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Pharmacotherapy for Chronic Obstructive Pulmonary Disease

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Abbreviations: COPD: Chronic Obstructive Pulmonary Disease; SABAs: Short Acting Beta-2-Agonists; FEV1: Forced Expiratory Volume; PDE4: Type 4 Phosphodiesterase

Introduction

Chronic obstructive pulmonary disease (COPD) increases public health concern, and its management is a challenge for healthcare professionals. According to the American Lung Association, COPD is the fourth leading disease-caused death in the United States, and treatment options are limited to alleviation of symptoms, mitigation of disease progression and exacerbation, and improvement on patient quality of life [1-4]. it was reported that the direct and indirect costs of COPD total over $50 billion in the United States alone [5] and the 20-year (2019-2039) discounted direct medical costs attributable to COPD are estimated to be more than $800 billion [6]. This area needs further research as the projections for cases of COPD are increasing globally, due to aging populations as well as continued introduction of risk factors that precipitate the disease [7]. COPD is characterized by tenacious dyspnea, cough, sputum production, and airflow limitation that is due to airway impediments usually caused by significant exposure to noxious particles or gases [8]. This chronic airway obstruction is instigated by bronchiolitis and is perpetuated with emphysema progression, but the extent of each varies between patients, making targeted therapy and diagnosis a difficult task. Smoking is the main risk factor for COPD, so smoking cessation is crucial in order to maximize the outcomes of therapy [1]. Once a diagnosis of COPD is made and the class of severity is determined, pharmacological treatment can be initiated in an effort to reduce the symptoms, reduce the frequency and severity of exacerbations, and improve exercise tolerance and overall health status [1]. The therapeutic regimens are individualized and escalated based on the symptoms, diagnosis and the severity of the disease as well as the presence of comorbidities. The major pharmacologic treatment classes are selective beta-2 agonists, antimuscarinic agents, methylxanthines, and anti-inflammatory agents such as inhaled corticosteroids and selective PDE4 inhibitors. The oral corticosteroids, antibiotics and mucolytics/antioxidants are added for management of the exacerbations [1,3,8]. Patient management of pharmacological treatment is the focus of this review, which will break down and evaluate the efficacy of the current pharmacotherapy options across groups.

Pharmacological Agents Used for Treatment of COPD

Bronchodilators are comprised of different duration beta$_2$-agonists and antimuscarinics. Short acting beta$_2$-agonists (SABAs), such as albuterol, are used on a regular and as-needed basis for immediate improvement of ventilation (measured as FEV_1) and relieving the shortness of breath [9]. The duration of SABAs are typically 4-6 hours, thus requiring continued usage throughout the day. Long acting beta$_2$-agonists (LABAs), such as salmeterol, have a duration of 12 or more hours and can be used alongside SABAs. LABAs provide twice daily dosing that significantly improves FEV_1, increases lung volumes, reduces dyspnea and exacerbation rate as well as reduces the number of hospitalizations and the costs of managements [10,11]. Indacaterol, oladaterol and vilanterol are LABAs which have a duration of 24 or more hours, but the use of LABAs as monotherapy is not recommended [12]. Treatment with beta-2 agonists can produce adverse effects such as cardiac rhythm disturbances and tremor especially with higher doses. Prior asthma research has raised concerns about possible loss of lung function and increased mortality with the use of beta bronchodilators, but this has not been reported with COPD [10,13,14]. Recently preclinical studies indicated that long term

use of β-2-adrenoceptor agonists may help to stimulate glucose uptake in skeletal muscle and improve glucose homeostasis, which may be beneficial for COPD patients with insulin resistance diabetic conditions [15].

