



# The Role of Tiotropium+Olodaterol Dual Bronchodilator Therapy in the Management of Chronic Obstructive Pulmonary Disease

David M. G. Halpin, M.A., D.Phil. M.B.B.S., F.R.C.P.

Department of Respiratory Medicine, Royal Devon and Exeter Hospital, Exeter, UK

Bronchodilator therapy is central to the management of chronic obstructive pulmonary disease and are recommended as the preferred treatment by the Global Obstructive Lung Disease Initiative (GOLD). Long acting anti-muscarinics (LAMA) and long acting  $\beta_2$  agonists (LABA) are both more effective than regular short-acting drugs but many patients remain symptomatic despite monotherapy with these drugs. Combination therapy with LAMA and LABA increases the therapeutic benefit while minimizing dose-dependent side effects of long-acting bronchodilator therapy. The TOviTO programme has investigated the benefits of treatment with a combination of tiotropium and olodaterol administered via a single inhaler. Tiotropium+olodaterol 5/5  $\mu\text{g}$  significantly improved forced expiratory volume in 1 second ( $\text{FEV}_1$ ) area under the curve from 0 to 3 hours, trough  $\text{FEV}_1$  health status and breathlessness versus the mono-components and placebo. Tiotropium+olodaterol 5/5  $\mu\text{g}$  also increased endurance time and reduced dynamic hyperinflation during constant work rate cycle ergometry. On the basis of these and other studies the 2017 GOLD report recommends escalating to dual bronchodilator therapy in patients in groups B and C if they remain symptomatic or continue to have exacerbations and as initial therapy for patients in group D.

**Keywords:** Pulmonary Disease, Chronic Obstructive; Tiotropium; Olodaterol

## Introduction

Although chronic obstructive pulmonary disease (COPD) is defined by the presence of persistent respiratory symptoms and airflow limitation<sup>1</sup> many people with COPD show a significant spirometric response to bronchodilators. For example, in both the Isolde and UPLIFT studies where patients were given

400  $\mu\text{g}$  salbutamol and 80  $\mu\text{g}$  ipratropium to assess the bronchodilator response at entry to the study, the mean increase in forced expiratory volume in 1 second ( $\text{FEV}_1$ ) was around 200 mL with some patients showing increases in  $\text{FEV}_1$  of over 500 mL<sup>2,3</sup>. As well as improving the  $\text{FEV}_1$ , which is largely a measure of large and medium airway caliber, bronchodilators have significant effects on small airway function (which is often reflected in changes in forced vital capacity [FVC]) and on static and dynamic hyperinflation<sup>4-7</sup>.

Although the impact of COPD on patients' functional capacity and quality of life is affected by many factors not reflected in the degree of spirometric impairment, in large populations improvements in  $\text{FEV}_1$  correlate with reductions in breathlessness (measured by the transitional dyspnea index [TDI]), health status (measured by the St George's Respiratory Questionnaire [SGRQ]), requirement for rescue medication use and the frequency of exacerbations<sup>8,9</sup>.

**Address for correspondence:** David M. G. Halpin, M.A., D.Phil. M.B.B.S., F.R.C.P.

Department of Respiratory Medicine, Royal Devon and Exeter Hospital, Barrack Road, Exeter EX2 5DW, UK

Phone: 44-(0)1392-402133, Fax: 44-(0)1392-402828

E-mail: d.halpin@nhs.net

Received: Aug. 19, 2017

Revised: Aug. 21, 2017

Accepted: Aug. 23, 2017

© It is identical to the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0/>).



Copyright © 2018  
The Korean Academy of Tuberculosis and Respiratory Diseases.  
All rights reserved.

