Use of single-inhaler triple therapy in the management of obstructive airway disease: Indian medical experts' review

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Shareable abstract (@ERSpublications)
SITT has been shown to reduce exacerbations and improve symptom control and QoL in OAD. Additionally, evidence suggests improved adherence with SITT. Further real-world studies are needed to substantiate the benefits of SITT in OAD, especially asthma. https://bit.ly/3IfwnUZ

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Abstract

Obstructive airway disease (OAD), which includes COPD and asthma, is the leading cause of morbidity and mortality in India. Long-acting bronchodilators (long-acting β2 agonists (LABAs) and/or long-acting muscarinic antagonists (LAMAs)) and inhaled corticosteroids (ICS) have a vital role in the management of patients with OAD. While symptom burden and exacerbations are common amongst treated patients, poor adherence to inhaler therapy is a frequent challenge. Better treatment options that optimise symptom control, improve quality of life, reduce exacerbation risk and improve adherence are desired. Triple therapy (ICS/LABA/LAMA) is recommended in the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2021 guidelines for symptomatic COPD patients on ICS/LABA or LABA/LAMA, and who are at increased risk for frequent or severe exacerbations. Similarly, add-on LAMA is recommended in uncontrolled asthma patients on medium- to high-dose ICS/LABA by the Global Initiative for Asthma (GINA) 2021 guideline. In the real world, high-risk and overlapping phenotypes exist, which necessitate early initiation of triple therapy. We aim to provide an expert review on the use of single-inhaler triple therapy (SITT) for OAD management in global and Indian settings, knowledge from which can be extrapolated for appropriate treatment of Indian patients. The OAD population in India may benefit from early optimisation to SITT characterised by a high burden of exacerbating OAD, nonsmoker COPD and asthma–COPD overlap.

Background

Obstructive airway disease (OAD), which includes asthma and COPD, is characterised by chronic inflammation of the pulmonary system [1, 2]. According to the Global Burden of Disease (GBD), COPD was the leading cause and asthma was the second most common cause of death and disability-adjusted life years (DALYs) worldwide [1]. According to a recent systematic survey the estimated worldwide mean prevalence of COPD was 13.1% while it was 12.4% in Europe, 13.9% in Africa, 13.2% in the USA and 13.5% in Asia [2]. The prevalence of COPD in China is between 4.4% and 16.7%, 14.5% in Australia, 5.6% in Indonesia, 13.4% in Korea, 8.6% in Japan and 4.7% in Malaysia [3]. India, with 20% of the world's total population, has a high prevalence of OAD with a significant clinical and economic burden. While COPD was the second leading cause of disease burden in India accounting for 8.7% of total deaths, asthma was responsible for 1.9% of total deaths [4]. When compared to global COPD-related deaths, India contributes to a significant and growing percentage of COPD mortality (>20%) [5].

India has a highly symptomatic and exacerbating OAD population comprising group B/D COPD patients, Step 4/5 asthma patients, along with difficult-to-treat asthma, and asthma–COPD overlap (ACO) patients

[1–8]. The prevalence of COPD group B/D in Indian studies ranged from 12.6% to 27% for group B and 29 to 42% for group D COPD [9, 10]. According to a prospective observational study, 57% of nonsmoker COPD patients were categorised as grade B COPD, while 80% of smokers fell into group D COPD [11]. According to an observational cross-sectional study that evaluated 200 patients with COPD, 56.5% were nonsmokers, whereas the remaining 43.5% were smokers [12]. Air pollution is the key risk factor for COPD in India. While smoking prevalence has reduced in India, the increase in respiratory disorders has been attributed to indoor air pollution from biomass fuels, outdoor air pollution from particulate matter, occupational exposure to dust from mines, crop dust and chemicals, and poor nutrition, poor socioeconomic status and overcrowding [13].

Healthcare utilisation is high among patients with grade B/D COPD, including emergency department visits, resulting in high median total cost per exacerbation episode [14], which can be unaffordable for patients who have lower economic status. More often, symptomatic COPD patients fail to seek care early due to low awareness. Also, the risk of underreporting of exacerbations by patients is common in the real world [15]. Acute exacerbations of COPD (AECOPD) have detrimental effects on pulmonary function, quality of life (QoL) and physical activity [8]. The mortality among COPD patients is directly proportional to the stage of COPD. Patients with severe COPD had mortality rates as high as 84% [9].

Asthma management in India remains very poor, with a significant proportion of patients experiencing challenging symptoms and worsened QoL. Asthma management is negatively influenced by certain cultural and social beliefs among Indians [7]. In the Asia-Pacific Asthma Insight and Management (AP-AIM) study, only 2% of patients were considered to be "completely controlled" across the entire region based on the Global Initiative for Asthma (GINA) guidelines. Overall, 59.4% of all respondents reported daytime symptoms; of these, 23% reported having daytime symptoms either every day or most days. Daytime shortness of breath and chest tightness was considered the most inconvenient symptom by over 60% of respondents. Among 45.2% of respondents who reported night-time symptoms, 44% reported symptoms at least once or twice per week. On average, patients with asthma in India reported 8.4 exacerbations per year, each lasting a mean of 4 days. Asthma patients in India tend to tolerate their symptoms and consider a certain amount of suffering as an inherent part of the disease process. This may be one of the reasons for the high exacerbation rate among these patients [6]. Poor symptom control and inadequate treatment of asthma patients in India may also have a role [16]. A recent multinational observational study has highlighted patient's overestimation of their asthma control and significant hidden burden associated with under-recognition of poor asthma control [17].

The goals of OAD management are to improve the individual patient's functional status and QoL by maintaining optimal airway function, improving symptoms, preventing recurrence, providing round-the-clock control and reducing the future risk of exacerbations and hospitalisation [18–21]. Assessing the severity of the spirometry abnormality, current nature and magnitude of patient's symptoms, history and future risk of exacerbations, and presence of comorbidities, is helpful in optimising OAD management [18]. The treatment decisions should also consider phenotype as well as patient preferences and practical issues such as inhaler technique, adherence and cost to the patient [19].

Real-world data (US Medicare) revealed that ICS/LABA was the most prescribed maintenance therapy (overall), while the use of triple therapy was observed across Global Initiative for Chronic Obstructive Lung Disease (GOLD) categories [22]. According to the SPIROMICS study, symptomatic COPD patients are often undertreated, while inhaler management in about 50% of patients with COPD is not aligned with GOLD recommendations [23]. The survey reported that mild disease is over-treated and moderate-to-severe disease is often undertreated. Median time to triple therapy varied between 17 and 42 months after COPD diagnosis [23]. While patients in Australia had the shortest time gap, patients in the UK had the longest time gap between COPD diagnosis and initiation of triple therapy. Patient adherence to triple therapy was better in Western countries, which might be due to the wide availability of SITT [24, 25]. However, there are several key issues pertinent to treatment, adherence and compliance with medications in Asian countries especially with regard to triple therapy. In a real-world setting, adherence to and persistence in multiple-inhaler triple therapy (MITT) in COPD management was found to be low [26]. Suboptimal adherence to medication in OAD was frequent, mainly due to the availability of multiple inhalers or complex regimens [6, 27, 28]. Treatment compliance was even low in severe cases of the disease. A meta-analysis reported that only 31% of patients knew the correct technique for using pressurised metered-dose inhalers (pMDIs) and dry powder inhalers (DPIs), while 41% of patients followed "acceptable" inhaler technique [29]. This proportion may decline further when two or more inhalers are being used [28].

The other major challenge in OAD management is the presence of distinct endotypes and phenotypes with variable clinical progression and clinical response. These variations are often difficult to diagnose and manage. Frequent exacerbators, rapid decliners and ACO phenotypes are usually associated with rapid clinical progression and a high risk of exacerbations and hospitalisation in COPD [30–32]. Similar evidence to determine whether there is a clinical phenotype or characteristic that would predict the benefit of add-on LAMA to ICS/LABA in asthma revealed clinical advantage of LAMA irrespective of phenotypes. This finding implies the need to always consider LAMA as an add-on to ICS/LABA in severe asthma management before escalation to phenotype-specific personalised biological therapies, in the stepwise process of gaining asthma control [33]. Therefore, early identification of "treatable traits" to improve the precision of starting SITT in the management of patients with OAD is vital.

Current GOLD guidelines recommend triple therapy for highly symptomatic and exacerbating group D COPD patients [18], and LAMA add-on to ICS/LABA is included in the GINA guidelines at step 4 or 5 if asthma is persistently uncontrolled despite medium- or high-dose ICS-LABA [19]. According to the Indian guidelines published by Indian Chest Society and National College of Chest Physicians (NCCP) in 2013, triple therapy (ICS plus LABA plus LAMA) has been suggested in patients with severe COPD (forced expiratory volume in 1 s (FEV$_1$) <50%) who are symptomatic despite single or dual bronchodilator therapy [34]. However, there have been no recent updates on the same. Moreover, clinicians in India widely follow the GOLD and GINA guidelines, which are updated annually.

A Delphi consensus from a Spanish group has revealed experts' perception about the benefit of SITT over double therapy regarding efficacy in improving dyspnoea, pulmonary function, QoL and reducing exacerbations. The effects were perceived to be higher against ICS/LABAs than LABA/LAMAs. However, the panel acknowledged the complexity and heterogeneity of COPD and the need for better positioning of SITT [35]. The intent of this narrative review is to evaluate the available literature related to SITT in OAD management and provide an expert perspective on the role of SITT in Indian settings.

