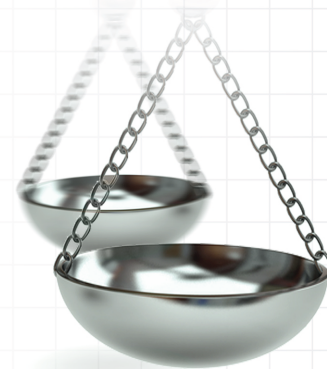




Budesonide/formoterol therapy: effective and appropriate use in asthma and chronic obstructive pulmonary disease

Journal of **Comparative Effectiveness Research**

Douglas W Mapel^{1,2}, Melissa H Roberts^{*,1}  & Jill Davis³

¹University of New Mexico College of Pharmacy, MSC09 5360, University of New Mexico, Albuquerque, NM 87131, USA

²LCF Research, 2309 Renard Place SE Ste 103, Albuquerque, NM 87106, USA

³AstraZeneca LP, 1800 Concord Pike, Wilmington, DE 19897, USA

*Author for correspondence: Tel.: +1 505 925 0953; MHRoberts@salud.unm.edu

Aim: Quality, real-world comparative effectiveness (CE) studies of asthma and chronic obstructive pulmonary disease therapy efficacy are scarce. We identified and evaluated peer-reviewed CE and appropriate-use evaluations of budesonide/formoterol combination (BFC) maintenance therapy. **Materials & methods:** Analyses were limited to retrospective, real-world utilization studies of BFC delivered by pressurized metered-dose inhalers. **Results:** In a CE study of BFC versus fluticasone/salmeterol combinations (FSC) in asthma, BFC users had fewer total exacerbations. In appropriate-use studies of asthma treatment, BFC patients were consistently more likely to meet treatment escalation recommendations. BFC comparisons with FSC or tiotropium for chronic obstructive pulmonary disease found differences in exacerbation rates and rescue inhaler use. **Conclusion:** We found available, good quality BFC CE and appropriate-use articles; however, all had limitations.

First draft submitted: 30 October 2019; Accepted for publication: 19 December 2019; Published online: 27 January 2020

Keywords: asthma • bronchodilator agents • budesonide • chronic obstructive pulmonary disease • comparative effectiveness • formoterol • health outcomes • review

Background

The development of combinations of inhaled corticosteroids (ICS) with long-acting β_2 -agonists (LABAs) has revolutionized the treatment of asthma and chronic obstructive pulmonary disease (COPD). ICS/LABA combination therapies were initially developed and approved for the treatment of asthma, as the efficacy of ICS/LABA compared with higher doses of ICS monotherapy makes them a valuable step-up option when low/medium-dosage ICS treatment cannot manage the severity of asthma symptoms or decrease the risk of exacerbations [1]. In addition, the convenience of simplified dosing makes them a preferred choice among patients with asthma and prescribers [2,3]. Subsequent proof of efficacy in COPD changed the treatment philosophy in this disease from a purely palliative approach to one emphasizing aggressive therapy [4]. ICS/LABA therapy is currently recommended for patients with a history of exacerbations with or without a higher level of symptoms as a more effective treatment option compared with either component alone for improving lung function and health status [5].

Two pivotal studies demonstrated greater efficacy and a similar safety profile of budesonide/formoterol combination (BFC) pressurized metered-dose inhaler (pMDI) compared with either component alone in patients with asthma [6,7]. In 2006, BFC was approved in the USA as a twice-daily treatment for asthma, and subsequently as a maintenance treatment for airflow obstruction and reducing exacerbations in patients with COPD [8–13]. [Table 1](#) presents a summary of treatment effect estimates observed in randomized clinical trials (RCTs) of BFC pMDI in chronic persistent asthma, and [Table 2](#) presents a summary of effect estimates in moderate-to-severe COPD.

BFC has a mechanism of action similar to fluticasone/salmeterol combination (FSC), another US FDA approved ICS/LABA; however, unlike salmeterol, formoterol is a full β_2 -receptor agonist and has a faster onset of action compared with FSC [14].

Table 1. Budesonide/formoterol combination in asthma: summary of randomized clinical trial outcomes[¶].

Study and outcomes (year)	Difference (95% CI)			
Mean change from baseline to 12 weeks in 12-h mean FEV ₁ , L				
Corren <i>et al.</i> (2007)	BFC 160/9 µg (N = 123)	BD 160 µg (N = 121)	Placebo (N = 122)	
– Day 1	0.41 ± 0.27	0.17 ± 0.24	0.15 ± 0.27	BFC-BD: 0.24 (0.17–0.31) [§] BFC-placebo: 0.25 (0.19–0.32) [§]
– Week 2	0.47 ± 0.37	0.30 ± 0.35	0.12 ± 0.33	BFC-BD: 0.18 (0.09–0.27) [§] BFC-placebo: 0.35 (0.26–0.44) [§]
– Week 12	0.50 ± 0.37	0.32 ± 0.37	0.12 ± 0.35	BFC-BD: 0.20 (0.11–0.29) [§] BFC-placebo: 0.39 (0.30–0.47) [§]
– Mean change from baseline to 12 weeks in predose FEV ₁ , L [#]	0.37 ± 0.37	0.23 ± 0.40	0.03 ± 0.44	BFC-BD: 0.15 (0.05–0.26) [‡] BFC-placebo: 0.34 (0.23–0.45) [§]
– Mean change from baseline to 12 weeks in symptom-free days ^{††}	26.47 ± 39.46	29.77 ± 38.19	7.52 ± 30.64	BFC-BD: -2.66 (-12.26–6.93) BFC-placebo: 21.05 (11.46–30.64) [§]
– Worsening asthma at 12 weeks, n (%) ^{‡‡}	23 (18.7)	26 (21.5)	69 (56.6)	BFC-BD: OR: 0.84 (0.45–1.57) BFC-placebo: OR: 0.18 (0.10–0.31) [§]
– Clinical asthma exacerbations at 12 weeks, n (%) ^{§§}	1 (0.8)	3 (2.5)	20 (16.4)	BFC-BD: OR: 0.32 (0.03–3.14) BFC-placebo: OR: 0.04 (0.01–0.32) [§]
– Mean change from baseline to 12 weeks in rescue medication use, inhalations/day	-2.01 ± 2.36	-1.86 ± 2.59	0.15 ± 2.72	BFC-BD: -0.23 (-0.80–0.34) BFC-placebo: -2.06 (-2.62 to -1.49) [§]
Noonan <i>et al.</i> (2007)	BFC 320/9 µg (N = 124)	BD 320 µg (N = 109)	Placebo (N = 125)	
– Day 1	0.37	0.11	0.09	BFC-BD: 0.26 (0.20–0.33) [§] BFC-placebo: 0.29 (0.22–0.35) [§]
– Week 2	0.34	0.15	-0.03	BFC-BD: 0.20 (0.11–0.28) [§] BFC-placebo: 0.37 (0.29–0.45) [§]
– Week 12	0.37	0.15	-0.03	BFC-BD: 0.23 (0.14–0.31) [§] BFC-placebo: 0.40 (0.32–0.48) [§]
– Mean change from baseline to 12 weeks in predose FEV ₁ , L [#]	0.19	0.10	-0.17	BFC-BD: 0.10 (0.00–0.21) [†] BFC-placebo: 0.37 (0.27–0.47) [§]
– Mean change from baseline to 12 weeks in symptom-free days ^{††}	23.14	9.50	2.37	BFC-BD: 15.47 (7.19–23.74) [§] BFC-placebo: 23.41 (15.44–31.38) [§]
– Worsening asthma at 12 weeks, n (%) ^{‡‡}	37 (29.8)	48 (44.0)	84 (67.2)	BFC-BD: OR: 0.54 (0.32–0.93) [†] BFC-placebo: OR: 0.21 (0.12–0.35) [§]
– Clinical asthma exacerbations at 12 weeks, n (%) ^{§§}	7 (5.6)	5 (4.6)	16 (12.8)	BFC-BD: OR: 1.25 (0.38–4.04) BFC-placebo: OR: 0.42 (0.17–1.06)
– Mean change from baseline to 12 weeks in rescue medication use, inhalations/day	-1.00	-0.78	0.83	BFC-BD: -0.51 (-1.05–0.03) BFC-placebo: -2.05 (-2.57 to -1.54) [§]
Values are mean ± standard deviation unless otherwise stated.				
†p ≤ 0.05.				
‡p < 0.01.				
§p ≤ 0.001.				
¶The authors only report on studies with budesonide/formoterol combination delivered by pressurized metered-dose inhalers.				
*Forced expiratory volume over 1 second recorded approximately 12 h after the last dose of study medication.				
††Days with no daytime or nighttime symptoms and no awakenings due to asthma.				
‡‡One or more of the following: a decrease in morning predose forced expiratory volume over 1 second of >20% from the value at randomization or a decrease to <45% of predicted normal, use of ≥12 actuations of albuterol per day on ≥3 days within any period of 7 consecutive days after randomization, a decrease in morning peak expiratory flow of ≥20% from baseline on ≥3 days within any period of 7 consecutive days after randomization, an awakening due to asthma requiring the use of rescue medication on ≥2 nights within any period of 7 consecutive days after randomization, or a clinical exacerbation requiring emergency treatment, hospitalization or use of asthma medication not allowed by the study protocol.				
§§Exacerbations requiring emergency treatment, hospitalization or use of an asthma medication not allowed by the study protocol.				
BD: Budesonide; BFC: Budesonide/formoterol combination; FEV ₁ : Forced expiratory volume over 1 second; OR: Odds ratio.				

Although RCTs are essential for demonstrating the efficacy of new therapies, they are typically conducted in selected populations that may not be fully representative of patients treated in the general population. Additionally, RCT study protocols and monitoring conditions may result in treatment adherence and outcomes that may be better than can be expected in real-world conditions. Conversely, real-world analyses more accurately reflect the unpredictable nature of asthma or COPD symptoms and exacerbations, their impact on perceived treatment efficacy [15,16], association with increased costs [17] and suboptimal medication adherence [18,19] – all of which are typically well controlled in RCTs [20]. Similarly, appropriate-use studies based on real-world data provide insights

Table 2. Budesonide/formoterol combination in chronic obstructive pulmonary disease: summary of randomized clinical trial outcomes[#].