Similarly, antimuscarinic therapy are comprised of short acting muscarinic antagonists (SAMAs, such as ipratropium) and long-acting muscarinic antagonists (LAMAs), which block acetylcholine-mediated bronchoconstriction effects caused by activating muscarinic receptors in airway smooth muscle. Long-acting muscarinic antagonists (LAMAs), such as tiotropium, have a prolonged bronchodilation effect due to their binding at M3 muscarinic receptors [16]. When comparing the therapeutic efficacy, more favorable improvements in lung function with antimuscarinics rather than $beta_2$ agonists[1,17-19].Treatment with antimuscarinics are typically associated with anticholinergic side effects, such as constipation and drying of mucus membranes [20]. In in patients with advanced COPD, these two classes of bronchodilator medications are frequently used in combination [1,3,21]. Methylxanthines are utilized when patients fail to respond to treatment options targeting adrenergic and/or muscarinic pathways. The addition of theophylline to the LABA salmeterol has shown an improvement in FEV_1 and breathlessness when compared to salmeterol alone [22]. effects such as nausea, vomiting, and headaches can occur within the therapeutic range of theophylline and the metabolism by cytochrome P450 introduces the possibility of significant medication interactions. The narrow therapeutic window of methylxanthines can lead to toxicities and ultimately limit its widespread usage in treatment of COPD. More recent trial results failed to confirm the therapeutic efficacy of theophylline [23]. Selective phosphodiesterase-4 (PDE4) inhibitors are used to reduce inflammation in patients who have a moderate to severe diagnosis and a history of exacerbations. The most commonly used PDE4 inhibitor roflumilast works by inhibiting the breakdown of intracellular cyclic AMP [24,25].This oral medication can be taken once daily to improve lung function, in combination with systemic corticosteroids, LABAs, or fixed-dose LABA/ICS combinations [26,27,28]. Systemic roflumilast causes more adverse effects than inhaled medications, but most of the adverse responses tend to occur at the initiation of treatment and subside with time [1]. The most common adverse effects are weight loss, nausea and dose-limiting emesis. The current recommendation is to use PDE4 inhibitors as an add-on medication. With itsanti-inflammatory action, it is possible that early administration of roflumilast may slow down the progression of the disease and reduce or avoid the chronic usage of oral corticosteroids in patients with severe This suggestion needs to be further studied.. Inhaled corticosteroids (ICS) are the most powerful anti-inflammatory agents, and they are always used in combination with $beta_2$-agonists or antimuscarinic agents in the management of COPD. Their anti-inflammatory effects alone do not modify the progressive decline of FEV_1 or mortality in patients with COPD, but they do provide benefit for patients with frequent exacerbations and exacerbation-related hospitalization [1,29]. ICS and LABA used in combination have shown to be more effective than either treatment alone in improving lung function, health status and reducing exacerbations. Nannini [30,31] risks associated with ICS use include increased prevalence of pneumonia and oral candidiasis among several other complications due to the immune suppression [1,29]. The discontinuation of ICS use is associated with withdrawal of lung function, along with increased symptoms and exacerbations [32], which makes the decision of discontinuation to use ICS difficult.

The purpose of this review is to highlight the clinical efficacy of pharmacological therapy for management of patients with COPD,the efficacies of these agents on pulmonary function improvements are compiled in Table 1. Spirometry is widely used in the diagnosis of COPD and FEV_1 remains a constant in the evaluation of medication efficacy. The focus points for this review were on the current treatment options, and their respective clinically significant improvements in FEV_1 among patients diagnosed with COPD. Data was collected using PubMed and the U.S. National Library of Medicine for clinical trials. The corresponding trails are listed in Table 2.

Table 1: Pharmacotherapy management of COPD.

Drug Class	Treatment Group	Name (Brand)	Effect on Pulmonary Function	Trials	Adverse Effects	Adult Dosing & Frequency	Inflammation Reduction
SABA	**Acute & Mild Symptoms**						
	Across all GOLD grades via 2015	Albuterol HFA (Proventil®, ProAir®, Ventolin®)	0.269L FEV1 improvement 1 hour post dose	1	Tachycardia, tremors, dizziness, pharyngitis	90m cg/puff, 2puffs inhaled Q4-6h PRN	N/A
	only studied in asthma patients	Levalbuterol HFA (Xopenex®)	Comparable to Albuterol vs placebo	15	Rash, diarrhea, tremors	45m cg/puff, 2puffs inhaled Q4-6h PRN	N/A