Methods

A narrative review was carried out that evaluated the literature related to SITT in the management COPD and asthma. A literature search was conducted across PubMed and Google Scholar to include all completed and ongoing clinical trials on SITT, both globally and in the Asia-Pacific region including India, since 2015. Relevant literature was then screened and deliberated during a focused group meeting involving the authors, and relevant information was segregated and included in the review.

Clinical trial evidence of SITT in OAD

An emerging body of evidence from randomised controlled clinical trials has shown that SITT in comparison with LABA/LAMA and ICS/LABA was associated with a significant reduction in the rates of moderate or severe exacerbations, significant decrease in the rate of severe exacerbation, significant improvement in trough FEV$_1$ and mean St. George's Respiratory Questionnaire (SGRQ) total score and improved all-cause mortality, without the increased risk of adverse events, serious adverse events or cardiovascular events among COPD patients [36, 37]. The risk of pneumonia events with SITT were greater compared to LABA/LAMA but similar to ICS/LABA [33, 35]. Similarly, for patients with persistent and uncontrolled asthma, the SITT improved lung function and reduced asthma exacerbations [38–40]. With favourable data from the CAPTAIN [39] and IRIDIUM trials [40], the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) have approved SITT for asthma. There is a dearth of Indian studies that have evaluated efficacy and safety of SITT in India. An open label, randomised, prospective study in India evaluated the effects of glycopyrronium 25 µg/formoterol 12 µg given concurrently with budesonide 400 µg in patients with moderate-to-severe COPD. The open triple therapy was associated with significant improvement in lung function and significant reduction in use of rescue medication [41]. A recent phase 3, randomised study in India evaluated the safety and efficacy of SITT containing glycopyrronium, formoterol and fluticasone in comparison to an open triple therapy (of the same combination) among people with COPD. Bronchodilation and lung function improvement with the SITT was comparable to open triple therapy; the SITT was safe and well tolerated [42]. Table 1 lists the approved SITTs for COPD and/or asthma by various regulatory bodies globally and in India. Table 2 summarises the clinical trials of SITT in OAD.

SITT benefits in OAD

Reduction in exacerbation risk

Exacerbations of COPD and asthma represent a potential clinical problem and have a significant negative impact on pulmonary function and QoL. They are also associated with cardiovascular complications, high

TABLE 1 List of approved SITT for COPD and/or asthma globally and in India

Approved by	SITT (brand/composition)	Device	Indication	Dosage
US FDA [43]	Trelegy Ellipta; GlaxoSmithKline FF/UMEC/VI	DPI	Maintenance treatment of both asthma and COPD	Once daily
EMA [44], CANADA [45]	Trelegy Ellipta; GlaxoSmithKline FF/UMEC/VI	DPI	Maintenance treatment of COPD	Once daily
US FDA [46]	BREZTRI; AstraZeneca BDP/FOR/GP	pMDI	Maintenance treatment of COPD	Twice daily
EMA [47]	Trimbow; Chiesi Pharmaceuticals BDP/FF/GP	pMDI	Maintenance treatment of COPD and asthma	Twice daily
EMA [48]	Enerzair Breezhaler; Novartis IND/GLY/MF	DPI	Maintenance treatment of COPD and asthma	Once daily
CDSCO [49]	Airz-FF; Glenmark GLY/FOR/FP	DPI	Maintenance treatment of COPD	Twice daily
CDSCO [49]	Glycohale-FB; Cipla GLY/FOR/BUD	DPI	Maintenance treatment of COPD	Twice daily

SITT: single-inhaler triple therapy; US FDA: United States Food and Drug Administration; FF/UMEC/VI: fluticasone furoate/umeclidinium/vilanterol; DPI: dry powder inhaler; EMA: European Medicines Agency; BDP/FF/GP: beclomethasone dipropionate/fluticasone furoate/glycopyrronium; BDP/FOR/GP: beclomethasone/formoterol/glycopyrronium; pMDI: pressurised metered-dose inhaler; IND/GLY/MF: indacaterol/glycopyrronium/mometasone furoate; GLY/FOR/FP: glycopyrronium/formoterol/fluticasone propionate; GLY/FOR/BUD: glycopyrronium/formoterol/budesonide; CDSCO: Central Drugs Standard Control Organisation.

mortality and increased healthcare costs [56–58]. Several studies have established the benefits of SITT in this clinical setting. In a meta-analysis of 12 randomised controlled trials (RCTs) involving >19 000 patients with moderate-to-severe COPD, SITT significantly reduced COPD exacerbations (relative risk 0.75; 95% CI 0.69–0.83; $p<0.01$) [59]. In another meta-analysis of 21 trials (19 RCTs) of patients with moderate-to-severe COPD, SITT significantly reduced the rate of moderate or severe exacerbations *versus* LAMA monotherapy (relative risk 0.71, 95% CI 0.60 to 0.85); LAMA-LABA (relative 0.78, 95% CI 0.70–0.88); and ICS-LABA (relative risk 0.77, 95% CI 0.66 to 0.91) [37]. The meta-analysis of ETHOS, KRONOS, IMPACT and TRILOGY studies reported that triple therapy was safe and more effective than LABA/LAMA and ICS/LABA in COPD patients, irrespective of eosinophil count [60]. Similarly, analysis of pivotal RCTs revealed that triple therapy has a superior protective effect against the risk of COPD exacerbation to LABA/LAMA and ICS/LABA [61]. The data from the KRONOS study also revealed that SITT was effective in reducing exacerbations even in symptomatic patients without a history of exacerbations (70% of patients had no exacerbations in the previous year) [53].

The pooled analysis of TRIMARAN and TRIGGER trials reported that risk of severe exacerbations among asthma patients was greatly reduced compared to conventional ICS/LABA in higher degree of reversibility (>400 mL) *versus* lower degree (relative risk 0.729; p=0.024); body mass index (BMI) <25 $kg \cdot m^{-2}$ *versus* higher BMI >25 $kg \cdot m^{-2}$ (relative risk 0.570; p=0.005); 1 exacerbation in the previous year *versus* >1 exacerbation (relative risk 0.731; p=0.009), nonsmokers *versus* smoking history (relative risk 0.764; p=0.013), age <65 years *versus* age >65 years (relative risk 0.770; p=0.17), and male *versus* female (relative risk 0.651; p =0.009) [38]. In a meta-analysis of phase 3 studies involving patients with uncontrolled asthma, triple therapy with high-dose ICS was found to be more effective ($p<0.05$) than triple therapy with medium-dose ICS. Additionally, triple therapy with high-dose ICS was better than medium- and high-dose ICS/LABA against moderate-to-severe asthma exacerbation (relative risk 0.61–0.80) and lung function improvement. Further, high-dose triple therapy was superior to medium-dose triple therapy in preventing severe exacerbations ($p<0.05$) but not moderate exacerbations [62].

Improving lung function and symptom control

FEV_1 is one of the core outcomes to measure disease severity and control. Evidence from a meta-analysis indicates that SITT was associated with improvement in lung function as measured by an absolute increase in FEV_1 change (mean difference (MD) 0.07 to 0.09; $p<0.01$) in moderate-to-severe COPD patients [57, 58]. Also, the WISDOM study showed a significant decline in lung function when ICS was withdrawn in COPD patients treated with ICS/LABA/LAMA [63].

Similarly, in asthma patients, lung function significantly improved with SITT compared to ICS/LABA (57 mL to 73 mL; $p<0.01$) [64]. In inadequately controlled asthma with ICS/LABA, treatment with SITT

