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Review Article

Severity Assessment and Management of Chronic Obstructive Pulmonary Disease

Rasha Khaled Sendy[1]*, Qusai Munir Dahlawi[2], Ziyad Saud Rasheed Al Mjlad[3], Muhammed Ibrahim[4], Abdulrahman Saleh Alaql[5], Sultan Anwar Aljudaibi[6], Malik Ahmad Ibrahim Alqubaie[7], Amjad Fawaz Alshammari[8], Mayssan Hussein Almalki[9], Amjad Meshal Allahyani[9], Esam Mousa Aqeeli[10], Abdullah Naif Albugami[11] and Abdulrahman Omar Mansy[12]

[1]King Fahad General Hospital, Jeddah, Saudi Arabia
[2]Alnoor Specialist Hospital, Makkah, Saudi Arabia
[3]King Saud Medcail City, Riyadh, Saudi Arabia
[4]Al Abeer International Medical Center, Saudi Arabia
[5]Aladel Primary Health Care, Jeddah, Saudi Arabia
[6]Ibn Sina National College, Jeddah, Saudi Arabia
[7]Assir Hospital, Assir, Saudi Arabia
[8]King Fahad Medical City, Riyadh, Saudi Arabia
[9]King Abdullah Medical Complex, Jeddah, Saudi Arabia
[10]Khulais General Hospital, Khulais, Saudi Arabia
[11]Security Forces Hospital, Riyadh, Saudi Arabia
[12]Taif University, Taif, Saudi Arabia

***Corresponding Author:** Rasha Khaled Sendy, Medical Registrar, King Fahad General Hospital, Jeddah, Saudi Arabia.

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Abstract

Introduction: Chronic obstructive pulmonary disease (COPD) is classified as a fatal disease, with a very high rate of morbidity and mortality. It is associated with acute exacerbations, so the patients are usually undergoing frequent hospitalizations and chronic therapy. Fortunately, the appropriate controlling of the disease has positive effects such as reducing the frequency, exacerbations, and improving the health overall.

Aim of the Work: In this review, we will outline the principles of assessment and management of patients with various severity of chronic obstructive pulmonary disease. In addition, we discussed some aspects related to COPD management during Covid-19 pandemic.

Methods: A non-systematic, thorough search of the biomedical literature between 2010 and 2020 was conducted. All observational and interventional studies addressing chronic obstructive lung disease were screened.

Conclusion: Avoidance of triggers exposures, vaccines used for respiratory infections, drugs-using learning, exacerbation identification and management are all general measures considered correct for all patients with COPD. For patients who are suffering from intermittent increasing in dyspnea, the drug of choice in this case is short acting bronchodilators. The recommendation for patients who are at low risks of exacerbation and more symptomatic is a regular use of a long-acting bronchodilator with short-acting bronchodilator, prescribed as-needed for intermittent increases in dyspnea. In patients with mMRC ≥ 2, CAT score ≥ 10 and a ≥ 2 exacerbations per year with one or more hospitalization, the best initial treatment in this case is long-acting anticholinergic agent. Recommendations do not advise the patients with COPD to stop any medications they are regularly taking, including corticosteroid. If the patient admitted to the hospital due to COVID-19, using of nebulized medications should be avoided to reduce infectious spreading.

Keywords: *COPD; Assessment; Pattern; Control; Management*

Introduction

Chronic obstructive pulmonary disease, known in the medical field as (COPD), is a respiratory disease that is caused by decreasing in the airflow [1]. This disease is classified as fatal disease, with a very high rate of morbidity and mortality [2]. It is associated with acute exacerbations, so the patients with COPD are usually suffering from frequent hospitalizations and chronic therapy [3]. Fortunately, the appropriate controlling of the disease has positive effects on the symptoms such as reducing the frequency, exacerbations and improving the health overall [4].

In this review, we will outline the principles of assessment and management of patients with various severity of chronic obstructive pulmonary disease. In addition, we discussed some aspects related to COPD management during Covid-19 pandemic.

