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Original Article

Evaluation of Empirical Usage of Respiratory Medications in Treatment of Patients Presenting With Chronic Lower Respiratory Symptoms During Spirometric Screening

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Abstract

Background: An observational and cross-sectional study was done to evaluate the empirical use of medications in respiratory diseases in 550 urban patients aged 18-60 years (both gender) presenting with chronic lower respiratory symptoms (LRS) referred from OPDs to attend spirometry testing.

Methods: After obtaining detailed clinical profile, patients were divided into two groups based on treatment history with respiratory medications: Treated [n=470] and Untreated [n=80] and Spirometry was carried out in each patient following recommendations of ATS / ERS (2005) at lung function laboratory, department of Physiology, RG. Kar Medical College and Hospital, Kolkata. Patients were categorized based on Spirometry variable FVC, FEV_1, FEV_1/FVC,FEF_{25-75} and PEFR values.

Results: It was found that empirical usage of medications without spirometry in patients with LRS is widespread with the possible future adverse outcome. Furthermore, under diagnosis, misdiagnosis, and over-diagnosis of obstructive lung diseases occurred significantly in clinical assessment as revealed by post-bronchodilator response (BDR) test.

Conclusion: Present study concludes that all chronic lower respiratory symptoms patients should have their diagnoses confirmed with Spirometry analysis prior to receiving medications to avoid incorrect diagnosis as well as unwanted adverse effects.

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Introduction

Lower respiratory symptoms like a cough, wheeze, dyspnea etc. are the most common complaints with which patients present to their primary care physician (1). The literature has shown a high probability of obstructive lung diseases among adults attending

clinics with a cough persisting for at least 2 weeks and not known to have asthma or other lung disorders (2). There is evidence that clinical data obtained with a thorough history and physical examination are often insufficient to have a high index of suspicion regarding bronchial asthma (3). Unfortunately, very few studies have been conducted till date focusing on diagnosis and initial management of patients attending clinics with chronic lower respiratory symptoms (4). Although empiric treatment of undiagnosed cough with bronchodilators and/or corticosteroids is not recommended in the literature (5), a recent study found that the majority of these patients are treated empirically and indiscriminately with respiratory medications targeting obstructive lung disease and that only a few have done additional tests including Spirometry (1). Many such patients are thereby labeled erroneously as having a chronic disease when none exists and this overdiagnosis can lead to inappropriate treatment, with increased risk of side effects. The patients also are to bear costs for respiratory medications without any purpose (6). On the other side symptoms assumed to be due to obstructive lung disease might instead signify another medical condition that then goes undiagnosed and untreated (7). For example, up to 80% of COPD cases remain undiagnosed even with spirometry until the disease is advanced and substantial end-organ damage is present (8-10). On the other side up to 25% of patients older than 40 years who are labeled as having asthma actually have COPD. Conversely, many patients in primary care are labeled as having COPD when they, in fact, have asthma (11-12) and a subset of patients may display symptoms of respiratory distress with psychological basis (psychogenic asthma due to anxiety, panic disorder etc in majority of female patients and related vocal cord dysfunction) requiring psychological intervention (13). Thus both under-diagnosis and overdiagnosis of asthma is common (6). An international guideline for use of Spirometry in primary care recommends that “Spirometry should be considered for patients presenting with undiagnosed respiratory symptoms like dyspnea, wheeze, and cough” (14). The reversibility test with bronchodilator is more sensitive for diagnosing airway obstruction (15). Normal Spirometry in the presence of persistent respiratory symptoms should prompt the physician to think of an alternative diagnosis rather than conventional obstructive lung disease (16).

Objective:

The objective of the study was to evaluate the usefulness of various respiratory medications among the patients presenting with chronic lower respiratory symptoms at a tertiary care hospital.

Methods

An observational and cross-sectional study was conducted between July and November 2015 on 550 patients who were suffering from chronic lower respiratory symptoms. At first ethical permission was obtained from Institutional Ethics Committee, R G Kar Medical College, and Hospital, Kolkata.

