COPD/Emphysema PubMed search results covering the period 23/10/2018 to 18/01/2019

Systematic reviews and clinical trials

Search strategy: (("pulmonary disease, chronic obstructive"[MeSH Terms] OR "emphysema"[MeSH Terms]) AND ((systematic[sb] OR Clinical Trial[ptyp]) AND English[lang]) AND ("2018/10/23"[CDAT] : "3000"[CDAT])) AND ((systematic[sb] OR Clinical Trial[ptyp]) AND English[lang]) AND ((systematic[sb] OR Clinical Trial[ptyp]) AND English[lang])

Aboumatar, H., M. Naqibuddin, et al. (2018). **"Effect of a Program Combining Transitional Care and Long-term Self-management Support on Outcomes of Hospitalized Patients With Chronic Obstructive Pulmonary Disease: A Randomized Clinical Trial."** Jama **320**(22): 2335-2343.

Importance: Patients hospitalized for chronic obstructive pulmonary disease (COPD) exacerbations have high rehospitalization rates and reduced quality of life. Objective: To evaluate a hospital-initiated program that combined transition and long-term self-management support for patients hospitalized due to COPD and their family caregivers. Design, Setting, and Participants: This single-site randomized clinical trial was conducted in Baltimore, Maryland, with 240 participants. Participants were patients hospitalized due to COPD, randomized to intervention or usual care, and followed up for 6 months after hospital discharge. Enrollment occurred from March 2015 to May 2016; follow-up ended in December 2016. Interventions: The intervention (n = 120) was a comprehensive 3-month program to help patients and their family caregivers with long-term self-management of COPD. It was delivered by COPD nurses (nurses with special training on supporting patients with COPD using standardized tools). Usual care (n = 120) included transition support for 30 days after discharge to ensure adherence to discharge plan and connection to outpatient care. Main Outcomes and Measures: The primary outcome was number of COPD-related acute care events (hospitalizations and emergency department visits) per participant at 6 months. The co-primary outcome was change in participants' health-related quality of life measured by the St George's Respiratory Questionnaire (SGRQ) at 6 months after discharge (score, 0 [best] to 100 [worst]; 4-point difference is clinically meaningful). Results: Among 240 patients who were randomized (mean [SD] age, 64.9 [9.8] years; females, 61.7%), 203 (85%) completed the study. The mean (SD) baseline SGRQ score was 63.1 (19.9) in the intervention group and 62.6 (19.3) in the usual care group. The mean number of COPD-related acute care events per participant at 6 months was 0.72 (95% CI, 0.45-0.97) in the intervention group vs 1.40 (95% CI, 1.01-1.79) in the usual care group (difference, 0.68 [95% CI, 0.22 to 1.15]; P = .004). The mean change in participants' SGRQ total score at 6 months was -1.53 in the intervention and +5.44 in the usual care group (adjusted difference, -6.69 [95% CI, -12.97 to -0.40]; P = .04). During the study period, there were 15 deaths (intervention: 7; usual care: 8) and 337 hospitalizations (intervention: 135; usual care: 202). Conclusions and Relevance: In a single-site randomized clinical trial of patients hospitalized due to COPD, a 3-month program that combined transition and long-term self-management support resulted in significantly fewer COPD-related hospitalizations and emergency department visits and better health-related quality of life at 6 months after discharge. Further research is needed to evaluate this intervention in other settings. Trial Registration: ClinicalTrials.gov Identifier: NCT02036294.

https://jamanetwork.com/journals/jama/article-abstract/2714645

Anzueto, A. R., K. Kostikas, et al. (2018). **"Indacaterol/glycopyrronium versus salmeterol/fluticasone in the prevention of clinically important deterioration in COPD: results from the FLAME study."** Respir Res **19**(1): 121.

BACKGROUND: Chronic obstructive pulmonary disease (COPD) is a progressive disease and a composite endpoint could be an indicator of treatment effect on disease worsening. This post-hoc analysis assessed whether indacaterol/glycopyrronium (IND/GLY) 110/50 mug once daily reduced the risk of clinically important deterioration (CID) versus salmeterol/fluticasone (SFC) 50/500 mug twice daily in moderate-to-very severe COPD patients from the FLAME study. METHODS: CID was defined as >/=100 mL decrease in forced expiratory volume in 1 s (FEV1) or >/= 4-unit increase in St. George's Respiratory Questionnaire

(SGRQ) total score or a moderate-to-severe COPD exacerbation. Changes from baseline in the rate of moderate and severe exacerbations, time to first moderate-to-severe exacerbation, and change from baseline in the SGRQ score, measured after Week 12 up to Week 52, were assessed by presence of early CID (CID+) or absence of CID (CID-) at Week 12. RESULTS: IND/GLY significantly delayed the time to CID (hazard ratio [HR] (95% confidence interval [CI]), 0.72 [0.67-0.78]; P < 0.0001), and reduced the incidences of CID versus SFC. Additionally, IND/GLY delayed the time to CID in all patient subgroups. After 12 weeks until 52 weeks, CID+ patients had a significantly higher rate of moderate-to-severe exacerbations versus CID- patients (P < 0.0001); moreover, CID+ patients experienced moderate-to-severe exacerbations significantly earlier versus CID- patients (P < 0.0001). CID+ patients had a comparable change in the SGRQ total score versus CID- patients. CONCLUSIONS: IND/GLY reduced the risk of CID versus SFC. CID had a significant impact on long-term exacerbation outcomes in patients with moderate-to-very severe COPD and a history of >/=1 exacerbations in the previous year. TRIAL REGISTRATION: Clinicaltrials.gov NCT01782326 .

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6011394/pdf/12931_2018_Article_830.pdf

Archontogeorgis, K., A. Voulgaris, et al. (2018). **"Mean Platelet Volume and Platelet Distribution Width in Patients With Obstructive Sleep Apnea Syndrome and Concurrent Chronic Obstructive Pulmonary Disease."** Clin Appl Thromb Hemost **24**(8): 1216-1222.

Evidence suggests that there is platelet activation in obstructive sleep apnea syndrome (OSAS) and chronic obstructive pulmonary disease (COPD). Our objective is to evaluate mean platelet volume (MPV) and platelet distribution width (PDW) in patients with overlap syndrome (OS), that is, concurrent COPD with OSAS. Mean platelet volume and PDW were assessed in consecutive patients who had undergone polysomnography and pulmonary function testing. They were divided into the following groups: controls (apnea-hypopnea index [AHI] <5/hour, and forced expiratory volume in 1st second [FEV1]/forced vital capacity [FVC] >70%), OSAS group (AHI >/=5/hour and FEV1/FVC >70%), and OS group (AHI >/=5/hour and FEV1/FVC <70%). A total of 485 patients (360 males and 125 females) were included. Mean platelet volume in controls was lower compared with the other groups: 10 +/- 0.9 fL for controls versus 10.3 +/- 1.2 fL for OSAS (P = .006), versus 10.7 +/- 1 fL for OS (P < .001). Additionally, MPV was higher in OS group than OSAS: 10.7 +/- 1 fL versus 10.3 +/- 1.2 fL, respectively (P = .002). Platelet distribution width was lower in controls compared with the other groups: 12.9 +/- 2 fL for controls versus 13.6 +/- 1.9 fL for OSAS (P = .007), versus 13.8 +/- 2.3 fL for OS (P = .008), while there was no difference between OS and OSAS groups. Mean platelet volume and PDW are increased in patients with OS compared with healthy controls, with respiratory function being the major contributor in platelet activation in this series.

Balla, A., S. Quaresima, et al. (2018). **"Ectopic air localizations after transanal procedures: A systematic literature review."** Int J Surg **56**: 167-173.

BACKGROUND: Aim of this study is to report and to analyze the incidence, clinical impact and treatment options of ectopic air localizations after transanal procedures. METHODS: A systematic literature review was performed using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The research was carried out using the PubMed database, identifying 40 articles with the following keywords: "transanal" AND "emphysema"; "transanal" AND "subcutaneous emphysema"; "transanal" AND "pneumomediastinum"; "transanal" AND "pneumothoraces"; "transanal" AND "pneumopericardium"; "transanal" AND "retropneumoperitoneum". RESULTS: Nineteen articles, published between 1993 and 2017, were included in the study for a total of 29 patients. The most frequent air localization was in the retroperitoneum, followed by subcutaneous tissues, mediastinum and neck. This condition was treated conservatively in 20 patients, with colostomy in 4 patients, with bowel resection and negative diagnostic laparoscopy in one patient each. In three cases the treatment was not specified. Ectopic air location resolved in all cases. CONCLUSIONS: Pneumo-mediastinum and pneumo-

retroperitoneum after transanal procedures are unusual complications with a dramatic radiological appearance but can be managed successfully with a completely benign course in most cases. Initially, a conservative approach is recommended. Surgical treatment should be reserved only in case of fluid collection or suture dehiscence.

Beeh, K. M., A. Emirova, et al. (2018). **"Dose-response of an extrafine dry powder inhaler formulation of glycopyrronium bromide: randomized, double-blind, placebo-controlled, dose-ranging study (GlycoNEXT)."** Int J Chron Obstruct Pulmon Dis **13**: 1701-1711.

Introduction: An extrafine formulation of the long-acting muscarinic antagonist, glycopyrronium bromide (GB), has been developed for delivery via the NEXThaler dry powder inhaler (DPI). This study assessed the bronchodilator efficacy and safety of different doses of this formulation in patients with COPD to identify the optimal dose for further development. Patients and methods: This was a multicenter, randomized, double-blind, placebo-controlled, incomplete block, three-way crossover study, including three 28-day treatment periods, each separated by a 21-day washout period. Eligible patients had a diagnosis of COPD and post-bronchodilator forced expiratory volume in 1 s (FEV1) 40%-70% predicted. Treatments administered were GB 6.25, 12.5, 25 and 50 mug or matched placebo; all were given twice daily (BID) via DPI, with spirometry assessed on Days 1 and 28 of each treatment period. The primary end point was FEV1 area under the curve from 0 to 12 h (AUC0-12 h) on Day 28. Results: A total of 202 patients were randomized (61% male, mean age 62.6 years), with 178 (88%) completing all the three treatment periods. For the primary end point, all the four GB doses were superior to placebo ($p<0.001$) with mean differences (95% CI) of 114 (74, 154), 125 (85, 166), 143 (104, 183) and 187 (147, 228) mL for GB 6.25, 12.5, 25 and 50 mug BID, respectively. All four GB doses were also statistically superior to placebo for all secondary efficacy end points, showing clear dose-response relationships for most of the endpoints. Accordingly, GB 25 mug BID met the criteria for the minimally acceptable dose. Adverse events were reported by 15.5, 16.2, 10.9 and 14.3% of patients receiving GB 6.25, 12.5, 25 and 50 mug BID, respectively, and 14.8% receiving placebo. Conclusion: This study supports the selection of GB 25 mug BID as the minimal effective dose for patients with COPD when delivered with this extrafine DPI formulation.

https://www.dovepress.com/getfile.php?fileID=42317

Boudewijn, I. M., A. Faiz, et al. (2017). **"Nasal gene expression differentiates COPD from controls and overlaps bronchial gene expression."** Respir Res **18**(1): 213.

BACKGROUND: Nasal gene expression profiling is a promising method to characterize COPD non-invasively. We aimed to identify a nasal gene expression profile to distinguish COPD patients from healthy controls. We investigated whether this COPD-associated gene expression profile in nasal epithelium is comparable with the profile observed in bronchial epithelium. METHODS: Genome wide gene expression analysis was performed on nasal epithelial brushes of 31 severe COPD patients and 22 controls, all current smokers, using Affymetrix Human Gene 1.0 ST Arrays. We repeated the gene expression analysis on bronchial epithelial brushes in 2 independent cohorts of mild-to-moderate COPD patients and controls. RESULTS: In nasal epithelium, 135 genes were significantly differentially expressed between severe COPD patients and controls, 21 being up- and 114 downregulated in COPD (false discovery rate < 0.01). Gene Set Enrichment Analysis (GSEA) showed significant concordant enrichment of COPD-associated nasal and bronchial gene expression in both independent cohorts (FDRGSEA < 0.001). CONCLUSION: We identified a nasal gene expression profile that differentiates severe COPD patients from controls. Of interest, part of the nasal gene expression changes in COPD mimics differentially expressed genes in the bronchus. These findings indicate that nasal gene expression profiling is potentially useful as a non-invasive biomarker in COPD. TRIAL REGISTRATION: ClinicalTrials.gov registration number NCT01351792 (registration date May 10, 2011), ClinicalTrials.gov registration number NCT00848406 (registration date

February 19, 2009), ClinicalTrials.gov registration number NCT00807469 (registration date December 11, 2008).

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5740586/pdf/12931_2017_Article_696.pdf

Calle Rubio, M., J. B. Soriano, et al. (2018). **"Testing for alpha-1 antitrypsin in COPD in outpatient respiratory clinics in Spain: A multilevel, cross-sectional analysis of the EPOCONSUL study."** PLoS One **13**(6): e0198777.

BACKGROUND: Alpha-1 antitrypsin deficiency (AATD) is the most common hereditary disorder in adults, but is under-recognized. In Spain, the number of patients diagnosed with AATD is much lower than expected according to epidemiologic studies. The objectives of this study were to assess the frequency and determinants of testing serum alpha1-antitrypsin (AAT) levels in COPD patients, and to describe factors associated with testing. METHODS: EPOCONSUL is a cross-sectional clinical audit, recruiting consecutive COPD cases over one year. The study evaluated serum AAT level determination in COPD patients and associations between individual, disease-related, and hospital characteristics. RESULTS: A total of 4,405 clinical records for COPD patients from 57 Spanish hospitals were evaluated. Only 995 (22.5%) patients had serum AAT tested on some occasion. A number of patient characteristics (being male [OR 0.5, p < 0.001], </=55 years old [OR 2.38, p<0.001], BMI</=21 kg/m2 [OR 1.71, p<0.001], FEV1(%)<50% [OR 1.35, p<0.001], chronic bronchitis [OR 0.79, p < 0.001], Charlson index >/= 3 [OR 0.66, p < 0.001], or history or symptoms of asthma [OR 1.32, p<0.001]), and management at a specialized COPD outpatient clinic [OR 2.73,p<0.001] were identified as factors independently associated with ever testing COPD patients for AATD. Overall, 114 COPD patients (11.5% of those tested) had AATD. Of them, 26 (22.8%) patients had severe deficiency. Patients with AATD were younger, with a low pack-year index, and were more likely to have emphysema (p<0.05). CONCLUSION: Testing of AAT blood levels in COPD patients treated at outpatient respiratory clinics in Spain is infrequent. However, when tested, AATD (based on the serum AAT levels </=100 mg/dL) is detected in one in five COPD patients. Efforts to optimize AATD case detection in COPD are needed.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6023216/pdf/pone.0198777.pdf

Chervinskaya, A. V. and K. V. Kotenko (2016). **"Efficiency of controlled halotherapy in rehabilitation of patients with occupational lung diseases."** Med Tr Prom Ekol(11): 38-40.

The study was aimed at features and efficiency of controlled halotherapy method in patients with occupational chronic obstructive lung disease (COLD). Examination covered 73 patients with occupational mild and moderate stages of COLD, aged 45 to 64. All the patients were randomized to 2 comparable groups - main and reference (37 and 36 examinees respectively). The main group in addition to conventional medical therapy received courses of controlled halotherapy (10 procedures with certain concentration of sodium chloride dry aerosol in accordance to methodic recommendations). Based on complex evaluation of clinical, functional and laboratory methods, the authors assessed efficiency of controlled halotherapy in patients with occupational COLD. Considerable improvement was seen: for mild COLD--in 40% of cases, for moderate COLD - in 30%, with general efficiency for these patients of 90 and 85% respectively. Analysis of the results obtained enables to evaluate controlled halotherapy as an effective method of rehabilitation and prevention in occupational COLD patients.

Eriksson Strom, J., J. Pourazar, et al. (2018). **"Cytotoxic lymphocytes in COPD airways: increased NK cells associated with disease, iNKT and NKT-like cells with current smoking."** Respir Res **19**(1): 244.

BACKGROUND: Cytotoxic lymphocytes are increased in the airways of COPD patients. Whether this increase is driven primarily by the disease or by smoking is not clear, nor whether it correlates with the rate of decline in lung function. METHODS: Bronchoscopy with BAL was performed in 52 subjects recruited from the longitudinal OLIN COPD study according to pre-determined criteria; 12 with COPD and a rapid decline in lung function (loss of FEV1 >/= 60 ml/year), 10 with COPD and a non-rapid decline in lung function (loss of FEV1 </= 30 ml/year), 15 current and ex-smokers and 15 non-smokers with normal lung function. BAL lymphocyte subsets were determined using flow cytometry. RESULTS: In BAL fluid, the proportions of NK, iNKT and NKT-like cells all increased with pack-years. Within the COPD group, NK cells - but not iNKT or NKT-like cells - were significantly elevated also in subjects that had quit smoking. In contrast, current smoking was associated with a marked increase in iNKT and NKT-like cells but not in NK cells. Rate of lung function decline did not significantly affect any of the results. CONCLUSIONS: In summary, increased proportions of NK cells in BAL fluid were associated with COPD; iNKT and NKT-like cells with current smoking but not with COPD. Interestingly, NK cell percentages did not normalize in COPD subjects that had quit smoking, indicating that these cells might play a role in the continued disease progression seen in COPD even after smoking cessation. TRIAL REGISTRATION: Clinicaltrials.gov identifier NCT02729220 .

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6286566/pdf/12931_2018_Article_940.pdf

Faner, R., G. Noell, et al. (2018). **"Distribution, temporal stability and association with all-cause mortality of the 2017 GOLD groups in the ECLIPSE cohort."** Respir Med **141**: 14-19.

BACKGROUND: In 2017, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) proposed a new classification of patients with chronic obstructive pulmonary disease (COPD). MATERIAL AND METHODS: We contrasted the distribution of COPD patients according to GOLD 2017 and 2011 classifications, the temporal stability of the 2017 groups during 3 years follow-up and their association with all-cause mortality in the ECLIPSE cohort. RESULTS: We found that GOLD 2017: (1) switched a substantial proportion of GOLD 2011C and D patients to A and B groups at recruitment; (2) about half of A, B and D patients remained in the same group at the end of follow-up, whereas 74% of C patients (the smallest group of all) changed, either because exacerbation rate decreased or dyspnea increased; and, (3) all-cause mortality by group was not significantly different between GOLD 2011 and 2017. Of note, mortality in B (16%) and D patients (18%) was similar, both with similar severity of airflow limitation, the best individual mortality risk factor. CONCLUSIONS: These results illustrate the cross-sectional and longitudinal effects of excluding FEV1 from GOLD 2017, and highlight both the clinical relevance of symptom assessment in the management of COPD and the prognostic capacity of FEV1.

https://www.resmedjournal.com/article/S0954-6111(18)30206-3/fulltext

Gregoriano, C., T. Dieterle, et al. (2018). **"Use and inhalation technique of inhaled medication in patients with asthma and COPD: data from a randomized controlled trial."** Respir Res **19**(1): 237.

BACKGROUND: The burden of asthma and COPD among patients is high and people affected are frequently hospitalized due to exacerbations. There are numerous reasons for the lack of disease control in asthma and COPD patients. It is associated with non-adherence to guidelines on the part of the health care provider and with poor inhalation technique and/or non-adherence to the prescribed treatment plan by the patient. This study aims to present data on inhaler technique and its impact on quality of life (QoL) and symptom control in a typical population of patients with chronic lung disease from a randomized controlled trial on medication adherence. METHODS: For this cross-sectional analysis, 165 asthma and COPD patients were analyzed. Correct application of inhaler devices was tested using pre-defined checklists for each inhaler type. QoL and symptom control were investigated using COPD Assessment Test (CAT) and Asthma Control Test (ACT). Spirometry was used to measure forced vital capacity (FVC) and forced expiratory volume in one second (FEV1). RESULTS: Overall, incorrect inhalation technique ranged from 0 to 53% depending on the type of inhaler. COPD patients with incorrect device application had a higher CAT sum score compared to those with a correct device application (P = .02). Moreover,

COPD patients with incorrect device application were more likely to suffer from cough (P = .03) and were more breathless while walking uphill or a flight of stairs (P = .02). While there was no significance found in asthma patients, COPD patients who used their devices correctly had a significantly better mean FEV1% predicted at baseline compared to those who applied their devices incorrectly (P = .04). CONCLUSIONS: Correct inhalation of prescribed medication is associated with improved health status and lung function. These findings should encourage health professionals to provide instructions on correct inhalation technique and to regularly re-evaluate the patients' inhalation technique. TRIAL REGISTRATION: ClinicalTrials.gov: NCT0238672 , Registered 14 February 2014.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6276152/pdf/12931_2018_Article_936.pdf

Huang, Q. D., Q. Wu, et al. (2018). **"Current Status of Forest Medicine Research in China."** Biomed Environ Sci **31**(7): 551-554.