Methods

A non-systematic, thorough search of the biomedical literature between 2010 and 2020 was conducted. All observational and interventional studies addressing chronic obstructive lung disease were screened. We used PubMed database and google scholar search engine to conduct the search process. We include articles encompassing assessment and/or management of COPD. The terms used in search include COPD, assessment, pattern, control, management.

Pattern and severity

An assessment system with a multi components has been developed to help physicians in taking the right decisions to initiate the therapy for COPD. This system, which is developed for Chronic Obstructive Lung Disease (GOLD), put the patients in categories based on symptoms, risk of exacerbations and hospitalizations [1].

Patients are classified into four groups. The instrument that is used to assess symptoms is called modified Medical Research Council (mMRC) or COPD assessment test (CAT) [1]. The risk of exacerbations depends on the history of the patient since last year. So, if the patient has two or more exacerbations that requires antibiotic or glucocorticoid, or needs one or more COPD hospitalization admission, then the patient has a greater risk to face future exacerbations [1]. The groups are named as group A (characterized by low risk of exacerbations, minimal symptoms and CAT score < 10 or mMRC grade 0 to 1; the patient have no previous hospitalization and 0 to 1 exacerbation per year), group B (characterized by low risk of exacerbations, more symptoms and CAT score ≥ 10 or mMRC grade ≥ 2; the patient have no previous hospitalization and 0 to 1 exacerbation per year), group C (characterized by high risk of exacerbations, minimal symptoms and CAT score < 10 or mMRC grade 0 to 1; the patient have ≥ 1 hospitalization and ≥ 2 exacerbation per year) and group D (characterized by high risk of exacerbations, more symptoms and CAT score ≥ 10 or mMRC grade mMRC grade ≥ 2; the patient have ≥ 1 hospitalization and ≥ 2 exacerbation per year).

For the confirmation of the diagnosis of COPD, we usually use spirometry, which is defined as FEV1 to FVC ratio (< 0.7). FEV1 is not included in the ABCD categories because FEV1 alone cannot predict the patients as induvial. In addition, Spirometry is used also to assess the progression of COPD and the need for surgical interventions. If we need to assess the individual risk of death and hospitalization, we usually use the BODE index but it is not recommended by GOLD to initiate the medication [1].

Management: General measures and main principles

Avoidance of inhaled particulate exposures, vaccines used for respiratory infections, drugs-using learning, exacerbation identification and management are all general measures considered correct for all patients with COPD.

The education on how to use inhalers is very important for adequate COPD control [5]. Showing a video for patients to teach them how to use different types of inhalers is highly recommended. It is preferred to use the valved holding chamber because it is easier to be

learned by the patients. Clinicians should review the using of inhaler with patients at every follow-up visit. Many factors should be taken in consideration when selecting the inhaler device such as hand arthritis, inspiratory flow rate, and cognitive function.

COPD exacerbations are known to be caused by infection. Vaccination (like Pneumococcal, influenza and pertussis) may minimize the risk by preventing infections. Taking vaccine against pneumococcus may help in reducing exacerbations related to acquired pneumonia. Influenza vaccine is also recommended for all patients with COPD because it reduces the cases of hospitalization. In according to pertussis vaccine, it is recommended in adults with ≥ 19 years for just one time.

One of the most important steps in the treatment of COPD is the patient counselling. It may be occurred at hospitalization as a step of pulmonary rehabilitation. Clinician must help patient to increase his adherence and concerns about the medications to enhance the results. Patient counselling may include teaching the risk factors (such as exposures, respiratory infections, smoking), treatment of current symptoms by administer the medication properly, be aware of complications and exacerbations and how to use supplemental oxygen. These steps will improve the health of the COPD patient and decrease the hospital admissions [6].

Smoking cessation is the most important step that is recommended in the management of COPD because it highly reducing the declining in lung function [1]. Many strategies should be followed to achieve the goal of smoking cessation such as nicotine replacement therapy, varenicline and bupropion.

There are many benefits may the patients have from the COPD self-management strategy including increasing the quality of life and decreasing the hospital admissions. This strategy will enhance the result of management plan.

