DOI: 10.7860/JCDR/2021/46060.14550

Review Article

Pharmacology Section

Triple Therapy of Fluticasone Furoate, Umeclidinium, Vilanterol- A Compelling Choice in Severe Chronic Obstructive Pulmonary Disease

B JAGAN NATHAN[1], MELINA I SAHAY[2], AK GAUTHAM[3], DK SRIRAM[4], MELVIN GEORGE[5]

ABSTRACT

Trelegy Ellipta (GlaxoSmithKlineTM) is the first single inhaler triple combination therapy comprising of umeclidinium, vilanterol and fluticasone approved by the United States Food and Drug Administration (US FDA) for patients with severe COPD in 2019. Clinical trials comparing this triple combination with dual therapy including a Long Acting β2-Agonist/Long Acting Muscarinic Antagonist (LABA/LAMA) or Long Acting β2-Agonist/Inhaled Corticosteroids (LABA/ICS) were evaluated. Triple combination did show improvement through the mean Forced Expiratory Volume per second (FEV1), St. George questionnaire, and reduced hospitalisation due to acute exacerbation of COPD. This medication should be prescribed cautiously for certain populations. Although this triple combination is used only in patients with the most advanced forms of disease who have frequent exacerbations and remain uncontrolled, there are certain additional indications that may be explored in future trials. The convenience associated with using a single device for three different classes of drugs could be its biggest trump card and it will not be surprising to see its preference among patients avoiding the need for multiple dosing. Nevertheless, it remains to be seen if this improved adherence would translate into improved outcomes such as reduced mortality in real world practice among patients with severe COPD. The availability of a single inhaler device for delivering a triple combination of LABA/LAMA/ICS is a small success story in the quest to identify better therapies for patients with severe COPD, who are so prone to repeat acute exacerbations which could eventually turn fatal.

Keywords: Adrenergic β2 receptor agonists, Bronchodilator, Exacerbations

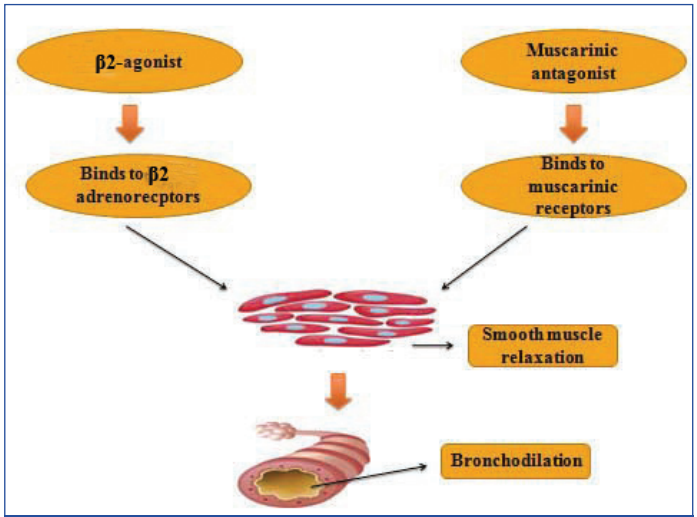
INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is characterised by airway obstruction leading to persistent respiratory symptoms, on account of exposure to noxious substances [1]. The primary aetiology of COPD is smoking, though in recent times, many other additional factors have also been identified. Patients with COPD complain of persistent cough, sputum production, and dyspnea [2]. A 90% of COPD related deaths have occurred in low-income countries [3]. In accordance with large epidemiological studies such as Burden of Obstructive Lung Disease (BOLD) showed that, with an increase in the prevalence of smoking in developing countries, the prevalence of COPD is expected to rise over the next 40 years [4,5]. There has been a somber forecast that, by 2060 over 5.4 million deaths would annually occur due to COPD and related conditions [6]. At present it is not curable, it can only ease symptoms, improve health-related quality of life, and reduce the risk of mortality [7]. Few studies have shown that "the intensity of systemic inflammation in severe COPD patients, including large numbers of neutrophils, macrophages, and lymphocytes is directly affects the health-related quality of life, airflow limitation, exercise intolerance, and comorbidities associated with COPD" [8-10].