All of the patients included in the study were aged between 18 to 60 years including male and female. All patients were suffering from chronic lower respiratory symptoms for more than three months duration. All belonged to urban areas of North 24–Pgs, West Bengal, India and were referred from the different outpatient department of R G Kar Medical College and Hospital (RGKMCH), Kolkata for spirometry for the first time to the dept. of Physiology, RGKMCH.

Exclusion criteria for the present study were patients not having LRS, patients coming for pre -anesthetic checkup, Pediatric and Geriatric patients, patients with acute illness, active hemoptysis and tuberculosis, patients with known cardiovascular, subdiaphragmatic and Otorhinolaryngological diseases.

Written consent was taken from each patient prior to the examination. Then they were asked to respond to a standardized respiratory symptoms questionnaire (ATS/DLD-78 A questionnaire) (17).

After obtaining detailed clinical profile, patients were divided in two groups: those who are receiving respiratory medications in several regimen within the last two years (including $Beta_2$ bronchodilators, steroids, anticholinergic, theophylline and leukotriene antagonist with antihistaminic combination) as written on patient's OPD card [Treated group (n=470)] and those not receiving respiratory medications [Untreated group (n=80)].

Spirometry was carried out by using electronic Spirometer (RMS HELIOS 702) which was preprogrammed according to the latest guidelines of the American Thoracic Society (ATS) and the European Respiratory Society (ERS) [ATS/ERS] (2005) (18) using 80% ethnic correction.

One of the authors had taken anthropometric measurements and clinical profile of the study subjects; another instructed the subjects to perform all the tests following ATS/ERS protocol and recorded the readings. Another author interpreted the findings and wrote the final impression and another author was responsible for overall supervision.

Daily calibration of the spirometer was done using a calibrated syringe according to latest ATS/ERS guidelines (18) during the tenure of the study. The author checked the syringe for leaks and damage prior the procedure and kept the syringe next to the spirometer. The largest observed values of FEV_1 and FVC available from among at least three acceptable and reproducible tests were taken as the key parameters for interpretation. After that the author made a training session for inhaler usage to the subjects as mentioned below, step by step as given in standard instruction manuals supplied with the medication as follows:

Shake the inhaler well before use (3-4 shakes) → Remove the cap from the inhaler → Put the inhaler in the mouth and the mouthpiece between your teeth and close your lips around it → Press the top of your inhaler once → Breathe in very slowly until you have taken a full breath → Hold your breath for about ten seconds, then breath out.

After completion of this demonstration regarding drug delivery system, the subject was asked to inhale short acting bronchodilator as per dose recommended in the ATS/ERS guidelines (0.4 mg salbutamol) (18). After ten minutes of taking the inhaler the subject was asked to perform the Spirometry once again and thus the reversibility test was done (18). The highest values of FVC and FEV_1 were selected. After completion of Spirometry we categorized all the patients as per existing standard criteria based on FVC, FEV_1, FEV_1/FVC, FEF_{25-75} and PEFR values- i) Normal (19-22); ii) COPD (23); iii) Restrictive Pattern (23); iv) Mixed Ventilatory Defect (24) and v) Small Airflow Obstruction (25-26).

Statistical Analysis:

The data wera expressed in Mean±Standard Deviation (SD). Descriptive analysis was performed using Fisher's Exact Test (for categorical variables) and two-sided unpaired t-tests (for continuous variables) to compare groups. All data of Spirometry variables were expressed in percentage (%) form. Mean values and standard deviation were calculated using Microsoft excel and rest of all the statistical analysis were done by using GraphPadQuickcalcs Software, California, USA. A p value of <0.05 was considered significant.

Results

TABLE I: Overall Demographic, Anthropometric, Clinical and Spirometry Profile of the Study Population.