In addition to the previous steps, pulmonary rehabilitation (such as physical exercises, adherence to the medication, psychological support) all are results in improving the quality of life and decreasing hospital admissions. For that, the GOLD strategy recommends to add the pulmonary rehabilitation to the medication plan [7].

It is useful for patients with COPD to follow a healthy diet in order to make their BMI as ideal as possible. In general, weight loss strategy is useful in these cases because it decreases dyspnea and increase the exercises capacity. COPD exacerbation is highly associated with vitamin D deficiency because it causes decreasing in the lung function and more hospital admissions [8,9].

The goal of the GOLD therapy in general is to improve patient life by improving the symptoms and to decrease exacerbations. Choosing the initial therapy is based on tow parameters: the risk of exacerbations and severity of symptoms. It is highly recommended to initiate the pharmacologic therapy along with non-pharmacologic therapy [1]. The medication adjustment depends on response to the current medication, level of symptoms and exacerbation risks.

The cornerstone therapy that is used for stable COPD are bronchodilators, especially muscarinic antagonists and beta agonists. Examples includes albuterol, ipratropium, and budesonide. The routes of administration are depending on hand held inhalation in different forms (dry powders inhalers, soft mist, and metered dose). Choosing the best medication depends on two parameters: the symptoms and the risk of future exacerbations.

Group A (Low risk of exacerbations, minimally symptomatic)

For patients who are suffering from intermittent increasing in dyspnea, the drug of choice in this case is short acting bronchodilators [1]. In addition, if the COPD symptoms are minimal with a low risk of exacerbation, then these bronchodilators are considered to be the only needed for treatment (when the mMRC is 0 to 1 or CAT score < 10 and 0 to 1 exacerbation per year) [1]. In general, these bronchodilators have a lot of benefits on the COPD symptoms, improvements of the airflow and increases the capacity of exercises [10]. We can use short-acting beta agonists and short-acting muscarinic antagonists, alone or in combination, for relieving symptoms of COPD. The

most important feature of short acting bronchodilators is their rapid onset of action. On the other hand, the disadvantage of using these short acting medications is short duration of action. However, the combination therapy has an advantage of greater response than the monotherapy [11].

Albuterol and levalbuterol, are short-acting beta agonists used to improve the lung function and symptoms [12]. These beta agonists are prescribed as needed basis, but not regularly [13]. Clinical trials proved that regular using of albuterol has no clinically important impacts on symptoms or lung function. In addition, risks of the overusing of beta agonists are possible in case the patients take higher doses than the usual. These risks are varying, may include reflex tachycardia, tremor and hypokalemia in severer cases. These beta agonist drugs seem to be safe, but high doses most likely cause cardiac arrythmia [14].

Ipratropium and tiotropium, a short-acting muscarinic antagonist (also called SAMA or anticholinergic) are drugs used to reduce the symptoms and make improvements on lung function [15]. In one clinical trial, patients with minimal symptoms of COPD are given tiotropium once daily, the results showed that the FEV1 in the tiotropium group is higher than the placebo group [16]. However, the GOLD strategy suggests using short-acting bronchodilators in patients with low-risk COPD instead of long-acting muscarinic antagonists [1].

Some clinical trials that make a comparison between Albuterol and ipratropium reveal that both medications have the same effects on improving the lung function [11,17], but the side effects are different between each of them.

Some clinical trials have studied the effect of combining the short-acting beta agonists and muscarinic antagonists. The results showed that the achieved degree of bronchodilation is additive, it increased the FEV1 more than the monotherapy, but has no effect on the frequency of exacerbations.

Group B (Low risk of exacerbations, more symptomatic)

The recommendation for patients who are at low risks of exacerbation and more symptomatic is a regular use of a long-acting bronchodilator with short-acting bronchodilator, prescribed as-needed for intermittent increases in dyspnea [1]. In patients with group B COPD, both long-acting beta agonist (LABA) and long-acting anticholinergic agent (LAMA) are approved for treatment [1]. In addition, SABA (short-acting beta agonist) is prescribed for rescue use in patients taking LAMA. But for patients taking LABA, we prescribe SABA or SABA-SAMA (short-acting muscarinic antagonist) as a combination for rescue use.