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	FEV1 between 45-70% predicted	Albuterol nebulizer solution (AccuNeb®)	0.199L FEV1 improvement 30 min post dose	17	Tachycardia, tremors, dizziness, pharyngitis	2.5m cg/3mL, via nebulizer Q4-6h PRN	N/A
	FEV1 between 45-70% predicted	Levalbuterol nebulizer solution (Xopenex®)	0.216L FEV1 improvement 1 hour post dose	17	Rash, diarrhea, teremors	0.063-1.25mg/3mL, via nebulizer Q4-6h PRN	N/A
LABA	**Moderate to severe diagnosis with persistent symptoms**						
	Moderate to severe GOLD diagnosis via 2008	Salmeterol DPI (Servent Diskus®)	0.11L FEV1 improvement compared to placebo	3	Headache, musculoskeletal pain	50mcg/inhalation, 1 inhalation twice daily	N/A
	Moderate to severe GOLD diagnosis via 2016	Formoterol (Foradil Aerolizer®)	0.117L FEV1 improvement compared to placebo	5	Headache, termor, Diarrhea, xerostomia	12mcg/single use-cap, 1 capsule Q12h	N/A
	Patients aged ≥40 years with a ≥10 pack years smoking history	Olodaterol (striverdi Respimat®)	0.129L FEV1 improvement over 6 weeks	6	Nasopharyngitis, URTI	5mcg/inhalation once daily	N/A
	Patients aged >40 years with a >10 pack years smoking history	Indacterol DPL (Arcapta Neohaler®)	0.10L FEV1 improvement compared to placebo	2	Headache, Cough, nasopharynigitis	75mcg/inhalation, 1 inhalation daily	N/A
	GOLD diagnosis of COPD for atleast 6 monts via 2016	Formoterol nebulizer soluction (Perforomist®)	0.122L FEV1 improvement after 12 hours	5	Headache, termor, Diarrhea, xerostomia	20mcg/2ml, 20mcg via nebulizer Q12h	N/A
	Patients aged ≥60 years with a ≥10 pack years smoking history	Arformoterol nebulizer soluction (Brovana®)	.084L FEV1 improvement	4	Chest pain, rash, diarrhea	15mcg/2ml, 15mcg via nebulizer Q12h	N/A
SAMA	**Acute & Moderate diagnosis**						
	Across all GOLD grades via 2015	Ipratropium MDI (Atrovent HFA®)	0.243L FEV1 improvement 1 hour post dose	1	Bitter taste, xerostomia, bronchitis, sinusitis	17mcg/puff, 2 puff inhaled Qgh	N/A
	patients aged ≥40 years with stable COPD	Ipratropium nebulizer solution (Atrovent®)	0.1699L FEV1 improvement after 3 days	24	xerostomia, bronchitis, sinusitis	0.5mg/2.5mL, 0.25-0.5mg via nebulizer Q6-8h	N/A
LAMA	**Servere diagnosis with persistent sympotoms**						
	Patients aged ≥40 years with an established history of moderate to severe COPD	Tiotropium DPI (Spiriva Handihaler®)	0.309L peak FEV1 improvement from baseline 6 hours post dose on day 7	10	Xerostomia, Headache, bronchitis, pharyngitis, sinusitis, URTI	18mcg/capsule, 1 cap inhaled daily	N/A
	Patients aged ≥40 years with a ≥10 pack years smoking history with a GOLD stage 2-4 via 2015	Tiotropium SIM (Spiriva Respimate®)	0.133L FEV1 improvement over 6 weeks	6	Xerostomia, Headache, bronchitis, pharyngitis, sinusitis, URTI	5mcg/puff, 2 puffs inhaled daily	N/A

