COPD/Emphysema PubMed search results covering the period 20/07/2019 to 25/10/19
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 ("2019/10/19"[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. (2019). **"Effect of a Hospital-Initiated Program Combining Transitional Care and Long-term Self-management Support on Outcomes of Patients Hospitalized With Chronic Obstructive Pulmonary Disease: A Randomized Clinical Trial."** Jama **322**(14): 1371-1380.

Importance: Patients hospitalized for chronic obstructive pulmonary disease (COPD) exacerbations have high rehospitalization rates and reduced quality of life. Objective: To evaluate whether a hospital-initiated program that combined transition and long-term self-management support for patients hospitalized due to COPD and their family caregivers can improve outcomes. Design, Setting, and Participants: Single-site randomized clinical trial 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) involved a comprehensive 3-month program to help patients and their family caregivers with long-term self-management of COPD. It was delivered by 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; 61.7% women), 203 (85%) completed the study. The mean (SD) baseline SGRQ score was 62.3 (18.8) in the intervention group and 63.6 (17.4) in the usual care group. The mean number of COPD-related acute care events per participant at 6 months was 1.40 (95% CI, 1.01-1.79) in the intervention group vs 0.72 (95% CI, 0.45-0.97) in the usual care group (difference, 0.68 [95% CI, 0.22-1.15]; P = .004). The mean change in participants' SGRQ total score at 6 months was 2.81 in the intervention group and -2.69 in the usual care group (adjusted difference, 5.18 [95% CI, -2.15 to 12.51]; P = .11). During the study period, there were 15 deaths (intervention: 8; usual care: 7) and 339 hospitalizations (intervention: 202; usual care: 137). 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 greater COPD-related hospitalizations and emergency department visits, without improvement in quality of life. Further research is needed to determine reasons for this unanticipated finding. Trial Registration: ClinicalTrials.gov Identifier: NCT02036294.

https://jamanetwork.com/journals/jama/articlepdf/2752467/jama_aboumatar_2019_oi_190089.pdf

Abukwaik, A. W., R. Mansukhani, et al. (2018). **"Long-Acting Bronchodilator Use in the Management of Stable COPD."** Ann Pharmacother **52**(6): 562-570.

OBJECTIVE: To review the management of chronic obstructive pulmonary disease (COPD), with a focus on updated information regarding the use of long-acting bronchodilators in the prevention of exacerbations and outcomes associated with this disease. DATA SOURCES: A literature search of the MEDLINE databases through November 2017 was conducted. All published articles regarding use of bronchodilator therapy in the management of COPD were evaluated. References of selected articles, data from poster presentations, and abstract publications were additionally reviewed. STUDY SELECTION AND DATA EXTRACTION: Available English-language data from reviews, abstracts, presentations, and clinical trials of the treatment of stable COPD with bronchodilator therapy in humans were reviewed; relevant clinical data were selected and included. DATA SYNTHESIS: COPD is a prevalent medical

condition worldwide that results in functional impairment, and worsened quality of life and overall health status. Numerous treatment options are available; the rationale for the optimal agents to utilize in a particular patient case is dependent on a multitude of patient-specific factors and severity of disease. In this review, a discussion of the role of long-acting bronchodilators, including long-acting beta agonists and long-acting muscarinic antagonists will be explored. Additionally, an update on the roles of novel delivery devices for delivering respiratory medications in this medical condition will be described. CONCLUSION: Although numerous treatment options are available, management of COPD remains a clinical challenge. Long-acting bronchodilators represent a significant class of medications that have the potential to reduce exacerbations and related hospitalizations and improve overall health outcomes.

Adamson, P. D., J. A. Anderson, et al. (2018). **"Cardiac Troponin I and Cardiovascular Risk in Patients With Chronic Obstructive Pulmonary Disease."** J Am Coll Cardiol **72**(10): 1126-1137.

