Original Paper

Discovering the Relative Efficacy of Inhaled Medications for Chronic Obstructive Pulmonary Disease: Multiple Treatment Comparisons

Ying Zhu^a Tong Zhang^a Haiyan Li^b YangYang^c Qiong Chen^d Lei Kong^e Bo Tai^f

^aDepartment of Geratology, ^bDepartment of Radiology, First People's Hospital of Yunnan Province,

^cFaculty of Life Science and Technology, Kunming University of Science and Technology, Kunming,

Yunnan, ^dLincang Health School of Yunnan Province, Lincang, Yunnan, ^eSchool Infirmary of Kunming

Medical University, ^fDepartment of Neurosurgery, First People's Hospital of Yunnan Province, Kunming, Yunnan, China

Key Words

Chronic obstructive pulmonary disease • Inhaled corticosteroids • Long-acting Beta 2-agonist • Long-acting muscarinic antagonist • tFEV1 • St George's Respiratory Questionnaire

Abstract

Background: Chronic obstructive pulmonary disease (COPD) is managed by three major classes of inhaled medications: inhaled corticosteroids (ICS), long-acting Beta 2-agonist (LABA), long-acting muscarinic antagonist (LAMA). Single inhaled medication is usually replaced by combined inhaled medications for efficacy enhancement. However, this practice should be supported by clinical evidence for large-scale implementations. **Methods:** The relative efficacy of inhaled medications is determined by three endpoints: changes in the trough forced expiratory volume in 1 second (tFEV₁), changes in the St George's Respiratory Questionnaire (SGRQ) score and the proportion of SGRQ responders which represents a reduction in SGRQ total score at week 24 of ≥ 4.0 . A total of 76 eligible studies were identified in PubMed and Embase. Relevant data were extracted for the purpose of evidence synthesis. Then, raw mean differences (MD) and odds ratios (ORs) were produced by using the network meta-analysis. **Results:** Patients with ICS + LABA, ICS + LABA + LAMA, LABA, LABA + LAMA, LAMA exhibited significant increases in the tFEV1 compared to those with placebo ($P < 0.05$). Moreover, patients with ICS + LABA + LAMA exhibited the largest increase in the average tFEV1 and the largest decrease in the average SGRQ scores compared to those with placebo. COPD patients with ICS + LABA + LAMA were far more likely to achieve a significant reduction in the SGRQ scores compared to those with placebo or other inhaled medications ($OR > 1$). **Conclusions:** The combined inhaled medication of ICS + LABA + LAMA may be more efficacious than other inhaled medications for COPD patients.

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Y. Zhu and T. Zhang are first authors.

Bo Tai

Department of Neurosurgery, First People's Hospital of Yunnan Province,
No. 157 Jinbi Road, Xishan District, Kunming, 650032, Yunnan (China)
Tel./Fax +86 0871-63638544, E-Mail qianwdr@126.com / taibo1976@163.com

Introduction

Chronic obstructive pulmonary disease (COPD) is an irreversible disease which is characterized by a progressive decline in pulmonary functions. COPD is often accompanied by some respiratory symptoms including dyspnea, cough and sputum production [1]. The high prevalence of COPD has become a global issue due to the large aging population [2]. A wide variety of inhaled medications have been developed and they appear to have different levels of efficacy with respect to lung function restoration and COPD symptom control [3, 4].

Current guidelines made by the Global Initiative for COPD (GOLD) recommend the use of inhaled medications such as long-acting β agonist (LABA) or long-acting muscarinic antagonist (LAMA) for symptomatic patients who suffered from moderate or severe COPD [5]. Both LAMA (Tiotropium, Glycopyrronium, Aclidinium Bromide) [6] and LABA (Salmeterol, Formoterol, Indacaterol) have been approved as inhaled medications for COPD patients [7, 8]. Alternatively, LAMA and LABA can be combined with each other in order to enhance the efficacy.

The current medication strategy for COPD patients is based on disease classification, but combined inhaled medications may be introduced if single inhaled medication is not effective [9]. For instance, LABA + LAMA may be more efficacious than single inhaled medication, but such combined medications have not been thoroughly investigated [10, 11]. The newly-adopted disease classification approach takes account both symptoms and exacerbation risks. As a result, combined inhaled medications may be introduced if patients exhibited specific symptoms. For instance, inhaled corticosteroids (ICS) can be combined with LABA or LAMA in the case that COPD is accompanied with asthma [12]. Also, ICS + LABA is able to suppress the exacerbation of COPD for those who had low forced expiratory volume [13]. Currently, incorporating ICS, LABA and LAMA has become popular in clinical practices. However, no conclusive evidence has been disclosed from the current literature and few systematic reviews have been performed to assess its relative efficacy [14, 15].

