A Prospective Study on Prescription Pattern in Chronic Obstructive Pulmonary Disease

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╭─ *ABSTRACT* ─╮

Background: *Irrational prescribing results produce a negative impact on health and economy of both individuals and society, leading to wastage of resources and widespread health hazards.*

Method: *Outpatients with mild, moderate, and severe COPD were included. Several parameters were noted: patient's age and gender, outpatient (OPD) ID number, date of admission, occupation, h/o smoking, alcohol consumption, etc, disease condition details (duration, gradation as mild, moderate and severe, and co-existing diseases), prescribed medication details (dose, frequency, route of administration, and duration). Drug selection was assessed as per GOLD guidelines, the severity of disease was categorized according to the same guidelines, and medication efficacy was evaluated by treatment outcome according to the modified MRC dyspnoea scale.*

Results: *Inhalation route (36.95%) was the most preferred route of drug administration in this study, followed by the parenteral route (34.34%), and enteral route (28.71%). Adherence to GOLD 2015: All patients (n=400) were categorized to Gold stages I to IV based on the severity of COPD. Amongst these patients, 11 were in stage I, 146 in stage II, 184 in stage III, and 59 in stage IV. The majority of subjects received fixed-dose combination therapy: levocetirizine + montelukast (77%) and least bromhexine + guaiphenesin + terbutaline + menthol (18%). Dyspnoea status was graded from 0 to 4 according to the modified MRC dyspnea scale. Out of the 400 patients, 18 had grade 0, 44 grade 1, 156 grade 2, 133 grade 3, and 49 grade 4.*

Conclusion: *Overall, data from this analysis suggest that adherence to GOLD guidelines does not have a perceivable impact on symptom prevalence, exacerbation rate or lung function. Male sex, asthma and severe co-morbidities as a cerebrovascular insult could be associated with a risk for frequent exacerbations.*

Keywords: chronic obstructive pulmonary disease, prescription pattern, GOLD guidelines, modified MRC dyspnoea scale.

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INTRODUCTION

All over the world, inappropriate/irrational prescribing pattern is a significant problem of healthcare delivery, especially in developing countries (1). Irrational prescribing has a negative impact on health and economy of both individuals and society, leading to wastage of resources and widespread health hazards (2).

Drug utilization studies are powerful tools to explore and ascertain the role of drugs in society. These studies contribute to sound sociomedical and health economic basis for healthcare decision making. Despite the complexity of drug use, several indicators have been developed, standardised and evaluated by the World Health Organization (WHO) (3). These indicators are used not only to measure drug use in outpatient facilities and provide measures of the optimal resource use in those facilities, but also to help correcting deviations from expected standards and planning.

The National Heart Lung and Blood Institute reports that there are 24 milion people with chronic obstructive pulmonary disease (COPD), of which only 10 milion adults are estimated to have been diagnosed with COPD, while the remaining 12 milion individuals are undiagnosed (4). COPD requires long-term treatment, which may lead to irrational drug use and certain sequela.

In COPD, pharmacotherapy aims to reduce symptoms, decrease the frequency and severity of exacerbations, improve health status and exercise tolerance. Bronchodilators represent the mainstay of pharmacological management of COPD. Short-acting bronchodilators are given for immediate symptom relief, one or more long-acting bronchodilators (long-acting beta 2 agonists (LAβAs) or long-acting muscarinic antagonist (LAMAs) are used for long term maintenance treatment in subjects with moderate to severe disease. Inhaled corticosteroids (ICS) are central to the treatment of asthma, but their role is controversial in the management of COPD. In COPD, ICS are primarily given to decrease the risk of exacerbations. The new Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategy recommends the addition of a second bronchodilator in patients with moderate airflow obstruction, reserving the ICS use along with a LABA and/or LAMA for those with severe or very severe airflow obstruction and/or two or more exacerbations of COPD *per* year (5).

But there is evidence that prescriptions are not always written according to GOLD recommendations or other national guidelines (6), resulting in a high proportion of patients being unnecessarily treated with ICS and exposed to the risk of side effects in an undue manner.

