Theophylline and Leukotriene Modifiers: Is There Any Compelling Role in COPD?

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Abstract

Chronic obstructive pulmonary disease (COPD) is considered to be an emerging global public health problem. Inhaled therapies are first-line maintenance treatment for COPD, whereas oral drug therapies are used as second or third line maintenance treatment. Oral drugs have modest bronchodilatory as well as anti-inflammatory activities but have lower potency as compared to inhaled therapies. Oral drug therapy can play an important role with several advantages that include distinctive pharmacologic mechanisms of action, prompt availability, ease of administration without the challenges of proper inhalational drug deposition in airways of lung and cost-effectiveness. Theophyllines and leukotriene modifiers are frequently prescribed oral drug therapies worldwide. Although evidence remains weak regarding the exact role of theophyllines in COPD, they are still used alone or as an add-on agent to inhaled therapies but at the expense of narrow therapeutic index leading to dose-dependent toxicities. Leukotriene modifiers are currently prescribed as add-on agents to inhaled therapies in moderate-to-severe asthma. However, the role of leukotriene modifiers in COPD is not very convincing with limited evidence. Overall, there is not any compelling evidence on the utility of theophyllines and leukotriene modifiers in the management of COPD.

Keywords: Chronic obstructive pulmonary disease, leukotriene modifiers, montelukast, theophylline

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a chronic airway disorder characterized by persistent symptoms and airflow limitation with a lack of significant bronchodilator reversibility in majority of cases as evident on spirometry when performed under appropriate conditions.^[1] COPD is considered to be an emerging public health problem with an estimated global prevalence of 11.7%.^[2] It has been currently ranked fourth among leading causes of mortality worldwide but is projected to be the third leading cause in subsequent years.^[3] More than 3 million deaths occurred ever year due to COPD accounting for 6% of all global deaths.^[4] The disease is associated with significant morbidity and mortality carrying substantial and expanding socioeconomic burden worldwide.^[5] The burden of COPD is increasing even in developing countries like India, although the magnitude of burden of disease is not exactly defined. The prevalence of COPD in India is estimated to be 3.67% with annual mortality rate of 500,000.^[6,7]

The use of drug therapy in COPD has expanded over the past several decades with a better outcome. Inhaled therapies play

a pivotal role as these are typically preferred for the first-line maintenance treatment of COPD.^[1,8] The advantages of inhaled therapies include direct delivery of medications into the airways leading to improvement in efficacy, rapid onset of action, and lesser risk for systemic adverse effects.^[8] Oral drug therapies are used for second or third line maintenance treatment of COPD. The most commonly used oral drugs are theophylline, leukotriene modifiers, macrolides, phosphodiesterase (PDE) inhibitors, and mucolytic agents. Oral drugs can play an important role as advantages include distinctive pharmacologic mechanisms of action, ease of administration, without the challenges of proper inhalational drug deposition in airways of lung and relatively cheaper than inhaled therapies.^[8] These

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agents have anti-inflammatory or immunomodulatory effects as the predominant pharmacologic mechanism of action for clinical benefit. Other mechanisms include reduction of exacerbations and fairly rapid bronchodilation but less than that achieved with inhaled therapies. There is uncertainty regarding the role of theophylline and leukotriene modifiers either used alone or in combination in patients having COPD. This review highlights the current evidence regarding the role of theophylline and leukotriene modifiers in COPD.

SEARCH STRATEGY

Published studies related to role of theophylline and leukotriene modifiers in COPD were searched involving principal electronic databases (PUBMED, National Library of Medicine, EMBASE, Web of Science, Index Copernicus, Google scholar, and IndMed) from 1950 till now, using the index terms (Medical Subject Headings) in combination: “Chronic Obstructive Pulmonary Disease” or “COPD,” and “Theophyllines” or “Methylxanthines” or “Xanthine derivatives” and “Leukotriene modifiers” or “Leukotriene receptor antagonists” or “Montelukast” or “Zileuton.” Other terms such as “Oral drug therapies” and “Obstructive lung diseases” were also used. A manual search was also performed in addition. Twenty-five articles including three systematic reviews have been identified. All articles with resulting titles and abstracts were screened. The full text of relevant articles was read and kept for reference.

