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A REVIEW ON MANAGEMENT OF COPD WITH SPCIFIED STUDY ON PRE-CLINICAL SCREENING METHODS FOR PHARMACOLOGICAL ACTIVITY

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ABSTRACT

Chronic Obstructive Pulmonary Disease (COPD) is characterized to be heterogenous lung disease, where patient experiences chronic cough, sputum production and exacerbation. Many people were diseased globally due to exposure of toxic substances, lack of respiratory hygiene and genetic abnormalities. As per Global Burden of Diseases COPD is "third leading cause of death worldwide". In concern of these challenges, Global Initiative for Chronic Obstructive Lung Disease have programmed policies and strategies in prevention and management of COPD. In this article we discuss about efficient diagnostic like Spirometry, CT, CBC, Lung Function test and treatment procedures like Medication, Oxygen therapy, Rehabitation, Vaccination and Surgical procedures. This article mainly highlights in detail on Pre-clinical screening methods like In-vitro and In-vivo model for Pharmacological activity.

Keywords: Chronic Obstructive Pulmonary Disease (COPD), Spirometry, CT, CBC, Medication, Oxygen therapy, Rehabitation, Vaccination

INTRODUCTION

According to Global Initiative for Chronic Obstructive Lung Disease(GOLD), Chronic obstructive pulmonary disease (COPD) is a heterogenous lung disease characterized by Chronic respiratory symptoms like dyspnea, Cough, sputum production and exacerbation due to often progressive airway obstructions**[1].**Emphysema and chronic bronchitis are themost common factors that contribute to COPD, but varies in terms of characterization and severity among individuals with COPD **[1]**. Chronic bronchitis is inflammation of the lining of the bronchial tubes of the lungs and characterized by daily cough and sputum production **[1]**. Whereas Emphysema is destruction and dilation of air spaces from distal to terminal bronchiole**[1].**

Epidemiology of COPD is described to be "third leading cause of death worldwide" by Global Burden of Diseases (GBD) **[1]**. Based on concern raised by GBD, an initiative lead by GOLD have came-up with policies and strategies with regard to awareness on diagnosis, prevention and management of COPD. As per 1st report published in 2001, it have documented development of Global Strategies with expertise individuals on COPD. It also affects annually about 300 million people worldwide, with death count of 3.5 to 4 million **[1]**. Nearly three billion individuals globally are exposed to household air pollutants, which pose a significant health risk for chronic obstructive pulmonary disease (COPD)**[2].** According to estimates, approximately one-quarter to one-third of all COPD cases worldwide are attributed to non-smoking exposure. Additionally, fourteen percent of the total COPD burden can be attributed to workplace exposures **[2]**.

COPD develops gradually over time, often resulting from a combination of risk factors

- Active or passive exposure of Tobacco, dusts, fumes or chemicals **[3]**.
- Early life events such as poor growth in utero, prematurity, and frequent or severe respiratory infections in childhood that prevent maximum lung growth **[3]**.
- Asthma in childhood **[3]**.
- A rare genetic condition called alpha-1 antitrypsin deficiency, which can cause COPD at a young age **[3]**.

PATHOPHYSIOLOGY

Toxic substances affect the Central and peripheral airways, in response it ruptures lung parenchyma, alveoli and pulmonary vasculature by subjecting to inflammation.

This phenomenon is main cause of narrowing respiratory pathways and decreasing elastic recoil by increasing mucus secretion that results in Pulmonary hypertension. This pathological condition lead to Chronic cough and sputum production as a Categorizing key of COPD **[4]**.

COPD symptoms often don't appear until significant lung damage has occurred, and they usually worsen over time with exacerbations, particularly if smoking exposure continues. On basis of examining signs and symptoms COPD is classified into four stages, the table below (Table-1) details about Signs and Symptoms along with FEV1 diagnostic parameters and recommended treatments **[4]**.

