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Chronic Obstructive Pulmonary Disease (COPD)

Month/Year of Review: July 2013 **Date of Last Review: February 2012**

PDL Classes: Beta$_2$ Agonists, Inhaled Corticosteroids, Anticholinergics **Source Document: OSU College of Pharmacy**

Current Status of PDL Class:

- **Preferred Agents:** IPRATROPIUM BROMIDE HFA AER AD, IPRATROPIUM BROMIDE SOLUTION, IPRATROPIUM/ALBUTEROL SULFATE AMPUL-NEB, TIOTROPIUM BROMIDE(SPIRIVA®) CAP W/DEV, BECLOMETHASONE DIPROPIONATE(QVAR®) AER W/ADAP, CICLESONIDE (ALVESCO®) HFA AER AD, FLUTICASONE PROPIONATE(FLOVENT DISKUS®) DISK W/DEV, FLUTICASONE PROPIONATE(FLOVENT HFA®) AER W/ADAP, FLUTICASONE/SALMETEROL (ADVAIR DISKUS®) DISK W/DEV, FLUTICASONE/SALMETEROL (ADVAIR HFA®) HFA AER AD, FORMOTEROL FUMARATE (FORADIL®) CAP W/DEV, SALMETEROL (SEREVENT®) DISKUS
- **Non-Preferred Agents:** BUDESONIDE, BUDESONIDE/FORMOTEROL, BUDESONIDE (PULMICORT®), BUDESONIDE (PULMICORT®) FLEXHALER, MOMETASONE (ASMANEX®) TWISTHALER, MOMETASONE/FORMOTEROL (DULERA®), OMALIZUMAB (XOLAIR®), AFORMOTEROL (BROVANA®), FORMOTEROL (PERFOROMIST), IPRATROPIUM/ALBUTEROL (COMBIVENT®) RESPIMAT, ROFLUMILAST (DALIRESP®), INDACATEROL (ARCAPTA®) NEOHALER, ACLIDINIUM (TUDORZA®) PRESSAIR

Current PA Criteria: Prior Authorization (PA) criteria is in place for long-acting beta(2)-agonists (LABAs) and inhaled corticosteroid (ICS) inhalers (Appendix 1) to ensure that they are being prescribed for appropriate diagnoses and therapy. Combination Short Acting Bronchodilator Inhalers (Appendix 2) require step therapy with a short acting beta agonist (SABA) or an inhaled short acting anticholinergic agent ensure appropriate drug use. Roflumilast (Appendix 3) requires a PA to ensure appropriate therapy for patients with severe Chronic Obstructive Pulmonary Disease (COPD) with a history of chronic exacerbations or prior exacerbations while being treated with a long-acting bronchodilator.

Research Questions:

- Is there new comparative evidence that there is a meaningful difference in LABAs, long-acting antimuscarinic agents (LAMAs), and ICSs or combinations thereof in long term clinical outcomes or safety that could justify changes in current PDL management?
- Is there any new relevant evidence to change current policy?

Recommendations:

- Recommend evaluating comparative costs in executive session.
- Bring back more detailed drug review of fluticasone furoate/vilanterol inhalation powder (Breo Ellipta®) at upcoming meeting.
- Make both Combivent Respimat and Combivent MDI preferred and abandon previous step therapy recommendations.

Previous Conclusions and Recommendations:

- There is insufficient comparative effectiveness evidence between inhaled corticosteroids and inhaled anticholinergics.
- There is no evidence demonstrating clinical superiority of aclidinium bromide over tiotropium, recommend making it non-preferred.
- There is moderate quality evidence that ipratropium bromide/albuterol Respimat inhaler is non-inferior to ipratropium bromide/albuterol MDI on lung function in the treatment of moderate to severe COPD.
- Make Combivent Respimat and Combivent MDI non-preferred and require a step through therapy with either component (short acting beta agonist OR a short acting anticholinergic). Grandfather current utilizers.

- Due to limited long term effectiveness or safety evidence compared to multiple alternatives, recommend making indacaterol a nonpreferred LABA.
- Recommend maintaining roflumilast as a non-preferred agent and include clinical PA criteria necessary for approval to ensure it is only used in the appropriate patient population:
    - Patient has severe or very severe COPD with chronic bronchitis and frequent exacerbation
    - Patient has documented failure with an ICS or ICS combination product or tiotropium
    - Patient is on a concurrent long acting controller medication (LABA or LAMA) as monotherapy or in combination with other therapies.

Methods:

A Medline literature search ending July 2013 for new systematic reviews and randomized controlled trials (RCT's) comparing ipratropium, tiotropium, beclomethasone, ciclesonide, fluticasone, salmeterol, formoterol,budesonide, mometasone, aformoterol, roflumilast, indacaterol, and aclidinium . The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, Clinical Evidence, Up To Date, Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts, and the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. The primary focus of the evidence is on high quality systematic reviews and evidence based guidelines for this class update. Randomized controlled trials (RCTs) will be emphasized if evidence is lacking or insufficient from those preferred sources. After review of the citations from Medline and the manual searches, seven systematic reviews, one guideline update and three head to head RCTs were identified.

Systematic reviews:

A new Cochrane Collaboration systematic review by Chong et al[1] evaluated the use of tiotropium versus LABAs. This review included seven randomized trials with 12,223 participants. All studies were of good methodological quality. However, there was a high amount of heterogenicity among the trials. The primary objective was to compare the relative clinical effects of tiotropium alone versus a LABA alone in quality of life, exacerbations, lung function and serious adverse events in people with chronic stable COPD. Tiotropium reduced the number of participants experiencing one or more exacerbations compared to the LABA (OR 0.86, 95% Confidence Interval (CI) 0.79 to 0.93). There was no difference seen among the different LABAs. Tiotropium was associated with a reduction in the number of COPD exacerbations leading to hospitalization compared to LABA treatment (OR 0.87; 95% CI 0.77 to 0.99), but the difference in overall hospitalizations or mortality. Symptom improvement and changes in lung function were similar between the two groups. There is not enough data to demonstrate clinical superiority of either tiotropium or LABAs.