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	Patients aged ≥40 with moderate to severe COPD with 87.8% in GOLD stage B or D via 2015	Aclidinium DPI (Tudorza Pressair®)	0.144L FEV1 improvement over 12 weeks	8	Headache, Cough, nasopharynigitis	400mcg/inhalation, 1 inhalation daily	N/A
	Patients aged ≥40 years with a >10 pack years smoking history, with the majority GOLD category B or D via 2015	Umeclidinium DPI (Incruse Ellipta®)	0.126L FEV1 improvement after 85 days	23	Nasopharynigitis, URTI	62.5mcg/inhalation, 1 inhalation daily	N/A
	COPD severity from moderate very severe	Glycopyrrolate DPI (Seebri Neohaler®)	0.223L peak FEV1 improvement at week 24	11	Dyspnea, Nasopharynigitis	18mcg/capsule, 1 capsule inhaled B.I.D	N/A
Inhaled Corticosteroids (ICS)	**Moderate to very severe or advance disease, with frequent exacerbations despite LAMA/ LABA**						
	Meta analysis of 55 studies with ICS use for ≥6 months	Fluticasone furoate DPI (Arnuity Ellipta®)	<0.0058L FEV1 improvrment with long term use	22	Backache, Headache, Cough, nosebleed	100 or 200mcg/inhalation, 2 inhalations B.I.D	N/A
	Meta analysis of 55 studies with ICS use for ≥6 months	Fluticasone propionate HFA (Flovent®)	<0.0058L FEV1 improvrment with long term use	22	Candidiasis od mouth esophagus, nausea and vomiting	110 or 200mcg/puff, 1-2 inhalation B.I.D	N/A
	Meta analysis of 55 studies with ICS use for ≥6 months	Fluticasone propionate DPI (Flovent Diskus®)	<0.0058L FEV1 improvrment with long term use	22	Candidiasis od mouth esophagus, nausea and vomiting	100 or 250mcg/inhalation, 1 inhalation B.I.D	N/A
	Patients aged 40-80 years with ≥10 pack years smoking history	Budesonide DPI (Pulmicort Flexhaler®)	0.143L Peak change from baseline FEV1 on day 15	14	Diarrhea, nausea, headache	320mcg/inhalation, 1-2 inhalation B.I.D	N/A
	Meta analysis of 55 studies with ICS use for ≥6 months	Budesonide nebulizer solution (Pulmicort Flexhaler®)	<0.0058L FEV1 improvrment with long term use	22	Diarrhea, nausea, headache	0.5mg or 1.0mg per 2mL, 0.5-1.0mg via nebulizer Q12h	N/A
	Meta analysis of 55 studies with ICS use for ≥6 months	Beclomethasone dipropionate HFA (QVAR®)	<0.0058L FEV1 improvrment with long term use	22	Headache	40 or 80mcg/ inhalation, 1-4 inhalations B.I.D	N/A
	Patients ≥ 40 years with moderate to very severe COPD	Mometasone HFA (Asmanex®)	0.054L FEV1 improvement from baseline after 4 weeks	21	Candidiasis od mouth esophagus, nausea and vomiting	100 or 200mcg/puff, 2 inhalations B.I.D	N/A
Combo ICS & LABA	**Moderate to servere diagnosis with frequent exacerbations**						

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	Patients aged 40-80 years with ≥ 10 pack years smoking history	Budesonide & Formoterol DPI (symbicort®)	0.138L peak change from baseline FEVl on day 28	14	Oral candidiasis, stomachache, vomiting	160/4.5mcg/inhalation, 2 inhalations B.I.D	N/A
	Patients aged 40 ≥ with a clinical history of COPD and a ≥10 Pack year somking history	Fluticasone furoate & Vilanterol (Breo Ellipta®)	0.230L weighted mean FEV1 change from baseline 0-4h post dose on day 84	12	Oral candidiasis, headache	100/25mcg/blister, 1 inhalation daily	N/A
	Patients aged 40 ≥ with a clinical history of COPD and a≥10 Pack year somking history	Fluticasone & Salmeterot DPI (Advair Diskus®)	0.201L weighted mean FEV1 change from baseline 0-4h post dose on day 84	12	Oral candidiasis, headache, musculoskeletal pain	250/50mcg /inhalation, 1 inhalation B.I.D	N/A
	Patients ≥40 years who are current or former smokers with ≥10 pack years history	Fluticasone & Salmeterol HFA (Advair HFA®)	0.155L mean FEV1 improvement after 2 hours	13	Oral candidiasis, headache, musculoskeletal pain	115/21mcg/puff, 2 puffs inhaled B.I.D	N/A
	Patients ≥40 years with moderate to very severe COPD	Mometasone & Fonnoterol DPI (Dulera®)	0.112L FEV1 improvement from baseline after 13 weeks	21	Headache, nasopharyngitis, sinusitis	400/10mcg/ inhalation, B.I.D	N/A
Combo SABA & SAMA	**Long term, Moderate maintenance treatment with frequent exacerbations**						
	Patients aged 40-80 years who have a ≥10 pack year smoking history with either severe or very Severe GOLD diagnosis via 2013	Albuterol nebulizer solution & lpratropium (Duoneb®)	0.23L FEV1 Improvement after 45 min	18	Tachycardia, tremors, dizziness, pharyngitis, xerostomia	2.5/0.5mg per 3mL, 3mLvia nebulizer Q.I.D	N/A
	Patients aged 40-80 years who have a ≥10 pack year smoking history with either severe or very Severe GOLD diagnosis via 2014	Albuterol SMI & lpratropium (Combivent Respimat®)	0.16L FEV1 improvement after 45 min with aero chamber	18	Headache, bronchitis, cough, dyspnea, pharyngitis, sinusitis, URTI	100/20mcg per puff,1 puff Q.I.D	N/A
Cmnbo LAMA & LABA	**Servere sympotoms with a high frequency of exacerbations**						