Study and outcomes (year)	Mean difference (95% CI), unless otherwise noted			
Szafranski <i>et al.</i> (2003)	BFC 320/9 µg (N = 208)	BD 400 µg (N = 198)	Placebo (N = 205)	
– Severe exacerbations, per patient-year ^{††}	1.42	1.59	1.87	BFC vs BD: 11% reduction (–15.9–31.8) BFC vs placebo: 24% reduction (1.9–41.4) [†]
– OCS courses associated with exacerbations, per patient-year	0.74	0.76	1.07	BFC vs placebo: 31% reduction [†]
Calverley <i>et al.</i> (2003)	BFC 320/9 µg (N = 254)	BD 320 µg (N = 257)	Placebo (N = 256)	
– Mean FEV ₁ as a % of baseline FEV ₁ ^{‡‡}				BFC vs BD: 11% higher BFC vs placebo: 14% higher
– Total exacerbations, per patient-year ^{††}	1.38	1.60	1.80	BFC vs BD: RR: 0.864 (0.679–1.100) BFC vs placebo: RR: 0.764 (0.600–0.973) [†]
– Exacerbations requiring OCS, per patient-year	0.63	0.87	0.91	BFC vs BD: RR: 0.718 (0.543–0.949) [†] BFC vs placebo: RR: 0.553 (0.420–0.728) [¶]
– Median time to first exacerbation, days	254	178	96	BFC vs BD: HR: 0.773 (0.611–0.980) [†] BFC vs placebo: HR: 0.715 (0.562–0.910) [‡]
– Rescue medication use, inhalations/day				BFC vs BD: –0.8 [‡] BFC vs placebo: –0.8 [‡]
Tashkin <i>et al.</i> (2008)	BFC 320/9 µg (N = 281)	BD 320 µg (N = 275)	Placebo (N = 300)	
– Mean change from baseline to 24 weeks predose FEV ₁ , L ^{§§}	0.07 ± 0.19	0.01 ± 0.19	0.01 ± 0.21	BFC vs BD: 0.06 (0.02–0.09) [§] BFC vs placebo: 0.05 (0.02–0.09) [‡]
– Mean change from baseline to 24 weeks 1 h postdose FEV ₁ , L	0.20 ± 0.20	0.04 ± 0.19	0.04 ± 0.21	BFC vs BD: 0.16 (0.13–0.20) [§] BFC vs placebo: 0.16 (0.13–0.20) [§]
– Mean change from baseline to 24 weeks in rescue medication use, inhalations/day	–1.24 ± 2.82	–0.39 ± 2.65	–0.14 ± 2.44	BFC vs BD: –0.93 (–1.32 to –0.63) [§] BFC vs placebo: –1.00 (–1.39 to –0.61) [§]
– Mean change from baseline to 24 weeks in rescue medication-free days (%) ^{¶¶}	21.39 ± 36.14	7.44 ± 33.83	7.07 ± 30.61	BFC vs BD: 13.41 (8.11–18.72) [§] BFC vs placebo: 12.42 (7.20–17.65) [§]
Rennard <i>et al.</i> (2009)	BFC 320/9 µg (N = 494)		Placebo (N = 481)	
– Total exacerbations, per patient-year ^{††}				BFC vs placebo: 41% reduction [¶]
– Exacerbations requiring OCS, per patient-year				BFC vs placebo: 42.9% reduction [‡]
Sharafkhaneh <i>et al.</i> (2012)	BFC 320/9 µg (N = 407)	BFC 160/9 µg (N = 408)	Formoterol 9 µg (N = 404)	
– Total exacerbations per patient-treatment year ^{††,##}	0.700 (0.084)	0.794 (0.092)	1.072 (0.119)	BFC 320/9 µg vs formoterol 9 µg: 34.6% reduction [¶] BFC 160/9 µg vs formoterol 9 µg: 25.9% reduction [‡]
– Total OCS-related exacerbations per patient-treatment year ^{##}	0.680 (0.082)	0.772 (0.090)	1.043 (0.116)	BFC 320/9 µg vs formoterol 9 µg: 34.8% reduction [¶] BFC 160/9 µg vs formoterol 9 µg: 25.9% reduction [‡]
– Total hospitalization-related exacerbations per patient-treatment year ^{##}	0.106 (0.014)	0.127 (0.015)	0.144 (0.016)	BFC 320/9 µg vs formoterol 9 µg: 26.8% reduction BFC 160/9 µg vs formoterol 9 µg: 12.2% reduction
– Time to first exacerbation, days	277.9	263.7	249.8	BFC 320/9 µg vs formoterol 9 µg: 21.2% reduction [†] BFC 160/9 µg vs formoterol 9 µg: 15.3% reduction
Ferguson <i>et al.</i> (2017)	BFC 320/9 µg (N = 606)	Formoterol 9 µg (N = 613)		
– Moderate/severe exacerbations per patient-year (on treatment) ^{†††, n (95% CI)}	0.85 (0.70, 1.03)	1.12 (0.93, 1.35)		BFC vs formoterol: 24% reduction [‡]
– Time to first exacerbation				BFC vs formoterol: 22% reduction [†]

Values are mean ± standard deviation unless otherwise stated.

[†]p < 0.05.[‡]p < 0.01.[§]p ≤ 0.001.[¶]p < 0.001.[#]The authors only report on studies with budesonide/formoterol combination delivered by pressurized metered-dose inhalers.^{††}Hospitalizations due to respiratory symptoms and/or use of oral corticosteroids and/or antibiotics (note, Rennard 2009 and Sharafkhaneh 2012 did not include antibiotic use in definition of exacerbation).^{‡‡}Mean of all available measurements during the 12-month treatment period.^{§§}Forced expiratory volume over 1 second recorded approximately 12 h after the last dose of study medication.^{¶¶}Days for which patients reported no daytime or nighttime rescue medication use.^{##}Estimated using a Poisson regression model adjusted for differential treatment exposure with person years as an offset variable and country (standard error).^{†††}Worsening of ≥2 major symptoms (increased dyspnea, sputum volume and sputum color/purulence) or one major symptom in combination with ≥1 minor symptom (sore throat, colds, fever without other cause, increased cough and increased wheeze) for ≥2 consecutive days and requiring treatment with oral corticosteroids for ≥3 days and/or antibiotics (moderate) and/or hospitalization (severe).BD: Budesonide; BFC: Budesonide/formoterol combination; FEV₁: Forced expiratory volume over 1 second; HR: Hazard ratio; OCS: Oral corticosteroids; RR: Rate ratio.

into how participants in RCTs may differ from patients using the product in the general population, as well as how closely prescribers follow guidelines concerning escalation of therapy. Thus, there is an urgent need for real-world effectiveness data on therapies beyond clinical efficacy outcomes [21,22]. The goal of this review was to identify and evaluate the comprehensive reporting of peer-reviewed evaluations of the comparative effectiveness (CE) of BFC pMDI treatment for asthma and COPD. Secondary objectives included review of appropriate-use studies of BFC pMDI and examination of the utility of currently available study quality assessment tools intended to improve the quality of respiratory disease outcomes publications. This review provides important data for clinicians and healthcare payers who are interested in the CE of treatments for asthma and COPD.

Methods

Inclusion/exclusion criteria

This review was structured based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for design and reporting of literature reviews. EMBASE was searched in November 2016, with a follow-up search conducted in August 2019, using keywords relating to asthma, COPD and BFC, alone or compared with similar products, and real-world efficacy or utility ([Supplementary Table 1](#)). Because BFC was first approved for use in asthma in 2006, the search was designed to capture only articles published on or after 1 January 2006.

Eligible studies involved patients with asthma or COPD and evaluated an aspect of real-world effectiveness, utility, health-related quality of life or appropriate use as an outcome and were based on data derived from insurance claims databases, healthcare administrative databases and population-based registries. *In vitro* studies, reviews, non-English publications and animal studies were excluded. Studies were also excluded if they were solely an abstract (e.g., conference proceedings).

Study quality assessment tools

A combined instrument to assess the quality, relevance and credibility of an observational study ([Supplementary Table 2](#)) was developed based on questions derived from three sources. Twenty-eight questions were extracted from the ISPOR-AMCP-NPC 2014 Good Practice Task Force Report on observational studies [23]. Twelve questions were adapted from the ISPOR 2009 Good Practice Task Force Report on the use of retrospective database studies for CE research [24]. In addition to overall reporting, questions from these two sources addressed methods and analyses used to minimize biases and confounding factors that could affect any measured difference in treatment outcomes. Eight questions were adapted from the Respiratory Effectiveness Group summary of quality standards for real-world research [25]. Respiratory Effectiveness Group standards stressed three points to ensure quality of included studies for analysis: preparation of research, analyses and reporting and discussion of results. The scoring instrument was modified for scoring appropriate use studies by either modifying items to make them valid for this application or eliminating those items ([Supplementary Table 2](#)).

Each included article was reviewed by ≥ 2 reviewers independently ([Supplementary Table 3](#)). The reviewers then conferred to determine an overall evaluation. To approximate an overall score, the percentage of checklist items that were satisfactorily addressed was converted to a 100-point score based on the number of items that applied to the study. The quality of each reviewed article was assumed to be related to the number of items on the checklist that were satisfactorily addressed in the published manuscript. No comparison was made on the relative importance of individual items, and no weighting was used.

Results

A PRISMA flow diagram of the literature search results is shown in [Figure 1](#). The literature yielded four evaluations related to treatment of asthma and six for COPD: six were CE evaluations, and four studies concerned initiation of treatment ([Table 3](#)). All evaluations were retrospective studies using claims data.

CE of BFC in asthma

The only CE study of BFC versus FSC use among patients with asthma conducted in the USA was published by Tunceli *et al.* [21]. This study compared patients with asthma newly initiated on ICS/LABA therapy with respect to exacerbations and healthcare resource utilization (HCRU). Patients with asthma were identified using the HealthCore Integrated Research Database between 1 June 2007 and 30 September 2010 to coincide with the approval of BFC for the treatment of asthma in the USA. Patients were aged 12–64 years and had a second

Table 3. Summary of real-world studies included in the review[†].

Article (year)	Outcomes assessed	Data source	Study design	Confounder adjustment method	Time period for treatment initiation	Exclusion criteria	Age (years)	Study period	Sample size (n)	Results: appropriate initiation
Asthma: comparative effectiveness studies										
Tunceli et al. (2014)	Asthma exacerbations (inpatient hospitalization, ED visit or a pharmacy claim for OCS); HCRU (all-cause and asthma-related)	HealthCore Integrated Research Database	Retrospective, ITT cohort analysis	Propensity-matching	1 June 2007–30 September 2010	Other respiratory or inflammatory diseases including COPD; Chronic OCS use or omalizumab treatment during the baseline period; Were switched to another ICS/LABA treatment during the follow-up period	12–64	12 months baseline; 12 months postinitiation	BFC, 3043; FSC, 3043	Mean asthma exacerbation rate: BFC, 0.85 vs FSC, 0.93; adjusted RR: 0.92 (95% CI: 0.85–0.99); p = 0.0255 Mean OCS prescription fills: BFC, 0.73 vs FSC, 0.79; AMD: -0.07 (95% CI: 0.12 to -0.01) Mean ED visits: BFC, 0.08 vs FSC, 0.10; AMD: -0.02 (95% CI: -0.03 to 0.00) Mean asthma-related hospitalization rates: BFC, 0.01 vs FSC, 0.01; AMD: 0.0 (95% CI: 0.00–0.00)
Asthma: appropriate-use studies										
Ye et al. (2009)	Appropriate initiation of ICS/LABA combination therapy	Insurance claims database for a large national health plan	Retrospective cohort study	Multiple regression	1 January 2006–31 December 2007	COPD, cystic fibrosis, lung cancer or tuberculosis; No prior ICS/LABA combination therapy during the baseline period	≥12	12 months post-ICS/LABA initiation	BFC, 993; FSC, 23,238	Appropriate initiation: BFC, 58.4% vs FSC, 36.7%; p < 0.001 Adjusted OR for appropriate initiation: 2.01 (95% CI: 1.76–2.30); p < 0.001
Blanchette et al. (2009)	Appropriate initiation of ICS/LABA combination therapy	PharMetrics Patient-Centric Database	Retrospective cohort study	Multiple regression	1 July 2007–30 June 2008	COPD	12–64	12 months post-ICS/LABA initiation	BFC, 1417; FSC, 14,788	Appropriate initiation: BFC, 55.6% vs FSC, 37.7%; p < 0.001 Adjusted OR for meeting ≥1 appropriateness criterion: BFC vs FSC, 1.79 (95% CI: 1.60–2.00); p < 0.001
Tunceli et al. (2014)	Appropriate initiation of ICS/LABA combination therapy	HealthCore Integrated Research Database	Retrospective cohort study	Multiple regression	1 June 2007–31 December 2010	COPD, cystic fibrosis, lung cancer, tuberculosis or exercise-induced asthma with no other asthma diagnosis; Switching to another ICS/LABA treatment during the follow-up period	12–64	12 months post-ICS/LABA initiation	BFC, 11,718; FSC, 38,697	Appropriate initiation: BFC, 57.3% vs FSC, 51.6%; Adjusted OR for appropriate initiation, BFC vs FSC, 1.21 (95% CI: 1.16–1.27); p < 0.0001

[†] The authors only report on studies with budesonide/formoterol combination delivered by pressurized metered-dose inhalers.

[‡] Excluding hypertension, dyslipidemia, atherosclerosis or myocardial infarction.