Cope at al[2] evaluated the use of indacaterol 75 µg versus fixed-dose combinations of an ICS and LABA for the treatment of COPD. Fifteen randomized, placebo-controlled trials including COPD patients were evaluated. All trials were analyzed simultaneously using a Bayesian network meta-analysis and relative treatment effects between all regimens were obtained. Outcomes of interest were trough FEV_1 and transitional dyspnea index at 12 weeks. Indacaterol resulted in greater improvement in FEV_1 at 12 weels compared with budesonide/formoterol 160/9 ug (change from baseline 0.09L; 95% CI 0.04 to 0.13), budesonide/formoterol 320/9 ug (change from baseline 0.07L; 95% CI 0.03 to 0.11), fluticasone/salmeterol 250/50 ug (change from baseline 0.00L; 95% CI -0.07 to 0.07), and fluticasone/salmeterol 500/50 ug (change from baseline 0.01L; 95% CI -0.04 to 0.05). Based on the results of a network meta-analysis with and without covariates, indacaterol 75 µg is expected to be at least as efficacious to budesonide/formoterol and comparable to fluticasone/salmeterol with respect to lung function, but the results of effects on dypsnea are inconclusive with available data.

Dong et al[3] evaluated the overall safety and cardiovascular death for inhaled medications in patients with COPD. Forty-two trials with 52,516 subjects were included. A mixed-treatment comparison meta-analysis with a fixed effect model

indicated tiotropium Soft Mist Inhaler was associated with a universally increased risk of overall death compared with placebo (OR 1.51; 95% CI 1.06 to 2.19), tiotropium HandiHaler (OR 1.65; 95% CI 1.13 to 2.43), LABA (OR 1.63; 95% CI 1.10 to 2.44) and LABA-ICS (OR 1.90; 95% CI 1.28 to 2.86). The risk was more evident for cardiovascular death, in patients with severe COPD, and at higher daily doses. LABA-ICS was associated with the lowest risk of death among all treatments. No excess risk was noted for tiotropium Handihaler or LABA.

Karner et al[4] evaluated the use of LABA and tiotropium versus either tiotropium or a LABA for the Cochrane Collaboration. Five trials were included in this review, mostly recruiting participants with moderate or severe COPD. All of them compared tiotropium in addition to LABAto tiotropium alone, but only one trial additionally compared a combination of the two types of bronchodilator with LABA(formoterol) alone. Two studies (moderate quality evidence) used the LABA indacaterol, two used formoterol and one used salmeterol. Compared to tiotropium alone (3263 patients), treatment with tiotropium plus LABA resulted in a slightly larger improvement in the mean health-related quality of life (St George's Respiratory Questionnaire (SGRQ) MD -1.61; 95% CI -2.93 to -0.29). In the control arm, tiotropium alone, the SGRQ improved by falling 4.5 units from baseline and with both treatments the improvement was a fall of 6.1 units from baseline (on average). There were no significant differences in the other primary outcomes (hospital admission or mortality).The secondary outcome of pre-bronchodilator FEV(1) showed a small mean increase with the addition of LABA (MD 0.07 L; 95% CI 0.05 to 0.09) over the control arm, which showed a change from baseline ranging from 0.03 L to 0.13 L on tiotropium alone. None of the other secondary outcomes (exacerbations, symptom scores, serious adverse events, and withdrawals) showed any statistically significant differences between the groups. The results from this review indicate a small mean improvement in health-related quality of life for patients on a combination of tiotropium and LABA compared to tiotropium alone, but it is not clear how clinically important this mean difference may be.

Nannini et al[5] evaluated the efficacy of ICS and LABA in a single inhaler with mono-component LABA alone for the Cochrane Collaborative. Fourteen studies were included, randomizing 11,794 people with COPD. Ten studies assessed fluticasone plus salmeterol and four assessed budesonide plus formoterol. All studies were well designed with a low risk for bias for randomization and blinding, but had high rates of attrition. There was low quality evidence that exacerbation rates in people using LABA/ICS inhalers were lower in comparison to those with LABA alone, from nine studies which randomized 9921 participants (rate ratio 0.76; 95% CI 0.68 to 0.84). This corresponds to one exacerbation per person per year on LABA and 0.76 exacerbations per person per year on ICS/LABA. When analyzed as the number of people experiencing one or more exacerbations over the course of the study, FPS lowered the odds of an exacerbation with an odds ratio (OR) of 0.83 (95% CI 0.70 to 0.98, 6 studies, 3357 participants). With a risk of an exacerbation of 47% in the LABA group over one year, 42% of people treated with LABA/ICS would be expected to experience an exacerbation. There was no significant difference in the rate of hospitalizations (rate ratio 0.79; 95% CI 0.55 to 1.13, very low quality evidence). There was no significant difference in mortality between people on combined inhalers and those on LABA, from 10 studies on 10,680 participants (OR 0.92; 95% CI 0.76 to 1.11, moderate quality evidence). Pneumonia occurred more commonly in people randomized to combined inhalers, from 12 studies with 11,076 participants (OR 1.55; 95% CI 1.20 to 2.01, moderate quality evidence) with an annual risk of around 3% on LABA alone compared to 4% on combination treatment. There were no significant differences between the results for either exacerbations or pneumonia from trials adding different doses or types of inhaled corticosteroid. Data were inconclusive as to the superiority of ICS/LABA over LABA alone in preventing COPD exacerbations. There was moderate quality evidence that combination therapy increased risk of pneumonia.

Rodrigo et al[6] explored the efficacy and safety of indacaterol in comparison with tiotropium or twice-daily dosed LABAs for the treatment of moderate to severe COPD. Five trials were included. Compared with tiotropium, indacaterol showed statistically and clinically significant reductions in the use of rescue medication and dyspnea(43% greater likelihood of achieving a minimal clinically important difference [MCID] in the transitional dyspnea index [TDI]; number needed to treat (NNT) = 10). Additionally, the MCID in health status was more likely to be achieved with indacaterol than with tiotropium (OR = 1.43; 95% CI, 1.22–1.68; P = .00001; NNT = 10). Trough FEV1 was statistically significantly higher at the end of treatment with indacaterol than with TD-LABAs (80 mL, p = .00001). Similarly, indacaterol significantly

improved dyspnea (61% greater likelihood of achieving an MCID in TDI, p = .008) and health status (21% greater likelihood of achieving an MCID in St. George's Respiratory Questionnaire, p = .04) than TD-LABA. Indacaterol showed similar levels of safety and tolerability to both comparators. There was moderate quality evidence showing indacaterol may be a useful alternative to tiotropium or twice-daily dosed LABAs.