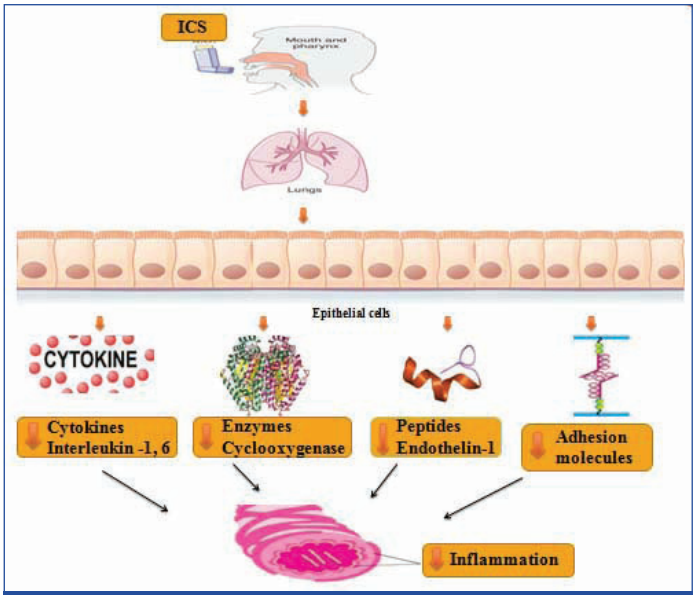
The pharmacological treatment of COPD largely revolves around three categories of drugs namely inhaled corticosteroids, muscarinic antagonists, and β2-agonists [11]. According to Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria, the management of COPD depends on the severity of the disease and the rate of exacerbations leading to hospitalisation [12]. A fixed dose combination of fluticasone furoate, umeclidinium and vilanterol (Trelegy Ellipta/GlaxoSmithKline) is a newly developed triple combination medication approved for use by US FDA for severe COPD patients in September 2017. It has the distinction of being the first fixed-dose triple combination approved by US FDA [13]. This review summarises the evidence on the safety, efficacy and other important pharmacological properties of this unique triple combination FDC product for use in severe COPD.

MECHANISM OF ACTION

The triple combination inhaler contains fluticasone, umeclidinium and vilanterol. These drugs represent three different classes of the active component such as inhaled corticosteroid, antimuscarinic agent, and β2-agonist. The detailed mechanisms of action for the individual component are described below [Table/Fig-1,2].



[Table/Fig-1]: Represents the mechanism of β2-agonist and Muscarinic antagonist [14].



[Table/Fig-2]: Represent the mechanism of Inhaled corticosteroids [15,16].
ICS: Inhaled corticosteroids

1) Fluticasone furoate

Fluticasone furoate is a potent glucocorticoid that is synthetic and chemically termed as triflourinated corticosteroid [17]. Corticosteroids play an essential role in the treatment of COPD, because of their excellent anti-inflammatory properties [18]. Fluticasone furoate binds with glucocorticoid receptors which help in the regulation of gene expression through glucocorticoid elements leading to inhibition of pro-inflammatory factors such as NF-KB [19,20]. It works by preserving epithelial integrity and permeability which occurs due to protease induced cell damage [Table/Fig-2].

2) Umeclidinium

Cholinergic parasympathetic nerves provide the pre-dominant innervations to the airway [21]. There are about 5 Muscarinic acetylcholine receptors, (mAChRs) M1 to M5 of which only M1 to M3 are well known in humans. These receptors are expressed abundantly in vagal nerve, pulmonary vasculature, smooth muscles, and sub mucosal glands in the lining of airway [22]. The mAChRs are single glycoprotein receptors combined by intra and extracellular loops which can be linked to ion channels (K+ or Ca2+). The binding of Acetylcholine ligand typically results in the activation of Adenylyl Cyclase (AC), activation of phospholipase C, and opening of the potassium channel. The released acetylcholine interacts with mAChRs to regulate contraction of smooth muscle in the airway, mucus secretion, and vasodilation. COPD is characterised by increased parasympathetic activity [23,24] which may be moderately reversed with anticholinergic agents such as umeclidinium and subsequently improve limitation in the airway [Table/Fig-1].

3) Vilanterol

Vilanterol is an effective bronchodilator that can ease the smooth muscle lining of airway [25]. They exert their effects by binding to the active site of β2-adrenoreceptors, which are present in abundance on smooth muscles [26]. The assumed cellular mode of action involves the signaling pathway such as activation of AC and production of intracellular cAMP, which in turn may activate the effector molecules of cAMP-dependent Protein Kinase A (PKA) and a Rap1, Epac guanine nucleotide exchange factor. PKA phosphorylates key regulatory proteins involved in the contraction of smooth muscle tone and cAMP which results in the sequestration of intracellular Ca2+, leading to relaxation of the smooth muscle [Table/Fig-1] [27].

