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RESEARCH ARTICLE

Effect of long-acting beta-2 agonists on small airways among patients with chronic lower respiratory symptoms - A clinicospirometric evaluation

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ABSTRACT

Background: Long-acting beta-2 agonists (LABA) are recommended for regular use to control chronic lower respiratory symptoms (LRS). However, LABAs may have the potency to modulate the lung pathology by suppressing the ongoing bronchial inflammation, leaving such patients at greater risk of severe complications. **Aims and Objectives:** The aim of this study was to evaluate the effect of inhaled LABA medications on small airways in patients with chronic LRS by spirometric screening at a tertiary hospital. **Materials and Methods:** A total of 240 urban patients (aged 25–50 years; both genders) with LRS referred from outdoor patients for spirometric screening were included in this study. After obtaining detailed clinical profile, patients were divided into two groups based on inhaled medications history: Lone LABA users (n = 130) and combined bronchodilator (BDRs) regimen (LABA + inhaled corticosteroids) users group (n = 110). Spirometry was carried out following recommendations of the American Thoracic Society/European Respiratory Society (2005). Patients were categorized based on forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1), FEV_1/FVC, $FEF_{25–75\%}$, and peak expiratory flow rate values. **Results:** A study revealed that those patients were treated with lone LABA inhalers chronically, persistence of small airways obstruction was significantly higher in them compared to combined BDRs regimen user group. **Conclusion:** The present study explores better efficacy of combined usage of combined BDRs regimen and potential masking effect of lone LABA in small airway diseases with respect to clinicospirometry study.

KEY WORDS: Long-acting Beta-2 Agonists; Small Airways Obstruction; Spirometry

INTRODUCTION

The small airway means bronchioles with <2 mm in internal diameters without cartilage which includes airways from the 4th to 16th generations of branching and offers little resistance to airflow that is laminar (and not turbulent). Although small airways contribute little to airway resistance in normal individual, these are the major site for several chronic obstructive airway diseases which present with a number of lower respiratory symptoms (LRS) such as wheeze, cough, and shortness of breath (SOB).[1] Small airway wall thickening caused by neutrophilic and CD4 lymphocytic infiltration is strongly associated with subsequent emphysematous destruction. Despite their importance, small airways related lung pathology have proven difficult to diagnose.[2] Small airway obstruction (SAO) can be identified by simple spirometry screening.[3] The forced expiratory flow at 25–75% of FVC (FEF25–75%) is the spirometric variable most commonly cited as an indicator of small airways obstruction.[2] Sensitivity of the spirometry procedure for diagnosing SAO will be increased further after reversibility test with bronchodilator.[4] There is limited data available on

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small airway pathology in uncontrolled as well as milder and/or in well-controlled bronchial asthmatics. Whether all or certain particular patients with complaining of LRS will have small airways involvement remains largely unknown till date. Researchers named this type of patient population having small airways involvement as "small airways phenotype."[2]

The use of long-acting beta-2 agonist (LABA) medications through inhalational route is very much popular age-old practice to treat LRS, either as monotherapy or in combination to other drugs such as corticosteroids as they offer quick symptomatic relief. However, in spite of a successful and optimistic introduction in early nineties (1990), LABAs were soon mired with controversy. In reviewing the history, it is worth to mention in this article that in the 1960s and 70s, the more potent short-acting beta-2 agonists were isoproterenol and fenoterol which were found to be associated with high asthmatic mortality. Subsequently, they were withdrawn from the market. With this background, there is always a concern about the safety measure of commonly used LABAs such as salmeterol and formoterol in India.[5] In general, LABAs have an acceptable safety profile in spite of having some adverse effects such as tachycardia, palpitations, transient decrease in PaO_2, and tremor;[6] based on clinical finding of the occurrences of severe asthma exacerbations in some patients with asthma, with some associated deaths among patients receiving these drugs chronically, Pulmonary-Allergy Drugs Advisory Committee of the Food and Drug Administration, USA, considered "Black Box" levels for LABAs.[7] However, there is unavailability of data to the investigators till date which can undoubtedly prove whether these drugs may have the potency to greatly increase the risk of asthma mortality or not.[6] Truly speaking very few long-term Indian studies[5] as well as in other parts of the world[8-12] have been conducted till date to evaluate the rationality of using LABA, particularly for SAO in spite of having the knowledge about the involvement of small airways among patients with acute and chronic LRS as well as mild-to-severe diseases.