Three popular efficacy endpoints were selected in order to determine the relative efficacy of inhaled medications: trough forced expiratory volume in 1 second (tFEV₁), St George's Respiratory Questionnaire (SGRQ) score and the proportion of SGRQ responders [16]. The implementation of network meta-analysis (NMA) may produce extra evidence which cannot be achieved by using conventional meta-analysis.

Material and Methods

Literature retrieval strategy

We began our research by conducting a systematic review of approved inhaled medications that are classified as ICS, LABA or LAMA. The following inhaled medications are included in our literature search and review process: aclidinium, arformoterol, beclomethasone, formoterol, budesonide, tiotropium, fluticasone furoate, vilanterol, fluticasone propionate, salmeterol, fluticasone, glycopyrronium, indacaterol, ipratropium, mometasone furoate, olodaterol, umeclidinium and vilanterol. Then, a rigorous literature searching strategy was designed and input into online databases including PubMed and Embase in order to retrieve relevant studies. The above searching process was conducted by two reviewers independently and only studies published in English were included. Additional literature search was conducted by reviewing the reference list of retrieved articles and key cited references were included in our study if they appeared to be relevant to our research objectives. The title, abstract and content of retrieved articles were sequentially reviewed by two independent reviewers. Any discrepancy with respect to literature search, identification and screening was solved by discussion.

Determine the eligibility of studies

We designed the following eligible criteria for studies to be included in our NMA: 1) double-blind randomized clinical trials (RCTs) that compared at least one of the above inhaled medications; 2) sufficient information with respect to tFEV₁, SGRQ scores or SGRQ responders; 3) studies carried out between 2005

and 2015 with study duration ranging from four weeks to two years; 4) studies published in English. Duplicated studies, case reports, reviews and studies without sufficient data were excluded from the eligible list.

Selection of clinical outcomes

The trough forced expiratory volume in 1 second (tFEV₁) is a popular measurement that can be used to assess lung function and monitor the progress of COPD over time and therefore it was selected as the primary efficacy outcome [17]. A significant increase in the tFEV₁ during the study period indicates significant improvements in lung functions. Since the included studies disclose the study duration instead of the medication duration, we assume the two to be approximately equal to each other. The second key outcome of our interest is the SGRQ score which is a standardized self-evaluated questionnaire for measuring both health status and well-being of patients with airway disease [18]. A total of 50 questions were incorporated in the SGRQ, which simultaneously quantifies disease severity, disease syndrome and life quality of patients. The score of SGRQ ranges between 0 and 100. A score of zero indicates that COPD does not have any effect on the daily activity of patients whereas a score of 100 indicates that COPD significantly impairs the well-being of COPD patients. More importantly, a change in SGRQ score ≥ 4 units is defined as clinical significant. We also selected the binary outcome of SGRQ responders: whether a COPD patient exhibited a reduction in SGRQ score ≥ 4 units during the study period. The above three endpoints were selected in three broad aspects: COPD symptoms control, lung function restoration and improvements in life quality.

Data extraction

Once the eligible study list was determined, data extraction was conducted by two independent reviewers and the corresponding results were examined by a third reviewer to ensure accuracy. A data extraction spreadsheet was used to record the following information of each eligible study: first author, publication year, included treatments, treatment classification, dose, study duration, sample size, average age of subjects, average pre-dose tFEV₁ in both liters and percentages, tFEV₁ time, average tFEV₁ at baseline and at endpoint in liters and their corresponding sample standard deviations (SD), average changes in the tFEV₁ over the study period (tFEV₁ at endpoint - tFEV₁ at baseline) and sample SD, SGRQ time, average SGRQ at baseline, average SGRQ at endpoint, average changes in SGRQ (average SGRQ at endpoint - average SGRQ at baseline) and the proportion of SGRQ responders in each study group. Missing data were estimated or imputed by using the approach described by Wan et al. [19].

Statistical analysis

We adopted the Bayesian Framework for implementing NMA and three outcomes were considered for evidence synthesis: changes in tFEV₁ from baseline, changes in SGRQ scores from baseline and the proportion of SGRQ responders. The implementation of NMA was performed by using the R statistical software (Version 3.2.4, The R project for statistical computing) in conjunction with the GEMTC package, and a random-effects model for each outcome is assumed to be appropriate. Moreover, a consistency model is simulated from the GEMTC package by using the Markov Chan Monte Carlo (MCMC) approach. Raw mean difference (MD) was used to synthesize evidence for continuous outcomes such as tFEV₁ and SGRQ scores, whereas odds ratios (ORs) were used to compare the likelihood of SGRQ responders who are treated by two treatments. The 95% credible interval (CrI) for each summary statistics was used to assess the statistical significance of each summary effect. Ranking of interventions was performed by comparing their corresponding surface under cumulative ranking area (SUCRA). Consistency between direct and indirect evidence with respect to a particular comparison was assessed by using the node splitting approach [20]. Finally, small study effects and publication bias which may affect the validity of NMA were examined using the funnel plot. The significant level of 0.05 was set for all statistical tests.