In a clinical trial [18] a comparison between LAMA and LABA is studied, the results shows that both medications reduce exacerbations, but in the case of LAMA the effects seem to be greater.

Various patients may choose one bronchodilator instead of other. This is happened because some patients may suffer from side effects related to one bronchodilator but not the other. For example, if a patient taking LABA experience a somatic tremor or resting tachycardia, it is better to him to take LAMA to bypass this side effect. LAMAs also may cause a dry mouth side effect; patient can rinse his mouth to decrease this bothersome side effect.

A meta-analysis trials is used to measure the efficacy of tiotropium in comparison with other LABAs [19]. The results showed no differences is important between them that may affect the quality of life or dyspnea. In addition, the cardiovascular side effects of LABAs or LAMAs is also studied in a clinical trial and showed that no significant issues are determined [20].

In a nested clinical trial that studied patients who have hospitalization admission with COPD for cardiovascular disease compared with patients without cardiovascular disease [21], results showed that newly LAMAs and LABAs medications causes more events that are related to cardiovascular disease. In another trial, indacaterol (which is LABA) was compared with tiotropium (each drug dosage is once daily) [22]. All the adverse events (such as high blood glucose, low serum potassium, and cardiac events) was the same across all treatments.

Salmeterol, formoterol, arformoterol (which is the only LABAs used as solution for nebulization), vilanterol (which is the only LABAs used as a component of a combination product), indacaterol and olodaterol are considered Beta-2 selective medications.

Salmeterol, which is given twice daily, have been studied alone, in comparing with fluticasone alone, placebo or in combination with fluticasone [23]. Results showed that salmeterol decreased exacerbation rates and improving both quality of life and lung function. The safety of this medication is considered good in comparison with placebo.

Formoterol, a twice daily inhaled medication, need around 12 minutes to take the onset of bronchodilation [24]. It is given as a solution for nebulization with a dose of 20 mg/2 mL every 12 hours. It is also used as a part of LABA-LAMA combination or LABA-glucocorticoid inhaler. However, arformoterol is given as a solution for nebulization with a dose of 15mcg every 12 hours [25].

Indacaterol, an approved drug to treat COPD, is given once daily [22]. It has a long duration of action with rapid onset of action. The approved daily dose of indacaterol is 75 mcg [26]. Studies show that increasing the dose to more than 75 mcg per day seems not to be effective in increasing the quality of life. However, increasing the dose to 300 mcg leads to increase in asthma exacerbations and respiratory-related deaths [26]. Indacaterol is considered as a P-glycoprotein transporter and CYP3A4 substrate. By the way, the agents that inhibit these pathways seems not to have any effects in the prescribed dose.

Olodaterol is a rapid onset LABA that is approved as a medication to treat the COPD. It is given once daily [27]. The results of trials showed that Olodaterol has improvement effects on airflow (such as quality of life, peak and trough FEV1) [28].

Vilanterol, which is a once daily LABA, is used in combination with fluticasone or umeclidinium, and not recommended to be used alone. However, the related relationship between using LABA and hospitalization or death because of cardiac arrythmia was examined, and it seems that newly using of LABA is associated with increased risk of arrythmia [14].

In according to long-acting anticholinergic medications, also known as LAMAs, Tiotropium is the most known medication. Other examples of LAMAs include aclidinium, umeclidinium and glycopyrrolate. Tiotropium is present as dry powder inhaler used once daily. Its function is for decreasing dynamic hyperinflation, exacerbations, dyspnea and increase the lung function. Patients who are suffering from renal impairment must be monitored when taking this drug because it is excreted by kidneys [9].

Other medications are Aclidinium (which is dry powder inhaled twice daily), Umeclidinium (which is also dry powder inhaled once daily) and Glycopyrrolate (which is present as capsule powder inhaler once or twice per day and a nebulizing solution). Revefenacin is a nebulizing solution taking once daily.

