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SINGLE-INHALER TRIPLE THERAPY IN COPD: INTEGRATING CLINICAL EFFICACY, DEVICE ERGONOMICS, AND COGNITIVE FACTORS FOR TREATMENT SUCCESS – A COMPREHENSIVE REVIEW

Honey Mariya Babu[1], Dr. Tamilselvan[3], Mrs. Vineetha S[2], Asika Dileep[4], Betty George [4], Jismi Jackson[4], Kadeejathul Hana KP[4]

[1]Fourth Semester, M Pharm Student, Department of Pharmacy Practice, Nehru College of Pharmacy, Thiruvilwamala, Thrissur,680588
[2]Associate Professor, Department of Pharmacy Practice, Nehru College of Pharmacy, Thiruvilwamala, Thrissur,680588
[3]HOD & Professor, Department of pharmacy, Nehru College of Pharmacy, Thiruvilwamala, Thrissur,680588
[4]Fourth Semester, M Pharm Students, Department of Pharmacy Practice, Nehru College of Pharmacy, Thiruvilwamala, Thrissur,680588

Abstract:
COPD remains a major cause of morbidity and mortality worldwide. Early optimization of bronchodilation in conjunction with anti-inflammatory medication has become more important in the management of moderate-to-severe illness. According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategy, patients with persistent symptoms and/or frequent exacerbations despite dual maintenance therapy are advised to use single-inhaler triple therapy (SITT), which combines a long-acting beta2-agonist (LABA), a long-acting muscarinic antagonist (LAMA), and an inhaled corticosteroid (ICS).
In addition to device-related performance features and cognitive factors influencing inhaler use, this thorough analysis summarizes data from significant randomized controlled trials and real-world investigations assessing the therapeutic efficacy of SITT. When compared to dual treatments, SITT consistently improves lung function and lowers rates of moderate-to-severe exacerbations across pivotal trials. However, real-world effectiveness is heavily influenced by device selection, inspiratory flow capacity, and patient-level cognitive and behavioural factors that affect inhaler technique.
Although mortality reductions have been reported in secondary analyses, these findings remain exploratory and require prospective confirmation. In general, combining pharmaceutical efficacy with customized device and cognitive evaluation is essential for therapeutic success.
***Keywords**: COPD; single-inhaler triple therapy; inhaler technique; device ergonomics; cognitive impairment; exacerbation prevention.*

Corresponding author:
Honey Mariya Babu,
4th Semester, M. Pharm Students,
Department of Pharmacy Practice,
Nehru College of 2Pharmacy,
Thiruvilwamala, Thrisssur, 680588

QR CODE

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INTRODUCTION:

Chronic Obstructive Pulmonary Disease (COPD) is a major global health concern, as well as the major cause of morbidity and mortality. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) states that triple therapy, which consists of a long-acting beta-2 agonist, a long-acting muscarinic antagonist, and an inhaled corticosteroid (LABA/LAMA/ICS), should be considered for patients who continue to have recurrent exacerbations or persistent symptoms despite dual bronchodilator therapy [8].

Recent GOLD findings support the use of single-inhaler triple treatment (SITT) in patients who continue to have exacerbations despite optimal dual therapy, particularly those with higher blood eosinophil levels and a high exacerbation load. Patients who have a blood eosinophil count of at least 300 cells/µL or who have experienced at least two moderate exacerbations or at least one hospitalization-related exacerbation in the past year are included in this [8].

Compared to multi-inhaler regimens, SITT eliminates essential inhaler-handling errors, enhances adherence, and streamlines complicated treatment regimens by integrating three pharmacologic classes into a single device [12]. In the past, triple therapy necessitated the use of many inhaler devices, which was linked to poor treatment compliance, a rise in technique-related mistakes, and greater medical expenses [5,12].