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	Patients aged ≥ 40 with an established history of moderate to severe COPD	Glycopyrrolate & Fetmoterol MDI (Bevespi Aerosohere®)	0.392L peak FEV1 lmprovement from baseline in 24 hours	10	Cough	9/4.8mcg/puff, 2 puffs inhaled B.I.D	N/A
	Patients ≥ 40 years with modersate to severe COPO and ≥10 pack year smoking history	Glycopyrrolate & indacaterol DPI (Utibron Neohaer®)	1.659L peak FEV1 on day 7	20	Hypertension, headache, nasopharyngitis	50/300mcg/capsule inhaled once daily	N/A
	Patients ≥ 40 years with symptomatic COPD, classified as GOLD stage B or D via 2017	Tiotropium & Olodaterol SMI (Stiolto Respimat®)	.141L FEV1 improvement over 4 weeks	7	Backache, nasopharvngitis	2.5/2.5mcg/puff ,2 puffs inhaled daily	N/A
	Patients aged ≥ 40 years with a GOLD stage 2-4 via 2016	Umeclidinium & Vilanterol DPI (Anro Ellipta®)	0.189L FEV1 improvement over 4 weeks	7	Chest pain, constipation, diarrhea	62.5/25mcg/puff, 1 inhalation daily	N/A
	Patients aged ≥ 40 years with moderate to severe COPD with 87.8% in GOLD stage B or D via 2015	Aclidinium & Formoterol	0.189L FEV1 improvement over 12 hours	8	Headache, cough, nasopharyngitis, tremor, diarrhea	400/6mcg/puff,1 puff B.I.D	N/A
Methylxanthine	**Failure to tolerate or respond to other agents**						
	Stable COPD with GOLD stage 1 or 2 via 2008	Theophylline	0.10L FEV1 improvement after 8 weeks	19	Dose related toxicities, peristent repetitive comiting and nausea	10mg/kg/day	
Phosphodiesterse-4 (PDE4) Inhibitors	**Add on therapy for a diagnosis of severe to very severe with a history of exacerbations**						**Inflammation Reduction**
	Patients ≥40 years with severe or very severe COPD, 2 or more exacerbations in the previous year	Roflumilast (Daliresp®)	0.053L mean improvement in FEV1 Predose at week 52 alongside LABA+ ICS	16, 25	Diarrhea, nausea, weight decrease, Headache	500mcg PO daily	Decrease of 51.4 Eosinophils mean cells per mm2 after 16 weeks

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Table 2: Clinical Trails Referred in Table 1.

