocol was previously published,[14] as such, the methods are only briefly summarised here.

MEDLINE, EMBASE and the Cochrane Library were searched for RCTs, cohort studies and case–control studies comparing six interventions with each other or placebo for individuals with COPD (online supplemental figure S1). Interventions were LABA, LAMA, LABA+LAMA, ICS, LABA+ICS and triple therapy (LABA+LAMA+ICS). Combinations included both open and fixed dose inhalers. The primary outcome was number of moderate-to-severe exacerbations short-term (<20 weeks of treatment) and long-term (≥20 weeks of treatment), with secondary outcomes including lung function as measured by forced expiratory volume in one second (FEV_1; studies with ≥12 weeks of treatment), health-related quality of life measured by St George's Respiratory Questionnaire (SGRQ), mortality and adverse events. Searching of the databases was based on a predefined search strategy.[13]

Two reviewers (ELA and AL) screened titles, abstract and full papers. References of found papers and previous systematic reviews were searched to identify other relevant literature. Data were extracted using the Population, Intervention, Comparison and Outcomes framework and detailed in the study protocol.[14] The primary reviewers (ELA and AL) assessed the risk of bias of each RCT using the 7-item Cochrane Risk of Bias Tool[15] and each observational study using a tool devised for this review based on the CASP system.[16] Any disagreements during the screening and bias review process were settled in consultation with a third reviewer (JKQ).

NMA was used to compare the effectiveness of interventions that have and have not been evaluated directly against each other.[17 18] A frequentist approach to the NMA was used.[19] Network geometry was illustrated using network maps with the size of the nodes being proportional to the number of studies evaluating each class of intervention.[20] The thickness of the edges is proportional to the number of studies of direct comparisons between interventions. After first testing for inconsistency in direct and indirect effects of treatments, a consistency model was used to compare interventions.[19] Mean summary effects and their 95% CIs were calculated and are presented due to the assumption of a common heterogeneity of variance across all pairwise comparisons in an NMA.[20] Surface under the cumulative ranking score (SUCRA) plots were used to illustrate the probability and of each class of treatment being the best, along with the ranking of each class of treatment.[21] Analyses were conducted in Stata V.15 using that software's NMA suite of programs.[22]

Observational studies were described narratively.

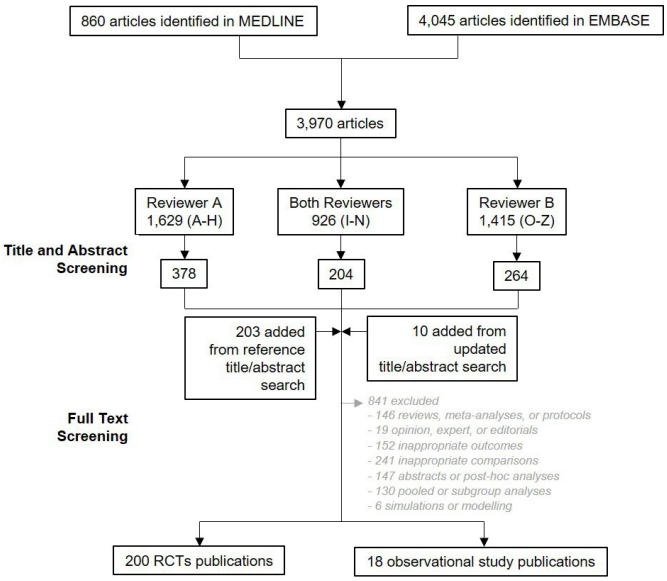


Figure 1 Study flow diagram. Maps the number of publications identified, included and excluded; lists reasons for exclusion at the full-text screening. RCTs, randomised controlled trials.

RESULTS

Study characteristics

We found 231 studies from 218 publications that met our inclusion and exclusion criteria (figure 1; table 1; online supplemental table S1). There were 212 RCTs and 19 observational studies represented in 218 publications, the majority published from 2011 onwards (57%). No studies identified from the grey literature had enough information available in the public domain to be included. The majority of RCTs were multi-continent (48.7%) or European (24.5%), while most observational studies were from Europe and North America (73.7%).

Risk of bias

Of the 200 publications reporting RCTs, two-thirds failed to adequately report their methods for random sequence generation and allocation concealment (online

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Table 1 Characteristics of included studies

Study characteristics	RCT	Observational studies
Number of studies*	N=231	
RCTs	212	~
Crossover	14	~
Open-label†	12	~
Withdrawal	2	~
Observational	~	19
Case–control	~	1
Cross-sectional	~	1
Cohort	~	15
Self-controlled case series	~	2
Year of publication		
1980–1990	0	0
1991–2000	18	1
2001–2010	77	3
2011–2018	117	15
Geographic region		
Africa	1	0
Asia	20	5
Australia/New Zealand	3	0
Europe	52	7
Multi-continent	103	0
North America	28	7
South America	0	0
Not reported	5	0
Setting		
Single centre	13	3
Multicentre (one country)	46	3
Multicentre (multi-country)	129	0
Multicentre (unknown)	3	0
Not reported	21	1
Database	0	11
Duration of treatment/follow-up		
0–≤6 weeks	27	1
>6–≤12 weeks	67	1
>12–≤24 weeks	29	2
>24–≤48 weeks	38	1
>48–≤72 weeks	39	9
>72–≤96 weeks	1	0
>96–≤120 weeks	2	0
>120 weeks	8	3
Event-driven	1	1
Not reported/cross-sectional	0	1

*From 218 publications, multiple studies, including extensions, may be reported in a single publication.
†At least one intervention or control was open-label.
RCT, randomised controlled trial.

supplemental figure S2). Additionally, 15% did not completely report outcomes data and 11% selectively reported data.