PHARMACOKINETICS

1) Fluticasone furoate

When fluticasone furoate was administered by inhalation, maximum Serum concentration (Cmax) occurred within 0.5 to 1 hour. Bioavailability was 15.2%. Steady state was estimated to be achieved within six hours. The volume of distribution was 661L. It is highly bound to human plasma protein and principally metabolised through hepatic metabolism via CYP3A4. The elimination half-life of the drug was 24 hours and excreted through feces and urine [Table/Fig-3] [28].

Pharmacokinetic parameters	Fluticasone furoate	Umeclidinium	Vilanterol
C_{max}	0.5 to 1 hours	5 to 15 minutes	5 to 15 minutes
Bioavailability	15.2%	13%	27.3%
Volume of distribution	661L	86L	165L
Metabolism	Hepatic via CYP3A4	Hepatic via CYP2D6	Hepatic via CYP3A4
Half life	24 hours	11 hours	11 hours
Excretion	Principally in feces and urine	Feces (58%); Urine (22%)	Urine (70%); Feces (30%)

[Table/Fig-3]: Pharmacokinetics characteristics of fluticasone furoate, umeclidinium and vilanterol [28].
Cmax: Maximum serum concentration

2) Umeclidinium

Upon inhalation of umeclidinium, Cmax was achieved within 5 to 15 minutes; Steady state was reached within 14 days. It binds to plasma protein and the volume of distribution was 86 L. It is metabolised through hepatic metabolism via CYP2D6. The elimination half-life of the drug was 11 hours and excreted through feces (58%) and urine (22%) [Table/Fig-3] [28].

3) Vilanterol

Cmax and steady state was achieved within 5 to 15 minutes, and 14 days respectively, upon inhalation of vilanterol. The drug is highly bound to plasma protein and has a distribution volume of 165L. It is metabolised by the liver via CYP3A4 with a half-life of 11 hours and excreted in urine (70%) and feces (30%) [Table/Fig-3] [28].

EFFICACY

Overview of lung parameters and health related quality of life among COPD patients in major trials [Table/Fig-4] [29-33].

Study	Trough FEV1	SGRQ	Rate of exacerbation	Rescue medication use
Siler TM et al., [29] (2015)	+	+	Not evaluated	+
Lipson DA et al., [30] (2018)	+	+	+	Not evaluated
Lipson DA et al., [31] (2017)	+	+	+	Not evaluated
Bremner PR et al., [32] (2018)	+	X	X	Not evaluated
Tabberer M et al., [33] (2018)	Not evaluated	+	Not evaluated	+

[Table/Fig-4]: Overview of lung parameters and health related quality of life among COPD patients in major trial; + - Improved, X-Unchanged; SGRQ: St. George questionnaire; FEV1: Forced expiratory volume per second

The Lung Function and Quality of Life Assessment in COPD with Closed Triple Therapy (FULFIL) trial evaluated the Trelegy Ellipta (GSK) (fluticasone furoate/umeclidinium/vilanterol) against budesonide/formoterol combination in patients with COPD, GOLD class D having an FEV1 <50% and COPD Assessment test ≥10 and having a moderate or severe exacerbation in the past one year. Tough FEV1 and St. George's Respiratory questionnaire total score showed remarkable improvement at the end of 24 weeks of therapy in the triple therapy group compared to the control group. Triple therapy had greater odds of favorable response in comparison to control with respect to SGRQ improvement. The annualised rate of exacerbations was lesser in triple therapy [31].

In 2018, results of InforMing the PAthway of COPD Treatment (IMPACT) trial were published, which compared Trelegy ellipta (GSK) once-daily single inhaler triple combination (fluticasone furoate/

umeclidinium/vilanterol) versus dual therapies i.e., fluticasone furoate/vilanterol or umeclidinium/vilanterol. It was a phase III, randomised trial with a total of 10,355 patients enrolled as intent to treat. The primary endpoint of the study was met, in terms of lower exacerbation rate in the triple combination therapy, when compared to either of the dual therapies. However, it is possible that the abrupt withdrawal of ICS in patients of the LABA/LAMA group could have triggered the increased risk of exacerbations when compared to the other groups. The annual hospital admissions due to severe exacerbations were significantly reduced. There was a high risk of pneumonia in triple therapy compared to umeclidinium/vilanterol. A trend towards lesser all-cause mortality in the triple therapy was reported, however finding needs to be explored further as it did not achieve statistical significance, due to the exploratory nature of the endpoint. It is speculated that the immunosuppressive effects of ICS increase the risk of pneumonia but its anti-inflammatory effect can mitigate the severity of pneumonia, thereby reducing the mortality [30].