	Trail Details
1	Sinch D, Zhu CQ, Sharma S, Church A. Kalberg O (2015) Dalty variation in lune function in COPO patients with combined albuterol and lpratropium: resutts from a 4-week, randomized, crossover study. Pulm Pharmacol Ther 31: 85-91.
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4	Mahler OA, Waterman LA, Ward J, Gifford AH (2014) Comparison of dry powder versus nebullzed beta-agonlst in patients with COPO who have suboptimal peak lnspiratocy flow rate. J Aerosol Med Pulm Drug Deliv 27(2): 103-109.
5	NCT027966Sl Fotmoterol Dose Ranging Study (ACHIEVE Dualdir USA Phase llb)
6	Beeh KM, Westerman J, Kirsten AM (2015) The 24-h lung-function profile of once-daily tiotropium andolodaterol fixed-dose combination in chronic obstructive pulmonary disease. Pulm Pharmacol Ther 32: 53-59.
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9	Malekli yazdl MR, Singh D, Anzueto A, Tombs L, Fahy WA, et al. (2017) Assessling Shot-term Deterioration in Maintenance-naive Patients with COPO Receiving Umeclidinium/Vilanterol and Tiotropium: A Pooled Analysis of Three Randomized Trials. Adv Ther 33(12): 2183-2199.
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11	Martinez FJ, Fabbri LM, Ferguson GT (2017) Baseline Symptom Score Impact on Benefits of Glycopyrrolate/Formoterol Metered Dose Inhaler in COPD. Chest 152(6): 1169-1178.
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13	Koser A, Westerman J, Sharma S, Emmett Av Crater GO (2010) Safety and efficacy of fluticasone propionate/salmeterol hydrofluoroalkane 134a metered-dose-inhaler compared with fluticasone propionate/salmeterol diskus in patients with chronic obstructive pulmonary disease. Open Respir Med J 4: 86-91.
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15	Lotvall J, Palmqvist M, Arvidsson P, Maloney A, Ventresca GP, et al. (2001) The therapeutic ratio of R-albuterol is comparable with that of RS-albuterol in asthmatic patients.J Allergy Clin Immunol 108(5): 726-731.
16	Martinez FJ, Rabe KF, Sethi S (2016) Effect of Roflumilast and inhaled Corticosteroid/Long-Acting β2-Agonist on Chronic Obstructive Pulmonary Disease Exacerbations (RE(2) SPOND). A Randomized Clinical Trial. Am J Respir Crit Care Med 194(5): 559-567.
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22	Yang IA, Clartt MS, Sim EH, Fons KM (2012) Inhaled corticosteroids for stable chronic obstructive pulmonary disease. Cochrane Database Syst Rev (7): CD002991.
23	Rheault T, Khindri S, Vahdati-bolouri M, Church A, Fahy WA (2016) A randomised, open-label study of umeclidinium versus glycopyrronium in patients with COPD. ERJ Open Res 2(2): 00101-2015.
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25	Rabe KF, Watz H, Baraldo S, Pedersen F, Blondini D, et al. (2018) Anti-lnflammatoty effects of roflumilast in chronic obstructive pulmonary disease (ROBERT): a 16-week, randomized, placebo-controlled trial. The Lancet Respiratory Medicine.

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Since the incidence of COPD increases with age, smoking status, and the presence of comorbidities, these factors can certainly contribute to the findings of each study. As the GOLD guidelines have adapted to new research and improved over the years, the staging and recommended treatment options have coincided. The table references trials conducted over the past decade, and their treatment groups reflect the patient management options available at those times. Comorbidities, airflow limitation, history of exacerbations and other independent factors should always be considered in the current diagnosis and treatment of patients with COPD. The table 1 has an emphasis upon FEV_1 improvement as well as inflammation reduction for the purpose of determining the optimal management of treatment. It will serve as a reference in the analysis of recommended pharmacotherapy per the GOLD 2018 guidelines [1]. Drug classes are listed beside their current place in therapy and individual therapies are separated by the specific treatment group evaluated in each respective study. Alongside the effect on pulmonary function, the corresponding trail data is numbered and listed at the end of this paper in Table 2. Common adverse effects as well as the dosage used to elicit the responses follow. Group A is excluded from the analysis due to the wide range of symptoms as well as treatment options.

Pharmacotherapy management for GOLD group B

Initial treatment of patients diagnosed to Group B consists of long-acting bronchodilators (LABA or LAMA). Cochrane systematic reviews have established long-acting bronchodilators to be superior to their short acting counterparts [1,33]. If patients in this group suffer from persistent symptoms or exacerbations, only then they are recommended a combination LABA and LAMA. In reference to Table 1, olodaterol has shown the greatest improvement in FEV_1 amongst LABAs and tiotropium amongst LAMAs. Olodaterol is highly selective with nearly full intrinsic activity at beta2 receptors and has been shown to effectively improve lung function aBouyssou & Koch [34,35]. In the Beeh study Beeh [36] of olodaterol, the primary end point was FEV_1 area under the curve response 0 to 24 hours after 6 weeks of treatment, resulting in an improvement of 0.129L from a once daily 5mcg dose. In the same study, 5mcg of tiotropium daily produced an improvement of 0.133L after 6 weeks which would lead to the assumption that they have similar effectiveness despite their different mechanisms of action.