A few studies have evaluated the patterns of drug therapy use relative to GOLD guidelines and have identified several gaps in the pharmacological management of COPD (7, 8).

Screening of prescriptions and evaluation of drug utilization can identify the issues regarding drug use and helps in contributing feedback to prescribers to create awareness about irrational drug use. Drug utilization studies provide useful insights into current prescribing practices and can thus help to reform and update practices in clinical medicine and pharmacotherapy (9). Keeping this in the background, the present study is undertaken to analyze the prescribing pattern, extent, rationality, frequency of drug use in COPD and adherence to GOLD guidelines (10) in the treatment of COPD. ❑

METHODOLOGY

This was an observational prospective sampling study, conducted on 400 consecutive cases of COPD between January – December 2017 in the Medicine Department OPD after taking consent from each patient or patient's guardian/relative as well as permission from the Institutional Ethics Committee (Ref No: BRIMS/Ethical Committee/57/2015). Relevant data were personally collected by the investigator from all patients, as indicated in a specially designed performa.

Inclusion criteria: patients with mild, moderate, and severe COPD attending the outpatient Department of Medicine.

Exclusion criteria: patients with tuberculosis or bronchial asthma, terminally ill cancer patients, patients in intensive care unit (ICU), and pregnant and lactating women.

Relevant data were collected, including the following details:
- demographic data: patient age, gender, OPD ID number, date of admission, occupation, h/o smoking, alcoholic, etc;
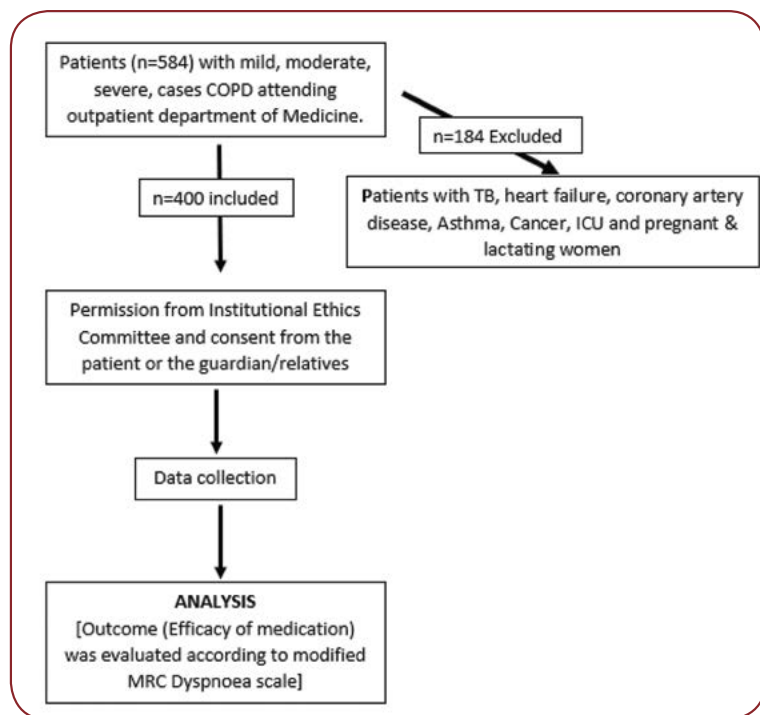
FIGURE 1. Flow chart of methodology

Disease	%
COPD only	22
COPD Infective exacerbation	2.4
COPD + Hypertension	0.7
COPD + Diabetes	1.9
COPD + Diabetes + Hypertension	0.7
COPD + Corpulmonale	5.6
COPD +Corpulmonale + Type 2 Respiratory Failure	6.1
COPD + Cardiovascular Disease	4.8
COPD + Gastrointestinal Disease	5
COPD + Multiple Disease	36.4
COPD + HIV	1.8
COPD + Other Lung diseases	12.6

TABLE 1. Disease comorbid status

- disease condition details: duration, gradation and co-existing diseases, if any;
- prescribed drug details: dose, frequency, route of administration, and duration.

