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REVIEW

Chronic Obstructive Pulmonary Disease Treatment and Pharmacist-Led Medication Management

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Abstract: Chronic obstructive pulmonary disease (COPD) is the fourth leading cause of death across the globe. Its repeated exacerbation will seriously worsen the quality of life, aggravate the patients' symptoms, and bring a heavy burden on the patients and the society. Understanding the current status of drug therapy and the role of pharmaceutical care is essential for the management of COPD. In addition to the drugs already on the market, recent clinical trials also show that emerging novel drugs for treating COPD are being developed to prevent the symptoms, reduce the frequency of acute exacerbation, and improve the quality of life. Recent progress in new drug research should lead to novel treatment options for COPD patients in future clinical practice. The pharmaceutical care has shown significantly favourable impacts on addressing drug-related problems, supporting its vital role in the management of COPD, especially when there are a wide range of therapeutic agents. This review not only provides an overview of current treatment strategies but also further underlines the importance of new drug development and pharmaceutical care for patients with COPD.

Keywords: chronic obstructive pulmonary disease, drugs, clinical trial, complications, pharmaceutical care

Introduction

Chronic obstructive pulmonary disease (COPD) is a chronic progressive airway disease characterized by gradual lung function decline and airway remodeling.[1] The clinical symptoms of COPD include sputum, chronic cough, wheezing, along with slow onset and long duration. Persistent COPD exacerbations will aggravate the patients' symptoms and seriously affect the patients' quality of life. Currently, COPD is the fourth leading cause of death across the globe, while the World Health Organization (WHO) predicts that COPD will become the third leading cause of death by 2030.[2]

The pathogenesis of COPD involves gene-related susceptibility, atopy, lung damages, immune regulation abnormalities, and repeated airway infection.[3,4] Meanwhile, smoking, biofuel smog, occupational dust exposure, and air pollution are key environmental factors for the onset of COPD.[5] Many studies have confirmed that lifestyle changes and risk factor avoidance could help to relieve the symptoms of COPD and reduce the frequency of the acute exacerbation of COPD (AECOPD).[6,7] AECOPD is a rapid deterioration of respiratory symptoms requiring hospital admission and escalation of pharmacological and non-pharmacological

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care including more severe cases of respiratory failure and admission to an intensive care unit (ICU).[8] Some COPD patients experience frequent exacerbations (≥2 per year) independently of disease severity, but are associated with impaired health-related quality of life, reduced physical activity and poor disease prognosis.[8] The cornerstone of pharmacotherapy for stable COPD is long-acting bronchodilators or combined with inhaled corticosteroids (ICS), while the treatment for AECOPD also includes anti-infective drugs.[9] The treatment strategies will be more complicated especially for patients with complex complications. Thus, the selection of drugs with different mechanisms and the pharmaceutical care will be of great importance in the management of COPD.

Here, we summarize the representative drugs for COPD treatment and other agents that may be effective in clinical trials, aimed at providing a comprehensive overview of current treatment strategies and the associated pharmacological mechanisms. Furthermore, the importance of pharmaceutical care and the development of new drugs is further emphasized.

Conventional Treatment Strategies in Patients

Although few strategies have been proven effective in reversing the gradual decline in lung function, many drugs have been developed to alleviate the symptoms, reduce the frequency and severity of acute exacerbation, and ultimately improve the quality of life for patients with COPD.

Bronchodilators

Clinically, the main measures to improve COPD symptoms are to dilate the bronchi and relieve airflow limitation. The primary pharmacologic treatments for both the maintenance and exacerbations of COPD is bronchodilator, including long-acting muscarinic antagonists (LAMAs), long-acting beta-agonists (LABAs), LAMA/LABAs, non-selective phosphodiesterase (PDE) inhibitors (such as theophylline) and newly discovered PDE-4 inhibitors (such as roflumilast). For the maintenance treatment of COPD, LAMAs, LAMA/LABAs and ICS/LABAs could lead to a significantly greater improvement in trough the forced expiratory volume in one second (FEV1) compared with placebo and short-acting muscarinic antagonists (SAMAs) monotherapy at weeks 12 and 24 in a frequentist meta-analysis, while LAMA/LABAs had the highest probabilities of being ranked the best agents in the transition dyspnea index, FEV1 improvement and St George's Respiratory Questionnaire outcomes.[10]