## Main Text

Bronchodilators are the mainstay of the pharmacologi-

cal management of COPD and are recommended by the Global Obstructive Lung Disease Initiative (GOLD) as the preferred treatment for people with COPD<sup>1</sup>. Short acting bronchodilators, both  $\beta_2$ -agonists and anti-muscarinics taken either as needed or regularly improve both breathlessness and lung function<sup>10</sup> and greater effects are seen if drugs of both classes are combined<sup>11,12</sup>. However, many patients remain symptomatic despite the use of short acting drugs or have levels of symptoms that require treatment with more effective bronchodilators. The long acting anti-muscarinics (long-acting muscarinic antagonist [LAMA]) and long-acting  $\beta_2$  agonists (LABA) are both more effective than regular short-acting drugs and more convenient. Long-acting bronchodilator monotherapy reduces airflow limitation<sup>13-18</sup> and dyspnoea<sup>13,14,18</sup> and improves physical activity/exercise capacity<sup>19-22</sup>, and health status<sup>13,14,16-18</sup> as well as reducing the risk of exacerbations<sup>23</sup>.

Tiotropium bromide was the first LAMA to be approved for maintenance treatment of COPD<sup>24</sup>. It is available in two formulations: dry powder (18 mg once daily) delivered via the breath-actuated HandiHaler, and aqueous solution (5 mg, two puffs 2.5 mg once daily) delivered via the Respimat Soft Mist Inhaler. It is effective when administered once daily as it has a long elimination half-life compared with other available LAMAs (27–45 hours following inhalation compared with, for example, just 2–3 hours with aclidinium)<sup>25</sup>. Tiotropium has occupied a central role in the management of COPD for the last decade.

Olodaterol is a once-daily LABA that is highly selective with nearly full intrinsic activity at  $\beta_2$  receptors<sup>26</sup> and which has been shown to be effective at improving lung function over 24 hours in patients with COPD<sup>27,28</sup> and improving patient-reported outcomes<sup>28</sup>.

Although long acting bronchodilators provide adequate control of symptoms for some patients, significant numbers of patients treated with long acting bronchodilator monotherapy continue to experience significant breathlessness. For example, in a study of nearly 700 patients in both primary care and specialist centers in the United States over half had a modified Medical Research Council breathlessness score (mMRC) of 2 or more despite treatment with a single long-acting bronchodilator<sup>29</sup>.

LABAs and LAMAs act via different mechanisms; when used together in patients with COPD, they exert additional bronchodilating effects<sup>30-32</sup>. By targeting different receptors using an anti-muscarinic and a  $\beta$  agonist it is possible to increase the therapeutic benefits while minimizing dose-dependent side effects. The complementary pharmacological profiles of tiotropium and olodaterol make them ideal partners and data from studies using them in separate inhalers support the benefits of combining them<sup>33,34</sup>. Following on from these studies, an extensive clinical trial programme (The TOViTO programme) has investigated the benefits of treatment with a combina-

tion of tiotropium and olodaterol administered via a single inhaler. Consolidating treatments into single devices ought to decrease the complexity of usage, improve compliance and improve outcomes, particularly if the device is a Respimat Soft Mist which is easy to use and gives good pulmonary deposition<sup>35,36</sup>. The TOViTO program consists of ten phase 3 studies evaluating the potential benefits and safety profile of the fixed-dose combination (FDC) of olodaterol and tiotropium through the Respimat inhaler. The program has studied over 15,000 patients with moderate-to-very-severe COPD in more than 50 countries<sup>37</sup>.

The two replicate TONADO trials were randomised, double-blind, parallel-group, multicentre trials which compared the efficacy and safety of tiotropium+olodaterol FDC administered via the Respimat device compared with the mono-components in patients with moderate to very severe COPD<sup>38</sup>. Current or ex-smokers aged 40 or more with at least a 10 pack year history of smoking and a post-bronchodilator FEV<sub>1</sub> of less than 80% of their predicted value and a post-bronchodilator FEV<sub>1</sub>/FVC less than 70% were randomized to receive tiotropium+olodaterol FDC 2.5/5  $\mu$ g or 5/5  $\mu$ g, tiotropium 2.5  $\mu$ g or 5  $\mu$ g, or olodaterol 5  $\mu$ g delivered once-daily via Respimat inhaler over 52 weeks. The primary end points were the FEV<sub>1</sub> area under the curve from 0 to 3 hours (AUC<sub>0-3</sub>) response, trough FEV<sub>1</sub> response and SGRQ total score at 24 weeks.