ROLE OF THEOPHYLLINES IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Theophylline is a drug extracted from a purine derivative (1, 3-dimethyl xanthine) and is naturally present in tea, cocoa, and beans. It was one of the drugs earlier used for the treatment of asthma, initially as aminophylline both in oral and intravenous forms. This drug had a very narrow therapeutic window as doses used at that time for bronchodilation, were also associated with severe gastrointestinal, cardiac, and central nervous system (CNS) adverse effects. Seizures, cardiac arrhythmias, and even mortality were also observed when blood concentrations became too high due to pharmacokinetic interactions. Subsequently, theophylline gained popularity with the availability of sustained release products and commercial automated assays that allowed convenient blood level monitoring. However, the utility of theophylline declined when inhaled bronchodilators were introduced since the past few decades.

Theophylline is usually prescribed at lower concentrations based on its anti-inflammatory effects in COPD and is a safer option currently than in the past. It usually acts as smooth muscle relaxant located in the bronchial airways and pulmonary blood vessels.^[9] It also reduces the airway responsiveness to various agents such as histamine, adenosine, methacholine, and allergens. There are two major pharmacological mechanisms of action for theophylline which include broad spectrum

PDE inhibition leading to increase in the concentration of intracellular cyclic adenosine monophosphate and guanosine monophosphate, activation of protein kinase A, inhibition of tumor necrosis factor alpha and leukotriene synthesis and another adenosine receptor antagonist leading to anti-inflammatory effects.^[8,9]

Other proposed mechanisms of action showing anti-inflammatory effects include inhibition of nuclear factor-kappa B leading to reduction of the expression of known inflammatory genes in COPD, enhancement of interleukin-10 secretion, increasing histone deacetylase 2 (HDAC 2) activity, inhibiting phosphoinositide 3-kinase-delta, decreasing poly (ADP-ribose) polymerase-1, and promotion of apoptosis of inflammatory cells such as T cells and neutrophils.^[9,10] All these actions occur at a higher therapeutic dosage ranging from 10 to 20 mcg/ml, whereas the effect on HDAC 2 is observed at a lower dosage ranging from 5 to 10 mcg/ml. Apart from anti-inflammatory effects, theophylline also exhibits mild bronchodilation (increase forced expiratory volume in 1 s [FEV1], decreased air-trapping, and improvement in gas exchange), decrease in work of breathing by improving diaphragm contractility, respiratory stimulation, promotion of mucociliary clearance, and suppression of cough.^[11]

Desired therapeutic concentrations of theophylline for children and adults are 5–15 mcg/ml and 10–20 mcg/ml, respectively, whereas toxicity is increased when concentration exceeds 20 mcg/ml.^[12] There are interactions with several drugs such as cimetidine, ciprofloxacin, erythromycin, clarithromycin, and rifampicin due to alterations in hepatic metabolism primarily with not only the CYP1A2 but also the CYP3A4 metabolizing enzymes. Therapeutic dose monitoring is required in various conditions such as congestive cardiac failure, liver disorders, viral infections, morbid obesity, atrial fibrillation, and smoking. Low doses of theophylline such as 100–200 mg twice daily as a sustained release with target blood levels of 5–10 mcg/mL is currently recommended considering the risk-benefit ratio. It is best to titrate the dose upward on initiation with monitoring of drug levels in blood as indicated for suspicion of toxicity. Dose-dependent toxicity is observed such as gastrointestinal (nausea, vomiting, and discomfort) and CNS (headache, sleeplessness, and seizures).^[13] Gastrointestinal side-effects and diuresis have been observed due to PDE inhibition, whereas cardiac arrhythmias and seizures are due to adenosine receptor antagonism that occurs at very high plasma concentrations.