AMD: Adjusted mean difference; BFC: Budesonide/formoterol combination; CAD: Coronary artery disease; CHF: Congestive heart failure; COPD: Chronic obstructive pulmonary disease; ED: Emergency department; FSC: Fluticasone propionate/salmeterol combination; HCRU: Healthcare resource utilization; HR: Hazard ratio; ICS: Inhaled corticosteroid; ICU: Intensive care unit; IPR: Ipratropium; ITT: Intent-to-treat; LABA: Long-acting β_2 -agonist; LAMA: Long-acting muscarinic antagonists; LTRA: Leukotriene receptor antagonist; MI: Myocardial infarction; MPR: Medication possession ratio; OCS: Oral corticosteroids; OR: Odds ratio; PDC: Proportion of days covered; PPV: Per patient-year; PVD: Peripheral vascular disease; RR: Rate ratio; SABA: Short-acting β_2 -agonist; SAMA: Short-acting muscarinic antagonist; SD: Standard deviation; TIA: Transient ischemic attack; TIO: Tiotropium.

Table 3. Summary of real-world studies included in the review[†] (cont.).

Article (year)	Outcomes assessed	Data source	Study design	Confounder adjustment method	Time period for treatment initiation	Exclusion criteria	Age (years)	Study period	Sample size (n)	Results: appropriate initiation
COPD: comparative effectiveness studies										
Roberts et al. (2011)	COPD- and pneumonia-related medical service events (including hospitalization, ED and outpatient visits) and COPD-related prescriptions; adherence; HCRU	PharMetrics Integrated Database	Retrospective, ITT cohort analysis	Propensity-matching	1 January 2007–31 January 2009	Respiratory tract cancer; OCS dependence (MPR ≥ 0.50 in the 6 months prior to baseline)	≥ 40	6 months baseline; 3–6 months postindex	BFC, 3385; FSC, 3385	Overall, no significant differences observed in postinitiation HCRU, with exceptions of SABA use: BFC, 34.7% vs FSC, 39.5%; $p < 0.001$, LABA use: BFC, 1.4% vs FSC, 0.9%; and IPR use: BFC, 7.8% vs FSC, 9.8%; $p = 0.005$ COPD-related medical service events: no significant cost differences between cohorts Rescue medications: no significant cost differences between cohorts Controller medication costs: BFC, US\$522.76 vs FSC, US\$566.10; $p < 0.001$. Adherence: similar for both cohorts, slightly higher percentage of FSC patients had an MPR >0.25 ; $p < 0.05$
Mapel et al. (2013)	Severe COPD exacerbations (hospitalization or ED visits with a primary respiratory diagnosis; COPD, pneumonia or respiratory distress) with stratification for baseline SABA use; exploration of whether baseline SABA use was an indicator for increased risk of severe exacerbations	PharMetrics Integrated Database	Retrospective, ITT cohort analysis	Propensity-matching	1 July 2006–30 June 2010	Respiratory tract cancer; OCS dependence (MPR ≥ 0.50 in the 6 months prior to baseline)	≥ 40	6 months baseline; 3–6 months postindex	BFC, 3852; FSC, 3852	Severe COPD exacerbations: overall no significant difference between cohorts Postinitiation decrease in COPD exacerbations for combined BFC and FSC groups only significant in patients with ≥ 2 SABA prescription fills at baseline: 9.0% vs 4.9%; $p < 0.001$ Postinitiation no SABA use: BFC, 59.3% vs FSC, 56.2%; $p < 0.01$

[†] The authors only report on studies with budesonide/formoterol combination delivered by pressurized metered-dose inhalers.

[‡] Excluding hypertension, dyslipidemia, atherosclerosis or myocardial infarction.

AMD: Adjusted mean difference; BFC: Budesonide/formoterol combination; CAD: Coronary artery disease; CHF: Congestive heart failure; COPD: Chronic obstructive pulmonary disease; ED: Emergency department; FSC: Fluticasone propionate/salmeterol combination; HCRU: Healthcare resource utilization; HR: Hazard ratio; ICS: Inhaled corticosteroid; ICU: Intensive care unit; IPR: Ipratropium; ITT: Intent-to-treat; LABA: Long-acting β_2 -agonist; LAMA: Long-acting muscarinic antagonists; LTRA: Leukotriene receptor antagonist; MI: Myocardial infarction; MPR: Medication possession ratio; OCS: Oral corticosteroids; OR: Odds ratio; PDC: Proportion of days covered; PPY: Per patient-year; PVD: Peripheral vascular disease; RR: Rate ratio; SABA: Short-acting β_2 -agonist; SAMA: Short-acting muscarinic antagonist; SD: Standard deviation; TIA: Transient ischemic attack; TIO: Tiotropium.

Table 3. Summary of real-world studies included in the review† (cont.).

Article (year)	Outcomes assessed	Data source	Study design	Confounder adjustment method	Time period for treatment initiation	Exclusion criteria	Age (years)	Study period	Sample size (n)	Results: appropriate initiation
Trudo <i>et al.</i> (2015)	Time to first COPD exacerbation; COPD exacerbations; HCRU; healthcare costs; treatment modification (BFC patients: any prescriptions for any other ICS/LABA or LAMA; TIO patients: any prescriptions for ICS/LABA or any other LAMA); adherence	HealthCore Integrated Research Database	Retrospective, ITT cohort analysis	Propensity-matching	1 March 2009–28 February 2012	Cancer diagnosis; ≥ 180 days of OCS use during the 12 months prior to baseline	≥ 40	12 months baseline; 12 months postinitiation	BFC, 1198; TIO, 1198	Time to first COPD exacerbation: BFC vs TIO: HR: 0.78 (95% CI: 0.70–0.87); $p < 0.001$ COPD exacerbations: BFC, 1.23 PPY vs TIO, 1.50 PPY; RR: 0.82 (95% CI: 0.73–0.91) HCRU: similar all-cause healthcare utilization, with exception of SABA use: BFC, 50.8% vs TIO, 54.3%; $p = 0.043$ COPD-related HCRU: inpatient hospitalizations: BFC, 7.5% vs TIO, 9.4%; OR: 0.78 (95% CI: 0.58–1.05); $p = 0.01$ ED visits: BFC, 13.7% vs TIO, 16.9%; OR: 0.77 (95% CI: 0.61–0.96); $p = 0.023$ Outpatient/office visits: BFC, 74.2% vs TIO, 86.8%; OR: 0.44 (95% CI: 0.35–0.55); $p < 0.001$ Any treatment modification: BFC, 17.5% vs TIO, 36.9%; OR: 0.36 (95% CI: 0.30–0.44); $p < 0.001$ Mean $\pm$ SD adherence (PDC): BFC, 0.28 $\pm$ 0.25 vs TIO, 0.37 $\pm$ 0.30 Mean index medication prescription fills: BFC, 3.3 vs FSC, 4.3; AMD: -1.01 (95% CI: -1.22 to -0.77) Mean $\pm$ SD healthcare costs: All-cause: BFC, US\$21,681 $\pm$ 60,517 vs TIO, US\$24,374 $\pm$ 46,428; AMD: -US\$2702 (95% CI: -US\$4160 to -US\$1119); $p = 0.001$ COPD-related costs: BFC, US\$4084 $\pm$ 7308 vs TIO, US\$5656 $\pm$ 10,056; AMD: -US\$1360 (95% CI: -US\$1715 to -US\$967); $p < 0.001$
Kern <i>et al.</i> (2015)	COPD exacerbations (inpatient, COPD-related ED visits, outpatient visits with antibiotics or OCS); time to first exacerbation; HCRU (COPD-related and all-cause); respiratory medication use; adherence; pneumonia events	HealthCore Integrated Research Database	Retrospective, ITT cohort analysis	Propensity-matching	1 March 2009–31 March 2012	Cancer diagnosis; ≥ 180 days of OCS use during the 12 months prior to baseline	≥ 40	12 months baseline; 12 months postinitiation	BFC, 3697; FSC, 3697	COPD exacerbations: no significant difference between cohorts Time to first exacerbation: no significant difference between cohorts HCRU: no significant difference between cohorts Respiratory medication use: no significant differences between cohorts Mean $\pm$ SD adherence (PDC): BFC, 0.33 $\pm$ 0.28 vs FSC, 0.34 $\pm$ 0.29 Mean $\pm$ SD index medication prescription fills: BFC, 3.8 $\pm$ 3.2 vs FSC, 4.0 $\pm$ 3.4; AMD: -0.20 (95% CI: -0.34 to -0.05); $p = 0.0071$ pneumonia events: no significant differences between cohorts

† The authors only report on studies with budesonide/formoterol combination delivered by pressurized metered-dose inhalers.

‡ Excluding hypertension, dyslipidemia, atherosclerosis or myocardial infarction.

AMD: Adjusted mean difference; BFC: Budesonide/formoterol combination; CAD: Coronary artery disease; CHF: Congestive heart failure; COPD: Chronic obstructive pulmonary disease; ED: Emergency department; FSC: Fluticasone propionate/salmeterol combination; HCRU: Healthcare resource utilization; HR: Hazard ratio; ICS: Inhaled corticosteroid; ICU: Intensive care unit; IPR: Ipratropium; ITT: Intent-to-treat; LABA: Long-acting β_2 -agonist; LAMA: Long-acting muscarinic antagonists; LTRA: Leukotriene receptor antagonist; MI: Myocardial infarction; MPR: Medication possession ratio; OCS: Oral corticosteroids; OR: Odds ratio; PDC: Proportion of days covered; PPY: Per patient-year; PVD: Peripheral vascular disease; RR: Rate ratio; SABA: Short-acting β_2 -agonist; SAMA: Short-acting muscarinic antagonist; SD: Standard deviation; TIA: Transient ischemic attack; TIO: Tiotropium.

Table 3. Summary of real-world studies included in the review† (cont.).

Article (year)	Outcomes assessed	Data source	Study design	Confounder adjustment method	Time period for treatment initiation	Exclusion criteria	Age (years)	Study period	Sample size (n)	Results: appropriate initiation
Davis <i>et al.</i> (2016)	Direct healthcare costs (COPD-related, pneumonia-related and all-cause); HCRU (hospitalization, ICU stays, ED visits, outpatient visits and medication); adherence	HealthCore Integrated Research Environment	Retrospective, ITT cohort analysis	Propensity-matching	1 March 2009–31 March 2012	Cancer diagnosis; ≥ 180 days of OCS use during the 12 months prior to baseline	≥ 40	12 months baseline; 12 months postinitiation	BFC, 3697; FSC, 3697	Overall, rates of COPD-related and all-cause HCRU were similar for the two cohorts during the 12-month follow-up period Mean $\pm$ SD COPD-related total healthcare costs: BFC, US\$4326 $\pm$ 9267 vs FSC, \$4846 $\pm$ 0627; AMD: -US\$316 (95% CI: -512 to -108); $p = 0.003$ COPD-related inpatient costs: BFC, US\$966 $\pm$ 6915 vs FSC, US\$1202 $\pm$ 7688; AMD: -US\$248 (95% CI: -337 to -147); $p < 0.001$ COPD-related outpatient/office visit costs: BFC, US\$1378 $\pm$ 3322 vs FSC, US\$1436 $\pm$ 2852; AMD: -US\$97 (95% CI: -186 to -1); $p = 0.048$ COPD-related pharmacy costs: BFC, US\$1482 $\pm$ 1634 vs FSC, US\$1609 $\pm$ 1712; AMD: -121 (95% CI: -193 to -45); $p = 0.002$ COPD-related ED visit costs: BFC, US\$257 $\pm$ 1120 vs FSC, US\$252 $\pm$ 1119; AMD: 26 (95% CI: 2-52); $p = 0.033$ Pneumonia-related total healthcare costs: BFC, US\$2855 $\pm$ 32,237 vs FSC, US\$3605 $\pm$ 23,095; AMD: -US\$716 (95% CI: -967 to -431); $p < 0.001$ Pneumonia-related inpatient costs: BFC, US\$2728 $\pm$ 32,033 vs FSC, US\$3409 $\pm$ 22,880; AMD: -US\$640 (95% CI: -894 to -349); $p < 0.001$ Total all-cause healthcare costs: BFC, US\$21,580 $\pm$ 46,376 vs FSC, US\$24,483 $\pm$ 45,324; AMD: -US\$1884 (95% CI: -2685 to -1047); $p < 0.001$ All-cause inpatient costs: BFC, US\$8519 $\pm$ 38,072 vs FSC, US\$10,314 $\pm$ 34,708; AMD: -US\$1242 (95% CI: -2082 to -288); $p = 0.012$ All-cause outpatient/office visit costs: BFC, US\$7310 $\pm$ 16,440 vs FSC, US\$7921 $\pm$ 17,873; AMD: -\$464 (95% CI: -778 to -135); $p = 0.006$

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Table 3. Summary of real-world studies included in the review[†] (cont.).