Both tiotropium+olodaterol fixed dose combinations significantly improved FEV<sub>1</sub> AUC<sub>0-3</sub> and trough FEV<sub>1</sub> response versus the mono-components in the two replicate studies. FEV<sub>1</sub> AUC<sub>0-3</sub> responses for tiotropium+olodaterol FDC 2.5/5  $\mu$ g, 5/5  $\mu$ g, tiotropium 2.5  $\mu$ g, 5  $\mu$ g, and olodaterol 5  $\mu$ g were 241, 256, 148, 139, and 133 mL, respectively, in one study, and 256, 268, 125, 165, and 136 mL, respectively, in the other study. Improvements in the adjusted mean FEV<sub>1</sub> AUC<sub>0-3</sub> with tiotropium+olodaterol FDC 5/5  $\mu$ g and 2.5/5  $\mu$ g over the corresponding individual components in the individual studies and the combined analysis were statistically significant ( $p < 0.0001$  for all comparisons)<sup>38</sup>.

After 24 weeks, the pre-specified analysis of the adjusted mean SGRQ total score showed statistically significant improvements for tiotropium+olodaterol FDC 5/5  $\mu$ g over corresponding individual components (vs. olodaterol 5  $\mu$ g: -1.693 [0.553],  $p < 0.01$ ; vs. tiotropium 5  $\mu$ g: -1.233 [0.551],  $p < 0.05$ ) but not for tiotropium+olodaterol FDC 2.5/5  $\mu$ g versus the individual components. An analysis of responder rates examining the proportion of patients who achieved a decrease in SGRQ total score by at least the minimum clinically important difference of 4.0 units was also performed. Over half of patients treated with the FDCs responded: the responder rates were 57.5% for tiotropium+olodaterol 5/5  $\mu$ g and 53.2% for 2.5/5. This compared to responder rates of 49.6%, 48.7%, and 44.8% for tiotropium 2.5  $\mu$ g, 5  $\mu$ g, and olodaterol 5  $\mu$ g, respectively. The increases in the responder rates for tiotropium+olodaterol

FDC 5/5 µg over its individual components was statistically significant<sup>38</sup>.

There was also a statistically significant improvement in the key secondary end point of the Mahler TDI focal score at 24 weeks in the combined data set for both tiotropium+olodaterol FDCs versus their mono-components (nominal  $p < 0.05$ ). Fifty-four point nine percentage of patients treated with tiotropium+olodaterol FDC 5/5 µg achieved the minimal clinically important difference of 1 unit improvement in the TDI compared to 50.6% with 5 µg tiotropium and 48.2% with 5 µg olodaterol.

With both tiotropium+olodaterol FDC 5/5 µg and 2.5/5 µg there was a reduction in adjusted weekly mean daily (24-hour) rescue medication use compared to the monotherapy components throughout the 52-week treatment period. Such reductions in rescue medication are important indicators of whether patients notice a benefit from their maintenance therapy<sup>39</sup>.

The TONADO studies were not designed to examine the effects of tiotropium+olodaterol FDC on exacerbation rates but data on exacerbations were collected and there was a trend for improvement in exacerbations with the FDCs versus the monotherapy components. The incidence of adverse events was comparable between the FDCs and the mono-components.

*Post-hoc* analysis of the TONADO studies showed tiotropium+olodaterol FDC improved lung function over the mono-components in patients with GOLD 2 and 3–4 disease, irrespective of prior LAMA or LABA maintenance therapy and most comparisons between the FDCs and their respective mono-components were statistically significant ( $p < 0.05$ )<sup>40</sup>. There was also no difference in the relative responses to tiotropium+olodaterol 5/5 µg compared to the mono-therapies in different age groups<sup>41</sup>.

Adverse event incidence was generally balanced across all treatment groups, with the majority being mild to moderate in severity and the incidence of adverse events was comparable between the FDCs and the mono-components.