Newer derivatives, such as doxofylline (1,3 dioxolane-2-yl methyl) and acebrophylline (ambroxol + theophylline-7-acetate) with decreased affinity for adenosine receptors, have been showing similar efficacy but have better cardiovascular and CNS toxicity profile as compared to theophyllines. A network meta-analysis has observed doxofylline to be the best xanthine in the treatment of COPD in terms of therapeutic efficacy and toxicity

Table 1: Review of literature showing existing role of theophyllines and leukotriene modifiers in chronic obstructive pulmonary disease

Author/ year	Type of study	Demographic profile of cohort	Results	Conclusion
Whitfield <i>et al.</i> , 1951 ^[32]	Lancet trial Comparative study No randomization	12 cases of emphysema without bronchospasm 6 healthy controls Lung volumes and tidal air tracings were determined before and after the oral administration of aminophylline in both groups	Healthy controls: No change in the lung volume or spirographic pattern Emphysema: Slight ↓ in TLV, FRC and RV following administration of drug in sitting position No change in lung volumes in recumbency position Tidal-air tracings in emphysematous group were unchanged	Aminophylline, in the absence of bronchospasm, has no place in the treatment of emphysema
Usery <i>et al.</i> , 2008 ^[33]	Systematic literature search of studies related to role of leukotriene modifiers in COPD (1950-2007)	7 studies identified (prospective=2, retrospective=1, randomized placebo controlled=1, <i>in vitro</i> =1, double blind cross-over=1, randomized, prospective, single blind, controlled=1)	No conclusive evidence available for benefit of leukotriene modifiers in COPD Drugs may offer benefits to patients with COPD, including effects that pertain to airflow limitation, neutrophil and lymphocyte chemotaxis, and neutrophil longevity	Reduction of symptoms, improvement of objective measures of disease and control of inflammation when added to conventional treatment Further studies are needed to determine the precise role
Woodruff <i>et al.</i> , 2011 ^[28]	Randomized double-blind, placebo controlled, parallel group study	Randomization: 60 COPD patients to Zileuton 600 mg PO QID versus 59 COPD patients to placebo Treatment for 14 days starting within 12 hours of hospital admission for COPD exacerbation Primary outcome: Hospital length of stay Secondary outcomes: Treatment failure and biomarkers of leukotriene production	No difference in hospital length of stay (3.75±2.19 vs. 3.86±3.06 days), $P=0.39$ No difference in treatment failure (23% vs. 27%, $P=0.63$) Significant decline in urinary LTE (4) levels in the drug-treated group as compared to placebo at 24 and 72 h	No convincing evidence suggesting benefit of drug in COPD due to insufficient sample size
Moosavi <i>et al.</i> , 2013 ^[34]	Interventional Quasi-experimental study	25 patients with moderate-to-severe COPD in stable state Treatment: 40 mg oral zafirlukast daily for 2 weeks Spirometry performed both at the baseline and at the end of the study Follow-up period: 2 weeks	Mean improvements in FVC, FEV1 and FEV1/FVC were 4.75% (SD=13.18), 3.71% (SD=9.19) and 9.33 (SD=27.08), respectively Zafirlukast produced a nonsignificant ($P>0.05$) bronchodilation, with maximum mean increase in FEV1 0.04 L (3%) above baseline	Zafirlukast has no considerable bronchodilatory effect in COPD Very short treatment period for observation of benefit Additional larger studies are needed to verify role
Lee <i>et al.</i> , 2015 ^[26]	Systematic review and meta-analysis	7 studies involving 342 COPD patients treated with leukotriene modifiers	Pooled estimation from 3 RCTs did not demonstrate any significant benefit with drugs ↑ FEV1 (overall effect: 0.09 L, 95 % CI: -0.04-0.21; $P=0.17$; I (2)=41.0%) ↑ FVC (overall effect: 0.04 L, 95 % CI: -0.04-0.11; $P=0.64$; I (2)=0.0%) No effect on level of myeloperoxidase (SMD, -0.15; 95% CI: -0.65-0.36) or LTB4 (SMD, -0.41; 95% CI: -0.96-0.13) ↓ frequency of dyspnea (RR 0.43; 95% CI: 0.29-0.64) and sputum (RR 0.37; 95% CI: 0.22-0.63)	Overall lack of evidence to support the therapeutic efficacy of leukotriene modifiers in patients with COPD Further large-scale, long-term studies are needed to identify predictive factors for COPD patients who may benefit from these agents
Devereux <i>et al.</i> , 2018 ^[18]	TWICS Multi-centric Double-blind placebo controlled pragmatic Randomized Controlled Trial	1578 proven COPD with at least 2 exacerbations (treated with antibiotics, oral corticosteroids, or both) in the previous year and were using an inhaled corticosteroid Randomization: 791 received low-dose theophylline (200 mg OD or BD daily) versus 787 received placebo	Data available for 1536/1578 participants (98%) 772 in theophylline group versus 764 in placebo group Total exacerbations noted 3430 1727 in the theophylline group versus 1703 in the placebo group Mean exacerbations per year 2.24 (95% CI: 2.10-2.38) in theophylline group versus 2.23 (95% CI: 2.09-2.37) in placebo group	Addition of low-dose theophylline, compared with placebo, did not reduce the number of annual COPD exacerbations No supporting evidence the for low-dose theophylline as adjunctive therapy to inhaled corticosteroids