La Torre, G., R. A. Cocchiara, et al. (2018). **"Counseling intervention to improve quality of life in patients with pre-existing acute myocardial infarction (AMI) or chronic obstructive pulmonary disease (COPD): a pilot study."** J Prev Med Hyg **59**(2): E153-e158.

Background: In the light of diagnostic and therapeutic advances, patients with a previous myocardial infarction or with a diagnosis of chronic obstructive pulmonary disease are vulnerable and need continuous monitoring over time. These pathological frameworks have a strong impact on the economy and on the status of the population and require effective and low-cost solutions. Aims: The objective of this clinical trial is to evaluate the efficacy in the short term of a telephone counseling intervention to modify the lifestyles of these two patient populations. Methods: In May 2015, all the patients included in the study underwent a questionnaire to evaluate their eating and smoking habits and their quality of life. After randomization in two groups, the intervention group received telephone counseling related to the correct lifestyles. The control group did not undergo any intervention. In September-October 2015, the same initial questionnaire was administered to evaluate changes in patients' behavior. Results: 64 patients were included in the study: 34 were assigned to the intervention group and 30 to the control group. The outcomes evaluated were: quality of life, assessment of eating habits and smoking status. After the telephone counseling, the intervention group (34 persons) showed a significant improvement in the score of adherence to the Mediterranean diet (p = 0.01) and a significant reduction in the percentage of smokers (p = 0.01) compared to the population that did not receive any intervention (30 persons). On the other hand, the changes related to the quality of life questionnaire were not significant. Conclusions: A single telephone counseling intervention is effective in modifying the lifestyles of patients with a previous myocardial infarction or diagnosed with chronic obstructive pulmonary disease in the short term, reducing their risk profile.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6069404/pdf/jpmh-2018-02-e153.pdf

Lahham, A., C. F. McDonald, et al. (2018). **"Acceptability and validity of a home exercise diary used in home-based pulmonary rehabilitation: A secondary analysis of a randomised controlled trial."** Clin Respir J **12**(6): 2057-2064.

INTRODUCTION: Evaluating adherence to home-based pulmonary rehabilitation (PR) could be challenging due to lack of direct supervision and the complex nature of the rehabilitation model. To measure adherence to home-based PR in the HomeBase trial, participants were encouraged to work towards a goal of at least 30 min of whole-body exercise on most days of the week and report their participation using a home exercise diary. OBJECTIVE: This project aimed to evaluate the acceptability and validity of the home

exercise diary. METHODS: Diary return and completion rates assessed acceptability of the home exercise diary. Home participants underwent physical activity (PA) monitoring using the Sensewear armband during the final week of an 8-week PR. The correlation between self-documented and objective daily exercise minutes was calculated. Objective exercise minutes were defined as bouts of >/=10 min spent in >/= moderate PA. Differences in self-documented weekly exercise minutes between sufficiently active (>/=7000 daily steps) and inactive participants were computed. RESULTS: Diaries were returned by 92% of programme completers. Of those who returned diaries, 72% have completed exercise documentation. Fifteen programme completers underwent PA monitoring [mean age 69 (9) (SD) years, FEV1 55 (19) %predicted]. A moderate correlation was observed between self-documented and objective mean daily exercise minutes (r = .59, P = .02). Active participants [n = 6, 10 253 (1521) daily steps] documented more exercise (111 min) during week eight compared with inactive participants [n = 9, 2705 (1772) daily steps, P = .002]. CONCLUSION: The self-documented home exercise diary is an acceptable and valid method to reflect exercise participation during home-based PR.

https://onlinelibrary.wiley.com/doi/abs/10.1111/crj.12773

Leitao Filho, F. S., S. W. Ra, et al. (2018). **"Serum IgG subclass levels and risk of exacerbations and hospitalizations in patients with COPD."** Respir Res **19**(1): 30.

BACKGROUND: The literature is scarce regarding the prevalence and clinical impact of IgG subclass deficiency in COPD. We investigated the prevalence of IgG subclass deficiencies and their association with exacerbations and hospitalizations using subjects from two COPD cohorts. METHODS: We measured IgG subclass levels using immunonephelometry in serum samples from participants enrolled in two previous COPD trials: Macrolide Azithromycin for Prevention of Exacerbations of COPD (MACRO; n = 976) and Simvastatin for the Prevention of Exacerbations in Moderate-to-Severe COPD (STATCOPE; n = 653). All samples were collected from clinically stable participants upon entry into both studies. IgG subclass deficiency was diagnosed when IgG subclass levels were below their respective lower limit of normal: IgG1 < 2.8 g/L; IgG2 < 1.15 g/L; IgG3 < 0.24 g/L; and IgG4 < 0.052 g/L. To investigate the impact of IgG subclass levels on time to first exacerbation or hospitalization, we log-transformed IgG levels and performed Cox regression models, with adjustments for confounders. RESULTS: One or more IgG subclass deficiencies were found in 173 (17.7%) and 133 (20.4%) participants in MACRO and STATCOPE, respectively. Lower IgG1 or IgG2 levels resulted in increased risk of exacerbations with adjusted hazard ratios (HR) of 1.30 (95% CI, 1.10-1.54, p < 0.01) and 1.19 (95% CI, 1.05-1.35, p < 0.01), respectively in the MACRO study, with STATCOPE yielding similar results. Reduced IgG1 or IgG2 levels were also associated with increased risk of hospitalizations: the adjusted HR for IgG1 and IgG2 was 1.52 (95% CI: 1.15-2.02, p < 0.01) and 1.33 (95% CI, 1.08-1.64, p < 0.01), respectively for the MACRO study; in STATCOPE, only IgG2 was an independent predictor of hospitalization. In our multivariate Cox models, IgG3 and IgG4 levels did not result in significant associations for both outcomes in either MACRO or STATCOPE cohorts. CONCLUSIONS: Approximately 1 in 5 COPD patients had one or more IgG subclass deficiencies. Reduced IgG subclass levels were independent risk factors for both COPD exacerbations (IgG1 and IgG2) and hospitalizations (IgG2) in two COPD cohorts. TRIAL REGISTRATION: This study used serum samples from participants of the MACRO (NCT00325897) and STATCOPE (NCT01061671) trials.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5813358/pdf/12931_2018_Article_733.pdf

Liang, J., M. J. Abramson, et al. (2018). **"Diagnosing COPD and supporting smoking cessation in general practice: evidence-practice gaps."** Med J Aust **208**(1): 29-34.

OBJECTIVES: To review the accuracy of diagnoses of chronic obstructive pulmonary disease (COPD) in primary care in Australia, and to describe smokers' experiences with and preferences for smoking cessation. DESIGN, SETTING AND PARTICIPANTS: Patients were invited to participate if they were at least 40 years old and had visited participating general practice clinics in Melbourne at least twice during the previous 12 months, reported being current or ex-smokers with a smoking history of at least 10 pack-years, or were being managed for COPD. Interviews based on a structured questionnaire and case finding

(FEV1/FEV6 measurement) were followed, when appropriate, by spirometry testing and assessment of health-related quality of life, dyspnoea and symptoms. RESULTS: 1050 patients attended baseline interviews (February 2015 - April 2017) at 41 practices. Of 245 participants managed for COPD, 130 (53.1%) met the spirometry-based definition (post-bronchodilator FEV1/FVC < 0.7) or had a clinical correlation; in 37% of cases COPD was not confirmed, and no definitive result was obtained for 9.8% of patients. Case finding and subsequent spirometry testing identified 142 new COPD cases (17.6% of participants without prior diagnosis; 95% CI, 15.1-20.5%). 690 participants (65.7%) were current smokers, of whom 360 had attempted quitting during the previous 12 months; 286 (81.0% of those attempting to quit) reported difficulties during previous quit attempts. Nicotine replacement therapy (205, 57.4%) and varenicline (110, 30.8%) were the most frequently employed pharmacological treatments; side effects were common. Hypnotherapy was the most popular non-pharmacological option (62 smokers, 17%); e-cigarettes were tried by 38 (11%). 187 current smokers (27.6%) would consider using e-cigarettes in future attempts to quit. CONCLUSIONS: COPD was both misdiagnosed and missed. Case finding and effective use of spirometry testing could improve diagnosis. Side effects of smoking cessation medications and difficulties during attempts to quit smoking are common. Health professionals should emphasise evidence-based treatments, and closely monitor quitting difficulties and side effects of cessation aids. TRIAL REGISTRATION: Australian New Zealand Clinical Trials Registry ACTRN12614001155684.

https://onlinelibrary.wiley.com/doi/abs/10.5694/mja17.00664

Magnussen, H., M. Arzt, et al. (2017). **"Aclidinium bromide improves symptoms and sleep quality in COPD: a pilot study."** Eur Respir J **49**(6)
https://erj.ersjournals.com/content/erj/49/6/1700485.full.pdf

Man, K. N., Z. Tian, et al. (2018). **"Satisfaction, preference and error occurrence of three dry powder inhalers as assessed by a cohort naive to inhaler operation."** Int J Chron Obstruct Pulmon Dis **13**: 1949-1963.
Background: Inhaled medication is central to the treatment of COPD. Various types of inhaler devices, which directly deliver medication to the lung, have been developed. However, patients often exhibit incorrect techniques of inhaler usage. Effectiveness of therapy may be affected by the ease of device usage, size, convenience of use, durability, clarity of instructions and device preferences of patients. This study compares the satisfaction and preference, as well as error occurrence, with the use of Genuair((R)), Ellipta and Breezhaler by healthy subjects in Hong Kong. Subjects and methods: One hundred and thirty healthy Hong Kong Chinese subjects aged >/=40 years without a previous diagnosis of COPD and asthma and with no experience of using dry powder inhalers (DPIs) were recruited. Subjects learned to use the three DPIs by initially reading the instructions and then observing a demonstration with verbal explanation. The number of errors committed was evaluated. Subjects also completed a questionnaire to indicate their satisfaction and preference. Results: The satisfaction score of comfort for Breezhaler was significantly higher than that for Ellipta (p</=0.05), while the satisfaction score on confidence to have inhaled the entire dose was highest for Genuair compared with Ellipta (p</=0.0001) or Breezhaler (p</=0.05). The overall satisfaction score was significantly higher for Genuair than Ellipta (p</=0.05) or Breezhaler (p</=0.01). After reading the instructions, the highest number of subjects committing one or more critical errors was with Breezhaler (97) followed by Genuair (70) and then Ellipta (33). Demonstration reduced the number of critical errors made by subjects for each DPI to one third or lower. Conclusion: Breezhaler seemed to be more comfortable and easy to carry, but users made less critical errors when using Ellipta after reading the instructions only. Genuair provided the clearest indication of correct dose preparation and inhalation.

https://www.dovepress.com/getfile.php?fileID=42633

Martinelli, B., V. A. Pires Di Lorenzo, et al. (2018). **"Cardiorespiratory repercussions according to the abdominal circumference measurement of men with obstructive respiratory disorder submitted to respiratory physiotherapy."** Physiother Theory Pract **34**(11): 835-845.

PURPOSE: To examine the effect of respiratory physiotherapy among men with obstructive respiratory disorder, in relation to abdominal circumference (AC). METHODS: Quasi-experimental study including 26 men split into two groups according to AC(cm): 1) < 102 (ACrisk-free); and 2) >/= 102 (ACrisk). Heart rate variability (HRV), diastolic blood pressure (DBP), oxygen saturation (SpO2), FEV1/FVC, slow vital capacity (SVC), inspiratory capacity (IC), maximal inspiratory pressure (PImax), thoracoabdominal amplitude (AI) were measured: before (M1); 5 min after the physiotherapy (i.e. breathing exercises for airway clearance and active kinesiotherapy) (M2); and at follow-up, 30 min after physiotherapy (M3). RESULTS: The groups differed in age, body mass index and body fat %. At M2 IC was different between groups (ACrisk-free< ACrisk). There was an increase in HRV indexes, PImax, SpO2, axillary AI, FEV1/FVC, and reduction in HR for ACrisk-free. There was a decrease in AI and an increase in DBP for ACrisk. CONCLUSION: In men with obstructive respiratory disorder, increased AC measurement limited the thoracoabdominal expansibility and induced a rise of the DBP. Respiratory physiotherapy promotes an increase of cardiac modulation and inspiratory capacity for men with obstructive respiratory disorder.

https://www.tandfonline.com/doi/full/10.1080/09593985.2018.1430195

Milosavljevic, A., T. Aspden, et al. (2018). **"Community pharmacist-led interventions and their impact on patients' medication adherence and other health outcomes: a systematic review."** Int J Pharm Pract **26**(5): 387-397.

INTRODUCTION: Medication adherence can be defined as the extent to which one's medication-taking behaviour follows that mutually agreed upon by the prescribing physician. Optimal medication adherence is often deemed crucial for the success of a patient's treatment, as suboptimal adherence may lead to treatment failure and unnecessary medical expenditure. Increasing evidence has highlighted the positive contribution community pharmacist-led interventions can have on improving patients' adherence and health outcomes. OBJECTIVES: To provide an overview of the published literature on community pharmacist-led interventions and their effectiveness in improving patients' adherence and health outcomes. METHODS: A search strategy was developed, aiming to retrieve published reports of community pharmacy interventions worldwide. Medline, EMBASE, International Pharmaceutical Abstracts, Google Scholar and ProQuest Dissertations and Theses databases were searched. Articles meeting the inclusion criteria were collated, relevant data extracted, and a risk of bias assessment undertaken. KEY FINDINGS: Twenty-two studies were included in the analysis, and their outcomes were reported in 26 peer-reviewed journal articles. Community pharmacist-led interventions have been shown to improve patients' adherence and contribute to better blood pressure control, cholesterol management, chronic obstructive pulmonary disease and asthma control. Studies in this review, however, did not report statistically significant effects of interventions on diabetes or depression control. CONCLUSION: Community pharmacist-led interventions have been shown to contribute to improved adherence and better disease control. Future research should attempt to better understand which particular intervention components make the greatest contribution towards improving adherence and health outcomes, for patients with different medical conditions.

https://onlinelibrary.wiley.com/doi/pdf/10.1111/ijpp.12462

Morrow, J. D., X. Zhou, et al. (2017). **"Functional interactors of three genome-wide association study genes are differentially expressed in severe chronic obstructive pulmonary disease lung tissue."** Sci Rep **7**: 44232.

In comparison to genome-wide association studies (GWAS), there has been poor replication of gene expression studies in chronic obstructive pulmonary disease (COPD). We performed microarray gene expression profiling on a large sample of resected lung tissues from subjects with severe COPD. Comparing 111

COPD cases and 40 control smokers, 204 genes were differentially expressed; none were at significant GWAS loci. The top differentially expressed gene was HMGB1, which interacts with AGER, a known COPD GWAS gene. Differentially expressed genes showed enrichment for putative interactors of the first three identified COPD GWAS genes IREB2, HHIP, and FAM13A, based on gene sets derived from protein and RNA binding studies, RNA-interference, a murine smoking model, and expression quantitative trait locus analyses. The gene module most highly associated for COPD in Weighted Gene Co-Expression Network Analysis (WGCNA) was enriched for B cell pathways, and shared seventeen genes with a mouse smoking model and twenty genes with previous emphysema studies. As in other common diseases, genes at COPD GWAS loci were not differentially expressed; however, using a combination of network methods, experimental studies and careful phenotype definition, we found differential expression of putative interactors of these genes, and we replicated previous human and mouse microarray results.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5347019/pdf/srep44232.pdf

Nevarez-Sida, A., A. J. Castro-Bucio, et al. (2017). **"Costos medicos directos en pacientes con enfermedad pulmonar obstructiva Cronica en Mexico."** Value Health Reg Issues **14**: 9-14.

INTRODUCTION: chronic obstructive pulmonary disease (COPD) is a progressive, incurable and potentially mortal. COPD generates a high burden of illness and decreased quality of life in patients. The aim of this study was to determine the direct medical cost of COPD and the primary variables associated. METHODOLOGY: We conducted a multicenter clinical study, based in a retrospective cohort as base of a partial economic evaluation in patients diagnosed with moderate to severe COPD. It was considered an institutional point of view to determine medical costs, with an annual time horizon. For analysis of associations between explanatory and end point variables, a generalized lineal regression model was developed. RESULTS: We analyzed data from 283 patients, Fifty-nine percent were women, the average age was 72 years +/- 11, Sixty-five percent of patients had a history of smoking and 57.6 % were exposed to wood smoke. The annual direct medical costs (MXN 2016) was 20,754 and 41,887 for patients with moderate and severe COPD, respectively, this difference is mainly due to the use of oxygen as well as longer hospital stay (12.9 vs. 24.7 days) of patients with severe COPD. CONCLUSIONS: Although the severity level is associated with greater health care costs, the quality of life of the patients should be considered carefully because it is inversely associated with the cost of care for patients with COPD.

https://ac.els-cdn.com/S2212109917300158/1-s2.0-S2212109917300158-main.pdf?_tid=66a88c84-5015-45a7-9867-162939bc694b&acdnat=1547772229_c697b4fa6f2cb9231ded7b4b2f26d954

Ostridge, K., N. P. Williams, et al. (2018). **"Relationship of CT-quantified emphysema, small airways disease and bronchial wall dimensions with physiological, inflammatory and infective measures in COPD."** Respir Res **19**(1): 31.

BACKGROUND: COPD is a complex, heterogeneous disease characterised by progressive development of airflow limitation. Spirometry provides little information about key aspects of pathology and is poorly related to clinical outcome, so other tools are required to investigate the disease. We sought to explore the relationships between quantitative CT analysis with functional, inflammatory and infective assessments of disease to identify the utility of imaging to stratify disease to better predict outcomes and disease response. METHODS: Patients from the AERIS study with moderate-very severe COPD underwent HRCT, with image analysis determining the quantity of emphysema (%LAA<- 950), small airways disease (E/I MLD) and bronchial wall thickening (Pi10). At enrolment subjects underwent lung function testing, six-minute walk testing (6MWT), blood sampling for inflammatory markers and sputum sampling for white cell differential and microbiological culture and PCR. RESULTS: 122 subjects were included in this analysis. Emphysema and small airways disease had independent associations with airflow obstruction (beta = - 0.34, p < 0.001 and beta = - 0.56, p < 0.001). %LAA<- 950 had independent associations with gas transfer (beta = - 0.37, p < 0.001) and E/I MLD with RV/TLC (beta = 0.30, p =0.003). The distance walked during the 6MWT was not associated with CT parameters, but exertional desaturation was

independently associated with emphysema (beta = 0.73, p < 0.001). Pi10 did not show any independent associations with lung function or functional parameters. No CT parameters had any associations with sputum inflammatory cells. Greater emphysema was associated with lower levels of systemic inflammation (CRP beta = - 0.34, p < 0.001 and fibrinogen beta = - 0.28, p =0.003). There was no significant difference in any of the CT parameters between subjects where potentially pathogenic bacteria were detected in sputum and those where it was not. CONCLUSIONS: This study provides further validation for the use of quantitative CT measures of emphysema and small airways disease in COPD as they showed strong associations with pulmonary physiology and functional status. In contrast to this quantitative CT measures showed few convincing associations with biological measures of disease, suggesting it is not an effective tool at measuring disease activity.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5819274/pdf/12931_2018_Article_734.pdf

Rabe, K. F., P. M. A. Calverley, et al. (2017). **"Effect of roflumilast in patients with severe COPD and a history of hospitalisation."** Eur Respir J **50**(1)
https://erj.ersjournals.com/content/erj/50/1/1700158.full.pdf

Reychler, G., E. Debier, et al. (2018). **"Intrapulmonary Percussive Ventilation as an Airway Clearance Technique in Subjects With Chronic Obstructive Airway Diseases."** Respir Care **63**(5): 620-631.
BACKGROUND: Airway clearance techniques are regularly proposed as a part of the treatment in chronic obstructive airway diseases. Intrapulmonary percussive ventilation (IPV) is used as an airway clearance technique in patients affected by excessive lung secretions. The aim of this systematic review is to summarize the physiological and clinical effects related to the use of IPV as an airway clearance technique in chronic obstructive airway diseases. METHODS: This systematic review followed the PRISMA guidelines. Randomized, controlled, comparative, and cohort studies investigating IPV as an airway clearance technique were identified and reviewed from 3 databases. Two reviewers independently assessed study quality and reviewed the selected studies. RESULTS: 278 subjects from 12 studies were included in the final analysis, with 3 diseases studied. Only one of the included studies had a sample size > 50 subjects. The main findings showed that IPV improves gas exchange during exacerbation and could reduce the hospital length of stay for patients with COPD. In subjects with cystic fibrosis, neither lung function nor other parameters were improved. CONCLUSIONS: The systematic use of IPV as an airway clearance technique in chronic obstructive airway diseases is not supported by sufficiently strong evidence to recommend routine use in this patient population.

http://rc.rcjournal.com/content/63/5/620.short

Rogliani, P., V. Brusasco, et al. (2018). **"Multidimensional approach for the proper management of a complex chronic patient with chronic obstructive pulmonary disease."** Expert Rev Respir Med **12**(2): 103-112.
INTRODUCTION: Chronic obstructive pulmonary disease (COPD) is frequently associated with comorbidities occurring either independently or as consequences of COPD. Areas covered: This review examines the interactions between the pathophysiology of COPD and the most frequent comorbidities, and highlights the need for multidimensional clinical strategies to manage COPD patients with comorbidities. Expert commentary: Most COPD patients need to be approached in a complex and multifactorial scenario. The diagnosis of COPD is necessarily based on the presence of chronic respiratory symptoms and poorly reversible airflow obstruction, but exacerbations and comorbidities need to be considered in the evaluation of disease severity and prognosis in individual patients. More importantly, defining the precise relationship between COPD and comorbidities for each patient is the basis for a correct therapeutic approach.

https://www.tandfonline.com/doi/full/10.1080/17476348.2018.1417041

Schuler, M., M. Wittmann, et al. (2018). **"Including changes in dyspnea after inpatient rehabilitation improves prediction models of exacerbations in COPD."** Respir Med **141**: 87-93.