Results

Study retrieval and selection

A total of 6,324 articles were identified by using the prescribed searching strategies. The number of articles retrieved from PubMed and Embase are 3,366 and 2,958, respectively. After the identification of articles, the corresponding results were examined before literature

screening. We also attempted to identify other records such as unpublished articles from other sources. However, no additional records were identified. Then, we started the literature screening process by removing all duplicated articles (2,367 duplicates). Once all duplicated articles were removed, we examined the title and abstract of the remaining 3,957 articles in order to determine whether they are relevant to our research topics and 3,366 articles appeared to be irrelevant. As a result, only 592 articles passed the initial screening process and were subject to full-text review. Then, the eligibility criteria were adopted in the process of full-text review. Any articles that do not fulfill the eligibility criteria or those without access to full-text content were removed and this led to an exclusion of 515 studies. Finally, 76 studies passed the entire literature retrieval and selection process [16, 21-95]. The above process was repeated for several times in order to ensure the accuracy of the eligible study list. Two independent reviewers were responsible for conducting this process and their results were cross-examined.

Study characteristic

The characteristics of 76 eligible studies are displayed in Table 1. Study information is summarized as author, publication year, trial ID, GOLD stage of patients, inhaled medication compared in each study, study duration and the corresponding clinical outcomes assessed. Evidence obtained from direct or indirect comparisons can be illustrated by network plots. A closed-loop network is formed if all nodes within a network can be connected by either solid or dashed lines. The total number of patients included in our analysis with respect to $tFEV_1$, SGRQ and SGRQ responders are 27,995, 19,702 and 36,152, respectively. The eligible studies cover all patients with GOLD stage I-IV. The minimum and maximum study duration is four weeks and four years, respectively. As suggested by Figure 1, comparators (inhaled medications) with respect to the endpoint of $tFEV_1$, SGRQ and SGRQ all form closed-loop networks. Therefore, both direct and indirect evidence can be synthesized by using the approach of NMA.

Comparing different inhaled medications by using $tFEV_1$

Since $tFEV_1$ measures the overall performance of lung function, a significant increase in $tFEV_1$ indicates the efficacy of inhaled medications. Average changes in $tFEV_1$ from baseline to endpoint for each eligible study were extracted and then a summary effect comparing the raw mean difference was produced by NMA. A summary effect which is significantly larger than zero suggests that one inhaled medication (single or combined) is potentially more efficacious than another and vice versa. COPD patients with five inhaled medications exhibited significant increase in the average $tFEV_1$ compared to those with placebo (ICS + LABA: 0.11 liters, 95% CrI = 0.08-0.15 liters; ICS + LABA + LAMA: 0.22 liters, 95% CrI = 0.16-0.29 liters; LABA: 0.07 liters, 95% CrI = 0.04-0.10 liters; LABA + LAMA: 0.16 liters 95% CrI = 0.13-0.19 liters; LAMA: 0.10 liters, 95% CrI = 0.07-0.13 liters). Our NMA suggests that COPD patients with ICS + LABA + LAMA exhibited the largest increase in the average $tFEV_1$ (Table 2, Fig. 2). Moreover, COPD patients with ICS + LABA + LAMA exhibited significant increase in the average $tFEV_1$ compared to those with other inhaled medications (all raw mean difference > 0). On the other hand, patients with LABA exhibited a significant decrease in the average $tFEV_1$ in reference to those with the other four mechanisms (all raw mean difference < 0; Table 2, Fig. 2).

Comparing different inhaled medications by using SGRQ scores

SGRQ score ranging from 0 to 100 measures how COPD affects the well-being of patients. A significant reduction in SGRQ score indicates the well-being of patients has been significantly improved by inhaled medications over the study duration. Patients with three inhaled medications exhibited significant reduction in the SGRQ scores compared to those with placebo: ICS + LABA (-3.20, 95% CrI = -5.13 to -1.29), ICS+LABA+LAMA (-3.69, 95% CrI = -6.95 to -0.41) and LABA (-2.03, 95% CrI = -3.64 to -0.45). Although ICS+LABA+LAMA appears to be significantly more efficacious than the placebo with respect to SGRQ, there