TABLE 2 Summary of clinical trials for SITT in OAD

Clinical trial	Trial design and end-points – primary/secondary	Patient population	Treatment and duration	Key findings
Global trials				
TRILOGY EU [50]	• Phase 3, randomised, double-blind, parallel-group • Pre-dose and 2-hour post-dose morning FEV_1 at week 26 and TDI score at week 26 • COPD exacerbation rate at 52 weeks	• Age ⩾40 years • Post-bronchodilator FEV_1 <50% • FEV_1/FVC <70% • ⩾1 moderate or severe COPD exacerbation within 1 year of study • Use of ICS/LAMA, LABA/LAMA or LAMA ⩾2 months • CAT score ⩾ 10 • BDI focal score ⩽10	Extrafine BDP/FF/GP pMDI 200/12/25 µg twice daily (n=687) vs Extrafine BDP/FF pMDI 200/12 µg twice daily (n=680) × 52 weeks	• SITT was superior to BDP/FF for pre-dose FEV_1 (MD 81 mL; p<0.001) and 2-hour post-dose FEV_1 (MD 117 mL; p<0.001) • TDI improved in both groups (MD 0.21 Units) • Moderate-to-severe exacerbations occurred in 31% and 35% for adjusted annual rate of 0.41 and 0.53 for SITT *versus* BDP/FF, respectively (RR 0.77; p=0.005) • Pneumonia rates were similar between the groups
TRINITY EU, South America, Mexico [51]	• Phase 3, randomised, double-blind, parallel-group • COPD exacerbation rate at 52 weeks • Pre-dose morning FEV_1 at week 26	• Current or ex-smokers • Age ⩾40 years • Post-bronchodilator FEV_1 <50% • FEV_1/FVC <70% • ⩾1 moderate or severe COPD exacerbation within 1 year • Use of ICS/LABA, ICS/LAMA, LABA/LAMA or LAMA ⩾2 months • CAT score ⩾10	Tiotropium DPI 18 µg QD(n=1076) vs Extrafine BDP/FF pMDI 200/12 µg twice daily plus tiotropium DPI 18 µg once daily (n=537) ×52 weeks	• SITT significantly improved pre-dose FEV_1 *versus* tiotropium (MD 61 mL; p<0.0001) • Rates of moderate-to-severe COPD exacerbations: SITT was superior to tiotropium (RR 0.80; p=0.0025) and similar to open TT • COPD exacerbation and pneumonia were similar in all treatment groups
TRIBUTE EU [52]	• Phase 3, randomised, double-blind, double-dummy, parallel-group • COPD exacerbation rate at 52 weeks • Pre-dose morning FEV_1	• Current or ex-smokers • Age ⩾40 years • Post-bronchodilator FEV_1 <50% • FEV_1/FVC <70% • ⩾1 moderate or severe COPD exacerbation within 1 year of study • Use of ICS/LABA, ICS/LAMA, LABA/LAMA or LAMA ⩾2 months • CAT score ⩾10	Extrafine BDP/FF/GP pMDI 200/12/25 µg twice daily (n=764) vs IND/GP DPI 85/43 µg once daily (n=768) ×52 weeks	• SITT significantly improved mean change from baseline in FEV_1 *versus* IND/GP at weeks 12 and 40 (MD 32 mL; p<0.01) • Rates of moderate-to-severe COPD exacerbations: SITT was superior to IND/GP (RR 0.85, p= 0.043) • COPD exacerbation and pneumonia were similar across all treatment groups
KRONOS Canada, China, Japan, USA [53]	• Phase 3, randomised, double-blind, parallel-group • COPD exacerbation rate at 24 weeks	• Current or ex-smokers (⩾10 pack-years) • Age 40–80 years • Post-bronchodilator FEV_1 ⩾25% to 80% • FEV_1/FVC <70% • Use of ⩾2 inhaled maintenance therapies for ⩾6 weeks • CAT score ⩾10	BUD/GP/FF pMDI 320/ 18/9.6 µg twice daily (n =639) vs GFF pMDI 18/9.6 µg (n= 625) vs BUD/FF pMDI 320/9.6 µg twice daily (n=314) vs OL BUD/FF DPI 400/ 12 µg twice daily (n=318) ×24 weeks	• SITT significantly improved FEV_1 AUC *versus* both GFF (LSMD 104 mL; p<0.0001) and BUD/FF (LSMD 91 mL; p<0.0001) • SITT significantly improved pre-dose morning trough FEV_1 *versus* GFF (22 mL; p=0.139) and BUD/FF pMDI (74 mL; p<0.0001) • TDI focal score was significantly improved with SITT *versus* OL BUD/FF but not *versus* GFF • Rates of moderate-to-severe COPD exacerbations: SITT was superior to GFF (p<0.001) • Pneumonia rates were similar between the groups

Continued

TABLE 2 Continued

Clinical trial	Trial design and end-points – primary/secondary	Patient population	Treatment and duration	Key findings
ETHOS Australia, Canada, China, EU, South America, USA, UK [54]	• Phase 3, randomised, double-blind, parallel-group • COPD exacerbation rate • Time to death	• Current or ex-smokers • Age ⩾40 years • Post-bronchodilator FEV_1 25–65% • ⩾1 moderate or severe COPD exacerbation within 1 year • Use of ICS or SAMA/SABA ⩾2 months • CAT score ⩾10	BDP/FF/GP MDI 160/9/4.8 µg twice daily (n=2137) vs BDP/FF/GP MDI 160/9/4.8 µg twice daily (n=2121) vs GP/FF MDI 9/4.8 µg twice daily (n=2120) vs BDP/FF MDI 160/4.8 µg twice daily (n=2131) × 52 weeks	• Rates of moderate-to-severe COPD exacerbations: 320-µg SITT was superior to GP/FF (RR 0.76; p<0.001), or BDP/FF 1.24 (RR 0.87; p<0.003); 160-µg SITT was superior to GP/FF (RR 0.75; p<0.001) or BDP/FF 1.24 (RR 0.86; p=0.002) • Low risk of mortality with 320-µg SITT: *versus* GP/FF (HR 0.54), *versus* BDP/FF (HR 0.78); low risk with 160-µg SITT *versus* GP/FF; HR 0.79) but higher *versus* BDP/FF (HR 1.13) • Pneumonia rates were high with high-dose SITT and BDP/FF
IMPACT Asia-Pacific, Canada, EU, South America, South Africa, USA, UK [55]	• Phase 3, randomised, double-blind, parallel-group • COPD exacerbation rate • Pre-dose morning FEV_1	• Ex-smokers • Age ⩾40 years • Post-bronchodilator FEV_1 <50 • ⩾1 moderate or severe COPD exacerbation within 1 year • Use of ICS or LAMA or LABA or in combination ⩾2 weeks • CAT score ⩾10	FF/UMEC/VI DPI 100/62.5/25 µg once daily (n=4151) vs UMEC/VI DPI 62.5/25 µg once daily (n=4134) vs FF/VI DPI 100/25 µg once daily (n=2070) × 52 weeks	• SITT significantly improved pre-dose FEV_1 *versus* UMEC/VI (MD 97 mL; p<0.001) and *versus* FF/VI (MD 54 mL; p<0.001) • Rates of moderate-to-severe COPD exacerbations: SITT was superior to UMEC/VI and FF/VI (RR 0.85 and 0.75, respectively; p<0.001 for both) • Significantly low risk of mortality with SITT *versus* UMEC/VI (HR 0.58, $p_{unadjusted}$=0.01) • Risk of clinician-diagnosed pneumonia was significantly higher with SITT *versus* UMEC/VI (HR 1.53; p<0.001)
TRIGGER EU [38]	• Phase 3, randomised, double-blind, parallel-group • Pre-dose morning FEV_1 • Asthma exacerbation rate	• Age 18–75 years • Uncontrolled asthma (ACQ-7 ⩾1.5) • Pre-bronchodilator FEV_1 <80% • At least one exacerbation within 1 year • Use of high-dose ICS/LABA ⩾4 weeks	BDP/FF/GP 200/6/10 µg MDI twice daily (n=573) vs BDP/FF 200/6 µg MDI twice daily (n=576) vs OL BDP/FF 200/6 µg MDI twice daily plus tiotropium 2.5 µg once daily (n=288) × 52 weeks	• SITT was superior to BDP/FF for pre-dose FEV_1 (improvement by 73 mL; p=0.0025) at week 26 • Rates of moderate-to-severe asthma exacerbations reduced by 12% for BDP/FF/GP *versus* BDP/FF, respectively (RR 0.88; p=0.11) • Pneumonia rates were similar between the groups
TRIMARAN EU [38]		• Similar to TRIGGER except use of medium-dose ICS/LABA ⩾4 weeks	BDP/FF/GP 100/6/10 µg MDI twice daily (n=579) vs BDP/FF 100/6 µg MDI twice daily (n=576) × 52 weeks	• SITT was superior to BDP/FF for pre-dose FEV_1 (improvement by 57 mL; p=0.0080) at week 26 • Rates of moderate-to-severe asthma exacerbations reduced by 15% for BDP/FF/GP *versus* BDP/FF, respectively (RR 0.85; p=0.033) • No increased incidence of pneumonia with SITT

Continued

TABLE 2 Continued

Clinical trial	Trial design and end-points – primary/secondary	Patient population	Treatment and duration	Key findings
CAPTAIN Australia, Canada, EU, Japan, South Korea, South America, South Africa, USA, UK [39]	• Phase 3, randomised, double-blind, parallel-group • Pre-dose morning FEV_1 • Asthma exacerbation rates	• Age 18–75 years • Uncontrolled asthma (ACQ-7 ⩾1.5) • Pre-bronchodilator FEV_1 30–85% • Post-bronchodilator FEV_1 ⩾12% and ⩾200 mL in 20–60 min • Use of ICS/LABA ⩾3 months	FF/UMEC/VI DPI 100/31.25/25 µg (n=405) once daily *versus* FF/UMEC/VI DPI 100/62.5/25 µg (n=406) once daily *versus* FF/UMEC/VI DPI 200/31.25/25 µg (n=404) once daily *versus* FF/UMEC/VI DPI 200/62.5/25 µg (n=408) once daily *versus* FF/VI 100/25 µg DPI (n=40) once daily *versus* FF/VI 200/25 µg DPI (n=406) once daily × 52 weeks	• High-dose LAMA SITT was superior to FF/VI 100/25 µg for pre-dose FEV_1 (LSMD, 110 mL; p<0.001); High-dose ICS SITT was superior to FF/VI 200/25 µg (92 mL; p<0.0001) • Adding UMEC 31.25 µg to FF/VI had similar outcomes; supported by FEV_1 at 3 hours post-dose • Rates of moderate-to-severe asthma exacerbation reductions were non-significant for FF/UMEC 62.5 µg/VI *versus* FF/VI (pooled analysis) • Pneumonia rates were similar between the groups
IRIDIUM Asia-Pacific, EU South America, UK [49]	• Phase 3, randomised, double-blind, double-dummy, parallel-group • Pre-dose morning FEV_1 • Asthma exacerbation rate	• Age 18–75 years • Uncontrolled asthma (ACQ-7 ⩾1.5) • Pre-bronchodilator FEV_1 <80% • Post-bronchidilator increase in FEV_1 of ⩾12% and ⩾200 mL • Use of ICS/ LABA ⩾3 months	MF/IND/GLY DPI 80/150/50 µg once daily (n=620) vs MF/IND/GLY DPI 160/150/50 µg once daily (n=619) vs MF/IND DPI 160/150 µg once daily (n=617) vs MF/IND DPI 320/150 µg once daily (n=618) vs FLU/SAL DPI 500/50 µg twice daily (n=618) × 52 weeks	• Medium and high-dose SITT was superior to corresponding doses of MF/IND for pre-dose FEV_1 (MD 76 mL; p<0.001 and MD 65 mL, respectively; p<0.001 for both) • Improvements in pre-dose FEV_1 were greater for both medium-dose SITT (99 mL; p<0.001) and high-dose triple therapy (119 mL; p<0.001) *versus* FLU/SAL at week 26 • Rates of moderate-to-severe asthma exacerbations reduced by 13% (medium dose) and 15% (high-dose) for SITT *versus* corresponding dose of MF/IND *versus* FLU/SAL • Pneumonia rates were similar between the groups
Indian trial				
Salvi *et al.*; Indian double-blind RCT [42]	• Phase 3, randomised, double-blind, active-control, parallel-group, noninferiority study • COPD patients • Change from baseline in trough FEV_1 at the end of 12 weeks	• COPD patients • Age ⩾40 to ⩽75 years, with FEV_1/FVC <0.70 • Using mono/dual therapy with ICSs, LAMAs, or LABAs for ⩾1 month	GB/FF/FP 12.5/12/250 µg twice daily (n=198) or GB/FF/FP 50/12/250 µg twice daily (n=198) for 12 weeks	• LSMD in pre-dose FEV_1 from baseline at 12 weeks was noninferior between the groups (p<0.05) • LSMD change from baseline in post-dose FEV_1 was comparable (p=0.38) • Comparable efficacy in terms of change in trough FEV_1