Of the 18 publications reporting observational studies, 17% did not clearly describe the representativeness of the exposed (online supplemental figure S3). Questions regarding adequacy of follow-up were raised for 11% of studies and another 11% had potentially insufficient lengths of follow-up.

Patient characteristics

There were no large differences in patient characteristics in RCT intervention groups in terms of average age, proportion of current smokers, pack-years, body mass index (BMI) or baseline health-related quality of life (online supplemental table S2). Disease severity and exacerbation history were inconsistently reported between studies (online supplemental table S1). In observational studies, intervention groups were similar in terms of age and BMI. LABA and LAMA patients had a higher proportion of current smokers and lower quality of life scores than the other intervention groups; however, very small numbers of comparisons reported on these outcomes (online supplemental table S3). Additionally, only one comparison in each treatment group, except LABA where there were no data, reported on pack-year history (online supplemental table S3). RCT participants were younger, with shorter smoking histories, than observational study participants.

NMAs of RCTs

We conducted eight NMAs of included RCTs investigating treatment efficacy in relation to exacerbations, change in FEV_1, change in SGRQ, deaths, adverse events and pneumonia. Network maps and interval plots for each analysis can be seen in figures 2–4. Heterogeneity was such that it was appropriate to pool the data in this way (figure 2). The thickness of the bold lines in each network map represents the number of trials available which compared the intervention nodes. The size of the nodes represents the total number of participants who have taken that intervention (ie, LABA). The larger the area under the SUCRA plotted curve lines, the higher the cumulative probability of that treatment being the best per outcome.

Exacerbations

A total of 219 comparisons of treatment efficacy for moderate-to-severe exacerbations were made, including 159 long-term (≥20 weeks of treatment) efficacy comparisons, representing 169 555 patients, and 60 short-term (<20 weeks of treatment) efficacy comparisons, representing 22 134 patients (figure 2A,B).

Compared with LABA+LAMA, the mean treatment effect of triple therapy on exacerbations long-term was HR 0.85 (95% CI: 0.78 to 0.94) (figure 3A) and short-term was HR 0.67 (95% CI: 0.49 to 0.92) (figure 3B), both statistically significant. In the long-term, triple therapy ranked the most effective at preventing exacerbations

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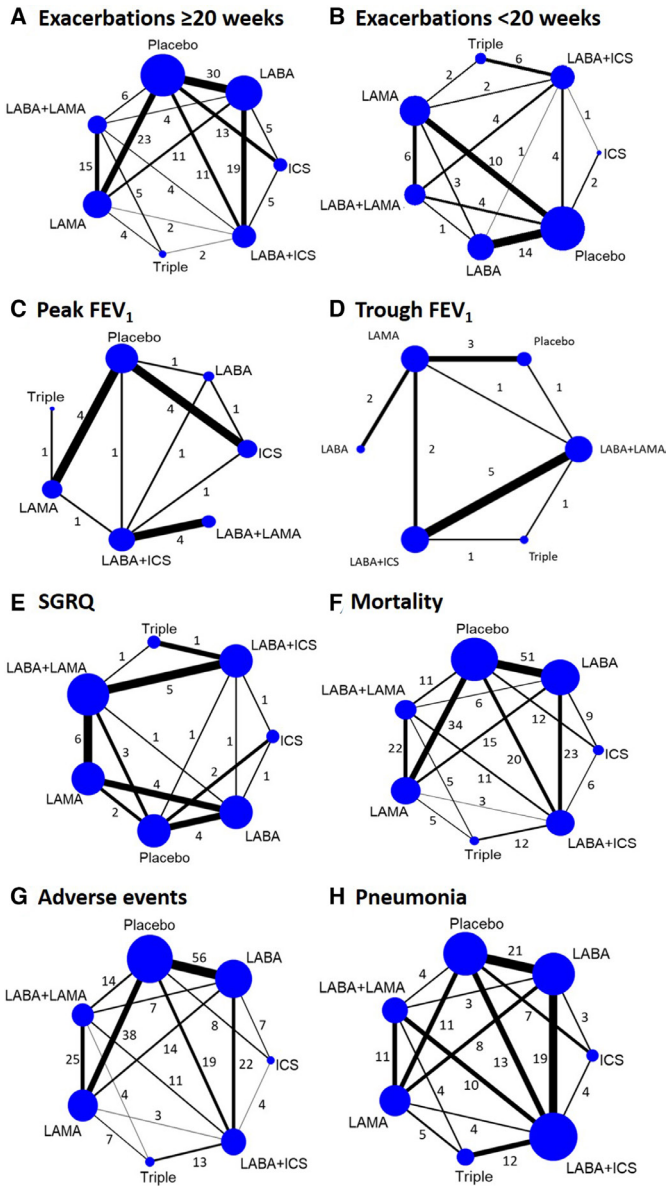