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Table 1: Contd...

Author/ year	Type of study	Demographic profile of cohort	Results	Conclusion
Liu <i>et al.</i> , 2018 ^[35]	Systematic review and meta-analysis including randomized controlled studies	Six studies including 221 COPD patients treated with LTRA	Pooled effect size No significant improvement in FEV1 (SMD: 0.28, 95% CI: 0.17-0.72, $P=0.227$) FVC (SMD: 0.54, 95% CI: 0.10-1.18, $P=0.597$) FEV1/FVC (SMD: 0.18, 95% CI: 0.09-0.46, $P=0.189$) Subgroup analysis Short-term (<1 year) (SMD: 0.47, 95% CI: -0.06-0.99, $P=0.082$) Long-term (≥ 1 year) (SMD: -0.13, 95% CI: -0.57-0.31, $P=0.561$)	No improvement in lung function of COPD patients Neither short-term nor long-term exposure of LTRA can improve lung function decline in COPD Large scale randomized controlled trials are urgently warranted
Jenkins <i>et al.</i> , 2019 ^[36]	TASCS Multi-centric Double-blind, double dummy placebo controlled three arm randomized trial	1670 moderate-to-very severe COPD patients Randomization to three groups a. Low-dose theophylline 100 mg BD + Prednisone 5 mg daily b. Low-dose theophylline 100 mg BD + Placebo c. Placebo BD + placebo daily Follow-up duration: 1 year	1211 completed study 43% reported annual exacerbation No difference in mean exacerbation rates among three groups 1.07 (0.92-1.3) versus 0.95 (0.81-1.11) versus 1.03 (0.88-1.21)	Addition of low-dose theophylline with oral steroids compared with other two groups, did not reduce the number of exacerbations over a 1-year period
NICE COPD 2018 ^[37]	Guideline for COPD patients with age 16 years or older	Theophylline should only be used after a trial of short-acting and long-acting bronchodilators, or for people who are unable to use inhaled therapy, as plasma levels and interactions need to be monitored Only use intravenous theophylline as an adjunct to exacerbation management if there is an inadequate response to nebulized bronchodilators Monitoring of drug levels recommended as there is pharmacokinetic interaction with other drugs as well as associated adverse events for both oral and intravenous formulations		
GOLD COPD (2018) ^[1]	Guideline	Theophylline exerts a small bronchodilator effect in stable COPD and associated with modest symptomatic benefits Theophylline is not recommended unless other long term bronchodilators are unavailable or unaffordable Theophyllines or methylxanthines are not indicated for the treatment of exacerbation due to increased adverse events profiles Leukotriene modifier has not been adequately tested in COPD patients		

COPD: Chronic obstructive pulmonary disease; TLV: Total lung volume; RV: Residual volume; FRC: Functional residual capacity; FVC: Forced vital capacity; SD: Standard deviation; SMD: Standardized mean deviation; GOLD: Global initiative for chronic obstructive lung disease; NICE: National Institute for Health and Care Excellence; LTRA: Leukotriene receptor antagonist; TWICS: Theophylline with inhaled corticosteroids in COPD; TASCS: Theophylline and systemic corticosteroids in COPD, CI: Confidence interval

profile, followed by aminophylline and theophylline.^[14] This class of drugs is currently indicated as add-on therapy primarily in advanced COPD continuing to have symptoms despite optimum inhaled therapy including inhaled corticosteroids (ICS), long acting beta agonist (LABA), and long acting muscarinic antagonist to achieve symptomatic relief, improvement in quality of life and possible reduction in exacerbations.^[1,15] It can be used as an alternative in COPD patients noncompliant with inhalers for any reason.^[15]