Article (year)	Outcomes assessed	Data source	Study design	Confounder adjustment method	Time period for treatment initiation	Exclusion criteria	Age (years)	Study period	Sample size (n)	Results: appropriate initiation
COPD: appropriate-use studies										
Kern et al. (2014)	Describe and evaluate demographic and clinical characteristics, HCRU and healthcare costs 12 months prior to treatment initiation	HealthCore Integrated Research Database	Retrospective cross-sectional study	No adjustment	1 March 2009–31 January 2012	Respiratory tract cancer	≥40	12-month period prior to initiation	BFC, 6940; TIO, 10,831	Mean ± SD age: BFC, 64.3 ± 12.1 years vs TIO, 66.9 ± 11.8 years; mean difference: -2.67 years (95% CI: -3.03 to -2.30); p < 0.0001 Females: BFC, 54.2% vs TIO, 50.6%; mean difference: 0.87 (95% CI: 0.82–0.92); p < 0.0001 Pulmonologist prescriber: BFC, 23.1% vs TIO, 26.6%; OR: 0.83 (95% CI: 0.77–0.89); p < 0.0001 Comorbidities: Hypertension: BFC, 59.0% vs TIO, 60.5%; OR: 0.94 (95% CI: 0.88–1.00); p = 0.0423 Asthma: BFC, 24.7% vs TIO, 12.7%; OR: 2.26 (95% CI: 2.09–2.44); p < 0.0001 Diabetes mellitus: BFC, 23.5% vs TIO, 22.2%; OR: 1.08 (95% CI: 1.00–1.16); p = 0.0449 Other CAD [‡] : BFC, 22.4% vs TIO, 28.1%; OR: 0.74 (95% CI: 0.69–0.80) CHF: BFC, 13.2% vs TIO, 16.2%; OR: 0.79 (95% CI: 0.72–0.86); p < 0.0001 Sinusitis: BFC, 10.4% vs TIO, 6.6%; OR: 1.65 (95% CI: 1.48–1.84); p < 0.0001 Allergic rhinitis: BFC, 8.0% vs TIO, 4.1%; OR: 2.04 (95% CI: 1.79–2.32); p < 0.0001 PVD/atherosclerosis: BFC, 7.5% vs TIO, 9.8%; OR: 0.75 (95% CI: 0.67–0.83); p < 0.0001 Stroke, TIA, or cerebrovascular disease: BFC, 6.9% vs TIO, 9.0%; OR: 0.75 (95% CI: 0.67–0.84); p < 0.0001 MI: BFC, 4.3% vs TIO, 6.0%; OR: 0.71 (95% CI: 0.62–0.82); p < 0.0001 Other lung diseases: BFC, 17.1% vs TIO, 19.3%; OR: 0.87 (95% CI: 0.80–0.94); p = 0.0003 Baseline respiratory medications (all p < 0.0001): Nebulizer treatment: BFC, 16.4% vs TIO, 11.0%; OR: 1.59 (95% CI: 1.46–1.74) ICS monotherapy: BFC, 11.1% vs TIO, 8.8%; OR: 1.29 (95% CI: 1.17–1.43) LTRA monotherapy: BFC, 11.6% vs TIO, 6.0%; OR: 2.05 (95% CI: 1.84–2.29) SABA use: BFC, 43.9% vs TIO, 34.8%; OR: 1.47 (95% CI: 1.38–1.56) SABA/SAMA combination: BFC, 16.5% vs TIO, 12.6%; OR: 1.37 (95% CI: 1.26–1.49)

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AMD: Adjusted mean difference; BFC: Budesonide/formoterol combination; CAD: Coronary artery disease; CHF: Congestive heart failure; COPD: Chronic obstructive pulmonary disease; ED: Emergency department; FSC: Fluticasone propionate/salmeterol combination; HCRU: Healthcare resource utilization; HR: Hazard ratio; ICS: Inhaled corticosteroid; ICU: Intensive care unit; IPR: Ipratropium; ITT: Intent-to-treat; LABA: Long-acting β_2 -agonist; LAMA: Long-acting muscarinic antagonists; LTRA: Leukotriene receptor antagonist; MI: Myocardial infarction; MPR: Medication possession ratio; OCS: Oral corticosteroids; OR: Odds ratio; PDC: Proportion of days covered; PPY: Per patient-year; PVD: Peripheral vascular disease; RR: Rate ratio; SABA: Short-acting β_2 -agonist; SAMA: Short-acting muscarinic antagonist; SD: Standard deviation; TIA: Transient ischemic attack; TIO: Tiotropium.

Table 3. Summary of real-world studies included in the review[†] (cont.).

Article (year)	Outcomes assessed	Data source	Study design	Confounder adjustment method	Time period for treatment initiation	Exclusion criteria	Age (years)	Study period	Sample size (n)	Results: appropriate initiation
										OCS monotherapy: BFC, 45.8% vs TIO, 34.6%; OR: 1.60 (95% CI: 1.50–1.70) Baseline HCRU: similar percentages for COPD-related inpatient stays or ER visits COPD outpatient visits: BFC, 68.4% vs TIO, 74.4%; OR: 0.75 (95% CI: 0.70–0.80) Outpatient visit with antibiotics or OCS: BFC, 44.0% vs TIO, 33.0%; OR: 1.59 (95% CI, 1.49–1.69) Baseline exacerbations: BFC, 50.2% vs TIO, 40.4% Driven by OCS requiring exacerbations: BFC, 45.8% vs TIO, 34.6% All-cause costs: Total: BFC, US\$17,259 vs TIO, US\$17,926; mean difference: -US\$667 (95% CI: -US\$1254 to -US\$88) Inpatient: BFC, US\$7459 vs TIO, US\$8599; mean difference: -US\$1140 (95% CI: -US\$1712 to -US\$521) COPD-related costs: Total: BFC, US\$1718 vs TIO, US\$1930; mean difference: -US\$213 (95% CI: -US\$302 to -US\$118) Inpatient: BFC, US\$627 vs TIO, US\$767; mean difference: -US\$140 (95% CI: -US\$190 to -US\$85)

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AMD: Adjusted mean difference; BFC: Budesonide/formoterol combination; CAD: Coronary artery disease; CHF: Congestive heart failure; COPD: Chronic obstructive pulmonary disease; ED: Emergency department; FSC: Fluticasone propionate/salmeterol combination; HCRU: Healthcare resource utilization; HR: Hazard ratio; ICS: Inhaled corticosteroid; ICU: Intensive care unit; IPR: Ipratropium; ITT: Intent-to-treat; LABA: Long-acting β_2 -agonist; LAMA: Long-acting muscarinic antagonists; LTRA: Leukotriene receptor antagonist; MI: Myocardial infarction; MPR: Medication possession ratio; OCS: Oral corticosteroids; OR: Odds ratio; PDC: Proportion of days covered; PPY: Per patient-year; PVD: Peripheral vascular disease; RR: Rate ratio; SABA: Short-acting β_2 -agonist; SAMA: Short-acting muscarinic antagonist; SD: Standard deviation; TIA: Transient ischemic attack; TIO: Tiotropium.

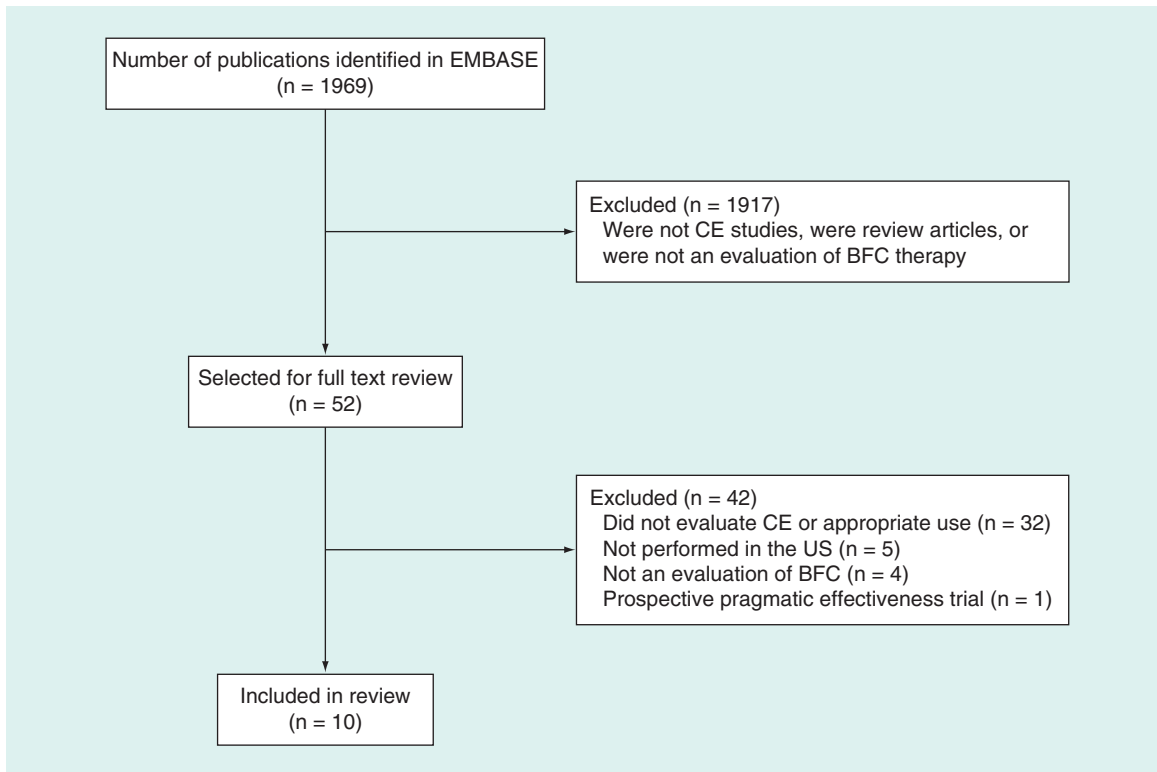


Figure 1. Preferred reporting items for systematic reviews and meta-analyses flow diagram.
BFC: Budesonide/formoterol combination; CE: Comparative effectiveness.

prescription fill of the same ICS/LABA combination during the 12-month follow-up period (Table 3). Propensity score matching was used to balance the study cohorts by age, sex and asthma-related utilization at baseline. From 3122 BFC and 8177 FSC patients meeting study criteria, 3043 BFC initiators were matched to 3043 FSC initiators.