Figure 2 Network maps for (A) exacerbations ≥20 weeks, (B) exacerbations <20 weeks, (C) peak forced expiratory volume in one second (FEV_1) ≥12 weeks, (D) trough FEV_1 ≥12 weeks, (E) St George's Respiratory Questionnaire (SGRQ), (F) mortality, (G) adverse events, (H) pneumonia. P values for overall consistency: (A) 0.81, (B) 0.63, (C) 0.53, (D) 0.99, (E) 0.97, (F) 0.47, (G) 0.89, (H) 0.19. P values for consistency within all comparisons: (A) all >0.08; (B) all >0.08; (C) all >0.09; (D) all >0.90; (E) all >0.19; (F) all >0.045; (G) all >0.15; (H) 0.005 for LABA+LAMA versus triple, 0.002 for LABA+ICS versus triple, remaining all >0.07. ICS, inhaled corticosteroids; LABA, long-acting beta-adrenoceptor agonists; LAMA, long-acting muscarinic antagonists.

(100% chance of being best therapy as determined by SUCRA curves; table 2, online supplemental figure S4); however, in the short-term triple therapy (50.7%) was only slightly more effective than ICS (47.0%).

Surface under the cumulative ranking curve (SUCRA). Exacerbations in studies with a treatment period ≥20 weeks or <20 weeks. Peak and trough forced expiratory volume in one second (FEV_1) in studies with a treatment period ≥12 weeks. St George's Respiratory Questionnaire (SGRQ) in studies with a treatment period ≥4 weeks. Deaths, adverse events, and pneumonia in all studies. Long acting beta-adrenoceptor agonists (LABA). Long-acting muscarinic antagonists (LAMA). Inhaled corticosteroids (ICS).

Change in peak FEV_1

There were 19 comparisons representing 10 620 patients with treatment periods ≥12 weeks (figure 2C). The mean treatment effect of triple therapy on peak FEV_1 was not statistically significantly different from LABA+LAMA at mean difference (MD) 0.02mls (95% CI: −0.10 to 0.14) (figure 3C). In the SUCRA analysis, triple therapy resulted in the greatest improvements in peak FEV_1 (62.5%), followed by LABA+LAMA (36.9%) (table 2, online supplemental figure S5).

Change in trough FEV_1

There were 16 comparisons representing 29 132 patients with treatment periods ≥12 weeks (figure 2C). The mean treatment effect of triple therapy on trough FEV_1 was not statistically significantly different from LABA+LAMA at MD: 0.03mls (95% CI: −0.04 to 0.11) (figure 3D). In the SUCRA analysis, triple therapy resulted in the greatest improvement in trough FEV_1 (78.6%), followed by LABA+LAMA (21.2%) (table 2, online supplemental figure S5).

Change in SGRQ

There were 33 comparisons with SGRQ data, representing 47 103 patients (figure 2E). No statistically significant differences in improving health-related quality of life, as determined by SGRQ, were detected when comparing LAMA+LABA with triple therapy (MD: −1.12 95% CI: −3.83 to 1.59) (figure 3E). The SUCRA analysis indicated that triple therapy led to the greatest improvements in SGRQ (78.8%) (table 2, online supplemental figure S5), followed by LAMA+LABA (17.5%) (table 2, online supplemental figure S5).

Mortality

For all-cause mortality, there were 245 comparisons representing 223 195 patients and 6559 deaths (figure 2F). Compared with LABA+LAMA, the mean treatment effect of triple therapy on mortality was HR: 0.72 (95% CI: 0.59 to 0.89) (figure 4A). In the SUCRA analysis, triple therapy was also ranked most effective in reducing deaths (90.8%) (table 2, online supplemental figure S5), followed by LABA+ICS (9.2%).