Drug selection was assessed as *per* GOLD guidelines (11), disease severity was categorized according to guidelines (12), and medication efficacy was evaluated by treatment outcome according to modified MRC dyspnoea scale (13). The methodology used by us is shown in the flow chart presented in Figure 1.

Drugs used in COPD were categorized into three categories: bronchodilators, anticholinergics, and steroids. Fixed drug combinations were calculated separately. Adherence to GOLD guidelines (10) was studied by assuming that drugs recommended as the first line should be the most frequently prescribed ones with the highest utilization. ❑

RESULTS

In the current study we analysed prescription data of 400 patients [278 males (69.5%) and 122 females (30.5%)], with a mean age of 42.7±13.7 years (42.8±13.6 for males and 42.6±13.9 for females).

Smoking and alcohol consumption history. The 400 patients were divided based on their addictive habits such as smoking and alcohol consumption. Thus, 158 (39.5%) patients were smokers and 62 (15.5%) alcoholics, 222 (55.5%) were non-smokers and 322 (80.5%) non-alcoholics, and 20 (5%) were ex-smokers and 16 (4%) ex-alcoholics.

Disease comorbid status. The majority of patients were suffering from comorbid conditions. Among the 400 COPD cases, 22% of patients had only COPD and 78% comorbid conditions (Table 1).

Dosage forms/routes of administration. Inhalation route (36.95%) was the most common route of drug administration in this study, followed by the parenteral route (34.34%) and enteral route (28.71%) (Table 2).

Drugs used by class. Antibiotics were given to all included patients, followed by bronchodilators, anticholinergic, short-acting β2 agonist and disease controlling drugs such as inhaled steroids and methylxanthine group drugs (Table 2).

The modified Medical Research Council (mMRC) scale. Before treatment, patients were interviewed for dyspnoea status, which was graded from 0 to 4, according to the modified MRC dyspnea scale (Figure 3).

Class of drugs	Drugs	No of prescriptions	%	Route of administration
Antibiotics	Amoxicillin & Clavulanic acid	78	19.5	Oral
	Ceftriaxone	176	44	Injection
	Azithromycin	47	12	Oral
	Levofloxacin	23	5.8	Oral
	Cefotaxime	164	41	Injection
Anticholinergic	Tiotropium	121	30.3	Inhalational
	Ipratropium	195	48.8	Inhalational
Antihistamines	Levocetrizine	203	50.8	Oral
Leukotriene Antagonists	Montelukast	192	48	Oral
Methyl xanthines	Theophylline	283	71	Oral/injection
Short acting β2 agonist (SABA)	Salbutamol	165	41.3	Inhalational
	Terbutaline	43	10.8	Oral
Long acting β2 agonist (LABA)	Formoterol	298	74.5	Inhalational
Inhaled steroids	Budesonide	254	63.5	Inhalational
	Fluticasone	86	21.5	Inhalational
Systemic steroids	Methylprednisolone	36	9	Oral
	Dexamethasone	41	10	Injection
	Beclomethasone	74	19	Oral/inhalational
	Hydrocortisone	103	25.8	Injection

TABLE 2. Drug utilisation pattern

Adherence to GOLD 2015. All the 400 patients were categorized to GOLD stages I to IV based on COPD severity. Amongst these patients, 11 were in stage I, 146 in stage II, 184 in stage III, and 59 in stage IV. Appropriate and inappropriate treatment approaches in different stages are presented in Table 3. ❑
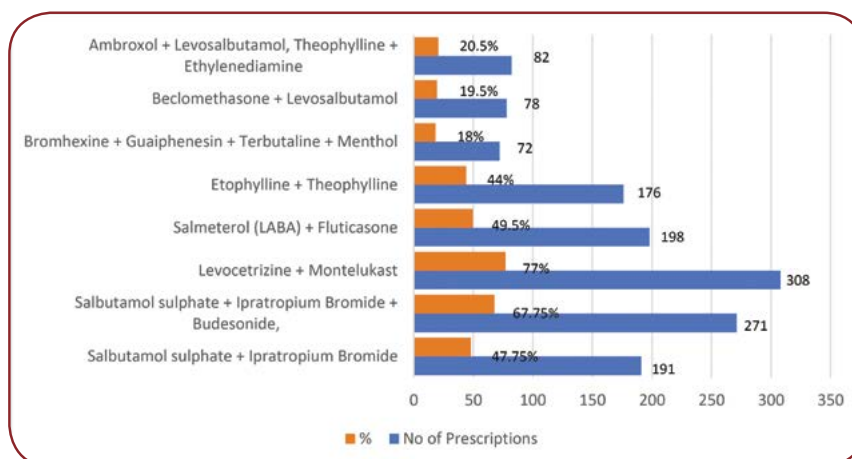