Tiotropium bromide, the first LAMA available for COPD in clinical practice, is safe and effective as a long-term and once-daily LAMA for the maintenance treatment of COPD and for reducing AECOPD.[11] The use of tiotropium bromide in low-grade COPD patients could increase FEV1 level and reduce its annual decline.[12] Recent clinical results indicated that treating patients who were maintenance naive at baseline with tiotropium/olodaterol resulted in greater improvements in lung function, health status and dyspnoea severity compared with tiotropium alone, without compromising patient safety.[13] It supports the use of dual bronchodilation (such as tiotropium/olodaterol) as first-line maintenance treatment in patients with COPD. Indacaterol/glycopyrronium, a new drug in LAMA/LABA, with 110/50 μg once daily, was demonstrated to improve lung function, daily symptoms, dyspnoea, health-related quality of life and lower exacerbation rates greater than mono LAMA in COPD patients.[14] It was also confirmed that indacaterol and salmeterol/fluticasone propionate could reduce all-cause mortality in patients with COPD.[15] The lung function was obviously improved during treatment with terbutaline and budesonide nebulized inhalation, accompanied by better clinical outcomes in preventing COPD deterioration.[16] With lung atomization inhalation, there will be fewer systemic adverse reactions and higher medication compliance, and worthy of routine use in COPD patients.

The representative theophylline drugs such as theophylline, aminophylline, doxofylline, can increase the concentration of cyclic adenosine monophosphate in airway smooth muscle cells with bronchodilator effects. Recent studies have confirmed that tiotropium combined with low-dose theophylline significantly improved the symptoms and general health of patients with stable COPD after 6 months of follow-up.[17] However, for patients with high risk of AECOPD, the addition of low-dose oral theophylline to a drug regimen that includes glucocorticoids confers no overall clinical or health economic benefits.[18] Besides, the safe blood concentration of theophylline is a narrow range with large individual differences, and thus its dosage should be adjusted accordingly. It has also been reported that tiotropium bromide combined with doxofylline could significantly improve the pulmonary function, relieve dyspnea, and increase clinical efficacy of patients with stable COPD.[19]

Therefore, doxofylline may be a better theophylline drug in combination with other regimens or alone for improving COPD symptoms.

Inhaled bronchodilators (ie, LABAs and LAMAs) are the main drugs in reducing lung hyperinflation secondary to reduced airway resistance and in turn relieving dyspnoea during AECOPD.[8,20] These drugs are also used in the treatment of stable COPD and AECOPD in the non-ICU or community setting. Recently developed drugs such as roflumilast, specific PDE-4 inhibitors, play a role in the prevention of exacerbations and hospitalizations in the real-world population with severe COPD.[21] Nevertheless, the most frequently reported adverse events (AE) of roflumilast were weight loss (10.8%), loss of appetite (10.8%) and nausea (8.4%), while 19.3% of them discontinued it due to AE.[21] Besides, it is worth noting that other drugs like quinolones have an effect on the metabolism of theophylline, the combination of which was reported to induce severe theophylline toxicity.[22,23] If clinically appropriate, alternative antibiotics should be considered especially for elderly COPD suffers when receiving theophylline treatment. During the use of bronchodilators and development of new drugs, both of the pharmacological effects and AE should be comprehensively evaluated, meanwhile, the pharmaceutical care should concern about the risks associated with drug interactions.

ICS

As reported, long-term use of ICS in the stable stage of COPD can not prevent the downward trend of FEV1.[3] But the long-term and regular use of ICS in the maintenance treatment of COPD is applicable to patients with FEV1 value less than 50% of the estimated value (grades III and IV) accompanied by repeated aggravation.[3] It also showed that oral use of glucocorticoids was beneficial for the treatment of AECOPD via promoting the remission of patients' symptoms and recovery of lung function, improving hypoxemia, reducing early relapses and failure rate, as well as shortening the length of hospital stay.[24] Atomization budesonide could not immediately reduce airflow restriction during AECOPD.[25] However, its combination with short-acting bronchodilators could improve the symptoms and lung function, increase the quality of life and reduce the frequency of AECOPD.[25] It also does not recommend the use of long-term oral glucocorticoids and single ICS in COPD patients.[3] Short-term (seven days) and long-term (ten to fifteen days) use of glucocorticoids were similarly effective in treating patients with AECOPD at the same daily dose.[26] In addition, COPD patients receiving ICS showed an increased risk of community-acquired pneumonia and deteriorative prognosis.[27] A pulmonary function test is often needed to determine whether a patient has the indication for long-term use of ICS.[3]