Rodrigo et al[7] evaluated the use of tiotropium plus a LABA ("dual" therapy), LABA/ICS ("combined" therapy), tiotropium plus a LABA/ICS ("triple" therapy), and tiotropium monotherapy in the maintenance treatment of moderate to severe COPD. Twenty trials (6803 participants) were included. "Dual" therapy showed significant improvements in FEV1, health-related quality of life (HRQoL), and dyspnea. However, it failed to reduce the risk of COPD exacerbations. Compared with tiotropium, "combined" therapy presented modest but significant effects on FEV1, HRQoL, and dyspnea. Again, there was no significant difference in exacerbations, but it was associated with a significant increase of serious adverse effects (SAE) (number need to harm = 20; 95% CI: 11-119). Finally, "triple therapy" increased FEV1, improved HRQoL (both benefits exceeded minimal important differences) and decrease COPD exacerbations in anon-significant way. (Odds ratio [OR] = 0.57; 95% CI: 0.24 to 1.37, p = 0.21). While treatments with tiotropium plus a LABA and tiotropium plus a LABA/ICS look promising, there is no data to support a recommendation of either therapy over the other. More studies are needed to examine long-term safety and efficacy of these combinations.

New drugs:

FDA approved the combination of fluticasone furoate and vilanterol inhalation powder (Breo Ellipta®)[8] in May 2013 for the long-term, once-daily, maintenance treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema. It is also approved to reduce exacerbations of COPD in patients with a history of exacerbations. Approval was based on two pivotal trials studying Breo Ellipta to fluticasone alone, vilanterol alone, or placebo. The primary efficacy variable was mean change from baseline in weighted mean FEV1 0-4 hour on day 168. Breo 100/25 (difference from placebo 0.17; 95% CI 0.12 to 0.22; p <0.001) was statistically significant from placebo, as was fluticasone 100mg alone (difference from placebo 0.05; 95% CI 0.00 to 0.10; p=0.04) and vilanterol alone (difference from placebo 0.10; 95% CI 0.05 to 0.15; p <0.001).There was not an active comparator.

FDA approved aclidinium bromide (Tudorza Pressair®)[9] in July 2012 (P&T reviewed this drug in January 2013). It is currently non-preferred due to a lack of evidence demonstrating clinical superiority of aclidinium bromide over tiotropium.

New Formulations

Ipratropium/albuterol (Combivent®) Respimat[10] inhalation spray was approved in October 2011 (P&T reviewed this drug in January 2013). Generic Combivent Inhalation Aerosol (ipratropium/albuterol sulfate) is currently a preferred inhaler on the preferred drug list. Evidence demonstrated that ipratropium/albuterol (Combivent®) Respimat inhaler is non-inferior to ipratropium bromide/albuterol (Combivent®) MDI on lung function as measured by FEV1 in the treatment of moderate to severe COPD. Ipratropium/albuterol Respimat is a new version of Combivent without chlorofluorcarbons and will be replacing the previous MDI inhaler. It will be the only product available as of January 1, 2014. Combivent Respimat and Combivent MDI are non-preferred and require a step through therapy with either component (short acting beta agonist or a short acting anticholinergic).

New FDA Safety Alerts:
None.

New Guidelines:

An update to the 2011 Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines was released in 2013.[11] This update redefines COPD as a mixture of airflow obstruction, alveolar destruction and chronic inflammation. Previous GOLD guidelines classified COPD severity by post-bronchodilator FEV1 alone. Grading was updated to include grades A-D based upon a combination of clinical symptoms, most notably dypsnea, FEV1 and number of yearly exacerbations. Drug therapy options for COPD were addressed. Indacaterol was included as a therapeutic option superior to salmeterol and formeterol, with similar efficacy to tiotropium (level A evidence). Roflumilast was included in the 2011 guidelines, but was again supported with level A evidence for its proven efficacy in reducing exacerbations in patients with severe COPD. Aclidinium was not added to the guidelines.

Randomized Controlled Trials

A total ofsix RCT's were identified in the literature search. Of these, there are three potentially relevant head to head clinical trials. Abstracts of these trials are located in Appendix 4.

Study	Comparison	Population	Primary Outcome	Results
Fuhr et al[12]	Aclidinium 400 ug BID with placebo and tiotropium (1:1:1)	Moderate to severe COPD N=30	Mean change from baseline in FEV1 AUC on day 15	Mean change from baseline in FEV1 at day 15 was significantly greater for aclidinium and tiotropium over placebo (p<0.0001)
Sharafkheneh et al[13]	BID budesonide/formoterol pMDI 320/9 ug, budesonide/formoterol pMDI 160/9 ug, or formoterol dry powder inhaler 9 ug (1:1:1)	COPD patients aged >= 40 years with an exacerbation history discontinued medications except ICSs N=1219	Exacerbation rates (number per patient-treatment year)	Budesonide/formoterol 320/9 ug and 160/9 ug reduced exacerbation rates by 34.6% and 25.9%, respectively, versus formoterol (p<= 0.002
Zhong et al[14]	Budesonide/formoterol 320/9 ug BID or budesonide 400 ug BID	Moderate to very severe COPD in Chinese population N=308	FEV1 change from baseline after 24 weeks	Budesonide/formoterol FEV1 improved by 0.18L vs 0.03L in budesonide alone group (p<0.001)

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Current PA (Appendix 1):

LABA/ICS Inhalers

Goal(s):

- *Approve LABA/ICS only for covered diagnosis (e.g. COPD or Asthma and on concurrent controller medication)*
- *LABA are only indicated for use in clients with Asthma already receiving treatment with an asthma controller medication (e.g. Inhaled corticosteroids or leukotriene receptor antagonists).*

Initiative: LABA/ICS Step Therapy

Length of Authorization: 6 months - 1 year

Covered alternatives that DO NOT require a PA:
See PDL list at http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml

Step Therapy Required prior to coverage:

Asthma: oral corticosteroid inhalers (see preferred drug list options at http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml),

COPD: short and long-acting beta-agonist inhalers, anticholinergics and inhaled corticosteroids (see preferred drug list options at http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml), DO NOT require prior authorization.

Requires PA: All combination inhaled corticosteroid/long-acting beta-agonist inhalers.

