



Experience of clinicians with dual bronchodilator therapy in COPD (EXPAND) in Nepal

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ABSTRACT

Introduction: Combination of bronchodilators, particularly long-acting muscarinic antagonists (LAMAs) and long-acting β 2-agonists (LABAs) have become the mainstay of pharmacological therapy for COPD. COPD is now a common non communicable disease in Nepal.

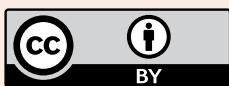
Objective: The study evaluated the current perception and experience of the clinicians in Nepal on diagnosis and management of COPD with focus on use of dual bronchodilator therapy.

Method: This cross-sectional, observational survey evaluated experiences of clinicians (n=96; pulmonologist-13, physician-57, general practitioner-26) in Nepal on diagnosis, management trends, and current perceptions on the use of dual bronchodilator therapy in COPD management.

Result: 93% of clinicians were practising in an urban setting for an average of 10 years and an average of 35% of their patients are of COPD. 61% of clinicians use mMRC with (34%) or without (27%) CAT score. 92% of clinicians perceived that most of their patients had 1 (32%) or >1 (59%) exacerbation/year. 54% of clinicians performed spirometry on all their patients with suspected COPD. 49% of clinicians measured blood EOS in their patients with severe COPD before adding ICS. 93% of clinicians preferred dual therapy (separate inhalers or a combination) for their COPD patients, but 83% of clinicians preferred LABA + LAMA in a single inhaler over inhalers given separately. 57% of clinicians preferred LABA + LAMA and 82% preferred the Tiotropium + Formoterol combination. 81% of clinicians stepped up or stepped down their treatment. 56% of patients were taking LABA + LAMA + ICS and 55% of clinicians co-prescribed ICS + LABA with LABA + LAMA. 80% of clinicians checked the inhalation technique at every visit and an average of 54% of their COPD patients were adherent (>80%) to the prescribed inhalation therapy. 78% of clinicians felt that dryness of mouth was the most common side effect of LABA + LAMA. 94% of clinicians believed that managing COPD better could improve cardiovascular outcomes in their patients with coexistent COPD.

Conclusion: In the EXPAND survey, Formoterol + Tiotropium was preferred by most clinicians in Nepal amongst the LABA + LAMA combination. There is a good scope for improvement in the utilization of tools like spirometry, mMRC, CAT, and blood EOS in the daily practice of clinicians in Nepal.

Keywords: Chronic Obstructive Pulmonary Disease; Bronchodilators; Inhaler Techniques; Formoterol; Tiotropium.



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INTRODUCTION

An estimated 384 million people are suffering from chronic obstructive pulmonary disease (COPD) globally. The global prevalence of COPD is 11.7%¹ and the annual mortality being 3 million,² which is further projected to increase to as high as 5.4 million by 2060.^{3,4} Low- and middle-income countries (LMICs) account for 80% of the 60% of non-communicable disease (NCDs) including chronic respiratory diseases related

mortality globally, which is the largest percentage of deaths caused by NCDs.⁵ According to World Health Organization (WHO), NCDs in the South-Asian LMIC, in Nepal accounted for 66% of mortality, of which chronic respiratory diseases