The exacerbation rate among BFC initiators, defined as the total number of exacerbations during the postindex period divided by the total follow-up time in person years, was lower than that of FSC initiators (0.83 vs 0.89 per patient-year, respectively). After adjustment for asthma severity and exacerbation risk, this difference remained statistically significant (0.85 vs 0.93, respectively; rate ratio [RR]: 0.92 [95% CI: 0.85–0.99; $p = 0.0255$]). The BFC cohort had significantly fewer oral corticosteroid (OCS) prescription fills (mean: BFC, 0.73; FSC, 0.79; $p = 0.0299$) and fewer emergency department (ED) visits (mean: BFC, 0.08; FSC, 0.10; $p = 0.0486$), but the numbers of patients with any asthma-related hospitalization were similar (BFC, $n = 45$; FSC, $n = 46$). An unadjusted, descriptive analysis of high-dosage (BFC, 160/4.5 μg [delivered dose]; FSC, 250/50 or 500/50 μg [metered dose]) or low-dosage (BFC, 80/4.5 μg ; FSC, 100/50 μg) treatments found that exacerbation rates (events per year) were similar for low-dosage treatments (BFC, 0.68; FSC, 0.66) but were slightly lower for BFC initiators among high-dosage treatments (BFC, 0.88; FSC, 0.95 [0.86 for 250/50 μg and 1.33 for 500/50 μg]). The percentage of patients needing short-acting β_2 -agonist (SABA) prescription fills was lower in the BFC cohort (66.4 vs 71.2%; $p = 0.0027$); the adjusted mean number of SABA fills per patient was also lower (2.4 vs 2.6; $p = 0.0221$). Treatment adherence (proportion of days covered), was minimally lower in the BFC cohort (adjusted mean proportion of days covered: 0.46 vs 0.49; $p < 0.001$), suggesting adherence differences did not explain the observed differences in health-related outcomes. In this study, patients had to have ≥ 2 BFC or FSC prescription fills for inclusion, making adherence figures biased toward increased usage compared with studies discussed later in this review.

The Tunceli *et al.* analysis rated highly in all categories of study quality (Table 4) [21]. The limitations were mostly related to inherent limitations of administrative claims data, including possible misclassification of asthma diagnosis or exacerbation events and questionable generalizability to populations not covered by commercial insurance or living outside of the USA. Formulary design and differential prescribing patterns between pulmonary specialists and primary care physicians have previously been found to result in a greater uptake of newly approved brand

Table 4. Budesonide/formoterol combination articles[†] rated by strengths: design, data, analysis, reporting, interpretation and overall quality.

	Outcomes postinitiation studies						Initiation of treatment studies			
	Roberts <i>et al.</i> (2011)	Mapel <i>et al.</i> (2013)	Tunceli <i>et al.</i> (2014a)	Kern <i>et al.</i> (2015)	Trudo <i>et al.</i> (2015)	Davis <i>et al.</i> (2016)	Blanchette <i>et al.</i> (2009)	Ye <i>et al.</i> (2009)	Tunceli <i>et al.</i> (2014b)	Kern <i>et al.</i> (2014)
Design (%)	79	79	81	94	89	86	77	73	81	71
Data (%)	90	80	95	90	93	87	100	81	94	69
Analysis (%)	38	50	63	33	58	33	50	33	75	17
Reporting (%)	86	79	82	86	86	71	86	79	89	64
Interpretation (%)	75	81	78	75	75	67	79	71	100	63
Overall (%) [‡]	79	78	83	83	84	76	83	74	89	65

Percentage of items satisfactorily addressed by each article within each domain of the quality assessment tool, plus the overall percentage of items on the questionnaire satisfactorily addressed.

[†]The authors only report on studies with budesonide/formoterol combination delivered by pressurized metered-dose inhalers.

[‡]All articles scored 100% on conflict of interest reporting (two items) which were included in the overall quality rating.

medications among patients with more severe asthma [26–28]. However, patients in each treatment group in the Tunceli *et al.* analysis were matched on asthma-related utilization at baseline. Thus, this analysis is less likely to have been affected by ‘novelty bias’, a form of indication or channeling bias in which patients with more severe disease have a greater likelihood of receiving prescriptions for novel or recently released medications [26].

Appropriate use of BFC in asthma

After BFC was approved for the treatment of asthma in the USA, the National Asthma Education and Prevention Program (NAEPP) released updated clinical practice guidelines for asthma [29]. These guidelines stated that ICS/LABA combination products should be reserved for patients whose disease requires two controller therapies or who are not adequately controlled with other maintenance therapies. The following appropriate-use studies investigated whether these recommendations were followed for patients treated in the general population. Exclusion criteria are presented in Table 3.

Blanchette *et al.* examined initiation of ICS/LABA combination therapy (BFC or FSC) based on preinitiation HCRU [30]. This analysis used a large national commercial insurance database and included patients with asthma aged 12–64 years continuously enrolled for 12 months prior to initiation of therapy from 1 July 2007–30 June 2008. Initiation of ICS/LABA therapy was considered appropriate if patients had claims during the preinitiation period for an ICS or leukotriene receptor antagonist (LTRA), an asthma-related ED visit or hospitalization, ≥ 2 courses of OCS or ≥ 6 canisters of a SABA. These criteria were based on the NAEPP guidelines and a comprehensive literature review; HCRU criteria assessed risk of exacerbations and the SABA criterion was used as a measure of poor disease control.

During the study period, 16,205 patients initiating ICS/LABA therapy met the inclusion/exclusion criteria. Of these, 788 of 1417 patients (55.6%) in the BFC group and 5572 of 14,788 patients (37.7%) in the FSC group met ≥ 1 criterion for appropriate use (odds ratio [OR]: 1.79; 95% CI: 1.60–2.00; $p < 0.001$). Greater percentages of BFC than FSC users met the individual criteria for appropriate use: previous ICS use (31.1 vs 11.0%), previous LTRA use (29.6 vs 18.6%), ≥ 2 courses of OCS (18.2 and 11.2%), and high SABA use (9.7 vs 6.1%; $p < 0.001$ for all comparisons). There were no differences in percentages of patients with asthma-related ED visits or hospitalizations (BFC, 5.6%; FSC, 5.9%). Factors potentially associated with appropriate use included receipt of the initial ICS/LABA prescription from a pulmonologist or allergist and presence of specific comorbidities (allergic rhinitis, sinusitis, gastroesophageal reflux disease and acute respiratory infection; all $p < 0.001$).

Ye *et al.* conducted a retrospective cohort study of commercially insured US patients with asthma aged ≥ 12 years who initiated BFC or FSC therapy in 2007 and were continuously enrolled for 12 months prior to the initial prescription fill [31]. Use of ICS/LABA combination therapy was considered appropriate if patients met any of the following criteria preinitiation: use of ICS or an LTRA, an asthma-related ED visit or hospital admission, ≥ 2 prescription claims for OCS with a days’ supply of < 21 days, or ≥ 6 SABA prescription fills.

During the study period, 203,348 patients with a claim for ICS/LABA therapy were identified, and 24,231 patients met inclusion criteria, with 993 initiated on BFC and 23,238 on FSC. The average age was 38.6 years, and 38.4% were male. Only 37.6% (9107 patients) in the total population were considered appropriate candidates for

initiating ICS/LABA (BFC, 58.4%; FSC, 36.7%; $p < 0.0001$). After adjusting for other factors, the odds that the BFC cohort was appropriately prescribed ICS/LABA compared with the FSC cohort were twofold greater (OR: 2.01; 95% CI: 1.76–2.30; $p < 0.001$). Odds of appropriate use decreased with increased age, greater number of comorbidities, increased prescription fills for other medications and visiting pulmonary or allergy specialists.

Tunceli *et al.* also conducted a retrospective appropriate-use study using the same large national commercial insurance database analyzed in their CE analysis [32]. Patients with asthma aged 12–64 years who later initiated ICS/LABA therapy between 1 June 2007 and 31 December 2010 were included. Appropriate use was defined using the same criteria as the Blanchette and Ye studies [30,31].

A total of 50,541 BFC, FSC and mometasone/formoterol fumarate users satisfied all study inclusion/exclusion criteria, but the latter were excluded because there were only 126 patients, leaving 11,718 in the BFC cohort and 38,697 in the FSC cohort. A higher percentage of BFC patients (BFC, 57.3%; FSC, 51.6%; adjusted OR: 1.21; [95% CI: 1.16–1.27]) met ≥ 1 of the appropriate-use criteria. The largest difference in appropriate-use criteria was in prior asthma medication usage, particularly ICS (BFC, 24.9%; FSC, 14.8%), but also LTRA (BFC, 26.8%; FSC, 21.4%). Percentage differences for high-risk utilization during the preinitiation period were mixed across the various criteria, including asthma-related ED visits (BFC, 9.8%; FSC, 12.1%), hospitalizations (BFC, 4.9%; FSC, 6.3%), ≥ 2 OCS fills (BFC, 17.4%; FSC, 14.6%) and fills of ≥ 6 SABA canisters (BFC, 8.3%; FSC, 7.0%), with $p < 0.001$ for all comparisons. Greater percentages of BFC patients were diagnosed with allergic rhinitis (41.4 vs 31.6%) and sinusitis (28.9 vs 25.1%), which may have accounted for some of the OCS and LTRA differences. More allergists/immunologists and pulmonologists prescribed BFC (30.5%) versus FSC (17.5%), which was also noted in the other two appropriate-use studies. A unique finding in this study, however, was that appropriate use of both agents decreased every year of the study. It is important to note that concepts about ‘appropriate use’ of ICS/LABA, and particularly ICS/formoterol, have evolved substantially since the 2007 NAEPP guidelines [29] that were the foundation of these three analyses. Current Global Initiative for Asthma (GINA) guidelines [33] recommend much broader application of ICS/formoterol, including use as a first-line treatment and in patients with milder disease.

Limitations of the Blanchette and Ye studies included limited information about the study populations and analysis methods [30,31]. Tunceli rated higher in these areas due to more detailed reporting [32]. There was also limited discussion about the clinical relevance of the results. The authors acknowledged that claims data do not contain information on asthma severity in terms of clinical symptoms and pulmonary function testing, which would have been appropriate indications for ICS/LABA therapy. Claims data also do not capture prescriptions that are not filled or medication samples obtained during an office visit. In addition, factors such as time of approval may impact appropriate-use results when comparing two treatments.

CE of BFC in COPD

Roberts *et al.* were the first to compare the effectiveness of BFC and FSC using data from the USA for healthcare costs, HCRU, adherence and COPD exacerbations [34]. For this study, administrative claims data from a database of > 50 million patients were used to identify those with COPD newly initiated on ICS/LABA therapy. Propensity-matching techniques were used to select highly similar BFC and FSC cohorts based on age, sex, geographic region, treatment initiation year, comorbid conditions, months of follow-up and preindex COPD episode utilization. Cost and effectiveness outcomes were total healthcare expenditures, exacerbation events (defined as hospitalizations, ED visits or outpatient visits associated with OCS or antibiotic prescription fills), treatment medication adherence, and claims for rescue medications and outpatient encounters during the 3–6-month follow-up period.

After all propensity-matching methods were applied, 6770 patients (3385 BFC and 3385 FSC) who initiated treatment during the study period (1 January 2007–31 January 2009) were compared. Fewer BFC patients had claims for SABAs (34.7 vs 39.5%; $p < 0.001$) and ipratropium (7.8 vs 9.8%; $p < 0.005$) than FSC patients, suggesting that they had better overall symptom control. No significant differences were seen in other clinical outcomes, including exacerbation events (BFC, $n = 2146$ [63.4%]; FSC, $n = 2116$ [62.5%]; $p = 0.45$). BFC patients had slightly fewer office visits related to pneumonia (patients with ≥ 1 visits: BFC, $n = 93$ [2.7%]; FSC, $n = 121$ [3.6%]; $p = 0.052$). However, the percentage of patients hospitalized for pneumonia was comparable (patients with ≥ 1 hospitalizations: BFC, $n = 60$ [1.8%]; FSC, $n = 65$ [1.9%]; $p = 0.652$).

The major limitations of this study are common to propensity-matched CE studies when one treatment is used much less commonly than the other [35]. BFC had just been approved for COPD treatment at the beginning of the study period, whereas FSC had already been available for this indication for 6 years; therefore, the pool of BFC patients meeting inclusion criteria was 3390 versus 90,070 for FSC [34]. Before matching, there were subtle

differences between the BFC and FSC populations (e.g., age). The large number of FSC patients allowed for near-complete matching of all BFC patients and a high degree of confidence about the results derived from the patients who were compared, but there is uncertainty about how well the results can be extrapolated to those with COPD who were not examined. In addition, the follow-up period for BFC was short (3–6 months), which does not measure 1-year exacerbation outcomes or the effect of seasonal issues, and also prevents comparison of potential longer-term differences in outcomes between BFC and FSC users.