ICS use has been restricted only to selected COPD patients mainly based on the risk of AECOPD. The patients can continue taking ICS-based therapy when the patients were on the presence of co-existence of asthma or high eosinophil counts and frequency of moderate or severe exacerbations in the previous 12 months.[28] However, several observational studies showed a high rate of prescribed ICS for COPD, irrespective of clinical recommendations, questioning the efficacy of these compounds in unselected patients, and leading to increased complications (weight gain, osteoporosis, cataract) and community-acquired pneumonia related to ICS use.[29,30] ICS treatment in COPD patients needs to be personalised based on whether the patient is currently receiving LABA/ICS or LAMA/LABA/ICS.[28] LAMA/LABA inhalers could be the maintenance therapy in COPD, especially in the longer duration trials, which may be able to successfully switch from current ICS/LABA therapy to LAMA/LABA inhalers, and potentially reduce the use of ICS.[30]

Anti-Infective Drugs

Pathogen (bacterial and/or viral) infection is a leading cause of AECOPD. AECOPD often follow increased airway inflammation, mainly due to infection, and lead to decreased airflow and increased lung hyperinflation relative to stable COPD.[8] The role of bacterial infection in AECOPD is mainly manifested by the primary bacterial infection in lower airway, secondary bacterial infection along with viral infection, followed by bacterial antigen-induced hyperresponsiveness of airway, and eosinophil inflammation.[31] *Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, Enterobacter*, and *Pseudomonas aeruginosa*, are prevailing bacteria classes in COPD patients. Moreover, *Staphylococcus aureus* and *Klebsiella pneumoniae* were identified more in mortality group of AECOPD.[32] A multicenter clinical trial confirmed that amoxicillin/clavulanic acid (500/125 mg three times daily for 8 days) was effective in treating mild to moderate COPD at a rate of 74.1%, and significantly prolonged the next time interval of AECOPD.[33] Levofloxacin has a good antibacterial effect on *Pseudomonas aeruginosa* infection. It has been reported

that levofloxacin synergism with imipenem or colistin, can be used as combination therapy for infections by multi-drug-resistant bacteria.[34] A randomized controlled trial found that three months of azithromycin for an infectious AECOPD requiring hospitalization significantly reduced the treatment failure during the highest-risk period.[35] As acute exacerbations are a main common and detrimental event in COPD patients, effective antimicrobial therapies and regimens should be optimized. Therefore, the selection of antibiotics should take into account the patients' bacterial infection, comorbidities or other high-risk factors. Clinical pharmacists need to follow the guidelines of COPD treatment and avoid the off-label use, overuse and inappropriate combination of antibiotics. Furthermore, the effectiveness and adverse reactions should be routinely evaluated to promote the rational use of antibiotics.

In COPD patients, viral infections also play a relevant role in worsening lung function, therefore, favor disease progression.[36] Virus infection in COPD was reported to alter the respiratory microbiome and precipitate secondary bacterial infection, indicating increased infection burden and potentially complex drug treatments.[37] Recent study further showed that reduced abundance of bacteriophages in COPD patients with viral pathogens implicates skewing of the virome during infection, with potential consequences for the bacterial populations, during infection.[38] Viral infection is prone to occur in the AECOPD phase.[39] Jafarinejad et al have discovered that the overall estimation of the prevalence of viral infection was 37.4%, while the highest and lowest prevalence rate was related to *rhinovirus* and *echovirus*, respectively.[39] It also demonstrated that all virus infections were seasonal, with *influenza virus* and *rhinovirus* mainly identified in the winter, *parainfluenza virus* in the summer, and *metapneumovirus* in the spring.[32] These studies will improve the management of COPD by using antibiotics and other treatments. For example, acyclovir and valacyclovir were proved better for curing viral infections in patients who used systemic glucocorticoids in patients with COPD.[40] The pharmaceutical care should consider the presence of virus infection during the hospitalization of COPD patients and the following antiviral therapy.

Expectorants

Cough and sputum are common symptoms in patients with COPD. However, antitussive should not be used if the sputum is difficult to cough up, especially the central antitussive. As the central antitussive can suppress the respiratory center, block cough reflex, and then leave the sputum in the airway, which not only affects breathing but also prone to secondary infections. A meta-analysis demonstrates that mucolytics are useful in preventing AECOPD as maintenance add-on therapy to patients with frequent exacerbations, the effectiveness of which is independent of the severity of airway obstruction and the use of inhaled corticosteroids.[41] *In vitro*, mucolytic agents like ambroxol, could regulate airway inflammation by inhibiting NF-κB activation through reducing the production of inflammatory cytokines during tracheal epithelial rhinovirus infection.[42] It suggests that ambroxol may be also beneficial for rhinovirus infection associated with COPD.