It has been proposed that there is the occurrence of steroid resistance even at higher doses in smokers with COPD due to neutrophilic infiltration of airways as well as sputum and also due to increase in survival life of neutrophils by inhibition of apoptosis. This could lead to impaired HDAC activity that can be restored by the addition of low-dose theophylline to ICS, showing the potential utility of drug.^[16]

A single-blinded, prospective, randomized, placebo-controlled study reported reduction in dyspnea, improvement in exercise

performance, and lung functions in 58 moderate-to-severe COPD patients when theophylline was added to LABA and ICS combination.^[17] However, a recent randomized control trial reported that the addition of low-dose theophylline to ICS in COPD patients having high risk of exacerbation did not reduce the annual number of exacerbations as compared to placebo.^[18] The findings do not support the use of low-dose theophylline as adjunctive therapy in the prevention of COPD exacerbations.

The existing Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines do not recommend oral or intravenous aminophylline in patients hospitalized with COPD exacerbations due to significant adverse effects.^[1] Theophylline exerts minimal bronchodilatory effects in COPD with modest symptomatic improvement. It improved FEV1 when added to LABA, such as salmeterol compared with LABA alone. However, GOLD also does not recommend these drugs as a long-term controller for COPD unless other agents are unavailable or unaffordable.^[1]

ROLE OF LEUKOTRIENE MODIFIERS IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE

The leukotriene modifiers are another class of oral drugs that include montelukast, zafirlukast, and zileuton.^[19] All these drugs show anti-inflammatory activity by acting on different sites in 5-lipoxygenase pathway. The first two drugs are selective leukotriene receptor antagonists that selectively block the CysLT1 receptor leading to prevention of leukotriene specifically LTD4 and LTE4 from binding to the CysLT1 receptor whereas the last is an inhibitor of the enzyme 5-lipo-oxygenase that is responsible for the production of leukotrienes (LTC4, LTD4, LTE4, and LTB4) which are potent bronchoconstrictors. The blockade of the leukotrienes leads to modest bronchodilation with an onset of action of 1–2 h. Zileuton has shown better improvement in FEV1 as compared to montelukast and zafirlukast because the former blocks the leukotriene pathway at the level of 5-lipoxygenase with additional effects occur on LTB4 as well as on the other leukotrienes.^[19]

Clinical benefits include symptom relief, modest bronchodilation, reduction in exacerbations, and relief of allergic rhinitis symptoms. Dosing of these drugs is as follows: montelukast 10 mg once daily; zafirlukast 20 mg twice daily on empty stomach; and zileuton 600 mg 4 times daily or 1200 mg twice daily for extended-release product. Potential drug interactions include zafirlukast with warfarin leading to increase in prothrombin time, decrease in levels of zafirlukast co-administered with erythromycin and increase in levels of theophylline when given concurrently with zafirlukast and zileuton. All these drugs are generally well-tolerated but may be associated with headache, dyspepsia, nausea, pharyngitis, flu-like symptoms, sleep disturbances, hallucinations, and drowsiness. Deranged liver function test was reported with zileuton. Churg-Strauss syndrome was rarely reported with leukotriene modifiers. All these drugs are indicated as an alternative therapy for mild asthma and also as an add-on agents given in combination with other therapies such as ICS/LABA for moderate-to-severe asthma.^[19,20]

Montelukast is also indicated for the acute prevention of exercise-induced bronchoconstriction as well as for the treatment of aspirin-induced asthma and allergic rhinitis.^[20] However, there is no current indication for using leukotriene modifiers in COPD as evidence is limited. These classes of drugs might show a promising role in patients of COPD. Studies have reported higher levels of LTB4 in the sputum of COPD patients than in controls and also overexpression of CysLT1 receptors in the bronchial mucosa of COPD patients having frequent exacerbations than in normal individuals or stable COPD.^[21–23] In a subset of COPD patients with exacerbations, increased infiltration of bronchial mucosa with eosinophils has been observed, and montelukast with or without ICS might be effective in reducing the number of eosinophils.^[8,19,21] A small retrospective series comprising 20 moderate-to-severe elderly COPD patients treated with

montelukast on long-term basis reported modest benefit with reduced symptoms, emergency department visits, required doses of ICS but no change in lung function as compared to that group treated without montelukast.^[24]

