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.
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 (FEV₁) <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 of 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 FEV₁ 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
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 risk 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·m⁻² versus higher BMI >25 kg·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

FEV₁ 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 FEV₁ 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 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] | Enenerzair 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.
### 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 | • Age ≥40 years                                                                      | Extrafine BDP/FF/GP pMDI 200/12/25 μg twice daily (n=687) vs Tiotropium DPI 18 μg twice daily (n=537) ×52 weeks | • SITT was superior to BDP/FF for pre-dose FEV₁ (MD 81 mL; p<0.001) and 2-hour post-dose FEV₁ (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 |
|                      | • Pre-dose and 2-hour post-dose morning FEV₁ at week 26 and TDI score at week 26 | • Post-bronchodilator FEV₁ <50%  
  • FEV₁/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 |                                                                                         |                                                                                                                                                                       |
|                      | • COPD exacerbation rate at 52 weeks             |                                                                                      |                                                                                         |                                                                                                                                                                       |
|                      | • Pre-dose morning FEV₁ at week 26               |                                                                                      |                                                                                         |                                                                                                                                                                       |
| TRINITY EU, South America, Mexico [51] | • Phase 3, randomised, double-blind, parallel-group | • Current or ex-smokers  
  • Age ≥40 years  
  • Post-bronchodilator FEV₁ <50%  
  • FEV₁/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 | 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 FEV₁, 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 |
|                      | • COPD exacerbation rate at 52 weeks             |                                                                                      |                                                                                         |                                                                                                                                                                       |
|                      | • Pre-dose morning FEV₁ at week 26               |                                                                                      |                                                                                         |                                                                                                                                                                       |
| TRIBUTE EU [52]      | • Phase 3, randomised, double-blind, double-dummy, parallel-group | • Current or ex-smokers  
  • Age ≥40 years  
  • Post-bronchodilator FEV₁ <50%  
  • FEV₁/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 IN/GP DPI 85/43 μg once daily (n=768) ×52 weeks | • SITT significantly improved mean change from baseline in FEV₁ 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 |
|                      | • COPD exacerbation rate at 2 weeks              |                                                                                      |                                                                                         |                                                                                                                                                                       |
|                      | • Pre-dose morning FEV₁ at week 26               |                                                                                      |                                                                                         |                                                                                                                                                                       |
| KRONOS Canada, China, Japan, USA [53] | • Phase 3, randomised, double-blind, parallel-group | • Current or ex-smokers  
  • Age 40–80 years  
  • Post-bronchodilator FEV₁ ≥25% to 80%  
  • FEV₁/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 FEV₁ 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 FEV₁ 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 |
|                      | • COPD exacerbation rate at 24 weeks             |                                                                                      |                                                                                         |                                                                                                                                                                       |

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 FEV₁ 25–65% | | | |
|              | • ≥1 moderate or severe COPD exacerbation within 1 year | | | |
|              | • Use of ICS or SAMA/SABA ≥2 months | | | |
|              | • CAT score ≥10 | | | |
|              | | | | |
|              | BDP/DD/GP MDI 160/9/4.8 µg twice daily (n=2137) vs BDP/DD/GP MDI 160/9/4.8 µg twice daily (n=2121) vs GP/DD MDI 9/4.8 µg twice daily (n=2120) vs BDP/DD 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/DD (RR 0.76; p=0.001), or BDP/DD 1.24 (RR 0.87; p=0.003); 160-µg SITT was superior to GP/DD (RR 0.75; p=0.001) or BDP/DD 1.24 (RR 0.86; p=0.002) | |
| 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 FEV₁ | | | |
|              | • Ex-smokers | | | |
|              | • Age ≥40 years | | | |
|              | • Post-bronchodilator FEV₁ 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 FEV₁ versus UMEC/VI (MD 97 mL; p<0.001) and versus FF/VI (MD 54 mL; p<0.001) | |
| TRIGGER       | EU [38] | | | |
|              | • Phase 3, randomised, double-blind, parallel-group | | | |
|              | • Pre-dose morning FEV₁ | | | |
|              | • Asthma exacerbation rate | | | |
|              | • Age 18–75 years | | | |
|              | • Uncontrolled asthma (ACQ-7 1.5) | | | |
|              | • Pre-bronchodilator FEV₁ <80% | | | |
|              | • At least one exacerbation within 1 year | | | |
|              | • Use of high-dose ICS/LABA ≥4 weeks | | | |
|              | | | | |
|              | BDP/DD/GP 200/6/10 µg MDI twice daily (n=573) vs BDP/DD 200/6 µg MDI twice daily (n=576) vs OL BDP/DD 200/6 µg MDI twice daily plus tiotropium 2.5 µg once daily (n=288) × 52 weeks | | Rates of moderate-to-severe asthma exacerbations reduced by 12% for BDP/DD/GP versus BDP/DD, respectively (RR 0.88; p=0.11) | |
| TRIMARAN      | EU [38] | | | |
|              | • Similar to TRIGGER except use of medium-dose ICS/LABA ≥4 weeks | | | |
|              | | | | |
|              | BDP/DD/GP 100/6/10 µg MDI twice daily (n=579) vs BDP/DD/GP 100/6 µg MDI twice daily (n=576) × 52 weeks | | SITT was superior to BDP/DD for pre-dose FEV₁ (improvement by 73 mL; p=0.0025) at week 26 | |