Antihypoxic Drugs

Red blood cells in patients with COPD have increased internal viscosity, reduced deformability, and enhanced aggregation due to pulmonary circulation hemodynamic disorders and hypoxia, CO_2 retention, acidosis or other factors.[43] At this time, the blood was hyperviscosity, prone to respiratory failure and acidosis. It has revealed that almitrine could reduce blood viscosity and blood flow resistance, improve oxygen carrying capacity of red blood cells, change intracellular fluid or intracellular viscosity, and thereby improve microcirculation of COPD patients.[44] Recent study showed that constant infusion of almitrine (8 μg/kg/min) significantly increased the patients' mean pulmonary artery pressure, pulmonary vascular resistance, and PaO_2 at a certain inhaled oxygen concentration.[45] During hypoxia, the increase in mean pulmonary pressure and pulmonary vascular resistance of patients with almitrine was three times higher than the placebo group, but had no significant differences in cardiac output and systemic hemodynamics.[45] In addition, almitrine significantly improved the arterial blood gas index and 6-minute walking test distance (an exercise test for the functional status of patients with moderate and severe cardiopulmonary disease) in patients with COPD and respiratory failure.[46] However, evidence from clinical trials in Spain showed that the long-term treatment of chronic hypoxemia with almitrine (1 mg/kg/day) was ineffective compared to placebo though COPD patients were better tolerant of almitrine (1 mg/kg/day) use for up to 6 to 12 months.[47] Currently, supplemental oxygen is the primary treatment modality for hypoxemia in COPD patients. There is still an urgent need for scholars to further develop new drugs that

can be used for a long time and effectively improve hypoxia in patients with COPD.

Treatment Strategies in Patients with Complications

COPD patients with edema often need to use diuretics. It has been reported that both intravenous injection and oral administration of furosemide (20 mg, once every 12 hours) combined with conventional treatment could effectively improve the clinical symptoms of AECOPD patients, but had no effect on renal function.[48] High plasma brain natriuretic peptide level is positively correlated with poor prognosis of COPD.[49] Intravenous diuretics in combination with vasodilators have been proven effective in reducing brain natriuretic peptide level in patients with AECOPD without cor pulmonale, indicating the benefits of diuretics in these patients.[50] The above investigations have shown that diuretics have an adjuvant effect in the treatment of patients with COPD, especially during the acute exacerbation. However, the application of diuretics can easily induce electrolyte disturbances and hypochloric alkalosis which should be detected regularly. The pharmaceutical care should be noted that diuretics should be discontinued if the patients' symptoms were under control.

Acid-inhibitory drugs are commonly used in COPD patients treated with glucocorticoids. As glucocorticoids will delay tissue healing, increase gastric acid secretion, reduce gastric mucosal resistance, induce and aggravate peptic ulcers. To prevent above adverse impacts that caused by glucocorticoids in treating COPD, acid-inhibitory drugs are often added at the same time. Proton pump inhibitor is more effective in preventing ulcers than H_2 receptor blockers due to the rapid increase of pH in the stomach to more than 4 by the former agent. COPD complicated with pneumonia is one of the leading causes of death. Proton pump inhibitor was reported to be positively related to the occurrence of pneumonia.[51] Nevertheless, recent review showed that the efficacy and safety profile of proton pump inhibitor for patients with COPD remains uncertain.[52] Further studies investigating its role in major clinical outcomes such as AECOPD rate, serious adverse events and quality of life are warranted.

Cor pulmonale, defined as right ventricular hypertrophy and dilatation secondary to pulmonary hypertension (PH) caused by respiratory disorders, affects the lung function and decreases exercise capacity in COPD.[53] However, the only treatment for cor pulmonale for the past 3 decades has been to rest on supplemental oxygen and a variety of measures aimed at the relief of airway obstruction.[54] Currently, supplemental oxygen is still the primary treatment modality for cor pulmonale in COPD patients. In addition, it is necessary to further clarify the histopathological concepts of COPD with respect to the progression of cor pulmonale, which treats the heart and lung as a single unit.[54] Furthermore, the effects of drugs used in pulmonary arterial hypertension should be tested in COPD patients with severe PH.[53]

Systemic inflammation in COPD patients also initiate or worsen other comorbid diseases, such as ischaemic heart disease, heart failure, osteoporosis, obstructive sleep apnoea syndrome, chronic renal failure, normocytic anaemia, sarcopenia, dysphagia, depression and diabetes.[55,56] Comorbid diseases will potentiate the morbidity of COPD, lead to increased hospitalisations, mortality and healthcare costs, and thus need to be evaluated carefully during the pharmaceutical care in the management of COPD. Besides, selected screening procedures are highly desirable to identify the frequently missed comorbidities of COPD via the approach of pharmacosurveillance, and distinguish from drug effects or drug–drug interaction effects.[56]