ACQ: Asthma Control Questionnaire; AE: adverse events; BDI: baseline dyspnoea index; BDP/FF/GP: beclomethasone/formoterol/glycopyrronium; BUD/GP/FF: budesonide/ glycopyrronium/formoterol fumarate; DPI: dry powder inhaler; CAT: COPD assessment test; FF/UMEC/VI: fluticasone furoate/umeclidinium/vilanterol; FEV_1: forced expiratory volume in 1 s; FEV_1 AUC: FEV_1 area under the curve; FVC: forced vital capacity; FLU/SAL: fluticasone propionate/salmeterol; GFF: glycopyrronium and formoterol fumarate; ICS: inhaled corticosteroid; LABA: long-acting β-agonist; LAMA: long-acting muscarinic antagonist; LSMD: least squares mean difference; MD: mean difference; MF/IND/GLY: mometasone/indacaterol/glycopyrronium; OAD: obstructive airway disease; OL: open label; pMDI: pressurised metered-dose inhalers; RR: rate ratio; SABA: short-acting β-agonists; SAMA: short-acting muscarinic antagonists; SGRQ: St. George's Respiratory Questionnaire; SITT: single-inhaler triple therapy; TDI: transition dyspnoea Index; TT: triple therapy.

(indacaterol/glycopyrronium/mometasone furoate (MF/IND/GLY)) improved lung function and moderate-to-severe exacerbations [40]. In a real-world setting, SITT has significantly improved lung function compared to dual therapy in ACO (p=0.004) [65].

Improving clinically important deterioration

In a pooled analysis of TRILOGY, TRINITY and TRIBUTE studies, beclomethasone/formoterol/glycopyrronium (BDP/FF/GP) significantly extended time to clinically important deterioration (CID) compared to BDP/FF (HR 0.61, p<0.001), tiotropium (0.72, p<0.001), and IND/GLY (0.82, p<0.001) in patients with symptomatic COPD, FEV_1 <50% and exacerbation history. The SITT also significantly extended the time to sustained CID compared to BDP/FF (HR 0.64, p<0.001) and tiotropium (0.80, p<0.001) [62]. In a *post hoc* analysis of the FULFIL study, only 25% of those on fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI), compared with 56% of those on budesonide/formoterol (BUD/FOR), experienced a clinically meaningful decline in lung function of >100 mL during the 26 weeks study period. The median time to CID was five times longer for triple therapy compared to dual therapy [66]. Data on improving CID in the asthma setting are lacking.

Improving QoL

In moderate-to-severe COPD patients, QoL as measured by SGRQ score significantly improved with SITT (MD −1.67 to −2.78, p<0.05) [59, 37]. Further, patients receiving BDP/FF/GP were significantly more likely to be SGRQ responders at week 52 than those receiving BDP/FF or IND/GLY [64]. Clinically meaningful improvements in QoL as measured by Asthma Quality of Life Questionnaire (AQLQ-S) were seen with MF/IND/GLY [40].

Mortality

In the COPD setting, triple therapy of FF/UMEC/VI was significantly associated with lower all-cause mortality than UMEC/VI (HR 0.58; p=0.01) [55]. Similarly, triple therapy of BDP/FF/GP with high-dose ICS lowered risk of all-cause mortality; 46% lower than GP/FF and 22% lower than BDP/FF therapy [53]. Survival benefits of SITT in the asthma setting are yet to be determined.

Safety of SITT

While SITT was associated with an increased risk of pneumonia among COPD patients when compared to LABA/LAMA (OR 1.25; 95% CI 1.03−0.97; p=0.03), no significant difference was found when compared to ICS/LABA (OR 1.11; 95% CI 0.95−1.29; p=0.19) [59]. The risk of pneumonia was greater with SITT, irrespective of the type of ICS [67]. However, the rate of serious adverse events or cardiovascular events was similar between SITT and LABA/LAMA or ICS/LABA [59].

Asthma exacerbation was the most common adverse event, while serious adverse events, such as cholelithiasis, pneumonia, lower respiratory tract infection and pulmonary embolism, were low and similar across SITT and dual therapy groups in the IRIDIUM trial involving asthma patients [40]. Similarly, in the CAPTAIN, TRIMARAN and TRIGGER trials, pneumonia and MACE events occurred in <1% of patients with SITT and were similar across treatment groups [38, 39]. Additionally, no clinically meaningful changes were observed in terms of clinical signs or ECG changes with SITT [54, 55]. No treatment-related major adverse cardiovascular outcomes (MACE) were reported across treatment groups in the IRIDIUM trial [40].

Adherence and compliance with SITT

A real-world study has reported that SITT was associated with better adherence and persistence *versus* MITT among COPD patients. Compared to MITT, patients with SITT had a significantly higher mean proportion of days covered (PDC) at 6 months (0.66 *versus* 0.48, p<0.001) and 1 year (0.60 *versus* 0.40); higher rate of adherence (PDC ⩾80) at 6 months and 1 year with SITT *versus* MITT (46.5% *versus* 22.3% and 43.2% *versus* 17.4%); and longer median persistence with SITT *versus* MITT at 6 months (325 *versus* 90 days); and two times more likely to be persistent at 1 year (HR 2.08; p<0.001) [26]. In an observational study, patients with complete adherence to SITT had less severe COPD compared to those with low adherence (49.2% predicted *versus* 59.2% predicted, respectively; p<0.001) [68]. Data on SITT adherence and compliance in asthma setting are lacking.

Key questions in using SITT in OAD

What are the pathways before and following SITT in OAD?

There are diverse pathways to indicate SITT in OAD patients. In an international multicenter study, the median time from initial COPD diagnosis to the first prescription of triple therapy ranged from 16.9 (5.7–36.2) months in Australia to 42.5 (13.9–87.4) months in the UK [24]. The most common treatment pathways to triple therapy initiation are starting with ICS/LABA, no therapy, LAMA alone, [24, 69] and LABA/LAMA [70]. A real-world study observed that patients who did not had exacerbations in the previous year often received ICS-containing therapy before escalation to triple therapy. Treatment with triple therapy remained constant across all groups of COPD patients irrespective of severity and level of risk [71]. Step-down following triple therapy, especially during the first 30 days, was to ICA/LABA (42.4%), LAMA (22.4%) alone or LABA/LAMA (18.9%). The step-down pattern was similar across different severities of COPD. Similarly, in a real-world asthma setting, a higher proportion of patients in the triple therapy group had received high-dose ICS at index compared to the ICS/LABA group (68.2% *versus* 27.6%). In both the asthma and ACO cohort, ICS/LABA was the most common prior therapy (99.6% and 80.8%, respectively) [72].

When to step-up or step-down SITT in OAD?

While dual therapy with bronchodilators tends to be more beneficial, triple therapy seems to provide modest benefit in the general COPD population. However, symptomatic patients not controlled by ICS/LABA, LAMA or LABA/LAMA and those with poor health-related QoL, frequent exacerbations and high eosinophil count should be stepped up to triple therapy (TT) [73]. Current GOLD guidelines recommend TT for severe disease, frequent exacerbations and persistent symptoms who were not adequately controlled with LABA/LAMA or ICS/LABA therapy [19]. However, several real-world studies reported progression to TT even in patients with no exacerbations in the previous year [69]. Landis *et al*. [74] reported that dyspnoea was the key driver for change in COPD therapy in the primary care setting. The subgroup analyses from the KRONOS trial also reported beneficial effects of TT *versus* dual therapy even in patients with no prior exacerbation history [75]. The Spanish COPD guidelines recommend the use of ICS in patients identified as ACO and/or frequent exacerbators [76].