Because the TONADO studies ran for 52 weeks, it was considered unethical to include a placebo group, but it is important to be able to assess the effects of mono-therapy and the FDCs on patient reported outcomes (PRO) compared to placebo and the OTEMTO studies were designed to do this. These again comprised two randomized, double-blind, parallel-group, multicentre trials which compared the efficacy and safety of tiotropium+olodaterol FDC administered via the Respimat device compared with the mono-components and placebo over 12 weeks in patients with moderate to severe COPD<sup>42</sup>. The three primary end points, measured at 12 weeks, were SGRQ total score, and FEV<sub>1</sub> AUC<sub>0–3</sub> and trough FEV<sub>1</sub> changes from baseline.

In OTEMTO 1 and 2, after 12 weeks tiotropium+olodaterol 5/5 µg significantly improved FEV<sub>1</sub> AUC<sub>0–3</sub> response com-

pared to placebo by 0.331 L and 0.299 L, respectively and improved trough FEV<sub>1</sub> response by 0.162 L and 0.166 L compared to placebo ( $p < 0.0001$ ).

Tiotropium+olodaterol 5/5 µg improved SGRQ total score at 12 weeks by 4.89 units and 4.56 units versus placebo ( $p < 0.0001$ ) in OTEMTO 1 and 2, respectively and the improvement compared to tiotropium 5 µg was 2.49 units ( $p = 0.0136$ ) and 1.72 units ( $p = 0.0780$ ), respectively<sup>42</sup>. After 12 weeks of treatment 52% of patients receiving tiotropium+olodaterol 5/5 µg were classed as SGRQ responders compared to 41% receiving tiotropium 5 µg ( $p < 0.01$ ) and 32% in the placebo group ( $p < 0.0001$ )<sup>43</sup>.

Changes in TDI were assessed as a secondary endpoint. Tiotropium+olodaterol 5/5 µg improved TDI score at 12 weeks by 2.05 units and 1.20 units versus placebo ( $p < 0.0001$ ) in OTEMTO 1 and 2. At week 12, 54% of patients receiving tiotropium+olodaterol 5/5 µg were classed as TDI responders compared to 41% receiving tiotropium ( $p < 0.001$ ) and 26% of patients receiving placebo ( $p < 0.0001$ )<sup>43</sup>.

*Post-hoc* analysis of the OTEMTO studies showed tiotropium+olodaterol fixed dose combination improved lung function, SGRQ and TDI compared to tiotropium and placebo in patients with GOLD 2 and 3–4 disease<sup>44</sup>. There was also no difference in the relative responses to tiotropium+olodaterol 5/5 µg compared to tiotropium and placebo in different age groups<sup>41</sup>. When analysed by baseline breathlessness assessed using the mMRC, the difference between SGRQ scores achieved by tiotropium+olodaterol 5/5 µg compared to tiotropium 5 µg was greatest in patients with an mMRC of 2 or more compared to those with an mMRC less than 2<sup>45</sup>. This shows that the greatest benefit of combination bronchodilator therapy is seen in the more symptomatic patients where it is most needed.

Multiple studies have assessed whether other LABA/LAMA combinations result in similar improvements in lung function, reductions in exacerbation rates, and achievement of minimal clinically important differences in TDI and SGRQ scores compared to monotherapy<sup>46</sup>.

Clinically, it is important to know if there is additional benefit of dual bronchodilator therapy in patients who have a good response to either LAMA or LABA monotherapy as well as those who do not. One study has examined the efficacy of dual bronchodilatation (umeclidinium+vilanterol 62.5/25 µg) in patients identified as responsive or non-responsive to mono-bronchodilatation (umeclidinium 62.5 µg, vilanterol 25 µg)<sup>47</sup>. Umeclidinium+vilanterol significantly increased lung function versus umeclidinium in umeclidinium-responders and versus vilanterol in vilanterol-responders. In umeclidinium and vilanterol non-responders, lung function was still significantly increased by dual therapy, but by a smaller amount.

The CRYSTAL study examined directly switching from various treatments to glycopyrronium (50 µg) or indacaterol+glycopyrronium (110/50 µg) in terms of lung function and

symptoms in symptomatic patients with moderate COPD<sup>48</sup>. This was a prospective, multicentre, 12-week, randomized, pragmatic, open-label trial designed to mimic clinical practice. Indacaterol+glycopyrronium significantly improved lung function and dyspnea after direct switch from LAMA or LABA.