Table 1. Characteristics of the included studies. ICS inhaled corticosteroid; LABA long-acting β_2 -agonist; LAMA long-acting muscarinic antagonists; tFEV1 trough forced expiratory volume in 1 second; SGRQ St George's Respiratory Questionnaire; GOLD Global Initiative for COPD

Author, Year	Trial ID	GOLD stage	Inhaled medication (single or combined)	Duration	Endpoints
Buhl, 2015 [29]	NCT01431274	2-4	LABA; LAMAL; LABA+LAMA	52 wks	Trough FEV1, SGRQ, SQRG Responders
Zhong, 2015 [21]	NCT01709903	2-3	LABA+LAMA; ICS+LABA	26 wks	Trough FEV1, SGRQ
Zheng, 2015 [22]	NCT01636713	2-4	LABA+LAMA; Placebo	24 wks	Trough FEV1, SGRQ, SQRG Responders
Singh, 2015 [23]	NCT01822899	-	LABA+LAMA; ICS+LABA	12 wks	Trough FEV1, SGRQ
Siler, 2015 [24]	NCT01957163	2-4	ICS+LABA+LAMA; ICS+LABA	12 wks	Trough FEV1, SGRQ, SQRG Responders
Maleki-Yazdi, 2015 [25]	NCT00452400	2-3	LABA; Placebo	4 wks	Trough FEV1
Lee, 2015 [26]	NCT01636401	2-3	LAMA; Placebo	12 wks	Trough FEV1, SGRQ
Ichinose, 2015 [16]	NCT00824382	2-4	LABA; Placebo	4 wks	Trough FEV1
Frith, 2015 [27]	NCT01513460	2-3	ICS+LABA+LAMA; ICS+LABA+LAMA	12 wks	Trough FEV1, SGRQ
Donohue, 2015 [28]	NCT01817764; NCT01879410	2-3	LABA+LAMA; ICS+LABA	12 wks	Trough FEV1
Buhl, 2015 [30]	NCT01120717	2-3	LABA+LAMA; LABA+LAMA	26 wks	SGRQ, SQRG Responders
Beeh, 2015 [31]	NCT01559116	2-4	LABA; LAMA	6 wks	Trough FEV1
Aalbers, 2015 [32]	NCT01040403	2-3	LABA; LABA+LAMA	4 wks	Trough FEV1
Trivedi, 2014 [34]	NCT01387230	2-4	LAMA; LAMA	12 wks	Trough FEV1, SGRQ
Pepin, 2014 [36]	NCT01395888	2-3	ICS+LABA; LAMA	12 wks	Trough FEV1
Ohar, 2014 [37]	NCT01110200	2-3	ICS+LABA; LABA	26 wks	Trough FEV1
Donohue, 2014 [42]	NCT00909779	2-3	LABA; Placebo	52 wks	Trough FEV1
ZuWallack, 2014 [33]	NCT01694771; NCT01696058	2-3	LAMA; LABA+LAMA	12 wks	Trough FEV1, SGRQ, SQRG Responders
Celli, 2014 [43]	NCT01313637	2-4	LABA+LAMA; LABA	24 wks	Trough FEV1, SGRQ, SQRG Responders
Singh, 2014 [35]	NCT1462942	-	LABA+LAMA; LABA	24 wks	SGRQ
Maltais, 2014 [38]	NCT01323660; NCT01328444	1-4	LABA+LAMA; LABA+LAMA	12 wks	Trough FEV1
Maleki-Yazdi, 2014 [39]	NCT01777334	2-4	LABA+LAMA; LABA	24 wks	Trough FEV1, SGRQ, SQRG Responders
Feldman, 2014 [40]	NCT00931385	2-4	LABA; Placebo	6 wks	Trough FEV1
	NCT00932646	2-4	LABA; Placebo	6 wks	Trough FEV1
D'Urzo, 2014 [41]	NCT01437397	2-3	LABA+LAMA; LABA	24 wks	SGRQ, SQRG Responders
Fukuchi, 2013 [44]	NCT01069289	2-3	ICS+LABA; LABA	12 wks	SGRQ, SQRG Responders
Donohue, 2013 [45]	NCT01313650	3-4	LABA+LAMA; LABA	24 wks	SGRQ, SQRG Responders
Decramer, 2013 [46]	NCT00845728		LABA; LABA	52 wks	Trough FEV1, SGRQ, SQRG Responders
Cooper, 2013 [47]	NCT00525512	2-3	LAMA; Placebo	2 yrs	SGRQ
Bateman, 2013 [48]	NCT01202188	2-3	LABA+LAMA; LABA; Placebo	26 wks	SGRQ
Tashkin, 2012 [49]	NCT00383435; NCT00383721	2-4	ICS+LABA; ICS; LABA; Placebo	52 wks	SGRQ, SQRG Responders
Sharafkhaneh, 2012 [50]	NCT00419744	2-4	ICS+LABA; LABA	52 wks	Trough FEV1, SGRQ
Scherr, 2012 [51]	NCT00860938	1-2	ICS+LABA; LABA	16 wks	SGRQ
Lotvall, 2012 [52]	NCT00731822	2-3	ICS+LABA; Placebo	4 wks	Trough FEV1