Table 1: Characterization and Treatment recommended for all stages of COPD

Stage	Signs & Symptoms	FEV1 Measurement	Recommended Treatment
Mild COPD	**May have no symptoms, but at time of physical exercise experiences difficulty in breathing.**	**≥80**	**Short-acting bronchodilator when needed [4].**
Moderate COPD	**Coughing, wheezing, breathlessness and frequent stops to catch breath.**	**79-50**	**Regular treatment with one or more bronchodilator. Rehabilitation [4].**
Severe COPD	**Low oxygen levels leading to constant shortness of breath, flareup and exacerbations can be life threatening.**	**49-30**	**Regular treatment with one or more bronchodilator [4].** **Inhaled corticosteroids for patients with repeated exacerbation or persistent symptoms despite bronchodilator therapy. Rehabilitation [4].**
Very Severe COPD	**Symptoms worsen by frequent flareup and exacerbations leads to hospitalization.**	**<30**	**Regular treatment with one or more bronchodilator [4].** **Inhaled corticosteroids if symptoms persist despite bronchodilator therapy [4].** **Rehabilitation [4].** **Long term 02 therapy if chronic respiratory failure [4].** **Surgical treatments considered [4].**

DIAGNOSIS

The traces of COPD were first referred as Catarrh by Badham in 1814, which means chronic cough and mucus hypersecretions. Initially disease is diagnosed by Spirometer, for magnifying efficient approach in imaging COPD many multi-purpose diagnostic tests are also employed. These tests are described in following **Table 2**.

Table 2: Diagnostic Procedures for COPD

Diagnostic test	Spirometry [5]	CT- Scan [6]	Complete Blood Count (CBC) [7]	Lung Function Tests [1]
Purpose	Measures lung function and airflow.	Detailed study of Chest imaging.	Analysis of Blood Components	Analysing lung function and capacity
Sample	Inhalation and exhalation of breath.	Screening suspected person.	Blood	Breathing maneuvers
Direction	Based on diagnosing choice one short acting Bronchodilator is suggestible to minimise variability.	Suggestible to not to intake any food and liquids to avoid impurities.	Suggestible to not to intake any food and liquids before few hours to avoid impurities.	Avoid Heavy foods and polluted inhalations.
Procedure	Tight inhalation and forceful exhalaltion.	Table Imaging Scan by assessing 5 lung lobes individually.	Collecting blood samples.	Taking deep breath and cough.
Testing Time	15-30 minutes	Few minutes	2-4 hours after sample collection	30-60 minutes
Parametric ranges	FEV1/FVC ratio > 0.7 FEV1 > 80% predicted FVC > 80% predicted	Based on infection score- Score-1 (< 5% area involved), Score-2 (5–25% area involved), Score-3 (25–50% area involved), Score-4 (50–75% area involved), Score-5 (> 75% area involved).	Each component of blood is evaluated based on age and sex. Particularly AAT levels are evaluated.	FEV1/FVC ratio = 0.7±0.3 FEV1 =3.1±0.2 , TLC = 5.9 ± 0.3
Accuracy	Accurate lung function test.	Accurate Chest Imaging.	Accurate at cellular range.	
Interpretation		When all 5 lobes show > 75% involvement.	Abnormal ranges blood analysis and AAT deficiency.	FEV1/FVC ratio = <0.7 FEV1 =1.9±0.2 TLC=6.7±0.2

TREATMENT

COPD is not curable, however it can be improved by quitting smoking, avoiding air pollution, and getting vaccinations. It is treatable with medications, oxygen, and pulmonary rehabilitation. The major therapies are inhaled medications that open and relieve edema in the airways. COPD medications and assistance are discussed in below **Table 3**.