The effects of dual bronchodilator therapy on exercise capacity were examined in the TORRACTO study<sup>49</sup>. This was a randomized, double-blind, placebo-controlled study to determine the effect of 12-week treatment of inhaled tiotropium+olodaterol FDC at two different doses (2.5/5 µg and 5/5 µg) delivered by the Respimat inhaler on exercise endurance time during constant work rate cycle ergometry in 390 patients with COPD. The geometric mean endurance time during constant work rate cycle ergometry was 527.51 seconds with tiotropium+olodaterol 5/5 µg (14% increase vs. placebo,  $p=0.021$ ). Tiotropium+olodaterol 5/5 µg increased pre-exercise inspiratory capacity versus placebo at 12 weeks by 234 mL ( $p<0.0001$ ) and at week 12, the slope of the intensity of breathing discomfort (Borg scale) during exercise decreased with tiotropium+olodaterol 5/5 µg ( $p=0.060$ ).

Tiotropium monotherapy is effective at reducing the risk of exacerbations<sup>23</sup> and LABA/inhaled corticosteroid (ICS) was not more effective than tiotropium at preventing exacerbations in the INSPIRE study<sup>50</sup>. Recently, the FLAME study showed that dual bronchodilator therapy with indacaterol+glycopyrronium was more effective than LABA/ICS at reducing exacerbation rates<sup>51</sup>. Currently, there are no data comparing tiotropium+olodaterol with tiotropium from studies with exacerbation rates as the primary outcome. The DYNAGITO study (registered as NCT02296138 at ClinicalTrials.gov) comparing the annualized rate of moderate-to-severe COPD exacerbations over 1 year in patients treated with tiotropium+olodaterol 5/5 µg or tiotropium 5 µg will provide these data. The study is still on going, but results are expected in late 2017 or early 2018.

## Conclusion

The GOLD report emphasises the fact that bronchodilators are central to the management of COPD<sup>1</sup>; however, many patients remain symptomatic despite mono-therapy with a LABA or LAMA. Dual bronchodilator therapy improves lung function and PRO compared to the mono-components, and reduces exacerbation rates compared to LABA/ICS.

Once-daily dosing of COPD therapy translates into significantly higher adherence than other dosing frequencies, thereby leading to reductions in healthcare resource utilization and cost<sup>52</sup>.

On the basis of the evidence for the effectiveness of dual bronchodilator therapy, the 2017 GOLD report recommends escalating to dual bronchodilator therapy in patients in group B (higher symptoms but low risk of exacerbations) if they have

persistent breathlessness on monotherapy. It also states that for patients with severe breathlessness initial therapy with two bronchodilators may be considered.

The GOLD report also recommends that patients in group C (low symptoms but high risk of exacerbations) with persistent exacerbations despite treatment with a LAMA may benefit from escalation to dual bronchodilator therapy. For patients in group D (high symptoms and high risk of exacerbations) the GOLD report recommends starting treatment with dual bronchodilators.

## Conflicts of Interest

Professor Halpin has received sponsorship to attend international meetings, and honoraria for lecturing, attending advisory boards and preparing educational materials from Astra-Zeneca, Boehringer Ingelheim, Chiesi, GSK, Novartis, Pfizer & Sandoz. He is a member of the GOLD Board of Directors and the GOLD Science Committee.