Kerwin, 2012 [53]	NCT00891462	2-3	LAMA; Placebo	12 wks	Trough FEV1, SGRQ
Kerwin, 2012 [54]	NCT00929110	2-3	LAMA; Placebo	52 wks	Trough FEV1, SGRQ
Jones, 2012 [55]	NCT01001494	2-3	LAMA; Placebo	24 wks	SGRQ
Hanania, 2012 [56]	NCT00606684	2-3	LABA; Placebo	4 wks	Trough FEV1
Hanania, 2012 [57]	NCT00784550	2-3	ICS+LABA+LAMA; LABA	24 wks	Trough FEV1
Kormann, 2011 [58]	NCT00567996	2-3	LABA; Placebo	12 wks	SGRQ, SQRG Responders
Kerwin, 2011 [59]	NCT01072448; NCT01068600	2-3	LABA; Placebo	12 wks	SGRQ
Jones, 2011 [60]	NCT00363896; NCT00358436	2-3	LAMA; Placebo	52 wks	SGRQ, SQRG Responders
D'Urzo, 2011 [61]	NCT01005901	2-3	LAMA; Placebo	26 wks	Trough FEV1, SGRQ
Chapman, 2011 [62]	NCT00677807	2-3	LABA; Placebo	52 wks	Trough FEV1
Buhl, 2011 [63]	NCT00900731	2-3	LABA; LABA	12 wks	Trough FEV1, SGRQ
Bogdan, 2011 [64]	NCT00628862	2-3	LABA; Placebo	12 wks	Trough FEV1, SGRQ, SQRG Responders
Donohue, 2010 [65]	NCT00463567	2-3	LABA; LABA; Placebo	26 wks	Trough FEV1, SGRQ
Calverley, 2010 [66]	NCT476099	3	ICS+LABA; LABA	48 wks	Trough FEV1, SGRQ
Bateman, 2010 [67]	NCT00387088	2-3	LAMA; Placebo	48 wks	Trough FEV1, SGRQ, SQRG Responders
Bateman, 2010 [68]	NCT00168844; NCT00168831	2-3	LAMA; Placebo	48 wks	Trough FEV1, SGRQ
Welte, 2009 [69]	NCT00496470		ICS+LABA+LAMA; LABA	12 wks	Trough FEV1, SGRQ, SQRG Responders
Tashkin, 2009 [70]			LABA+LAMA; LABA	12 wks	Trough FEV1, SGRQ
Rennard, 2009 [71]	NCT00206167	2-4	ICS+LABA; LABA; Placebo	52 wks	SGRQ
Wedzicha, 2008 [72]	NCT00361959	3-4	ICS+LABA; LABA	2 yrs	SGRQ, SQRG Responders
Tonnel, 2008 [73]		2-3	LAMA; Placebo	9 mths	SGRQ, SQRG Responders
Tashkin, 2008 [74]	NCT00206154	2-4	ICS+LABA; LABA; Placebo	6 mths	Trough FEV1, SGRQ
Tashkin, 2008 [75]	NCT00144339	2-4	LAMA; Placebo	4 yrs	SQRG Responders
Sin, 2008 [76]	NCT00120978	2-3	ICS+LABA; Placebo	4 wks	SGRQ
Rabe, 2008 [77]	NCT00239421	2	LABA+LAMA; ICS+LABA	6 wks	Trough FEV1
Gross, 2008 [78]	NCT00215436	2-3	LABA; Placebo	12 wks	Trough FEV1, SGRQ
Calverley, 2008 [79]		2-3	ICS; Placebo	52 wks	Trough FEV1, SGRQ
Bateman, 2008 [80]		2-4	LAMA; ICS+LABA	6 wks	Trough FEV1
Zheng, 2007 [81]			ICS+LABA; Placebo	24 wks	Trough FEV1, SGRQ
Um, 2007 [82]			LAMA; ICS+LABA	6 wks	Trough FEV1, SGRQ, SQRG Responders
Kardos, 2007 [83]		3	ICS+LABA; LABA	44 wks	SGRQ, SQRG Responders
Freeman, 2007 [84]	NCT00274079	1-3	LAMA; Placebo	12 wks	Trough FEV1
Choudhury, 2007 [85]	NCT00440687		ICS; Placebo	52 wks	SGRQ
Chan, 2007 [86]			LAMA; Placebo	48 wks	Trough FEV1, SGRQ, SQRG Responders
Cazzola, 2007 [87]		3-4	ICS+LABA; LABA; ICS+LABA+LAMA	3 mths	Trough FEV1
Baumgartner, 2007 [88]			LABA; Placebo	12 wks	Trough FEV1, SGRQ
Aaron, 2007 [89]			LAMA; LABA+LAMA; ICS+LABA+LAMA	52 wks	Trough FEV1, SGRQ
Verkindre, 2006 [90]		2-3	LAMA; Placebo	12 wks	Trough FEV1, SGRQ, SQRG Responders
Stockley, 2006 [91]			LABA; Placebo	52 wks	SGRQ
Wouters, 2005 [92]			LABA; ICS+LABA	52 wks	SGRQ
Covelli, 2005 [93]			LAMA; Placebo	12 wks	Trough FEV1
Casaburi, 2005 [94]			LAMA; Placebo	25 wks	Trough FEV1, SGRQ
Briggs, 2005 [95]		2-3	LAMA; LABA	12 wks	Trough FEV1