Another study used montelukast on a short-term basis in moderate-to-severe COPD patients and reported that the addition of this drug to routine treatment protocol produced additional improvement on lung function, dyspnea score, and quality of life in patients with stable COPD suggesting need for an additional anti-inflammatory treatment.^[25] A systematic review and meta-analysis in 2015 reviewed leukotriene inhibitor therapy for COPD and observed that there was a modest improvement in lung function and symptom scores and found no improvement in lung function and no reduction of myeloperoxidase/neutrophilic inflammation markers or LTB4.^[26] A study reported that leukotriene synthesis inhibitor did not benefit COPD patients, although there was a modest reduction in neutrophilic inflammation with a 14-day therapy.^[27] There is a lack of evidence to support the therapeutic efficacy of anti-leukotriene agents in COPD but more number of studies, including well-designed randomized controlled trials with larger sample size, are required.

A larger study reported that the addition of zileuton to routine care had no impact on treatment outcomes in patients hospitalized with exacerbations of COPD.^[28] Patients with characteristics of both COPD and asthma sometimes referred to as asthma COPD overlap (ACO), may be more likely to benefit from montelukast therapy. A retrospective study of inner city veterans with COPD reported that 2 years of montelukast therapy is associated with decreased emergency department and urgent care utilization for exacerbations (from 34 to 22, 35%: $P = 0.03$).^[29] One well-designed trial in 39 smoking asthmatics likely representing ACO subgroup suggested that a better response to montelukast was observed as compared to ICS as compared to nonsmoking asthmatics.^[30] Leukotriene modifiers have been prescribed frequently in patients of COPD in view of presumed diagnosis of ACO.^[31] More studies are required to prove definite role of leukotriene modifiers in ACO.

CONCLUSION

Whether theophyllines and leukotriene modifiers are still to be considered for treatment or to be withdrawn remains inconclusive. The existing review of literature supporting their roles remain weak, as shown in Table 1.^[1,18,26,28,32–37] Despite the controversy about the exact role of these drugs whether used alone or in combination, they remain the most commonly used drugs worldwide on a traditional basis due to cost-effectiveness, availability, and ease of administration as compared to inhaled therapies. Studies have reported that most of the prescriptions by general practitioners are not always in accordance with GOLD guidelines. These two groups of drugs have been prescribed frequently either alone or along with inhaled therapies in multiple irrational combinations among COPD patients at various tertiary care centers leading

Table 2: Validated and proposed phenotypes of chronic obstructive pulmonary disease with treatment options