As the detailed picture about the actual therapeutic efficacy of LABA for LRS patients is yet to establish[13] and correct answer to the management of drugs with "black box" warnings still unclear, there is, therefore, an urgent need not only to understand whether treating this airway region impacts on patient symptoms but also to establish a proper treatment protocol for better control of the disease state.

The objective of the study was to evaluate the effect of inhaled LABA medications on small airways in patients with chronic LRS at a tertiary health-care setup.

MATERIALS AND METHODS

An observation and cross-sectional study was conducted between July and October 2016 on 240 patients aged 25–50 years (both gender) including smokers who were using LABA inhalers either alone or in combination with corticosteroids for chronic LRS for >3 months duration. All study subjects were legal residents of the state of West Bengal. Therefore, they could be assigned as Bengali by ethnicity. They were referred from different outpatient departments to the pulmonary function testing laboratory at physiology department of a tertiary hospital, Kolkata, for the 1st time for spirometric evaluation. In this study period, 240 patients were selected using complete enumeration sampling technique and of course maintaining proper inclusion and exclusion criteria. Ethical permission was obtained from the Institutional Ethics Committee, R G Kar Medical College and Hospital, Kolkata, before study and written consent was taken from each of the subject before the testing procedure. Inclusion criteria have already been mentioned. Exclusion criteria for the present study were asymptomatic patients coming for follow-up spirometry study, for pre anaesthetic check-up, patients having LRS less than three months duration, those who have been treated with oral medications and/or inhalers other than above mentioned drugs, patients below 25 years and above 50 years of age, debilitated patients, active haemoptysis and tuberculosis, patients with known cardiovascular, sub-diaphragmatic diseases and known Otorhinolaryngological diseases. However, patients with allergic-rhinitis or rhino-sinusitis were included in the study as sino-nasal symptoms in COPD may persist due to inflammatory condition and/or pathological neurogenic reflexes or even directly by products of smoking.[14] On the other side, allergens, dust, microbes, and non-specific respiratory irritants typically narrow the airways by excessive mucus production, thereby exacerbating COPD symptoms.[15,16]

The selected patients were at first asked to respond to a standardized respiratory symptoms questionnaire (American Thoracic Society [ATS]/Division of Lung Disease-78questionnaire),[17] and subsequently, a detailed history of the disease and treating medications were obtained from their prescription slip. The names and duration of the usage of different medications for at least 90 days as well as clinical profile including general survey and systemic examination of respiratory and cardiovascular system were documented at hospital outdoor patient (OPD) tickets. Afterward, patients were divided into two groups based on their medication history of >3 months duration documented from the OPD prescriptions: Inhaled lone LABA user group (n = 130) and combined BDRs regimen (LABA + inhaled corticosteroids [ICS]) users group users (n = 110). LABAs such as salmeterol and formoterol were included in the first group, whereas combined BDRs such as salmeterol/fluticasone propionate and formoterol/budesonide. Drugs were chosen for other groups in this study. Smoking history was obtained separately and subjects were categorized as per US Centers for Disease Control and Prevention definition of "never smokers" - adults who have never smoked a cigarette or who smoked fewer than 100 cigarettes in their entire lifetime. Rests of the subjects were marked as smokers. Spirometry was carried out using