BACKGROUND: Reducing the probability of future exacerbations is one of the main goals of pulmonary rehabilitation (PR) in COPD. Recent studies identified predictors of future exacerbations. However, PR might alter both predictors and number of exacerbations. OBJECTIVES: This secondary analysis examined which predictors assessed at both the beginning and the end of PR predict the risk of moderate (i.e. use of cortisone and/or antibiotics) and severe (hospitalization) exacerbations in the year after PR. METHODS: A total of n=383 COPD patients (34.7% female, mean age=57.8 years (SD=7.1), mean FEV1%pred=51.0 (SD=14.9)) who attended a 3-week inpatient PR were included. Number of moderate and severe exacerbations were assessed one year after PR (T2) via questionnaires. Potential predictors were assessed at the beginning (T0) and the end (T1) of PR. Negative binomial regression models were used. RESULTS: The mean numbers of severe (Ms)/moderate (Mm) exacerbations in the year after PR (Ms,t2=0.19; Mm, t2=1.07) was reduced compared to the numbers of exacerbations in the year before PR (Ms,t1=0.50, p<0.001; Mm,t1=1.21, p=0.051). Previous exacerbations, retirement, change in dyspnea (for severe exacerbations) and dyspnea at T1 (for moderate exacerbations) were identified as significant predictors. CONCLUSIONS: PR might alter associations between predictors and future exacerbations. Dyspnea at the end of PR or change in dyspnea are better predictors than dyspnea at the beginning of PR.

https://www.resmedjournal.com/article/S0954-6111(18)30225-7/fulltext

Suzuki, M., S. Muro, et al. (2018). **"Effects of acupuncture on nutritional state of patients with stable chronic obstructive pulmonary disease (COPD): re-analysis of COPD acupuncture trial, a randomized controlled trial."** BMC Complement Altern Med **18**(1): 287.

BACKGROUND: There are an increasing number of evidences that chronic obstructive pulmonary disease (COPD) is a systemic illness and that bodyweight loss is its prominent manifestation. We focused on the nutritional outcomes to find out the effectiveness of acupuncture on nutritional state of COPD patients and on their prognosis in our previous interventional study. METHODS: The present study is re-analysis of our previous interventional study, COPD Acupuncture Trial (CAT) published in 2012. Data from CAT was re-analyzed in terms of nutritional status, inflammatory biomarkers, and prognostic index. Nutritional states were evaluated by the measurements of body weight, body composition, and muscle strength, and the nutritional hematological examination results (retinol-binding protein (RBP), prealbumin (PA), transferrin (Tf), and hemoglobin (Hb) in serum), and inflammation biomarkers such as carboxyhemoglobin (COHb), High sensitivity C-reactive protein (Hs-CRP), Tumor Necrosis Factor-alpha (TNF-alpha), Interleukin 6 (IL-6), and Serum Amyloid A (SAA) were measured. The BODE index was measured in terms of prognosis. These measurements were compared between the real acupuncture group (RAG) and the placebo acupuncture group (PAG). All data are presented as mean (SD) or mean (95% CI). The difference between baseline and final volumes was compared using analysis of covariance (ANCOVA). Moreover, correlations between nutritional hematological examination scores and inflammation biomarker parameters were assessed using Spearman's rank correlation coefficient. RESULTS: After 12 weeks, the change in body weight was significantly greater in the RAG compared with the PAG (mean [SD] difference from baseline: 2.5 [0.4] in RAG vs - 0.5 [1.4] in PAG; mean difference between the groups: 3.00, 95% CI, 2.00 to 4.00 with ANCOVA). Patients in RAG also had improvements in the results of nutritional hematological examination (RBP, PA, Tf, Hb), Inflammation biomarkers (TNF-alpha, IL-6, SAA, Hs-CRP, COHb) and the BODE index. CONCLUSION: This study demonstrated some clear evidences that acupuncture can be a useful adjunctive therapy to improve nutritional state of COPD patients. TRIAL REGISTRATION: UMIN Clinical Trials Registry (UMIN000001277). Retrospectively registered.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6201549/pdf/12906_2018_Article_2341.pdf

Tashkin, D. P., M. Miravitlles, et al. (2018). **"Concomitant inhaled corticosteroid use and the risk of pneumonia in COPD: a matched-subgroup post hoc analysis of the UPLIFT(R) trial."** Respir Res **19**(1): 196.

BACKGROUND: Use of inhaled corticosteroids (ICS) increases the risk of pneumonia in chronic obstructive pulmonary disease (COPD), but the magnitude of risk with different ICS remains unclear. METHODS: A post hoc analysis of the 4-year UPLIFT(R) trial to assess whether pneumonia risk differed by type of ICS (fluticasone propionate [FP], other ICS, or no ICS) in permanent users (defined by use until end of study) or in users at baseline (sensitivity analysis). RESULTS: For the permanent-users analysis, 825 patients receiving FP throughout the trial, 825 patients receiving other ICS and 825 patients not receiving ICS were matched on relevant baseline features 1:1:1. A significantly greater risk of pneumonia was observed for FP versus no ICS: the hazard ratio (HR) for risk of pneumonia was 1.33 (95% confidence interval [CI] 1.00, 1.75; p = 0.046) and the rate ratio (RR) was 1.58 (95% CI 1.05, 2.37; p = 0.028). A greater risk was also found for FP versus other ICS: HR 1.28 (95% CI 0.97, 1.68; p = 0.078) and RR 1.48 (95% CI 1.00, 2.19; p = 0.049). A higher proportion of patients on FP were hospitalized with pneumonia (7.9%) versus other ICS (6.7%) or no ICS (5.9%). Whilst other ICS use was associated with the highest number of fatal pneumonia events, the total number of fatal pneumonia incidents was low. A similar pattern was observed in the sensitivity analyses, which included 4002 patients on different treatments at baseline (FP, other ICS, and no ICS) and considered potential switches during the study. CONCLUSION: The results support existing evidence of an increased pneumonia risk with FP use compared with other ICS and no ICS use in patients with COPD. Healthcare professionals should evaluate the risk-benefit ratio of using ICS when making treatment decisions with their patients. TRIAL REGISTRATION: Post hoc analysis of UPLIFT(R). ClinicalTrials.gov number: NCT00144339 . Retrospectively registered September 2, 2005.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6173940/pdf/12931_2018_Article_874.pdf

Vanderlei, F. M., F. Zandonadi, et al. (2018). **"Acute Effects of Different Types of Resistance Training on Cardiac Autonomic Modulation in COPD."** Respir Care **63**(8): 1050-1059.

BACKGROUND: An exercise modality that has been gaining significant importance in the rehabilitation of subjects with COPD is resistance training. When considering that patients with COPD present alterations in autonomic cardiac modulation caused by the disease itself, it is necessary to investigate the behavior of the autonomic nervous system in relation to this type of exercise. Thus, the objective of this study was to compare the acute effects of resistance training with elastic tubes, elastic bands, and conventional weightlifitng on the behavior of cardiac autonomic modulation in post-exercise recovery in subjects with COPD. METHODS: Thirty-four subjects with COPD performed an single session of resistance training divided according to the therapeutic resource used: elastic tubes (n = 10), elastic bands (n = 11), and conventional bodybuilding (n = 13). For analysis of cardiac autonomic modulation, the heart rate was obtained beat to beat at rest and immediately after the end of the session for 60 min in a seated position. Heart rate variability indices were obtained in the time and frequency domains. RESULTS: The 3 therapeutic resource types used in the single session of resistance training promoted changes in heart rate variability linear indices in the time and frequency domains; however, post-exercise recovery time was similar for all protocols performed. CONCLUSIONS: After single resistance training the elastic tubes group presented a minimum alteration in the post-exercise recovery of cardiac autonomic modulation in the subjects with COPD; however, at 5 min after exercising, the subjects with COPD had already recovered. Therefore, if the purpose of the training is to restore autonomic cardiac modulation, the use of elastic tubes is suggested, when considering their low cost and versatility.

http://rc.rcjournal.com/content/63/8/1050.short

Varas, A. B., S. Cordoba, et al. (2018). **"Effectiveness of a community-based exercise training programme to increase physical activity level in patients with chronic obstructive pulmonary disease: A randomized controlled trial."** Physiother Res Int **23**(4): e1740.

BACKGROUND AND PURPOSE: The exercise training included in pulmonary rehabilitation (PR) programmes improves exercise capacity and quality of life in patients with chronic obstructive pulmonary disease (COPD). Nevertheless, the duration of these effects is limited, and the implementation of PR is still insufficient. Moreover, the physical activity level of COPD patients is low, and it is not modified with the classic PR programmes. The purpose of this study was to assess the effects of a community-based PR programme designed to increase physical activity in COPD patients. METHODS: Stable COPD patients were assigned to either an experimental group (EG, n = 17) who followed a community-based 8-week programme consisting of exercise training through walking and a plan to increase activity, using a pedometer for feedback; or a control group (n = 16), who followed general recommendations to walk more every day. The following were evaluated postintervention, after 3 months, and after 12 months: exercise capacity (endurance shuttle test [EST]), physical activity (steps/day and modified Baecke questionnaire), quality of life (St. George's Respiratory Questionnaire [SGRQ]), dyspnoea (modified Medical Research Council scale), and exacerbations. RESULTS: Postintervention, the EG showed significant improvements in EST times (7.6 min [4.4, 10.7]), distance (549 m [282, 815]; $p < 0.01$, both), number of steps (3,361 [1,553, 5,118]), and Baecke scores (1.6 [0.2, 3.1], $p < 0.01$). SGRQ scores decreased (-5.4 [-8.6, -2.4], $p < 0.01$). These results remained evident after 3 and 12 months ($p < 0.01$). There were no differences between the groups nor in the exacerbations or dyspnoea. A significant association was found between increase in physical activity level, improvement in exercise capacity, and quality of life during the period monitored. CONCLUSIONS: A community-based programme of exercise training through walking and increased physical activity, using pedometers as feedback, produces short- and long-term improvements in exercise capacity, physical activity level, and quality of life in COPD patients.

https://onlinelibrary.wiley.com/doi/abs/10.1002/pri.1740

Vitacca, M., D. Kaymaz, et al. (2018). **"Non-invasive ventilation during cycle exercise training in patients with chronic respiratory failure on long-term ventilatory support: A randomized controlled trial."** Respirology **23**(2): 182-189.

BACKGROUND AND OBJECTIVE: The role of non-invasive ventilation (NIV) during exercise training (ET) in patients with chronic respiratory failure (CRF) is still unclear. The aim of this study was to test whether NIV during ET had an additional effect in increasing the 6-min walking distance (6MWD) and cycle endurance time compared with ET alone. METHODS: All patients underwent 20 sessions of cycle training over 3 weeks and were randomly assigned to ET with NIV or ET alone. Outcome measures were 6MWD (primary outcome), incremental and endurance cycle ergometer exercise time, respiratory muscle function, quality of life by the Maugeri Respiratory Failure questionnaire (MRF-28), dyspnoea (Medical Research Council scale) and leg fatigue at rest. RESULTS: Forty-two patients completed the study. Following training, no significant difference in 6MWD changes were found between groups. Improvement in endurance time was significantly greater in the NIV group compared with the non-NIV training group (754 +/- 973 vs 51 +/- 406 s, P = 0.0271); dyspnoea improved in both groups, while respiratory muscle function and leg fatigue improved only in the NIV ET group. MRF-28 improved only in the group training without NIV. CONCLUSION: In CRF patients on long-term NIV and long-term oxygen therapy (LTOT), the addition of NIV to ET sessions resulted in an improvement in endurance time, but not in 6MWD.

https://onlinelibrary.wiley.com/doi/pdf/10.1111/resp.13181

Watz, H., K. Tetzlaff, et al. (2018). **"Spirometric changes during exacerbations of COPD: a post hoc analysis of the WISDOM trial."** Respir Res **19**(1): 251.

BACKGROUND: Exacerbations of chronic obstructive pulmonary disease (COPD) are associated with loss of lung function and poor outcomes for patients. However, there are limited data on the time course of changes

in forced expiratory volume in 1 s (FEV1) preceding the first reported symptom and after the start of an exacerbation. METHODS: WISDOM was a multinational, randomized, double-blind, active-controlled, 52-week study in patients with severe-to-very severe COPD. Patients received triple therapy (long-acting muscarinic antagonist and long-acting beta2-agonist/inhaled corticosteroid [ICS]) for 6 weeks, and were randomized to continue triple therapy or stepwise withdrawal of the ICS (dual bronchodilator group). After suitable training, patients performed daily spirometry at home using a portable, battery-operated spirometer. In the present post hoc analysis, patients who continued to perform daily home spirometry and completed at least one measurement per week for a 56-day period before and after the start of a moderate or severe exacerbation were included. Missing values were imputed by linear interpolation (intermittent), backfilling (beginning) or carry forward (end). Exacerbation onset was the first day of a reported symptom of exacerbation. RESULTS: Eight hundred and eighty-eight patients in the WISDOM study had a moderate/severe exacerbation after the complete ICS withdrawal visit; 360 of them contributed at least one FEV1 measure per week for the 8 weeks before and after the event and are included in this analysis. Mean daily FEV1 began to decline from approximately 2 weeks before the onset of symptoms of an exacerbation, dropping from 0.907 L (mean Days - 56 to - 36 before the exacerbation) to 0.860 L on the first day of the exacerbation. After the exacerbation, mean FEV1 improved but did not return to pre-exacerbation levels (mean Days 36-56 after the exacerbation, 0.875 L). The pattern of FEV1 changes around exacerbations was similar in the triple therapy and dual bronchodilator groups, and a similar pattern was seen in moderate and severe exacerbations when analysed separately. CONCLUSIONS: Mean lung function starts to decline prior to the first reported symptoms of an exacerbation, and does not recover to pre-exacerbation levels 8 weeks after the event. TRIAL REGISTRATION: WISDOM (ClinicalTrials.gov number, NCT00975195).

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6293570/pdf/12931_2018_Article_944.pdf

Wu, W., X. Liu, et al. (2018). **"Effectiveness of water-based Liuzijue exercise on respiratory muscle strength and peripheral skeletal muscle function in patients with COPD."** Int J Chron Obstruct Pulmon Dis **13**: 1713-1726.

Objects: The purpose of this study was to quantitatively assess the effects of water-based Liuzijue exercise on patients with COPD and compare it with land-based Liuzijue exercise. Materials and methods: Participants were randomly allocated to one of three groups: the water-based Liuzijue exercise group (WG), the land-based Liuzijue exercise group (LG), and the control group (CG). CG participants accepted no exercise intervention, while training groups performed Liuzijue exercise according to Health Qigong Liuzijue (People's Republic of China) in different environments for 60-min sessions twice a week for 3 months. Results: Of the 50 patients enrolled, 45 (90%) completed the 3-month intervention. The CG showed decreased expiratory muscle strength, extensor and flexor endurance ratio (ER) of the elbow joints and flexor peak torque (PT), total work (TW), and ER of the knee joints ($p<0.05$). Both training groups showed improved respiratory muscle strength, which differed from the CG ($p<0.001$). In addition, extensor and flexor TW of the elbow joints in the training groups were increased ($p<0.01$), and the WG differed from the CG in extensor TW and ER and flexor TW ($p<0.01$), while the LG differed from the CG in flexor TW and extensor ER ($p<0.05$). PT, PT/body weight (BW), and TW in the knee joint extensor in the training groups were increased as well (PT and PT/BW: $p<0.05$, TW: $p<0.01$), and the WG differed from the CG in terms of knee joints outcomes, while the LG differed from the CG in flexor TW only ($p<0.05$). Conclusion: Water-based Liuzijue exercise has beneficial effects on COPD patients' respiratory muscle strength and peripheral skeletal muscle function, and additional benefits may exist in endurance of upper limbs and strength and endurance of lower limbs when compared with land-based Liuzijue exercise.

https://www.dovepress.com/getfile.php?fileID=42315

Yoshimura, K., Y. Suzuki, et al. (2018). **"Utility of serum Aspergillus-galactomannan antigen to evaluate the risk of severe acute exacerbation in chronic obstructive pulmonary disease."** PLoS One **13**(6): e0198479.

BACKGROUND: Recent studies have shown that the microbiome, namely Aspergillus species, play a previously unrecognized role in both stable and exacerbated chronic obstructive pulmonary disease (COPD). Galactomannan is a major component of the Aspergillus cell wall that has been widely used as a diagnostic marker. OBJECTIVES: To explore whether serum levels of Aspergillus-galactomannan antigen could be used to evaluate the risk of severe acute exacerbation of COPD (AE-COPD). METHODS: We measured the Aspergillus-galactomannan antigen levels of 191 patients with stable COPD, and examined its clinical relevance including AE-COPD. RESULTS: There were 77 (40.3%) patients who were positive for serum Aspergillus-galactomannan antigen (>/=0.5). High Aspergillus-galactomannan antigen level (>/=0.7) was associated with older age and presence of bronchiectasis and cysts on computed tomography images. Compared to patients with low Aspergillus-galactomannan antigen level (<0.7), patients with high Aspergillus-galactomannan antigen level had significantly higher incidence of severe AE-COPD (P = 0.0039, Gray's test) and respiratory-related mortality (P = 0.0176, log-rank test). Multivariate analysis showed that high Aspergillus-galactomannan antigen level was independently associated with severe AE-COPD (hazard ratio, 2.162; 95% confidence interval, 1.267-3.692; P = 0.005). CONCLUSION: Serum Aspergillus-galactomannan antigen was detected in patients with COPD, and elevated serum Aspergillus-galactomannan antigen was associated with severe AE-COPD.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5988315/pdf/pone.0198479.pdf

You, K., R. Bendl, et al. (2018). **"Randomized clinical trial of elective resection versus observation in diverticulitis with extraluminal air or abscess initially managed conservatively."** Br J Surg **105**(8): 971-979.

BACKGROUND: The aim of this RCT was to determine whether elective resection following successful non-operative management of a first episode of acute sigmoid diverticulitis complicated by extraluminal air with or without abscess is superior to observation in terms of recurrence rates. METHODS: This was a single-centre, sequential design RCT. Patients were randomized to elective surgery or observation following non-operative management and colonoscopy. Non-operative management included nil by mouth, intravenous fluids, intravenous antibiotics, CT with intravenous contrast on arrival at hospital, and repeat CT with intravenous and rectal contrast on day 3 in hospital. The primary endpoint was recurrent diverticulitis at 24 months. Patients with a history of sigmoid diverticulitis, immunosuppression or peritonitis were not included. RESULTS: Of 137 screened patients, 107 were assigned randomly to elective surgery (26) or observation (81), and underwent the allocated intervention after successful non-operative management. Conservative management failed in 15 patients. Groups were similar in age, sex, BMI, co-morbidities and colorectal POSSUM. Rates of recurrent diverticulitis differed significantly in the elective surgery and observation groups (8 versus 32 per cent; P = 0.019) at a mean(s.d.) follow-up of 37.8(8.6) and 35.2(9.2) months respectively. There was also a significant difference in time to recurrence (median 11 versus 7 months; P = 0.015). A total of 28 patients presented with recurrent diverticulitis complicated by extraluminal air and/or abscess (2 elective surgery, 26 observation), all of whom recovered with repeat non-operative management. CONCLUSION: The majority of patients observed following conservative management of diverticulitis with local extraluminal air do not require elective surgery. Registration number: NCT01986686 (http://www.clinicaltrials.gov).

https://onlinelibrary.wiley.com/doi/abs/10.1002/bjs.10868

Zhang, X., Y. Chen, et al. (2018). **"Pharmacological mechanism of roflumilast in the treatment of asthma-COPD overlap."** Drug Des Devel Ther **12**: 2371-2379.