Tiotropium is traditionally dosed at 18mcg daily, and in the Tashkin study [37] it was administered open label as its brand name Spiriva HandiHaler ®. As a secondary endpoint in this study, tiotropium resulted in a peak change in FEV_1 over 6 hours post-dose on day 7 Although this improvement appears proportional to the increase in dosage from the Beeh [36] study, peak FEV_1 over 3 hours at week 6 from 5mcg olodaterol and 5mcg tiotropium resulted in 0.291L and 0.300L respectively. These results lead to the conclusion that tiotropium is slightly more efficacious than olodaterol in FEV_1 improvement. Based on this data, it would be reasonable to suggest that Group B COPD patients start therapy with a LAMA such as tiotropium or umeclidinium rather than a LABA. In a recent head-to-head study, the efficacy of umeclidinium 62.5mcg was shown to be greater than 18mcg tiotropium in terms of the least squares mean change from baseline in trough FEV_1. [38]. In a following-up study by Feldman [39], the efficacy of tiotropium and olodaterol once-daily fixed-dose combination was analyzed versus the once-daily umeclidinium and vilanterol combination. This was the first study to analyze the components when delivered through a single device. Tiotropium/olodaterol was administered once daily via the Respimat ® inhaler, as two puffs of 2.5/2.5mcg. Umeclidinium and vilanterol were administered once daily via the Ellipta ® inhaler at 62.5/25mcg respectively. The trough FEV1 change from baseline to week 4 resulted in 0.141L for TIO/OLO and 0.189L for UMEC/VI [39]. When this data is compared to the data from Table 1, it becomes clear that the combination of a LAMA and LABA provides a small but substantial improvement over monotherapy and thus supports the escalation to dual therapy upon persistent symptoms in Group B patients.

Pharmacotherapy management for GOLD group C

Patients diagnosed to Group C are initially started on a LAMA and if they suffer from increased exacerbations, therapy is extended to a LAMA plus LABA, or alternatively a LABA plus ICS. The preferred treatment in this group is LAMA and LABA, because ICS usage increases the risk of developing pneumonia in some cases [1]. These treatment options do not differ much from the Group B therapy, besides the addition of ICS. When comparing LAMA and LABA against LABA and ICS treatments, Table 1 again demonstrates a greater improvement in FEV_1 with glycopyrrolate and formoterol (LABA and LAMA) therapy rather than fluticasone furoate and vilanterol (ICS and LABA). The difference is greater

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than 100mL, but treatment with ICS may be more beneficial in certain patients with frequent exacerbations when considering time to onset. A 2017 Cochrane review of LAMA and LABA versus LABA and ICS analyzed eleven studies, which found fewer exacerbations and a larger improvement in FEV_1 in the LAMA + LABA group, along with a lower risk of pneumonia [40]. These data support the current intensification of treatment for Group C with anti-inflammatory agents and indicate the importance of reducing chronic inflammation in the management of COPD. This may prompt the beneficial effects of using selective PDE4 inhibitor roflumilast in early stage of COPD patients. When comparing the optimum FEV_1 values from Table 1, treatment with the LAMA tiotripium 18mcg once daily has a 0.309L improvement opposed to a 0.230L improvement with the combination LABA/ICS vilanterol and fluticasone furoate 25/100mcg once daily [37,41]. These values point towards a better response with the monotherapy of a LAMA over the combination of LABA and ICS, but the frequency of exacerbations and individual patient quality of life must be taken into consideration when balancing the immediate improvement in ventilation and slowing down the inflammation-related disease progression and exacerbations. In a Cochrane database review of fluticasone furoate and vilanterol versus tiotropium, no statistically significant differences were found for the improvement of symptoms in COPD assessment Test (CAT) score nor FEV_1 after 84 days. The authors Sliwka et al. [42] suggested that further trials with longer duration are needed to determine if there is an advantage of either therapy since the current data is not strong enough to establish differences in efficacy or equivalency. The introduction of a PDE4 inhibitor in the addition of a LAMA or LABA here may be an alternative route to explore for the treatment of further exacerbations in Group C rather than an ICS. Table 1 demonstrates the use of ICS results in minimal FEV_1 improvement, specifically <0.0058L with long term use [29]. Roflumilast dosed at 500mcg once daily by mouth resulted in a FEV_1 improvement of 0.053L, and significantly reduced the rate of moderate or severe exacerbations in patients with a history of more than three in the past year [43]. Use of roflumilast could potentially decrease the rate of disease progression from patients from Group C to Group D.