Adverse events and pneumonia

There were 252 comparisons of adverse events, representing 204 251 patients (figure 2G). Compared with LABA+LAMA, the mean treatment effect of triple therapy on adverse events was HR: 1.02 (95% CI: 0.96 to 1.08) (figure 4B). In the SUCRA analysis, LABA+LAMA treatment resulted in the fewest adverse events (35.1%),

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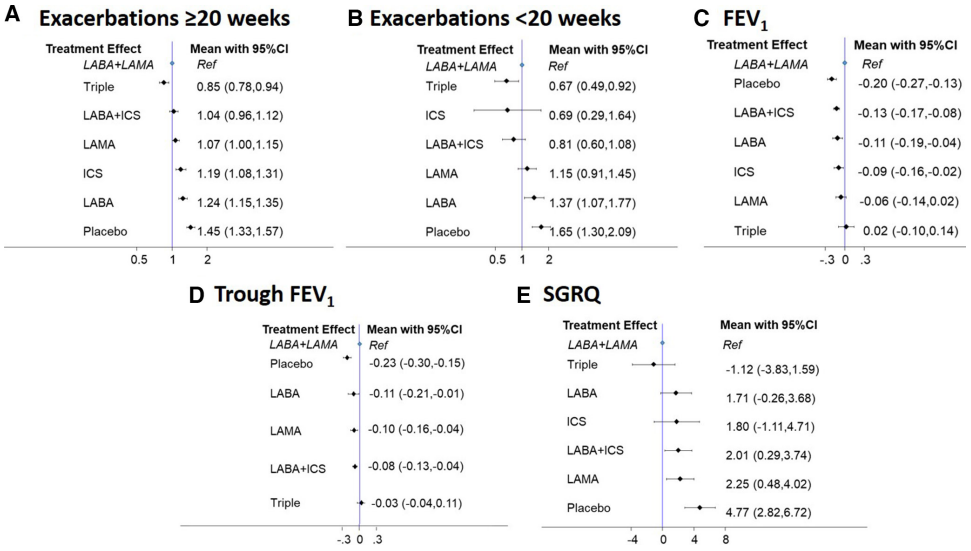


Figure 3 Interval plots for treatment efficacy compared with LABA+LAMA therapy for (A) exacerbations ≥20 weeks, (B) exacerbations <20 weeks, (C) peak forced expiratory volume in one second (FEV_1) ≥12 weeks, (D) trough FEV_1 ≥12 weeks, (E) St George's Respiratory Questionnaire (SGRQ). ICS, inhaled corticosteroids; LABA, long-acting beta-adrenoceptor agonists; LAMA, long-acting muscarinic antagonists.

followed by LAMA (18.5%) and placebo (18.0%) (table 2, online supplemental figure S5).

There were 139 comparisons of pneumonia events, representing 158 043 patients (figure 2H). Compared with LABA+LAMA, triple therapy statistically significantly increased the risk of pneumonia with a mean treatment effect of HR: 1.35 (95% CI: 1.10 to 1.67) (figure 4C). In the SUCRA analysis, LAMA therapy resulted in the fewest pneumonia cases (69.9%), followed by LABA+LAMA (19.6%) (table 2, online supplemental figure S5).

Observational study results

There were not enough data from observational studies to conduct an NMA as the number of comparisons made for each outcome was very small (online supplemental table S1). Here, we narratively summarise 18 publications reporting observational studies.

LAMA versus LABA

Kirchmayer *et al*[23] (n=33 891) found no difference in mortality between new users of LAMA compared with new users of LABA in 1 year of follow-up. Suissa *et al*[24] (n=52 884) found significantly lower risk of pneumonia in LAMA users compared with LABA users in 1 year of follow-up.

LABA+LAMA versus LAMA

Eguchi *et al*[25] (n=38) observed significantly improved FEV_1 following LABA+LAMA treatment compared with LAMA alone after 8 weeks. Eguchi *et al* also observed significantly improved SGRQ following LABA+LAMA treatment as compared with LAMA.

LABA+LAMA versus LABA or LAMA

Tsai *et al*[26] (n=596) found patients treated with LABA+LAMA experienced increased incidence of stroke than patients on either LABA or LAMA.

ICS versus no ICS

McEvoy *et al*[27] (n=187) investigated risk of vertebral fracture comparing patients with COPD who were never corticosteroid users with ICS users. All participants in this study had to have been using a beta-agonist inhaler for at least a year. Inhaled steroid users were those who had had

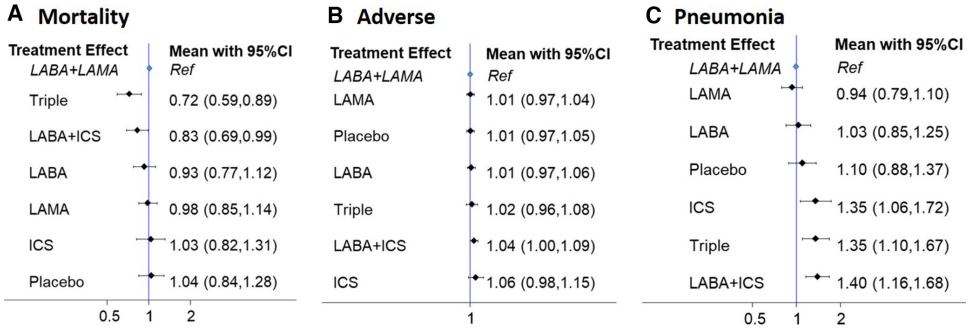


Figure 4 Interval plots for treatment safety compared with LABA+LAMA therapy for (A) mortality, (B) adverse events, (C) pneumonia. ICS, inhaled corticosteroids; LABA, long-acting beta-adrenoceptor agonists; LAMA, long-acting muscarinic antagonists.