Approval Criteria		
1. Does patient have asthma or reactive airway disease (ICD-9: 493, 493.0-493.93)?	**Yes:** Go to **2**	**No:** Go to **3**
2. Has patient: • failed an inhaled corticosteroid or other controller medication OR • Had ≥2 exacerbations requiring oral systemic corticosteroids in the past year, OR • Is there documentation of step 3 asthma or higher OR • Is there a hospital admission or ER visit related to asthma or reactive airway disease within last 60 days?	**Yes**: Document the following: Date of trial, drug, reason(s) for failure or contraindications OR chart notes of asthma severity in the PA record Approve for 1 year if this is patient's first prescription for a combination inhaler or if this is a continuation of therapy and patient is well controlled on current dose.	**No**: **PASS TO RPH DENY (Medical Appropriateness).**
3. Does patient have COPD (ICD-9 496) or Chronic bronchitis (491.1-2.) and/or emphysema (492.xx)?	**Yes:** Go to **4**	**NO: PASS TO RPH DENY (Medical Appropriateness).** *Need a supporting diagnosis. If prescriber believes diagnosis appropriate inform them of the provider reconsideration process for Medical Director Review.*
4. Has patient failed a combination of **short acting** (ipratroprium or	**Yes:** Document the following: Date of trial, drug, reason(s) for failure or contraindications in the	(**No:** Pass to RPH; Deny, (Medical Appropriateness). *Gold*

ipratroprium/albuterol) **and long-acting** (salmeterol, formoterol and/or tioptropium) inhaled bronchodilators?	PA record**.** Approve for 1 year if this is patient's first prescription for a combination inhaler or if this is a continuation of therapy and patient is well controlled on current dose.	*guidelines recommend addition of inhaled corticosteroid if disease severity persistent despite use of combination of short acting and long-acting bronchodilators. http://www.goldcopd.org/uploads/users/files/GOLDReport_April112011.pdf*

Appendix 2:

Combination Short Acting Bronchodilator Inhalers

Goal(s):

- *Promote preferred drugs that are selected based on evidence based reviews.*
- *To ensure appropriate drug use .*

Initiative: Short Acting Bronchodilator Step Therapy

Length of Authorization: 1 year

Covered alternatives that DO NOT require a PA:
See PDL list at http://www.orpdl.org/

Step Therapy Required prior to coverage:

Requires PA: non-preferred combination short acting bronchodilators

Approval Criteria		
1. What diagnosis is being treated?	**Record ICD9 code**	
2. Does the patient have COPD (ICD-9 496)?	**Yes**: Go to #3	**No**: Pass to RPh; Deny (Medical Appropriateness).
3. Will the prescriber change to a preferred product?	**Yes:** Inform provider of covered alternatives in class	**NO:** Go to #4
4. Has patient failed an inhaled Short acting beta agonist (albuterol) OR An inhaled short acting anticholinergic agent (ipratropium)?	**Yes:** Approve for one year	**No:** Pass to RPh, Deny (medical appropriateness)

Appendix 3

Roflumilast

Goal(s):

- Decrease the number of COPD exacerbations in patients with severe COPD and chronic bronchitis and a history of prior exacerbations.

Length of Authorization: 1 year

Covered Alternatives: Listed at; http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml

Approval Criteria		
1. What is the diagnosis?	Record ICD-9 code	
2. Is the diagnosis an OHP covered diagnosis?	**Yes:** Go to #3.	**No:** Pass to RPh, Deny for OHP Coverage.
3. Does the patient have documented severe or very severe (Stage III or Stage IV) COPD?	**Yes:** Go to #4	**No:** Deny (medical inappropriateness)
4. Does the patient have a history of chronic bronchitis AND Prior COPD exacerbations?	**Yes:** Go to #5	**No:** Deny (medical inappropriateness)
5. Is the patient currently on a long-acting bronchodilator?	**Yes:** Go to #6	**No:** Deny. Recommend trial of preferred long-acting bronchodilators
6. Has the patient tried an inhaled corticosteroid (ICS), and ICS combination, or tiotropium (LAMA)?	**Yes:** Approve up to 1 year	**No:** Deny. Recommend trial of preferred long-acting ICS or LAMA

Appendix 4: RCT Abstracts

Furh, R., H. Magnussen, et al. (2012). "Efficacy of aclidinimium bromide 400 ug twice daily compared with placebo and tiotropium in patients with moderate to severe COPD." Chest **141**(3): 745-752.

BACKGROUND: The efficacy and safety of aclidinium bromide bid, a novel, long-acting, muscarinic antagonist, was assessed in patients with moderate to severe COPD.

METHODS: In this phase IIa randomized, double-blind, double-dummy, crossover trial, patients with moderate to severe COPD received aclidinium 400 ug bid, tiotropium 8 ug once daily, and placebo for 15 days, with a 9- to 15-day washout between treatment periods. Treatments were administered through the Genuair or HandiHaler dry powder inhalers. The primary end point was mean change from baseline in FEV(1) AUC(0-12 /12h)(area under the curve where the numbers represent the time period for which data were collected divided by the number of hours over which the data are averaged [eg, 0-12 h postdose divided by 12h]) on day 15. Secondary end points were changes from baseline in FEV(1) AUC(12-24/12h), FEV(1) AUC(0-24/24h), morning predose FEV(1), peak FEV(1), and COPD symptom scores.

RESULTS: Thirty patients with COPD were randomized, and 27 completed the study. Mean change from baseline in FEV(1) AUC(12-24/12h) at day 15 was significantly greater for aclidinium and tiotropium over placebo (P < .0001). Mean changes from baseline in FEV(1) AUC(12-24/12h), FEV(1) AUC(0-24/24h), morning predose FEV(1), and peak FEV(1) at day 15 were significantly greater for aclidinium and tiotropium over placebo (P < .0001 for all except P <.001 for FEV(1) AUC(12-24/12h) tiotropium vs placebo). Improvements were significantly greater with aclidinium vs tiotropium on day 1 for all of the normalized AUC values of FEV(1) as well as on day 15 for FEV(1) AUC(12-24/12h) (P < .05 for all). COPD symptoms were significantly improved from baseline with aclidinium vs placebo (P < .05) but not with tiotropium.

CONCLUSIONS: In patients with COPD, aclidinium 400 ug bid compared with placebo provided clinically meaningful improvements in 24-h bronchodilation that generally were comparable to tiotropium 18 ug daily but with significant differences in favor of aclidinium observed in the average nighttime period. Larger studies with longer treatment duration are ongoing to confirm the efficacy of aclidinium 400 ug bid on bronchodilation and COPD symptoms. Trial registry: ClinicalTrials.gov; No.: NCT00868231; URL: www.clinicaltrials.gov.

Sharafkhaneh, A., J. G. Southard, et al. (2012). "Effect of budesonide/formoterol pMDI on COPD exacerbations: a double-blind, randomized study." Respiratory Medicine **106**(2):257-268.