## References

1. Vogelmeier CF, Criner GJ, Martinez FJ, Anzueto A, Barnes PJ, Bourbeau J, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease 2017 report. GOLD Executive Summary. *Am J Respir Crit Care Med* 2017;195:557-82.
2. Calverley PM, Burge PS, Spencer S, Anderson JA, Jones PW. Bronchodilator reversibility testing in chronic obstructive pulmonary disease. *Thorax* 2003;58:659-64.
3. Tashkin DP, Celli B, Senn S, Burkhart D, Kesten S, Menjoge S, et al. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. *N Engl J Med* 2008;359:1543-54.
4. Pisi R, Aiello M, Zanini A, Tzani P, Paleari D, Marangio E, et al. Small airway dysfunction and flow and volume bronchodilator responsiveness in patients with chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis* 2015;10:1191-7.
5. Walker PP, Calverley PM. The volumetric response to bronchodilators in stable chronic obstructive pulmonary disease. *COPD* 2008;5:147-52.
6. Calverley PM. AJRCCM: 100-year anniversary. Physiology and chronic obstructive pulmonary disease in the blue journals. *Am J Respir Crit Care Med* 2017;195:1088-90.
7. O'Donnell DE, Revill SM, Webb KA. Dynamic hyperinflation and exercise intolerance in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001;164:770-7.
8. Jones PW, Donohue JE, Nedelman J, Pascoe S, Pinault G, Lassen C. Correlating changes in lung function with patient outcomes in chronic obstructive pulmonary disease: a pooled analysis. *Respir Res* 2011;12:161.