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Table 2 Probability of best therapy, SUCRA values and ranking of therapy

Treatment	Probability of being the best therapy (%)	SUCRA value (%)	Mean ranking
Outcome: exacerbations (≥20 weeks)			
LABA	0.0	20	5.9
LAMA	0.0	50	3.8
LABA+LAMA	0.0	80	2.2
ICS	0.0	30	5.1
LABA+ICS	0.0	70	2.9
Triple	100	100	1.0
Placebo	0.0	0	7.0
Outcome: exacerbations (<20 weeks)			
LABA	0	20	5.9
LAMA	0	40	4.8
LABA+LAMA	0.1	50	3.9
ICS	47.0	80	2.3
LABA+ICS	2.2	70	2.6
Triple	50.7	90	1.5
Placebo	0.0	0	7.0
Outcome: change in peak FEV_1 (≥12 weeks)			
LABA	0.1	30	4.9
LAMA	0.5	60	3.1
LABA+LAMA	36.9	90	1.7
ICS	0.0	50	4.3
LABA+ICS	0.0	20	5.5
Triple	62.5	90	1.4
Placebo	0.0	0	7.0
Outcome: change in trough FEV_1 (≥12 weeks)			
LABA	0.2	40	4.2
LAMA	0.0	40	4.1
LABA+LAMA	21.2	80	1.8
ICS	–	–	–
LABA+ICS	0.0	50	3.6
Triple	78.6	100	1.2
Placebo	0.0	0	6.0
Outcome: change in SGRQ			
LABA	0.8	50	4.1
LAMA	0.0	30	4.9
LABA+LAMA	17.5	80	2.0
ICS	2.9	50	4.2
LABA+ICS	0.0	40	4.5
Triple	78.8	100	1.3
Placebo	0.0	0	7.0
Outcome: deaths			
LABA	0.0	60	3.5
LAMA	0.0	40	4.8
LABA+LAMA	0.0	30	5.1

Continued

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Table 2 Continued

Treatment	Probability of being the best therapy (%)	SUCRA value (%)	Mean ranking
ICS	0.0	20	5.6
LABA+ICS	9.2	80	2.0
Triple	90.8	100	1.1
Placebo	0.0	20	5.8
Outcome: adverse events			
LABA	8.1	50	3.7
LAMA	18.5	70	2.9
LABA+LAMA	35.1	80	2.4
ICS	3.1	10	6.1
LABA+ICS	0.1	20	5.9
Triple	17.1	50	4.0
Placebo	18.0	70	2.9
Outcome: pneumonia			
LABA	7.8	70	2.8
LAMA	69.9	90	1.4
LABA+LAMA	19.6	80	2.4
ICS	0.0	20	5.9
LABA+ICS	0.0	10	6.3
Triple	0.0	20	5.8
Placebo	2.7	60	3.6

Exacerbations in studies with a treatment period ≥20 weeks or <20 weeks. Peak and trough forced expiratory volume in one second (FEV_1) in studies with a treatment period ≥12 weeks. St George's Respiratory Questionnaire (SGRQ) in studies with a treatment period ≥4 weeks. Deaths, adverse events and pneumonia in all studies.
ICS, Inhaled corticosteroids; LABA, long-acting beta-adrenoceptor agonists; LAMA, long-acting muscarinic antagonists; SUCRA, surface under the cumulative ranking curve.

a minimum of four puffs a day for at least 6 months in the previous year and minimal use of oral steroids. No further information was available regarding other inhaled medication use. Authors found that use of ICS significantly increased the odds of vertebral fracture.

LABA+ICS versus LABA

Gershon *et al*[28] (n=5594) demonstrated a reduced risk of death associated with LABA+ICS treatment compared with LABA. Mapel *et al*[29] (n=2664) found treatment with LABA+ICS reduced mortality compared with LABA, but this was not significant. Rossi *et al*[30] (n=816) observed no change in FEV_1 or exacerbation rate in patients following withdrawal of ICS to LABA over 6 months.

LABA+ICS versus LAMA

Dalal *et al*[31] (n=4150) found that the number of exacerbations resulting in outpatient visits or rehospitalisation was no different between patients taking LABA+ICS and those taking LAMA within 30 days of an initial COPD-related hospitalisation. Dalal *et al*[32] (n=2849) found that in the 1-year period following a moderate exacerbation, patients taking LABA+ICS experienced a significantly lower risk of exacerbation than those taking LAMA. Dalal *et al*[33] (n=4001) similarly found a lower risk of exacerbation and lower exacerbation-related hospitalisation rates in patients with COPD with comorbid depression/anxiety taking LABA+ICS compared with those taking LAMA.

LABA+ICS versus ICS

Mapel *et al*[29] (n=2664) found that LABA+ICS reduced mortality compared with ICS, but this was not significant.