BACKGROUND: Treatment of an inhaled corticosteroid (ICS) and long-acting bronchodilator is recommended for severe/very severe chronic obstructive pulmonary disease (COPD) patients with repeated exacerbations This randomized, double-blind, double-dummy, parallel-group, 12-month multicenter study evaluated the effect of budesonide/formoterol pressurized metered-dose inhaler (pMDI) on COPD exacerbations.

METHODS: Following a 2-week run-in during which COPD patients aged >=40 years with an exacerbation history discontinued medications except ICSs, 1219 patients were randomized 1:1:1 to twice-daily budesonide/formoterol pMDI 320/9 ug, budesonide/formoterol 160/9 ug, or formoterol dry powder inhaler 9 ug. An exacerbation was defined as COPD worsening requiring oral corticosteroids and/or hospitalization. A post hoc analysis, with antibiotic treatment added to the exacerbation definition, was also performed.

RESULTS: Budesonide/formoterol 320/9 and 160/9 rediced exacerbation rates (number per patient-treatment year) by 34.6% and 25.9%, respectively, versus formoterol (p ,= 0.002). Budesonide/formoterol320/9 prolonged time to first exacerbation versus formoterol, corresponding to a 21.2% reduction in hazard ration (0.788 [95% CI: 0.639, 0.972]; p = 0.026). Exacerbation rates (number per patient-treatment year) including antibiotic treatment (post hoc analysis) were reduced by 25.9% and 18.7% with budesonide/formoterol 320/9 and 160/9, respectively, versus formoterol (p <= 0.023). Both budesonide/formoterol 320/9, 160/9 and formoterol groups.

CONCLUSIONS: Over 12 months, both budesonide/formoterol doses reduced the exacerbation rate (defined with or without antibiotic treatment) versus formoterol. Budesonide/formoterol pMDI is an appropriate treatment for reducing exacerbations in COPD patients with a history of exacerbations. (NTC00419744).

Zhong, N., J. Zheng, et al. (2012). "Efficacy and safety of budesonide/formoterol via a dry powder inhaler in Chinese patients with chronic obstructive pulmonary disease. Current Medical Research & Opinion 28**(2):** 257-265**.**

OBJECTIVE: To evaluate the efficacy and safety of budesonide (BUD)/formoterol (FORM) compared with BUD, both administered by way of a dry powder inhaler (Turbuhaler).

METHODS: This was a 6-month, multicenter, randomized, parallel-group, double-blind, double-dummy design study (NCT 00421122). Patients were randomized to either BUD/FORM 160/9 twice daily or BUD 400 ug, twice daily. Improvement of lung function, daily symptoms, reliever use and health-related quality-of-life (St. George's Respiratory Questionaire [SGRQ] score) were compared between the two treatment groups.

RESULTS: A total of 308 patients with moderate to very severe COPD from 12 centers in China were randomized to BUD/FORM (n=156) or BUD (n=152). The primary endpoint, 1-hour post-dose forced expiratory volume in 1 second (FEV1), in the BUD/FORM group improved by 0.18L (from 0.83L at baseline to 1.01L) and this was significantly better (p<0.001) than the small increase (0.03L) observed in the BUD group after 24 weeks' treatment. Increases in pre-dose and 15-min post-does FEV(1) together with 1-hour post-dose forced vital capacity were also significantly larger with BUD/FORM than BUD (p<0.001 for all). Compared with BUD alone, BUD/FORM improved COPD total symptom scores (-1.04+/-0.16 vs -0.55+/-0.17; p=0.03), reduced reliever use (-0.85+/-0.16 puffs/day vs -0.31+/-0.16 puffs/day; p=0.012) and improved health-related quality-of-life (mean change of total SGRQ score -4.5 points (p=0182). Overall, both treatment groups were well tolerated.

CONCLUSIONS: In Chinese patients with moderate to very severe COPD, fixed combination treatments with BUD/FORM resulted in clinically meaningful improvements in lung function, health-related quality-of-life, COPD symptoms and a reduction in reliever use, compared with BUD use alone and both treatments were well tolerated. Treatment of BNUD/FORM for milder patients with COPD and head to head comparison of Chinese and Caucasians in future studies will be helpful to expand upon the findings of the current clinical trial.

Appendix 5: Abstracts of Meta Analyses

Chong M. J., C. Karner, et al. (2102). "Tiotropium versus long-acting beta-agonists for stable chronic obstructive pulmonary disease." ¨Cochrane Database of Systemic Reviews 9: CD009157.

BACKGROUND: Tiotropium and long-acting beta(2)-agonists (LABAs) are both accepted in the routine management for people with stable chronic obstructive pulmonary disease (COPD). There are new studies which have compared tiotropium with LABAs, including some that have evaluated recently introduced LABAs.

OBJECTIVES: To compare the relative clinical effects of tiotropium bromide alone versus LABA alone, upon measures of quality of life, exacerbations, lung function and serious adverse events, in people with stable COPD. To critically appraise and summarize current evidence on the costs and cost-effectiveness with tiotropium compared to LABA in people with COPD.

SEARCH METHODS: We identified randomized controlled trials (RCTs) from the Cochrane Airwasys Group Specialised Register of trials and economic evaluations from searching NHS EED and HEED (date of last search February 2012). We found additional trials from web-based clinical trial registers.

SELECTION CRITERIA: We included RCTs and full economic evaluations if they compared effects of tiotropium alone with LABAs alone in people with COPD. We allowed co-administration of standard COPD therapy.

DATA COLLECTION AND ANALYSIS: Two review authors independently assessed studies for inclusion, then extracted data on study quality and outcomes .We contacted study authors and trial sponsors for additional information. We analyzed data using the Cochrane Review Manager (RevMan 5.1) software.