Ongoing Clinical Trials

COPD is often associated with a variety of complications and therefore complex treatment decisions need to be made. Currently, the treatment strategy for COPD patients has not lived up to expectations, and the development of new drugs is ongoing. As shown in Table 1, increasing clinical trials are under recruitment for COPD treatment (https://www.clinicaltrials.gov/). These frontier studies include the exploration of drug repurposing and new drugs for treating COPD in clinical.[57]

Ongoing Clinical Trials with Old Drugs

Exploring new use of old drugs is one of the important strategies for developing new agents. In two ongoing multicenter studies, the investigators try to expound that fentanyl (a powerful narcotic analgesic) may reduce dyspnea that caused by COPD with less side effects than morphine,[58] or compared with bronchodilator.[59] There are two studies evaluating the effects of treprostinil, a drug originally used to treat PH, on improving exercise tolerance for patients with COPD.[60,61] Sildenafil is another drug treating PH and is now brewing to investigate whether it can effectively and safely improve the symptoms of severe PH caused by COPD.[62] In

Table 1 Ongoing Clinical Trials

Interventions	Sponsor	Stages	Ref.
Fentanyl, Morphine Retard	Huib A.M. Kerstjens	Phase 4	[58]
Salbutamol	University of Saskatchewan	Phase 4	[59]
Inhaled Treprostinil	Inova Health Care Services	Phase 2	[60]
Inhaled treprostinil solution	United Therapeutics	Phase 3	[61]
Sildenafil Citrate	Chinese Academy of Medical Sciences, Fuwai Hospital	Not Applicable	[62]
Sertraline	Duke University	Not Applicable	[63]
Liraglutide	Claus Bogh Juhl	Phase 4	[64]
Interferon Beta-1A	Synairgen Research Ltd.	Phase 2	[65]
Arbidol	Shengjing Hospital	Phase 4	[66]
Umeclidinium/Vilanterol Dry Powder Inhaler	Gary L. Pierce	Phase 4	[67]
Indacaterol/Glycopyrrolate	University of Michigan	Phase 3	[68]
Tiotropium/Salmeterol/Fluticasone Fixed Dose Combination	Neutec Ar-Ge San ve Tic A.Ş	Phase 4	[69]
Tiotropium & olodaterol, fluticasone furoate and vilanterol	University of Dundee	Phase 4	[70]
Indacaterol/Glycopyrronium	Taipei Medical University Shuang Ho Hospital	Phase 4	[71]
ICS/LAMA/LABA, Fluticasone furoate/umeclidinium/vilanterol	GlaxoSmithKline	Phase 4	[72]
Salbutamol (Ventolin®), Tiotropium Bromide (Spiriva®), Salmeterol/fluticasone (Seretide®), YCC capsule Drug: BL capsule	Henan University of Traditional Chinese Medicine	Phase 3	[73]
PUL-042 Inhalation Solution	Pulmotect, Inc.	Phase 2	[74]
Quercetin	Temple University	Phase 1 Phase 2	[75]
Dupilumab SAR231893, ICS, LAMAs, LABAs	Sanofi	Phase 3	[76]
Ivacaftor	University of Alabama at Birmingham	Phase 2	[77]
CHF6523	Chiesi Farmaceutici S.p.A.	Phase 1	[78]

Abbreviations: COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroids; LAMAs, long-acting muscarinic antagonists; LABAs, long-acting beta-agonists; Ref., reference.

a prospective study, the researchers intend to determine whether antidepressant therapy (Sertraline) can improve the dyspnea scores of COPD patients.[63] There is also a 44-week prospective, randomized and two-center trial hypothesizing that liraglutide (3 mg), which is for treating type II diabetes in adults, can improve lung function and the quality of life in COPD patients.[64]

In clinical, when COPD patients suffer from a cold or flu, the symptoms will worsen, and then result in a reduced quality of life. A recent clinical study is designed to explore the efficacy of a natural antiviral protein containing interferon beta (IFN-β) for COPD patients with a common cold.[65] Besides, another study speculates that arbidol (umifenovir), an anti-influenza virus drug, may effectively control COPD with upper respiratory virus infection, thereby benefit AECOPD.[66] Recently, there are also many studies evaluating the effects of the combination of two or three old drugs on COPD, including LAMA/LABAs (umeclidinium/vilanterol; glycopyrrolate/indacaterol; tiotropium/olodaterol), ICS/LABAs (fluticasone/salmeterol; fluticasone/vilanterol), and ICS/LAMA/LABA (fluticasone/tiotropium/salmeterol).[67–73] The results of these clinical trials, focusing on older drugs, are urgently expected.