a non-heated spirometer (RMS HELIOS 702) following the American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines.[18] The instrument was properly calibrated as per the ATS/ERS protocol before the procedure at each time. The largest observed values of forced expiratory volume in 1 s (FEV_1) and FVC available from at least three acceptable and reproducible tests were taken as the key parameters for interpretation. Then, the subject was asked to inhale short-acting BDRs such as levosalbutamol or ipratropium bromide in the pre-prescribed doses.[18] After 10 min of taking the inhaler, the subject was asked to perform the spirometry once again and thus the reversibility test done.[19] The highest values of FVC and FEV_1 were selected. Spirometric parameters recorded were FVC, FEV_1, FEV_1/FVC, $FEF_{25–75\%}$, and peak expiratory flow rate (PEFR) and percent predicted values were used to categorize all the study subjects as per existing standard criteria - (i) normal spirometric finding, (ii) COPD, (iii) restrictive pattern; (iv) mixed ventilatory defect, and (v) SAO.[20] The sentence was deleted due to irrelevent in this context. As the present study was of observation and cross-sectional nature, so no confounding variable such as age and smoking could be ascertained. However, these were important variables which influenced the overall outcome. Therefore, in this study, patients were categorized based on these spirometric indices and compared the different groups to deduce the study results.

Statistical Analysis

Descriptive analyses were performed using Fisher's exact test (for categorical variables) and two-sided unpaired t-tests (for continuous variables) to compare groups. As all the data were collected at a point of time (cross-sectional data) with no known confounding variable, so unpaired *t*-test was applied to compare these two groups. All data of spirometric variables were expressed in percent predicted form. Statistical analyses were done using GraphPad Quickcalcs Software, California, USA. $P < 0.05$ was considered statistically significant.

RESULTS

Characteristics of the study population are presented in Table 1. Subjects treated with combined BDRs regimen users were significantly more likely to be smokers, having high persistence of LRS like wheeze and more number of prior physician-diagnosed cases of asthma, allergic rhinitis, and COPD compared to other population in this study. Strikingly post-medication reversibility test results mean values of FVC, FEV_1, FEV_1/FVC, and PEFR were significantly much less among combined drug users than that of lone LABA using patients. Moreover, there were no significant differences regarding mean age, weight, height, body mass index (BMI), gender, and LRS other than wheeze such as dyspnea, dry cough, wet cough, as well as spirometric mean value of $FEF_{25–75\%}$ also between these two populations.

Table 2 had shown that occurrence of spirometry diagnosed COPD and mixed ventilator defect was significantly more in combined BDRs using population compared to lone LABA using population, whereas small airways obstruction (SAO) was significantly much higher among lone LABA users than that of the other groups in this study. Moreover, exactly half of the combined drug's users and nearly two-fifth of lone LABA users were having normal spirometry result (Figure 1).

DISCUSSION

This present study was conducted to evaluate the effect of inhaled LABA medications on small airways in patients with chronic LRS by spirometry. The result of this study observed higher prevalence of persistent SAO with lesser clinical finding like wheeze among patients using LABA as monotherapy for at least 3-month duration compared to combined BDRs regimen user group, whereas testing results revealed significantly higher number of COPD and mixed ventilatory defects among combined regimen users than the other groups in this study. Over and above a large of subjects in this study population were reported normal test results in spite of having ongoing symptoms for which they were treated with the inhaled medications.

At first, this study was chosen those patients having LRS and received treatment from their physician with above-mentioned inhaled drugs for at least 3 months. A 90-day period was chosen because respiratory medications for chronic LRS among patients such as asthma and COPD are usually prescribed for 3 months at a time.[21]

Previously, Lazarus *et al*. were conducted a study on LABA monotherapy versus continued therapy with ICS and observed that ICSs were more effective than inhaled LABA as far as relief of persistent symptoms asthma was concerned, though there were no significant differences in spirometric parameters.[22] However, researchers had already shown the better efficacy using combination therapy of ICSs and LABA than monotherapy with either agent alone[23,24]