SAFETY

The adverse effects of triple combination therapy are a reflection of the individual components of the inhaler. For instance, vilanterol by virtue of its sympathetic activation can cause tachycardia, a rise in blood pressure, and cardiac arrhythmia including supraventricular tachycardia and extra systoles [34]. One should be extremely cautious when prescribing this combination in patients with hypertension or coronary artery disease. Patients with thyrotoxicosis or seizure disorder are more prone to the worsening of the disease with vilanterol [35]. ICS is known to potentially cause worsening of intraocular pressure, glaucoma, and increase the risk of cataracts among COPD patients. Some of these issues such as glaucoma worsening can occur even with umeclidinium due to its anticholinergic property. An increased predilection to Candida infection of the oral cavity can be reduced with proper rinsing of the mouth to a certain extent [36]. Paradoxical bronchospasm, reduction in bone mineral density, adrenal suppression are some of the other troublesome effects that can be potentially seen among users of the triple combination. Headache, diarrhea, cough, dyspepsia, and back pain are some of the minor adverse events associated with the triple combination inhaler [28].

CURRENT STATUS AND FUTURE PERSPECTIVES

Currently, the triple combination of umeclidinium/vilanterol/fluticasone is approved in patients with COPD who are already consuming LABA-LAMA combination or LABA-ICS combination and still not achieving adequate control [37]. The drug is also indicated in patients who have been using fluticasone-vilanterol combination and umeclidinium as two separate medications, as using the triple therapy would enhance compliance due to convenience and also helps the patients to stick to the treatment regimen to avoid exacerbation, and persistent symptoms [38]. The triple combination is available as a dry powder inhaler. Besides this, another triple therapy comprising of budesonide, glycopyrronium, and formoterol has also been approved by the European Medicines agency (EMA) based on the positive results from TRIBUTE study. In this study, a single inhaler triple combination of Beclomethasone Dipropionate, Formoterol Fumarate, and Glycopyrronium (BDP/FF/GLY) compared with single inhaler dual combination of indacaterol and glycopyrronium (IND/GLY). It showed BDP/FF/GLY reduced exacerbations rate compared to IND/GLY [Table/Fig-5] [39,40].

It remains to be seen how these two inhalers would fare against each other in head to head trials in future. There has not been a piece of definite evidence to prove that providing the same drugs in a single inhaler is superior to giving them the drugs separately. Nevertheless, there are data to suggest that within one year of diagnosis; almost 32% of patients require triple therapy eventually [41]. It has also been suggested that in a new COPD patient who has been hospitalised for acute exacerbations, there is a strong case for providing them on triple therapy after discharge from the hospital for a few months at least. The drugs could be gradually tapered subsequently for these patients based on the response of the patient [42]. However, this has to be evaluated in a trial setting. All scenarios that warrant avoiding ICS in COPD patients apply even for triple therapy. For instance, HIV patients receiving Highly Active Antiretroviral Therapy (HAART) may have the metabolism of ICS impaired due to hepatic enzyme inhibition potential, resulting in an increased predilection for Cushing's syndrome. Patients with active tuberculosis or any other infection should also not be prescribed ICS, and hence triple therapy [43]. Despite these challenges, triple therapy is bound to be increasingly used in advanced COPD owing to its convenience from the patient's vantage point [44]. Finally, in terms of cost analysis, Fluticasone Furoate/Umeclidinium/Vilanterol (FF/UMEC/VI) established a cost-effective treatment option for patients with COPD when compared to treatment with Beclometasone/formoterol/glycopyrronium [45-47].