A population-based study in Spain observed that the probability of de-escalation following TT was more likely in patients with severe disease (frequent exacerbators and patients with ACO) and during the first year of COPD. The step-down from TT was 50% within 5 years [69]. The de-escalation from TT is attributable to either lack of efficacy with TT, or effective disease stability with TT. More frequent contacts of severe patients with the healthcare providers may increase the probability of treatment changes, including de-escalation from TT. In a latest real-world study, which included mostly infrequent exacerbators, withdrawal of ICS from TT was not associated with risk of exacerbation [77]. Current guidelines based on RCTs also propose safe withdrawal of ICS in patients with stable COPD, particularly in non-exacerbators with low blood eosinophil counts [78, 79].

Recent approval of SITT in severe uncontrolled asthma is a positive addition to treatment options; however, clinical questions continue. Current GINA guidelines recommend triple therapy in severe asthma before step-up to oral corticosteroids or biologics. The guidelines also highlight the fact that asthma severity may vary over time [19]. Consequently, the intensity of treatment will have to change based on disease severity. Step-down from triple therapy offers a minimal level of treatment efficient in providing asthma control, but it could be difficult, particularly if patients well under control will not want to interrupt a therapy that they perceive effective.

What is the role of biomarkers in SITT?

Blood eosinophil count is a useful biomarker of eosinophilic exacerbations of COPD. Evidence supports the determination of eosinophils in patients with repeated COPD exacerbations and the use of ICS if they are elevated [80]. The ICS treatment reduces exacerbation rates in COPD patients with higher blood eosinophil counts [81]. Withdrawal of ICS treatment is associated with an increased exacerbation risk only in patients with elevated blood eosinophil counts [82]. Exacerbation risk associated with eosinophilic inflammation should be treated with ICS on top of LABA/LAMA. Triple therapy was found to be more effective than dual bronchodilation and LAMA monotherapy in reducing AECOPD at a cut-off value of $\geqslant$100 eosinophil cells$\cdot\mu L^{-1}$ [18]. In patients with $\geqslant$300 eosinophil cells$\cdot\mu L^{-1}$ and more than two AECOPD in the previous year, step-down from triple therapy by withdrawing ICS led to an increased risk of AECOPD [73]. However, in the Indian scenario, because of the high parasitic infection rate, eosinophil count might be high in many patients [83], necessitating confirmation of threshold values for blood eosinophil count above which triple therapy is useful. In nonsmokers' COPD, which is prevalent in the Indian population, the eosinophil count is high, and these patients might respond better to ICS treatment [84]. Further, pneumonia risk following ICS treatment is lower among patients with high blood eosinophil counts [85].

The current GINA guideline recommends LAMA add-on for patients aged $\geqslant$6 years whose asthma is not well controlled with ICS/LABA [6] indicating that biomarker testing is not needed for LAMA add-on.

Similarly, the National Asthma Education and Prevention Program conditionally recommends adding a LAMA to ICS-LABA therapy compared with continuing the same dose of ICS-LABA therapy in patients aged ⩾12 years or older with uncontrolled persistent asthma [20].

How long should we continue SITT?

A real-world study showed that mean time to step-down following TT initiation was 38.9 months (95% CI 51.3–57.9) and this was similar across GOLD subgroups. At 5 years, overall, 50% of patients were likely to de-escalate from TT [69].

In a real-world asthma setting, the proportion of patients continuing triple therapy decreased from 62.8% at 3 months after index date to 38.5% at 1 year for patients with asthma, and from 55.6% to 44.4% for patients with ACO [72]. Nevertheless, the duration of SITT administration is often based on clinical judgement, and there can be inter-individual differences in this aspect.

What should be the frequency of SITT – once or twice a day?

Round-the-clock symptom control in COPD is relevant in highly symptomatic patients due to nocturnal and early morning symptom burden. The night-time symptoms especially were associated with high mortality and exacerbations due to various factors resulting from a supine position, increased vagal stimulation causing more inflammation and airway resistance [86]. Therefore, management based on circadian variations supports twice-daily usage, which may improve bronchodilation and overall symptom control. The option of SITT with twice-daily dosing will be beneficial in patients with night-time or early morning symptoms [30].

However, a real-world study in asthma has shown better adherence and lower risk of discontinuing treatment with once-daily dosing, suggesting that once-daily dosing might improve adherence and persistence compared with twice-daily alternatives [87]. Nevertheless, the choice of frequency for SITT should be discussed with the patient in the context of his or her symptoms and adherence to prior therapy, while ensuring that the optimal daily dose is targeted for maximal symptom relief.

What is the choice of device in SITT?

The selection of an appropriate device is dependent on patient preferences, and characteristics. SITT delivered by DPI devices are widely available worldwide, including India. An RCT demonstrated similar efficacy and safety with DPI and pMDI formulations of SITT in COPD patients [88].

From the environmental perspective, pMDIs contain hydrofluorocarbons, which are likely to contribute to the global warming effect. The production and disposal of pMDIs also have a carbon footprint thereby contributing to climate change. DPIs are more environmentally friendly in terms of a lower carbon footprint. Usage of SITT with newer DPI devices including breath-actuated ones appears to be the more prudent option when overall benefit is considered [89–91]. But the possibility of delivering SITT using different devices (DPI, pMDI, nebuliser) allows therapy to be tailored to a patient's characteristics.

Owing to the recent smartphone boom in India, there are more smartphone users in India than any other country in the world. By utilising the rapid upsurge in mobile technologies, smartphones can be employed to monitor the use of inhalers in the home setting. Mobile apps that connect to sensors on inhalers can also be used to monitor medication adherence as well as inhalation airflow [92].

Patient profiles for starting SITT in clinical practice

Patient groups with OAD that could benefit from optimisation to SITT have been enumerated in the following sections.

COPD patients uncontrolled on dual therapy

Several phase 3 trials assessed the safety and efficacy of SITT in COPD patients uncontrolled on dual therapy. These trials also included individuals who are current or ex-smokers with one or more moderate or severe exacerbations in the previous year. Patients with FEV_1/forced vital capacity (FVC) <70%, COPD assessment test (CAT) score ⩾10 or baseline dyspnoea index focal score ⩽10 have shown superiority of SITT *versus* dual therapy [43–46]. Further, in a real-world study, while ∼5% of GOLD 1 and 9% of GOLD 2 patients used triple therapy, 20% and 17% of patients categorised as GOLD 3 and 4, respectively, used triple therapy [93].

Non-smoking COPD

The burden of non-smoking COPD (NSCOPD) is high in India (∼65%), especially in rural areas due to biomass exposure and indoor pollution. The condition is characterised by lower FVC but slower FEV_1 decline, greater small airway obstruction, air trapping and less emphysema. This cohort also has a high eosinophil count, and SITT containing ICS might provide a better response [84].

COPD frequent exacerbators profile

The number of exacerbations constitutes the most important distinguishing criterion of clinical phenotypes. Patients with frequent exacerbator COPD phenotype characterised by more than two exacerbations in a year, high symptom presentation, high morbidity and mortality, risk of myocardial infarction and stroke, and worsening lung function and QoL might benefit from SITT [68, 32]. In a meta-analysis of 523 studies, triple therapy was associated with reduction of moderate or severe exacerbation rates annually in the range of 15–52% compared with LABA/LAMA, 15–35% compared with ICS/LABA and 20% compared with LAMA alone. The absolute treatment benefit was more emphasised in patients with higher eosinophil counts or higher frequency of exacerbations and ex-smokers [94].

COPD rapid lung function decliners

Large cohort studies have shown that close to 30% of COPD patients lose lung function at a faster rate ($30\ mL \cdot year^{-1}$) [30]. Rapid lung function decline is independently associated with higher mortality. Evidence suggests that of all COPD patients, one-third of them exhibit a rapid decline in lung function [77]. In a *post hoc* analysis of the FULFIL study, a clinically meaningful decline in lung function was seen in 25% treated with triple therapy compared with 56% treated with dual therapy. The median time to CID was five times longer for triple therapy compared to dual therapy. Further, rapid decline in lung function is particularly noted in COPD patients with self-reported late-onset asthma. These data suggest that triple therapy can be considered in COPD patients with rapid lung function decline [66].

COPD with a history of ACO

The ACO phenotype also has a considerable burden across India. These patients are characterised by features of both asthma and COPD, presence of eosinophils and/or neutrophils in sputum and >400 mL airflow reversibility [95]. The prevalence of ACO among patients in an observational study in the northern part of India was 21.8% [96], while another study in southern India reported a prevalence of 27% [97]. In a pilot study of 19 ACO patients, inspiratory capacity (IC), an index of hyperinflation of the lung, was 2.11 L after treatment with triple therapy compared to 1.85 L after dual therapy ($p<0.02$). Four-week treatment of ACO patients with budesonide/formoterol/glycopyrrolate (BUD/FORM/GLY) triple therapy resulted in significant improvement from baseline in lung function, including IC, compared with BUD/FORM dual therapy, with a comparable safety profile [98].