9. Donohue JF, Jones P, Bartels C, Marvel J, D'Andrea P, Banerji D, et al. Relationship between change in trough FEV1 and COPD patient outcomes: pooled analysis of 23 clinical trials in patients with COPD. *Eur Respir J* 2015;46(Suppl 59):PA1013.
10. Ram FS, Sestini P. Regular inhaled short acting  $\beta_2$  agonists for the management of stable chronic obstructive pulmonary disease: Cochrane systematic review and meta-analysis. *Thorax* 2003;58:580-4.
11. Gross N, Tashkin D, Miller R, Oren J, Coleman W, Linberg S. Inhalation by nebulization of albuterol-ipratropium combination (Dey combination) is superior to either agent alone in the treatment of chronic obstructive pulmonary disease. Dey Combination Solution Study Group. *Respiration* 1998;65:354-62.
12. 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* 1994;105:1411-9.
13. Donohue JF, van Noord JA, Bateman ED, Langley SJ, Lee A, Wittek TJ Jr, et al. A 6-month, placebo-controlled study comparing lung function and health status changes in COPD patients treated with tiotropium or salmeterol. *Chest* 2002;122:47-55.
14. D'Urzo A, Ferguson GT, van Noord JA, Hirata K, Martin C, Horton R, et al. Efficacy and safety of once-daily NVA237 in patients with moderate-to-severe COPD: the GLOW1 trial. *Respir Res* 2011;12:156.
15. Calverley PM, Anderson JA, Celli B, Ferguson GT, Jenkins C, Jones PW, et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Engl J Med* 2007;356:775-89.
16. Rossi A, Kristufek P, Levine BE, Thomson MH, Till D, Kottakis J, et al. Comparison of the efficacy, tolerability, and safety of formoterol dry powder and oral, slow-release theophylline in the treatment of COPD. *Chest* 2002;121:1058-69.
17. Chapman KR, Rennard SI, Dogra A, Owen R, Lassen C, Kramer B, et al. Long-term safety and efficacy of indacaterol, a long-acting  $\beta_2$ -agonist, in subjects with COPD: a randomized, placebo-controlled study. *Chest* 2011;140:68-75.
18. Kerwin EM, D'Urzo AD, Gelb AF, Lakkis H, Garcia Gil E, Caracta CF, et al. Efficacy and safety of a 12-week treatment with twice-daily aclidinium bromide in COPD patients (ACCORD COPD I). *COPD* 2012;9:90-101.
19. Beeh KM, Singh D, Di Scala L, Drollmann A. Once-daily NVA237 improves exercise tolerance from the first dose in patients with COPD: the GLOW3 trial. *Int J Chron Obstruct Pulmon Dis* 2012;7:503-13.
20. Maltais F, Celli B, Casaburi R, Porszasz J, Jarreta D, Seoane B, et al. Aclidinium bromide improves exercise endurance and lung hyperinflation in patients with moderate to severe COPD. *Respir Med* 2011;105:580-7.
21. O'Donnell DE, Fluge T, Gerken F, Hamilton A, Webb K, Aguilaniu B, et al. Effects of tiotropium on lung hyperinflation, dyspnoea and exercise tolerance in COPD. *Eur Respir J* 2004;23:832-40.
22. O'Donnell DE, Casaburi R, Vincken W, Puente-Maestu L, Swales J, Lawrence D, et al. Effect of indacaterol on exercise endurance and lung hyperinflation in COPD. *Respir Med* 2011;105:1030-6.
23. Halpin DM, Vogelmeier C, Pieper MP, Metzendorf N, Richard F, Anzueto A. Effect of tiotropium on COPD exacerbations: a systematic review. *Respir Med* 2016;114:1-8.
24. Busch-Petersen J, Laine DI. Inhaled long-acting muscarinic antagonists in chronic obstructive pulmonary disease. *Future Med Chem* 2011;3:1623-34.
25. Keating GM. Tiotropium bromide inhalation powder: a review of its use in the management of chronic obstructive pulmonary disease. *Drugs* 2012;72:273-300.
26. Bouyssou T, Casarosa P, Naline E, Pestel S, Konetzki I, Devillier P, et al. Pharmacological characterization of olodaterol, a novel inhaled  $\beta_2$ -adrenoceptor agonist exerting a 24-hour-long duration of action in preclinical models. *J Pharmacol Exp Ther* 2010;334:53-62.
27. Ferguson GT, Feldman GJ, Hofbauer P, Hamilton A, Allen L, Korducki L, et al. Efficacy and safety of olodaterol once daily delivered via Respimat(R) in patients with GOLD 2-4 COPD: results from two replicate 48-week studies. *Int J Chron Obstruct Pulmon Dis* 2014;9:629-45.
28. Koch A, Pizzichini E, Hamilton A, Hart L, Korducki L, De Salvo MC, et al. Lung function efficacy and symptomatic benefit of olodaterol once daily delivered via Respimat(R) versus placebo and formoterol twice daily in patients with GOLD 2-4 COPD: results from two replicate 48-week studies. *Int J Chron Obstruct Pulmon Dis* 2014;9:697-714.
29. Dransfield MT, Bailey W, Crater G, Emmett A, O'Dell DM, Yawn B. Disease severity and symptoms among patients receiving monotherapy for COPD. *Prim Care Respir J* 2011;20:46-53.
30. Singh D. New combination bronchodilators for chronic obstructive pulmonary disease: current evidence and future perspectives. *Br J Clin Pharmacol* 2015;79:695-708.
31. Tashkin DP, Ferguson GT. Combination bronchodilator therapy in the management of chronic obstructive pulmonary disease. *Respir Res* 2013;14:49.
32. Cohen JS, Miles MC, Donohue JF, Ohar JA. Dual therapy strategies for COPD: the scientific rationale for LAMA + LABA. *Int J Chron Obstruct Pulmon Dis* 2016;11:785-97.
33. Aalbers R, Maleki-Yazdi MR, Hamilton A, Waitere-Wijker S, Zhao Y, Amatto VC, et al. Randomized, double-blind, dose-finding study for tiotropium when added to olodaterol, administered via the Respimat(R) inhaler in patients with chronic obstructive pulmonary disease. *Adv Ther* 2015;32:809-22.
34. ZuWallack R, Allen L, Hernandez G, Ting N, Abrahams R. Efficacy and safety of combining olodaterol Respimat((R)) and tiotropium HandiHaler((R)) in patients with COPD: results of two randomized, double-blind, active-controlled studies. *Int J Chron Obstruct Pulmon Dis* 2014;9:1133-44.