Table 3: Management of COPD

Treatment Option	Purpose	Medication	Dosage/Frequency	Side Effects	Notes
Short-acting Bronchodilators [8]	**Quick relief of symptoms during flare-ups.**	**Albuterol (Proventil, Ventolin), Ipratropium**	**As needed during flare-ups.**	**Tremor, rapid heart rate, low potassium, and shakiness.**	**For moderate COPD, an inhaled anticholinergic, such as ipratropium, may be prescribed alone or in combination with a short-acting beta-agonist.**
Long-acting Bronchodilators [8]	**Maintenance therapy to prevent symptoms.**	**Formoterol (Perforomist), Salmeterol (Serevent)**	**Daily as prescribed.**	**Increased heart rate, increased blood pressure, and tremor.**	**Long-acting bronchodilators include long-acting beta-agonists (LABAs) and long-acting muscarinic antagonists (LAMAs).**
Inhaled Corticosteroids [8]	**Reduce inflammation and prevent exacerbations.**	**Fluticasone (Flovent), Budesonide (Pulmicort)**	**Daily as prescribed.**	**Oral thrush, hoarseness, and throat irritation.**	**Inhaled corticosteroids (ICS) are used in combination with LABAs in patients with moderate to severe COPD and a history of exacerbations.**
Oxygen Therapy [8]	**Improve survival and quality of life.**	**Oxygen concentrator, Liquid oxygen, Compressed oxygen**	**As needed, typically 15 hours/day.**	**Dry or bloody nose, skin irritation, and nasal congestion.**	**Essential for severe COPD with low oxygen levels.**
Pulmonary Rehabilitation Programs [8]	**Enhance exercise capacity and quality of life.**	**Exercise training, Education, Support**	**Regular sessions as prescribed.**	**Fatigue, muscle soreness, and shortness of breath.**	**Comprehensive programs designed to address the physical, emotional, and social aspects of living with COPD.**
Surgical Treatments [8]	**Considered in severe cases with specific criteria.**	**Lung volume reduction surgery (LVRS), Lung transplant**	**Case-specific considerations.**	**Risks associated with surgery, including infection and complications.**	**Reserved for a small subset of patients with very severe COPD and specific criteria**
Vaccinations [8]	**Prevent respiratory infections.**	**Influenza vaccine, Pneumococcal vaccine**	**As recommended by healthcare provider.**	**Mild soreness at the injection site.**	**Vaccinations are crucial to prevent respiratory infections, which can exacerbate COPD symptoms.**

PROGNOSIS AND COMPLICATIONS

The severity of the condition, the existence of concomitant conditions, and the patient's reaction to treatment all affect the prognosis of COPD. Being a progressive disease, COPD can result in substantial disability and a diminished quality of life as it progresses. Complications from severe COPD may include pneumonia, cardiac issues, and respiratory failure, among others are discussed in below **Table 4**.

Table 4: Prognosis and Complications of COPD

Complication	Description	Treatment/Management	Prevention Strategies	Prognosis
Respiratory Failure [9]	**Inability of the respiratory system to maintain adequate oxygenation.**	**Oxygen therapy, mechanical ventilation.**	**Avoidance of smoking, adherence to prescribed medications.**	**Variable, depends on the severity and response to treatment [9].**
Pneumonia [10]	**Inflammation of the lung tissue often caused by bacterial or viral infections.**	**Antibiotics, antiviral medications.**	**Vaccination against influenza and pneumonia.**	**Can be serious, especially in those with advanced COPD [10].**
Cor Pulmonale [11]	**Right-sided heart failure due to long-term high blood pressure in the pulmonary arteries.**	**Diuretics, oxygen therapy.**	**Management of COPD, avoidance of exacerbations.**	**Variable, may lead to significant disability and reduced quality of life [11].**
Acute Exacerbations [12]	**Sudden worsening of COPD symptoms, often triggered by infections or other factors.**	**Bronchodilators, corticosteroids, antibiotics.**	**Vaccination, smoking cessation, early management of symptoms.**	**Can be recurrent and contribute to disease progression [12].**

PREVENTION

The main focus of COPD prevention methods is on modifiable risk factors. The most effective way to prevent COPD and stop its progression is to stop smoking. Public health initiatives, such lowering exposure to toxins in the environment and work-related risks, are also vital. Vaccinations against pneumonia and influenza can also stop respiratory infections that could make COPD symptoms worse. The COPD preventive strategies that GOLD formats are these are discussed in below **Table 5 [1]**.