Ongoing Clinical Trials with New Drugs

In addition to the exploration of drug repurposing, emerging progress has been made in developing new drugs for COPD therapy. The effects of inhaled PUL-042 which is comprised

of synthetic ligands for toll-like receptor (TLR) 2/6 and TLR 9, on rhinovirus-induced lower respiratory symptoms in early COPD subjects will be examined in a single-center, double-blind, placebo-controlled study.[74] A current double-blinded placebo-controlled study is designed to determine whether quercetin supplementation can reduce inflammation and oxidative stress in patients with COPD.[75] There is a rigorously designed study evaluating the efficacy, safety, and tolerability of dupilumab, a fully human monoclonal antibody against interleukin-4 receptor α, in patients with moderate to severe COPD with type 2 inflammation.[76] A Phase II study is then devised to explore the safety and effectiveness of a drug called ivacaftor (a selective enhancer for cystic fibrosis transmembrane regulator) in COPD patients.[77] Besides, as an exploratory assessment, the anti-inflammatory effect of CHF6523, a phosphoinositide-3-kinase inhibitor, will be evaluated in a randomised, double-blind, placebo-controlled study in COPD subjects.[78] We look forward to getting good feedback from these well-designed clinical trials.

Completed Clinical Trials

COPD is one of the leading causes of death among chronic diseases, but limited new drugs have been proven effective and widely used in clinical in the last decades.[79] Recently, the resurgence of the development for COPD treatment is fueled by a greater understanding of its pathophysiology, a growing prevalence and an aging population. Expectantly, more than six hundred records of clinical trial drugs for COPD treatment are currently in the completed stage (https://www.clinicaltrials.gov/), partly shown in Table 2.

Among them, a study confirmed that RPL554 (a phosphodiesterase PDE3/4 inhibitor) can significantly improve the symptoms of patients with moderate and severe COPD.[80] RPL554 in combination with tiotropium is more effective than tiotropium alone for patients with COPD.[81] There is a 26-week, randomized, double-blind, parallel-group multicenter study showing that indacaterol/glycopyrronium (QVA149, 110/50μg daily) is more effective for treating COPD than tiotropium (18 μg daily) plus salmeterol/fluticasone propionate (50/500 μg daily),[82] but another study indicates that it can not improve the night-time blood oxygenation.[83] In two multicentre studies, the researchers determine that both SUN101 (a nebulized glycopyrrolate formulation) and GSK233705 (a new LAMA) have significant effects on COPD patients with dose–response curves.[84,85] Another 12-week phase II study shows that taking AQX-1125 (a novel oral SHIP1 activator) once a day has significant protective effects when compared with placebo treatment after the deterioration of COPD.[86] Revefenacin (TD-4208; GSK1160724), a potent LAMA agent, is proved to significantly increase the peak FEV1 in relative to baseline for treating COPD compared to placebo,[87] while its incidence of adverse events is similar to tiotropium.[88] In a recent study, trospium inhalation powder (a quaternary amine LAMA) is confirmed to have a certain therapeutic effect on COPD.[89] In a phase IIa, multi-centre, double-blind, 3 periods, and crossover study, the investigators show that

Table 2 Completed Clinical Trials

Interventions	Sponsor	Stages	Results	Ref.
RPL554 suspension	Verona Pharma plc	Phase 2	Positive	[80]
RPL554 plus tiotropium, Placebo plus tiotropium	Verona Pharma plc	Phase 2	Positive	[81]
QVA149, Tiotropium+Salmeterol/fluticasone	Novartis Pharmaceuticals	Phase 4	Positive	[82]
QVA149	Novartis Pharmaceuticals	Phase 4	Negative	[83]
SUN101	Sunovion Respiratory Development Inc.	Phase 2	Positive	[84]
GSK233705B	GlaxoSmithKline	Phase 2	Positive	[85]
AQX-1125	Aquinox Pharmaceuticals (Canada) Inc.	Phase 2	Negative	[86]
TD-4208	Theravance Biopharma	Phase 2	Positive	[87]
TD-4208, Tiotropium	Theravance Biopharma	Phase 3	Negative	[88]
Trospium inhalation powder (TrIP)	Alkermes, Inc.	Phase 2	Positive	[89]
AZD8871	AstraZeneca	Phase 2	Positive	[90]
BYM338	Novartis Pharmaceuticals	Phase 2	Positive	[91]
GW642444	GlaxoSmithKline	Phase 2	Positive	[92]
QAW039	Novartis Pharmaceuticals	Phase 2	Terminated	[93]
Amoxicillin and clavulanic acid	Catalan Society of Family Medicine	Phase 4	Positive	[94]
Azithromycin	University of Alabama at Birmingham	Not Applicable	Positive	[95]
Mepolizumab 100 mg SC	GlaxoSmithKline	Phase 3	Positive	[96]