Fig. 1. Network plot of inhaled medications compared in our network meta-analysis. The width of the lines represents the cumulative number of trials for each comparison.

Table 2. Network meta-analysis results of raw mean differences and odds ratios between inhaled medications. Treatment: A = Placebo; B = ICS + LABA; C = ICS + LABA + LAMA; D = LABA; E = LABA + LAMA; F = LAMA. Abbreviation: Trough FEV₁ = trough forced expiratory volume in 1 second; SGRQ = St George's Respiratory Questionnaire

Trough FEV ₁	A	0.11 (0.08, 0.15)	0.22 (0.16, 0.29)	0.07 (0.04, 0.10)	0.16 (0.13, 0.19)	0.10 (0.07, 0.13)
	-0.11 (-0.15, -0.08)	B	0.11 (0.05, 0.17)	-0.05 (-0.08, -0.01)	0.05 (0.01, 0.08)	-0.02 (-0.05, 0.02)
	-0.22 (-0.29, -0.16)	-0.11 (-0.17, -0.05)	C	-0.15 (-0.22, -0.09)	-0.06 (-0.13, 0.00)	-0.12 (-0.19, -0.06)
	-0.07 (-0.10, -0.04)	0.05 (0.01, 0.08)	0.15 (0.09, 0.22)	D	0.09 (0.06, 0.12)	0.03 (-0.00, 0.06)
	-0.16 (-0.19, -0.13)	-0.05 (-0.08, -0.01)	0.06 (-0.00, 0.13)	-0.09 (-0.12, -0.06)	E	-0.06 (-0.10, -0.03)
	-0.10 (-0.13, -0.07)	0.02 (-0.02, 0.05)	0.12 (0.06, 0.19)	-0.03 (-0.06, 0.00)	0.06 (0.03, 0.10)	F
SGRQ Scores	A	3.20 (1.29, 5.13)	3.69 (0.41, 6.95)	2.03 (0.45, 3.64)	2.00 (-0.02, 4.09)	1.42 (-0.47, 3.39)
	-3.20 (-5.13, -1.29)	B	0.50 (-2.18, 3.09)	-1.17 (-2.85, 0.49)	-1.19 (-3.37, 1.11)	-1.76 (-4.01, 0.48)
	-3.69 (-6.95, -0.41)	-0.50 (-3.09, 2.18)	C	-1.63 (-4.77, 1.52)	-1.68 (-5.08, 1.85)	-2.26 (-5.61, 1.30)
	-2.03 (-3.64, -0.45)	1.17 (-0.49, 2.85)	1.63 (-1.52, 4.77)	D	-0.04 (-2.02, 2.10)	-0.61 (-2.34, 1.17)
	-2.00 (-4.09, 0.02)	1.19 (-1.11, 3.37)	1.68 (-1.85, 5.08)	0.04 (-2.10, 2.02)	E	-0.58 (-2.67, 1.53)
	-1.42 (-3.39, 0.47)	1.76 (-0.48, 4.01)	2.26 (-1.30, 5.61)	0.61 (-1.17, 2.34)	0.58 (-1.53, 2.67)	F
SGRQ Responders	A	1.76 (1.52, 2.05)	2.23 (1.78, 2.82)	1.42 (1.29, 1.59)	1.94 (1.75, 2.19)	1.44 (1.33, 1.57)
	0.57 (0.49, 0.66)	B	1.27 (1.02, 1.59)	0.80 (0.70, 0.92)	1.10 (0.94, 1.28)	0.82 (0.71, 0.93)
	0.45 (0.36, 0.56)	0.79 (0.63, 0.98)	C	0.64 (0.51, 0.80)	0.87 (0.69, 1.10)	0.64 (0.52, 0.80)
	0.70 (0.63, 0.78)	1.24 (1.09, 1.42)	1.57 (1.25, 1.98)	D	1.37 (1.22, 1.53)	1.01 (0.92, 1.11)
	0.52 (0.46, 0.57)	0.91 (0.78, 1.07)	1.15 (0.91, 1.45)	0.73 (0.65, 0.82)	E	0.74 (0.67, 0.81)
	0.70 (0.64, 0.75)	1.22 (1.07, 1.41)	1.55 (1.24, 1.94)	0.99 (0.90, 1.09)	1.35 (1.23, 1.49)	F