Name of the drugs	Fluticasone/umeclidinium/vilanterol	Beclometasone/formoterol/glycopyrronium
Mode of delivery	Dry powder inhaler	Metered-dose inhaler
Dose	FF 100 mcg/umec 62.5 mcg/vi 25 mcg	BDP 87 mcg/FF 5 mcg/GP 9 mcg
Frequency	Once daily	Twice daily
Brand name	Trelegy Ellipta	Trimbow
Manufacturer	GSK/Innoviva Inc.	ChiesiFarmaceutici
Cost for 28 days	£41.53	£41.53
Approved by	FDA (Sep 2017), EMA (Nov 2017), NMPA (Nov 2019)	EMA (July 2017)

[Table/Fig-5]: Characteristics of Trelegy Ellipta and Trimbow [28,40].
FDA: Food and drug administration; EMA: European medicines agency; NMPA: National medical products administration

CONCLUSION(S)

The pharmacological management of patients with COPD continues to remain daunting in patients with advanced stage of disease. Besides LAMA, LABA, and ICS there have not been any other drugs that have revolutionised the care of these patients. The availability of a single inhaler device for delivering a triple combination of LABA/LAMA/ICS is a small success story in the quest to identify better therapies for patients with COPD, who are so prone to repeat acute exacerbations which could eventually turn fatal. With appropriate use of the medication, the combination of umeclidinium/vilanterol/fluticasone could add to the limited arsenal in the fight against COPD.

REFERENCES

[1] Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease [Internet]. Goldcopd.org. 2020 [cited 9 May 2020]. Available from: www.goldcopd.org/wp-content/uploads/2020/03/GOLD-2020-POCKET-GUIDE-ver1.0_FINAL-WMV.pdf.

[2] Wacker ME, Kitzing K, Jörres RA, Leidl R, Schulz H, Karrasch S, et al. The contribution of symptoms and comorbidities to the economic impact of COPD: An analysis of the German COSYCONET cohort. Int J Chron Obstruct Pulmon Dis. 2017;12:3437-48.

[3] Chronic obstructive pulmonary disease (COPD) [Internet]. Who.int. 2020 [cited 9 May 2020]. Available from: www.who.int/news-room/fact-sheets/detail/chronic-obstructive-pulmonary-disease-(copd).

[4] Buist AS, McBurnie MA, Vollmer WM, Gillespie S, Burney P, Mannino DM, et al. International variation in the prevalence of COPD (the BOLD Study): A population-based prevalence study. Lancet. 2007;370:741-50.

[5] GBD 2016 Risk Factors Collaborators. Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990-2016: A systematic analysis for the Global Burden of Disease Study 2016. Lancet. 2017;390(10100):1345-422.

[6] Salvi S, Kumar GA, Dhaliwal RS, Paulson K, Agrawal A, Koul PA, et al. The burden of chronic respiratory diseases and their heterogeneity across the states of India: The Global Burden of Disease Study 1990-2016. The Lancet Global Health. 2018;6(12):e1363-74.

[7] Ng TP, Niti M, Tan WC, Cao Z, Ong KC, Eng P. Depressive symptoms and chronic obstructive pulmonary disease: Effect on mortality, hospital readmission, symptom burden, functional status, and quality of life. Archives of Internal Medicine. 2007;167(1):60-67.