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were the second highest cause of death (10%)⁶. Further it was reported that the third most common cause of outpatient department morbidity in Nepal is also COPD.⁷ To tackle the ever-increasing issue of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) collaborates with medical experts and public health representatives globally to increase COPD awareness and enhance the disease's prevention and management. As per the GOLD 2024 strategy report the main treatment goals of COPD are to reduce the symptoms and future risk of exacerbations.³ Combination of bronchodilators, particularly long-acting muscarinic antagonists (LAMAs) and long-acting β 2-agonists (LABAs) have been the backbone of pharmacological therapy for COPD.¹ The GOLD 2024 strategy report suggests the initial pharmacological management for group B COPD should be the LABA + LAMA combination. The patients are labelled as group B COPD based on their mMRC and CATTM scores as ≥ 2 and ≥ 10 respectively (mMRC: modified Medical Research Council dyspnea questionnaire, CATTM: COPD Assessment TestTM), and those patients with 0 or 1 moderate exacerbation which is not leading to any hospital admission.³ The LABA + LAMA combination is also labelled as the preferred choice for initial therapy in group E COPD⁸ who had ≥ 2 moderate exacerbations or ≥ 1 exacerbation leading to hospitalization.³ Different LAMAs available in the market include Tiotropium, Aclidinium, Umeclidinium, Glycopyrrolate, etc.⁹ Tiotropium, a long-acting muscarinic antagonist, is reported to possess high selectivity for M3 muscarinic receptors, and a prolonged M3 receptor blockade leads to over 24 hours of bronchodilation action resulting in once daily prescription.¹⁰ Similarly several LABAs are also available for the management of COPD including Formoterol, Salmeterol, Indacaterol, Vilanterol, Olodaterol, etc.¹¹ Formoterol is a long-acting β 2-adrenergic receptor agonist. Formoterol's interaction with β 2-receptors is present on airway smooth muscle cell membranes, resulting in persistent bronchodilation. The approximate duration of action of formoterol is 12 hours, resulting in twice daily prescription.¹² Previous reports have suggested that there exists a probable complementary action when LABA and LAMA is administered in combination.^{13,14} Interestingly, a meta-analysis involving 8 randomized clinical trials showed significant improvement among COPD patients treated with the Tiotropium + Formoterol combination compared to Tiotropium alone in different spirometric indices, which includes trough FEV1 and FVC, peak FEV1 and FVC, transitional dyspnea index (TDI), St. George Respiratory Questionnaire (SGRQ) and exacerbations.¹⁵ There is not much data on how clinicians perceive the diagnosis and management trends of COPD and current perceptions and experiences of clinicians in Nepal on the use of dual bronchodilator therapy for the management of COPD. Nepal is one of Asia's lower- and middleincome countries as per the international guidelines. Hence doctor surveys are essential to keep track of the use of diagnosing methods, management therapies, pharmacological effects, ease of using the technologies, and the factors that affect COPD in Nepal. Keeping all this in mind, this survey was planned to evaluate the experience of clinicians with the use of dual

bronchodilator therapy in COPD management in Nepalese patients. This survey was also planned to understand the diagnosis and management trends of the clinicians on COPD in Nepal.

METHOD:

This questionnaire-based, observational, cross-sectional survey evaluated experiences of randomly chosen pulmonologists (13), physicians (57), and general practitioners (26) (cumulatively mentioned as 'clinicians' henceforth) in Nepal on the diagnosis, management trends, and current perceptions on the use of dual bronchodilator therapy for COPD management. Principal investigators helped to develop the survey questionnaire and reviewed the survey protocol and consent procedures to ensure data confidentiality and safety. **[Fig. 1]** Purposive sampling was used to choose physicians who treat a significant number of COPD patients and have respiratory practice. The survey procedure guaranteed data security and privacy, doctor agreement, full disclosure of the survey's creator and design, and the option to voluntarily leave the research. Data sharing consent was obtained from the clinicians prior to filling the questionnaire. 100 clinicians participated in the online survey, and 96 completed it. The survey questionnaire consisted of 29 closed-ended questions; some required a single answer while others offered multiple-choice answers. The surveys were not monetarily sponsored.

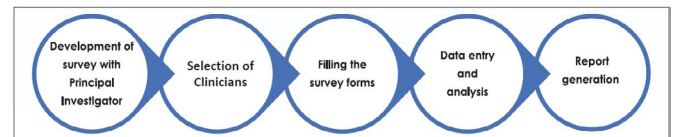


Figure 1: Scheme depicting the execution of the study

RESULTS:

The total percentage of clinicians [consulting pulmonologists (13.54%), physicians consulting respiratory medicines (59.38%), and general practitioners (27.08%)] **[Table 1]** who responded to the questions were of an average age of 39.68 years and average practice tenure of 10.09 years.