Asthma-COPD overlap (ACO) is a type of incomplete obstructive airway disease that has a high incidence and mortality. Nevertheless, there is currently no clear definition of ACO and no effective intervention. The newly discovered phosphodiesterase-4 inhibitor, roflumilast, has shown initial efficacy for treating

asthma, COPD, and ACO. The mechanism of roflumilast, however, remains unclear, and there has been no interpretation through systematic review to date. The determination of a definite mechanism of roflumilast will guide the clinician's decisions regarding medication use, standardized diagnosis, and treatment guidelines. For this reason, we have systematically reviewed the therapeutic mechanism of roflumilast for ACO and provided reference for the clinical application of roflumilast in ACO.

https://www.dovepress.com/getfile.php?fileID=43435

Systematic reviews and clinical trials – In Process

Search strategy: (COPD[Title] OR Emphysema[Title] OR Chronic Obstructive Pulmonary Disease[Title] OR Chronic Bronchitis[Title]) AND (inprocess[sb] OR Publisher[sb]) AND ("meta-analysis"[All Fields] OR "meta-analyses"[All Fields] OR "randomised"[All] OR "random"[All Fields]) AND English[lang]

Asamoah-Boaheng, M., L. Acheampong, et al. (2018). **"Association between early history of asthma and COPD diagnosis in later life: a systematic review and meta-analysis."** Int J Epidemiol **47**(6): 1865-1876.

Background: Whereas most studies have reported prior history/diagnosis of asthma as an independent risk factor for chronic obstructive pulmonary disease (COPD) development in later life, no systematic review and meta-analysis has been conducted to synthesize these observational studies. The aim of this review is to investigate associations between prior history of asthma and later development of COPD. Methods: We conducted a comprehensive search in PubMed, CINAHL and EMBASE for studies related to prior history of asthma and COPD diagnosis. Articles were screened for relevance by two independent reviewers. Methodological quality was independently assessed and data extracted for qualitative and quantitative review. We explored heterogeneity and performed a publication bias check. Results: From the 1260 articles retrieved, 9 were included in the qualitative review and 7 in the meta-analysis. History of asthma was associated with developing COPD in later life (Inverse Variance Random-effects model, odds ratio: 7.87, 95% confidence interval: 5.40-11.45, $p < 0.00001$). Conclusions: Studies with high methodological quality provided sufficient evidence to suggest that individuals with previous history of asthma have an increasing likelihood of developing COPD in later life.

https://academic.oup.com/ije/article-abstract/47/6/1865/5113268?redirectedFrom=fulltext

Aziz, M. I. A., L. E. Tan, et al. (2018). **"Comparative efficacy of inhaled medications (ICS/LABA, LAMA, LAMA/LABA and SAMA) for COPD: a systematic review and network meta-analysis."** Int J Chron Obstruct Pulmon Dis **13**: 3203-3231.

Purpose: To assess the comparative efficacy of short-acting muscarinic antagonists (SAMAs), long-acting muscarinic antagonists (LAMAs), LAMA in combination with long-acting beta-agonists (LABAs; LAMA/LABAs) and inhaled corticosteroids (ICS) in combination with LABA (ICS/LABAs) for the maintenance treatment of COPD. Materials and methods: We systematically reviewed 74 randomized controlled trials (74,832 participants) published up to 15 November 2017, which compared any of the interventions (SAMA [ipratropium], LAMA [aclidinium, glycopyrronium, tiotropium, umeclidinium], LAMA/LABA [aclidinium/formoterol, indacaterol/glycopyrronium, tiotropium/olodaterol, umeclidinium/vilanterol] and ICS/LABA [fluticasone/vilanterol, budesonide/formoterol, salmeterol/fluticasone]) with each other or with placebo. A random-effects network meta-analysis combining direct and indirect evidence was conducted to examine the change from baseline in trough FEV1, transition dyspnea index, St George's Respiratory Questionnaire and frequency of adverse events at weeks 12 and 24. Results: Inconsistency models were not statistically significant for all outcomes. LAMAs, LAMA/LABAs and ICS/LABAs led to a significantly greater improvement in trough FEV1 compared with placebo and SAMA monotherapy at weeks 12 and 24. All LAMA/LABAs, except aclidinium/formoterol, were statistically significantly better than LAMA monotherapy and ICS/LABAs in improving trough FEV1. Among the LAMAs, umeclidinium showed statistically significant improvement in trough FEV1 at week 12 compared to tiotropium and glycopyrronium, but the results were not clinically significant. LAMA/LABAs had the highest probabilities of being ranked the best agents in FEV1 improvement. Similar trends were observed for the transition dyspnea index and St George's Respiratory Questionnaire outcomes. There were no significant differences in the incidences of adverse events among all treatment options. Conclusion: LAMA/LABA showed the greatest improvement in trough FEV1 at weeks 12 and 24 compared with the other inhaled drug classes, while SAMA showed the least improvement. There were no significant differences among the LAMAs and LAMA/LABAs within their respective classes.

https://www.dovepress.com/getfile.php?fileID=45136

Bajaj, M. K., D. R. Burrage, et al. (2019). **"COPD patients hospitalized with exacerbations have greater cognitive impairment than patients hospitalized with decompensated heart failure."** Clin Interv Aging **14**: 1-8.

Purpose: People with COPD have cognitive dysfunction, which is greater in those hospitalized for exacerbations than in stable outpatients. We tested the hypothesis that cognitive dysfunction at exacerbation is a disease-specific feature of COPD, rather than a nonspecific feature of hospitalization for acute illness, by comparing cognition between patients hospitalized for acute COPD exacerbations and those with worsening heart failure (HF). Patients and methods: A total of 40 hospital inpatients were recruited, 20 patients with COPD exacerbations and 20 patients with congestive or left-sided HF. Exclusion criteria included previous stroke, known neurological disease, and marked alcohol excess. Participants completed the Montreal cognitive assessment (MoCA) and Hospital Anxiety and Depression Scale (HADS) and underwent spirometry and review of clinical records. Results: Age (mean+/-SD, COPD 73+/-10; HF 76+/-11 years), acute illness severity (Acute Physiology and Chronic Health Evaluation [APACHE]-II, COPD 15.4+/-3.5; HF 15.9+/-3.0), comorbidities (Charlson index, COPD 1.3+/-1.9; HF 1.6+/-1.5), and educational background were similar between COPD and HF groups. MoCA total was significantly lower in COPD than in HF (COPD 20.6+/-5.6; HF 24.8+/-3.5, P=0.007); however, significance was lost after correction for age, sex, and pack year smoking history. When compared with HF patients, the COPD cohort performed worse on the following domains of the MoCA: visuospatial function (median [IQR], COPD 0 [1]; HF 2 [1], P=0.003), executive function (COPD 2 [1]; HF 3 [1], P=0.035), and attention (COPD 4 [3]; HF 6 [2], P=0.020). Age (P=0.012) and random glucose concentration (P=0.041) were associated with cognitive function in whole group analysis, with pack year smoking history reaching borderline significance (P=0.050). Conclusion: Total MoCA score for COPD and HF indicated that both groups had mild cognitive impairment, although this was greater in people with COPD. Mechanisms underlying the observed cognitive dysfunction in COPD remain unclear but appear related to blood glucose concentrations and greater lifetime smoking load.

https://www.dovepress.com/getfile.php?fileID=47036

Bayat, A., N. Saki, et al. (2019). **"Is COPD associated with alterations in hearing? A systematic review and meta-analysis."** Int J Chron Obstruct Pulmon Dis **14**: 149-162.

Background and aims: COPD is an irreversible or persistent airflow obstruction, which affects up to 600 million people globally. The primary purpose of this systematic review was to explore the COPD-based alteration in the auditory system function by conducting a quantitative analysis of presently published data. Materials and methods: We systematically searched seven diverse electronic databases and manual searching of references to identify relevant studies. Data from the selected studies were rated by two investigators independently in a blinded fashion. Meta-analysis was done on pooled data using Cochrane's Review Manager 5.3. Results: Sixteen articles received suitable scores and were thus included for further processes. Hearing loss (HL) was defined as a change in pure tone audiometry (PTA) thresholds, auditory brainstem response (ABR), and auditory P300 parameters. ABR wave was significantly elongated in patients with COPD than in controls (standardized mean difference [SMD]=0.27, 95% CI: 0.05-0.48, P=0.02). PTA was significantly higher in patients with COPD when compared with controls (SMD=1.76, 95% CI: 0.43-3.08, P=0.0004). We found that patients with COPD had a significantly higher latency than controls (SMD=1.30, 95% CI: 0.79-1.80, P=0.0001). Conclusion: COPD patients had considerably greater incidence of HL when compared with controls. Interestingly, although the mean PTA thresholds at every frequency for COPD patients were higher than those for controls, these values were still in the slight to mild HL ranges. Prolonged ABR wave latencies in the COPD patients suggest retro-cochlear involvement. Thus, COPD most frequently clusters with HL, but it is worth noting that alteration in hearing is not always recognized by medical experts as a frequent comorbidity associated with COPD.

https://www.dovepress.com/getfile.php?fileID=47276

Beijers, R., S. M. D. Huysmans, et al. (2018). **"The effect of acute and 7-days dietary nitrate on mechanical efficiency, exercise performance and cardiac biomarkers in patients with chronic obstructive pulmonary disease."** Clin Nutr **37**(6 Pt A): 1852-1861.

BACKGROUND & AIMS: Many COPD patients have a reduced exercise capacity and mechanical efficiency and are at increased cardiometabolic risk. This study aimed to assess acute and 7-days effects of dietary nitrate on mechanical efficiency, exercise performance and cardiac biomarkers in patients with COPD. METHODS: This double-blind, randomized cross-over placebo controlled trial included 20 mild-to-moderate COPD patients (66.6 +/- 7.5 years) with moderate exercise impairments and decreased mechanical efficiency, normal BMI (26 +/- 3 kg/m(2)) but high prevalence of abdominal obesity (83.3%). Subjects were randomly allocated to the treatment order of 7 days sodium nitrate ingestion (approximately 8 mmol/day) and 7 days placebo (NaCl solution) or vice versa, separated by a washout period. Before (Day-1) and after (Day-7) both intervention periods resting metabolic rate and the metabolic response during submaximal cycle ergometry, cycling endurance time, plasma nitrate and nitrite levels, cardiac plasma biomarkers (e.g. cardiac troponin T, Nt-proBNP and creatinine kinase) and blood pressure were measured. Subsequently, gross, net and delta mechanical efficiency were calculated. RESULTS: Plasma nitrate and nitrite concentrations increased at Day-1 and Day-7 after sodium nitrate but not after placebo ingestion. Systolic and diastolic blood pressure did not change following nitrate ingestion. Furthermore, no differences were observed in gross, net, and delta mechanical efficiency during submaximal exercise, cycling endurance time and cardiac biomarkers between nitrate and placebo on Day-1 and Day-7. Meta-analysis of all available studies in COPD also showed no beneficial effect of beetroot juice on systolic and diastolic blood pressure. CONCLUSION: Acute as well as 7-days sodium nitrate supplementation does not modulate mechanical efficiency, blood pressure or cardiac biomarkers in mild-to-moderate COPD patients.

https://www.clinicalnutritionjournal.com/article/S0261-5614(17)31384-5/fulltext

Cazzola, M., P. Rogliani, et al. (2018). **"Triple therapy versus single and dual long-acting bronchodilator therapy in COPD: a systematic review and meta-analysis."** Eur Respir J **52**(6)We performed a meta-analysis to compare the impact of triple combination therapy with inhaled corticosteroids (ICS), long-acting beta2-agonists (LABAs) and long-acting muscarinic receptor antagonists (LAMAs) versus LABA/LAMA combination therapy or single long-acting bronchodilator therapy in chronic obstructive pulmonary disease. The ICS/LABA/LAMA combination reduced the risk of exacerbation (relative risk 0.70, 95% CI 0.53-0.94) and improved trough forced expiratory volume in 1 s (mean difference in mL +37.94, 95% CI 18.83-53.89) versus LABA/LAMA combination therapy. The protective effect of triple combination therapy versus LABA/LAMA combination therapy against risk of exacerbation was greater in patients with blood eosinophil counts >/=300 cells.microL(-1) (relative risk 0.57, 95% CI 0.48-0.68). While approximately 38 patients had to be treated for 1 year with ICS/LABA/LAMA combination therapy to prevent one exacerbation compared to LABA/LAMA combination therapy, the number needed to treat (NNT) was approximately 21 when compared to single long-acting bronchodilator therapy. The person-based NNT per year of ICS/LABA/LAMA combination therapy versus LABA/LAMA combination therapy was significantly ($p<0.05$) lower in patients with eosinophil counts >/=300 cells.microL(-1) (NNT value: 8.58) than in those with counts <300 cells.microL(-1) (NNT value: 46.28). The risk of pneumonia did not differ between ICS/LABA/LAMA combination therapy and its comparators. The number needed to harm was approximately 195. This meta-analysis suggests that patients on single long-acting bronchodilator therapy or LABA/LAMA combination therapy, who still have exacerbations and have blood eosinophil counts >/=300 cells.microL(-1), could benefit from ICS/LABA/LAMA combination therapy.

https://erj.ersjournals.com/content/52/6/1801586

Cui, Y., L. Luo, et al. (2018). **"Long-term macrolide treatment for the prevention of acute exacerbations in COPD: a systematic review and meta-analysis."** Int J Chron Obstruct Pulmon Dis **13**: 3813-3829.

Background: Acute exacerbation of COPD (AECOPD) is associated with an increased hospitalization and mortality. Azithromycin and erythromycin are the recommended drugs to reduce the risk of exacerbations. However, the most suitable duration of therapy and drug-related adverse events are still a matter of debate. The aim of this meta-analysis was to assess the current evidence regarding the efficacy and safety of long-term macrolide treatment for COPD. Materials and methods: We comprehensively searched PubMed, Embase, the Cochrane Library, and the Web of Science and performed a systematic review and cumulative meta-analysis of all randomized controlled trials (RCTs) and retrospective studies. Results: Eleven RCTs and one retrospective study including a total of 2,151 cases were carried out. Long-term macrolide treatment significantly reduced the total number of cases with one or more exacerbations (OR=0.40; 95% CI=0.24-0.65; P<0.01) and the rate of exacerbations per patient per year (risk ratio [RR]=0.60; 95% CI=0.45-0.78; P<0.01). Subgroup analyses showed that the minimum duration for drug efficacy for both azithromycin and erythromycin therapy was 6 months. In addition, macrolide therapy could improve the St George Respiratory Questionnaire (SGRQ) total score (P<0.01) but did not achieve the level of clinical significance. The frequency of hospitalizations was not significantly different between the treatment and control groups (P=0.50). Moreover, chronic azithromycin treatment was more likely to increase adverse events (P<0.01). Conclusion: Prophylactic azithromycin or erythromycin treatment has a significant effect in reducing the frequency of AECOPD in a time-dependent manner. However, long-term macrolide treatment could increase the occurrence of adverse events and macrolide resistance. Future large-scale, well-designed RCTs with extensive follow-up are required to identify patients in whom the benefits outweigh risks.

https://www.dovepress.com/getfile.php?fileID=46404

Ding, Z., K. Wang, et al. (2019). **"Association between glutathione S-transferase gene M1 and T1 polymorphisms and chronic obstructive pulmonary disease risk: A meta-analysis."** Clin Genet **95**(1): 53-62.

Chronic obstructive pulmonary disease (COPD) is a severe lung disease characterized by long-term breathing problems. A series of studies have indicated that the glutathione S-transferase genes M1 and T1 are associated with COPD susceptibility; however, the result still remains inconclusive. This meta-analysis was performed to estimate the effect of GSTM1 and GSTT1 polymorphisms in COPD risk. Eligible case-control studies published between January 2000 and December 2017 was searched and retrieved. A total of 37 articles were screened out, including 4674 COPD patients and 5006 controls. Overall, our results found that GSTM1 and GSTT1 null genotypes significantly increased the risk of COPD (GSTM1: odds ratio [OR] = 1.52, 95% confidence interval [CI] = 1.31-1.77, P <.00001; GSTT1: OR = 1.28, 95% CI = 1.09-1.50, P = .003). Subgroup analysis by ethnicity suggested that there was a close association between GSTM1 null polymorphism and COPD susceptibility in each studied ethnicity, while GSTT1 null polymorphism only showed association with Asian COPD patients. Moreover, we also found that joint GSTM1/GSTT1 null genotypes showed a high association with increased COPD susceptibility (OR = 1.42, 95% CI = 1.21-1.66, P < .0001). In conclusion, our results indicated that GSTM1 null, GSTT1 null, and the combined GSTM1/GSTT1 null genotypes might be risk factors in the development of COPD. However, future case-control studies with large-scale participants are still required to further estimate these associations.

https://onlinelibrary.wiley.com/doi/abs/10.1111/cge.13373

Early, F., I. Wellwood, et al. (2018). **"Interventions to increase referral and uptake to pulmonary rehabilitation in people with COPD: a systematic review."** Int J Chron Obstruct Pulmon Dis **13**: 3571-3586.

Pulmonary rehabilitation (PR) reduces the number and duration of hospital admissions and readmissions, and improves health-related quality of life in patients with COPD. Despite clinical guideline recommendations, under-referral and limited uptake to PR contribute to poor treatment access. We

reviewed published literature on the effectiveness of interventions to improve referral to and uptake of PR in patients with COPD when compared to standard care, alternative interventions, or no intervention. The review followed recognized methods. Search terms included "pulmonary rehabilitation" AND "referral" OR "uptake" applied to MEDLINE, EMBASE, CINAHL, PsycINFO, ASSIA, BNI, Web of Science, and Cochrane Library up to January 2018. Titles, abstracts, and full papers were reviewed independently and quality appraised. The protocol was registered (PROSPERO # 2016:CRD42016043762). We screened 5,328 references. Fourteen papers met the inclusion criteria. Ten assessed referral and five assessed uptake (46,146 patients, 409 clinicians, 82 hospital departments, 122 general practices). One was a systematic review which assessed uptake. Designs, interventions, and scope of studies were diverse, often part of multifaceted evidence-based management of COPD. Examples included computer-based prompts at practice nurse review, patient information, clinician education, and financial incentives. Four studies reported statistically significant improvements in referral (range 3.5%-36%). Two studies reported statistically significant increases in uptake (range 18%-21.5%). Most studies had methodological and reporting limitations. Meta-analysis was not conducted due to heterogeneity of study designs. This review demonstrates the range of approaches aimed at increasing referral and uptake to PR but identifies limited evidence of effectiveness due to the heterogeneity and limitations of study designs. Research using robust methods with clear descriptions of intervention, setting, and target population is required to optimize access to PR across a range of settings.

https://www.dovepress.com/getfile.php?fileID=45737

Faner, R., J. D. Morrow, et al. (2019). **"Do sputum or circulating blood samples reflect the pulmonary transcriptomic differences of COPD patients? A multi-tissue transcriptomic network META-analysis."** Respir Res **20**(1): 5.

BACKGROUND: Previous studies have identified lung, sputum or blood transcriptomic biomarkers associated with the severity of airflow limitation in COPD. Yet, it is not clear whether the lung pathobiology is mirrored by these surrogate tissues. The aim of this study was to explore this question. METHODS: We used Weighted Gene Co-expression Network Analysis (WGCNA) to identify shared pathological mechanisms across four COPD gene-expression datasets: two sets of lung tissues (L1 n = 70; L2 n = 124), and one each of induced sputum (S; n = 121) and peripheral blood (B; n = 121). RESULTS: WGCNA analysis identified twenty-one gene co-expression modules in L1. A robust module preservation between the two L datasets was observed (86%), with less preservation in S (33%) and even less in B (23%). Three modules preserved across lung tissues and sputum (not blood) were associated with the severity of airflow limitation. Ontology enrichment analysis showed that these modules included genes related to mitochondrial function, ion-homeostasis, T cells and RNA processing. These findings were largely reproduced using the consensus WGCNA network approach. CONCLUSIONS: These observations indicate that major differences in lung tissue transcriptomics in patients with COPD are poorly mirrored in sputum and are unrelated to those determined in blood, suggesting that the systemic component in COPD is independently regulated. Finally, the fact that one of the preserved modules associated with FEV1 was enriched in mitochondria-related genes supports a role for mitochondrial dysfunction in the pathobiology of COPD.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6325784/pdf/12931_2018_Article_965.pdf

Felcar, J. M., V. S. Probst, et al. (2018). **"Effects of exercise training in water and on land in patients with COPD: a randomised clinical trial."** Physiotherapy **104**(4): 408-416.