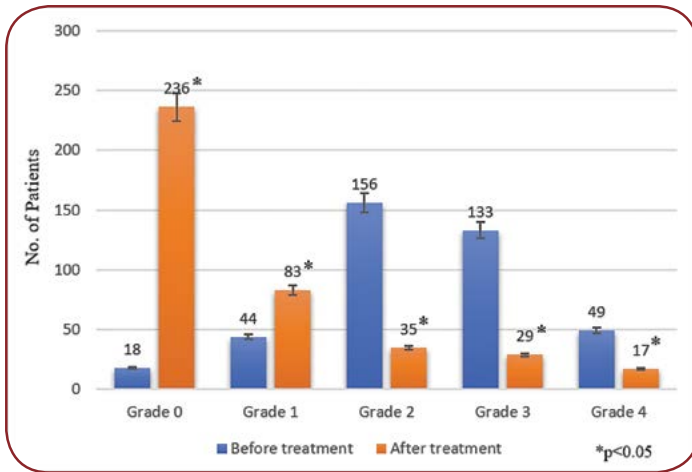**FIGURE 2.** Drugs prescribed in fixed dose combinations

FIGURE 3. Efficacy of drugs as *per* the mMRC scale

DISCUSSION

Effect of gender. In our study, the incidence of COPD was higher in males than females, which was in accordance with the reports of Niffy A. *et al* (13) and Gigi A. *et al*. (14).

Effect of the season. The COPD patient inflow was the highest in October (14.5%) and the lowest in May (2%). *The American Journal of Respiratory and Critical Care Medicine* published an article showing that individuals with COPD and seasonal allergies were more likely to exhibit symptoms of wheezing and chronic coughing (15). A new study at Johns Hopkins University suggested that individuals with COPD and allergic disease are at higher risk for COPD exacerbations (16).

Effect of smoking. The present study results were in accordance with those of Niffy A. *et al*. (13). Tobacco smoking affects multiple organ systems, resulting in numerous so-called tobacco-related diseases, including various chronic respiratory diseases, mainly chronic obstructive pulmonary disease (COPD) as well as enhanced levels of carbohydrate deficient transferrin (CDT), an increased number of T lymphocytes and macrophages, and oxidants–antioxidants imbalance (17).

Effect of alcohol consumption on COPD. The present study results were in accordance with those of Niffy A *et al*. (13). Garshick E *et al*. (18) reported that lifetime alcohol consumption was a significant predictor of chronic cough and chronic phlegm but no symptoms. Smoking and alcohol consumption interactions were inversely correlated to the independent effects of alcohol. Frantz S *et al*. (19) showed an association between increased CDT and T lymphocytes and lower FEV1 as well as a diffusing capacity for carbon monoxide (DL, CO) in subjects drinking alcohol, also after adjustments for potential confounders. No such associations were observed in never-smokers.

Drug therapy. All the 400 prescriptions for subjects of our study contained more than three drugs, which is in accordance with the previous studies of Unni A. *et al* (20) and Niffy A. *et al* (13). The prescription of more than three drugs (multidrug therapy) for one patient may suggest the possibility of some patients presenting with an acute and chronic exacerbation of COPD and bronchial asthma with or without co-morbid conditions, which requires antibiotic and corticosteroid treatment.