If the patient comes suffering from severe decreasing in breath (that means CAT ≥ 20), then the best therapy choice to begin with is LABA-LAMA combination because it causes great relief of the symptoms. However, patients who have less symptoms of breathlessness can use short-acting bronchodilators. In according to patients with ACO, we suggest to control the symptoms by using a LABA-inhaled glucocorticoid combination [29].

Group C (High risk of exacerbation, minimally symptomatic)

In general, if the patient has mMRC between 0 to 1, CAT score < 10 with ≥ 2 exacerbations per year in addition to one or more leading to hospitalization, then the best choice therapy to begin with is LAMA, because LAMA is known to reduce exacerbation rate [1]. In one study which comparing many LAMAs (formoterol, salmeterol and tiotropium) [19], the results showed that tiotropium is the most effective medication that used to decrease the exacerbations (it increases the time to the first exacerbation of COPD and provided the best protection against exacerbations). A study comparing patients with moderate to severe COPD, they take tiotropium or salmeterol with or without glucocorticoids, results showed that tiotropium has decrease the risk of developing an exacerbation [30].

Group D (High risk of exacerbation, more symptomatic)

In patients with mMRC ≥ 2, CAT score ≥ 10 and a ≥ 2 exacerbations per year with one or more hospitalization, the best initial treatment in this case is LAMA [1], but if the patients come with blood eosinophil of ≥ 300 cells/microL and symptoms of asthma-COPD overlapping, then the best medication in this case is ICS (LABA inhaled glucocorticoid). A combination of LAMA-LABA is usually used in severe breathlessness cases because it improves the symptoms of dyspnea. A fixed dose of LAMA-LABA showed a better result on adherence. When we compared tiotropium alone with LAMA-LABA combination, the combination showed better increasing in the quality of life and FEV1 than the tiotropium alone.

A combination of tiotropium-olodaterol is used once daily to control the symptoms of COPD. It causes increasing in the FEV1 and improving health status when compared with monotherapy. Also, a combination of umeclidinium-vilanterol inhaler is used once daily to treat COPD achieved a greater increasing in mean peak FEV1.

Glycopyrronium-indacaterol inhaler, which is used twice daily, is a good choice for decrease using of rescue medication [31]. It improves the lung function, dyspnea and quality of life. Patients that are suffering from renal impairment must be controlled for side effects of this combination because it is excreted renally.

A combination of glycopyrrolate-formoterol, which is inhaled twice daily, is also approved for treating COPD. It shows a better increasing from baseline in FEV1 than the placebo [32]. Aclidinium-formoterol, a dry powder inhaler combination is taken also twice daily and have a good impact on decreasing the exacerbations. In addition, the FDC (fixed-dose LAMA-LABA combination) is reducing exacerbations, but not all the FDA recommend it to reduce exacerbations in patients with COPD.

LABA-ICS combination showed a reduction in mortality and exacerbations when compared with monotherapy. When we compared glycopyrronium-indacaterol with fluticasone-salmeterol in patients with moderate to severe COPD, results showed that glycopyrronium-indacaterol combination is better in reducing COPD exacerbations and fewer episodes of pneumonia compared to fluticasone-salmeterol [1]. The GOLD strategy recommends the regular treatment with LABA-ICS as an alternative for patients who are suffering from frequent COPD exacerbations and blood eosinophils ≥ 300 cells/microL. This combination showed improving on the health status, lung function and decreasing in the rate of exacerbations, but have a minimally decreasing in the mortality rate (in spite of the risk of death in the combination is lower than the fluticasone alone). The combination of salmeterol-fluticasone showed a good improving in the health status, but the pneumonia is more frequent in this combination despite of the lower mortality.

Other LABA-ICS combination examples includes budesonide-formoterol (twice-daily inhaler), mometasone-formoterol (twice-daily inhaler also) and fluticasone furoate-vilanterol (once-daily inhaler) [33]. The fluticasone furoate-vilanterol combination showed improvement in the lung function and increasing in trough FEV1. When we compared vilanterol-fluticasone with vilanterol alone in COPD patients, the results showed that the combination modestly reduced the exacerbation compared with vilanterol, but the rate of pneumonia is higher in the combination.