MAIN RESULTS: Seven clinical studies totaling 12,223 participants with COPD were included in the review. The studies used similar designs and were generally of good methodological quality. Inclusion criteria for RCTs were similar across the included studies, although studies varied in terms of smoking history and COPD severity of participants. They compared tiotropium (which was delivered by HandiHaler in all studies) with salmeterol (four studies, 8936 participants), formoterol (one study, 431 participants) and indacaterol (two studies, 2856 participants). All participants were instructed to discontinue anticholinergic or LABAbronchodilators during treatment, but could receive inhaled corticosteroids (ICS) at a stable dose. Study duration ranged from 3 to 12 months. We extracted data for 11,223 participants. In general, the treatment groups were well matched at baseline. Overall, the risk of bias across the included RCTs was low. In the analysis of the primary outcomes in this review, a high level of heterogenicity amongst studies meant that we did not pool data for St. George's Respiratory Questionnaire quality of life score. Subgroup analyses based on the type of LABA found statistically significant differences among effects on quality of life depending on whether tiopropium was compared with salmeterol, formoterol, or indacaterol. Tiotropium reduced the number of participants experiencing one or more exacerbations compared with LABA (odds ratio (OR) 0.86; 95% confidence interval (CI) 0.79 to 0.93). For this outcome, there was no difference seen among the different types of LABA. There was no statistical difference in mortality observed between the treatment groups. For secondary outcomes, tiotropium was associated with a reduction in the number of COPD exacerbations leading to hospitalisation compared with LABA treatment (OR 0.87; 95% CI 0.77 to 0.99), but not in the overall rate of all-cause hospitalizations. There was no statisticallysignificant difference in forced expiratory volume in one second FEV(!) or symptom score between tiotropium and LABA-treated participants. There was a lower rate of non-fatal serious adverse events recorded with tiotropium compared with LABA (OR 0.88; 95% CI 0.78 to 0.99). The tiotropium group was also associated with a lower rate of study withdrawals (OR 0.89; 95% CI 0.81 to 0.99). We identified six full economic evaluations assessing the cost and cost-effectiveness of tiotropium and salmeterol. The studies were based on an economic model or empirical analysis of clinical data from RCTs. They all looked at maintenance costs and the costs for COPD exacerbations,

including respiratory medications and hospitalizations. The setting for the evaluations was primary and secondary care in the UK, Greece, Netherlands, Spain and US> All the studies estimated tiotropium to be superior to salmeterol based on better clinical outcomes (exacerbations or quality of life_ and/or lower total costs. However, the authors of all evaluations reported there was substantial uncertainty around the results.

AUTHORS' CONCLUSIONS: In people with COPD, the evidence is equivocal as to whether or not tiotropium offers greater benefit than LABAs in improving quality of life; however, this is complicated by differences in effect among the LABA types. Tiotropium was more effective than LABAs as a group in preventing COPD exacerbations and disease-related hospitalizations, although there were no statistical differences between groups in overall hospitalization rates or mortality during the study periods. There were fewer serious adverse events and study withdrawals recorded with tiotropium compared with LABAs. Symptom improvement and changes in lung function were similar between the treatment groups. Given the small number of studies to date, with high levels of heterogeneity among them, one approach may be to give a COPD patient a substantial trial of tiotropium, followed by a LABA (or vice-versa), then to continue prescribing the long-acting bronchodilator that the patient prefers. Further studies are needed to compare tiotropium with different LABAs, which are currently ongoing. The available economic evidence indicates that tiotropium may be cost-effective compared with salmeterol in several specific setting, but there is considerable uncertainty around this finding.

Cope, S., M. Kraemer, et al. (2012). "Efficacy of indacaterol 75 ug versusfixed-dose combinations of formoterol-budesonide or salmeterol-fluticasone for COPD: a network meta-analysis." Ïnternational Journal of Copd 7: 415-420.

BACKGROUND: The purpose of this study was to update our network meta-analysis in order to compare the efficacy of indacaterol 75 µg with that of a fixed-dose combination of formoterol and budesonide (FOR/BUD) and a fixed-dose combination salmeterol and fluticasone (SAL/FP) for the treatment of chronic obstructive pulmonary disease (COPD) based on evidence identified previously in addition to two new randomized clinical trials.

METHODS: Fifteen randomized, placebo-controlled clinical trials including COPD patients were evaluated: indacaterol 75 µg once daily (n = 2 studies), indacaterol 150 µg once daily (n = 5), indacaterol 300 µg once daily (n = 4), FOR/BUD 9/160 µg twice daily (n = 2), FOR/BUD 9/320 µg twice daily (n = 2), SAL/FP 50/500 µg twice daily (n = 4), and SAL/FP 50/250 µg twice daily (n = 1). All trials were analyzed simultaneously using a Bayesian network meta-analysis and relative treatment effects between all regimens were obtained. Treatment-by-covariate interactions were included where possible to improve the similarity of the trials. Outcomes of interest were trough forced expiratory volume in 1 second (FEV(1)) and transitional dyspnea index at 12 weeks.

RESULTS: Based on the results without adjustment for covariates, indacaterol 75 µg resulted in a greater improvement in FEV(1) at 12 weeks compared with FOR/BUD 9/160 µg (difference in change from baseline 0.09 L [95% credible interval 0.04-0.13]) and FOR/BUD 9/320 µg (0.07 L [0.03-0.11]) and was comparable with SAL/FP 50/250 µg (0.00 L [-0.07-0.07]) and SAL/FP 50/500 µg (0.01 L [-0.04-0.05]). For transitional dyspnea index, data was available only for indacaterol 75 µg versus SAL/FP 50/500 µg (-0.49 points [-1.87-0.89]).

CONCLUSION: Based on results of a network meta-analysis with and without covariates, indacaterol 75 µg is expected to be at least as efficacious as FOR/BUD (9/320 µg and 9/160 µg) and comparable with SAL/FP (50/250 µg and 50/500 µg) in terms of lung function. In terms of breathlessness (transitional dyspnea index) at 12 weeks, the results are inconclusive given the limited data.

Dong, Y.. –H., H.-H. Lin, et al. (2013). "Comparative safety of inhaled medications in patients with chronic obstructive pulmonary disease: systematic review and mixed treatment comparison meta-analysis of randomized controlled trials." ¨Thorax 65(1): 48-56.

BACKGROUND: The active-treatment comparative safety information for all inhaled medications in patients with chronic obstructive pulmonary disease (COPD) is limited. We aimed to compare the risk of overall and cardiovascular death for inhaled medications in patients with COPD.

METHODS: Through systematic database searching, we identified randomised controlled trials of tiotropium Soft Mist Inhaler, tiotropium HandiHaler, long-acting β2 agonists (LABAs), inhaled corticosteroids (ICS), and LABA-ICS combination with at least a 6-month treatment duration. Direct comparison and mixed treatment comparison (MTC) meta-analyses were conducted to estimate the pooled ORs of death for each comparison.