Table 1: Baseline characteristics

Baseline characteristics	Total number (n=96)	Percentage (%)
The speciality of participating clinicians		
Pulmonologist	13	13.54
Physician	57	59.38
General practitioner	26	27.08
Primary area of practice		
City	56	58.33

Town	33	34.38
Rural	7	7.29
Type of practice setting		
Hospital	33	34.38
Clinic	15	15.63
Both	48	50.00

92.7% of clinicians were practising in urban (city + town) settings for an average of 10 years and an average of 34.64% of their patients have COPD. An average of 41.02% are women COPD patients. 61% of clinicians use mMRC with (34.38%) or without (27.08%) CAT score for the diagnosis of COPD. **[Fig. 2]** Among the users of the mMRC scale in their practice, clinicians found that most patients (85.71%) have a symptom severity score of 2 or 3 as per mMRC. 91.66% of clinicians perceived that most of their patients had 1 (32.29%) or >1 (59.38%) exacerbation per year. **[Fig. 3]**

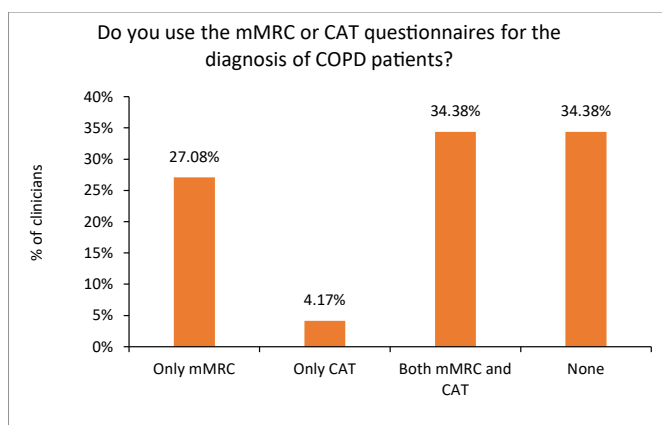


Fig. 2: Clinicians using mMRC or CAT for the diagnosis of COPD

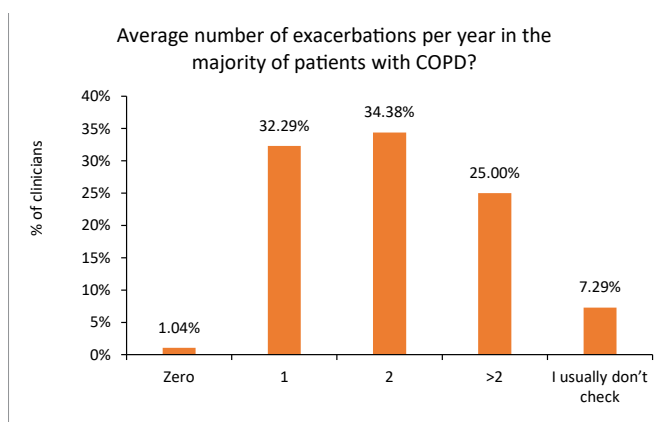


Fig. 3: Exacerbations per year in the majority of COPD patients

On average, 54.16% of clinicians performed spirometry on all patients with suspected COPD. Before administering ICS, 48.95% of the clinicians who assessed the blood eosinophil levels in their severe COPD patients also verified that 87.23%

of the time, they perform this test at least twice per year for their patients.

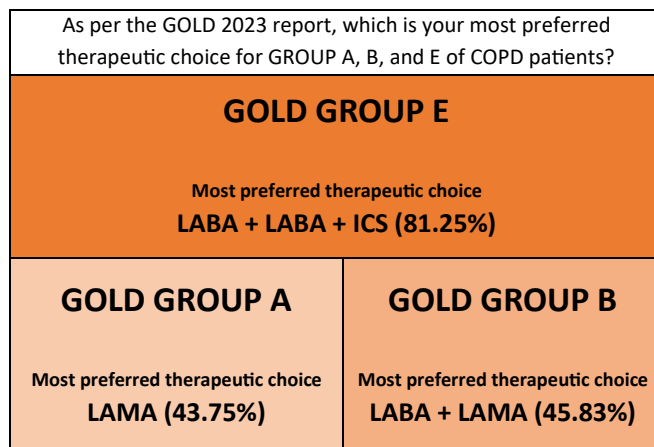


Fig. 4: Most preferred therapeutic choice for GROUP A, B, and E of COPD patients

As per the GOLD 2023 strategy report of managing COPD, the clinicians found their most preferred therapeutic choice for GOLD severity GROUP A, B, and E are LAMA (43.75%), LABA + LAMA (45.83%) and LABA + LABA + ICS (81.25%) respectively. **[Fig. 4]**