OBJECTIVES: To compare the effects of two similar 6-month protocols of high-intensity exercise training, in water and on land, in patients with chronic obstructive pulmonary disease (COPD). DESIGN: Randomised controlled trial. SETTING: University-based outpatient clinic. PARTICIPANTS: Thirty-six patients with predominantly moderate-to-severe COPD completed the study. INTERVENTION: Patients were evaluated at baseline, at 3 months and at the end of the programme (i.e. 6 months). For both groups, the 6-month protocol consisted of high-intensity endurance and strength exercises with gradual increase in time

and/or workload, totalling 60 sessions. MAIN OUTCOMES: Objective monitoring of physical activity in daily life (PADL, primary outcome), lung function, peripheral and respiratory muscle strength, body composition, maximal and submaximal exercise capacity, functional status, quality of life, and symptoms of anxiety and depression. RESULTS: After 6 months of training, a significant improvement in PADL was seen for both groups [mean difference (95% confidence interval): land group 993 (358 to 1628) steps/day; water group 1669 (404 to 2934) steps/day]. Significant improvements were also seen in inspiratory, expiratory and peripheral muscle strength; maximal and submaximal exercise capacity; quality of life and functional status for both groups. There were no significant improvements in lung function, body composition, and symptoms of anxiety and depression for either group. No difference was found in the magnitude of improvement between the two types of training for any outcome. CONCLUSION: High-intensity exercise training in water generates similar effects compared with training on land in patients with moderate-to-severe COPD, rendering it an equally beneficial therapeutic option for this population. CLINICAL TRIAL REGISTRATION NUMBER: NCT01691131.

https://www.physiotherapyjournal.com/article/S0031-9406(18)30043-9/fulltext

Fricke, K., H. Schneider, et al. (2018). **"Nasal high flow, but not supplemental O2, reduces peripheral vascular sympathetic activity during sleep in COPD patients."** Int J Chron Obstruct Pulmon Dis **13**: 3635-3643.

Introduction: Patients with COPD have increased respiratory loads and altered blood gases, both of which affect vascular function and sympathetic activity. Sleep, particularly rapid eye movement (REM) sleep, is known to exacerbate hypoxia and respiratory loads. Therefore, we hypothesize that nasal high flow (NHF), which lowers ventilatory loads, reduces sympathetic activity during sleep and that this effect depends on COPD severity. Methods: We performed full polysomnography in COPD patients (n=17; FEV1, 1.6+/-0.6 L) and in matched controls (n=8). Participants received room air (RA) at baseline and single night treatment with O2 (2 L/min) and NHF (20 L/min) in a random order. Finger pulse wave amplitude (PWA), a measure of vascular sympathetic tone, was assessed by photoplethysmography. Autonomic activation (AA) events were defined as PWA attenuation >/=30% and indexed per hour for sleep stages (AA index [AAI]) at RA, NHF, and O2). Results: In COPD, sleep apnea improved following O2 (REM-apnea hypopnea index [AHI] with RA, O2, and NHF: 18.6+/-20.9, 12.7+/-18.1, and 14.4+/-19.8, respectively; P=0.04 for O2 and P=0.06 for NHF). REM-AAI was reduced only following NHF in COPD patients (AAI-RA, 21.5+/-18.4 n/h and AAI-NHF, 9.9+/-6.8 n/h, P=0.02) without changes following O2 (NHF-O2 difference, P=0.01). REM-AAI reduction was associated with lung function expressed as FEV1 and FVC (FEV1: r=-0.59, P=0.001; FEV1/FVC: r=-0.52 and P=0.007). Conclusion: NHF but not elevated oxygenation reduces peripheral vascular sympathetic activity in COPD patients during REM sleep. Sympathetic off-loading by NHF, possibly related to improved breathing mechanics, showed a strong association with COPD severity.

https://www.dovepress.com/getfile.php?fileID=45900

Gendron, L. M., A. Nyberg, et al. (2018). **"Active mind-body movement therapies as an adjunct to or in comparison with pulmonary rehabilitation for people with chronic obstructive pulmonary disease."** Cochrane Database Syst Rev **10**: Cd012290.

BACKGROUND: Active mind-body movement therapies (AMBMTs), including but not limited to yoga, tai chi, and qigong, have been applied as exercise modalities for people with chronic obstructive pulmonary disease (COPD). AMBMT strategies have been found to be more effective than usual care; however, whether AMBMT is inferior, equivalent, or superior to pulmonary rehabilitation (PR) in people with COPD remains to be determined. OBJECTIVES: To assess the effects of AMBMTs compared with, or in addition to, PR in the management of COPD. SEARCH METHODS: We searched the Cochrane Airways Group Specialised Register of trials and major Chinese databases, as well as trial registries from inception to July 2017. In addition, we searched references of primary studies and review articles. We updated this search in July 2018 but have not yet incorporated these results. SELECTION CRITERIA: We included (1) randomised controlled trials (RCTs) comparing AMBMT (i.e. controlled breathing and/or focused meditation/attention interventions for which patients must actively move their joints and muscles for at

least four weeks with no minimum intervention frequency) versus PR (any inpatient or outpatient, community-based or home-based rehabilitation programme lasting at least four weeks, with no minimum intervention frequency, that included conventional exercise training with or without education or psychological support) and (2) RCTs comparing AMBMT + PR versus PR alone in people with COPD. Two independent review authors screened and selected studies for inclusion. DATA COLLECTION AND ANALYSIS: Two review authors independently selected trials for inclusion, extracted outcome data, and assessed risk of bias. We contacted study authors if necessary to ask them to provide missing data. We calculated mean differences (MDs) using a random-effects model. MAIN RESULTS: We included in the meta-analysis 10 studies with 762 participants across one or more comparisons. The sample size of included studies ranged from 11 to 206 participants. Nine out of 10 studies involving all levels of COPD severity were conducted in China with adults from 55 to 88 years of age, a higher proportion of whom were male (78%). Nine out of 10 studies provided tai chi and/or qigong programmes as AMBMT, and one study provided yoga. Overall, the term 'PR' has been uncritically applied in the vast majority of studies, which limits comparison of AMBMT and PR. For example, eight out of 10 studies considered walking training as equal to PR and used this as conventional exercise training within PR. Overall study quality for main comparisons was moderate to very low mainly owing to imprecision, indirectness (exercise component inconsistent with recommendations), and risk of bias issues. The primary outcomes for our review were quality of life, dyspnoea, and serious adverse events.When researchers compared AMBMT versus PR alone (mainly unstructured walking training), statistically significant improvements in disease-specific quality of life (QoL) (St. George's Respiratory Questionnaire (SGRQ) total score) favoured AMBMT: mean difference (MD) -5.83, 95% confidence interval (CI) -8.75 to -2.92; three trials; 249 participants; low-quality evidence. The common effect size, but not the 95% CI around the pooled treatment effect, exceeded the minimal clinically important difference (MCID) of minus four. The COPD Assessment Test (CAT) also revealed statistically significant improvements favouring AMBMT over PR, with scores exceeding the MCID of three, with an MD of 6.58 units (95% CI -9.16 to - 4.00 units; one trial; 74 participants; low-quality evidence). Results show no between-group differences with regard to dyspnoea measured by the modified Medical Research Council Scale (MD 0.00 units, 95% CI -0.37 to 0.37; two trials; 127 participants; low-quality evidence), the Borg Scale (MD 0.44 units, 95% CI -0.88 to 0.00; one trial; 139 participants; low-quality evidence), or the Chronic Respiratory Questionnaire (CRQ) Dyspnoea Scale (MD -0.21, 95% CI -2.81 to 2.38; one trial; 11 participants; low-quality evidence). Comparisons of AMBMT versus PR alone did not include assessments of generic quality of life, adverse events, limb muscle function, exacerbations, or adherence.Comparisons of AMBMT added to PR versus PR alone (mainly unstructured walking training) revealed significant improvements in generic QoL as measured by Short Form (SF)-36 for both the SF-36 general health summary score (MD 5.42, 95% CI 3.82 to 7.02; one trial; 80 participants; very low-quality evidence) and the SF-36 mental health summary score (MD 3.29, 95% CI 1.45 to 4.95; one trial; 80 participants; very low-quality evidence). With regard to disease-specific QoL, investigators noted no significant improvement with addition of AMBMT to PR versus PR alone (SGRQ total score: MD -2.57, 95% CI -7.76 to 2.62 units; one trial; 192 participants; moderate-quality evidence; CRQ Dyspnoea Scale score: MD 0.04, 95% CI -2.18 to 2.26 units; one trial; 80 participants; very low-quality evidence). Comparisons of AMBMT + PR versus PR alone did not include assessments of dyspnoea, adverse events, limb muscle function, exacerbations, or adherence. AUTHORS' CONCLUSIONS: Given the quality of available evidence, the effects of AMBMT versus PR or of AMBMT added to PR versus PR alone in people with stable COPD remain inconclusive. Evidence of low quality suggests better disease-specific QoL with AMBMT versus PR in people with stable COPD, and evidence of very low quality suggests no differences in dyspnoea between AMBMT and PR. Evidence of moderate quality shows that AMBMT added to PR does not result in improved disease-specific QoL, and evidence of very low quality suggests that AMBMT added to PR may lead to better generic QoL versus PR alone. Future studies with adequate descriptions of conventional exercise training (i.e. information on duration, intensity, and progression) delivered by trained professionals with a comprehensive understanding of respiratory physiology, exercise science, and the pathology of COPD are needed before definitive conclusions can be drawn regarding treatment outcomes with AMBMT versus PR or AMBMT added to PR versus PR alone for patients with COPD.

Guillien, A., T. Soumagne, et al. (2019). **"COPD, airflow limitation and chronic bronchitis in farmers: a systematic review and meta-analysis."** Occup Environ Med **76**(1): 58-68.

INTRODUCTION: The current definition of chronic obstructive pulmonary disease (COPD) associates persistent airflow limitation and chronic respiratory symptoms. Agricultural work has been associated with an increased risk of developing COPD, but the prevalence and definition of the disease vary greatly between studies. This meta-analysis aimed to assess the association between agricultural work and COPD using the most widely used definitions of the disease. METHODS: Inclusion criteria were: (1) design: cross-sectional or longitudinal, (2) groups: at least one group of farmers and a control group of non-farmers, (3) outcome: prevalence or unadjusted OR of COPD, airflow limitation and/or chronic bronchitis, (4) study subjects: groups of exposed subjects comprising >/=30 individuals and with a mean age >/=40 years and (5) language: English and French language, full-length, original publications in peer-reviewed journals. RESULTS: In total, 22 manuscripts were included in the meta-analysis. Eight studies assessed only the prevalence of airflow limitation, nine assessed only the prevalence of chronic bronchitis and four assessed the prevalence of both these parameters. Only one assessed the prevalence of COPD according to its current definition, and this study also provided the prevalence of airflow limitation. Ten studies showed a positive association between farming exposure and airflow limitation or chronic bronchitis, and 12 showed no association (OR (95% CI)=1.77 (1.50 to 2.08), p<0.001). Cattle, swine, poultry and crop farming were associated with either airflow limitation or chronic bronchitis. CONCLUSION: Although some features of COPD are associated with some agricultural work, well-designed studies with appropriate diagnostic criteria should be conducted to draw strong conclusions about the relationship between COPD and farming.

https://oem.bmj.com/content/76/1/58.long

Gulea, C., R. Zakeri, et al. (2018). **"Effect of beta-blocker therapy on clinical outcomes, safety, health-related quality of life and functional capacity in patients with chronic obstructive pulmonary disease (COPD): a protocol for a systematic literature review and meta-analysis with multiple treatment comparison."** BMJ Open **8**(11): e024736.

INTRODUCTION: Patients with chronic obstructive pulmonary disease (COPD) who have a clinical indication for beta-blocker therapy, are often not prescribed such medication, despite evidence suggesting that beta-blockers are not associated with adverse respiratory outcomes. The primary objective of this systematic review and meta-analysis is to examine the class effect of beta-blocker use in patients with COPD. We will focus on a broad range of endpoints including, clinical, safety, and patient-centric outcomes such as health related quality of life (HRQoL) and functional capacity. A secondary objective is to explore potential within-class variation in the effects of beta-blockers among patients with COPD, and rank individual agents according to their relative benefit(s). METHODS AND ANALYSIS: MEDLINE, Embase, The Cochrane Library and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) databases will be systematically searched, from inception to present, to identify randomised controlled trials (RCTs) and other prospective and interventional studies of beta-blocker use in patients with COPD which report on the outcomes of interest. Relative treatment effects with respect to mortality, COPD exacerbations, all-cause hospitalisation, lung function, HRQoL and exercise capacity will be summarised by meta-analysis. Individual treatments (agents) will be compared in a Bayesian network meta-analysis including RCT and observational data, if feasible. ETHICS AND DISSEMINATION: The results of the study will be submitted for publication in a peer-reviewed journal. Only previously published aggregate data will be used for the purpose of this review. PROSPERO REGISTRATION NUMBER: CRD42018098983.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6252680/pdf/bmjopen-2018-024736.pdf

Hansen, E. F., J. D. Hove, et al. (2018). **"Automated oxygen control with O2matic((R)) during admission with exacerbation of COPD."** Int J Chron Obstruct Pulmon Dis **13**: 3997-4003.

Purpose: It is a challenge to control oxygen saturation (SpO2) in patients with exacerbations of COPD during admission. We tested a newly developed closed-loop system, O2matic((R)), and its ability to keep SpO2

within a specified interval compared with manual control by nursing staff. Patients and methods: We conducted a crossover trial with patients admitted with an exacerbation of COPD and hypoxemia (SpO2 </=88% on room air). Patients were monitored with continuous measurement of SpO2. In random order, they had 4 hours with manually controlled oxygen and 4 hours with oxygen delivery controlled by O2matic. Primary outcome was time within a prespecified SpO2 target interval. Secondary outcomes were time with SpO2 <85%, time with SpO2 below target but not <85%, and time with SpO2 above target. Results: Twenty patients were randomized and 19 completed the study. Mean age was 72.4 years and mean FEV1 was 0.72 L (33% of predicted). Patients with O2matic-controlled treatment were within the SpO2 target interval in 85.1% of the time vs 46.6% with manually controlled treatment (P<0.001). Time with SpO2 <85% was 1.3% with O2matic and 17.9% with manual control (P=0.01). Time with SpO2 below target but not <85% was 9.0% with O2matic and 25.0% with manual control (P=0.002). Time with SpO2 above target was not significantly different between treatments (4.6% vs 10.5%, P=0.2). Patients expressed high confidence and a sense of safety with automatic oxygen delivery. Conclusion: O2matic was able to effectively control SpO2 for patients admitted with an exacerbation of COPD. O2matic was significantly better than manual control to maintain SpO2 within target interval and to reduce time with unintended hypoxemia.

https://www.dovepress.com/getfile.php?fileID=46990

Hayden, L. P., M. H. Cho, et al. (2018). **"Childhood asthma is associated with COPD and known asthma variants in COPDGene: a genome-wide association study."** Respir Res **19**(1): 209.

BACKGROUND: Childhood asthma is strongly influenced by genetics and is a risk factor for reduced lung function and chronic obstructive pulmonary disease (COPD) in adults. This study investigates self-reported childhood asthma in adult smokers from the COPDGene Study. We hypothesize that childhood asthma is associated with decreased lung function, increased risk for COPD, and that a genome-wide association study (GWAS) will show association with established asthma variants. METHODS: We evaluated current and former smokers ages 45-80 of non-Hispanic white (NHW) or African American (AA) race. Childhood asthma was defined by self-report of asthma, diagnosed by a medical professional, with onset at < 16 years or during childhood. Subjects with a history of childhood asthma were compared to those who never had asthma based on lung function, development of COPD, and genetic variation. GWAS was performed in NHW and AA populations, and combined in meta-analysis. Two sets of established asthma SNPs from published literature were examined for association with childhood asthma. RESULTS: Among 10,199 adult smokers, 730 (7%) reported childhood asthma and 7493 (73%) reported no history of asthma. Childhood asthmatics had reduced lung function and increased risk for COPD (OR 3.42, 95% CI 2.81-4.18). Genotype data was assessed for 8031 subjects. Among NHWs, 391(7%) had childhood asthma, and GWAS identified one genome-wide significant association in KIAA1958 (rs59289606, p = 4.82 x 10(- 8)). Among AAs, 339 (12%) had childhood asthma. No SNPs reached genome-wide significance in the AAs or in the meta-analysis combining NHW and AA subjects; however, potential regions of interest were identified. Established asthma SNPs were examined, seven from the NHGRI-EBI database and five with genome-wide significance in the largest pediatric asthma GWAS. Associations were found in the current childhood asthma GWAS with known asthma loci in IL1RL1, IL13, LINC01149, near GSDMB, and in the C11orf30-LRRC32 region (Bonferroni adjusted p < 0.05 for all comparisons). CONCLUSIONS: Childhood asthmatics are at increased risk for COPD. Defining asthma by self-report is valid in populations at risk for COPD, identifying subjects with clinical and genetic characteristics known to associate with childhood asthma. This has potential to improve clinical understanding of asthma-COPD overlap (ACO) and enhance future research into ACO-specific treatment regimens. TRIAL REGISTRATION: ClinicalTrials.gov, NCT00608764 (Active since January 28, 2008).

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6206739/pdf/12931_2018_Article_890.pdf

Herath, S. C., R. Normansell, et al. (2018). **"Prophylactic antibiotic therapy for chronic obstructive pulmonary disease (COPD)."** Cochrane Database Syst Rev **10**: Cd009764.

BACKGROUND: There has been renewal of interest in the use of prophylactic antibiotics to reduce the frequency of exacerbations and improve quality of life in chronic obstructive pulmonary disease (COPD). OBJECTIVES: To determine whether or not regular (continuous, intermittent or pulsed) treatment of COPD patients with prophylactic antibiotics reduces exacerbations or affects quality of life. SEARCH METHODS: We searched the Cochrane Airways Group Trials Register and bibliographies of relevant studies. The latest literature search was performed on 27 July 2018. SELECTION CRITERIA: Randomised controlled trials (RCTs) that compared prophylactic antibiotics with placebo in patients with COPD. DATA COLLECTION AND ANALYSIS: We used the standard Cochrane methods. Two independent review authors selected studies for inclusion, extracted data, and assessed risk of bias. We resolved discrepancies by involving a third review author. MAIN RESULTS: We included 14 studies involving 3932 participants in this review. We identified two further studies meeting inclusion criteria but both were terminated early without providing results. All studies were published between 2001 and 2015. Nine studies were of continuous macrolide antibiotics, two studies were of intermittent antibiotic prophylaxis (three times per week) and two were of pulsed antibiotic regimens (e.g. five days every eight weeks). The final study included one continuous, one intermittent and one pulsed arm. The antibiotics investigated were azithromycin, erythromycin, clarithromycin, doxycyline, roxithromycin and moxifloxacin. The study duration varied from three months to 36 months and all used intention-to-treat analysis. Most of the pooled results were of moderate quality. The risk of bias of the included studies was generally low.The studies recruited participants with a mean age between 65 and 72 years and mostly at least moderate-severity COPD. Five studies only included participants with frequent exacerbations and two studies recruited participants requiring systemic steroids or antibiotics or both, or who were at the end stage of their disease and required oxygen. One study recruited participants with pulmonary hypertension secondary to COPD and a further study was specifically designed to asses whether eradication of Chlamydia pneumoniae reduced exacerbation rates.The co-primary outcomes for this review were the number of exacerbations and quality of life.With use of prophylactic antibiotics, the number of participants experiencing one or more exacerbations was reduced (odds ratio (OR) 0.57, 95% CI 0.42 to 0.78; participants = 2716; studies = 8; moderate-quality evidence). This represented a reduction from 61% of participants in the control group compared to 47% in the treatment group (95% CI 39% to 55%). The number needed to treat for an additional beneficial outcome with prophylactic antibiotics given for three to 12 months to prevent one person from experiencing an exacerbation (NNTB) was 8 (95% CI 5 to 17). The test for subgroup difference suggested that continuous and intermittent antibiotics may be more effective than pulsed antibiotics (P = 0.02, I(2) = 73.3%).The frequency of exacerbations per patient per year was also reduced with prophylactic antibiotic treatment (rate ratio 0.67; 95% CI 0.54 to 0.83; participants = 1384; studies = 5; moderate-quality evidence). Although we were unable to pool the result, six of the seven studies reporting time to first exacerbation identified an increase (i.e. benefit) with antibiotics, which was reported as statistically significant in four studies.There was a statistically significant improvement in quality of life as measured by the St George's Respiratory Questionnaire (SGRQ) with prophylactic antibiotic treatment, but this was smaller than the four unit improvement that is regarded as being clinically significant (mean difference (MD) -1.94, 95% CI -3.13 to -0.75; participants = 2237; studies = 7, high-quality evidence).Prophylactic antibiotics showed no significant effect on the secondary outcomes of frequency of hospital admissions, change in forced expiratory volume in one second (FEV1), serious adverse events or all-cause mortality (moderate-quality evidence). There was some evidence of benefit in exercise tolerance, but this was driven by a single study of lower methodological quality.The adverse events that were recorded varied among the studies depending on the antibiotics used. Azithromycin was associated with significant hearing loss in the treatment group, which was in many cases reversible or partially reversible. The moxifloxacin pulsed study reported a significantly higher number of adverse events in the treatment arm due to the marked increase in gastrointestinal adverse events (P < 0.001). Some adverse events that led to drug discontinuation, such as development of long QTc or tinnitus, were not significantly more frequent in the treatment group than the placebo group but pose important considerations in clinical practice.The development of antibiotic resistance in the community is of major concern. Six studies reported on this, but we were unable to combine results. One study found newly colonised participants to have higher rates of antibiotic resistance. Participants colonised with moxifloxacin-sensitive pseudomonas at initiation of therapy rapidly became resistant with the quinolone treatment. A further study with three active treatment arms found an increase in the degree of antibiotic resistance of isolates in all three arms after 13 weeks treatment. AUTHORS' CONCLUSIONS: Use of continuous and intermittent prophylactic antibiotics results in a clinically significant benefit in reducing exacerbations in COPD patients. All studies of continuous and intermittent antibiotics used macrolides, hence the noted benefit applies only to the

use of macrolide antibiotics prescribed at least three times per week. The impact of pulsed antibiotics remains uncertain and requires further research.The studies in this review included mostly participants who were frequent exacerbators with at least moderate-severity COPD. There were also older individuals with a mean age over 65 years. The results of these studies apply only to the group of participants who were studied in these studies and may not be generalisable to other groups.Because of concerns about antibiotic resistance and specific adverse effects, consideration of prophylactic antibiotic use should be mindful of the balance between benefits to individual patients and the potential harms to society created by antibiotic overuse. Monitoring of significant side effects including hearing loss, tinnitus, and long QTc in the community in this elderly patient group may require extra health resources.