Although fixed-dose SITT is an important therapeutic and lifestyle development, the patient's contact with the delivery system plays a major role in translating its efficacy from controlled clinical trials to the real world [17]. Device mechanics, inspiratory flow needs, physical coordination, and the patient's neurocognitive capacity to successfully execute complex breathing manoeuvres all have an impact on clinical results [19,21]. Additionally, long-term respiratory symptoms such as productive cough may impede the delivery of medications, underscoring the significance of good maintenance techniques to stop the progression of the illness and clinical decline [18,19].

Therefore, the clinical effectiveness of single-inhaler triple therapy in COPD is examined in this thorough analysis, with a focus on key clinical trial data, device ergonomics, inhalation physiology, and cognitive factors that affect treatment success in the real world.

CLINICAL EFFICACY OF SINGLE-INHALER TRIPLE THERAPY

EVIDENCE FROM MAJOR CLINICAL TRIALS

Large randomized controlled studies assessing various pharmacological combinations and inhaler platforms provide evidence in favor of SITT.

In symptomatic patients with previous exacerbations, the IMPACT study showed that fluticasone furoate/umeclidinium/vilanterol significantly reduced moderate-to-severe exacerbations when compared with dual therapy [1]. Comparative findings against monotherapy regimens [9] further validated this finding. Comparing budesonide-based triple treatment to dual bronchodilation, the ETHOS study found lower exacerbation rates [25].

Although it was not particularly enriched for frequent exacerbators, the KRONOS study showed improvements in lung function and symptom control in a larger COPD group [2]. These advantages persisted even in patients switching straight from previous ICS/LABA combination treatments, according to later post-hoc analyses of the KRONOS data [3]. Completing the core registration trials, the TRIBUTE trial successfully proved the superiority of this extra fine formulation over LAMA/LABA dual bronchodilation [13], while the TRILOGY trial confirmed improvements in lung function and a decrease in exacerbations with extra fine beclomethasone dipropionate/formoterol/glycopyrronium compared with ICS/LABA therapy [4].

LUNG FUNCTION AND SYMPTOM OUTCOMES

SITT consistently improves trough FEV1 (around 50–100 mL compared to dual therapy) in pivotal trials, and it also significantly lowers dyspnoea scores and rescue drug use [2,24]. Reduced lung hyperinflation and better mechanical unloading of the respiratory muscles during exercise are the underlying physiological mechanisms of dyspnoea reduction [20]. Patients with higher baseline symptom load and frequent exacerbation risks benefit most clinically from these combined effects, which result in observable improvements in health-related quality of life.

MORTALITY OUTCOMES (CAUTIOUS INTERPRETATION)

Secondary studies from the IMPACT and ETHOS datasets found that SITT could reduce all-cause mortality relative to dual treatment [6]. However, these results must be regarded cautiously as hypothesis-generating since mortality was not a key endpoint in these protocols. The most likely biological mechanism is indirect, mediated by a decrease in the frequency and severity of acute exacerbation events, which are known to cause abrupt respiratory failure and cardiovascular problems.

ICS BENEFIT–RISK CONSIDERATIONS

The inclusion of inhaled corticosteroids in SITT necessitates careful patient selection due to the increased risk of pneumonia in susceptible populations [28]. Patients with low blood eosinophil counts (less than 100 cells/µl), a history of pneumonia, old age, or physical weakness are more at risk. The significance of correctly matching the anti-inflammatory component to the patient's unique phenotypic risk is shown by long-term safety evaluations of long-acting bronchodilator solutions [16].

On the other hand, ICS-containing regimens provide the best protection for patients with elevated eosinophil counts (>300 cells/µl) and frequent exacerbations. As a result, ICS utilization in SITT should be significantly customized in accordance with guidelines [8,28].

DEVICE ERGONOMICS AND INHALATION PHYSIOLOGY

DRY POWDER INHALERS (DPI)

Drug fluidization and de-aggregation in DPIs are fully dependent on patient-generated inspiratory flow. The internal resistance profile of the particular device determines the necessary peak inspiratory flow rate (PIFR), which can occasionally need efforts greater than 60 L/min in high-resistance systems [21].