Pharmacotherapy management for GOLD group D

Current recommendations for patients in the Group D stage are dependent on the patient's previous treatment. LABA and LAMA combination is the recommended starting therapy which is consistent with the previous treatment of choice in groups B and Group D patients have been shown to be at a higher risk of developing pneumonia when treated with ICS [44] due to the disease progression and the suppression of immune defense system of the body by chronic and large amount of steroid exposure. The risk of pneumonia is an important concern in the selection of treatment, but some patients in Group benefit from LABA and ICS use especially if they have been suspected of or have a history of asthma-COPD overlap [1]. After determining the proper initial treatment, any further exacerbations or persistent symptoms would escalate treatment to triple therapy of LAMA, LABA, and ICS. Only after triple therapy is roflumilast considered if the patient is still experiencing exacerbations. Specifically, in patients with an FEV_1 < 50% predicted, chronic bronchitis, or particularly if they have had at least one hospitalization for an exacerbation in the previous year[28,43,45]. Results of roflumilast (thirty-four randomized controlled trials) in patients including Group B-D stages showed a significant improvement in FEV_1 by 0.0515L compared to placebo Chong [46], as shown in Table 1.

AntiInflammatory Therapy and COPD Management

The PDE4 inhibitor roflumilast is currently not recommended by the GOLD guidelines unless the patient reaches a Group D diagnosis. Previous studies have analyzed the effect of roflumilast in conjunction with traditional therapies, but its use alone for the prevention of COPD progression has not been evaluated. In the RE (2) SPOND trail, the difference in mean change from baseline in pre-dose FEV1 was 0.053L when orally taking roflumilast 500mcg once daily [43]. Although this change in FEV_1 is below the normally considered minimum clinically important difference of 100mL, it still provides considerable evidence for its use outside of a last line add on therapy [47]. In comparison to the FEV_1 mean improvement of 0.047L by steroid fluticasone, this anti-inflammatory agent may provide more benefits than currently ascribed [48]. Several studies have focused on the use of roflumilast in the prevention of exacerbations and have exhibited the efficacy that supports its recommended usage. In a 2017 Cochrane Library review of PDE4 use in COPD, the number needed to treat for a single person to be exacerbation-free was found to be 20 (95% CI 16 to 26) [46] . These discoveries suggest that PDE4 inhibitors in patients with COPD are acting independently of the other treatments and could be supportive of its broad anti-inflammatory efficacy [27]. The recently published ROBERT trial [49] looked specifically at the anti-inflammatory effects of roflumilast in COPD. Bronchial biopsies were taken at baseline and week 16 of treatment to evaluate: CD8, CD68, CD4, CD45, neutrophils, eosinophils per mm2 in the submucosa, as well as CD8 and CD68 cells in the bronchial epithelium. The primary endpoint (change in CD8 cellsby roflumilast) was not significantly different from placebo . However, as a secondary outcome, the decrease in eosinophils was significantly greater than placebo as shown in Table 1 by a value of 51.4 mean cells per mm^2. This decrease of eosinophil counts not only in the bronchial biopsy specimens but also in the induced sputum samples presents a new opportunity to evaluate the efficacy of different COPD treatments. The findings of ROBERT trial that blood eosinophilia counts do not necessarily reflect the lung eosinophilia as reported by Kolsum et al. [50]. Specific studies to determine eosinophil count of both blood and lung biopsies in COPD patients could help in the diagnosis as well as in decision making for pharmacotherapy.

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Summary

The treatment of COPD has progressed with the increased data collected on bronchodilators and anti-inflammatory therapies. GOLD guidelines have improved upon their diagnosis and treatment algorithms to better manage this chronic illness. With the current available treatment, COPD is still not a reversible or curable disease. New treatment options and studies must continue to understand the pathophysiology in order to advance patient care outcomes. Current therapy is able to help alleviate and manage symptoms. The use of PDE4 inhibitors may be underutilized in the treatment of patients in Groups B & C. Future studies should consider a more extensive approach over the disease progression and focus on the long-term effects of treatment options as well as developing new treatment for inflammatory markers. In addition, more specific studies based upon gender, age, and race are needed to help better identify which patients benefit most from the treatment algorithms.

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