In according to ICS, it causes decreases in the inflammation related to COPD, decrease exacerbations and somehow slowing the progression of respiratory symptoms, but its effect on lung function and mortality seems to be little. It is used as a combination regimen to control the COPD but not used as monotherapy [1].

COVID-19 advices

Patients with COPD who are infected with COVID-19 have a higher tendency to enter the ICU, requiring an invasive ventilation and in some cases death. This is happened because of SARS-COVID2 (severe acute respiratory syndrome coronavirus 2) [2]. The experts recom-

mend that patients with COPD should take care of themselves to avoid infecting with COVID-19 by social distancing and using the hand hygiene. Recommendations do not advise the patients with COPD to stop any medications they are regularly taking, including corticosteroid. If the patient admitted to the hospital due to COVID-19, using of nebulized medications should be avoided to reduce infectious spreading.

Conclusion

Patients are classified into four groups. The instrument that is used to assess symptoms is called modified Medical Research Council (mMRC) or COPD assessment test (CAT). The risk of exacerbations depends on the history of the patient since last year. So, if the patient has two or more exacerbations that requires antibiotic or glucocorticoid, or needs one or more COPD hospitalization admission, then the patient has a greater risk to face future exacerbations.

Avoidance of triggers exposures, vaccines used for respiratory infections, drugs-using learning, exacerbation identification and management are all general measures considered correct for all patients with COPD.

For patients who are suffering from intermittent increasing in dyspnea, the drug of choice in this case is short acting bronchodilators. The recommendation for patients who are at low risks of exacerbation and more symptomatic is a regular use of a long-acting bronchodilator with short-acting bronchodilator, prescribed as-needed for intermittent increases in dyspnea. In patients with mMRC ≥ 2, CAT score ≥ 10 and a ≥ 2 exacerbations per year with one or more hospitalization, the best initial treatment in this case is long-acting anticholinergic agent.

Patients with COPD who are infected with COVID-19 have a higher tendency to enter the ICU, requiring an invasive ventilation and in some cases death. Recommendations do not advise the patients with COPD to stop any medications they are regularly taking, including corticosteroid. If the patient admitted to the hospital due to COVID-19, using of nebulized medications should be avoided to reduce infectious spreading.

Bibliography

1. Global Initiative for Chronic Obstructive Lung Disease (GOLD). "Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease" (2020).

2. Guan WJ., *et al.* "Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis". *European Respiratory Journal* (2020): 55.

3. Buist AS., *et al.* "International variation in the prevalence of COPD (the BOLD Study): a population-based prevalence study". *Lancet* 370 (2007): 741.

4. Rennard SI and Vestbo J. "COPD: the dangerous underestimate of 15%". *Lancet* 367 (2006): 1216.

5. National Jewish Health Video Library. "Devices to inhale medication (Asthma inhalers, COPD inhalers)" (2018).

6. Make B. "Collaborative self-management strategies for patients with respiratory disease". *Respiratory Care* 39 (1994): 566.

7. McCarthy B., *et al.* "Pulmonary rehabilitation for chronic obstructive pulmonary disease". *Cochrane Database of Systematic Reviews* (2015): CD003793.

8. Malinovschi A., *et al.* "Severe vitamin D deficiency is associated with frequent exacerbations and hospitalization in COPD patients". *Respiratory Research* 15 (2014): 131.

9. Rafiq R., *et al.* "Prevention of exacerbations in patients with COPD and vitamin D deficiency through vitamin D supplementation (PRECOVID): a study protocol". *BMC Pulmonary Medicine* 15 (2015): 106.

10. Hanania NA., *et al.* "Bronchodilator reversibility in COPD". *Chest* 140 (2011): 1055.

11. In chronic obstructive pulmonary disease, a combination of ipratropium and albuterol is more effective than either agent alone. An 85-day multicenter trial. COMBIVENT Inhalation Aerosol Study Group". *Chest* 105 (1994): 1411.

12. Ram FS and Sestini P. "Regular inhaled short acting beta2 agonists for the management of stable chronic obstructive pulmonary disease: Cochrane systematic review and meta-analysis". *Thorax* 58 (2003): 580.