RESULTS: 42 trials with 52 516 subjects were included. The MTC meta-analysis with the fixed effect model indicated tiotropium Soft Mist Inhaler was associated with an universally increased risk of overall death compared with placebo (OR 1.51; 95% CI 1.06 to 2.19), tiotropium HandiHaler (OR 1.65; 95% CI 1.13 to 2.43), LABA (OR 1.63; 95% CI 1.10 to 2.44) and LABA-ICS (OR 1.90; 95% CI 1.28 to 2.86). The risk was more evident for cardiovascular death, in patients with severe COPD, and at a higher daily dose. LABA-ICS was associated with the lowest risk of death among all treatments. No excess risk was noted for tiotropium

HandiHaler or LABA. The results were similar for MTC and direct comparison meta-analyses, with less precision in the random effects model.

CONCLUSION: Our study provided a comparative safety spectrum for each category of inhaled medications. Tiotropium Soft Mist Inhaler had a higher risk of mortality and should be used with caution.

Karner, C. & Cates, C. J. "LABAin addition to tiotropium versus either tiotropium or LABAalone for chronic obstructive pulmonary disease." Cochrane Database Syst Rev 4, CD008989 (2012).

BACKGROUND: Long-acting bronchodilators comprising long-acting beta(2)-agonists and the anticholinergic agent tiotropium are commonly used for managing persistent symptoms of chronic obstructive pulmonary disease. Combining these treatments, which have different mechanisms of action, may be more effective than the individual components. However, the benefits and risks of combining tiotropium and long-acting beta(2)-agonists for the treatment of chronic obstructive pulmonary (COPD) disease are unclear.

OBJECTIVES: To assess the relative effects of treatment with tiotropium in addition to LABA compared to tiotropium or LABA alone in patients with chronic obstructive pulmonary disease.

SEARCH METHODS: We searched the Cochrane Airways Group Specialised Register of trials and clinicaltrials.gov up to January 2012.

SELECTION CRITERIA: We included parallel group, randomised controlled trials of three months or longer comparing treatment with tiotropium in addition to LABA against tiotropium or LABA alone for patients with chronic obstructive pulmonary disease.

DATA COLLECTION AND ANALYSIS: Two review authors independently assessed trials for inclusion and then extracted data on trial quality and the outcome results. We contacted study authors for additional information. We collected information on adverse effects from the trials.

MAIN RESULTS: Five trials were included in this review, mostly recruiting participants with moderate or severe chronic obstructive pulmonary disease. All of them compared tiotropium in addition to LABA to tiotropium alone, but only one trial additionally compared a combination of the two types of bronchodilator with LABA (formoterol) alone. Two studies used the LABA indacaterol, two used formoterol and one used salmeterol. Compared to tiotropium alone (3263 patients), treatment with tiotropium plus LABA resulted in a slightly larger improvement in the mean health-related quality of life (St George's Respiratory Questionnaire (SGRQ) MD -1.61; 95% CI -2.93 to -0.29). In the control arm, tiotropium alone, the SGRQ improved by falling 4.5 units from baseline and with both treatments the improvement was a fall of 6.1 units from baseline (on average). High withdrawal rates in the trials increased the uncertainty in this result, and the GRADE assessment for this outcome was therefore moderate. There were no significant differences in the other primary outcomes (hospital admission or mortality).The secondary outcome of pre-bronchodilator FEV(1) showed a small mean increase with the addition of LABA (MD 0.07 L; 95% CI 0.05 to 0.09) over the control arm, which showed a change from baseline ranging from 0.03 L to 0.13 L on tiotropium alone. None of the other secondary outcomes (exacerbations, symptom scores, serious adverse events, and withdrawals) showed any statistically significant differences between the groups. There were wide confidence intervals around these outcomes and moderate heterogeneity for both exacerbations and withdrawals. The results from the one trial comparing the combination of tiotropium and LABA to LABA alone (417 participants) were insufficient to draw firm conclusions for this comparison.

AUTHORS' CONCLUSIONS: The results from this review indicate a small mean improvement in health-related quality of life for patients on a combination of tiotropium and LABA compared to tiotropium alone, but it is not clear how clinically important this mean difference may be. Hospital admission and mortality have not been shown to be altered by adding long-acting beta(2)-agonists to tiotropium. There were not enough data to determine the relative efficacy and safety of tiotropium plus LABA compared to LABA alone. There were insufficient data to make comparisons between the different long-acting beta(2)-agonists when used in addition to tiotropium.

Nannin, L. J., T. J. Lasserson, et al. (2012). "Combined corticosteroid and LABA in one inhaler versus long-acting beta(2)-agonists for chronic obstructive pulmonary disease." Cochrane Database of Systematic Reviews **9: CD006829.**

BACKGROUND: Both inhaled steroids (ICS) and long-acting beta(2)-agonists (LABA) are used in the management of chronic obstructive pulmonary disease (COPD). This updated review compared compound LABA plus ICS therapy (LABA/ICS) with the LABA component drug given alone.

OBJECTIVES: To assess the efficacy of ICS and LABA in a single inhaler with mono-component LABA alone in adults with COPD.

SEARCH METHODS: We searched the Cochrane Airways Group Specialised Register of trials. The date of the most recent search was November 2011.

SELECTION CRITERIA: We included randomised, double-blind controlled trials. We included trials comparing compound ICS and LABA preparations with their component LABA preparations in people with COPD.

DATA COLLECTION AND ANALYSIS: Two authors independently assessed study risk of bias and extracted data. The primary outcomes were exacerbations, mortality and pneumonia, while secondary outcomes were health-related quality of life (measured by

validated scales), lung function, withdrawals due to lack of efficacy, withdrawals due to adverse events and side-effects. Dichotomous data were analysed as random-effects model odds ratios or rate ratios with 95% confidence intervals (CIs), and continuous data as mean differences and 95% CIs. We rated the quality of evidence for exacerbations, mortality and pneumonia according to recommendations made by the GRADE working group.