[8] Barnes PJ, Celli BR. Systemic manifestations and comorbidities of COPD. Eur Respir Rev. 2009;33(5):1165-85.
[9] Agustí A. Systemic effects of chronic obstructive pulmonary disease: What we know and what we don't know (but should). Proc Am Thorac Soc. 2007;4:522-25.
[10] Garcia-Rio F, Miravitlles M, Soriano JB, Muñoz L, Duran-Tauleria E, Sánchez G, et al. Systemic inflammation in chronic obstructive pulmonary disease: A population-based study. Respir Res. 2010;11(63):01-15.
[11] Horita N, Goto A, Shibata Y, Ota E, Nakashima K, Nagai K, et al. Long-Acting Muscarinic Antagonist (LAMA) plus Long-Acting Beta-Agonist (LABA) versus LABA plus Inhaled Corticosteroid (ICS) for stable Chronic Obstructive Pulmonary Disease (COPD). Cochrane Database Syst Rev. 2017;2(2):CD012066.
[12] Russi EW, Karrer W, Brutsche M, Eich C, Fitting JW, Frey M, et al. Diagnosis and management of chronic obstructive pulmonary disease: The Swiss guidelines. Respiration. 2013;85(2):160-74.
[13] Albertson TE, Murin S, Sutter ME, Chenoweth JA. The Salford Lung Study: A pioneering comparative effectiveness approach to COPD and asthma in clinical trials. Pragmatic and Observational Research. 2017;8:175-81.
[14] DeBellis RJ. Mechanism of action of long-acting bronchodilators Clin Pulm Med. 2005;12(4):S10-12.
[15] Williams DM. Clinical pharmacology of corticosteroids. Respiratory Care. 2018;63(6):655-70.
[16] Barnes PJ. Inhaled Corticosteroids. Pharmaceuticals (Basel). 2010;3(3):514-40.
[17] FDA. VeramystTM (fluticasone furoate) nasal spray: |US prescribing information [online] Accessed 2020 Nov 05.
[18] Suissa S, McGhan R, Niewoehner D, Make B. Inhaled corticosteroids in chronic obstructive pulmonary disease. Ann Am Thorac Soc. 2007;4(7):535-42.
[19] Horvath G, Wanner A. Inhaled corticosteroids: Effects on the airway vasculature in bronchial asthma. Eur Respir Rev. 2006;27(1):172-87.
[20] Ericson-Neilsen W, Kaye AD. Steroids: Pharmacology, complications, and practice delivery issues. Ochsner Journal. 2014;14(2):203-07.
[21] Belmonte KE. Cholinergic pathways in the lungs and anticholinergic therapy for chronic obstructive pulmonary disease. Ann Am Thorac Soc. 2005;2(4):297-304.
[22] Babu KS, Morjaria JB. Umeclidinium in chronic obstructive pulmonary disease: Latest evidence and place in therapy. Therapeutic Advances in Chronic Disease. 2017;8(4-5):81-91.
[23] Wessler IK, Kirkpatrick CJ. The nonneuronal cholinergic system: An emerging drug target in the airways. Pulm Pharmacol Ther. 2001;14:423-34.
[24] Gosens R, Zaagsma J, GrootteBromhaar M, Nelemans A, Meurs H. Acetylcholine: A novel regulator of airway smooth muscle remodelling? Eur J Pharmacol. 2004;500:193-201.
[25] Cazzola M, Page CP, Rogliani P, Matera MG. β2-agonist therapy in lung disease. Am J Respir Crit Care Med. 2013;187(7):690-96.
[26] Billington CK, Ojo OO, Penn RB, Ito S. cAMP regulation of airway smooth muscle function. Pulm Pharmacol Ther. 2013;26:112-20.
[27] Billington CK, Hall IP. Novel cAMP signalling paradigms: Therapeutic implications for airway disease. Br J Pharmacol. 2012;166:401-10.
[28] US Food and Drug Administration. Trelegy®Ellipta® highlights of prescribing information. Updated September 2017 [cited 9 May 2020]. https://www.accessdata.fda.gov/drugs at fda _docs/label /2017/20948 2s000 lbl.pdf.
[29] Siler TM, Kerwin E, Sousa AR, Donald A, Ali R, Church A. Efficacy and safety of umeclidinium added to fluticasone furoate/vilanterol in chronic obstructive pulmonary disease: Results of two randomised studies. Respir Med Res. 2015;109(9):1155-63.
[30] Lipson DA, Barnhart F, Brealey N, Brooks J, Criner GJ, Day NC, et al. Once-daily single-inhaler triple versus dual therapy in patients with COPD. N Engl J Med. 2018;378(18):1671-80.
[31] Lipson DA, Barnacle H, Birk R, Brealey N, Locantore N, Lomas DA, et al. FULFIL trial: once-daily triple therapy for patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2017;196(4):438-46.
[32] Bremner PR, Birk R, Brealey N, Ismaila AS, Zhu CQ, Lipson DA. Single-inhaler fluticasone furoate/umeclidinium/vilanterol versus fluticasone furoate/vilanterol plus umeclidinium using two inhalers for chronic obstructive pulmonary disease: A randomised non-inferiority study. Respir Med Res. 2018;19(1):19.