Route of administration. Maintenance therapy with nebulizers should be employed in elderly patients as well as in those with severe disease and frequent exacerbations. For some patients, using both nebulizers and pressurized metered-dose inhalers provided the best combination in terms of efficacy and convenience. Our study results are supported by those of Dhand R. *et al*. (21). Aerosol therapy is an important administration route in the treatment of COPD to assure drug delivery to the lungs. Virchow J. C. *et al* (22) suggested that the inhaler technology has the potential to improve asthma and COPD management.

Drugs. It was found that antibiotics were given to all patients, while the second most commonly prescribed drugs included anticholinergics, short-acting β2 agonists and disease controlling drugs such as inhaled steroids and methylxanthine group drugs. Our study results are in correlation with those of Vikneswari *et al* (23).

In a study by Sharon Sunil *et al* (24), 45% of patients received combination therapy, in which salbutamol + ipratropium bromide + budesonide (40%) was the preferred combination, followed by etophylline + theophylline (22%) and budesonide + formoterol (14%).

In the study of Faheemuddin M. D. *et al*. (25), COPD patients received a combination of bronchodilators consisting in an β2 agonist and an anticholinergic (salbutamol + ipratropium bromide).

GOLD Stage	Appropriate Treatment	n (%)	Inappropriate Treatment	n (%)
I	Short acting Bronchodilators when needed	2 (18.2)	LAMA	2 (18.2)
			LAMA+LABA	1 (9.1)
			LABA+ICS	1 (9.1)
			LAMA+T	2 (18.2)
			LABA+ICS+LAMA	3 (27.3)
	Total	2 (18.2)	Total	9 (81.8)
II	LAMA	8 (5.5)	ICS	4 (2.7)
	LAMA+LABA	12 (8.2)	LAMA+ICS	17 (11.6)
	LAMA+T	3 (2.1)	LABA+ICS	2 (1.4)
			ICS+SABA+SAMA	1 (0.7)
			LAMA/LAMA+ICS+T	6 (4.1)
			LABA+ICS+LAMA	68 (46.6)
			LABA+ICS+LAMA+T	20 (13.7)
	Total	23 (15.8)	Total	123 (84.2)
III	LABA+ICS	10 (5.4)	LABA	1 (0.5)
	LAMA+ICS	1 (0.5)	LAMA	6 (3.3)
	LABA/LAMA+ICS+T	10 (5.4)	T	5 (2.7)
	LABA+ICS+LAMA	92 (50)	ICS	3 (1.6)
	LABA+ICS+LAMA+T	39 (21.2)	LABA+T	4 (2.2)
			LAMA+T	4 (2.2)
			LABA+LAMA	2 (1.1)
			LABA+LAMA+T	3 (1.6)
			ICS+SABA+SAMA	4 (2.2)
	Total	152 (82.6)	Total	32 (17.4)
IV	LABA+ICS	10 (17)	LABA	1 (1.7)
	LAMA+ICS	1 (1.7)	LAMA	1 (1.7)
	LABA/LAMA+ICS+T	4 (6.8)	ICS	5 (8.5)
	LABA+ICS+LAMA	20 (34)	LABA+LAMA	3 (5.1)
	LABA+ICS+LAMA+T	12 (20.3)	LABA+T	1 (1.7)
			LABA+LAMA+T	1 (1.7)
	Total	47 (79.7)	Total	12 (20.3)
Total		224 (56)	Total	176 (44)

TABLE 3. Treatment adherence to GOLD 2015

In the present study, the most used combinations included levocetirizine + montelukast (77%), salbutamol sulphate + ipratropium bromide + budesonide (67.75%), and salmeterol (LABA) + fluticasone (49.5%) (Figure 2). Drug combinations were used to decrease COPD symptoms, increase drug effectiveness and decrease the medication dose. Mir S. Adil et al. (26) reported that LABA/SABA-ICS combination therapy was far better than LABA/SABA monotherapy in controlling COPD, because it not only reduced the risk of exacerbations but also improved QOL and airflow measures. Due to its antiinflammatory activity, combination therapy may help in reducing the risks of re-hospitalization or death.