Variables	*Treated (n=470)*	*Untreated (n=80)*	*p-value*
GENDER [n (%)]	Male: 210 (44.68) Female: 260 (55.32)	Male: 45 (56.25) Female: 35 (43.75)	0.0685
AGE (years) (Mean±SD)	40.56±12.81	34.81±12.51	0.0002*
WEIGHT (kg) (Mean±SD)	55.48±12.27	52.87±11.84	0.077
HEIGHT (cm) (Mean±SD)	155.73±8.69	159.12±10.21	0.001*
BMI (kg/m^2) (Mean±SD)	22.96±4.89	20.98±2.89	0.0005*
Smoking status[a] [n (%)]	Ever Smoker: 110 (23.40) Never Smoker: 360 (76.60)	Ever Smoker: 30 (37.5) Never Smoker: 50 (62.5)	0.0119*
Dyspnea[b] [n (%)]	Yes: 470 (100.00) No: 00 (0.00)	Yes: 80 (100.00) No: 00 (0.00)	1.000
Dry cough[c] [n (%)]	Yes: 170 (36.17) No: 300 (63.83)	Yes: 35 (43.75) No: 45 (56.25)	0.2118
Wet cough [n (%)]	Yes: 140 (29.79) No: 330 (70.21)	Yes: 5 (6.25) No: 75 (93.75)	<0.0001*
Wheeze [n (%)]	Yes: 40 (8.51) No: 430 (91.49)	Yes: 00 (0.00) No: 80 (100.00)	0.0021*
Physician diagnosed asthma[d] [n (%)]	Yes: 55 (11.7) No: 415 (88.3)	Yes: 0 (0.00) No: 80 (100.00)	0.0002*
Physician diagnosed COPD[e] [n (%)]	Yes: 45 (9.57) No: 425 (90.43)	Yes: 00 (0.00) No: 80 (100.00)	0.0013*
Physician diagnosed allergic rhinitis[f] [n (%)]	Yes: 240 (51.06) No: 230 (48.94)	Yes: 20 (25.00) No: 60 (75.00)	<0.0001*
FVC[g] (Mean±SD)	1 14.56±34.79	103.75±7.8	0.005*
FEV_1[h] (Mean±SD)	96.04±51.66	105.75±34.5	0.105
FEV_1/FVC (Mean±SD)	85.62±30.25	93.5±29.03	0.030*
FEF_{25-75}[i] (Mean±SD)	67.45±36.86	82.06±30.13	0.0008*
PEFR[j] (Mean±SD)	64.22±34.47	78.31±29.93	0.0006*

[SD: Standard Deviation, BMI: Body Mass Index. a. Smoking status defined as ever/never smoker of cigarette, beedi or hukka. b. Patients were asked: do you have to walk slower than people of your age on the level because of breathlessness? (SOB grade II). c. AChronic cough defined as acough on most days of the month, for three 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. g. Forced Vital Capacity. h. Forced Expiratory Volume in one second. i. Forced Expiratory Flow 25-75%. j. Peak Expiratory Flow Rate.]

The study observations represented in Table I that are statistically significant are as follows:

1] Treated population wasolder (mean age was 40 years) than untreated population
2] Mean body mass index (BMI) of the treated subjects was higher than untreated subjects.
3] Incidence of smoking habit was higher in untreated subjects compared with treated population.
4] Treated group of patients had a higher incidence of lower respiratory symptoms like wet cough, wheeze and more number of physician-diagnosed asthma, COPD and allergic rhinitis.
5] Post-bronchodilator Spirometry mean values of FEV_1/FVC, FEF_{25-75} and PEFR were significantly lower except FVC in treated population than the untreated population.

TABLE IIa : Distribution of Post Bronchodilatation Spirometry Results.

Spirometry result	*Treated (n=470)*	*Untreated (n=80)*	*p value*
Normal Pattern[k] [n (%)]	Yes: 240 (51.06) No: 230 (48.94)	Yes: 55 (68.75) No: 25 (31.25)	0.0035*
Small airways obstruction[l] [n(%)]	Yes: 125 (26.6) No: 345 (73.4)	Yes: 15 (18.75) No: 65 (81.25)	0.7964
COPD[m] [n(%)]	Yes: 65 (13.83) No: 405 (86.17)	Yes: 10 (12.5) No: 70 (87.5)	0.861
Mixed Ventilatory Defect[n] [n(%)]	Yes: 35 (7.44) No: 435 (92.56)	Yes: 00 (0.00) No: 80 (0.00)	0.0054*
Restrictive Pattern[o] [n(%)]	Yes: 5 (1.07) No: 465 (98.93)	Yes: 00 (0.00) No: 80 (100.00)	1.00

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

The study observations represented in Table IIa are as follows:

1] The proportion of patients in the treated group showing normal post-bronchodilator spirometry result was significantly less when compared to that in the untreated group.
2] The proportion of patients in the treated group showing mixed ventilatory defect pattern in post-bronchodilator spirometry was significantly more compared to that in the untreated group.
3] In the untreated group, 31.25% of patients were found to have small airway obstruction and COPD pattern by post-bronchdilatorspirometric results.