35. Keating GM. Tiotropium Respimat((R)) Soft Mist inhaler: a review of its use in chronic obstructive pulmonary disease. *Drugs* 2014;74:1801-16.
36. Brand P, Hederer B, Austen G, Dewberry H, Meyer T. Higher lung deposition with Respimat Soft Mist inhaler than HFA-MDI in COPD patients with poor technique. *Int J Chron Obstruct Pulmon Dis* 2008;3:763-70.
37. Spiolto Respimat in COPD [Internet]. Ingelheim am Rhein: Boehringer Ingelheim; 2017 [cited 2017 Jul 1]. Available from: <http://www.boehringer-ingelheim.com/copd/copd/information-tovito-clinical-trial-program>.
38. Buhl R, Maltais F, Abrahams R, Bjermer L, Derom E, Ferguson G, et al. Tiotropium and olodaterol fixed-dose combination versus mono-components in COPD (GOLD 2-4). *Eur Respir J* 2015;45:969-79.
39. Punekar YS, Sharma S, Pahwa A, Takyar J, Naya I, Jones PW. Rescue medication use as a patient-reported outcome in COPD: a systematic review and regression analysis. *Respir Res* 2017;18:86.
40. Ferguson GT, Flezar M, Korn S, Korducki L, Gronke L, Abrahams R, et al. Efficacy of tiotropium + olodaterol in patients with chronic obstructive pulmonary disease by initial disease severity and treatment intensity: a post hoc analysis. *Adv Ther* 2015;32:523-36.
41. Ferguson GT, Karpel JP, Clerisme-Beaty E, Gronke L, Voss F, Buhl R. Efficacy and safety of tiotropium + olodaterol maintenance treatment in patients with COPD in the TONADO(R) and OTEMTO(R) studies: a subgroup analysis by age. *Int J Chron Obstruct Pulmon Dis* 2016;11:2701-10.
42. Singh D, Ferguson GT, Bolitschek J, Gronke L, Hallmann C, Bennett N, et al. Tiotropium + olodaterol shows clinically meaningful improvements in quality of life. *Respir Med* 2015; 109:1312-9.
43. Ferguson GT, Karpel J, Bennett N, Clerisme-Beaty E, Gronke L, Voss F, et al. Effect of tiotropium and olodaterol on symptoms and patient-reported outcomes in patients with COPD: results from four randomised, double-blind studies. *NPJ Prim Care Respir Med* 2017;27:7.
44. Singh D, Gaga M, Schmidt O, Bjermer L, Gronke L, Voss F, et al. Effects of tiotropium + olodaterol versus tiotropium or placebo by COPD disease severity and previous treatment history in the OTEMTO(R) studies. *Respir Res* 2016;17:73.
45. Martinez FJ, Abrahams R, Ferguson GT, Bjermer L, Gronke L, Vob F, et al. Effects of symptom severity at baseline on lung-function and SGRQ responses in the OTEMTO studies. *Am J Respir Crit Care Med* 2016;193:A6787.
46. Thomas M, Halpin DM, Miravittles M. When is dual bronchodilation indicated in COPD? *Int J Chron Obstruct Pulmon Dis* 2017;12:2291-305.
47. Donohue JF, Singh D, Munzu C, Kilbride S, Church A. Magnitude of umeclidinium/vilanterol lung function effect depends on monotherapy responses: results from two randomised controlled trials. *Respir Med* 2016;112:65-74.
48. Vogelmeier CF, Gaga M, Aalamian-Mattheis M, Greulich T, Marin JM, Castellani W, et al. Efficacy and safety of direct switch to indacaterol/glycopyrronium in patients with moderate COPD: the CRYSTAL open-label randomised trial. *Respir Res* 2017;18:140.
49. Maltais F, Galdiz Iturri JB, Kirsten A, Singh D, Hamilton A, Tetzlaff K, et al. Effects of 12 weeks of once-daily tiotropium and olodaterol fixed-dose combination on exercise endurance in patients with COPD. *Thorax* 2014;69(Suppl 2):A186-7.
50. Wedzicha JA, Calverley PM, Seemungal TA, Hagan G, Ansari Z, Stockley RA, et al. The prevention of chronic obstructive pulmonary disease exacerbations by salmeterol/fluticasone propionate or tiotropium bromide. *Am J Respir Crit Care Med* 2008;177:19-26.
51. Wedzicha JA, Banerji D, Chapman KR, Vestbo J, Roche N, Ayers RT, et al. Indacaterol-glycopyrronium versus salmeterol-fluticasone for COPD. *N Engl J Med* 2016;374:2222-34.
52. Toy EL, Beaulieu NU, McHale JM, Welland TR, Plauschinat CA, Swensen A, et al. Treatment of COPD: relationships between daily dosing frequency, adherence, resource use, and costs. *Respir Med* 2011;105:435-41.