BACKGROUND: Patients with chronic obstructive pulmonary disease (COPD) have increased risk of cardiovascular events. OBJECTIVES: This study evaluated the association between high-sensitivity cardiac troponin I concentration and cardiovascular events in patients with COPD and heightened cardiovascular risk. METHODS: In a double-blind randomized controlled trial, 16,485 patients with COPD and cardiovascular disease or risk factors were randomized to once daily inhaled placebo, fluticasone furoate (100 mug), vilanterol (25 mug), or their combination. Plasma high-sensitivity cardiac troponin I concentrations were measured in a subgroup of 1,599 patients. Outcomes were on-treatment cardiovascular events and COPD exacerbations over a median of 18 months, and cardiovascular death over a median of 27 months. RESULTS: Baseline plasma cardiac troponin I concentrations were above the limit of detection (1.2 ng/l) in 1,542 (96%) patients. Concentrations were unaffected by inhaled therapies at 3 months ($p > 0.05$). Compared with the lowest quintile (cardiac troponin <2.3 ng/l), patients in the highest quintile (>/=7.7 ng/l) were at greater risk of cardiovascular events (hazard ratio [HR] 3.7; 95% confidence interval [CI]: 1.3 to 10.1; $p = 0.012$) and cardiovascular death (HR: 20.1; 95% CI: 2.4 to 165.2; $p = 0.005$) after adjustment for risk factors. By contrast, there were no differences in exacerbations between quintiles (HR: 1.1; 95% CI: 0.8 to 1.5; $p = 0.548$). CONCLUSIONS: In patients with COPD and heightened cardiovascular risk, plasma cardiac troponin I concentrations are a specific and major indicator of future cardiovascular events and cardiovascular death. Inhaled therapies did not affect cardiac troponin I concentrations consistent with their neutral effect on mortality and cardiovascular outcomes. (Study to Evaluate the Effect of Fluticasone Furoate/Vilanterol on Survival in Subjects With Chronic Obstructive Pulmonary Disease [SUMMIT]; NCT01313676).

Ahmadi, Z., J. Sandberg, et al. (2018). **"Is chronic breathlessness less recognised and treated compared with chronic pain? A case-based randomised controlled trial."** Eur Respir J **52**(3)

Alma, H., C. de Jong, et al. (2018). **"Clinically relevant differences in COPD health status: systematic review and triangulation."** Eur Respir J **52**(3)The minimal clinically important difference (MCID) quantifies when measured differences can be considered clinically relevant. This study aims to review and triangulate MCIDs of chronic obstructive pulmonary disease (COPD) health status tools.A systematic search in PubMed, EMBASE and Cochrane Library was conducted (Prospero #CRD42015023221). Study details, patient characteristics, MCID methodology and estimates were assessed and extracted by two authors. A triangulated mean was obtained for each tool's MCID, with two-thirds weighting for anchor-based and one-third for distribution-based results. This was then multiplied by a weighted factor based

upon the study size and quality rating.Overall, 785 records were reviewed of which 21 studies were included for analysis. MCIDs of 12 tools were presented. General quality and risk of bias were average to good. Triangulated MCIDs for the COPD Assessment Test (CAT), Clinical COPD Questionnaire (CCQ) and St. George's Respiratory Questionnaire (SGRQ) were -2.54, -0.43 and -7.43 for improvement. Too few and/or too diverse studies were present to triangulate MCIDs of other tools.Evidence for the MCID of the CAT and CCQ was strong and triangulation was valid. Currently used MCIDs in clinical practice for the SGRQ (4) and Chronic Respiratory Questionnaire (0.5) did not match the reviewed content, for which the MCIDs were much higher. Using too low MCIDs may lead to an overestimation of the interpretation of treatment effects. MCIDs for deterioration were scarce, which highlights the need for more research.

Araujo, Z. T. S., K. Mendonca, et al. (2019). **"Pulmonary rehabilitation for people with chronic obstructive pulmonary disease: A protocol for an overview of Cochrane reviews."** Medicine (Baltimore) **98**(38): e17129.

BACKGROUND: Pulmonary rehabilitation (PR) is an indispensable component in the nonpharmacological management of patients with chronic obstructive pulmonary disease (COPD) with significant improvements in quality of life and exercise capacity. It is strongly supported by systematic reviews (SR) as part of the treatment of these patients. However, it is not known which PR components are essential, such as duration, ideal locations, type and intensity of training, degree of supervision, adherence, cost-effectiveness challenge, and how long the program effects last. This overview aims to evaluate and describe different pulmonary rehabilitation interventions for individuals with COPD. METHODS: Only systematic reviews of randomized controlled trials (RCTs) published in the Cochrane Database of Systematic Reviews will be included. The following results were analyzed: health-related quality of life, functional capacity, mortality, dyspnea, cost-effectiveness, and adverse events. The risk of bias will be assessed by the Risk of Bias in Systematic Reviews (ROBIS). The methodological quality will be analyzed through the Assessment of Multiple Systematic Reviews (AMSTAR-2). We will use the evaluations of the Classification of Recommendations, Evaluation, Development and Evaluation (GRADE) of the authors of the included systematic reviews. The screening of systematic reviews, eligibility evaluation, data extraction, methodological quality, and quality of evidence will be performed in pairs by independent reviewers. The results that have been reported in the included reviews will be summarized in an "Overview of Reviews" table. The main conclusions about the effects of the interventions studied in the included reviews will be summarized and organized in clinically meaningful categories. RESULTS: The article in this overview will be submitted for publication in a peer-reviewed journal. The results will also be included in a doctoral thesis and disclosed in medical conferences. CONCLUSIONS: We expect to compile evidence from multiple systematic reviews of pulmonary rehabilitation in people with COPD in an accessible and useful document. REGISTRATION NUMBER PROSPERO: CRD42019111564.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6756730/pdf/medi-98-e17129.pdf

Baker, E. and F. Fatoye (2019). **"Patient perceived impact of nurse-led self-management interventions for COPD: A systematic review of qualitative research."** Int J Nurs Stud **91**: 22-34.