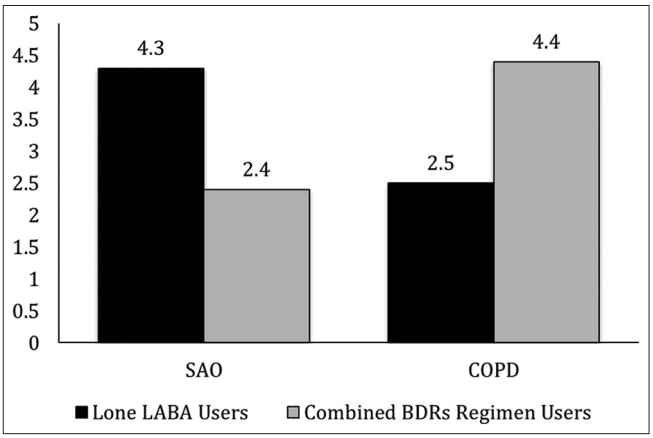

Figure 1: Spirometric analysis of obstructive airway diseases

Table 1: Overall demographic, anthropometric, clinical, and spirometric profile of the study population

Variable	Lone LABA users (*n*=130)	Combined BDRs regimen users (*n*=110)	*P*
Gender (*n* [%])	Male: 50 (38.46) Female: 80 (61.54)	Male: 50 (45.45) Female: 60 (54.55)	0.295
Age (years) (Mean±SD)	40.38±10.92	42.54±14.16	0.1834
Weight (kg) (Mean±SD)	55.61±8.86	57.86±14.96	0.1506
Height (cm) (Mean±SD)	154.65±7.69	156.31±10.57	0.1614
BMI (kg/m^2) (Mean±SD)	23.42±4.26	23.63±5.44	0.7378
Smoking statusa (*n* [%])	Ever smoker: 25 (19.23) Never smoker: 105 (80.77)	Ever smoker: 40 (36.36) Never smoker: 70 (63.64)	0.0035*
Dyspnea (SOB)[b] (*n* [%])	Yes: 130 (100.00) No: 00 (0.00)	Yes: 110 (100.00) No: 00 (0.00)	1.00
Dry cough[c] (*n* [%])	Yes: 40 (30.76) No: 90 (69.24)	Yes: 40 (36.36) No: 70 (63.64)	0.4102
Wet cough (*n* [%])	Yes: 50 (38.46) No: 80 (61.54)	Yes: 35 (31.81) No: 75 (68.19)	0.3422
Wheeze (*n* [%])	Yes: 5 (3.84) No: 125 (96.16)	Yes: 15 (13.63) No: 95 (86.37)	0.0088*
Physician-diagnosed asthma[d] (*n* [%])	Yes: 0 (0.00) No: 130 (100.00)	Yes: 25 (22.7) No: 85 (77.28)	<0.0001*
Physician-diagnosed COPD[e] (*n* [%])	Yes: 5 (3.84) No: 125 (96.16)	Yes: 25 (22.72) No: 85 (77.28)	<0.0001*
Physician-diagnosed allergic rhinitis[f] (*n* [%])	Yes: 40 (30.77) No: 90 (69.23)	Yes: 75 (68.18) No: 35 (31.82)	<0.0001*
FVC[g] (Mean±SD)	123±42.09	105.5±26.95	0.0002*
FEV1[h] (Mean±SD)	97.96±38.09	78.31±49.29	0.0006*
FEV_1/FVC (Mean±SD)	87±22.58	78.81±34.54	0.0285*
$FEF^{25–75\%}$ [i] (Mean±SD)	62.5±28.31	63.22±40.04	0.871
PEFR[j] (Mean±SD)	65.46±28.47	54.54±33.94	0.0072*

SD: Standard deviation, BMI: Body mass index. (a). Smoking status defined as ever/never smoker of cigarette, beerie, or huqqa. (b). Patients were asked: Do you have to walk slower than people of your age on the level due to breathlessness? Shortness of breath (SOB) (Grade II): To evaluate SOB NYHA standard guidelines were followed. (c). Chronic cough defined as cough on most days of month, for 3 consecutive months or more in a year. (d). Physician-diagnosed asthma defined as asthma confirmed by a doctor. (e). Physician-diagnosed COPD defined as COPD confirmed by a doctor. (f). Physician-diagnosed allergic rhinitis defined as allergic rhinitis confirmed by a doctor which is clinically most reliable factor in detection of allergy. (g). Forced vital capacity. (h). Forced expiratory volume in 1 s. (i). Forced expiratory flow 25–75%. (j). Peak expiratory flow rate, BDR: Bronchodilator