In another comparison of BFC and FSC using the same database, Mapel *et al.* examined the medications' effectiveness in reducing COPD exacerbations and SABA use [36]. Using propensity-score methods to create clinically similar cohorts, 3852 BFC patients from a large national database were matched 1:1 to FSC patients at initiation of treatment with either combination. Exacerbations resulting in an ED visit or hospitalization for COPD were captured during the periods 6 months before and after initiation of BFC or FSC. Patients were also compared by their SABA prescription fills before and after initiation of treatment and were stratified as no fills (no SABA prescription fills), low (one fill) or high numbers of fills (≥ 2).

Hospitalizations for COPD exacerbation were reduced by approximately 20% among initiators of either treatment (BFC = 6.2% patients with exacerbation prior to treatment vs 4.9% post; $p = 0.008$; FSC = 5.8% prior vs 4.7% post; $p = 0.023$). Increased SABA use was associated with higher numbers of exacerbations during the baseline period (9% in high fills, 6.6% in low fills and 4.9% in no fills), and increased SABA use at baseline was also a significant predictor of exacerbations during the follow-up period (high fill number vs no fills, hazard ratio [HR]: 1.38 [95% CI: 1.08–1.76]; low fills vs no fills, HR: 1.58 [95% CI: 1.21–2.06]). Most of the decrease in COPD-related ED visits or hospitalizations after initiation of ICS/LABA treatment was found among the patients with a high number of SABA fills (change in percentage of population with exacerbations: -4.1% [$p < 0.01$], +0.1% [not significant] and -0.6% [not significant] among high, low and no fill patients, respectively). SABA use was reduced overall after initiation of either ICS/LABA, but a higher percentage of BFC patients had no SABA fills after initiation (59.3 vs 56.2%; $p < 0.01$).

This study has a similar design as the Roberts analysis [34] and shares the same benefits and limitations introduced by the propensity score-matching technique. Adherence to treatment, a factor that potentially could have affected outcomes, was not examined, and the 6-month follow-up period was relatively short.

Kern *et al.* conducted a CE study among patients with COPD initiating BFC versus FSC to examine exacerbation rates during a 12-month period [37]. A US national health insurance database of >31 million people from 1 March 2009 to 31 March 2012 was used to create the study cohort. New users of BFC or FSC aged ≥ 40 years with a diagnosis of COPD were included. A total of 3697 BFC initiators were matched 1:1 to FSC patients using propensity score-matching techniques.

There were no significant differences in the adjusted exacerbation rates between BFC (0.88) and FSC (0.86) during the follow-up period and no differences between treatments when stratified by type of exacerbation. Additionally, there were no significant differences between cohorts in a series of sensitivity and secondary analyses, including time to first exacerbation. During the follow-up period, 48% of BFC and 47% of FSC patients experienced ≥ 1 exacerbation event, and 6.2% of BFC and 6.9% of FSC patients had ≥ 1 COPD-related hospitalization. Adherence was poor in both groups: BFC patients averaged 3.8 prescription fills during the 12-month follow-up period versus 4.0 for FSC ($p = 0.01$), and 33.9% of BFC patients filled only their initial prescription versus 32.7% of FSC patients. In contrast to the previous two studies, there were no significant differences in SABA, short-acting muscarinic antagonist, or combination SABA/short-acting muscarinic antagonist inhaler utilization.

The Kern study was propensity score matched. The percentage of patients using BFC was more balanced than in the previous two studies, making the results more generalizable. Of the 10,227 patients with COPD who met all inclusion/exclusion criteria, 3788 (37.0%) initiated BFC, and among these, 3697 (97.6%) were matched to an FSC patient. This study also captured pneumonia-related events and found no significant difference in the percentage of patients having pneumonia after treatment initiation, either by total events (BFC, 17.3%; FSC, 19.0%; $p = 0.1926$) or only among those hospitalized (BFC, 8.9%; FSC, 10.3%; $p = 0.0937$).

In a subsequent analysis using the same database as Kern and the same matched patients, Davis *et al.* compared HCRU and costs among patients with COPD newly initiated on ICS/LABA therapy during the first 12 months after initiating BFC or FSC [38]. HCRU differences between the BFC and FSC populations did not reach statistical significance, but there were trends toward greater utilization among the FSC cohort. For example, the percentages of patients with all-cause hospitalizations (BFC, 30.6%; FSC, 31.9%), COPD-related hospitalizations (BFC, 6.2%; FSC, 6.9%), pneumonia-related hospitalizations (BFC, 8.9%; FSC, 10.3%) and all-cause intensive care

unit admissions (BFC, 6.0%; FSC, 6.5%) were all higher among FSC patients. The 12-month mean all-cause hospitalization cost was US\$8519 per BFC patient and US\$10,314 per FSC patient (adjusted mean difference [AMD]: US\$1242 [95% CI: -2082 to -288; $p = 0.01$]), the mean COPD-related hospitalization cost was US\$966 per BFC patient and US\$1202 per FSC patient (AMD: US\$248 [95% CI: -377 to -147; $p < 0.001$]) and the mean pneumonia-related hospitalization cost was US\$2728 per BFC patient and US\$3409 per FSC patient (AMD: US\$640 [95% CI: -894 to -349; $p < 0.001$]). Significantly higher costs for FSC relative to BFC in outpatient visits and COPD-related pharmacy costs resulted in a total mean cost of US\$21,580 per BFC patient and US\$24,483 per FSC patient (AMD: US\$1884 [95% CI: -2685 to -1047; $p < 0.001$]).

The Kern and Davis studies rated high on the quality assessment tool (Table 4), with both having the major limitation of lacking detailed information about comorbidities other than asthma [38,39]. The quality assessment tool also emphasizes sensitivity analyses for testing key assumptions of study design or modeling, which can be difficult when using a propensity score-matching system because the purpose of matching is to neutralize the effects of the known confounding variables.

Trudo *et al.* published the only CE study of patients with COPD initiating BFC or tiotropium (TIO) in the USA [40]. Using the same database as the Kern and Davis studies and almost the same study period (1 March 2009–28 February 2012), 4051 patients with COPD without prolonged OCS use who were new users of BFC or TIO were identified. Of these, 1381 initiated BFC; 1198 were matched 1:1 to TIO initiators using propensity score-matching methods similar to the previous studies. Patients were followed for ≥ 12 months for the primary outcome of time to first exacerbation, with prespecified secondary outcomes including exacerbation rates, HCRU and costs, adherence and other COPD-related medication prescription fills.

The median time to first COPD exacerbation was 352 days in the BFC cohort and 243 days in the TIO cohort, with a significant HR of 0.78 (95% CI: 0.70–0.87; $p < 0.001$), and 51% of BFC patients had ≥ 1 exacerbation during the follow-up period compared with 59% of TIO patients. The sensitivity and subgroup analyses were consistent with these results, including an examination limited to patients without any prior asthma diagnosis, who had a median time to exacerbation of 343 days on BFC and 273 days on TIO (HR: 0.83; 95% CI: 0.72–0.96; $p = 0.011$). Exacerbation rates were correspondingly lower in the total BFC cohort (BFC, 1.23 per patient-year; TIO, 1.50 per patient-year; RR: 0.82 [95% CI: 0.73–0.91; $p < 0.001$]).

All-cause HCRU was not significantly different between BFC and TIO, but the number of patients with ≥ 1 COPD-related hospitalization (BFC, $n = 90$ [7.5%]; TIO, $n = 113$ [9.4%]; $p = 0.01$) or COPD-related outpatient visits (BFC, $n = 889$ [74.2%]; TIO, $n = 1040$ [86.8%]; $p < 0.001$) were significantly different. Substantially fewer BFC patients added TIO ($n = 162$, 13.5%) than TIO patients added an ICS/LABA to their treatment regimen ($n = 441$, 36.8%), accounting for much of the difference in COPD-related mean outpatient pharmacy costs per patient (BFC, US\$1310; TIO, US\$1750; $p < 0.001$). The COPD-related hospitalization and outpatient visit differences translated to significantly higher mean costs per patient for hospitalization (BFC, US\$982; TIO, US\$1433; $p < 0.001$) and outpatient visits (BFC, US\$1287; TIO, US\$1745; $p < 0.001$). The increased COPD-related medical and pharmacy costs accounted for slightly more than half of the difference in mean per-patient total all-cause costs between the BFC (US\$21,681) and TIO (US\$24,374) cohorts.

In terms of adherence, 41% of BFC patients filled their index medication once versus 31% of the TIO patients. The average fills for the BFC cohort (3.3 for 12 months) were also lower than TIO (4.3). However, treatment modifications among BFC patients were less common than for TIO patients (18 and 37% of each cohort, respectively), and the time to first treatment modification was later for BFC patients (HR: 0.41 [95% CI: 0.35–0.49]).

The Trudo study rated highly in all quality categories for the quality assessment tool (Table 4). However, the poor adherence in a retrospective analysis of intent-to-treat cohorts suggests that the results must be considered with caution. Unmeasured clinical factors related to outcomes, such as disability and comorbidities, may have influenced treatment choice, and residual bias by indication could exist. For example, the TIO patients meeting all inclusion/exclusion criteria for this study prior to propensity matching had substantially more COPD-related hospitalizations (28.4 vs 19.0%) and ED visits (31.9 vs 24.8%) during the baseline year.

Appropriate use of BFC (COPD)

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) report for COPD treatment is updated annually, but in general the report has recommended starting with long-acting bronchodilators first and reserving ICS/LABA therapy for patients with high risk of COPD exacerbations (GOLD group C or D); long-acting

muscarinic antagonists (LAMA)/LABAs are also recommended for patients with persistent symptoms or further exacerbations (GOLD group B, C or D) [5].

The only published comparison of BFC and long-acting bronchodilator initiation and appropriate use in COPD was conducted by Kern *et al.* [39]. Using the same database analyzed for the authors' BFC versus TIO COPD CE study [37], the clinical and demographic characteristics and resource utilization in the 12-month preinitiation period were examined. However, patients who had used any controller therapy in the preinitiation period other than that cohort's affiliated therapy were included. A total of 6940 BFC and 10,831 TIO patients met all inclusion/exclusion criteria.

BFC patients tended to be younger (mean age: 64.3 vs 66.9 years), female (54.2 vs 50.6%), with more having respiratory comorbidities (particularly asthma [24.7 vs 12.7%]), and had ≥ 1 OCS prescription fill during the preinitiation year (45.8 vs 34.6%), with $p < 0.0001$ for all comparisons. However, similar percentages of BFC and TIO patients had exacerbations requiring hospitalization (7.1 vs 7.0%) or ED visits (7.7 vs 8.6%). The prevalence of most chronic nonpulmonary comorbidities was generally similar except for cardiovascular diseases, which were less common in the BFC cohort.

As a descriptive observational study, this study had difficulty meeting some criteria of the quality assessment tool because most of the analyses were descriptive rather than hypothesis testing. HCRU databases also do not collect pulmonary function testing data, although guidelines have recently been amended to focus more on symptoms and exacerbations as the basis for COPD severity assessments [5]. The demographic differences in the groups may reflect appropriate use since the guidelines support use of ICS/LABA in patients with a history of exacerbations and features of asthma [5]. Nevertheless, this study does reveal some of the important factors associated with prescribers' choices of initial COPD treatment.

Discussion

This review of current BFC CE and appropriate-use literature identified several clinically useful findings, and this is among the first applications of recently compiled quality assessment tools for this type of research. These instruments demonstrate that the BFC CE articles addressed most of the areas cited by expert panels as important considerations for this area of research. A few of the items included in these instruments were not applicable to appropriate-use analyses; nevertheless, the instruments were still useful for objectively comparing the quality of the appropriate-use articles. The instruments also identified some important areas for which more investigation is needed, such as the impact of comorbidities on clinical outcomes and appropriate treatment choices.