TABLE IIb : Statistical Analysis of Obstructive Lung Disease between Physician Diagnosed and Post-Bronchodilator Spirometry Observation among Treated Population.

Category	*Yes [n (%)]*	*No [n (%)]*	*p-value*
Spirometry Observation[p]	190(40.43)	280(59.57)	0.0001*
Physician Diagnosis[q]	100(21.27)	370(78.73)	

[p: Small Airways Obstruction (26.6%) and COPD (13.83%). q: Asthma (11.7%) and COPD (9.57%)]

The study observations represented in Table 2b is:

Among treated population post-bronchodilator, Spirometry showing obstructive features was significantly higher than physician diagnosis of obstructive lung disease prior to Spirometry.

TABLE III : Comparison of Subgroup of Normal Spirometric Result between Treated and Untreated Patients.

Parameter	*Treated [normal result] (n=240)*	*Untreated [normal result] (n=55)*	*p value*
Gender [n (%)]	Female: 150 (62.5) Male: 90 (37.5)	Female: 25 (45.46) Male: 30 (54.54)	0.0229*
BMI (kg/m^2) [Mean ±SD]	24.27±4.49	21.27±2.97	<0.0001*
Dry cough [n (%)]	Yes: 90 (37.5) No: 150 (62.5)	Yes: 35 (63.63) No: 20 (36.37)	0.00005*
Wet cough [n (%)]	Yes: 70 (29.17) No: 170 (70.83)	Yes: 5 (9.09) No: 50 (90.91)	0.0017*
Wheeze [n (%)]	Yes: 20 (8.33) No: 220 (91.67)	Yes: 00 (0.00) No: 55 (100.00)	0.0316*

The study observations represented in Table 3 are as follows:

1] Treated population with normal spirometry was female predominant
2] Treated group had significantly higher BMI than untreated patients.
3] Treated population had significantly more prevalence of respiratory symptoms like a dry cough, wheeze and wet cough than untreated normal spirometry population.

TABLE IV : Different Types of Respiratory Medications Used by the Treated Population (N=470).

Type of medications	*% Of treated population*
Oral $Beta_2$ Agonists (short acting)	36.17
Oral Theophylline Derivatives	24.47
Oral Leukotriene antagonist and Antihistaminic Drug Combination	34.04
Oral Corticosteroids	2.13
Inhaled Lone $Beta_2$ Agonist	23.40
Combination Inhalers (Including $Beta_2$ Agonist [Long/Short]±Anti cholinergic± Corticosteroids)	46.81*

The study observations represented in Table 4 are as follows:

1] Treated group of patients used a wide variety of respiratory medications prior to undergoing spirometry procedure.
2] Near about half of the patients who used medications prior to spirometry used combination therapy with $Beta_2$ agonist [Long/Short] ± anticholinergic ± corticosteroids through an inhalation route.
3] A majority (>70%) of this population used $Beta_2$ agonists through inhalation route either alone or in combination and a good number of them (>36%) had also used short-acting oral $Beta_2$ agonists.

Discussion

The present study focuses on the outcome of the empirical use of respiratory medications among the patients with chronic lower respiratory symptoms. A few population-based studies are there regarding the use of respiratory medications and the factors influencing their use. In recent past Montes de OM

et al. in the Platino study had shown that the subjects treated with respiratory medication empirically were more likely to be older, women, had higher mean body mass index {BMI} (27) and a greater number of smokers. In the present study, we also observed that most of the treated population was elderly smokers with significantly higher BMI. Another observation in the present study was that there was a gender difference in medication users group, with a higher prevalence among female though the difference was statistically non-significant. It might be due to a higher prevalence of asthma among adult female than male (28).