Table 2: Categorization of post-medication reversibility test results

Spirometric finding	Lone LABA users (*n*=130)	Combined BDRs regimen users (*n*=110)	*P*
Normal[k] (*n* [%])	Yes: 55 (42.30) No: 75 (57.7)	Yes: 55 (50.00) No: 55 (50.00)	0.2447
SAO[l] (*n* [%])	Yes: 60 (46.15) No: 70 (53.85)	Yes: 15 (13.64) No: 95 (86.36)	<0.0001*
COPD[m] (*n* [%])	Yes: 10 (7.70) No: 120 (92.3)	Yes: 25 (22.72) No: 85 (77.28)	0.0015*
Mixed ventilatory defectn (*n* [%])	Yes: 00 (0.00) No: 130 (100.00)	Yes: 15 (13.64) No: 95 (86.36)	<0.0001*
Restrictive pattern[o] (*n* [%])	Yes: 5 (3.85) No: 125 (96.15)	Yes: 00 (0.00) No: 110 (100.00)	0.0642

(k). FVC: 80%–120% predicted; FEV_1: 80%–120% predicted; FEV_1/FVC: 70%–85%; $FEF_{25–75}$: Values ranging from 50% to 60% and up to 130% of the average, PEFR: >60% predicted value. (l). $FEF_{25–75}$<50% predicted mainly. (m). FEV1/FVC<70% and FEV_1 value<100% predicted: Mild COPD or higher. (n). FEV1/FVC<0.7 and FVC<80% of predicted. (o). FVC<80%, FEV1≤80% (normal/decreased) and FEV1/FVC≥0.7

before that study. Although this present study was observed significantly more number of physician diagnosed asthma, COPD and allergic rhinitis as well as spirometric finding of COPD cases among combined BDRs regimen using

population compared to the other group. At a glance, these findings were not similar to the previous research works. However, further analysis of data revealed that these findings were not at all surprising because in this study combined BDRs regimen users group had significantly more number of smokers than lone LABA using population. Previously, Eisner *et al*.[25] had shown the fact that by far the single most important as well as the novel cause for developing COPD was smoking. There was no significant difference regarding mean age, weight, height, BMI, gender, and LRS such as dyspnea, dry cough, wet cough, and post-BDRs mean value of $FEF_{25–75\%}$ between these two populations. This implies that smokers were having a subjective feeling of worsening symptoms than non-smokers while suffering from similar type of active lung disease and, therefore, were prescribed more intensively with drugs. Furthermore, all of the medicines were prescribed without spirometry screening, which is basically a malpractice by physicians as documented in a pilot study by the same authors[26] and other researchers as well[27] before conducting this present study. Therefore, although the diagnostic algorithm starts with a thorough history and physical examination (including a discussion of family history, risk factors for respiratory and cardiac diseases, and occupational history), these clinical data are insufficient to diagnose patients having LRS appropriately leading to undiagnosed, misdiagnosed, and under or over diagnosed could be resulted.[26,27] Similarly, this present study also documented normal spirometry results among a good number of study population in spite of using medications continuously which could again be a supportive evidence of the malpractice in the community.