[33] Tabberer M, Lomas DA, Birk R, Brealey N, Zhu CQ, Pascoe S, et al. Once-daily triple therapy in patients with COPD: patient-reported symptoms and quality of life. Advances in Therapy. 2018;35(1):56-71.
[34] Vestbo J, Leather D, Barkerly ND, New J, Gibson JM, McCorkindale S, et al. Effectiveness of Fluticasone Furoate-Vilanterol for COPD in Clinical Practice. N Engl J Med. 2016;375(13):1253-60.
[35] Lotvall J, Bateman ED, Bleecker ER, Busse WW, Woodcock A, Follows R, et al. 24-h duration of the novel LABA vilanterol trifenatate in asthma patients treated with inhaled corticosteroids. ERJ Open Res. 2012;40:570-79.
[36] Tashkin DP, Strange C. Inhaled corticosteroids for chronic obstructive pulmonary disease: What is their role in therapy? Int J Chron Obstruct Pulmon Dis. 2018;13:2587-601.
[37] Malerba M, Nardin M, Santini G, Mores N, Radaeli A, Montuschi P. Single-inhaler triple therapy utilizing the once-daily combination of fluticasone furoate, umeclidinium and vilanterol in the management of COPD: The current evidence base and future prospects. Ther Adv Respir Dis. 2018;12:1753466618760779.
[38] Gaduzo S, McGovern V, Roberts J, Scullion JE, Singh D. When to use single-inhaler triple therapy in COPD: A practical approach for primary care health care professionals. Int J Chron Obstruct Pulmon Dis. 2019;14:391-401.
[39] Papi A, Vestbo J, Fabbri L, Corradi M, Prunier H, Cohuet G, et al. Extrafine inhaled triple therapy versus dual bronchodilator therapy in chronic obstructive pulmonary disease (TRIBUTE): A double-blind, parallel group, randomised controlled trial. Lancet. 2018;391(10125):1076-84.
[40] Trimbow [Internet]. Ema.europa.eu. 2020 [cited 9 November 2020]. Available from: www.ema.europa.eu/en/documents/product-information/trimbow-epar-product-information_en.pdf.
[41] Brusselle G, Price D, Gruffydd-Jones K, Miravitlles M, Keininger DL, Stewart R, et al. The inevitable drift to triple therapy in COPD: An analysis of prescribing pathways in the UK. Int J Chron Obstruct Pulmon Dis. 2015;10:2207-17.
[42] Reis AJ, Alves C, Furtado S, Ferreira J, Drummond M, Robalo-Cordeiro C. COPD exacerbations: Management and hospital discharge. Pulmonology. 2018;24(6):345-50.
[43] Raveendran AV. Inhalational Steroids and Iatrogenic Cushing's Syndrome. The Open Respir Med Res. 2014;8(1):74-84.
[44] Vanfleteren LE, Ullman A, Nordenson A, Andersson A, Andelid K, Fabbri LM. Triple therapy (ICS/LABA/LAMA) in COPD: Thinking out of the box. ERJ Open Research 2019;5(1):00185-2018.
[45] Ismaila AS, Risebrough N, Schroeder M, Shah D, Martin A, Goodall EC, et al. Cost-effectiveness of once-daily single-inhaler triple therapy in COPD: The IMPACT trial. Int J Chron Obstruct Pulmon Dis. 2019;14:2681.
[46] Schroeder M, Benjamin N, Atienza L, Biswas C, Martin A, Whalen JD, et al. Cost-effectiveness analysis of a once-daily single-inhaler triple therapy for patients with Chronic Obstructive Pulmonary Disease (COPD) using the FULFIL trial: A Spanish perspective. Int J Chron Obstruct Pulmon Dis. 2020;15:1621.
[47] Schroeder M, Shah D, Risebrough N, Martin A, Zhang S, Ndirangu K, et al. Cost-effectiveness analysis of a single-inhaler triple therapy for patients with advanced chronic obstructive pulmonary disease (COPD) using the FULFIL trial: A UK perspective. Respir Med X. 2019;1:100008.

PARTICULARS OF CONTRIBUTORS:
1. Intern, Department of Clinical Research, Hindu Mission Hospital, Chennai, Tamil Nadu, India.
2. Intern, Department of Clinical Research, Hindu Mission Hospital, Chennai, Tamil Nadu, India.
3. Consultant, Department of General Medicine, Hindu Mission Hospital, Chennai, Tamil Nadu, India.
4. Consultant, Department of Diabetology, Hindu Mission Hospital, Chennai, Tamil Nadu, India.
5. Consultant, Department of Clinical Research, Hindu Mission Hospital, Chennai, Tamil Nadu, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Melvin George,
103, GST Road, West Tambaram, Chennai, Tamil Nadu, India.
E-mail: drmelvingeorge@hindumissionhospital.org

PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Jul 26, 2020
- Manual Googling: Dec 30, 2020
- iThenticate Software: Jan 20, 2021 (11%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was informed consent obtained from the subjects involved in the study? NA
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Jul 22, 2020**
Date of Peer Review: **Oct 21, 2020**
Date of Acceptance: **Jan 02, 2021**
Date of Publishing: **Feb 01, 2021**