Montes de OM et al had also shown that among patients with one or more respiratory symptoms who were using respiratory medications for obstructive lung disease, two-thirds had Physician diagnosed obstructive lung disease and many of these patients had no obstruction in reality when tested with Spirometry. Although among the two third physician-diagnosed cases only one-third had a documented evidence of obstruction in Spirometry testing (27). The present study had also shown that over half of the treated patients had normal spirometry finding (51.06%).

Obstructive features (including small airway obstruction and COPD) in Spirometry result was significantly much higher compared to physician diagnosed obstructive lung disease (asthma and COPD) in this treated population. It would be an evidence of diagnostic delay due to medication usage without confirmatory Spirometry similar to the study conducted by Koefoed et al. among Danish adults initiating medication targeting obstructive lung disease (4). It is needless to mention that these patients were diagnosed incorrectly before Spirometry (6); which could be avoided by routine Spirometry screening.

Previously Simoni et al. had observed that anti-asthmatic medications were in wide usage before the confirmatory diagnosis of asthma (29); though the global prevalence of adult asthma and COPD in the general population is only 5–10% and 9–10%, respectively (30-31). In the present Study, we found that physician-diagnosed asthma and COPD was only 10% and 8.18% of study samples respectively but 85.46% of the total population were receiving medications merely on a symptomatic basis.

The mean values of post broncodilatation Spirometry parameters among treated population were significantly less than untreated population except for FVC. Furthermore, the post bronchodilatation test normal finding was proportionately less significant in treated patients (51.06%) compared to untreated patients (68.75%). Although the presence of wet cough and wheezeing were significantly more common (29.79% and 8.51%, respectively) in treated population compared to untreated population which was similar to the study of Tálamo C et al (32). Therefore, it was likely that the presence of wheezeing could lead to the use or prescription of respiratory medication in patients who actually had no airway obstruction. Jackson C made a famous quote more than 150 years ago that ‘all that wheezes is not asthma’ (33). This is well established by numerous future studies most recently by Collins BF et al. (34).

One key finding had been noted in this study that a wide variety of drug regimen had been used in the study population empirically prior to spirometry analysis. Most probably they were used in accordance with other factors like air pollution, local guidelines, local socio-economical factors, and health care system resources as shown by Montes de OM et al. in their Platino study (27), but this was entirely inappropriate with respect to standard treatment guidelines of obstructive lung disease and furthermore statistical implication of this issue could not be analyzed here. Out of the respiratory medications, empiric and indiscriminate prescription of $Beta_2$ agonists (both in oral and inhalation route, short acting±long acting) by the physicians prior spirometry procedure were very much common for lower respiratory symptoms and that might be expected to have deleterious cardiovascular effects. Researchers had demonstrated an association between $Beta_2$ agonist use and increased risk of myocardial infarction, congestive heart failure, cardiac arrest, and sudden cardiac death (35). Moreover, recent researches had also shown that $Beta_2$ agonist use increased respiratory deaths more than twofold

compared with placebo, without significantly affecting hospitalization or total mortality (36-37).

Moreover, reason for existence of significantly higher proportion of mixed ventilatory defect among treated patients compared to untreated patients could not be discussed here as further investigations (plethysmography) will be required to clarify the reason for the diminished vital capacity.

Limitation

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 of BMI (which could be a confounding variable) and impaired lung function with chronic lower respiratory symptoms and therefore role of individual medication could not be analyzed here.

Conclusion

Present study concludes that prescribing respiratory medications empirically and indiscriminately without Spirometry screening to patients with undifferentiated, nonspecific chronic lower respiratory symptoms often leads to incorrect diagnosis and brings unwanted adverse effects. Spirometry screening provides a more accurate diagnosis, which is essential to avoid inappropriate use of respiratory medications and also to make correct diagnosis of bronchial diseases in patients with history of chronic lower respiratory symptoms.

Future follow-up research with larger study population is required targeting for logical implementation of obstructive lung disease treatment protocol in patients presenting with chronic lower respiratory symptoms to ensure that only patients for whom medication is relevant receive it.

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