Izquierdo, J. L. and B. G. Cosio (2018). **"The dose of inhaled corticosteroids in patients with COPD: when less is better."** Int J Chron Obstruct Pulmon Dis **13**: 3539-3547.

Background: The use of inhaled corticosteroids (ICS) in combination with bronchodilators in patients with COPD has been shown to decrease the rate of disease exacerbations and to improve the lung function and patients' quality of life. However, their use has also been associated with an increased risk of pneumonia. Materials and methods: We have reviewed existing clinical evidence on the risks and benefits of ICS in COPD, including large randomized clinical trials, meta-analyses, and clinical reviews. Results: A large body of evidence supports the clinical benefits of ICS in patients with COPD in terms of exacerbations, symptoms, lung function, and quality of life. The incidence of adverse events related to ICS, including pneumonia, varies strongly among the studies and seems to be dose dependent, with recent well-designed, large studies on low-dose ICS reporting similar safety profiles in ICS and non-ICS groups. Conclusion: The benefits of ICS in COPD continue to outweigh the risks, especially when lower ICS doses are employed. Given that the data on ICS withdrawal in COPD are scarce and conflicting, we argue that using reduced doses of ICS could be an optimal strategy to manage patients with COPD.

https://www.dovepress.com/getfile.php?fileID=45626

Jolly, K., M. S. Sidhu, et al. (2018). **"Systematic review of the effectiveness of community-based self-management interventions among primary care COPD patients."** NPJ Prim Care Respir Med **28**(1): 44.

COPD self-management reduces hospital admissions and improves health-related quality of life (HRQoL). However, whilst most patients are managed in primary care, the majority of self-management trials have recruited participants with more severe disease from secondary care. We report the findings of a systematic review of the effectiveness of community-based self-management interventions in primary care patients with COPD. We systematically searched eleven electronic databases and identified 12 eligible randomised controlled trials with seven included in meta-analyses for HRQoL, anxiety and depression. We report no difference in HRQoL at final follow-up (St George's Respiratory Questionnaire total score -0.29; 95%CI -2.09, 1.51; I(2) 0%), nor any difference in anxiety or depression. In conclusion, supported self-management interventions delivered in the community to patients from primary care do not appear to be effective. Further research is recommended to identify effective self-management interventions suitable for primary care populations, particularly those with milder disease.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6251904/pdf/41533_2018_Article_111.pdf

Karlsson, S. L., V. Backer, et al. (2019). **"A single administration of glucocorticoid increases exercise capacity in men with stable chronic obstructive pulmonary disease."** Dan Med J **66**(1)INTRODUCTION: Oral use of glucocorticoids is a well-described therapy in the treatment of acute exacerbations of chronic

obstructive pulmonary disease (COPD). Patients with COPD occasionally report subjective benefits of glucocorticoids in terms of fewer symptoms and better exercise performance, even when they do not experience exacerbation. This study investigated whether a single high therapeutic dose of oral glucocorticoid improves short-term exercise tolerance in patients with moderate-to-very severe COPD. METHODS: In a double-blinded crossover design, patients were randomised to either 100 mg of prednisolone or placebo. The study consisted of a baseline visit and two study visits, each seven days apart. The primary endpoint was time to exhaustion (TTE) on an ergometer bike using a submaximal exercise test on 70% of the maximal workload. On every study visit, spirometry, the COPD Assessment Test, maximal inspiratory/expiratory pressure and maximal voluntary contraction of the quadriceps muscle were measured. A total of 14 male patients with grade C/D COPD were randomised. RESULTS: The mean TTE was significantly longer at the prednisolone visit (p = 0.019), whereas no differences were seen on other parameters such as lung function, respiratory symptoms or muscle strength. CONCLUSION: Our finding suggests that COPD patients experience improvements in exercise tolerance from a single high dose of glucocorticoid even in the stable phase of their disease. FUNDING: none. TRIAL REGISTRATION: EudraCT 2012-004503-13.

Koch, R., G. V. G. Rapello, et al. (2018). **"Is Inspiratory Muscle Weakness a Determinant of Endurance Exercise Tolerance During NIV-Supported Exercise in Patients With COPD?"** J Cardiopulm Rehabil Prev **38**(6): E9-e11.

PURPOSE: Previous research has reported that inspiratory muscle weakness is critical to decreased exercise tolerance and exercise tolerance improves with 10 cmH2O pressure support ventilation in patients with chronic obstructive pulmonary disease (COPD). The purpose of this study was to evaluate the effects of proportional assist ventilation (PAV) and continuous positive airway pressure (CPAP) compared with sham on exercise tolerance in patients with and without inspiratory muscle weakness. METHODS: In a prospective design, 12 of 54 patients were eligible after clinical and comprehensive lung function evaluation, including maximum inspiratory pressure (MIP) measurement. Using baseline measures, participants were divided into 2 age-matched groups that differed in regard to MIP (Group 1, MIP <60 cmH2O, and Group 2, MIP >/=60 cmH2O). Each participant performed 3 constant work rate tests with noninvasive support (PAV, CPAP, sham) in random order on different days at 80% of maximal incremental power. RESULTS: During the endurance tests, heart rate, peripheral oxygen saturation (SpO2), dyspnea perception scale, and exercise tolerance were measured. There were no significant differences between groups for heart rate, SpO2, dyspnea perception, or exercise tolerance during PAV, CPAP, or sham-supported exercise (P > .05 for all). CONCLUSIONS: In this small representative group of patients with COPD, inspiratory muscle weakness was not a determining factor of performance during CPAP or PAV-supported aerobic exercise.

Kopsaftis, Z. A., N. S. Sulaiman, et al. (2018). **"Short-acting bronchodilators for the management of acute exacerbations of chronic obstructive pulmonary disease in the hospital setting: systematic review."** Syst Rev **7**(1): 213.

BACKGROUND: Currently, there is a lack of guidelines for the use of short-acting bronchodilators (SABD) in people admitted to hospital for acute exacerbation of chronic obstructive pulmonary disease (AECOPD), despite routine use in practice and risk of cardiac adverse events. AIM: To review the evidence that underpins use and optimal dose, in terms of risk versus benefit, of SABD for inpatient management of AECOPD and collate the results for future guidelines. METHODS: Medline, Embase, the Cochrane Central Register of Controlled Trials, clinicaltrials.gov and International Clinical Trials Registry Platform were searched (inception to November 2017) for published and ongoing studies. Included studies were randomised controlled trials or controlled clinical trials investigating the effect of SABD (beta2-agonist and/or ipratropium) on inpatients with a diagnosis of AECOPD. This review was undertaken in

accordance with PRISMA guidelines and a pre-defined protocol. Due to heterogeneous methodologies, meta-analysis was not possible so the results were synthesised qualitatively. RESULTS: Of 1378 studies identified, 10 met inclusion criteria. Narrative synthesis of 10 studies revealed no significant differences in most outcomes of interest relative to dose, delivery via inhaler or nebuliser, and type of beta2-agonist used. However, some evidence demonstrated significantly increased cardiac side effects with increased dosage of beta2-agonist (45% versus 24%), P<0.05). CONCLUSION: This review identified a paucity of methodologically rigorous evidence evaluating use of SABD among AECOPD. The available evidence did not identify any additional benefits for participants receiving higher doses of short-acting beta2-agonists compared to lower doses, or based on type of delivery method or beta2-agonists used. However, there was a small increase in some adverse events for participants using higher doses of beta2-agonists.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6264607/pdf/13643_2018_Article_860.pdf

Liu, X., P. Li, et al. (2019). **"Effects of home-based prescribed pulmonary exercise by patients with chronic obstructive pulmonary disease: study protocol for a randomized controlled trial."** Trials **20**(1): 41.

BACKGROUND: Chronic obstructive pulmonary disease (COPD) not only affects pulmonary function but also leads to skeletal muscle dysfunction. The various characteristics of different forms of traditional Chinese exercise lead to inconsistent clinical effects in COPD patients. Hence, the present study carefully combined and rearranged liuzijue, wuqinxi, baduanjin, and yijinjing into a pulmonary exercise program targeting COPD patients. METHODS/DESIGN: This study is a single-blind, randomized controlled trial. A random number table will be generated by an independent person. Each number will be placed in a sealed opaque envelop to blind assignment. All outcome assessors will be blinded to group assignment. COPD patients between 40 and 80 years of age, with stable medical treatment and no regular participation in regular exercise in the last 6 months will be included. All participants will be recruited from the Respiratory Medicine Department of Yue-Yang Integrative Medicine Hospital Affiliated to Shanghai University of Traditional Chinese Medicine. All participants will continue to follow their medical treatment. They will be randomly assigned to one of four groups in a 1:1:1:1 ratio: (1) usual care (control group, CG), (2) pulmonary exercise group (PG), (3) resistance exercise group (RG), or (4) combined pulmonary exercise and resistance exercise group (PRG). CG participants will receive medical treatment only. PG participants will perform 60 min of exercise twice a day 7 days a week for 3 months, with 1 day's exercise per week at hospital under guidance and supervision. RG participants will perform 60 min of resistance exercise once a day, three times a week for 3 months, with 1 day's exercise per week at hospital under guidance and supervision. PRG participants will perform 60 min of prescribed pulmonary exercise combined with resistance exercise for 3 months. The outcomes include the isokinetic strength of peripheral skeletal muscle, surface electromyography, 6-min walking distance, 30-s arm curl test, pulmonary function, respiratory muscle strength, dyspnea, body composition, physical activity, quality of life, and Chronic Disease Self-Efficacy Scale. DISCUSSION: The results of this study will compensate for the current inadequate understanding of prescribed pulmonary exercise and may provide a new, simple, convenient, and effective home-based exercise intervention for COPD patients. TRIAL REGISTRATION: Chinese Clinical Trial Registry, ChiCTR-1800017405 . Registered on 28 July 2018.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6330445/pdf/13063_2018_Article_3149.pdf

Maricoto, T., L. Monteiro, et al. (2019). **"Inhaler Technique Education and Exacerbation Risk in Older Adults with Asthma or Chronic Obstructive Pulmonary Disease: A Meta-Analysis."** J Am Geriatr Soc **67**(1): 57-66.

OBJECTIVES: To evaluate the effect of inhaler education programs on clinical outcomes and exacerbation rates in older adults with asthma or chronic obstructive pulmonary disease (COPD). DESIGN: Systematic review and meta-analysis. SETTING AND PARTICIPANTS: Older adults with asthma or COPD, either in primary or secondary health care and pharmacy setting. MEASUREMENTS: We searched the Medline, Embase, and Central databases according to the main eligibility criteria for inclusion: systematic reviews, meta-

analysis, clinical trials and quasi-experimental studies; participants aged 65 and older; education on inhaler technique and reporting of disease control and exacerbation rates. We used the Grading of Recommendations, Assessment, Development and Evaluations scale for quality assessment and used a random-effect model with Mantel-Haenszel adjustment to perform a meta-analysis. RESULTS: We included 8 studies (4 randomized, 4 quasi-experimental) with a total of 1,812 participants. The most frequent type of intervention was physical demonstration of inhaler technique, training with placebo devices. Five studies showed significant reduction in exacerbation rates (pooled risk ratio=0.71, 95% confidence interval=0.59-0.86; p < .001), although effect on disease control and quality of life showed high discrepancy in the reported results, and all randomized studies revealed uncertainty in their risk of bias assessment. CONCLUSION: All interventions seemed to improve inhaler performance and clinically relevant outcomes, but a placebo device could be the most effective. There is evidence that interventions reduce exacerbation risk in older adults, although to an overall moderate degree. J Am Geriatr Soc 67:57-66, 2019.

https://onlinelibrary.wiley.com/doi/abs/10.1111/jgs.15602

Mostafaei, S., A. Kazemnejad, et al. (2018). **"Identification of Novel Genes in Human Airway Epithelial Cells associated with Chronic Obstructive Pulmonary Disease (COPD) using Machine-Based Learning Algorithms."** Sci Rep **8**(1): 15775.

The aim of this project was to identify candidate novel therapeutic targets to facilitate the treatment of COPD using machine-based learning (ML) algorithms and penalized regression models. In this study, 59 healthy smokers, 53 healthy non-smokers and 21 COPD smokers (9 GOLD stage I and 12 GOLD stage II) were included (n = 133). 20,097 probes were generated from a small airway epithelium (SAE) microarray dataset obtained from these subjects previously. Subsequently, the association between gene expression levels and smoking and COPD, respectively, was assessed using: AdaBoost Classification Trees, Decision Tree, Gradient Boosting Machines, Naive Bayes, Neural Network, Random Forest, Support Vector Machine and adaptive LASSO, Elastic-Net, and Ridge logistic regression analyses. Using this methodology, we identified 44 candidate genes, 27 of these genes had been previously been reported as important factors in the pathogenesis of COPD or regulation of lung function. Here, we also identified 17 genes, which have not been previously identified to be associated with the pathogenesis of COPD or the regulation of lung function. The most significantly regulated of these genes included: PRKAR2B, GAD1, LINC00930 and SLITRK6. These novel genes may provide the basis for the future development of novel therapeutics in COPD and its associated morbidities.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6202402/pdf/41598_2018_Article_33986.pdf

Ni, H., S. Moe, et al. (2018). **"Combined aclidinium bromide and long-acting beta2-agonist for chronic obstructive pulmonary disease (COPD)."** Cochrane Database Syst Rev **12**: Cd011594.

BACKGROUND: Several dual bronchodilator combinations of long-acting beta2-agonist (LABA) and long-acting muscarinic antagonist (LAMA) have been approved for treatment of stable chronic obstructive pulmonary disease (COPD). The current GOLD (Global Initiative for Chronic Obstructive Lung Disease) recommendations suggest the use of LABA/LAMA combinations in people with group B COPD with persistent symptoms, group C COPD with further exacerbations on LAMA therapy alone and group D COPD with or without inhaled corticosteroids (ICS). Fixed-dose combination (FDC) of aclidinium/formoterol is one of the approved LABA/LAMA therapies for people with stable COPD. OBJECTIVES: To assess the efficacy and safety of combined aclidinium bromide and long-acting beta2-agonists in stable COPD. SEARCH METHODS: We searched the Cochrane Airways Group Specialised Register (CAGR), ClinicalTrials.gov, World Health Organization (WHO) trials portal, United States Food and Drug Administration (FDA) and manufacturers' websites as well as the reference list of published trials up to 12 October 2018. SELECTION CRITERIA: Parallel-group randomised controlled trials (RCTs) assessing combined aclidinium bromide and LABAs in people with stable COPD. DATA COLLECTION AND ANALYSIS: We used standard methodological procedures expected by Cochrane for data collection

and analysis. The primary outcomes were exacerbations requiring a short course of an oral steroid or antibiotic, or both; quality of life measured by a validated scale and non-fatal serious adverse events (SAEs). Where the outcome or study details were not reported, we contacted the study investigators or pharmaceutical company trial co-ordinators (or both) for missing data. MAIN RESULTS: We identified RCTs comparing aclidinium/formoterol FDC versus aclidinium, formoterol or placebo only. We included seven multicentre trials of four to 52 weeks' duration conducted in outpatient settings. There were 5921 participants, whose mean age ranged from 60.7 to 64.7 years, mostly men with a mean smoking pack-years of 46.4 to 61.3 of which 43.9% to 63.4% were current smokers. They had a moderate-to-severe degree of COPD with a mean postbronchodilator forced expiratory volume in one second (FEV1) between 50.5% and 61% of predicted normal and the baseline mean FEV1 of 1.23 L to 1.43 L. We assessed performance and detection biases as low for all studies whereas selection, attrition and reporting biases were either low or unclear.FDC versus aclidiniumThere was no evidence of a difference between FDC and aclidinium for exacerbations requiring steroids or antibiotics, or both (OR 0.95, 95% CI 0.71 to 1.27; 2 trials, 2156 participants; moderate-certainty evidence); quality of life measured by St George's Respiratory Questionnaire (SGRQ) total score (MD -0.92, 95% CI -2.15 to 0.30); participants with significant improvement in SGRQ score (OR 1.17, 95% CI 0.97 to 1.41; 2 trials, 2002 participants; moderate-certainty evidence); non-fatal SAE (OR 1.19, 95% CI 0.79 to 1.80; 3 trials, 2473 participants; moderate-certainty evidence); hospital admissions due to severe exacerbations (OR 0.62, 95% CI 0.29 to 1.29; 2 trials, 2156 participants; moderate-certainty evidence) or adverse events (OR 0.95, 95% CI 0.76 to 1.18; 3 trials, 2473 participants; moderate-certainty evidence). Compared with aclidinium, FDC improved symptoms (Transitional Dyspnoea Index (TDI) focal score: MD 0.37, 95% CI 0.07 to 0.68; 2 trials, 2013 participants) with a higher chance of achieving a minimal clinically important difference (MCID) of at least one unit improvement (OR 1.34, 95% CI 1.11 to 1.62; high-certainty evidence); the number needed to treat for an additional beneficial outcome (NNTB) being 14 (95% CI 9 to 39).FDC versus formoterolWhen compared to formoterol, combination therapy reduced exacerbations requiring steroids or antibiotics, or both (OR 0.78, 95% CI 0.62 to 0.99; 3 trials, 2694 participants; high-certainty evidence); may decrease SGRQ total score (MD -1.88, 95% CI -3.10 to -0.65; 2 trials, 2002 participants; low-certainty evidence; MCID for SGRQ is 4 units); increased TDI focal score (MD 0.42, 95% CI 0.11 to 0.72; 2 trials, 2010 participants) with more participants attaining an MCID (OR 1.30, 95% CI 1.07 to 1.56; high-certainty evidence) and an NNTB of 16 (95% CI 10 to 60). FDC lowered the risk of adverse events compared to formoterol (OR 0.78, 95% CI 0.65 to 0.93; 5 trials, 3140 participants; high-certainty evidence; NNTB 22). However, there was no difference between FDC and formoterol for hospital admissions, all-cause mortality and non-fatal SAEs.FDC versus placeboCompared with placebo, FDC demonstrated no evidence of a difference in exacerbations requiring steroids or antibiotics, or both (OR 0.82, 95% CI 0.60 to 1.12; 2 trials, 1960 participants; moderate-certainty evidence) or hospital admissions due to severe exacerbations (OR 0.55, 95% CI 0.25 to 1.18; 2 trials, 1960 participants; moderate-certainty evidence), although estimates were uncertain. Quality of life measure by SGRQ total score was significantly better with FDC compared to placebo (MD -2.91, 95% CI -4.33 to -1.50; 2 trials, 1823 participants) resulting in a corresponding increase in SGRQ responders who achieved at least four units decrease in SGRQ total score (OR 1.72, 95% CI 1.39 to 2.13; high-certainty evidence) with an NNTB of 7 (95% CI 5 to 12). FDC also improved symptoms measured by TDI focal score (MD 1.32, 95% CI 0.96 to 1.69; 2 studies, 1832 participants) with more participants attaining at least one unit improvement in TDI focal score (OR 2.51, 95% CI 2.02 to 3.11; high-certainty evidence; NNTB 4). There were no differences in non-fatal SAEs, adverse events and all-cause mortality between FDC and placebo.Combination therapy significantly improved trough FEV1 compared to aclidinium, formoterol or placebo. AUTHORS' CONCLUSIONS: FDC improved dyspnoea and lung function compared to aclidinium, formoterol or placebo, and this translated into an increase in the number of responders on combination treatment. Quality of life was better with combination compared to formoterol or placebo. There was no evidence of a difference between FDC and monotherapy or placebo for exacerbations, hospital admissions, mortality, non-fatal SAEs or adverse events. Studies reported a lower risk of moderate exacerbations and adverse events with FDC compared to formoterol; however, larger studies would yield a more precise estimate for these outcomes.

Oba, Y., E. Keeney, et al. (2018). **"Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): a systematic review and network meta-analysis."** Cochrane Database Syst Rev **12**: Cd012620.