BACKGROUND: Self-management interventions are increasingly implemented to manage the health impact and economic burden of the growing prevalence of chronic obstructive pulmonary disease. Nurses are the primary providers of self-management education, yet there have been few attempts to assess their contribution in delivering these programmes. Qualitative evidence that explores patients' perceptions of the benefits of self-management is limited. OBJECTIVE: To synthesize qualitative evidence on patient perceived benefits of nursing interventions to support self-management. DESIGN: Systematic review and qualitative synthesis. METHODS: Data were collected from six electronic databases: British Nursing Index (BNI, Proquest), MEDLINE (Ovid), CINAHL (EBSCO), AMED (Ovid), Embase (Ovid), and PsycINFO (Ovid). Pre-defined keywords were used to identify qualitative or mixed methods English-language studies published in any year. The included studies were selected by screening titles, abstracts and full-texts

against inclusion and exclusion criteria that were established a priori. The Critical Appraisal Skills Programme tool was used to undertake a quality review. Data were analysed with a framework approach using categories of self-management outcomes reported in a previous review as a coding structure. RESULTS: Fourteen articles were included in the review. Four key themes were identified from the original research: Empowerment through new knowledge, Psychological wellbeing, Expanding social worlds and Increased physical activity. CONCLUSIONS: When provided with adequate knowledge and support, patients gained self-confidence and their coping behaviour increased. Social and psychological support were identified as key aspects of self-management interventions that patients found improved their sense of wellbeing. Group exercise components of self-management programmes were also favourably evaluated due to a perceived sense of increased well-being and enhanced social interaction.

Bellou, V., L. Belbasis, et al. (2019). **"Prognostic models for outcome prediction in patients with chronic obstructive pulmonary disease: systematic review and critical appraisal."** Bmj **367**: l5358.

OBJECTIVE: To map and assess prognostic models for outcome prediction in patients with chronic obstructive pulmonary disease (COPD). DESIGN: Systematic review. DATA SOURCES: PubMed until November 2018 and hand searched references from eligible articles. ELIGIBILITY CRITERIA FOR STUDY SELECTION: Studies developing, validating, or updating a prediction model in COPD patients and focusing on any potential clinical outcome. RESULTS: The systematic search yielded 228 eligible articles, describing the development of 408 prognostic models, the external validation of 38 models, and the validation of 20 prognostic models derived for diseases other than COPD. The 408 prognostic models were developed in three clinical settings: outpatients (n=239; 59%), patients admitted to hospital (n=155; 38%), and patients attending the emergency department (n=14; 3%). Among the 408 prognostic models, the most prevalent endpoints were mortality (n=209; 51%), risk for acute exacerbation of COPD (n=42; 10%), and risk for readmission after the index hospital admission (n=36; 9%). Overall, the most commonly used predictors were age (n=166; 41%), forced expiratory volume in one second (n=85; 21%), sex (n=74; 18%), body mass index (n=66; 16%), and smoking (n=65; 16%). Of the 408 prognostic models, 100 (25%) were internally validated and 91 (23%) examined the calibration of the developed model. For 286 (70%) models a model presentation was not available, and only 56 (14%) models were presented through the full equation. Model discrimination using the C statistic was available for 311 (76%) models. 38 models were externally validated, but in only 12 of these was the validation performed by a fully independent team. Only seven prognostic models with an overall low risk of bias according to PROBAST were identified. These models were ADO, B-AE-D, B-AE-D-C, extended ADO, updated ADO, updated BODE, and a model developed by Bertens et al. A meta-analysis of C statistics was performed for 12 prognostic models, and the summary estimates ranged from 0.611 to 0.769. CONCLUSIONS: This study constitutes a detailed mapping and assessment of the prognostic models for outcome prediction in COPD patients. The findings indicate several methodological pitfalls in their development and a low rate of external validation. Future research should focus on the improvement of existing models through update and external validation, as well as the assessment of the safety, clinical effectiveness, and cost effectiveness of the application of these prognostic models in clinical practice through impact studies. SYSTEMATIC REVIEW REGISTRATION: PROSPERO CRD42017069247.

https://www.bmj.com/content/bmj/367/bmj.l5358.full.pdf

Celli, B., J. A. Anderson, et al. (2018). **"Long-Acting beta-Agonist/Inhaled Corticosteroid in Patients with Chronic Obstructive Pulmonary Disease with Cardiovascular Disease or Risk: A Factorial Analysis of the SUMMIT Clinical Trial."** Am J Respir Crit Care Med **197**(12): 1641-1644.