Triple versus LAMA

Chatterjee *et al*[34] (n=3333) found triple therapy significantly reduced the risk of exacerbations compared with LAMA alone. Feng *et al*[35] (n=113) saw significant improvements in FEV_1 in triple therapy compared with LAMA over their 12-week study period; however, while Hanada *et al*[36] (n=44) saw some improvement in FEV_1 over their 3-year study period in patients treated with triple therapy, it was not significantly different from those seen in LAMA. Feng *et al* also saw significantly improved SGRQ scores after 12 weeks in triple therapy patients compared with LAMA patients.

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Triple versus LABA+LAMA

Buhl *et al*[37] in the DACCORD Study (n=2092 analysed) investigated the effect of triple therapy as compared with LABA+LAMA using pair-matching over 1 year. Significantly fewer patients on LABA+LAMA experienced exacerbations and patients on LABA+LAMA also experienced a significantly lower rate of exacerbations compared with triple therapy.

Triple versus LABA+ICS

In the OUTPUL Study, Ferroni *et al*[38] (n=5717) observed no difference in mild, moderate or severe exacerbation risk between patients treated with triple versus LABA+ICS during their 1-year follow-up; however, when narrowing to a pool of frequent exacerbators, triple therapy significantly reduced their risk of moderate exacerbations. Short *et al*[39] (n=2853) observed reduced risk of exacerbations leading to oral corticosteroid prescription or hospitalisation in patients on triple therapy compared with LABA+ICS during their average follow-up of 4.65 years. Perng *et al*[40] (n=46) saw significantly improved FEV_1 following the addition of LAMA to LABA+ICS and a significant decrease following the withdrawal of LAMA 4 weeks later. The larger and longer Short *et al* study did not see any clinically significant changes in FEV_1 from baseline in either the triple or LABA+ICS treatments. Perng *et al*[40] saw significant improvements in SGRQ during triple therapy over 4 weeks compared with LABA+ICS. Short *et al*[39] observed significantly decreased all-cause, respiratory and cardiovascular mortality in patients receiving triple therapy compared with patients receiving LABA+ICS.

DISCUSSION

Summary of findings

Ours is the largest meta-analysis, representing 255 857 patients, to investigate the effectiveness of inhaled COPD therapies, including triple therapy. Triple therapy was statistically significantly more effective at reducing moderate-to-severe exacerbations and mortality compared with LABA+LAMA at the expense of increased pneumonia risk. There was not a significant difference between the two therapies in improving peak or trough FEV_1, improving health-related quality of life or reducing adverse events. Observational evidence generally supports the RCT NMA, particularly favouring triple therapy compared with LAMA or LABA+ICS for reducing exacerbations, improving FEV_1 and improving quality of life according to SGRQ. However, there is some evidence that certain patient groups may benefit from some therapies more than others.

Relevance to previous studies

Exacerbations

Triple therapy significantly reduced moderate-to-severe exacerbations by 33% in the short-term, attenuating to a 15% reduction in the long-term, compared with LABA+LAMA. These results are in line with previous meta-analyses that found triple therapy more effective than LABA+LAMA in reducing moderate-to-severe exacerbations, though without stratifying for treatment duration.[10 11 41 42] The attenuation of triple therapy effectiveness in reducing exacerbations over long treatment periods has been seen in individual trials, such as IMPACT[43] and TRIBUTE.[44] However, it is worth noting that the inclusion criteria for IMPACT and TRIBUTE resulted in more severe patients with a history of exacerbations being selected, something we could not take into account in our analysis due to heterogeneity in reporting detail from other studies. Our results similarly demonstrate that the benefits of triple therapy wane in the long-term (≥20 weeks); however, triple therapy remained statistically more effective than LABA+LAMA.

The agreement between our meta-analysis of RCTs and observational studies with regards to treatment effectiveness in reducing exacerbations was mixed. The DACCORD Study observed significantly lower rates of exacerbations in patients taking LABA+LAMA compared with those on triple therapy.[37] This disagrees with our combined RCT evidence where triple therapy was shown to be more effective than LABA+LAMA in reducing exacerbations. Rossi *et al*[30] found no difference, and Dalal *et al*[31] found no difference in exacerbation-related readmission within 30 days of initial COPD-related hospitalisation between LABA+ICS and LAMA-treated patients. This is in-line with our meta-analysis results showing that there was no statistically significant difference between LABA+ICS and LAMA in short-term treatment. In longer-term observational studies, LABA+ICS proved more effective at reducing exacerbations than LAMA[32 33]; however, in our meta-analysis there was no statistically significant difference between the two treatments in the long-term, though LABA+ICS was ranked higher than LAMA in SUCRA analysis. With a variable follow-up period, up to 1 year with a median of 20 weeks, Chatterjee *et al*[34] found triple therapy significantly more effective at reducing exacerbations than LAMA. In the short-term, our meta-analysis found no statistically significant difference between triple therapy and LAMA; however, in the long-term, triple therapy was statistically more effective than LAMA. In line with our meta-analysis, observational studies comparing triple therapy and LABA+ICS found no significant difference in effectiveness reducing exacerbations.[38 39] More pragmatic trial data are needed before any conclusions on the relative effectiveness of these therapies can be made.