Fig. 2. Forest plots indicating the relative efficacy of inhaled medications (single or combined) with respect to tFEV₁, SGRQ and SGRQ responders.

is no significant difference in changes of SGRQ scores between any other pairs of inhaled medications (Table 2, Fig. 2).

Comparing different inhaled medications by using SGRQ responders

The relative efficacy of inhaled medications is also assessed by using the binary outcome of SGRQ responders which indicates whether a patient had at least 4-unit reduction in SGRQ total score during the study period (from baseline to endpoint at the 24th week). Significantly increased ORs of SGRQ responders suggest that the inhaled medication is potentially more efficacious than the reference inhaled medication. Patients with all five inhaled medications exhibited significantly increased OR of SGRQ responders in reference to those with placebo (all ORs > 1). Besides that, patients with ICS + LABA + LAMA exhibited more favorable results compared to those with the following inhaled medications: ICS+LABA (OR = 1.76, 95% CrI = 1.52-2.05), LABA (OR = 1.42, 95% CrI = 1.29-1.59) and LAMA (OR = 1.44, 95% CrI = 1.33-1.57; Table 2, Fig. 2).

Fig. 3. Rank grams showing the cumulative probability of each inhaled medication for being the best, the second best and so on. Higher ranking are more preferable than lower rankings.

Fig. 4. Forest plots for node splitting methods suggesting the consistence between direct and indirect evidence for each comparison.

Ranking of inhaled medications by using SUCRA

Table 3 provides a comprehensive ranking of various inhaled medications when tFEV₁, SGRQ and SGRQ responders were considered. The corresponding ranking of inhaled medications with respect to each endpoint is consistent with the results produced by our NMA. Incorporating ICS, LABA and LAMA for is ranked as the most preferable with respect to tFEV₁ (SUCRA = 0.828). A similar ranking tendency of ICS + LABA + LAMA is observed in the other two endpoints: SGRQ (SUCRA = 0.700) and SGRQ responders (SUCRA = 0.812). On the contrary, single inhaled medication of LABA or LAMA appears to have substantially lower values of SUCRA compared to that of ICS + LABA + LAMA. A ranking histogram comparing various inhaled medications (single or combined) with respect to tFEV₁, SGRQ and SGRQ responders is presented in Figure 3. As suggested by the SUCRA values, combined triple inhaled medications may be more efficacious than single or dual inhaled medications.

Fig. 5. Funnel plots for visualizing asymmetry patterns due to the presence of significant publication bias or small-study effects.

Assessing inconsistency between direct and indirect evidence

One fundamental assumption in our NMA is the adoption of a consistency model, in which the extent of consistency between direct and indirect evidence is validated by using the node splitting method. Evidence for each pairwise comparison obtained from direct evidence, indirect evidence and the network is compared using a node splitting forest plot (Fig. 4). A *P*-value of less than 0.05 suggests potentially significant inconsistency for that comparison. Hence, the consistency model assumption may be violated for that comparison. There is no significant inconsistency detected for each comparison with respect to $tFEV_1$ or SGRQ (all *P*-value > 0.05). However, the consistency model may not be appropriate for comparing placebo with LABA (*P*-value = 0.001) with respect to SGRQ responders. Since this is the only case in which potential significant inconsistency may arise from, we did not replace the consistency model in our NMA.

Assessing small study effects and publication bias

Although we did not conduct any formal statistical tests for small study effects or publication bias, a funnel plot was produced for each clinical outcome for this purpose. There is no obvious asymmetry pattern displayed in all of the three funnel plots. Thus, we do not have sufficient evidence to conclude significant small study effects or publication bias (Fig. 5).

Discussion

This NMA extends typical meta-analysis by simultaneously comparing several inhaled medications for COPD patients. In our study, COPD patients with the combined inhaled medications of ICS+LABA+LAMA were significantly associated with improved $tFEV_1$, SGRQ and SGRQ Responders compared to those with single inhaled medication of LABA or LAMA. The above results were confirmed by both pooled row mean differences and ORs produced by our NMA. Furthermore, such a trend is consistent with the ranking scheme which is based on the SUCRA values of inhaled medications.