**Continued**
### Clinical trial

| Clinical trial  | Trial design and end-points - primary/secondary | Patient population | Treatment and duration | Key findings |
|-----------------|-------------------------------------------------|--------------------|------------------------|--------------|
| CAPTAIN         | • Phase 3, randomised, double-blind, parallel-group | • Age 18–75 years | 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 | • High-dose LAMA SITT was superior to FF/VI 100/25 μg for pre-dose FEV₁ (LSMD, 110 mL; p<0.001); High-dose ICS SITT was superior to FF/VI 200/25 μg (92 mL; p<0.0001) |
|                 | • Pre-dose morning FEV₁ | • Uncontrolled asthma (ACQ-7 ≥1.5) | versus FF/UMEC/VI DPI 100/31.25/25 μg (n=404) once daily versus FF/UMEC/VI DPI 200/31.25/25 μg (n=404) 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 | • Adding UMEC 31.25 μg to FF/VI had similar outcomes; supported by FEV₁ at 3 hours post-dose |
|                 | • Asthma exacerbation rates                          | • Pre-bronchodilator FEV₁ 30–85% | | • Rates of moderate-to-severe asthma exacerbation reductions were non-significant for FF/UMEC 62.5 μg/VI versus FF/VI (pooled analysis) |
|                 | • Post-bronchodilator FEV₁ ≥12% and ≥200 mL in 20–60 min | • Post-bronchodilator increase in FEV₁ of ≥12% and ≥200 mL | | • Pneumonia rates were similar between the groups |
|                 | • Use of ICS/LABA ≥3 months                          | • Use of ICS/LABA ≥3 months | | |
| IRIDIUM         | • Phase 3, randomised, double-blind, double-dummy, parallel-group | • Age 18–75 years | MF/IND/GLY DPI 80/150/50 μg once daily (n=620) versus MF/IND/GLY DPI 160/150/50 μg once daily (n=619) versus MF/IND DPI 160/150 μg once daily (n=617) versus MF/IND DPI 320/150 μg once daily (n=618) versus 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 FEV₁ (MD 76 mL; p<0.001 and MD 65 mL, respectively; p=0.001 for both) |
|                 | • Pre-dose morning FEV₁                              | • Uncontrolled asthma (ACQ-7 ≥1.5) | | • Improvements in pre-dose FEV₁ 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 |
|                 | • Asthma exacerbation rate                           | • Pre-bronchodilator FEV₁ <80% | | • 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 |
|                 |                                                        | • Post-bronchodilator increase in FEV₁ of ≥12% and ≥200 mL | | • Pneumonia rates were similar between the groups |
|                 |                                                        | • Use of ICS/LABA ≥3 months | | |
| Indian trial    | • Phase 3, randomised, double-blind, active-control, parallel-group, noninferiority study | • COPD patients | 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 FEV₁ from baseline at 12 weeks was noninferior between the groups (p=0.05) |
|                 | • COPD patients                                      | • Age ≥40 to ≤75 years, with FEV₁/FVC <0.70 | | • LSMD change from baseline in post-dose FEV₁ was comparable (p=0.38) |
|                 | • COPD patients                                      | • Using mono/dual therapy with ICs, LAMAs, or LABAs for ≥1 month | | • Comparable efficacy in terms of change in trough FEV₁ |
|                 | • Change from baseline in trough FEV₁ at the end of 12 weeks | | | |

**Key:** 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; FEV₁: forced expiratory volume in 1 s; FEV₁ AUC: FEV₁ 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, FEV₁ <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 bronchodilator and LAMA monotherapy in reducing AECOPD at a cut-off value of $\geq 100$ eosinophil cells·μL$^{-1}$ [18]. In patients with $\geq 300$ eosinophil cells·μL$^{-1}$ 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 $\geq 6$ 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 FEV1/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 FEV1 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·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 FEV1 30–85% of predicted normal value), post-bronchodilator FEV1 ≥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.

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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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