Table 5: Prevention Strategies for COPD

Prevention measure	Description	Recommendations	Key considerations
Smoking cessation [1]	**Discontinuing tobacco use is the most effective way to prevent COPD.**	**Behavioral support, pharmacotherapy.**	**Tailor interventions to individual needs and provide ongoing support.**
Avoidance of environmental pollutants [1]	**Reducing exposure to air pollutants, occupational hazards, and indoor pollutants.**	**Use of protective equipment, workplace regulations.**	**Promote awareness and adherence to occupational safety measures.**
Vaccinations [1]	**Influenza and pneumococcal vaccines can prevent respiratory infections.**	**Annual influenza vaccination, pneumococcal vaccination as recommended.**	**Ensure accessibility and promote awareness of vaccination programs.**
Early management of respiratory infections [1]	**Prompt and appropriate treatment of respiratory infections to prevent exacerbations.**	**Timely use of prescribed medications.**	**Educate individuals with on recognizing and managing early symptoms.**

PRECLINICAL SCREENING METHODS FOR PHARMACOLOGICAL ACTIVITY

Alternative methodologies must be investigated and implemented based on how complex the research question is and how well the currently used animal models simulate human exposure and physiology. Realistic inhalation exposure in animals is difficult to achieve due to significant differences in lung architecture and physiology between regularly used animal species and the human respiratory system. Methods used in vitro provide a way to assess important features of in vivo impacts. Target identification, dosage calculation by cellular screening, evaluation of pharmacokinetic and pharmacodynamic characteristics, and safety and bioavailability assessments are all included in this step. Evaluations of reproductive toxicity, immunotoxicity, teratogenicity, mutagenicity, carcinogenicity, and acute and chronic toxicity are all part of safety studies using animal models.

In-vitro Methods [13]

1. Spasmolytic activity in isolated guinea pig lung strips
2. Spasmolytic activity in trachea
3. Reactivity of isolated perfused trachea
4. Vascular and airway responses in the isolated lung.

Table 6: In-vitro screening methods for Pharmacological activity

Experiment	Purpose and Rationale	Procedure	Method	Evaluation
A. Spasmolytic Activity in Isolated Guinea Pig Lung Strips [13].	**To assess spasmolytic activity induced by histamine and calcium ionophores [13].**	**- Animal: Albino guinea pigs**	**1. Animals sacrificed by ether overdoses and lungs isolated. 2. Isolated organs dissected into 5cm strips in PSS. 3. Strips mounted in organ bath, bubbled with carbogen at 37°C, and left to equilibrate for 30-60 mins. 4. Carbachol added to test contractility for 20 mins, then spasmogen added consecutively at 20-min intervals, recording pre-values. 5. Contractile response determined by adding test compound in cumulative doses at 5-10 min intervals. 6. Spasmogens: - Histamine dihydrochloride 10^{-6} g/ml for 5 min Calonophore 5×10^{-6} g/ml for 5 min Leukotriene LTC4 10^{-9} to 10^{-8} g/ml for 10 min Leukotriene LTD4 $10^{-9}$to 10^{-8} g/ml for 10 min [13].**	**Percentage inhibition of spasmogen-induced contraction is calculated [13].**
B. Spasmolytic Activity in Isolated Trachea [13]	**To check inhibition of bronchospasm by Beta-blocking activity induced by Beta sympathomimetic,**	**- Animal: Albino guinea pigs**	**1. Animal sacrificed by CO_2 narcosis, trachea dissected into individual rings (2-3 cartilaginous rings wide) 12-15 rings tied together with silk threads and mounted in an organ bath**	**Inhibition of spasmogen-induced contractions. ED50 can be calculated from the dose-response curve [13].**