On the other part of this present study, it was observed that not only significantly higher prevalence of persistent SAO as shown in spirometric analysis but also less persistence of LRS like wheezing was noted among LABA monotherapy users compared to the other group. In the 1990s, Spitzer *et al*. first observed that the usage of beta-2 agonists was linked to excess asthma-related mortality mainly due to a limitation in small airways of respiratory tract.[28] In many articles from time to time, the authors tried to analyze the molecular basis of the above findings. Conventionally, LABAs act on beta-2-adrenoceptors on airway smooth muscle (ASM), which initiates a signaling cascade and as a result of chemical events relaxation of ASM will be achieved.[6] However, it has become increasingly clear that the chemical pathway is considerably more complex and sophisticated than was previously considered, although most of the picture is still unclear till date.[29] Some researchers thought that tolerance to BDR and bronchoprotective effect to LABA using chronically might be due to reduction in both number and affinity of peripheral beta-2-adrenoceptors pointed toward deregulation and desensitization and receptor gene expression at terminal airways.[30,31] Moreover, chronic beta-2 agonists usage had been linked to heightened airway responsiveness to allergen exposure and produced tolerance to relieving effect from methacholine and allergen-induced bronchoconstriction. Postulated primary mechanisms of airway hyperresponsiveness were abnormalities of ASM such as increased ASM bulk, aberrant autonomic control, hyperactive reflex pathways, and physical damage to the airway epithelium as documented by the researchers.[28] These findings might be possibly explained the link between LABA use as monotherapy and loss of asthma control. Beasley *et al*. hypothesized that this could be due to the pro-inflammatory effect of LABA resulting from augmentation of allergic inflammation and T-Helper-2 responses specifically through the activation of signal transducer and activator of transcription 6.[32] Some studies were also documented the fact that chirality of LABA may also contribute SAO as R-enantiomer of these drugs has therapeutic importance, whereas S-enantiomer of racemes of beta-2 agonists appears to be responsible for rebound bronchial hyperresponsiveness.[33,34] In recent years, attention has been drawn to beta-2 agonist polymorphisms also. Studies have shown that asthmatics that are homozygous for arginine (Arg-16) have an impaired therapeutic response to salmeterol in spite of using ICSs concomitantly.[5] However, these polymorphisms may be more common in patients of different ethnic backgrounds and potentially alter clinical effects; it warrants further study for complete evaluation of this fact to abolish all contradictory findings.[34]

Furthermore, previously few small studies were observed the fact that actual lung function parameters worsen strongly with prolongation of treatment with lone LABA. Researchers commented that this might be due to potential masking effects of salmeterol in airway inflammation in asthmatic population with LRS, i.e., by simple BDRs beta-2 agonists relieve symptoms without arresting the principal inflammation causing COPD.[30,35] Similarly less persistence of wheezing, a conventional clinical marker for obstruction (blockage) or narrowing of the small bronchial tubes in the periphery of respiratory airways,[36] might be supportive evidence for potential masking effect of underlying lung pathology like SAO in the population using LABA as monotherapy. This could lead to delay in developing awareness about worsening of LRS and airway inflammation in this population. Researchers had shown that even a single dose of LABA can also mask the clinical symptoms and airway inflammation cell influx following challenge.[30,37,38] According to Cates *et al*.,[39] reducing the use of these drugs ultimately solved this problem, but whether the enhanced mortality was due to cardiovascular toxicity, masking of chronic LRS or another cause remained to be established.[20]

Limitations of the Study

This study had few limitations that need to be considered. Due to cross-sectional nature of the study, it was difficult to establish causal association between impaired lung function and LRS. Moreover, reason for the existence of significantly higher proportion of mixed ventilatory defect among

combined BDRs using patients compared with lone LABA users could not be discussed here as further investigations (plethysmography) will be required to clarify the reason for the diminished vital capacity. Due to cross-sectional nature, the diagnostic variations of individual pharmacological agent (including formoterol, salmeterol, and their combination with corticosteroids) in spirometric analysis as well as therapeutic significance in drug regimen (like single use or multiple uses at a time or in a day) could not be analyzed in this present study. Over and above this study had beyond the scope to analyze the effect of drug delivery systems to periphery of airways like whether the subjects were using dry powder inhalers or puffed metered dose inhalers with or without valve holding chambers or spacers as these data could not be retrieved from the OPD prescriptions of the hospital. Although researchers had shown that not only particle size of the drug but also the drug delivery system influences the efficiency of inhaled medications to heal lung pathology.[40] Finally, as this was a small, observational study performed in a single center with a homogeneous population, the results may vary in studies with larger and relatively heterogeneous population. Despite these limitations, we believe that our observations will provide valuable clue on future modifications of the ongoing therapeutic guidelines in treating patients suffering from LRS.

CONCLUSION

The present study points toward the better efficacy of combined BDRs regimen in patients with chronic LRS. Regular usage of lone LABA was associated with potential masking effect in patients with LRS and enhanced SAO. Future large-scale clinical trials are required for serial assessments of drug response and/or disease progression, to design appropriate drug combination and to customize drug protocol according to the age, sex, and BMI to improve small airways function.