Phenotype	Salient features	Treatment options
Validated phenotypes		
Emphysema/ hyperinflation (Type A)	Pathological, permanent dilatation of distal airways due to the destruction of walls of the airways without fibrotic changes Dyspnea is predominant symptom Radiological evidence of emphysema Rare hypercarbia and cardiovascular co-morbidities Increased lung volumes and impaired DLCO Pink puffer	LABA or LAMA LABA+LAMA ±Theophyllines ±Mucolytics ±LVRS or BLVR
Chronic Bronchitis (Type B)	Presence of productive cough or expectoration for >3 months per year and >2 consecutive years Cough and sputum production is predominant symptom Hypoxia, Hypercarbia, cyanosis, pulmonary hypertension, erythrocytosis, and cardiovascular/sleep disorder comorbidities Bronchial wall thickness on radiological imaging Normal lung volumes and preserved DLCO Blue bloater	LABA or LAMA LABA+ICS LABA+LAMA
Asthma-COPD overlap	History of smoking Persistent airflow limitation History of previous asthma <40 years of age Demonstration of eosinophilic inflammation in sputum or increased peripheral eosinophilia Documentation of enhanced reversibility in airflow obstruction after the bronchodilator test especially marked response (>400 mL in FEV ₁) or at least two positive bronchodilator tests is required Atopy and/or elevated serum IgE levels Higher levels of FENO	LABA+ICS LAMA+ICS LABA+ICS+LAMA ±Theophyllines, LTRA, macrolides in severe cases ±Biologicals - anti-IgE, anti-IL-5 in severe cases
Non or rare or infrequent exacerbator	Defined as <2 exacerbations per year based on clinical records or patient's history	LABA or LAMA LABA+LAMA ±Theophyllines in emphysema
Frequent exacerbator with chronic bronchitis or emphysema	Defined as ≥2 exacerbations/year Frequent exacerbator with chronic bronchitis Associated more with chronic bronchitis than emphysema Bronchial hypersecretion with increased airway inflammation and increased risk of bronchial colonization and respiratory infection Frequent exacerbator with emphysema Typical clinical and radiological signs of emphysema without chronic cough and sputum production	Chronic bronchitis LABA or LAMA+ICS LABA+LAMA+ICS ±PDE4 inhibitors (Roflumilast) in severe airflow limitation (FEV ₁ < 50%) Macrolides in former smokers Emphysema LABA+LAMA±ICS ±Theophyllines ±Mucolytics
Proposed phenotypes		
COPD-Bronchiectasis overlap	Diagnosis of COPD HRCT thorax showing evidence of bronchiectasis	LABA+ICS Postural drainage Mucolytics Long term antibiotics including macrolides
Exacerbation phenotype	Exacerbation in chronic bronchitis associated with bacterial and viral	Antibiotics including macrolides in bacterial exacerbation
Bacterial	Exacerbation in ACO with eosinophilic inflammation	Oral corticosteroids in eosinophilic predominant
Viral	Exacerbation in emphysema with pauci-inflammatory	LAMA in case of pauci-inflammatory
Eosinophilic predominant	Overlap of features can be evident	
Pauci-inflammatory		
Sustained lung function phenotype	Sustained lung function every year as documented by spirometric surveillance along with radiological changes	LABA or LAMA LABA+LAMA
Slow decliner phenotype	Slow decline in lung function Annual decline of FEV ₁ by 30 ml	LABA or LAMA LABA+LAMA±ICS

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Table 2: Contd...

Phenotype	Salient features	Treatment options
Fast or rapid decliner phenotype	Rapid decline in lung function Annual decline of FEV1 by 60 ml	LABA+LAMA LABA+LAMA+ICS Aggressive disease management including LVRS and pulmonary rehabilitation Referral for Lung transplantation
Wheezing phenotype	COPD patients having wheezing as symptom More associated with chronic bronchitis Tendency to have frequent exacerbations	Treatment similar for chronic bronchitis phenotype
Pulmonary cachexia phenotype/Low BMI	COPD patients with BMI less than 21 kg/m ²	Nutritional supplementation Pulmonary rehabilitation
Co-morbidities or Systemic phenotype with increased mortality	COPD having any degree of airflow limitation Associated with various comorbidities such as cardiovascular disorders (acute coronary syndrome, congestive cardiac failure, atrial fibrillation, hypertension), diabetes mellitus, obesity, anxiety, or depression Higher mortality More associated with chronic bronchitis	Aggressive management of co-morbidities Psychosocial support/behavioural therapy in case of anxiety or depression
COPD with lung cancer	COPD patients detected with co-existing diagnosis of lung cancer Poorer prognosis	Treatment of lung cancer
COPD with disproportionate pulmonary hypertension	Progressive dyspnea Normal spirometry Diffuse emphysema on radiological imaging Pulmonary hypertension ≥ 40 mmHg Marked reduction in DLCO Rule out other associated causes of pulmonary hypertension Suspect co-existing Group 3 and Group 1 pulmonary hypertension	Long-term oxygen therapy Diuretics, anticoagulation Pulmonary vasodilators either single or dual can be used Lung transplantation
COPD-SDB overlap	COPD with any degree of airflow limitation Polysomnography proven sleep disordered breathing in the form of obstructive sleep apnea, hypocapnic central sleep apnea with or without periodic breathing, hypercapnic central sleep apnea and sleep linked hypoventilation	Treatment of sleep disordered breathing with appropriate PAP devices OSA- CPAP Hypocapnic CSA with LVEF $\leq 45\%$ - CPAP, oxygen therapy, acetazolamide, positional therapy Hypocapnic CSA with LVEF $> 45\%$ - ASV OSA requiring higher pressures of CPAP, Hypoventilation - BIPAP Hypercapnic CSA, hypoventilation - BIPAP S/T
Emphysema predominant phenotype with hyperinflation	Large bullae Heterogeneous emphysema with upper lobe involvement and poor exercise tolerance Homogeneous emphysema	Bullectomy in case of bullae Either LVRS or BLVR (valve, coil, vapor ablation) in heterogeneous or homogeneous emphysema Valve not indicated in case of collateral ventilation Lung transplantation in those cases not candidates for LVRS, BLVR, and bullectomy
Genetic susceptibility Alpha 1 antitrypsin deficiency Telomerase polymorphisms	Early onset emphysema Unopposed effects of neutrophil elastase and other serine proteases Mutation of the telomerase gene TERT creating short telomeres -leading to cellular senescence Early onset emphysema Female predominant Increased risk of pneumothorax	Alpha 1 antitrypsin augmentation therapy
Persistent inflammatory phenotype	Presence of persistent systemic inflammation by measuring biomarkers such as WBC, CRP, IL-6, IL-8, fibrinogen, and TNF- α	Treatment similar to chronic bronchitis phenotype
No-smoking COPD Biomass fuel exposure/ Outdoor or indoor air pollution	Predominant small airway disease with little emphysema	Treatment similar to chronic bronchitis phenotype