According to Basavaraju Thejur Jayadeva et al (27), short-acting β2 agonists (i.e., salbutamol) are so commonly prescribed due to their rapid onset and low cost. In our study, injection hydrocortisone (61%) was also used in managing an acute asthma attack. It prevents the side effect of inhaled medication, which irritates the respiratory tract.

In a study conducted by Niffy Abraham et al (13), the majority of patients received a fixed dose combination therapy, including salbutamol sulphate + ipratropium bromide (23.19%) and salbutamol sulphate + ipratropium bromide + budesonide (42.23%). In another study (28), most of the patients were given the same combination therapy, consisting in salbutamol sulphate + ipratropium bromide (23.19%) and salbutamol sulphate + ipratropium bromide + budesonide (42.23%).

Efficacy of COPD medication as *per* the mMRC scale. The modified MRC score was >2 in the majority of COPD subjects before treatment. After receiving specific COPD medication, the score was improved in a significant number

of patients, proving the efficacy of drugs used for the treatment of COPD.

Adherence to GOLD 2015. Our study results showed that the overall adherence to GOLD guideline treatment recommendations for different stages of COPD was 56%. Appropriate and inappropriate treatment approaches in different stages are presented in Table 3.

In stage I (n=11), only one patient (18.18%) was treated with an appropriate regimen, and others were overtreated with regular long-acting bronchodilators or combination of bronchodilators and ICSs. The common treatment option was LABA-ICS-LAMA (27.27%).

In stage II (n=146), adherence to GOLD recommendations was 15.75%, and this group was also overtreated by a combination of bronchodilators and ICSs. In this stage, frequently preferred treatment options included LABA-ICS-LAMA (46.6%), LABA-ICS-LAMA theophylline (T) (13.7%), and LABA-ICS (11.6%). Of all stage II patients (n=146), 84.3% received an ICS-based treatment.

In stage III (n=184), adherence to guidelines increased to 82.6% due to the wide use of bronchodilator ICS combinations. The most preferred drug combination consisted in LABA-ICS-LAMA (50%), followed by LABA-ICS-LAMA-T (21.2%). Undertreatment was due to inappropriate treatment with regular long-/short-acting bronchodilators without ICS use, 1.6% of patients receiving ICS alone without any bronchodilators.

In stage IV (n=59), the appropriate treatment rate was also high, as 79.7% of subjects were given dual, triple, and quadruple therapies with bronchodilators and ICSs. The most preferred regimens were LABA-ICS-LAMA (34%) and LABA-ICS-LAMA-T (20.3%) combinations. Of all stage IV patients, 88.1% received an ICS-based medication. Inappropriate treatment approaches were represented by administering one or more long-acting bronchodilators without ICS or using only ICS (8.5%).

Stage I patients were overtreated with regular long-acting bronchodilators or combination of bronchodilators and ICSs, while guidelines recommended short-acting bronchodilators as initial therapy. Only 15.8% of stage II patients received an appropriate treatment, and this was mainly due to overtreatment, which was combined with long-acting bronchodilators and ICS in 84.3% of subjects. The ICS-based medication was frequently used for patients in all stages (36.4% in stage I, 84.3% in stage II, 84.7% in stage III, and 88.1% in stage IV), mostly as a part of combination therapy (Table 3).

Overall, 56% of patients were treated according to guideline recommendations. Most of the provider's guideline adherence studies have described the current practices of general practitioners. Two studies have also reported similar rates of adherence to guideline recommendations for COPD patients (37.9%–54.7%) among pulmonologists in other countries (29, 30). ❏

CONCLUSION

Our study showed that COPD treatment had low rates of adherence to GOLD guidelines. Overall, data provided by this analysis suggest that adherence to GOLD guidelines does not have a perceivable impact on symptom prevalence, exacerbation rate or lung function. Male sex, asthma and severe co-morbidities as a cerebrovascular insult could be associated with a risk for frequent exacerbations.

We suggest that new strategies are needed to achieve a standardized approach for the treatment of COPD, aiming to improve adherence to guideline recommendations, with particular focus on therapeutic indications and overtreatment. ❏

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