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REFERENCES

1. Hogg JC, Macklem PT, Thurlbeck WM. Site and nature of airway obstruction in chronic obstructive lung disease. N Engl J Med 1968;278:1355-60.
2. Burgel PR. The role of small airways in obstructive airway diseases. Eur Respir Rev 2011;20:23-33.
3. Stewart JI, Criner GJ. The small airways in chronic obstructive pulmonary disease: Pathology and effects on disease progression and survival. Curr Opin Pulm Med 2013;19:109-15.
4. Pérez-Padilla R, Hallal PC, Vázquez-García JC, Muiño A, Máquez M, López MV, *et al.* Impact of bronchodilator use on the prevalence of COPD in population-based samples. COPD 2007;4:113-20.
5. Gogtay JA, Chhowala SB. Are long acting beta agonists safe? Assoc Physicians India 2012;22:382-5.
6. Cazzola M, Page CP, Rogliani P, Matera MG. β2-agonist therapy in lung disease. Am J Respir Crit Care Med 2013;187:690-6.
7. Aaronson DW. The "black box" warning and allergy drugs. J Allergy Clin Immunol 2006;117:40-4.
8. Wagner EM, Liu MC, Weinmann GG, Permutt S, Bleecker ER. Peripheral lung resistance in normal and asthmatic subjects. Am Rev Respir Dis 1990;141:584-8.
9. Hyde DM, Hamid Q, Irvin CG. Anatomy, pathology, and physiology of the tracheobronchial tree: Emphasis on the distal airways. J Allergy Clin Immunol 2009;124:S72-7.
10. Kraft M, Djukanovic R, Wilson S, Holgate ST, Martin RJ. Alveolar tissue inflammation in asthma. Am J Respir Crit Care Med 1996;154:1505-10.
11. Kraft M, Pak J, Martin RJ, Kaminsky D, Irvin CG. Distal lung dysfunction at night in nocturnal asthma. Am J Respir Crit Care Med 2001;163:1551-6.
12. Kaminsky DA, Irvin CG, Gurka DA, Feldsien DC, Wagner EM, Liu MC, *et al.* Peripheral airways responsiveness to cool, dry air in normal and asthmatic individuals. Am J Respir Crit Care Med 1995;152:1784-90.
13. Gordona T, Balakrishnanb K, Deyc S, Rajagopaland S, Thornburge J, Thurstona G, *et al.* Air pollution health research priorities for India: Perspectives of the IndoU.S. Communities of Researchers. Environment International 2018;119:100-8.
14. Fabbri L, Pauwels RA, Hurd SS, GOLD Scientific Committee. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary updated 2003. COPD 2004;1:105-41.
15. Håkansson K, Konge L, Thomsen SF, Backer V, von Buchwald C. Sinonasal inflammation in COPD: A systematic review. Eur Respir J 2013;42:1402-11.
16. Jovinelly J. COPD and Allergies: Avoiding Pollutants and Allergens. Health line Medically Reviewed by University of Illinois-Chicago, College of Medicine News Letter; 2016.
17. Celed´on JC, Burchard EG, Schraufnagel D, Castillo-Salgado C, Marc Schenker M, Balmes J, *et al.* An American Thoracic Society/National Heart, Lung, and Blood Institute Workshop Report: Addressing Respiratory Health Equality in the United States. Annals ATS 2017 May; 14(5): 814-26.
18. Ferris BG. Epidemiology standardization project (American thoracic society). Am Rev Respir Dis 1978;118:1-20.
19. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, *et al.* Standardisation of spirometry. Eur Respir J 2005;26:319-38.
20. HELIOS 702 (Portable Spirometer) Evaluation of 51 Vital Parameters with Interpretation. Copy Writes 2010-2013 Accurate. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5483657/.
21. Ekström MP, Hermansson AB, Ström KE. Effects of cardiovascular drugs on mortality in severe chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2013;187:715-20.
22. Lazarus SC, Boushey HA, Fahy JV, Chinchilli VM, Lemanske RF Jr., Sorkness CA, *et al.* Long-acting beta2-agonist monotherapy vs continued therapy with inhaled corticosteroids