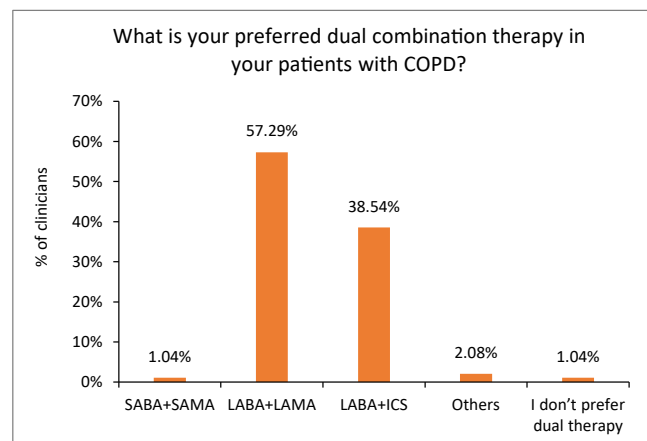


Fig. 5: Preferred dual combination therapy in patients with COPD

92.7% of clinicians preferred dual therapy (either as separate inhalers or a combination) for their COPD patients. 57.29% of clinicians preferred the LABA + LABA combination to manage COPD patients **[Fig. 5]** and the Formoterol + Tiotropium combination (82.29%) was their most preferred choice compared to Glycopyrronium-Formoterol (6.25%). In their practice, an average of 19.7% and 20.02% of clinicians felt

that their COPD patients remain uncontrolled despite being treated with a LABA + LAMA or LABA + ICS combination, respectively. 81.25% of clinicians step up (from dual to triple therapy) or step down (from triple to dual therapy) their treatment for their patients with COPD. Clinicians confirmed that out of their total number of patients with COPD, only 55.65% of their patients were taking LABA + LAMA + ICS. 55.20% of clinicians also like to co-prescribe ICS + LABA with LABA + LAMA. Based on their clinical experience, 30.21% of clinicians believe that improving quality of life is the most important benefit of LABA + LAMA when prescribed in COPD patients. [Fig. 6] 83.33% of clinicians preferred LABA + LAMA in a single inhaler as the more practical option over inhalers given separately.

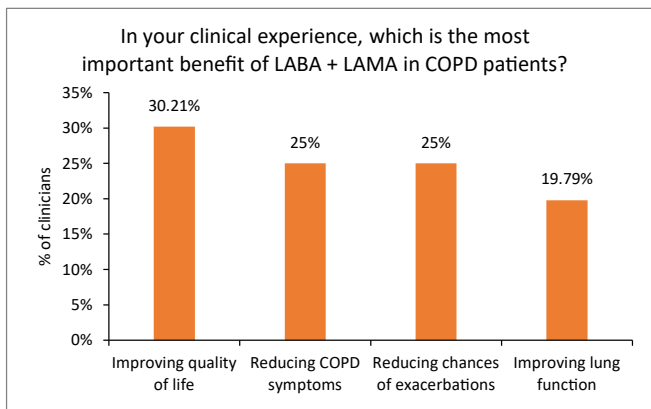


Fig 6: Most important benefit of LABA + LAMA when prescribed in COPD patients

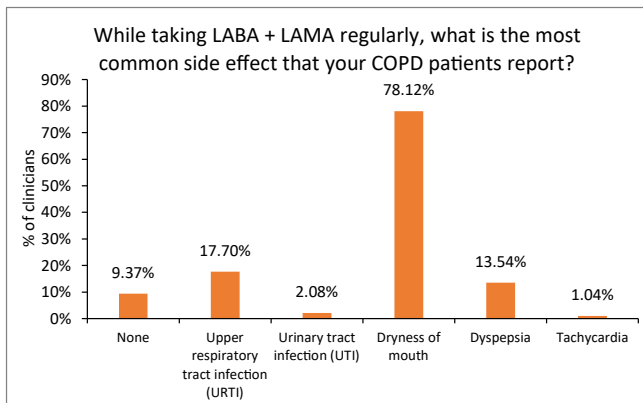


Fig 7: Most reported side effect of LABA + LAMA

Clinicians found equal benefits while prescribing a once-daily LAMA or LABA + LAMA combination in the morning or evening, for patients with COPD. 78.12% of clinicians felt that among all, dryness of mouth was the most reported side effect of LABA + LAMA. [Fig. 7]