ACO: Asthma-COPD overlap, ASV: Adaptive servo-ventilation, BIPAP: Bi-level positive airway pressure, BIPAP ST: Bi-level positive airway pressure Spontaneous/Timed, BLVR: Bronchoscopic lung volume reduction, BMI: Body mass index, COPD: Chronic obstructive pulmonary disease, CPAP: Continuous positive airway pressure, CRP: C-reactive protein, CSA: Central sleep apnea, DLCO: Diffusion lung capacity for carbon monoxide, FENO: Fractional exhalation of nitric oxide, FEV1: Forced expiratory volume in one second, ICS: Inhaled corticosteroids, IL-Interleukin, LABA: Long acting beta2 agonist, LAMA: Long acting muscarinic antagonist, LTRA: Leukotriene receptor antagonist, LVEF: Left ventricular ejection fraction, LVRS: Lung volume reduction surgery, OSA-Obstructive sleep apnea, PAP: Positive airway pressure, PDE4: Phosphodiesterase 4, SDB: Sleep disordered breathing, TNF alpha: Tumor necrosis factor alpha, WBC: White blood cell

to increased incidence of adverse drug reactions (ADRs).^[38-40] Polypharmacy has been associated with multiple ADRs with few of them overlapping or being additive as one or more class of drugs can be responsible. The use of oral theophylline in particular requires cautious therapeutic monitoring and dose individualization.^[41] There is a requirement of increased awareness among physicians regarding the rational use of these drugs among patients with COPD. In summary, there is no compelling evidence of benefit of theophyllines and leukotriene modifiers in the treatment of COPD. Their role needs to be justified by strong evidence.

PHENOTYPING OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE: FUTURE PROSPECTS

COPD has now been considered to be a heterogeneous disease, such as asthma and lung cancer. The concept of heterogeneity arises from the fact that COPD patients manifest with diverse clinical features (symptoms, comorbidities, and frequency of exacerbation) for a similar degree of airflow limitation based on FEV1. The concept of universal therapy for all seems to be outdated and personalized therapy is required. Several phenotypes have been proposed based on expanding evidence over the last decade.^[42-45] However, only few of them have been validated as described in Table 2. Categorization of all COPD patients into a particular phenotype seems to be practically difficult as many of them will have overlapping clinical manifestations and comorbidities. The phenotyping approach to COPD based on various parameters related to three domains (severity, activity, and impact) will potentiate targeted therapy that can guide clinicians to prescribe appropriate drugs. This approach will promote precision medicine in COPD leading to change in clinical practice but larger trials are required for validation in the near future.

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