in patients with persistent asthma: A randomized controlled trial. JAMA 2001;285:2583-93.
23. Greening AP, Ind PW, Northfield M, Shaw G. Added salmeterol versus higher-dose corticosteroid in asthma patients with symptoms on existing inhaled corticosteroid. Allen and hanburys limited UK study group. Lancet 1994;344:219-24.
24. Woolcock A, Lundback B, Ringdal N, Jacques LA. Comparison of addition of salmeterol to inhaled steroids with doubling of the dose of inhaled steroids. Am J Respir Crit Care Med 1996;153:1481-8.
25. Eisner MD, Anthonisen N, Coultas D, Kuenzli N, Perez-Padilla R, Postma D, *et al.* An official American thoracic society public policy statement: Novel risk factors and the global burden of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2010;182:693-718.
26. Mukerjee S, Das, Debajyoti, Banerjee G, Singhamahapatra AB. Evaluation of empirical usage of respiratory medications in treatment of patients presenting with chronic lower respiratory symptoms during spirometric screening. Indian J Physiol Pharmacol 2017;61:30-7.
27. Kaplan A, Stanbrook M. Must family physicians use spirometry in managing asthma patients? YES. Can Fam Physician 2010;56:126, 128, 130,132.
28. Spitzer WO, Suissa S, Ernst P, Horwitz RI, Habbick B, Cockcroft D, *et al.* The use of beta-agonists and the risk of death and near death from asthma. N Engl J Med 1992;326:501-6.
29. Billington CK, Hall IP. Novel cAMP signalling paradigms: Therapeutic implications for airway disease. Br J Pharmacol 2012;166:401-10.
30. Mcivor RA, Pizzichini E, Turner MO, Hussack P, Hargreave FE, Sears MR, *et al.* Potential masking effects of salmeterol on airway inflammation in asthma. Am J Respir Crit Care Med 1998;158:924-30.
31. Aziz I, Wilson AM, Lipworth BJ. Effects of once-daily formoterol and budesonide given alone or in combination on surrogate inflammatory markers in asthmatic adults. Chest 2000;118:1049-58.
32. Beasley R, Pearce N, Crane J, Burgess C. Beta-agonists: What is the evidence that their use increases the risk of asthma morbidity and mortality? J Allergy Clin Immunol 1999;104:S18-30.
33. Handley D. The asthma-like pharmacology and toxicology of (S)-isomers of beta agonists. J Allergy Clin Immunol 1999;104:S69-76.
34. Deenay C. Do adverse respiratory effects of beta2-agonists contribute to asthma morbidity and mortality? Pharm J 2006;193:1-5.
35. Gardiner PV, Ward C, Booth H, Allison A, Hendrick DJ, Walters EH, *et al.* Effect of eight weeks of treatment with salmeterol on bronchoalveolar lavage inflammatory indices in asthmatics. Am J Respir Crit Care Med 1994;150:1006-11.
36. Weiss LN. The diagnosing of wheezing in children. Am Fam Physician 2008;77:1109-14.
37. Wong BJ, Dolovich J, Ramsdale EH, O'Byrne P, Gontovnick L, Denburg JA, *et al.* Formoterol compared with beclomethasone and placebo on allergen-induced asthmatic responses. Am Rev Respir Dis 1992;146:1156-60.
38. Pizzichini MM, Kidney JC, Wong BJ, Morris MM, Efthimiadis A, Dolovich J, *et al.* Effect of salmeterol compared with beclomethasone on allergen-induced asthmatic and inflammatory responses. Eur Respir J 1996;9:449-55.
39. Cates CJ, Cates MJ, Lasserson TJ. Regular treatment with formoterol for chronic asthma: serious adverse events. Cochrane Database Syst Rev 2008;(4):CD006923.
40. Usmani OS. Treating the small airways. Respiration 2012;84:441-53. Available from: https://www.karger.com/Article/FullText/343629

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