Inadequate internal velocity generation causes inefficient lung deposition, inadequate peripheral dosage, and increased oropharyngeal drug waste in patients with severe airflow limitation or during severe acute exacerbations [19,22]. Because they lack the skeletal muscle strength to overcome significant internal device resistance, older populations are more at risk [27].

PRESSURIZED METERED-DOSE INHALERS (PMDI)

pMDIs are appropriate for patients with low inspiratory flow capabilities because they use propellant-driven mechanisms to deliver aerosolized medication without requiring inspiratory effort [15]. However, excellent coordination is required for optimal lung deposition in order to synchronize actuation with the beginning of a gradual, deep inhalation.

Phospholipid microparticle-based advanced co-suspension technology greatly enhances dose uniformity and suspension stability inside the canister [2], but it does not remove the fundamental behavioural requirements of appropriate shaking and handling techniques.

SPACER DEVICES

Spacer devices improve pMDI delivery dynamics by lowering aerosol velocity, allowing large propellant droplets to dissipate, and eliminating the requirement for precise hand-breath coordination. Because of this optimization, they are strongly advised for older people and those who exhibit cognitive impairments [23].

Table 1. COMPARATIVE DEVICE PROFILE

Factor	Dry Powder Inhaler (DPI)	Pressurized Metered-Dose Inhaler (pMDI)
Inspiratory Requirement	High (Flow-dependent)	Low (Volume-dependent)
Coordination Demand	Low (Breath-actuated)	High (Requires simultaneous hand-breath sync)
Spacer Compatibility	Not applicable	Recommended in selected patients / elderly
Primary Failure Mode	Low peak inspiratory flow	Timing and coordination errors

COGNITIVE DETERMINANTS OF INHALER USE

COPD is commonly associated with systemic vascular dysfunction and hypoxemia-related cognitive impairment, which can significantly reduce a patient's ability to maintain correct inhaler technique and retain treatment instructions over time [17]. Cognitive impairment affects approximately 10–60% of patients with COPD, depending on disease severity and assessment methodology. Deficits in attention, executive function, memory, and processing speed may compromise the correct execution of inhaler techniques and adherence to long-term maintenance therapy. Consequently, cognitive assessment should be considered an important component of individualized inhaler selection and patient education strategies [17].

COGNITIVE DOMAINS

Effective inhaler use is a multi-step process that strongly relies on working memory (for technique step retention), executive function (for sequential step execution), and visuospatial ability (for physical device positioning and spatial manipulation) [17].

SCREENING TOOLS

In ordinary practice, quick, validated clinical assessments like the Montreal Cognitive Assessment (MoCA) and the Mini-Cog are very helpful in proactively identifying patients who are at risk of inhaler usage, technique degradation, and subsequent treatment failure [17,23].