Conclusions: BFC CE studies (asthma)

The study of BFC versus FSC use published by Tunceli found that BFC users had fewer exacerbations, a difference that remained significant after adjustment for asthma severity and exacerbation risk [21]. Most of the difference was found among patients using high-dosage treatments. A Cochrane analysis of five RCTs comparing BFC and FSC in adults and children with asthma (total N = 5537 adults) was unable to make definitive conclusions about the superiority of either product due to uncertainty about asthma exacerbation measures [20]. Additional CE analysis of retrospective databases or prospective pragmatic clinical trials of real-world asthma populations would be useful to examine the relative benefits of BFC versus other asthma treatments in the USA.

Conclusions: BFC appropriate-use studies (asthma)

Perhaps the most remarkable finding among the appropriate-use studies in asthma is the consistency of the findings across studies. A slight majority of patients with asthma initiating BFC [21,30,31] met the definition of appropriate use by having utilization levels that indicated they were at greater risk of exacerbations based on ED visits or hospitalizations for asthma, or increased OCS use, or had tried other controllers first (ICS alone and/or LTRAs + SABA) before stepping up treatment. Also, each study found that patients with asthma initiating FSC during the study periods were less likely to have met these objective measures based on utilization. Clinically, asthma severity is based primarily on subjective measures that are not likely to be captured in healthcare administrative data, such as the presence of wheezing on physical exam or patient-reported incidence of nighttime symptoms. The fact that retrospective data demonstrate such reproducible objective evidence of increased asthma-related HCRU supports the validity of this approach as a proxy for estimating asthma severity in healthcare-based populations. It is also remarkable that factors associated with appropriate use were consistent among these studies, such as provider type (i.e., pulmonary or allergy specialist vs primary care provider) and regional differences across the USA. The

finding that asthma specialists were more likely than primary care providers to prescribe BFC suggests the potential for the novelty bias discussed previously.

It is important to note that the definition of ‘appropriate use’ for ICS/LABA treatment in asthma has changed substantially since the 2007 NAEPP guidelines, which were heavily influenced by the FDA ‘black box’ warning about LABA use in asthma, and recommended use only after failing more conservative therapy [26]. Since that time, studies have demonstrated that ICS/LABA treatment does not result in significantly more serious adverse events than ICS monotherapy [41,42]. The black box warning for LABA-containing treatments was removed in 2017 [43]. The current GINA guidelines now recommend ICS/LABA as a first-line asthma treatment. Furthermore, GINA recommends low-dose ICS/formoterol for those with infrequent symptoms, and as both a maintenance and reliever inhaler for patients with asthma who have moderate persistent symptoms. These new applications are considered ‘off label’ use per US FDA approved prescribing information. Nevertheless, our findings suggest that guidelines do impact asthma treatment utilization and that this research approach can provide useful and reproducible insights into clinical decisions about asthma treatment.

Conclusions: BFC CE studies (COPD)

COPD exacerbations were an outcome evaluated by the RCTs summarized in Table 2 and were also examined by all five of the BFC studies. In the four studies that compared patients who initiated BFC or FSC, exacerbation rates during the follow-up periods were similar, an expected result given that both are ICS/LABA combinations with subtle differences in pharmacology and delivery. There were trends favoring BFC in exacerbations defined as outpatient visits associated with OCS or antibiotic prescription fills in the Mapel study and BFC in exacerbations giving rise to hospitalizations for COPD in the Kern and Davis studies [36–38]. Although the comparison groups were closely matched, these are retrospective observational studies, so it is possible that the observed differences are due to selection bias or residual confounding. Nevertheless, the economic study by Davis demonstrates that even small differences in COPD exacerbation rates could result in substantial cost impacts [38].

Comparing BFC to TIO, the Trudo study found that BFC patients had substantially lower exacerbation rates and longer time to first exacerbation [40]. These differences are noteworthy given that they confirm, using real-world data, results that have been demonstrated in clinical trials. After initial therapy, far more TIO patients added an ICS/LABA than BFC patients added TIO, a phenomenon also observed in a recent comparison of FSC and TIO [44]. Similar reductions in COPD exacerbations were reported in BFC versus TIO effectiveness in a study from Canada [45]; however, the study was conducted using a BFC device not approved in the USA. It is possible that the patient identification and matching methods applied biased selection toward populations that were predisposed to having a more favorable response to ICS/LABA treatment. The observation of such large differences in FSC and TIO CE suggests that a tailored approach to COPD treatment could yield improvements in exacerbation outcomes.

Several other useful observations were made in these studies. The rate of exacerbations decreased by 20–25% after initiation of ICS/LABA treatment in the Mapel study, which is consistent with the reduction in exacerbations noted in RCTs (Table 2). Davis noted reductions in the percentage of patients with ≥ 1 COPD-related hospitalization (11.4% before BFC treatment, 6.2% after) and ≥ 1 COPD-related ED visit (14.1% before BFC, 12.3% after), which was similar to the reductions among matched FSC patients [38]. Roberts demonstrated that SABA use decreased after initiation of therapy, with the reduction being significantly greater among BFC users [34]. However, Mapel demonstrated that reduced SABA use was mostly driven by patients with higher baseline SABA use [36]. The reduction in SABA use suggests that patients being treated with BFC have less need for ‘rescue’ bronchodilator use to treat acute respiratory symptoms [38]. Increased SABA use was correlated with increased exacerbation risk at baseline and was also predictive of future exacerbations [36], confirming that SABA fills are a valid indicator of COPD severity. Pneumonia-related events were uncommon, but Roberts found a slightly lower rate among BFC users which was not seen in the Kern study [34,37]. A systematic review addressing the risk of pneumonia with ICS versus placebo or LABA in patients with COPD found no increased risk of pneumonia with budesonide-containing inhaled therapies, whereas therapies containing fluticasone propionate were associated with a 43–78% increased risk of pneumonia [46].

Conclusions: BFC appropriate-use studies (COPD)

The most notable finding in the Kern study is that two inhaled treatments with the same indication can have substantially different HCRU based on patient demographic characteristics, comorbidities and prior respiratory

medication utilization [37]. It is interesting to note that the utilization observed during the 2009–2012 study period more closely resembles current GOLD COPD treatment recommendations than the recommendations for ‘appropriate use’ of that time. These observational data support the concept that COPD is a heterogeneous syndrome; patients with COPD may benefit from a personalized approach to treatment.

Limitations of the reviewed studies

Limitations of research in this area include lack of information about comorbidities, particularly concomitant asthma and pneumonia in patients with COPD. Poor adherence to any of these long-acting respiratory medications casts some doubt about the causality of the relationship between the initiated treatment and observed outcomes. At the time these studies were conducted, use of FSC was more widespread than use of BFC pMDI, which may have introduced a ‘novelty bias’, wherein more patients with more severe disease were more likely to be prescribed the newer medication and thus could have affected appropriate use and CE measures. Although an intent-to-treat design provides information on the CE of the initial treatment decision, future analyses may benefit from implementing newer approaches that incorporate adherence and treatment switching into the analysis, such as marginal structural models and microsimulation techniques.

Future perspective

COPD is the third leading cause of death in the USA, and one in 13 Americans (~25 million people) have asthma. Development of ICS/long-acting β -agonist combinations such as budesonide/formoterol represented a breakthrough in the treatment of both respiratory diseases. Newer combination therapies of inhaled treatments and innovative biologic therapies have recently been released and many more are in development, but their roles in treatment are uncertain, and how they will affect outcomes among patients in the general population is also unclear. CE studies of BFC provide insights into the specific benefits of treatment among asthma and COPD in the general population, opportunities for improvement in treatment, and benchmarks for measuring the impact of newer generations of treatment. This application of recently developed assessment tools for the quality of CE research in respiratory studies also demonstrates how they can guide future outcomes research in asthma and COPD.

Summary points

Background

- Interest in comparative effectiveness (CE) studies of asthma and chronic obstructive pulmonary disease (COPD) treatments has increased commensurate with the availability of many new treatment options.
- Expert panels have recently provided objective tools for assessing the quality and comprehensiveness of CE research studies in respiratory diseases.
- This review applied these tools to published peer-reviewed CE and appropriate use evaluations of budesonide/formoterol combination (BFC) inhalers for the treatment of asthma and COPD.

Results

- A systematic search (January 2006–August 2019) of EMBASE using keywords relating to asthma, COPD and BFC, alone or compared with similar products yielded four evaluations related to treatment of asthma and six for COPD that met all inclusion and exclusion criteria.
- Based on the factors identified by the CE evaluation tools, we found that the available BFC CE and appropriate-use articles were of good quality, but each also had specific limitations.
- Comparisons of BFC versus fluticasone/salmeterol combination in asthma found total exacerbations were lower among BFC users, even after adjustment for factors associated with asthma severity and exacerbation risk. Appropriate-use studies for asthma treatment consistently found that BFC patients were more likely to have met guideline recommendations for escalation of treatment.
- BFC comparisons with fluticasone/salmeterol combination or tiotropium for COPD found differences in exacerbation rates and use of rescue inhalers. A comparison of appropriate use between BFC and tiotropium in COPD revealed several factors associated with choice of treatment and differences in clinical outcomes.

Conclusion

- This review demonstrates how recent respiratory disease expert panel and good research and practice recommendations for CE research can be usefully applied.
- Current CE and appropriate use studies in BFC for asthma and COPD confirm that treatment efficacy translates to clinical effectiveness in a range of important outcomes and identify opportunities for improving CE research in newer respiratory treatments.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/cer-2019-0161

Author contributions

D Mapel contributed to the study design and protocol development, article review and final selection and manuscript writing and editing. M Roberts identified parameters of the literature search, identified potential review tools, developed the quality assessment tool, reviewed articles, summarized findings and drafted the manuscript. J Davis was involved with the study design, review/rating of articles and manuscript review. All authors provided final approval of the manuscript prior to submission.

Financial & competing interests disclosure

D Mapel has participated in randomized clinical trials of asthma and COPD treatments that were sponsored by AstraZeneca and clinical trials and retrospective COPD treatment studies that were sponsored by GlaxoSmithKline. M Roberts did not receive compensation for work involved with this review. She has received grant funding for other respiratory-related research projects from GlaxoSmithKline, Pfizer and Boehringer Ingelheim. J Davis is an employee of AstraZeneca. This review was supported by AstraZeneca. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Editorial support was provided by Shane Walton, PhD, of MedErgy (PA, USA), which was in accordance with Good Publication Practice (GPP3) and was funded by AstraZeneca (DE, USA).