80.20% of clinicians checked the inhalation technique at every visit, and an average of 53.71% of their COPD patients were adherent (>80%) to the prescribed inhalation therapy. 93.75% of clinicians believed that managing COPD better could improve cardiovascular outcomes in their patients with coexistent COPD.

DISCUSSION:

The present survey was conducted in one of the LMIC country Nepal with an intention to understand the experience of clinicians with dual bronchodilator therapy in the management of COPD. The country is diversified into various specialties who manage patients with COPD. This includes pulmonologists, physicians, general practitioners who are cumulatively labelled as clinicians in this survey. These randomly chosen clinicians are practicing either in hospitals and/or in their personal clinics. They are primarily from the cities or towns and few from the rural areas of Nepal.

With a significant and growing economic and social cost, COPD is one of the world's major causes of morbidity and mortality. With the world's population ageing and prolonged exposure to COPD risk factors, the prevalence and impact of COPD will rise during the next several decades.³ A systematic analysis of the Global Burden of Disease Study done in 2016 suggests that COPD has become the fourth leading cause of all-age disability-adjusted life-years (DALYs) in Nepal.¹⁶ A study done in US comparing dual therapy of LABA + LAMA with monotherapy like LAMA demonstrated greater therapeutic benefits like improving total COPD symptoms scores with dual therapy.¹⁷ Another study done in a LMIC like India demonstrated the COPD management with dual therapy administered via a single inhaler produced a superior bronchodilator response than only LAMA alone over a period of 24 hours.¹⁸ The current study was carried out in another LMIC Nepal to evaluate the current perceptions and experiences of clinicians in Nepal on using dual bronchodilator therapy for the management of COPD. Also, to understand the perceptions regarding diagnosis and management trends of the clinicians on COPD in Nepal.

COPD diagnosis and determination of the COPD group to which the patient belongs is imperative in prescribing the therapy. Hashimoto N. et al. in their study emphasize the importance of an appropriate diagnosis for the management of COPD.¹⁹ A mixed evaluation technique based on the degree of symptoms for the diagnosis of COPD was also suggested by the GOLD strategy report as an alternative to the current simple spirometric grading system for disease severity assessment and therapy.³ Modified Medical Research Council (mMRC) scale has been used as a comprehensive symptom assessment tool. In this study, it was found that 61% of clinicians reported the use mMRC scale for the diagnosis of COPD. Among the users of the mMRC scale in their practice, clinicians found that most patients (85.71%) have a symptom severity score of 2 or 3 as per mMRC. The use of the mMRC scale has been seen in the study in Nepal by Shrestha SK et al., where they used the scale to diagnose COPD associated with Pulmonary Hypertension.²⁰ The use of a similar mMRC scale for COPD diagnosis can be similarly seen even in a 40year-old study from Nepal.²¹

A previous study describing knowledge, practice patterns, and attitude toward asthma management among physicians

in Nepal, showed that 37% of the doctors always used a spirometer as the lung function measuring tool for their patients.²² But in this study, on an average, 54.16% of clinicians performed spirometry on all patients with suspected COPD. Comparatively, spirometer use was slightly higher in COPD diagnosis as compared to asthma diagnosis. This could be because the GOLD strategy report suggests that the use of spirometry is mandatory to find the presence of a postbronchodilator FEV1/FVC < 0.7 to establish the diagnosis of COPD.³