BACKGROUND: Long-acting bronchodilators such as long-acting beta-agonist (LABA), long-acting muscarinic antagonist (LAMA), and LABA/inhaled corticosteroid (ICS) combinations have been used in people with moderate to severe chronic obstructive pulmonary disease (COPD) to control symptoms such as dyspnoea and cough, and prevent exacerbations. A number of LABA/LAMA combinations are now available for clinical use in COPD. However, it is not clear which group of above mentioned inhalers is most effective or if any specific formulation works better than the others within the same group or class. OBJECTIVES: To compare the efficacy and safety of available formulations from four different groups of inhalers (i.e. LABA/LAMA combination, LABA/ICS combination, LAMA and LABA) in people with moderate to severe COPD. The review will update previous systematic reviews on dual combination inhalers and long-acting bronchodilators to answer the questions described above using the strength of a network meta-analysis (NMA). SEARCH METHODS: We identified studies from the Cochrane Airways Specialised Register, which contains several databases. We also conducted a search of ClinicalTrials.gov and manufacturers' websites. The most recent searches were conducted on 6 April 2018. SELECTION CRITERIA: We included randomised controlled trials (RCTs) that recruited people aged 35 years or older with a diagnosis of COPD and a baseline forced expiratory volume in one second (FEV1) of less than 80% of predicted. We included studies of at least 12 weeks' duration including at least two active comparators from one of the four inhaler groups. DATA COLLECTION AND ANALYSIS: We conducted NMAs using a Bayesian Markov chain Monte Carlo method. We considered a study as high risk if recruited participants had at least one COPD exacerbation within the 12 months before study entry and as low risk otherwise. Primary outcomes were COPD exacerbations (moderate to severe and severe), and secondary outcomes included symptom and quality-of-life scores, safety outcomes, and lung function. We collected data only for active comparators and did not consider placebo was not considered. We assumed a class/group effect when a fixed-class model fitted well. Otherwise we used a random-class model to assess intraclass/group differences. We supplemented the NMAs with pairwise meta-analyses. MAIN RESULTS: We included a total of 101,311 participants from 99 studies (26 studies with 32,265 participants in the high-risk population and 73 studies with 69,046 participants in the low-risk population) in our systematic review. The median duration of studies was 52 weeks in the high-risk population and 26 weeks in the low-risk population (range 12 to 156 for both populations). We considered the quality of included studies generally to be good.The NMAs suggested that the LABA/LAMA combination was the highest ranked treatment group to reduce COPD exacerbations followed by LAMA in the both populations.There is evidence that the LABA/LAMA combination decreases moderate to severe exacerbations compared to LABA/ICS combination, LAMA, and LABA in the high-risk population (network hazard ratios (HRs) 0.86 (95% credible interval (CrI) 0.76 to 0.99), 0.87 (95% CrI 0.78 to 0.99), and 0.70 (95% CrI 0.61 to 0.8) respectively), and that LAMA decreases moderate to severe exacerbations compared to LABA in the high- and low-risk populations (network HR 0.80 (95% CrI 0.71 to 0.88) and 0.87 (95% CrI 0.78 to 0.97), respectively). There is evidence that the LABA/LAMA combination reduces severe exacerbations compared to LABA/ICS combination and LABA in the high-risk population (network HR 0.78 (95% CrI 0.64 to 0.93) and 0.64 (95% CrI 0.51 to 0.81), respectively).There was a general trend towards a greater improvement in symptom and quality-of-life scores with the combination therapies compared to monotherapies, and the combination therapies were generally ranked higher than monotherapies.The LABA/ICS combination was the lowest ranked in pneumonia serious adverse events (SAEs) in both populations. There is evidence that the LABA/ICS combination increases the odds of pneumonia compared to LAMA/LABA combination, LAMA and LABA (network ORs: 1.69 (95% CrI 1.20 to 2.44), 1.78 (95% CrI 1.33 to 2.39), and 1.50 (95% CrI 1.17 to 1.92) in the high-risk population and network or pairwise OR: 2.33 (95% CI 1.03 to 5.26), 2.02 (95% CrI 1.16 to 3.72), and 1.93 (95% CrI 1.29 to 3.22) in the low-risk population respectively). There were significant overlaps in the rank statistics in the other safety outcomes including mortality, total, COPD, and cardiac SAEs, and dropouts due to adverse events.None of the differences in lung function met a minimal clinically important difference criterion except for LABA/LAMA combination versus LABA in the high-risk population (network mean difference 0.13 L (95% CrI 0.10 to 0.15). The results of pairwise meta-analyses generally agreed with those of the NMAs. There is no evidence to suggest intraclass/group differences except for lung function at 12 months in the high-risk population. AUTHORS' CONCLUSIONS: The LABA/LAMA combination was the highest ranked treatment group to reduce COPD exacerbations although there was some uncertainty in the results. LAMA containing inhalers may have an advantage over those without a LAMA for preventing COPD exacerbations based on the rank statistics.

Combination therapies appear more effective than monotherapies for improving symptom and quality-of-life scores. ICS-containing inhalers are associated with an increased risk of pneumonia.Our most comprehensive review including intraclass/group comparisons, free combination therapies, 99 studies, and 20 outcomes for each high- and low-risk population summarises the current literature and could help with updating existing COPD guidelines.

O'Neill, B., O. O'Shea, et al. (2018). **"Clinician-Facilitated Physical Activity Intervention Versus Pulmonary Rehabilitation for Improving Physical Activity in COPD: A Feasibility Study."** Copd **15**(3): 254-264.

Pulmonary rehabilitation (PR) may not suit all individuals with chronic obstructive pulmonary disease (COPD) and may not result in increased physical activity. Higher levels of physical activity are associated with reduced mortality and morbidity. The aim of this study was to assess the feasibility of conducting a trial to investigate the effectiveness of a clinician-facilitated physical activity intervention (PAI) versus PR in improving physical activity in patients with COPD referred to PR. In this randomised controlled mixed methods feasibility study, all patients referred to PR who were eligible and willing were assessed at baseline and then randomised to the PAI or to PR. The assessments were repeated post-intervention and at 3-month follow-up. The main outcome was step count measured by Actigraph. Semi-structured interviews were conducted post-intervention. The N = 50 patients; mean (SD) age, 64.1(8.6) years, 24M were recruited and randomised; N = 23 (PAI) and n = 26 (PR): one patient was excluded from the analysis as that person did not meet the GOLD diagnostic criteria. Key feasibility criteria were met; recruitment was 11%, dropouts in PAI were 26% (n = 6) and 50% (n = 13/26) PR. Participants in both groups experienced a range of health benefits from their respective programmes. The PAI appears to be effective in increasing step counts in people with COPD: mean change (standard deviation) [confidence interval] for the PAI group was 972.0(3230.3)[-1080.3 to 3024.4], n = 12 and 4.3(662.7)[-440.9 to 449.5], n = 11 for the PR group. The PAI met all domains of fidelity. This study provides key information to inform a future-randomised controlled trial in physical activity.

https://www.tandfonline.com/doi/full/10.1080/15412555.2018.1486396

Pollok, J., J. E. van Agteren, et al. (2018). **"Pharmacological interventions for the treatment of depression in chronic obstructive pulmonary disease."** Cochrane Database Syst Rev **12**: Cd012346.

BACKGROUND: Studies report that up to 80% of individuals with chronic obstructive pulmonary disease (COPD) may struggle with symptoms of depression. However, this major comorbidity in COPD is rarely managed effectively. A number of recent studies indicate that left untreated, COPD-related depression is associated with worse quality of life, worse compliance with COPD treatment plan, increased exacerbations, hospital admissions, and healthcare costs when compared to individuals with COPD without depression. Regrettably, COPD practice guidelines do not provide conclusive treatment recommendations for the use of antidepressants in patients with COPD, and base their guidelines on findings from trials in the general population. This may be problematic, as there is an elevated risk of respiratory issues associated with antidepressant treatment and COPD. Evaluating effectiveness and safety of pharmacological interventions specifically for patients with COPD and depression was therefore paramount. OBJECTIVES: To assess the effectiveness and safety of pharmacological interventions for the treatment of depression in patients with COPD. SEARCH METHODS: The last search was performed on 26 November 2018. We initially searched the following databases via the Specialised Trials Registers of the Cochrane Airways and Common Mental Disorders Groups (to June 2016): MEDLINE, Embase, PsycINFO, CINAHL, AMED, and the Cochrane Library trials register (CENTRAL). Searches from June 2016 to November 2018 were performed directly on Ovid MEDLINE, Embase, PsycINFO and the Cochrane Library (Issue 11, 2018). We searched ClinicalTrials.gov, the ISRCTN registry, and the World Health Organization International Clinical Trials Registry Platform to 26 November 2018. We searched the grey literature databases to identify studies not indexed in major databases and the reference lists of studies initially identified for full-text screening. SELECTION CRITERIA: All published and unpublished

randomised controlled trials (RCTs) comparing the efficacy of pharmacological interventions with no intervention, placebo or co-intervention in adults with diagnosed COPD and depression were eligible for inclusion. DATA COLLECTION AND ANALYSIS: Two review authors independently assessed articles identified by the search for eligibility. Our primary outcomes were change in depressive symptoms and adverse events. The secondary outcomes were: change in quality of life, change in dyspnoea, change in forced expiratory volume in one second (FEV1), change in exercise tolerance, change in hospital utilisation (length of stay and readmission rates), and cost-effectiveness. For continuous outcomes, we calculated the pooled mean difference (MD) or standardised mean difference (SMD) with 95% confidence interval (CI) as appropriate. For dichotomous outcomes, we calculated the pooled odds ratio (OR) and corresponding 95% CI using a random-effects model. We assessed the quality of evidence using the GRADE framework. MAIN RESULTS: Of the 1125 records screened for eligibility, four RCTs (N = 201 participants), and one on-going study, met the inclusion criteria. Two classes of antidepressants were investigated in two separate comparisons with placebo: a tricyclic antidepressant (TCA) and selective serotonin reuptake inhibitors (SSRIs).TCA versus placeboOnly one RCT (N = 30 participants) provided results for this comparison.Primary outcomesThe TCA (nortriptyline) reduced depressive symptoms post-treatment compared to placebo (MD -10.20, 95% CI -16.75 to -3.65; P = 0.007; very low-quality evidence), as measured by the Hamilton Depression Rating Scale (HAM-D). Three participants withdrew from the trial due to adverse events related to the tested antidepressant (dry mouth, sedation, orthostatic hypotension).Secondary outcomesThe overall results post-treatment indicated that nortriptyline was not effective in improving the quality of life of individuals with COPD, as measured by the Sickness Impact Profile (MD -2.80, 95% CI -11.02 to 5.42; P = 0.50; very low-quality evidence).The results for the change in dyspnoea for the domains examined (e.g. dyspnoea scores for 'most day-to-day activities') post-treatment showed no improvement in the intervention group (MD 9.80, 95% CI -6.20 to 25.80; P = 0.23; very low-quality evidence).No data were reported for change in FEV1, change in exercise tolerance, change in hospital utilisation, or cost-effectiveness. The TCA study provided short-term results, with the last follow-up data collection at 12 weeks.The quality of the evidence for all the outcomes evaluated was very low due to a small sample size, imprecision, attrition, and selection and reporting bias.SSRIs versus placeboThree RCTs (N = 171 participants) provided results for this comparison.Primary outcomesThe pooled results for two studies showed no difference for the change in depressive symptoms post-intervention (SMD 0.75, 95% CI -1.14 to 2.64; 148 participants; 2 studies; P = 0.44; very low-quality evidence). High heterogeneity was observed (I(2) = 95%), limiting the reliability of these findings.While it was not possible to meta-analyse the total adverse events rates across the studies, it was possible to combine the results for two medication-specific adverse effects: nausea and dizziness. There were no significant post-treatment group differences for nausea (OR 2.32, 95% CI 0.66 to 8.12; 171 participants; 3 studies; P = 0.19; very low-quality evidence) or dizziness (OR 0.61, 95% CI 0.09 to 4.06; 143 participants; 2 studies; P = 0.61; very low-quality evidence).Secondary outcomesThe pooled analysis of two trials reporting data for the change in quality of life did not show improvement post-treatment in the intervention group compared to placebo (SMD 1.17, 95% CI -0.80 to 3.15; 148 participants; 2 studies; P = 0.25; very low-quality evidence).There was no difference between groups in change in FEV1 post-treatment (MD 0.01, 95% CI -0.03 to 0.05; 148 participants; 2 studies; P = 0.60; low-quality evidence). However, two trials reported improvement in exercise tolerance in the SSRI group versus the placebo group (MD 13.88, 95% CI 11.73 to 16.03; 148 participants; 2 studies; P < 0.001; very low-quality evidence).The trials included in this comparison did not report data related to the change in dyspnoea, hospital utilisation rates, or cost-effectiveness. AUTHORS' CONCLUSIONS: There is insufficient evidence to make definitive statements about the efficacy or safety of antidepressants for treating COPD-related depression. New RCTs are needed; with better methodological quality and more accurate reporting of the methods used. Moreover, longer-term follow-up data collection is needed, including outcomes such as adverse events, hospital utilisation and cost-effectiveness.

Qiao, D., A. Ameli, et al. (2018). **"Whole exome sequencing analysis in severe chronic obstructive pulmonary disease."** Hum Mol Genet **27**(21): 3801-3812.

Chronic obstructive pulmonary disease (COPD), one of the leading causes of death worldwide, is substantially influenced by genetic factors. Alpha-1 antitrypsin deficiency demonstrates that rare coding variants of

large effect can influence COPD susceptibility. To identify additional rare coding variants in patients with severe COPD, we conducted whole exome sequencing analysis in 2543 subjects from two family-based studies (Boston Early-Onset COPD Study and International COPD Genetics Network) and one case-control study (COPDGene). Applying a gene-based segregation test in the family-based data, we identified significant segregation of rare loss of function variants in TBC1D10A and RFPL1 (P-value < 2x10-6), but were unable to find similar variants in the case-control study. In single-variant, gene-based and pathway association analyses, we were unable to find significant findings that replicated or were significant in meta-analysis. However, we found that the top results in the two datasets were in proximity to each other in the protein-protein interaction network (P-value = 0.014), suggesting enrichment of these results for similar biological processes. A network of these association results and their neighbors was significantly enriched in the transforming growth factor beta-receptor binding and cilia-related pathways. Finally, in a more detailed examination of candidate genes, we identified individuals with putative high-risk variants, including patients harboring homozygous mutations in genes associated with cutis laxa and Niemann-Pick Disease Type C. Our results likely reflect heterogeneity of genetic risk for COPD along with limitations of statistical power and functional annotation, and highlight the potential of network analysis to gain insight into genetic association studies.

https://academic.oup.com/hmg/article-abstract/27/21/3801/5060721?redirectedFrom=fulltext

Rabe, K. F., H. Watz, et al. (2018). **"Anti-inflammatory effects of roflumilast in chronic obstructive pulmonary disease (ROBERT): a 16-week, randomised, placebo-controlled trial."** Lancet Respir Med **6**(11): 827-836.

BACKGROUND: The clinical effects of roflumilast, a selective phosphodiesterase-4 inhibitor, are well established, but little is known about the anti-inflammatory mechanisms underlying the drug's efficacy. The aim of the ROflumilast Biopsy European Research Trial (ROBERT) was to assess the anti-inflammatory effects of roflumilast on bronchial mucosal inflammation in patients with moderate-to-severe chronic obstructive pulmonary disease (COPD) and chronic bronchitis. METHODS: ROBERT was a randomised, double-blind, placebo-controlled trial done at 18 sites in five countries. Eligible patients were aged 40-80 years, had COPD, and had had a chronic productive cough for 3 months in each of the two previous years. Patients also had to have a post-bronchodilator predicted FEV1 30-80% and a post-bronchodilator FEV1/forced vital capacity ratio of 70% or less. Patients entered a 6-week run-in period before being randomly assigned (1:1) via a computerised central randomisation system to roflumilast 500 mug once daily or placebo for 16 weeks, in addition to bronchodilator therapy (inhaled corticosteroids were not permitted). Randomisation was stratified by concomitant use of long-acting beta agonist. Both participants and investigators were masked to group assignment. Roflumilast and placebo were supplied as identical yellow, triangular tablets. Airway inflammation was assessed by quantification of inflammatory cells in bronchial biopsy samples and induced sputum samples. The primary endpoint was the change in the number of CD8 inflammatory cells in bronchial biopsy submucosa from randomisation to week 16 in the intention-to-treat population. Changes in cell counts of additional inflammatory markers, including eosinophils, were assessed as secondary endpoints. This trial is registered with ClinicalTrials.gov, number NCT01509677, and is closed to new participants, with follow-up completed. FINDINGS: Between Jan 4, 2012, and Feb 11, 2016, 158 patients were randomly assigned: 79 to the roflumilast group, and 79 to the placebo group. At week 16, the change in the number of CD8 cells in the bronchial submucosa did not differ significantly between the roflumilast and placebo groups (treatment ratio 1.03 [95% CI 0.82-1.30]; p=0.79). However, compared with placebo, roflumilast was associated with a significant reduction in eosinophils in bronchial biopsy samples at week 16 (treatment ratio 0.53 [95% CI 0.34-0.82]; p=0.0046). Significant reductions in both absolute (p=0.0042) and differential (p=0.0086) eosinophil cell counts in induced sputum were also noted with roflumilast compared with placebo, but peripheral blood eosinophil counts were not significantly affected. We noted no other significant effects of roflumilast on bronchial mucosal inflammatory cells. The most common (ie, occurring in >5% patients) moderate adverse events were worsening of COPD (three [4%] patients in the roflumilast group vs seven [9%] in the placebo group), cough (six [8%] vs four [5%]), diarrhoea (four [5%] vs three [4%]), and nasopharyngitis (three [4%] vs five [6%]). Severe adverse events included worsening of COPD, which occurred in four (5%) patients in the roflumilast group and two (3%) in the placebo group. No deaths occurred during the study. Serious adverse events occurred in eight (10%) patients in the roflumilast

group and five (6%) in the placebo group. INTERPRETATION: 16 weeks of treatment with roflumilast did not affect the number of CD8 cells in bronchial submucosa compared with placebo. However, we noted significant reductions in eosinophil cell counts in bronchial biopsy samples and induced sputum, generating the hypothesis that the effect of roflumilast in COPD could be mediated by an effect on lung eosinophils. FUNDING: Takeda and AstraZeneca.

https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(18)30331-X/fulltext

Rea, F., G. Calusi, et al. (2018). **"Adherence of Elderly Patients with Cardiovascular Disease to Statins and the Risk of Exacerbation of Chronic Obstructive Pulmonary Disease: Evidence from an Italian Real-World Investigation."** Drugs Aging **35**(12): 1099-1108.

OBJECTIVE: The objective of this study was to investigate the relationship between adherence to statin therapy and the risk of exacerbation among elderly individuals affected by chronic obstructive pulmonary disease and cardiovascular disease. METHODS: Using the healthcare utilisation databases of five Italian territorial units accounting for nearly 35% of the Italian population, we recruited a cohort of 6263 elderly persons (i.e. aged 65 years or older) with co-existing chronic obstructive pulmonary disease and cardiovascular disease who initiated statin therapy. Exposure was adherence to statins measured by the proportion of days of follow-up covered. Outcome was the first hospital admission for chronic obstructive pulmonary disease occurring in the period of observation. A proportional hazards model was used to estimate the hazard ratio and 95% confidence intervals for the exposure-outcome association, after adjusting for several covariates. A set of sensitivity analyses was performed to account for sources of systematic uncertainty. RESULTS: During an average follow-up of about 4 years, 1307 cohort members experienced the outcome. Compared with patients with low adherence (proportion of days of follow-up covered </= 40%), those with intermediate (proportion of days of follow-up covered 41-80%) and high (proportion of days of follow-up covered > 80%) adherence exhibited a lower risk of exacerbation of 16% (95% confidence interval 3-27) and 23% (95% confidence interval 10-34). CONCLUSIONS: In a real-world setting, we observed evidence that adherence to statin therapy markedly reduced the risk of chronic obstructive pulmonary disease exacerbations in elderly patients with co-existing chronic obstructive pulmonary disease and cardiovascular disease. Given the limited and controversial evidence from trials, more randomised controlled trials are urgently needed to better examine the potential benefits of statins as adjunct therapy in chronic obstructive pulmonary disease.

https://link.springer.com/article/10.1007%2Fs40266-018-0600-0

Soriano, J. B., F. Garcia-Rio, et al. (2018). **"A multicentre, randomized controlled trial of telehealth for the management of COPD."** Respir Med **144**: 74-81.