13. Cook D., *et al.* "Regular versus as-needed short-acting inhaled beta-agonist therapy for chronic obstructive pulmonary disease". *American Journal of Respiratory and Critical Care Medicine* 163 (2001): 85.

14. Wilchesky M., *et al.* "Bronchodilator use and the risk of arrhythmia in COPD: part 2: reassessment in the larger Quebec cohort". *Chest* 142 (2012): 305.

15. Wadbo M., *et al.* "Effects of formoterol and ipratropium bromide in COPD: a 3-month placebo-controlled study". *European Respiratory Journal* 20 (2002): 1138.

16. No Zhou Y., *et al.* "Tiotropium in Early-Stage Chronic Obstructive Pulmonary Disease". *The New England Journal of Medicine* 377 (2017): 923.

17. Dorinsky PM., *et al.* "The combination of ipratropium and albuterol optimizes pulmonary function reversibility testing in patients with COPD". *Chest* 115 (1999): 966.

18. Donohue JF., *et al.* "A 6-month, placebo-controlled study comparing lung function and health status changes in COPD patients treated with tiotropium or salmeterol". *Chest* 122 (2002): 47.

19. Chong J., *et al.* "Tiotropium versus long-acting beta-agonists for stable chronic obstructive pulmonary disease". *Cochrane Database of Systematic Reviews* (2012): CD009157.

20. Tashkin DP., *et al.* "A 4-year trial of tiotropium in chronic obstructive pulmonary disease". *The New England Journal of Medicine* 359 (2008): 1543.

21. Gershon A., *et al.* "Cardiovascular safety of inhaled long-acting bronchodilators in individuals with chronic obstructive pulmonary disease". *JAMA Internal Medicine* 173 (2013): 1175.

22. Donohue JF., *et al.* "Once-daily bronchodilators for chronic obstructive pulmonary disease: indacaterol versus tiotropium". *American Journal of Respiratory and Critical Care Medicine* 182 (2010): 155.

23. Calverley PM., *et al.* "Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease". *The New England Journal of Medicine* 356 (2007): 775.

24. Kew KM., *et al.* "Long-acting beta2-agonists for chronic obstructive pulmonary disease". *Cochrane Database of Systematic Reviews* (2013): CD010177.

25. Donohue JF., *et al.* "One-year safety and efficacy study of arformoterol tartrate in patients with moderate to severe COPD". *Chest* 146 (2014): 1531.

26. Chowdhury BA., *et al.* "The risks and benefits of indacaterol--the FDA's review". *The New England Journal of Medicine* 365 (2011): 2247.

27. Joos GF., *et al.* "A randomised, double-blind, four-way, crossover trial comparing the 24-h FEV1 profile for once-daily versus twice-daily treatment with olodaterol, a novel long-acting β2-agonist, in patients with chronic obstructive (2015).

28. Koch A., *et al.* "Lung function efficacy and symptomatic benefit of olodaterol once daily delivered via Respimat® versus placebo and formoterol twice daily in patients with GOLD 2-4 COPD: results from two replicate 48-week studi (2014).

29. Wise RA., *et al.* "Tiotropium Respimat inhaler and the risk of death in COPD". *The New England Journal of Medicine* 369 (2013): 1491.

30. Vogelmeier C., *et al.* "Tiotropium versus salmeterol for the prevention of exacerbations of COPD". *The New England Journal of Medicine* 364 (2011): 1093.

31. Frampton JE. "QVA149 (indacaterol/glycopyrronium fixed-dose combination): a review of its use in patients with chronic obstructive pulmonary disease". *Drugs* 74 (2014): 465.

32. Martinez FJ., *et al.* "Pooled Analyses from PINNACLE-1 and -2: The Novel LAMA/LABA Co-Suspension Technology Glycopyrrolate/Formoterol Fixed-Dose Combination Delivered by MDI Shows Improvement Versus Monocomponents in Patient".

33. Sharafkhaneh A., *et al.* "Effect of budesonide/formoterol pMDI on COPD exacerbations: a double-blind, randomized study". *Respiratory Medicine* 106 (2012): 257.

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