In this study the clinicians reported that their most preferred therapeutic choice for GOLD severity GROUP A, B, and E are LAMA (43.75%), LABA + LAMA (45.83%), and LABA + LAMA + ICS (81.25%) respectively. This is in line with the strategy plan suggested by the GOLD 2024 strategy report of initial pharmacological management. The shifting of group E COPD patients from LABA + LAMA to LABA + LAMA + ICS is planned based on an elevated blood eosinophil count of ≥ 300 .³ In this study more than 81% of clinicians reported LABA + LAMA + ICS as their preferred choice for group E COPD patients and 49% of them check the blood eosinophil levels for this group. A study by Chokhani et al. in 2021 highlighted a similar preferred therapeutic choice of physicians as LABA + LAMA (40.67%) for Group B COPD patients which is in line with this study showing 45.83% clinicians' preferred choice.¹⁸ Amongst different LABA+LAMA combinations, 82.29% of clinicians preferred the Formoterol + Tiotropium combination whereas only 6.25% of clinicians preferred combination was Formoterol + Glycopyrronium. The actual reason behind their choice is not covered in this article as it was out of the scope of this survey. However, previous studies have shown that combination therapy of formoterol + tiotropium is non-inferior to formoterol + glycopyrrolate in terms of efficacy and safety profile of patients with COPD along with good tolerability and comparable adverse effect profile.^{23,24} 81.25% of clinicians step up (from dual to triple therapy) or step down (from triple to dual therapy) their treatment for their patients with COPD. A review by Marc Miravittles et al. published in 2022 on LABA + LAMA in COPD showed a similar recommendation for LABA + LAMA over monotherapy in patients with COPD and triple should only be used as a step-up option from the dual therapy.²⁵ 83.33% of clinicians preferred LABA + LAMA in a single inhaler as the more practical option over inhalers given separately. ATS guidelines also showed similar strong recommendations for LABA + LAMA combination therapy over LAMA or LABA monotherapy in patients with COPD.²⁶ Patients initiating therapy with single inhaler with combination drugs had significantly better adherence and persistence compared with multiple inhaler initiators.²⁷

30.21% of clinicians believe that improving quality of life is the most important benefit of LABA + LAMA when prescribed in COPD patients, followed by reducing symptoms and chances of exacerbations (25% each) and improving lung

function (19.79%). Similar importance of dual therapy in COPD treatment is also reported that for majority of COPD patients, dual bronchodilation is a treatment option that improves lung function, quality of life, and health-related symptoms while reducing exacerbations.²⁸

In this study 78.12% of clinicians felt that among all, dryness of mouth was the most reported side effect of LABA + LAMA. This is in accordance with previous studies on tiotropium bromide which demonstrated that tiotropium's sole notable adverse effect was dry mouth, which affected between 10 to 16% of patients but is safe and well tolerated by patients.¹⁰

In this study, 93.75% of clinicians believed that managing COPD better could improve cardiovascular outcomes in their patients with coexistent COPD. This corresponds to a previous study involving 32,696 COPD patients with coexistent cardiovascular risk factors, which confirmed coexistence is common but are inadequately monitored, undertreated, and poorly controlled. To lower morbidity and mortality in this high-risk patient population, novel strategies can enhance risk factor control and boost the acceptance of simple, affordable cardiovascular medications.²⁹

STRENGTHS AND LIMITATIONS:

This study includes participants from different geographies of Nepal which includes cities, towns, and rural regions. The clinicians who participated in this survey have also been diversified into multiple specialities who are involved in their practice managing patients with COPD symptoms like pulmonologists, physicians, and general practitioners. This gives a robust angle to the cumulated data. The main limitation of the study is that the survey is only restricted to the perceptions of clinicians regarding their diagnosis and management trends on COPD and not extended to the perceptions of their respective patients.

CONCLUSION:

There are no recent data on the clinician's perception and experience with the diagnosis and management of COPD specifically on the use of dual bronchodilators in Asia's lower- and middle-income countries including Nepal. In the EXPAND survey, Formoterol + Tiotropium was preferred by most clinicians in Nepal amongst all LABA + LAMA combinations. This survey also directed for further outcomes that might need to be contextualized to different study settings, allowing for adequate scope for future research and opinions of the patients suffering from similar respiratory diseases.

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Compliance with Ethics Guidelines: During the survey, no information about a specific patient was gathered, and no interventions were made. Ethics clearance is not needed for this project.

Data Availability: The corresponding author can provide the data sets created and/or analyzed during the current work upon reasonable request.

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