Uncontrolled asthma on optimal ICS/LABA

Several phase 3 trials assessed the safety and efficacy of SITT in patients with asthma uncontrolled on dual therapy [38–40]. These trials also included individuals with at least one exacerbation in the previous year, pre-bronchodilator FEV_1 30–85% of predicted normal value), post-bronchodilator FEV_1 ⩾12% and ⩾200 mL. These trials have shown superiority of SITT *versus* dual therapy. The TRIMARAN and TRIGGER trials have demonstrated the effectiveness of SITT in patients with poorly controlled asthma despite high doses of ICS/LABA. Single-inhaler triple therapy (BDP/FF/GP) was significantly associated with a reduced rate of severe asthma exacerbation and reduced treatment with systemic steroids in patients with asthma uncontrolled on medium- or high-dose BDP/FF [38]. Similarly, the IRIDIUM trial has shown significant effectiveness of SITT MF/IND/GLY for patients with asthma uncontrolled on ICS/LABA [40]. Data from the CAPTAIN trial showed that single-inhaler FF/UMEC/VI with a high FF dose reduced the rate of exacerbations, especially in patients with raised biomarkers of type 2 airway inflammation [39].

Chronic asthmatic smokers

In a small RCT of 16 smoking patients with asthma, SITT budesonide/olodaterol/tiotropium (BDP/OLO/TIO) was found to be superior to BDP/OLO in improving small airways dysfunction for both resistance and compliance. Significant improvements at trough for all outcomes of impulse oscillometry (IOS, a measure of small airway dysfunction), except for R20, was seen with triple therapy treatment *versus* dual therapy [99].

Use of SITT may be considered for newly diagnosed COPD with severe airway obstruction, exacerbation and peripheral eosinophilia. Patients discharged from hospital after an acute exacerbation of COPD, and in whom COPD is diagnosed for the first time (because of the severe exacerbation), can also be considered for SITT. These rare cases could be put on maintenance therapy at least for the first 1–3 months and then narrowly considered for step-down [70].

OAD management in India: gaps, challenges and future

Significant gaps have been reported in primary healthcare delivery and clinical approach in the management of OAD in India. This has been attributed to discrepancies in the diagnosis, lack of proper labelling (such as bronchial asthma, COPD) and appropriate management of the disease. The Indian Medical Association has also highlighted the underdiagnosis or incorrect diagnosis and poor management of patients with asthma. Oral therapy is still widely used in the management of asthma in India despite guidelines recommending inhaler therapy, which is associated with poor asthma control and increased hospitalisations. Nevertheless, increased availability of affordable drugs (including inhalers) and easier accessibility to investigation tools such as spirometry and peak flow meters have helped improve diagnosis and management of OAD in India. Due consideration should be given to non-smoking-related risk factors such as childhood lower respiratory tract infections, biomass exposure, prior history of tuberculosis and environmental pollution while managing OAD patients in India. Use of clinical prediction for future exacerbation risk will help in further optimising patient care.

Few observations have been made by experts on SITT based on the available literature and clinical nuances in OAD in India (table 3). Symptom control and compliance were the two most common factors influencing the choice of SITT. While the burden of ACO and NSCOPD is higher in India, there is no direct evidence about the effectiveness of SITT in this set of population. However, ICS is likely to be more beneficial in such patients than in those with smoker COPD. Notably, owing to higher eosinophil counts among individuals with NSCOPD, there may be an increased need for ICS in this population. Though advantages of SITT are certain, open triple therapy still find its place in the subset of unstable patients considering the flexibility in terms of dose titration (specifically for the ICS component) and splitting the components, especially LABA and LAMA (as noted in clinical practice).

TABLE 3 Summary of India-specific issues related to OAD characteristics, management, SITT therapy and research requirement

OAD population characteristics	• India has a highly symptomatic and exacerbating OAD population comprising group B and D COPD patients, step 4/5 asthma patients, difficult-to-treat asthma patients and ACO patients • >20% of the global COPD-related mortality is in India • Sociodemographic divide in terms of the prevalence of asthma with higher prevalence in the rural areas compared to urban areas • Asthma patients tend to tolerate their symptoms and consider a certain amount of suffering as an inherent part of the disease process • The rate of COPD is higher among nonsmokers compared to smokers • High burden of NSCOPD (~65%), especially in rural areas due to biomass exposure and indoor pollution • Risk factors, such as childhood lower respiratory tract infections, biomass exposure, history of tuberculosis and environmental pollution, are high • High nonadherence rate (27.2%) to inhalers among asthma patients
Gaps in diagnosis and management of OAD	• Significant gaps are reported in primary healthcare delivery and clinical approach in the management of OAD • Discrepancies in the diagnosis, lack of proper labelling (such as bronchial asthma or COPD) and appropriate management of the disease • Asthma management in India remains very poor, with a significant proportion of patients experiencing challenging symptoms and worsened quality of life • Many patients do not use their inhaler device correctly • Asthma management is negatively influenced by certain cultural and social beliefs among Indians • Despite guideline recommendations of inhalation therapy in asthma, oral therapy is still widely used
Choice of SITT	• Both SITT and open triple therapy are used in clinical practice • Physicians decide the choice (SITT *versus* open triple therapy) based on factors such as stable *versus* unstable OAD, titration flexibility of ICS dose, patient compliance and device options
Gaps in SITT adaptation	• SITT options in India are limited to twice-daily DPI formulations • SITT is not yet approved for asthma by the drug regulatory body in India
Need for research	• Threshold values for blood eosinophil count in Indian population needs to be evaluated • The effectiveness of SITT in patients with ACO and NSCOPD in India needs to be established • Data related to SITT in asthma in India are lacking • Indian guidelines related to management of OAD need to be frequently updated

OAD: obstructive airway disease; SITT: single-inhaler triple therapy; ACO: asthma–COPD overlap; NSCOPD: nonsmoker chronic obstructive pulmonary disease; ICS: inhaled corticosteroids; DPI: dry powder inhaler.

SITT with once-daily dosing is not yet available in India, leaving a void for optimal compliance benefit. Additionally, SITT is not approved for asthma by the drug regulatory body in India. Hence, data related to SITT in asthma are also lacking. However, off-label use of SITT in asthma is often noticed in clinical practice.

Conclusion

Obstructive airway disease remains an important cause of mortality and morbidity with a significant healthcare burden. SITT is now becoming an important treatment modality in OAD management as it reduces exacerbations and improves symptom control and QoL. Additionally, evidence suggests improved adherence with SITT. However, device choices for SITT are currently not available globally. Studies related to the efficacy and safety of SITT in NSCOPD and ACO patients are required in the Indian context. Cost-effectiveness studies will also be advantageous to patients living in low- and middle-income countries like India. Further real-world studies are also needed to substantiate the benefits of SITT in OAD, especially asthma.

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References

1 GBD Chronic Respiratory Disease Collaborators. Prevalence and attributable health burden of chronic respiratory diseases, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet Respir Med* 2020; 8: 585–596.
2 Blanco I, Diego I, Bueno P, *et al.* Geographic distribution of COPD prevalence in the world displayed by Geographic Information System maps. *Eur Respir J* 2019; 54: 1900610.
3 Cheng SL, Lin CH. COPD Guidelines in the Asia-Pacific regions: similarities and differences. *Diagnostics (Basel)* 2021; 11: 1153.
4 India State-Level Disease Burden Initiative CRD Collaborators. The burden of chronic respiratory diseases and their heterogeneity across the states of India: the Global Burden of Disease Study 19902016. *Lancet Glob Health* 2018; 6: e1363–e1374.
5 Bhome AB. COPD in India: iceberg or volcano? *J Thorac Dis* 2012; 4: 298–209.
6 Salvi SS, Apte KK, Dhar R, *et al.* Asthma insights and management in India: lessons learnt from the Asia Pacific – asthma insights and management (AP-AIM) Study. *J Assoc Physicians India* 2015; 63: 36–43.
7 Dhar R, Ip M, Kulkarni T, *et al.* Challenges faced in managing adult asthma: a perspective from Asian countries. *Respirology* 2020; 25: 1235–1242.
8 Hurst JR, Vestbo J, Anzueto A, *et al.* Susceptibility to exacerbation in chronic obstructive pulmonary disease. *N Engl J Med* 2010; 363: 1128–1138.
9 Koul PA, Dar HA, Jan RA, *et al.* Two-year mortality in survivors of acute exacerbations of chronic obstructive pulmonary disease: a North Indian study. *Lung India* 2017; 34: 511–516.
10 Batra A, Chhabra G, Gupta PK. Helplessness in chronic obstructive pulmonary disease patients: assessment and correlation with sociodemographic factors and spirometry-based severity. *Indian J Respir Care* 2018; 7: 83–87.
11 Bajpai J, Kant S, Bajaj DK, *et al.* Clinical, demographic and radiological profile of smoker COPD versus nonsmoker COPD patients at a tertiary care center in North India. *J Family Med Prim Care* 2019; 8: 2364–2368.