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References

Papers of special note have been highlighted as: ● of interest; ●● of considerable interest

1. National Asthma Education Prevention Panel. Expert Panel Report 3: guidelines for the diagnosis and management of asthma summary report 2007. *J. Allergy Clin. Immunol.* 120, S94–S138 (2007).
2. Su KC, Tsai CC, Kuo LC, Kuo SH, Perng DW. Budesonide/formoterol combination as a maintenance and rescue therapy: physicians' perspectives. *J. Asthma* 46(7), 647–651 (2009).
3. Johansson G, Stallberg B, Tornling G *et al.* Asthma treatment preference study: a conjoint analysis of preferred drug treatments. *Chest* 125(3), 916–923 (2004).
4. Celli BR. Update on the management of COPD. *Chest* 133(6), 1451–1462 (2008).
5. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease (2018 Report) (2018). <https://goldcopd.org/gold-reports>
6. Corren J, Korenblat PE, Miller CJ, O'Brien CD, Mezzanotte WS. Twelve-week, randomized, placebo-controlled, multicenter study of the efficacy and tolerability of budesonide and formoterol in one metered-dose inhaler compared with budesonide alone and formoterol alone in adolescents and adults with asthma. *Clin. Ther.* 29(5), 823–843 (2007).
7. Noonan M, Rosenwasser LJ, Martin P, O'Brien CD, O'Dowd L. Efficacy and safety of budesonide and formoterol in one pressurized metered-dose inhaler in adults and adolescents with moderate to severe asthma: a randomised clinical trial. *Drugs* 66(17), 2235–2254 (2006).
8. Szafranski W, Cukier A, Ramirez A *et al.* Efficacy and safety of budesonide/formoterol in the management of chronic obstructive pulmonary disease. *Eur. Respir. J.* 21(1), 74–81 (2003).
9. Calverley PM, Boonsawat W, Cseke Z, Zhong N, Peterson S, Olsson H. Maintenance therapy with budesonide and formoterol in chronic obstructive pulmonary disease. *Eur. Respir. J.* 22(6), 912–919 (2003).
10. Tashkin DP, Rennard SI, Martin P *et al.* Efficacy and safety of budesonide and formoterol in one pressurized metered-dose inhaler in patients with moderate to very severe chronic obstructive pulmonary disease: results of a 6-month randomized clinical trial. *Drugs* 68(14), 1975–2000 (2008).
11. Rennard SI, Tashkin DP, McElhattan J *et al.* Efficacy and tolerability of budesonide/formoterol in one hydrofluoroalkane pressurized metered-dose inhaler in patients with chronic obstructive pulmonary disease: results from a 1-year randomized controlled clinical trial. *Drugs* 69(5), 549–565 (2009).
12. Ferguson GT, Tashkin DP, Skarby T *et al.* Effect of budesonide/formoterol pressurized metered-dose inhaler on exacerbations versus formoterol in chronic obstructive pulmonary disease: the 6-month, randomized RISE (Revealing the Impact of Symbicort in reducing Exacerbations in COPD) study. *Respir. Med.* 132, 31–41 (2017).

13. Sharafkhaneh A, Southard JG, Goldman M, Uryniak T, Martin UJ. Effect of budesonide/formoterol pMDI on COPD exacerbations: a double-blind, randomized study. *Respir. Med.* 106(2), 257–268 (2012).
14. Grembale RD, Pelaia G, Naty S, Vatrella A, Tranfa CM, Marsico SA. Comparison of the bronchodilating effects of inhaled formoterol, salmeterol and salbutamol in asthmatic patients. *Pulm. Pharmacol. Ther.* 15(5), 463–466 (2002).
15. Ismaila A, Corriveau D, Vaillancourt J *et al.* Impact of adherence to treatment with tiotropium and fluticasone propionate/salmeterol in chronic obstructive pulmonary diseases patients. *Curr. Med. Res. Opin.* 30(7), 1427–1436 (2014).
16. Brixner DI, Lenhart G, Young DC, Samuelson WM. The effect of fixed combination of fluticasone and salmeterol on asthma drug utilization, asthma drug cost, and episodes of asthma exacerbations. *Curr. Med. Res. Opin.* 23(11), 2887–2895 (2007).
17. Schoening SK. Issues and challenges for managed care in the treatment of asthma and chronic obstructive pulmonary disease. *Am. J. Manag. Care* 10(Suppl. 5), S158–S163 (2004).
18. Makhinova T, Barner JC, Richards KM, Rascati KL. Asthma controller medication adherence, risk of exacerbation, and use of rescue agents among Texas Medicaid patients with persistent asthma. *J. Manag. Care Spec. Pharm.* 21(12), 1124–1132 (2015).
19. Vestbo J, Anderson JA, Calverley PM *et al.* Adherence to inhaled therapy, mortality and hospital admission in COPD. *Thorax* 64(11), 939–943 (2009).
20. Lasserson TJ, Ferrara G, Casali L. Combination fluticasone and salmeterol versus fixed dose combination budesonide and formoterol for chronic asthma in adults and children. *Cochrane Database Syst. Rev.* (12), CD004106 (2011).
21. Tunceli O, Williams SA, Kern DM *et al.* Comparative effectiveness of budesonide-formoterol combination and fluticasone-salmeterol combination for asthma management: a United States retrospective database analysis. *J. Allergy Clin. Immunol. Pract.* 2(6), 719–726 (2014).
22. Garrison LP Jr, Neumann PJ, Erickson P, Marshall D, Mullins CD. Using real-world data for coverage and payment decisions: the ISPOR Real-World Data Task Force report. *Value Health* 10(5), 326–335 (2007).
- **Provides a thoughtful assessment of the benefits and limitations of using real-world effectiveness data from observational studies that review effectiveness of therapies beyond clinical efficacy outcomes (traditionally done using randomized control trials).**
23. Berger ML, Martin BC, Huseareau D *et al.* A questionnaire to assess the relevance and credibility of observational studies to inform health care decision making: an ISPOR-AMCP-NPC Good Practice Task Force report. *Value Health* 17(2), 143–156 (2014).
- **One of three core articles that are recommended reading for gaining a better understanding of real-world observational studies. To be an aid in decision making, study findings must be relevant as well as credible. This article highlights assessment of those qualities as well as fatal flaws that would exclude using an article.**
24. Cox E, Martin BC, Van Staa T, Garbe E, Siebert U, Johnson ML. Good research practices for comparative effectiveness research: approaches to mitigate bias and confounding in the design of nonrandomized studies of treatment effects using secondary data sources: the International Society for Pharmacoeconomics and Outcomes Research Good Research Practices for Retrospective Database Analysis Task Force Report—Part II. *Value Health* 12(8), 1053–1061 (2009).
- **One of three core articles that are recommended reading for gaining a better understanding of real-world observational studies. This article is one of a three-part series on using nonrandomized studies for comparative effectiveness research. The authors highlight key issues related to measurement of exposure and outcome that must be considered to minimize bias and confounding.**
25. Roche N, Reddel H, Martin R *et al.* Quality standards for real-world research. Focus on observational database studies of comparative effectiveness. *Ann. Am. Thorac. Soc.* 11(Suppl. 2), S99–S104 (2014).
- **One of three core articles that are recommended reading for gaining a better understanding of real-world observational studies. Standards set forth by the Respiratory Effectiveness Group stressed three points to ensure quality of included studies for analysis: preparation of research, analyses and reporting, and discussion of results.**
26. Filion KB, Eberg M, Ernst P. Confounding by drug formulary restriction in pharmacoepidemiologic research. *Pharmacoepidemiol. Drug Saf.* 25(3), 278–286 (2016).
27. Florentinus SR, Heerdink ER, Van Dijk L, Griens AM, Groenewegen PP, Leufkens HG. Is new drug prescribing in primary care specialist induced? *BMC Health Serv. Res.* 9, 6 (2009).
28. Blais L, Ernst P, Suissa S. Confounding by indication and channeling over time: the risks of beta 2-agonists. *Am. J. Epidemiol.* 144(12), 1161–1169 (1996).
29. National Heart Lung and Blood Institute. National asthma education and prevention program. Expert panel report 3: guidelines for the diagnosis and management of asthma. Full report 2007. (2007). <https://www.nhlbi.nih.gov/health-topics/guidelines-for-diagnosis-management-of-asthma>
30. Blanchette CM, Culler SD, Ershoff D, Gutierrez B. Association between previous health care use and initiation of inhaled corticosteroid and long-acting beta2-adrenergic agonist combination therapy among US patients with asthma. *Clin. Ther.* 31(11), 2574–2583 (2009).
31. Ye X, Gutierrez B, Zarotsky V, Nelson M, Blanchette CM. Appropriate use of inhaled corticosteroid and long-acting beta(2)-adrenergic agonist combination therapy among asthma patients in a US commercially insured population. *Curr. Med. Res. Opin.* 25(9), 2251–2258 (2009).

32. Tunceli O, Kern DM, Williams SA, Pethick N, Suchower L, Ramachandran S. Initiation of inhaled corticosteroid and long-acting b2-adrenergic agonist (ICS/LABA) in asthma. *Am. J. Pharm. Ben.* 6(3), e70–e78 (2014).
33. Global Initiative for Asthma. Global strategy for asthma management and prevention (2019). <https://ginasthma.org/gina-reports/>
34. Roberts M, Mapel D, Petersen H, Blanchette C, Ramachandran S. Comparative effectiveness of budesonide/formoterol and fluticasone/salmeterol for COPD management. *J. Med. Econ.* 14(6), 769–776 (2011).
35. Streiner DL, Norman GR. The pros and cons of propensity scores. *Chest* 142(6), 1380–1382 (2012).
- **This article is a timely reminder that although propensity scores can be a powerful tool, they are a tool that must be used thoughtfully, and optimally will also include sensitivity analyses.**
36. Mapel D, Roberts MH, Blanchette CM, Petersen H, Ramachandran S. Effectiveness of inhaled combined corticosteroid/long-acting bronchodilator treatment in reducing COPD exacerbations and short-acting bronchodilator use. *J. Clin. Outcomes Manag.* 20(2), 60–68 (2013).
37. Kern DM, Davis J, Williams SA *et al.* Comparative effectiveness of budesonide/formoterol combination and fluticasone/salmeterol combination among chronic obstructive pulmonary disease patients new to controller treatment: a US administrative claims database study. *Respir. Res.* 16, 52 (2015).
38. Davis JR, Kern DM, Williams SA *et al.* Health care utilization and costs after initiating budesonide/formoterol combination or fluticasone/salmeterol combination among COPD patients new to ICS/LABA treatment. *J. Manag. Care Spec. Pharm.* 22(3), 293–304 (2016).
39. Kern DM, Williams SA, Tunceli O *et al.* A US database study characterizing patients initiating a budesonide-formoterol combination versus tiotropium bromide as initial maintenance therapy for chronic obstructive pulmonary disease. *Int. J. Chron. Obstruct. Pulmon. Dis.* 9, 775–783 (2014).
40. Trudo F, Kern DM, Davis JR *et al.* Comparative effectiveness of budesonide/formoterol combination and tiotropium bromide among COPD patients new to these controller treatments. *Int. J. Chron. Obstruct. Pulmon. Dis.* 10, 2055–2066 (2015).
41. Cates CJ, Schmidt S, Ferrer M, Sayer B, Waterson S. Inhaled steroids with and without regular salmeterol for asthma: serious adverse events. *Cochrane Database Syst. Rev.* doi:10.1002/14651858.CD006922.pub4 (2018) (Epub ahead of print).
42. Janjua S, Schmidt S, Ferrer M, Cates CJ. Inhaled steroids with and without regular formoterol for asthma: serious adverse events. *Cochrane Database Syst. Rev.* doi:10.1002/14651858.CD006924.pub4 (2019) (Epub ahead of print).
43. U.S. Food and Drug Administration. FDA review finds no significant increase in risk of serious asthma outcomes with long-acting beta agonists (LABAs) used in combination with inhaled corticosteroids (ICS) (2017). <https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-review-finds-no-significant-increase-risk-serious-asthma-outcomes>
44. Mapel D, Laliberte F, Roberts MH *et al.* A retrospective study to assess clinical characteristics and time to initiation of open-triple therapy among patients with chronic obstructive pulmonary disease, newly established on long-acting mono- or combination therapy. *Int. J. Chron. Obstruct. Pulmon. Dis.* 12, 1825–1836 (2017).
45. Blais L, Forget A, Ramachandran S. Relative effectiveness of budesonide/formoterol and fluticasone propionate/salmeterol in a 1-year, population-based, matched cohort study of patients with chronic obstructive pulmonary disease (COPD): effect on COPD-related exacerbations, emergency department visits and hospitalizations, medication utilization, and treatment adherence. *Clin. Ther.* 32(7), 1320–1328 (2010).
46. Janson C, Stratelis G, Miller-Larsson A, Harrison TW, Larsson K. Scientific rationale for the possible inhaled corticosteroid intraclass difference in the risk of pneumonia in COPD. *Int. J. Chron. Obstruct. Pulmon. Dis.* 12, 3055–3064 (2017).