	H1 blocking, and leukotriene blocking [13].		**containing Krebs-Henseleit solution at 37°C and gassed with carbogen. 2. Isometric contractions recorded via strain-gauge transducer on a polygraph for 45 mins equilibration before administering spasmogen. The following spasmogens are used: Carbachol ($2x10^{-7}$ g/ml), Histamine (10^{-7} g/ml), Calonophore for the release of leukotrienes, Leukotriene LTC4 ($10^{-9}$to 10^{-8} g/ml), Leukotriene LTD4 ($10^{-9}$to 10^{-8} g/ml). 3. After initial spasm-test drug-contraction recorded at max [13].**	
C. Reactivity of Isolated Perfused Trachea [13]	**To check epithelium effects on the reactivity of tracheal musculature. Contractile agonists added to serosal (extraluminal) or mucosal surface (intraluminal) [13].**	**- Animal: Guinea pig**	**1. Sacrificed animal subjected to removal of trachea (4cm) and perfused with modified Krebs-Henseleit solution at 37°C. 2. Isolated trachea attached to perfusion holder, gassed with 95% O_2 and 5% CO_2. 3. Responses obtained by measuring changes of Anteroposterior (AP) in the inlet-outlet present between the side holes of indwelling catheters. Agonists added in step-wise increasing, cumulative concentrations. 4. The preparation washed every 15 min, and two consecutive dose-response curves obtained at a time gap of 1.5 hours [13].**	**Responses quantified as change in pressure in centimeters of H_2O [13].**
D. Vascular and Airway Responses in Isolated Lung [13]	**Isolated perfused rat lung allows simultaneous constriction of pulmonary vascular and airway responses to various drugs [13].**	**- Animal: Sprague-Dawley rats**	**1. Animal anesthetized by I.P. pentobarbital sodium. Trachea cannulated, connected to a rodent ventilator, and ventilated with room air enriched with 95% O_2 and 5% CO_2. 2. Rats heparinized and exsanguinated, lungs removed and suspended in a humidified water-jacketed chamber. 3. Perfusate solution in reservoir, lungs perfused with peristaltic roller pump to maintain physiological baseline pulmonary arterial pressure. 4. Pulmonary arterial perfusion pressure, airway pressure, and reservoir blood level continuously monitored and recorded [13].**	**Changes in pulmonary arterial pressure after the injection of a test drug measured in mm Hg and compared with baseline values [13].**

In-vivo Methods [13]