12 Mahmood T, Singh RK, Kant S, *et al.* Prevalence and etiological profile of chronic obstructive pulmonary disease in nonsmokers. *Lung India* 2017; 34: 122–126.
13 India State-Level Disease Burden Initiative CRD Collaborators. The burden of chronic respiratory diseases and their heterogeneity across the states of India: the Global Burden of Disease Study 1990–2016. *Lancet Glob Health* 2018; 6: e1363–e1374.
14 Koul PA, Nowshehri AA, Khan UH, *et al.* Cost of severe chronic obstructive pulmonary disease exacerbations in a high burden region in North India. *Ann Glob Health* 2019; 85: 1–5.
15 Monteagudo M, Nuñez A, Solntseva I, *et al.* Treatment pathways before and after triple therapy in COPD: a population-based study in primary care in Spain. *Arch Bronconeumol (Engl Ed)* 2021; 57: 205–213.
16 Koul PA, Patel D. Indian guidelines for asthma: adherence is the key. *Lung India* 2015; 32: 1–2.
17 Kritikos V, Price D, Papi A, *et al.* A multinational observational study identifying primary care patients at risk of overestimation of asthma control. *NPJ Prim Care Respir Med* 2019; 29: 43.
18 Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for Prevention, Diagnosis and Management of COPD. Available from: https://goldcopd.org/
19 Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention. Available from: www.https://ginasthma.org/
20 Cloutier MM, Dixon AE, Krishnan JA, *et al.* Managing asthma in adolescents and adults: 2020 asthma guideline update from the national asthma education and prevention program. *JAMA* 2020; 324: 2301–2317.
21 Vogelmeier CF, Román-Rodríguez M, Singh D, *et al.* Goals of COPD treatment: focus on symptoms and exacerbations. *Respir Med* 2020; 166: 105938.
22 Bengtson LGS, DePietro M, McPheeters J, *et al.* Real-world outcomes in patients with chronic obstructive pulmonary disease initiating long-acting mono bronchodilator therapy. *Ther Adv Respir Dis* 2018; 12: 1753466618772750.
23 Labaki W, Fernando M, Meilan H. Insights into chronic obstructive pulmonary disease epidemiology, phenotypes and outcomes from SPIROMICS. *Barcelona Respiratory Network* 2019; 5: 233-248.
24 Quint JK, O'Leary C, Venerus A, *et al.* Prescribing pathways to triple therapy: a multi-country, retrospective observational study of adult patients with chronic obstructive pulmonary disease. *Pulm Ther* 2020; 6: 333–350.
25 Ghosh S, Anderson WH, Putcha N, *et al.* Alignment of inhaled chronic obstructive pulmonary disease therapies with published strategies. Analysis of the global initiative for chronic obstructive lung disease recommendations in SPIROMICS. *Ann Am Thorac Soc* 2019; 16: 200–208.
26 Bogart M, Stanford RH, Laliberté F, *et al.* Medication adherence and persistence in chronic obstructive pulmonary disease patients receiving triple therapy in a USA commercially insured population. *Int J Chron Obstruct Pulmon Dis* 2019; 14: 343–352.
27 Montes de Oca M, Menezes A, Wehrmeister FC, *et al.* Adherence to inhaled therapies of COPD patients from seven Latin American countries: The LASSYC study. *PLoS One* 2017; 12: e0186777.
28 Ingebrigtsen TS, Marott JL, Nordestgaard BG, *et al.* Low use and adherence to maintenance medication in chronic obstructive pulmonary disease in the general population. *J Gen Intern Med* 2015; 30: 51–59.
29 Sanchis J, Gich I, Pedersen S. Systematic review of errors in inhaler use: has patient technique improved over time? *Chest* 2016; 150: 394–406.
30 Celli BR. Pharmacological therapy of COPD: reasons for optimism. *Chest* 2018; 154: 1404–1415.
31 Vanfleteren LEGW, Boonen LMC, Spruit MA, *et al.* The superexacerbator phenotype in patients with COPD: a descriptive analysis. *ERJ Open Res* 2019; 5: 00235-2018.
32 Le Rouzic O, Roche N, Cortot AB, *et al.* Defining the "Frequent Exacerbator" phenotype in COPD: a hypothesis-free approach. *Chest* 2018; 153: 1106–1115.
33 Kerstjens HA, Moroni-Zentgraf P, Tashkin DP, *et al.* Tiotropium improves lung function, exacerbation rate, and asthma control, independent of baseline characteristics including age, degree of airway obstruction, and allergic status. *Respir Med* 2016; 117: 198–206.
34 Gupta D, Agarwal R, Aggarwal AN, *et al.* Guidelines for diagnosis and management of chronic obstructive pulmonary disease: Joint ICS/NCCP (I) recommendations. *Lung India* 2013; 30: 228–267.
35 López-Campos JL, Alcázar Navarrete B, Riesco Miranda JA, *et al.* A Delphi consensus document on the use of single-inhaler fixed-dose triple therapies in COPD patients. *Int J Chron Obstruct Pulmon Dis* 2020; 15: 1801–1811.
36 Li Y, Lim J, Stemkowski S, *et al.* Initiation of triple therapy maintenance treatment among patients with COPD. *Am J Manag Care* 2020; 26: e106–e112.
37 Zheng Y, Zhu J, Liu Y, *et al.* Triple therapy in the management of chronic obstructive pulmonary disease: systematic review and meta-analysis. *BMJ* 2018; 363: k4388.
38 Virchow JC, Kuna P, Paggiaro P, *et al.* Single inhaler extrafine triple therapy in uncontrolled asthma (TRIMARAN and TRIGGER): two double-blind, parallel-group, randomised, controlled phase 3 trials. *Lancet* 2019; 394: 1737–1749.

39 Lee LA, Bailes Z, Barnes N, *et al.* Efficacy and safety of once-daily single-inhaler triple therapy (FF/UMEC/VI) versus FF/VI in patients with inadequately controlled asthma (CAPTAIN): a double-blind, randomised, phase 3A trial. *Lancet Respir Med* 2021; 9: 69–84.
40 Kerstjens HAM, Maspero J, Chapman KR, *et al.* Once-daily, single-inhaler mometasone-indacaterol-glycopyrronium versus mometasone-indacaterol or twice-daily fluticasone-salmeterol in patients with inadequately controlled asthma (IRIDIUM): a randomised, double-blind, controlled phase 3 study. *Lancet Respir Med* 2020; 8: 1000–1012.
41 Cipla Ltd. Indian experience with glycopyrronium 25 µg/formoterol 12 µg when given concurrently with budesonide 400 µg; Data on File 2019.
42 Salvi S, Balki A, Krishnamurthy S, *et al.* Efficacy and safety of single-inhaler triple therapy of glycopyrronium, formoterol and fluticasone in patients with COPD: a double-blind, randomised controlled trial. *ERJ Open Res* 2021; 7: 00255-2021.
43 Trelegy Ellipta (fluticasone furoate, umeclidinium, and vilanterol inhalation powder) [Prescribing Information]. 2018. NC, USA, GlaxoSmithKline.
44 Trelegy Ellipta. Summary of product characteristics. 2018. Dublin, GlaxoSmithKline.
45 CADTH Canadian Drug Expert Committee Recommendation. Fluticasone furoate/umeclidinium/vilanterol (Trelegy Ellipta). 2018. www.cadth.ca/ Date last accessed: 21 July 2021.
46 Bevespi Aerosphere™ (glycopyrrolate and formoterol fumarate) [Prescribing Information]. 2016. Wilmington, AstraZeneca Pharmaceuticals.
47 Trimbow (beclometasone/formoterol/glycopyrronium bromide). Summary of product characteristics. 2017. Via Palermo, Chiesi Farmaceutici.
48 Enerzair Breezhaler. Summary of product characteristics. 2020. Dublin, Novartis Europharm Limited.
49 Central Drugs Standard Control Organization. List of FDC & Subsequent New Drugs Approved in India. https://cdsco.gov.in/opencms/opencms/system/modules/CDSCO.WEB/elements/download_file_division.jsp?num_id=NzUxOQ== Date last accessed: 11 November 2021.
50 Singh D, Papi A, Corradi M, *et al.* Single inhaler triple therapy versus inhaled corticosteroid plus long-acting β2-agonist therapy for chronic obstructive pulmonary disease (TRILOGY): a double-blind, parallel group, randomised controlled trial. *Lancet* 2016; 388: 963–973.
51 Vestbo J, Papi A, Corradi M, *et al.* Single inhaler extrafine triple therapy versus long-acting muscarinic antagonist therapy for chronic obstructive pulmonary disease (TRINITY): a double-blind, parallel group, randomised controlled trial. *Lancet* 2017; 389: 1919–1929.
52 Papi A, Vestbo J, Fabbri L, *et al.* Extrafine inhaled triple therapy versus dual bronchodilator therapy in chronic obstructive pulmonary disease (TRIBUTE): a double-blind, parallel group, randomised controlled trial. *Lancet* 2018; 391: 1076–1084.
53 Ferguson GT, Rabe KF, Martinez FJ, *et al.* Triple therapy with budesonide/glycopyrrolate/formoterol fumarate with co-suspension delivery technology versus dual therapies in chronic obstructive pulmonary disease (KRONOS): a double-blind, parallel-group, multicentre, phase 3 randomised controlled trial. *Lancet Respir Med* 2018; 6: 747–758.
54 Rabe KF, Martinez FJ, Ferguson GT, *et al.* Triple inhaled therapy at two glucocorticoid doses in moderate-to-very-severe COPD. *N Engl J Med* 2020; 383: 35–48.
55 Lipson DA, Barnhart F, Brealey N, *et al.* Once-daily single-inhaler triple versus dual therapy in patients with COPD. *N Engl J Med* 2018; 378: 1671–1680.
56 Halpin DM, Miravitlles M, Metzdorf N, *et al.* Impact and prevention of severe exacerbations of COPD: a review of the evidence. *Int J Chron Obstruct Pulmon Dis* 2017; 12: 2891–2908.
57 Hurst JR, Skolnik N, Hansen GJ, *et al.* Understanding the impact of chronic obstructive pulmonary disease exacerbations on patient health and quality of life. *Eur J Intern Med* 2020; 73: 1–6.
58 Rennard SI, Farmer SG. Exacerbations and progression of disease in asthma and chronic obstructive pulmonary disease. *Proc Am Thorac Soc* 2004; 1: 88–92.
59 Zayed Y, Barbarawi M, Kheiri B, *et al.* Triple versus dual inhaler therapy in moderate-to-severe COPD: a systematic review and meta-analysis of randomized controlled trials. *Clin Respir J* 2019; 13: 413–428.
60 Calzetta L, Ritondo BL, de Marco P, *et al.* Evaluating triple ICS/LABA/LAMA therapies for COPD patients: a network meta-analysis of ETHOS, KRONOS, IMPACT, and TRILOGY studies. *Expert Rev Respir Med* 2021; 15: 143–152.
61 Ritondo BL, Puxeddu E, Calzetta L, *et al.* Efficacy and safety of triple combination therapy for treating chronic obstructive pulmonary disease: an expert review. *Expert Opin Pharmacother* 2021; 22: 611–620.
62 Rogliani P, Ritondo BL, Calzetta L. Triple therapy in uncontrolled asthma: a network meta-analysis of Phase III studies. *Eur Respir J* 2021; 58: 2004233;
63 Magnussen H, Disse B, Rodriguez-Roisin R, *et al.* Withdrawal of inhaled glucocorticoids and exacerbations of COPD. *N Engl J Med* 2014; 371: 1285–1294.
64 Singh D, Clini E, Papi A, *et al.* A pooled analysis of the TRILOGY, TRINITY and TRIBUTE studies. *Eur Respir J* 2020; 56: 979.