Change in FEV_1

There was no statistically significant difference between triple therapy and LABA+LAMA in improving peak FEV_1. No previous reviews have assessed the impact of inhaled therapies on peak FEV_1. Recent meta-analyses reported that triple therapy was significantly more effective than LABA+LAMA at improving trough FEV_1.[10 11] According to table 2 above, SUCRA analysis showed triples were 78.6% likely to be the best therapy for trough FEV_1. However,

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in our analyses the two therapies were not statistically different. We retrieved limited data comparing triple and dual therapies for trough FEV_1, and results from additional trials such as the ETHOS trial[45] are required with trough FEV_1 as an outcome measure which may help substantiate these head-to-head combination treatment comparisons.

Health-related quality of life

There was no statistically significant difference between LABA+LAMA and triple therapy, LABA or ICS in improving health-related quality of life as measured by the SGRQ. As in our analysis, Eguchi *et al*[25] observed LABA+LAMA as more effective and Feng *et al*[35] observed triple therapy as more effective than LAMA in improving health-related quality of life. Perng *et al*[40] observed significant improvement in health-related quality of life following triple therapy compared with LABA+ICS; while our analysis did not reach statistical significance, triple therapy was ranked higher than LABA+ICS in SUCRA analysis.

Mortality

Triple therapy statistically significantly reduced all-cause mortality by 28% compared with LABA+LAMA and was ranked the best by SUCRA analysis. Triple therapy was 90.8% likely to be the best therapy for all-cause mortality (table 2). LABA+ICS also reduced all-cause mortality significantly by 17% compared with LABA+LAMA. As in our meta-analysis, Kirchmayer *et al*[23] observed no difference in mortality between LABA and LAMA users. Gershon *et al*[28] found a reduced risk of death with LABA+ICS treatment compared with LABA, while Mapel *et al*[29] observed the same direction of efficacy it was not significant. Our results are more in-line with Mapel *et al*, showing LABA+ICS as more effective than LABA at reducing mortality, but the effect not reaching statistical significance. As in Mapel *et al*,[29] we did not see a statistically significant difference in mortality between LABA+ICS and ICS. We did not see a statistically significant difference between triple therapy and LABA+ICS in mortality reduction, unlike Short *et al*[39] in their observational study.

Adverse events

There was no statistically significant difference between any of the treatments, including placebo, and LABA+LAMA in terms of reducing adverse events. LABA+LAMA was the most effective treatment for reducing adverse events, followed by LAMA. Similarly, Cazzola *et al*[10] found no difference in the occurrence of severe adverse events between LABA+LAMA and triple therapy; however, unlike us, they did find a significant difference between triple therapy and monotherapies. Treatment with LABA+LAMA was not statistically different in terms of reducing pneumonia events than LABA, LAMA or placebo. Based on the SUCRA rankings, LAMA was most effective at reducing pneumonia, followed by LABA+LAMA. Observationally, Suissa *et al*[24] found LAMA more effective at reducing pneumonia than LABA; however, there was no statistical difference between the two therapies in our meta-analysis. Treatment with ICS, triple therapy and LABA+ICS statistically significantly increased the number of pneumonia events experienced compared with LABA+LAMA. This is in-line with recent meta-analysis findings[10] and suggests that ICS increases pneumonia risk. There is evidence that pneumonia risk differs with different types of ICS, and there are other risks associated with ICS use such as developing type 2 diabetes mellitus or osteoporosis, but these were not explored here.[46] Given the heterogeneity in detail given for the studies included, we cannot tell from this work which patients are at most risk and so a risk/benefit decision needs to be made on an individual patient basis.

Patient characteristics

Some of our findings differ from other recent systematic reviews, and some findings that are statistically significant may not be clinically significant. There is evidence that patient characteristics may play an important role in therapeutic efficacy, including exacerbation history and eosinophils; two key characteristics that we could not include here, and the heterogeneity in the literature has likely contributed to the differences in advice from GOLD and NICE. Additionally, the OUTPUL[38] observational study found no difference in risk for exacerbation comparing triple therapy to LABA+ICS; however, when narrowed to a pool of frequent exacerbators, they saw a significantly reduced risk for moderate exacerbations in triple therapy patients.

Unfortunately, few studies, RCT or observational, report outcomes based on subgroup characteristics such as sex, smoking status or exacerbator phenotype, making it extremely difficult to tease out the limits of therapeutic efficacy. There is an urgent need for prospective studies to identify these subgroups of patients as doing so will aid in the balancing of risks and benefits integral to clinical decision making.