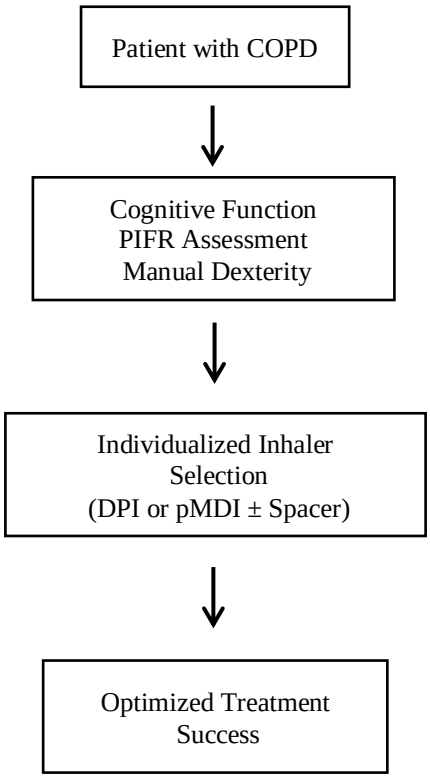
Table 2. CRITICAL INHALER ERRORS

Device Class	Critical Error	Clinical Consequence
DPI	Exhalation directly into the mouthpiece	Powder aggregation, moisture clumping, and severe dose loss
DPI / pMDI	Failure to perform a post-inhalation breath-hold	Reduced sedimentation, premature exhalation of fine particles
pMDI	Incorrect actuation timing (late/early)	Heavy oropharyngeal deposition, lack of lower airway entry
All Devices	Incorrect sequential preparation steps	Sub-therapeutic dosing or total therapeutic failure

DISCUSSION:

Single-inhaler triple therapy improves general adherence patterns, lowers out-of-pocket expenses, and greatly simplifies advanced COPD management. By lowering resource use brought on by serious medical failures, formal economic modelling shows that SITT offers a more affordable intervention method than open triple combinations [7]. Consolidation into a single device, however, also concentrates operational risk because all maintenance alternatives are stored together, making it possible for a single significant error to completely nullify the patient's entire maintenance schedule [12].

Clinician decisions must shift from typical protocol-driven models to a holistic framework that balances pharmaceutical benefit, device resistance, inspiratory flow dynamics, and cognitive ability in order to optimize real-world results [19,21]



Maintaining long-term illness stability requires pharmacist-led educational interventions, device demonstrations, and systematic technique reassessments at each clinical transition point [5,23,26]. Digital inhaler monitoring systems with integrated electronic sensors can provide real-time telemetry on objective adherence and execution quality, verifying proper handling outside of the clinic setting, to support these instructional initiatives [14]. Lastly, physical treatments should be combined with appropriate maintenance pharmacotherapy; the greatest functional improvements in overall exercise tolerance and quality of life are achieved when optimized SITT is combined with structured home-based pulmonary rehabilitation and frequent exercise programs [10]

PATIENT-CENTERED CONSIDERATIONS IN SITT

Although single-inhaler triple therapy has demonstrated substantial clinical efficacy in randomized clinical trials, treatment success in routine practice is strongly influenced by patient-specific factors [1,2,25]. Inspiratory flow capability, cognitive function, manual dexterity, health literacy, and treatment adherence all contribute to the effective use of inhaler devices and achievement of optimal therapeutic outcomes [17,19,21,23]. Failure to account for these factors may reduce clinical benefit despite the use of evidence-based pharmacological regimens [12,17]. Therefore, optimal implementation of SITT requires a patient-centered approach that integrates clinical characteristics with individualized device selection, inhaler education, and ongoing technique reassessment [5,12,23,26].

LIMITATIONS

The clinical heterogeneity across large randomized controlled trials, which includes differences in stringent patient selection criteria, particular baseline inhaler devices, and varying historical

definitions of what constitutes a clinical exacerbation, all restrict direct head-to-head comparability and limit this review. Moreover, compared to closely controlled settings, large-scale registration trials lack objective technique tracking and real-world prospective adherence data.

The mortality results are still limited by secondary exploratory characteristics and need to be verified through specific prospective safety trials [6]. Finally, evaluating absolute risk-benefit safety limits may be complicated by the considerable variation in prior baseline ICS doses across study populations [28].

CONCLUSION:

Single-inhaler triple treatment is a very effective, evidence-based standard of care for individuals with moderate-to-severe COPD who have had previous exacerbations. Major clinical trials consistently demonstrate superior
exacerbation reduction and improvements in lung function
compared with dual therapy [1,4,25].
However, real-world success is still largely dependent on patient-level cognitive and physical abilities as well as device ergonomics [12,17,19]. Highly individualized device selection, frequent pharmacist-led evaluation, objective screening for cognitive obstacles, and accurate, biomarker-guided assessment of long-term ICS hazards are all necessary to maximize the real-world clinical effectiveness of SITT [8,28].

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