MAIN RESULTS: Fourteen studies met the inclusion criteria, randomising 11,794 people with severe COPD. We looked at any LABA plus ICS inhaler (LABA/ICS) versus the same LABA component alone, and then we looked at the 10 studies which assessed fluticasone plus salmeterol (FPS) and the four studies assessing budesonide plus formoterol (BDF) separately. The studies were well-designed with low risk of bias for randomisation and blinding but they had high rates of attrition, which reduced our confidence in the results for outcomes other than mortality. Primary outcomes There was low quality evidence that exacerbation rates in people using LABA/ICS inhalers were lower in comparison to those with LABA alone, from nine studies which randomised 9921 participants (rate ratio 0.76; 95% CI 0.68 to 0.84). This corresponds to one exacerbation per person per year on LABA and 0.76 exacerbations per person per year on ICS/LABA. Our confidence in this effect was limited by statistical heterogeneity between the results of the studies (I(2) = 68%) and a risk of bias from the high withdrawal rates across the studies. When analysed as the number of people experiencing one or more exacerbations over the course of the study, FPS lowered the odds of an exacerbation with an odds ratio (OR) of 0.83 (95% CI 0.70 to 0.98, 6 studies, 3357 participants). With a risk of an exacerbation of 47% in the LABA group over one year, 42% of people treated with LABA/ICS would be expected to experience an exacerbation. Concerns over the effect of reporting biases led us to downgrade the quality of evidence for this effect from high to moderate. There was no significant difference in the rate of hospitalisations (rate ratio 0.79; 95% CI 0.55 to 1.13, very low quality evidence due to risk of bias, statistical imprecision and inconsistency). There was no significant difference in mortality between people on combined inhalers and those on LABA, from 10 studies on 10,680 participants (OR 0.92; 95% CI 0.76 to 1.11, downgraded to moderate quality evidence due to statistical imprecision). Pneumonia occurred more commonly in people randomised to combined inhalers, from 12 studies with 11,076 participants (OR 1.55; 95% CI 1.20 to 2.01, moderate quality evidence due to risk of bias in relation to attrition) with an annual risk of around 3% on LABA alone compared to 4% on combination treatment. There were no significant differences between the results for either exacerbations or pneumonia from trials adding different doses or types of inhaled corticosteroid. Secondary outcomes ICS/LABA was more effective than LABA alone in improving health-related quality of life measured by the St George's Respiratory Questionnaire (1.58 units lower with FPS; 2.69 units lower with BDF), dyspnoea (0.09 units lower with FPS), symptoms (0.07 units lower with BDF), rescue medication (0.38 puffs per day fewer with FPS, 0.33 puffs per day fewer with BDF), and forced expiratory volume in one second (FEV(1)) (70 mL higher with FPS, 50 mL higher with BDF). Candidiasis (OR 3.75) and upper respiratory infection (OR 1.32) occurred more frequently with FPS than SAL. We did not combine adverse event data relating to candidiasis for BDF studies as the results were very inconsistent.

AUTHORS' CONCLUSIONS: Concerns over the analysis and availability of data from the studies bring into question the superiority of ICS/LABA over LABA alone in preventing exacerbations. The effects on hospitalisations were inconsistent and require further exploration. There was moderate quality evidence of an increased risk of pneumonia with ICS/LABA. There was moderate quality evidence that treatments had similar effects on mortality. Quality of life, symptoms score, rescue medication use and FEV(1) improved more on ICS/LABA than on LABA, but the average differences were probably not clinically significant for these outcomes. To an individual patient the increased risk of pneumonia needs to be balanced against the possible reduction in exacerbations. More information would be useful on the relative benefits and adverse event rates with combination inhalers using different doses of inhaled corticosteroids. Evidence from head-to-head comparisons is needed to assess the comparative risks and benefits of the different combination inhalers

Rodrigo, G.J. and H. Neffen (2012). “Comparison of indacaterol with tiotropium or twice-daily long-acting agonists for stale COPD: a systematic review.” Chest 142(5) 1104-1110.

BACKGROUND: Bronchodilators are central to the symptomatic management of patients with COPD. Previous data have shown that inhaled indacaterol improved numerous clinical outcomes over placebo.

METHODS: This systematic review explored the efficacy and safety of indacaterol in comparison with tiotropium or bid long-acting β 2 -agonists (TD-LABAs) for treatment of moderate to severe COPD. Randomized controlled trials were identified after a search of different databases of published and unpublished trials.

RESULTS: Five trials (5,920 participants) were included. Compared with tiotropium, indacaterol showed statistically and clinically significant reductions in the use of rescue medication and dyspnea(43% greater likelihood of achieving a minimal clinically important difference [MCID] in the transitional dyspnea index [TDI]; number needed to treat for benefit [NNTB] 5 10). Additionally, the MCID in health status was more likely to be achieved with indacaterol than with tiotropium (OR = 1.43; 95% CI, 1.22–1.68; P = .00001; [NNTB]= 10). Trough FEV 1 was significantly higher at the end of treatment with indacaterol than with TD-LABAs (80 mL, P = .00001). Similarly, indacaterol significantly improved dyspnea (61% greater likelihood of

achieving an MCID in TDI, P = .008) and health status (21% greater likelihood of achieving an MCID in St. George's Respiratory Questionnaire, P 5 .04) than TD-LABA. Indacaterol showed similar levels of safety and tolerability to both comparators.

CONCLUSIONS: Available evidence suggests that indacaterol may prove useful as an alternative to tiotropium or TD-LABA due to its effects on health status, dyspnea, and pulmonary function.

Rodrigo, G. J., Plaza, V. & Castro-Rodríguez, J. A. "Comparison of three combined pharmacological approaches with tiotropium monotherapy in stable moderate to severe COPD: a systematic review." Pulm Pharmacol Ther **25,** 40–47 (2012).

BACKGROUND: Guidelines recommend the use of inhaled long-acting bronchodilators, inhaled corticosteroids (ICS) and their combinations for maintenance treatment of moderate to severe COPD. However, there are limited data supporting combination therapy.

METHODS: This systematic review assessed the efficacy of three therapeutic approaches: tiotropium plus long-acting beta2-agonist (LABA) ("dual" therapy), LABA/ICS ("combined" therapy), and tiotropium plus LABA/ICS ("triple" therapy), all compared with tiotropium monotherapy. Randomized controlled trials were identified after a search of different databases of published and unpublished trials.

RESULTS: Twenty trials (6803 participants) were included. "Dual" therapy showed significant improvements in forced volume in the first second (FEV(1)), health-related quality of life (HRQoL), and dyspnea. However, it failed to reduce the risk of COPD exacerbations. Compared with tiotropium, "combined" therapy presented modest but significant effects on FEV(1), HRQoL, and dyspnea. Again, there was no significant difference in exacerbations, but it was associated with a significant increase of serious adverse effects (SAE) (number need to treat for harm [NNTH] = 20; 95% CI: 11-119). Finally, "triple therapy" increased FEV(1), improved HRQoL (both benefits exceeded minimal important differences) and decrease COPD exacerbations in anon-significant way. (Odds ratio [OR] = 0.57; 95% CI: 0.24 to 1.37, p = 0.21).

CONCLUSIONS: "Dual" and "triple" therapy seem like the most promising for patients with moderate to very severe COPD. However, data are still scarce and studies too short to generate a strong recommendation. Future studies should examine long-term efficacy and safety**.**