Outcomes

Several additional important endpoints that were not measured or analysed in this report on inhaled therapies for COPD would be useful to investigate in the future. These include: (1) rates of medication adherence over the trial periods as these may vary between single, dual and triple therapies; (2) rates of COPD hospitalisations; (3) rates of pneumonia hospitalisations; and (4) to compare therapies in terms of minimal clinical important differences and numbers needed for treatment benefit or harm. Additionally, there are a number of topics, beyond the scope of this review, which may be of interest for future reviews. Particularly of interest may be: (1) the role of dose/duration of treatment on therapeutic efficacy, (2) the role of COPD severity on therapeutic efficacy, and (3) the interplay between inhaled therapies and other COPD medications, such as nebulised drugs,

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mucolytics,[47] antibiotics and inhaled colomycin,[48 49] and phosodiesterase-4 inhibitors.[50]

Strengths and limitations

Our work expands on previous research by examining the relationship between RCT evidence and real-world data from observational studies. To date, analyses from the NICE have not used real-world data.[51] Additionally, our work distinguishes between short-term and long-term treatment efficacy in terms of exacerbations in order to minimise study selection bias for the length of study.

The majority of RCTs reported on outcomes adequately, minimising risk of bias; however, the majority of RCTs also failed to adequately report their methodology for random sequence generation and allocation concealment, making it impossible to accurately gauge their risk of bias in these areas. Further expansion of methods in supplement material and/or editorial boards requiring RCTs provide adequate information for risk of bias assessment per Cochrane recommendations[15] would strengthen the health-related quality of RCT reporting.

In their pairwise meta-analysis of exacerbations, Cazzola *et al*[10] determined that the IMPACT[43] and WISDOM[52] Studies were contributing heavily to heterogeneity, but on removing those studies from their analysis the effect of triple therapy versus LABA+LAMA on moderate-to-severe exacerbations remained significant, though attenuated relative risk 0.78 (95% CI: 0.69 to 0.89) in complete analysis versus 0.87 (95% CI: 0.82 to 0.92) in sensitivity analysis.[10] Statistically, we found little evidence of inconsistency in our results when we grouped the drugs together in classes (see p values for consistency in figure 2).

The problem of bias due to systematically differing entry criteria in RCTs or observational studies was not something we could prevent beyond the application of our inclusion and exclusion criteria. Subgroup analysis based on patient characteristics such as exacerbation history and disease severity were not possible due to inconsistent reporting of these measures and various methods of reporting, however we know from the inclusion and exclusion criteria of studies that there is a large amount of variation in these characteristics. For example, in relation to exacerbation history: some papers report number of patients with 0, 1, 2+exacerbations in year prior, others report average exacerbation rate in the year prior, others report total number of exacerbations in year prior and others did not report. While each of these measures is informative in its own way, it is not possible to pool them. Similarly, the majority of studies reported moderate and severe exacerbations together; though definitions varied, most required a change in treatment and/or hospitalisation.

Oba *et al*[53] analysed data based on groups of 'high-risk' and 'low-risk' patients, where 'high risk' are those patients in trials that explicitly required participants to have had at least one exacerbation in the year prior to the study; all other studies would be considered 'low risk'. We decided against a similar approach due to concerns that a disproportionate number of 'high-risk' patients would be classed as 'low risk' due to study inclusion criteria allowing for the participation of patients regardless of their exacerbation history. We are also aware given the amount of grey literature we came across in which we could not obtain the details we needed for inclusion that our review will suffer from publication bias.

Twenty-five out of the 231 trials evaluated the efficacy of the inhaled triple therapy and of these, only six investigated the three inhaled classes of drugs (inhaled anti-muscarinics, beta2-agonists and glucocorticoids) administered through a single inhaler.[38 43 44 54–56] This reflects the novelty in the method of delivery of the three types of medication, while the other 18 RCTs evaluate the inhaled triple therapy administered by multiple inhalers. Therefore, there is a bias in data reporting for triple therapy towards comparisons using multiple inhalers for triple therapy.

Our quality analysis of observational studies did not focus on the mandatory reporting of baseline characteristics, issues of adherence to medication according to treatment group or crossing over of individuals into alternate arms, and therefore judgement on quality of observational trials may be exaggerated. These factors should be considered in future analyses and considered when reviewing the results.

CONCLUSIONS

Triple therapy proved most effective in reducing moderate-to-severe exacerbations compared with LABA+LAMA; however, with the potential risk of increasing pneumonia risk. Evidence from RCTs and observational studies suggest certain patient groups may benefit from triple therapy, such as those with a high eosinophil count or frequent exacerbators, however studying this in detail was not possible given the heterogeneity of reporting from other studies. This highlights the need for more prospective trials to address the risk/ benefit of triple therapy in treating people with COPD in order to fully understand the characteristics of patient subgroups whom may benefit from triple therapy and those for whom the extra risk of adverse events may outweigh any benefits.

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Contributors ELA coordinated the review and drafted the manuscript. ELA and AL screened citations and full-text articles, abstracted data and conducted risk of bias assessment. JP conducted the network meta-analyses. ELA qualitatively compared trial and real-world data. ELA, AL, JP, MP, SD, HV, and JKQ contributed to the initial scoping discussions of the research and participated in decisions regarding the risk of bias assessment strategies. ELA, AL, JP, HV, MP, SD and JKQ reviewed the final manuscript. JKQ is the guarantor of the review.

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