BACKGROUND: Evidence is needed to determine the role of telehealth (TH) in COPD management. METHODS: PROMETE II was a multicentre, randomized, 12-month trial. Severe COPD patients in stable condition were randomized to a specific monitoring protocol with TH or routine clinical practice (RCP). The primary objective was to reduce the number of COPD exacerbations leading to ER visits/hospital admissions between groups. RESULTS: Overall, 237 COPD patients were screened, and 229 (96.6%) were randomized to TH (n=115) or RCP (n=114), with age of 71+/-8 years and 80% were men. Overall, 169 completed the full follow-up period. There were no statistical differences at one year between groups in the proportion of participants who had a COPD exacerbation (60% in TH vs. 53.5% in RCP; p=0.321). There was, however, a marked but non-significant trend towards a shorter duration of hospitalization and days in ICU in the TH group (18.9+/-16.0 and 6.0+/-4.6 days) compared to the RCP group (22.4+/-19.5 and 13.3+/-11.1 days). The number of all-cause deaths was comparable between groups (12 in TH vs. 13 in RCP) as was total resource utilization cost (7912euro in TH vs. 8918euro in RCP). Telehealth was evaluated highly positively by patients and doctors. CONCLUSIONS: Remote patient management did not reduce COPD-related ER visits or hospital admissions compared to RCP within 12 months.

https://www.resmedjournal.com/article/S0954-6111(18)30314-7/fulltext

Stewart, F., G. Caldwell, et al. (2018). **"Building capacity in primary care: the implementation of a novel 'Pharmacy First' scheme for the management of UTI, impetigo and COPD exacerbation."** Prim Health Care Res Dev **19**(6): 531-541.

AimThis service aimed to improve patient access to treatment for urinary tract infections (UTI), impetigo and exacerbation of chronic obstructive pulmonary disease (COPD) and relieve pressure on general practice and out of hours services. BACKGROUND: In 2016, a service (Pharmacy First) was introduced in Forth Valley for the management of UTI, impetigo and exacerbation of COPD using patient group directions in community pharmacies. Trained pharmacists supplied a limited range of prescription medicines. Pathways for GP referral were defined. After 5 months of implementation, the service was evaluated. METHODS: A quantitative evaluation was undertaken. Feedback was sought from patients, GPs, pharmacists and GP reception staff, using structured questionnaires. Pharmacy records were used to assess referrals and pharmacy data summarised the number and type of consultations. Basic cost data was obtained from the Health Board.FindingsIn all, 75 pharmacies (of 76), and all 55 GP practices in the area, participated in the service. Over a 5-month period, 1189 cases were managed, the majority being for UTI (75.4%) followed by impetigo (15.2%), then COPD (9.3%). Of all cases, 77.9% were prescribed medication by the pharmacist, 9.1% were given advice only and 16.7% were referred to the GP. Independent clinical assessment of a random sample of 30 GP referrals considered all to be 'appropriate'. Feedback was received from 69 pharmacists, 34 GPs, 54 reception staff and 73 patients. Patients were very satisfied with the service, most frequently citing the 'quick and efficient' access to treatment, and a 'professional service'. Two thirds of GPs (67%) and 59% of reception staff found the service useful, mainly because it reduced pressure on GP appointments. A further cost benefit evaluation would allow objective assessment of the value of this service.

https://www.cambridge.org/core/services/aop-cambridge-core/content/view/081495A4B038588DD036C5BB92A14797/S1463423617000925a.pdf/div-class-title-building-capacity-in-primary-care-the-implementation-of-a-novel-pharmacy-first-scheme-for-the-management-of-uti-impetigo-and-copd-exacerbation-div.pdf

Vollenweider, D. J., A. Frei, et al. (2018). **"Antibiotics for exacerbations of chronic obstructive pulmonary disease."** Cochrane Database Syst Rev **10**: Cd010257.

BACKGROUND: Many patients with an exacerbation of chronic obstructive pulmonary disease (COPD) are treated with antibiotics. However, the value of antibiotics remains uncertain, as systematic reviews and clinical trials have shown conflicting results. OBJECTIVES: To assess effects of antibiotics on treatment failure as observed between seven days and one month after treatment initiation (primary outcome) for management of acute COPD exacerbations, as well as their effects on other patient-important outcomes (mortality, adverse events, length of hospital stay, time to next exacerbation). SEARCH METHODS: We searched the Cochrane Central Register of Controlled Trials (CENTRAL), in the Cochrane Library, MEDLINE, Embase, and other electronically available databases up to 26 September 2018. SELECTION CRITERIA: We sought to find randomised controlled trials (RCTs) including people with acute COPD exacerbations comparing antibiotic therapy and placebo and providing follow-up of at least seven days. DATA COLLECTION AND ANALYSIS: Two review authors independently screened references and extracted data from trial reports. We kept the three groups of outpatients, inpatients, and patients admitted to the intensive care unit (ICU) separate for benefit outcomes and mortality because we considered them to be clinically too different to be summarised as a single group. We considered outpatients to have a mild to moderate exacerbation, inpatients to have a severe exacerbation, and ICU patients to have a very severe exacerbation. When authors of primary studies did not report outcomes or study details, we contacted them to request missing data. We calculated pooled risk ratios (RRs) for treatment failure, Peto odds ratios (ORs) for rare events (mortality and adverse events), and mean differences (MDs) for continuous outcomes using random-effects models. We used GRADE to assess the quality of the evidence. The primary outcome was treatment failure as observed between seven days and one month after treatment initiation. MAIN RESULTS: We included 19 trials with 2663 participants

(11 with outpatients, seven with inpatients, and one with ICU patients).For outpatients (with mild to moderate exacerbations), evidence of low quality suggests that currently available antibiotics statistically significantly reduced the risk for treatment failure between seven days and one month after treatment initiation (RR 0.72, 95% confidence interval (CI) 0.56 to 0.94; I(2) = 31%; in absolute terms, reduction in treatment failures from 295 to 212 per 1000 treated participants, 95% CI 165 to 277). Studies providing older antibiotics not in use anymore yielded an RR of 0.69 (95% CI 0.53 to 0.90; I(2) = 31%). Evidence of low quality from one trial in outpatients suggested no effects of antibiotics on mortality (Peto OR 1.27, 95% CI 0.49 to 3.30). One trial reported no effects of antibiotics on re-exacerbations between two and six weeks after treatment initiation. Only one trial (N = 35) reported health-related quality of life but did not show a statistically significant difference between treatment and control groups.Evidence of moderate quality does not show that currently used antibiotics statistically significantly reduced the risk of treatment failure among inpatients with severe exacerbations (i.e. for inpatients excluding ICU patients) (RR 0.65, 95% CI 0.38 to 1.12; I(2) = 50%), but trial results remain uncertain. In turn, the effect was statistically significant when trials included older antibiotics no longer in clinical use (RR 0.76, 95% CI 0.58 to 1.00; I(2) = 39%). Evidence of moderate quality from two trials including inpatients shows no beneficial effects of antibiotics on mortality (Peto OR 2.48, 95% CI 0.94 to 6.55). Length of hospital stay (in days) was similar in antibiotic and placebo groups.The only trial with 93 patients admitted to the ICU showed a large and statistically significant effect on treatment failure (RR 0.19, 95% CI 0.08 to 0.45; moderate-quality evidence; in absolute terms, reduction in treatment failures from 565 to 107 per 1000 treated participants, 95% CI 45 to 254). Results of this trial show a statistically significant effect on mortality (Peto OR 0.21, 95% CI 0.06 to 0.72; moderate-quality evidence) and on length of hospital stay (MD -9.60 days, 95% CI -12.84 to -6.36; low-quality evidence).Evidence of moderate quality gathered from trials conducted in all settings shows no statistically significant effect on overall incidence of adverse events (Peto OR 1.20, 95% CI 0.89 to 1.63; moderate-quality evidence) nor on diarrhoea (Peto OR 1.68, 95% CI 0.92 to 3.07; moderate-quality evidence). AUTHORS' CONCLUSIONS: Researchers have found that antibiotics have some effect on inpatients and outpatients, but these effects are small, and they are inconsistent for some outcomes (treatment failure) and absent for other outcomes (mortality, length of hospital stay). Analyses show a strong beneficial effect of antibiotics among ICU patients. Few data are available on the effects of antibiotics on health-related quality of life or on other patient-reported symptoms, and data show no statistically significant increase in the risk of adverse events with antibiotics compared to placebo. These inconsistent effects call for research into clinical signs and biomarkers that can help identify patients who would benefit from antibiotics, while sparing antibiotics for patients who are unlikely to experience benefit and for whom downsides of antibiotics (side effects, costs, and multi-resistance) should be avoided.

Wang, K., S. Liu, et al. (2018). **"Mind-Body Exercise (Wuqinxi) for Patients with Chronic Obstructive Pulmonary Disease: A Systematic Review and Meta-Analysis of Randomized Controlled Trials."** Int J Environ Res Public Health **16**(1)Objective: This study is the first meta-analysis investigating the rehabilitative effects of Wuqinxi for patients with chronic obstructive pulmonary disease (COPD). Methods: Five electronic databases (PubMed, Web of Science, Scopus, CNKI, and Wanfang) from inception until early November 2018 were searched. All randomized controlled trials (RCT) using Wuqinxi as the main intervention component were included for meta-analysis. The pooled effect sizes (Standardized mean difference, SMD) were calculated to determine the magnitude of the Wuqinxi intervention effect. Moderator analysis was only conducted for total training time. Results: Overall results of the meta-analysis indicated that Wuqinxi exercise significantly improved exercise capability (SMD = 1.18, 95% CI 0.53 to 1.84, e < 0.001, I(2) = 84.97%), FEV1 (SMD = 0.44, 95% CI 0.12 to 0.77, e < 0.001, I(2) = 33.77%), FEV1% (SMD = 0.59, 95% CI 0.24 to 0.93, e < 0.001, I(2) = 63.79%), FEV1/FVC (SMD = 0.65, 95% CI 0.37 to 0.93, e = 0.006, I(2) = 44.32%) and CCQ (SMD = 1.23, 95% CI 0.31 to 2.14, e = 0.01, I(2) = 93.32%). Conclusions: With no occurrence of adverse event, clinicians could try to incorporate Wuqinxi exercise into their first-line rehabilitation regime for COPD patients.

https://res.mdpi.com/ijerph/ijerph-16-00072/article_deploy/ijerph-16-00072.pdf?filename=&attachment=1

Wang, Y., T. R. Zijp, et al. (2018). **"Effects of prophylactic antibiotics on patients with stable COPD: a systematic review and meta-analysis of randomized controlled trials."** J Antimicrob Chemother **73**(12): 3231-3243.

Background: As bacterial infections provoke exacerbations, COPD patients may benefit from prophylactic antibiotics. However, evidence regarding their overall benefit-risk profile is conflicting. Objectives: To update previous evidence and systematically evaluate the beneficial effects and side effects of prophylactic antibiotics in stable COPD patients. Methods: Several databases were searched up to 26 April 2017 for randomized controlled trials (RCTs) on prophylactic antibiotics in stable COPD patients. The primary outcomes were exacerbations and quality of life. Duration and schedule of antibiotics were considered in subgroup analyses. Results: Twelve RCTs involving 3683 patients were included. Prophylactic antibiotics significantly reduced the frequency of exacerbations [risk ratio (RR) 0.74, 95% CI 0.60-0.92] and the number of patients with one or more exacerbations (RR 0.82, 95% CI 0.74-0.90). Erythromycin and azithromycin appeared the most effective, with the number needed to treat ranging from four to seven. Quality of life was also significantly improved by prophylactic antibiotics (mean difference -1.55, 95% CI -2.59 to -0.51). Time to first exacerbation was prolonged in six studies, with one conflicting result. Neither the rate of hospitalization nor the rate of adverse events was significantly changed. Furthermore, no significant changes were observed in lung function, bacterial load and airway inflammation. However, antibiotic-resistant isolates were significantly increased (OR 4.49, 95% CI 2.48-8.12). Conclusions: Prophylactic antibiotics were effective in preventing COPD exacerbations and improving quality of life among stable patients with moderate to severe COPD. The choice of prophylactic antibiotics should be analysed and considered case by case, especially for long and continuous use.

https://academic.oup.com/jac/article-abstract/73/12/3231/5090548?redirectedFrom=fulltext

Xuan, L., F. Han, et al. (2018). **"Association between chronic obstructive pulmonary disease and serum lipid levels: a meta-analysis."** Lipids Health Dis **17**(1): 263.

BACKGROUND: Metabolic syndrome is a common extrapulmonary comorbidity in patients with chronic obstructive pulmonary disease (COPD). However, the reported relationship of COPD with dyslipidemia, an important component of metabolic syndrome, is ambiguous. The aim of this meta-analysis is to investigate the association between COPD and the serum levels of high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), total cholesterol (TC), and triglyceride (TG). METHODS: The PubMed and Embase databases were searched to find potential studies using the search terms of ("dyslipidemia" or "HDL" or "LDL" or "cholesterol" or "triglyceride") and COPD. We also performed subgroup analysis enrolling patients who were not receiving treatment for dyslipidemia. Mean differences (MD) with 95% confidence intervals (CI) were estimated with random effects models. RESULTS: A total of 11 studies comprising 615 cases and 471 controls were included in the study. No significant differences were found in the HDL (MD = -2.55, 95% CI [-6.03, 0.93], P = 0.15), LDL (MD = -2.25, 95% CI [-13.36, 8.86], P = 0.69), TC (MD = -2.69, 95% CI [-13.30, 7.92], P = 0.62), and TG (MD = 6.90, 95% CI [-2.81, 16.60], P = 0.16) levels of the 2 groups. However, subgroup analysis enrolling patients who were not receiving treatment for dyslipidemia showed that TG levels were higher in patients with stable COPD than in healthy individuals (MD = 16.35, 95% CI [5.90, 26.80], P = 0.002). CONCLUSIONS: Excluding the impact of hypolipidemic treatment on serum lipid profile, TG levels were higher in patients with COPD than in healthy individuals. This meta-analysis suggested that physicians should screen COPD patients for elevated TG levels to reduce the risk of cardiovascular morbidity and mortality.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6249772/pdf/12944_2018_Article_904.pdf

Yang, J., R. Lin, et al. (2019). **"Significance of Pulmonary Rehabilitation in Improving Quality of Life for Subjects With COPD."** Respir Care **64**(1): 99-107.

BACKGROUND: Increasingly, studies have shown that application of pulmonary rehabilitation (PR) may improve the quality of life (QOL) of patients with COPD. However, some studies remain controversial and were limited to small number of participants. We designed a systematic review and meta-analysis to evaluate the efficacy of PR in improving the QOL for subjects with COPD. METHODS: We searched the Cochrane Library, PubMed, EMBASE, and Web of Science up to March 29, 2018, to identify relevant randomized controlled trials that analyzed and evaluated the efficacy of PR in subjects with COPD. Participants were randomly assigned to receive PR (intervention group) or usual care (control group). We used Chronic Respiratory Questionnaire scores, which include 4 important domains (ie, Fatigue, Emotion, Mastery, and Dyspnea) as the evaluating indicators of QOL. Mean differences with 95% CI were estimated to compare the outcomes of the groups. We also performed subgroup analysis for the pooled results of PR effects in subjects with COPD. In addition, a sensitivity analysis was performed to examine the stability of the combined results. Two reviewers assessed trial quality and extracted data independently. RESULTS: Seventeen randomized controlled trials (N = 1,649 participants) were identified for the present analysis. In comparing PR groups with usual care groups, we identified significant effects in QOL improvement as measured by the Chronic Respiratory Questionnaire scores for fatigue (Mean difference 0.60, 95% CI 0.36-0.84, P < .001), mastery (Mean difference 0.59, 95% CI 0.32-0.85, P < .001), and dyspnea (Mean difference 0.70, 95% CI 0.46-0.94, P < .001), but no clinically important improvement was found in emotion (Mean difference 0.45, 95% CI 0.23-0.67, P < .001) according to the minimal clinically important difference that we defined as mean difference >/= 0.5 units. CONCLUSION: PR may constitute an important component of COPD management and may be beneficial in improving QOL.

http://rc.rcjournal.com/content/64/1/99.short

Ye, L., X. Huang, et al. (2018). **"PRISMA-compliant meta-analysis: association of metabolic syndrome and its components with the risk of chronic obstructive pulmonary disease."** Biosci Rep **38**(6)A preferred reporting items for systematic reviews and meta-analyses-compliant meta-analysis was conducted to test the association of metabolic syndrome and its components with the risk of chronic obstructive pulmonary disease (COPD) based on observational studies. Literature retrieval, article selection and data extraction were done by two researchers independently. Total 16 articles (20 independent studies) were analyzed with 3915 COPD patients and 25,790 control participants. Overall analysis indicated that metabolic syndrome was significantly associated with 1.53-fold (95% confidence interval [CI]: 1.23-1.9, P<0.001) increased risk of COPD, with moderate heterogeneity (I (2) = 74.3%). Of four metabolic components, hypertension was significantly associated with 1.55-fold (95% CI: 1.14-2.11, P=0.005) increased risk, and averaged levels of systolic blood pressure (weighted mean difference [WMD] = 3.626 mmHg, 95% CI: 1.537-5.714, P<0.001) and glucose (WMD = 2.976 mmol/l, 95% CI: 0.141-5.812; P=0.04) were significantly higher in COPD patients than in control participants, yet that of body mass index (WMD = -1.463 kg/m(2), 95% CI: -2.716 to -0.211, P=0.022) were significantly lower. Gender, race, source of control participants, matched status and sample size were identified as accountable factors for significant heterogeneity. Altogether, the presence of metabolic syndrome, especially its component hypertension, was associated with significantly increased risk of COPD.

http://www.bioscirep.org/content/ppbioscirep/38/6/BSR20181199.full.pdf

Zheng, Y., J. Zhu, et al. (2018). **"Triple therapy in the management of chronic obstructive pulmonary disease: systematic review and meta-analysis."** Bmj **363**: k4388.

OBJECTIVE: To compare the rate of moderate to severe exacerbations between triple therapy and dual therapy or monotherapy in patients with chronic obstructive pulmonary disease (COPD). DESIGN: Systematic review and meta-analysis of randomised controlled trials. DATA SOURCES: PubMed, Embase, Cochrane databases, and clinical trial registries searched from inception to April 2018. ELIGIBILITY CRITERIA: Randomised controlled trials comparing triple therapy with dual therapy or monotherapy in patients

with COPD were eligible. Efficacy and safety outcomes of interest were also available. DATA EXTRACTION AND SYNTHESIS: Data were collected independently. Meta-analyses were conducted to calculate rate ratios, hazard ratios, risk ratios, and mean differences with 95% confidence intervals. Quality of evidence was summarised in accordance with GRADE methodology (grading of recommendations assessment, development, and evaluation). RESULTS: 21 trials (19 publications) were included. Triple therapy consisted of a long acting muscarinic antagonist (LAMA), long acting beta agonist (LABA), and inhaled corticosteroid (ICS). Triple therapy was associated with a significantly reduced rate of moderate or severe exacerbations compared with LAMA monotherapy (rate ratio 0.71, 95% confidence interval 0.60 to 0.85), LAMA and LABA (0.78, 0.70 to 0.88), and ICS and LABA (0.77, 0.66 to 0.91). Trough forced expiratory volume in 1 second (FEV1) and quality of life were favourable with triple therapy. The overall safety profile of triple therapy is reassuring, but pneumonia was significantly higher with triple therapy than with dual therapy of LAMA and LABA (relative risk 1.53, 95% confidence interval 1.25 to 1.87). CONCLUSIONS: Use of triple therapy resulted in a lower rate of moderate or severe exacerbations of COPD, better lung function, and better health related quality of life than dual therapy or monotherapy in patients with advanced COPD. STUDY REGISTRATION: Prospero CRD42018077033.

https://www.bmj.com/content/bmj/363/bmj.k4388.full.pdf

Zhou, J., L. Pang, et al. (2018). **"Whole-body vibration training - better care for COPD patients: a systematic review and meta-analysis."** Int J Chron Obstruct Pulmon Dis **13**: 3243-3254.

Purpose: Whole-body vibrating training (WBVT) is a modality aiming to improve neuromuscular performance of patients with COPD. However, a consensus on the effects of WBVT has not been reached. We aimed to clarify the effects of WBVT on functional exercise capacity, pulmonary function, and quality of life in COPD patients. Patients and methods: PubMed, Web of Science, and EMBASE were searched through April 5, 2018. We calculated the pooled weight mean difference (WMD) using a random-effects model. Quality assessment and publication bias analyses were also performed. Results: We included eight randomized control trials involving 365 patients. Compared with control group, WBVT increased 6-minute walking distance (6-MWD) (WMD: 62.14 m; 95% CI: 48.12-76.16; P<0.001), the change of 6-MWD (Delta6-MWD) (WMD: 42.33 m; 95% CI: 15.21-69.45; P=0.002), the change of the time to finish five repeated sit-to-stand tests (WMD: -2.07 seconds; 95% CI: -4.00 to -0.05; P=0.04), and decreased the change of St George's Respiratory Questionnaire score (WMD: -6.65 points; 95% CI: -10.52 to -2.78; P<0.001). However, no significant difference was found between the two groups regarding forced expired volume in 1 second (FEV1) (% predicated), change of FEV1 (% predicated), sit-to-stand test, 6-MWD (% predicated), change of 6-MWD (% predicated), St George's Respiratory Questionnaire score, COPD Assessment Test score, and change of COPD Assessment Test score. Conclusion: WBVT has beneficial effects on functional exercise capacity for COPD patients.

https://www.dovepress.com/getfile.php?fileID=45180