65 Ishiura Y, Fujimura M, Ohkura N, *et al.* Effect of triple therapy in patients with asthma-COPD overlap. *Int J Clin Pharmacol Ther* 2019; 57: 384–392.
66 Naya I, Compton C, Ismaila AS, *et al.* Preventing clinically important deterioration with single-inhaler triple therapy in COPD. *ERJ Open Res* 2018; 4: 00047-2018.
67 Hartley BF, Barnes NC, Lettis S, *et al.* Risk factors for exacerbations and pneumonia in patients with chronic obstructive pulmonary disease: a pooled analysis. *Respir Res* 2020; 21: 5.
68 Humenberger M, Horner A, Labek A, *et al.* Adherence to inhaled therapy and its impact on chronic obstructive pulmonary disease (COPD). *BMC Pulm Med* 2018; 18: 2525319.
69 Monteagudo M, Barrecheguren M, Solntseva I, *et al.* Clinical characteristics and factors associated with triple therapy use in newly diagnosed patients with COPD. *NPJ Prim Care Respir* 2021; 31: 16.
70 Vanfleteren LEGW, Ullman A, Nordenson A, *et al.* Triple therapy (ICS/LABA/LAMA) in COPD: thinking out of the box. *ERJ Open Res* 2019; 5: 00185-2018.
71 Singh D, Fabbri LM, Corradi M, *et al.* Extrafine triple therapy in patients with symptomatic COPD and history of one moderate exacerbation. *Eur Respir J* 2019; 53: 1900235.
72 Suzuki T, Fairburn-Beech J, Sato K, *et al.* Clinical characteristics, treatment patterns, disease burden, and persistence/adherence in patients with asthma initiating inhaled triple therapy: real-world evidence from Japan. *Curr Med Res Opin* 2020; 36: 1049-1057.
73 Papaioannou AI, Loukides S, Bakakos P, *et al.* Dual bronchodilator in the era of triple therapy. *Int J Chron Obstruct Pulmon Dis* 2020; 15: 2695–2705.
74 Landis SH, Pimenta JM, Yang Y, *et al.* Association between blood eosinophils and acute exacerbation of COPD risk in patients with COPD in primary care. *Respiratory Medicine: X* 2019; 1: 100011.
75 Fernando M, Ferguson G, Bourne E, *et al.* Budesonide/glycopyrrolate/formoterol fumarate metered dose inhaler, formulated using co-suspension delivery technology, improves lung function and exacerbation outcomes in patients with COPD without a recent history of exacerbations: subgroup analysis of KRONOS study. *Chest* 2019; 156: A2276–A2277.
76 Miravitlles M, Soler-Cataluña JJ, Calle M, *et al.* Spanish guidelines for management of chronic obstructive pulmonary disease (GesEPOC) 2017. Pharmacological treatment of stable phase. *Arch Bronconeumol* 2017; 53: 324–335.
77 Magnussen H, Lucas S, Lapperre T, *et al.* Withdrawal of inhaled corticosteroids versus continuation of triple therapy in patients with COPD in real life: observational comparative effectiveness study. *Respir Res* 2021; 22: 25.
78 Nici L, Mammen MJ, Charbek E, *et al.* Pharmacologic management of chronic obstructive pulmonary disease. An official American Thoracic Society clinical practice guideline. *Am J Respir Crit Care Med* 2020; 201: e56–e69.
79 Chang AB, Fortescue R, Grimwood K, *et al.* European Respiratory Society guidelines for the management of children and adolescents with bronchiectasis. *Eur Respir J* 2021; 11: 2002990.
80 Celli BR, Criner GJ. Using the peripheral blood eosinophil count to manage patients with chronic obstructive pulmonary disease. *Ann Am Thorac Soc* 2019; 16: 301–303.
81 Pascoe S, Locantore N, Dransfield MT, *et al.* Blood eosinophil counts, exacerbations, and response to the addition of inhaled fluticasone furoate to vilanterol in patients with chronic obstructive pulmonary disease: a secondary analysis of data from two parallel randomised controlled trials. *Lancet Respir Med* 2015; 3: 435–442.
82 Watz H, Tetzlaff K, Wouters EF, *et al.* Blood eosinophil count and exacerbations in severe chronic obstructive pulmonary disease after withdrawal of inhaled corticosteroids: a post-hoc analysis of the WISDOM trial. *Lancet Respir Med* 2016; 4: 390–398.
83 Rasool QI, Bhat JH, Parry AA. Incidence of eosinophilia in rural population of northern region of Kashmir in India (a study at tertiary care hospital). *GJRA* 2019; 8: 2277–8160.
84 Salvi SS, Brashier BB, Londhe J, *et al.* Phenotypic comparison between smoking and non-smoking chronic obstructive pulmonary disease. *Respir Res* 2020; 21: 50.
85 Vedel-Krogh S, Nordestgaard BG, Lange P, *et al.* Blood eosinophil count and risk of pneumonia hospitalisations in individuals with COPD. *Eur Respir J* 2018; 51: 1800120.
86 Braghiroli A, Braido F, Piraino A, *et al.* Day and night control of COPD and role of pharmacotherapy: a review. *Int J Chron Obstruct Pulmon Dis* 2020; 15: 1269–1285.
87 Averell CM, Laliberté F, Duh MS, *et al.* Characterizing real-world use of tiotropium in asthma in the USA. *J Asthma Allergy* 2019; 12: 309–321.
88 Beeh KM, Kuna P, Corradi M, *et al.* Comparison of Dry-powder inhaler and pressurized metered-dose inhaler formulations of extrafine beclomethasone dipropionate/formoterol fumarate/glycopyrronium in patients with COPD: the TRI-D randomized controlled trial. *Int J Chron Obstruct Pulmon Dis* 2021; 16: 79–89.
89 Singh RB. Inhalers for the Indian subcontinent: therapeutic and environmental imperatives. *Respiratory Drug Delivery* 2010; 1: 147–152.
90 Starup-Hansen J, Dunne H, Sadler J, *et al.* Climate change in healthcare: exploring the potential role of inhaler prescribing. *Pharmacol Res Perspect* 2020; 8: e00675.

91 Himes BE, Leszinsky L, Walsh R, *et al.* Mobile health and inhaler-based monitoring devices for asthma management. *J Allergy Clin Immunol Pract* 2019; 7: 2535–2543.

92 Dhadge N, Shevade M, Kale N, *et al.* Monitoring of inhaler use at home with a smartphone video application in a pilot study. *NPJ Prim Care Respir Med* 2020; 30: 46.

93 Wallace AE, Kaila S, Bayer V, *et al.* Health care resource utilization and exacerbation rates in patients with COPD stratified by disease severity in a commercially insured population. *J Manag Care Spec Pharm* 2019; 25: 205–217.

94 Langham S, Lewis J, Pooley N, *et al.* Single-inhaler triple therapy in patients with chronic obstructive pulmonary disease: a systematic review. *Respir Res* 2019; 20: 242.

95 Sharma R. Prevalence and profile of asthma COPD overlap (ACO) in previously diagnosed COPD patients – an observational study from north India. *Respirology* 2017; 22: 88–278.

96 Kumar KS, Mathew JV, Robert KGV. Prevalence of ACOS among elderly reporting to emergency of a tertiary hospital in south India. *JAPI* 2018; 66.

97 Knight A. Managing the overlap of asthma and chronic obstructive pulmonary disease. *Aust Prescr* 2020; 43: 7–11.

98 Ishiura Y, Fujimura M, Ohkura N, *et al.* Triple therapy with Budesonide/Glycopyrrolate/Formoterol fumarate improves inspiratory capacity in patients with asthma-chronic obstructive pulmonary disease overlap. *Int J Chron Obstruct Pulmon Dis* 2020; 15: 269–277.

99 Jabbal S, Kuo CR, Lipworth B. Randomised controlled trial of triple versus dual inhaler therapy on small airways in smoking asthmatics. *Clin Exp Allergy* 2020; 50: 1140–1147.