Abbreviations: COPD, chronic obstructive pulmonary disease; Ref., reference.

navafenterol (AZD8871), a novel dual-pharmacology (LAMA and LABA) molecule, has a certain effect on COPD by improving FEV1.[90] Besides, a multicenter study find that bimagrumab (BYM338), a human dual-specific anti-ActRIIA/ActRIIB antibody, has a significant improvement effect on COPD and cachexia by comparing that with placebo treatment.[91] There is a clinical trial exploring the efficacy of GW642444 in patients with COPD, and then determined its safety and effective dose.[92] There is also a multicenter study using fevipiprant (QAW039), an oral antagonist of the prostaglandin D2 receptor 2, to alleviate eosinophilia in COPD patients.[93] Unfortunately, this clinical trial had been terminated on June 9, 2020, no results were posted yet.

The efficacy of amoxicillin and azithromycin is also investigated in treating patients with acute exacerbation of mild to moderate COPD.[94,95] In a clinical trial of monoclonal antibodies, the use of mepolizumab (a humanized interleukin-5 antagonist monoclonal antibody) has protective effects on AECOPD by regulating the growth, activation and survival of eosinophils.[96] Numerous clinical studies may bring new treatment strategies for COPD patients. However, the quality of research design varies greatly or some results of individual clinical studies are inconsistent. Besides, few clinical trials were focused on AECOPD. Furthermore, the potential increase in the number of effective drugs for COPD therapy will be a major challenge for physicians in selecting suitable drugs, and for pharmacists in conducting pharmaceutical care service.

Non-Pharmaceutical Strategies

Though we have important advances in the treatment of COPD by using bronchodilators, inhaled steroids as well as other new mechanism drugs, non-pharmaceutical strategies like pulmonary rehabilitation have to be used throughout the life time of COPD patients as main components of therapy.

Recent study has reported four lifestyle profiles that are associated with the highest number of disease-free years included a body mass index less than 25 (calculated as weight in kilograms divided by height in meters squared) and at least 2 of the following factors: never smoking, physical activity, and moderate alcohol consumption.[97] Cigarette smoking is one of the leading preventable causes of death worldwide and a major risk factor for COPD, meanwhile, nonsmokers with second-hand smoke exposure also suffer significant adverse respiratory effects.[98] Smoking cessation at any age confers substantial health benefits in COPD, but the uptake by patients remain limited due to the lack of publicity on smoking cessation and health education for patients. Huang et al reported that music therapy is effective in reducing dyspnea and anxiety, which may also improve sleep quality and physiological parameters of subjects with COPD.[99] Pulmonary rehabilitation, including an individualised plan of physical activities, retraining exercises, therapeutic education, psychosocial and self-management support, whether performed at home or in a specialised centre, is effective in managing COPD.[100]

There are no doubts as to the effectiveness of oxygen therapy in the treatment of acute and respiratory failure in different clinical scenarios.[101] A recent official guideline has made strong recommendations for long-term oxygen use in patients with COPD (moderate-quality evidence) or ILD (low-quality evidence) with severe chronic resting hypoxemia, which also has recommended that COPD patients and their caregivers should receive education on oxygen equipment and safety.[102] Recently, new devices have been developed that automatically adjust oxygen flow rates to the needs of each patient, in order to maintain stable oxygen saturation levels, which can potentially reduce medical error, improve morbidity and mortality, and reduce care costs.[101] These advances in non-drug therapy and future exploration will improve the understanding of COPD and its health management.

Impact of Pharmacist-Led Medication Management

Despite the availability of many effective strategies for treating COPD, the therapeutic goals are often not achieved. Combined with drug therapy, clinical pharmacist interventions have been reported effective in improving the clinical and humanistic outcomes in COPD patients. Emerging trials suggest that pharmaceutical care has a positive impact on treatment outcomes in COPD patients, especially in the treatment of AECOPD.[103–105]

In a randomised, controlled, prospective clinical trial, the structured education on COPD and the management of its symptoms which were provided by clinical pharmacists, could significantly improve patients' COPD knowledge, medication adherence, medication beliefs, and hospitalization rates.[106] Another pharmaceutical care programme initiated at the emergency department showed positive clinical benefits due to the reduced number and prevalence of drug-related negative outcomes.[103] In a pre- and post-intervention study over a period of 12 months, the percentage of COPD patients

with better adherence was significantly increased from 37.4% to 53.2% through pharmacist-led pharmaceutical care.[104]

Furthermore, it was demonstrated that individualized pharmaceutical care also improved inhalation technique, reduced readmissions and elevated health-related quality of life (HRQoL) in patients with COPD.[105,107–111] In addition, the pharmacists as educators for COPD patients could also reduce medical costs, smoking behavior, and the frequency of lung deterioration.[112–114]

These clinical practices demonstrated that the pharmaceutical care had shown favourable impacts on addressing drug-related problems such as medication adherence, hospital admission and medical costs, thus supporting its vital role in the management of COPD, especially when there is a wide range of therapeutic agents.