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) suggests several diagnosis approaches for COPD: symptom evaluations, patient history evaluations, exposure to risk factors as well as post-bronchodilator spirometric assessments [96]. Once a COPD diagnosis is confirmed, a new disease classification approach which takes both symptoms and exacerbation risks into consideration can be used to categorize patients into four groups [96]. Inhaled medications are usually recommended to patients based on disease classification. Moreover, several inhaled medications may be combined for those who are classified as severe COPD.

LAMAs differ not only in their pharmacological characteristics but also in their mechanisms. For instance, the symptoms of COPD patients can be alleviated by Tiotropium whereas enhancing pulmonary functions can be achieved by using Glycopyrronium [97-

99]. On the other hand, LABAs are particularly effective in broncho protection [7, 8]. However, a single long-acting bronchodilator such as LAMA or LABA often does not provide adequate relief for some COPD patients. As a result, combining LABA with LAMA has been recommended by clinicians [10]. This recommendation has been confirmed in our NMA which revealed that COPD patients with LABA + LAMA exhibited stronger improvements in both $tFEV_1$ and SGREQ scores compared to those with LABA or LAMA. This conclusion is consistent with results produced by other studies [2, 100, 101].

Another study conducted by Montuschi et al. indicated that triple inhaled medications (ICS+LABA+LAMA) may be particularly effective in patients with severe or very severe COPD. For those patients with severe COPD, maximizing bronchodilatation is the main objective. Results of Montuschi et al. are supported by the treatment recommendation guidelines provided by GOLD [102]. Also, our study appears to support the above conclusions because patients with ICS+LABA+LAMA were significantly associated with better $tFEV_1$, SGRQ and SGRQ Responders in relation to those with other inhaled medications. However, the potential for increased side effects with combining therapies has not been taken into consideration [29, 33], and the use of steroids may raise potential risk for pneumonia [37]. As a result, whether the combination of ICS+LABA+LAMA can be a best choice for clinicians still need further proofs. Besides, stratified analysis by the severity of COPD is not feasible in our analysis due to the lack of information. Therefore the enhanced efficacy of triple inhaled medication should be further verified. As suggested by another retrospective study, COPD patients with TIO+LABA+ICS were associated with a reduced risk of mortality, COPD exacerbations and hospitalizations compared to matched COPD patients with LABA + ICS [102]. Simultaneously exploiting different inhaled medications may trigger additive or synergetic effects and may result in enhanced efficacy. This kind of enhancement may not be achievable by simply increasing the dose of a single bronchodilator [102, 103]. However, some inappropriate prescriptions of triple inhaled medications have been conducted by clinicians. The implementation of COPD guidelines should be strictly followed by clinicians in order to avoid the overuse of triple inhaled medications, particularly those with low risks or with less severe symptoms [104].

As the first Bayesian NMA, our study compares six inhaled medications by synthesizing all available evidence in the current literature. However, a few limitations contained in this study should be concerned. Firstly, there is significant variation in the number of studies for each inhaled medication (unbalanced design). For instance, the number of studies involved in ICS+LABA+LAMA is significantly fewer than that of others. This tends to result in wider confidence interval and lower statistical power. Secondly, variation in the sample size and study duration as well as other study characteristics may cause significant heterogeneity and thereby pooling evidence from individual studies with significant heterogeneity may not be comparable. Thirdly, we used a self-evaluated questionnaire (SGRQ) for assessing the health recovery status of COPD patients. However, the included studies did not disclose any information about non-responses to such a questionnaire. If a large proportion of patients in the included studies did not respond to the SGRQ, then the overall conclusion may be inaccurate. Another major limitation of our study is that the safety of triple inhaled medication was not assessed by our study. For instance, COPD patients with ICS+LABA were associated with an increased risk of adverse pneumonia events [105, 106]. Therefore, clinicians should be mindful of the safety profile of dual or triple inhaled medications when making prescriptions. Besides, duration time of included studies are not consistent, and not all studies with long duration time such as 52 weeks or so have illustrated outcomes in 12 or 24 weeks, resulting in the difficulty and insufficiency of making a meta-analysis according to duration period.

For summary, combined inhaled medication of ICS+LABA+LAMA exhibited significant improvements in $tFEV_1$, SGRQ and SGRQ Responders. Apart from that, combined dual inhaled medications such as LABA+LAMA and ICS+LABA are potentially more efficacious than single inhaled medication. Large scale randomized trials should be designed and implemented to confirmed the above conclusions.

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Disclosure Statement

No conflict of interest among all authors.

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