1. Bronchospasmolytic activity in anesthetized guineapig (Konzett-Rossler method)

2. Effect of arachidonic acid or PAF on respiratory function

3. Pneumotachography in anesthetized guinea pigs

4. Airway microvascular leakage.

Table 6: In-vivo screening methods for Pharmacological activity

Experiment	Purpose and Rationale	Procedure	Testing Compounds	Evaluation
A. Bronchospasmolytic Activity in Anesthetized Guinea Pig (Konzett-Rossler Method) [13]	**To quantify bronchospasmolyti--c effect by measuring volume of air not taken up by the lungs after bronchospasm [13].**	**Animal: Guinea pig Sex: M/F Weight: 250-500g**	**Spasmogens (i.v): - Acetylcholine hydrochloride (20-40 µg/kg) Histamine dihydrochloride (5-20 µg/kg) Bradykinin triacetate (10-20 µg/kg) Ovalbumin (1 mg/kg) PAF (25-50 ng/ml) Leukotrienes LTC4, LTD4 (about 1 µg/kg) Substance P (0.5 µg/kg) [13].** **Standard Compounds: - Atropine sulfate (0.01 mg/kg, i.v.) Aminophylline (6 mg/kg, i.v.) Tolpropamine-HCl (0.2 mg/kg) Imipramine-HCl (3-5 mg/kg) [13].** **Testing Compounds: Administered I.V./P.O./S.C./Intraduodenally [13].**	**Results expressed as percent inhibition of induced bronchospasm over control agonistic responses. ED50 value calculated [13].**
B. Effect of Arachidonic Acid or PAF on Respiratory Function In Vivo [13]	**Evaluate sites of action of drugs interfering with mechanisms of bronchoconstriction and thrombocytopenia [13].**	**Animal: Guinea pigs Sex: M Weight: 300-600g**	**Standard Compounds: - DazoxibenHCl (inhibitor of thromboxane synthetase, TSI) Acetylsalicylic acid (inhibitor of cyclo-oxygenase, COI) [13].**	**% inhibition/increase of bronchospasm, reduction in BP, thrombocytopenia, leukocytopenia, and hematocrit evaluated. Mechanism of test drug concluded based on profile of influence [13]. Inhibition of thromboxane synthetase and cyclo-oxygenase evaluated [13].**
C. Pneumotachograph in Anesthetized Guinea Pigs [13]	**Simultaneous measurements of respiratory and circulatory parameters in anesthetized guinea pigs [13].**	**Animal: Guinea pigs (Pirbright white) Weight: 300-400g**	**Parameters presented: - Circulation: Systolic blood pressure, diastolic blood pressure, mean blood pressure [13]. Respiration: Tidal volume, respiratory volume per minute, respiratory rate [13]. Pulmonary mechanics: Airway resistance, dynamic compliance, end-respiratory work [13].**	**Data averaged over time intervals [13].**
D. Airway Microvascular Leakage [13]	**Determine plasma exudation in guinea-pig airways in vivo using Evans Blue dye. Study antagonism against bradykinin- and PAF-induced airway microvascular leakage and vagal stimulation-induced airway responses [13].**	**Animal: Dunkin-Hartley guinea pigs Sex: Female Weight: 380-600g**	**Procedures include tracheal cannulation, mechanical ventilation, injection of spasmogens and test drugs, bronchoconstriction induction, and Evans Blue dye injection [13].**	**Evans Blue dye concentration and lung resistance compared between treated and control groups [13].**

CONCLUSION

Patients with chronic obstructive pulmonary disease (COPD) encounter significant difficulties due to its complex nature, which is why it is essential to have a thorough grasp of the various facets involved in managing this condition. This exhaustive analysis sheds light on the intricate mechanisms underlying COPD and pinpoints areas that require urgent attention from medical experts. Firstly, we must acknowledge that COPD is a major public health concern globally, ranking as the third leading cause of mortality. Therefore, there is an imperative need for coordinated efforts in detection, diagnosis, and treatment to mitigate the adverse consequences of this illness. Our examination of the available literature has uncovered crucial knowledge regarding the application of spirometry, computed tomography (CT) scans, complete blood count (CBC), and other respiratory function tests in accurately classifying and staging COPD cases. By having a clear understanding of these diagnostic techniques, clinicians can tailor individualized care plans for their patients based on established criteria.

Furthermore, we recognize the significance of adopting a holistic strategy when tackling COPD management. This entails integrating multiple approaches, such as drug therapy, supplemental oxygen administration, rehabilitation programs, immunizations, and surgical interventions. Each component plays a vital role in improving patient outcomes by addressing different aspects of the disease process. For instance, medications are designed to alleviate symptoms like shortness of breath or coughing; meanwhile, oxygen therapy helps restore optimal oxygen levels in the body. Rehabilitation programs promote physical exercise and education to empower individuals with COPD to manage their conditions more effectively. Vaccines protect against viruses that exacerbate COPD symptoms, while surgery may be necessary for advanced cases requiring more invasive measures.

To gain further insight into potential therapeutic options, our investigation also explored pre-clinical screening methods for assessing pharmacological activities. We describe various in vitro and in vivo experiments that evaluate the efficacy of new compounds aimed at treating COPD. From measuring spasmolytic effects in isolated guinea pig lung tissues to evaluating bronchial responsiveness in anesthetized animals, these assays offer invaluable data toward developing novel treatments for this debilitating disorder.

Ultimately, this extensive study serves as a comprehensive reference source for healthcare providers and scientists invested in understanding and managing COPD. By synthesizing the most recent findings across multiple disciplines within respiratory medicine, we hope to accelerate progress toward improved patient outcomes through evidence-based practices.

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