Perspectives for the Drug Therapy and Medication Management

COPD is emphysema and/or chronic bronchitis characterized by long-term breathing problems and poor airflow that occurs in response to the exposure of inhaled irritants, chemicals, as well as allergens.[115] COPD seriously impairs the patients' body functioning, reduces the quality of life and causes lots of death worldwide, and has currently become a major public health problem. The treatment strategies for COPD should be considered from the perspective of prevention of disease progression and management of clinical deterioration.

With global efforts, several kinds of drugs have been developed to improve the symptoms of COPD patients, but they also pose more medication problems. In the present review, multiple drugs including bronchodilators, antimicrobial drugs, glucocorticoids as well as expectorants for treating COPD are briefly outlined. Besides, the benefits of pharmaceutical care in the management of COPD is also emphasized. A growing number of clinical trials on new drugs further indicate that the drugs for COPD treatment will be more complex, because the potential representative drugs listed here seem the tip of the iceberg and therefore require comprehensive pharmaceutical care on drug use.

The clinical pharmacists are an integral part of patients' health-care team by making recommendations or interventions related to the medication-related problems, especially in the treatment of chronic diseases including COPD.[116] The current physician-centric healthcare has limited emphasis on patient education and counselling, especially the physicians often have no time to do these multifarious work.[117] Thus, involving non-physician health professionals such as the pharmacists, should be the best strategy to improve this situation. Recent studies have shown that pharmacists' involvement in the management of COPD not only helps patients gain better knowledge of their disease and drug treatment but also addresses drug-related problems, improves disease control and treatment effectiveness, and reduces treatment costs, demonstrating the benefits of pharmaceutical care for COPD sufferers. Pharmacists play a significant role in all critical phases of care for COPD patient, from early detection to further management plans, including advice, counselling regarding medications, inhaler techniques and medication adherence. It shows that pharmacists are well suited to supplement doctor-based management for COPD patients. Additional areas requiring consideration should include pharmacist training, increased awareness of pharmacist role, as well as physician-pharmacist collaboration.[118,119] Nevertheless, there are many barriers in the implementation of pharmaceutical care plan, including insufficient time, imperfect drug monitoring software and excessive administrative burden, which should be fully considered if the pharmaceutical care was implemented.[120]

To obtain more reasonable medication suggestions and improve clinical outcomes when treating COPD patients, clinical pharmacists could provide professional advice in the comprehensive aspects of antimicrobial classes, dressing changes, repeated treatments, drug interactions, allergic reactions, drug doses, frequency of medications, and dose adjustment for abnormal renal function and so forth.[121,122] Clinical pharmacists should provide timely and high-quality pharmaceutical services for COPD patients on the basis of patient safety, effectiveness and compliance. In addition, drug therapy teams should consider integrating pharmacists into a collaborative care team in clinical practice. Further studies should also identify the benefits of different means of pharmacist intervention such as over telephone, WeChat, or face to face, all of which will be the focus of future researches. It is also worth noting that the use of the Internet for drug alerts and drug monitoring should become the mainstream for adherence improvement in the near future.[123–125] The last but not least, drug therapy alone is sometimes difficult to achieve satisfactory curative effects, thus the combination of non-drug therapy, such as functional training, should be a beneficial supplement for the treatment of COPD.

In conclusion, the present review has reviewed the representative drugs and clinical trial drugs for the treatment of COPD. It not only provides an overview of

current treatment strategies for patients with COPD but also further underlines the importance of pharmaceutical care and the development of new drugs. Further researches are warranted to determine the optimal pharmacist intervention for reducing drug-related problems and evaluate their comprehensive role in the management of COPD.

Abbreviations

AE, adverse events; AECOPD, acute exacerbation of chronic obstructive pulmonary disease; COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in one second; HRQoL, health-related quality of life; ICS, inhaled corticosteroids; ICU, intensive care unit; IFN-β, interferon beta; LAMAs, long-acting muscarinic antagonists; LABAs, long-acting beta-agonists; PDE, phosphodiesterases; PH, pulmonary hypertension; SAMAs, short-acting muscarinic antagonists; TLR, Toll-like receptor; WHO, World Health Organization.

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All authors made significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting, revising or critically reviewing the article; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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Disclosure

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