Chapman, K. R., J. R. Hurst, et al. (2018). **"Long-Term Triple Therapy De-escalation to Indacaterol/Glycopyrronium in Patients with Chronic Obstructive Pulmonary Disease (SUNSET): A Randomized, Double-Blind, Triple-Dummy Clinical Trial."** Am J Respir Crit Care Med **198**(3): 329-339.

RATIONALE: There are no studies on withdrawal of inhaled corticosteroids in patients on long-term triple therapy in the absence of frequent exacerbations. OBJECTIVES: To evaluate the efficacy and safety of direct de-escalation from long-term triple therapy to indacaterol/glycopyrronium in nonfrequently exacerbating patients with chronic obstructive pulmonary disease (COPD). METHODS: This 26-week, randomized, double-blind, triple-dummy study assessed the direct change from long-term triple therapy to indacaterol/glycopyrronium (110/50 mug once daily) or continuation of triple therapy (tiotropium [18 mug] once daily plus combination of salmeterol/fluticasone propionate [50/500 mug] twice daily) in nonfrequently exacerbating patients with moderate-to-severe COPD. Primary endpoint was noninferiority on change from baseline in trough FEV1. Moderate or severe exacerbations were predefined secondary endpoints. MEASUREMENTS AND MAIN RESULTS: A total of 527 patients were randomized to indacaterol/glycopyrronium and 526 to triple therapy. Inhaled corticosteroids withdrawal led to a reduction in trough FEV1 of -26 ml (95% confidence interval, -53 to 1 ml) with confidence limits exceeding the noninferiority margin of -50 ml. The annualized rate of moderate or severe COPD exacerbations did not differ between treatments (rate ratio, 1.08; 95% confidence interval, 0.83 to 1.40). Patients with >/=300 blood eosinophils/mul at baseline presented greater lung function loss and higher exacerbation risk. Adverse events were similar in the two groups. CONCLUSIONS: In patients with COPD without frequent exacerbations on long-term triple therapy, the direct de-escalation to indacaterol/glycopyrronium led to a small decrease in lung function, with no difference in exacerbations. The higher exacerbation risk in patients with >/=300 blood eosinophils/mul suggests that these patients are likely to benefit from triple therapy. Clinical trial registered with www.clinicaltrials.gov (NCT 02603393).

Choi, H. S., Y. B. Park, et al. (2019). **"Exacerbations of Chronic Obstructive Pulmonary Disease Tool to assess the efficacy of acute treatment."** Int J Chron Obstruct Pulmon Dis **14**: 471-478.

Background and objective: The Exacerbations of Chronic Obstructive Pulmonary Disease Tool-Patient-Reported Outcomes (EXACT-PRO) has been suggested as a reliable and valid measure for early assessment of COPD exacerbations and perceived recovery. However, there has been no evidence for EXACT-PRO efficacy in assessing recovery from treatment in a randomized controlled trial. The study evaluated the reliability, validity, and responsiveness of EXACT-PRO for the evaluation of the efficacy of acute treatment in patients with COPD exacerbation. Methods: In a Phase III randomized controlled study for assessing the efficacy of antibiotic treatment on COPD exacerbation, EXACT-PRO was evaluated in the responders and non-responders. Results: A total of 295 patients were analyzed (259 responders and 37 non-responders). Cronbach's alpha was 0.96 for EXACT total, 0.96 for the breathlessness domain, 0.89 for the cough and sputum domain, and 0.93 for the chest symptoms domain. The EXACT score correlated with the COPD assessment test (CAT) score (r=0.8, P<0.01). A stronger decrease in the EXACT score was found in the responder group than in the non-responder group from the fifth day after treatment. The difference in the EXACT score from exacerbation onset to recovery was -6.3 in responders and -1.9 in non-responders (P=0.01). Conclusion: EXACT-PRO is a comprehensive and sensitive method for assessing symptomatic resolution of COPD exacerbations during treatment.

Cox, N. S., C. C. Oliveira, et al. (2017). **"Pulmonary rehabilitation referral and participation are commonly influenced by environment, knowledge, and beliefs about consequences: a systematic review using the Theoretical Domains Framework."** J Physiother **63**(2): 84-93.

QUESTION: What are the barriers and enablers of referral, uptake, attendance and completion of pulmonary rehabilitation for people with chronic obstructive pulmonary disease (COPD)? DESIGN: Systematic review of qualitative or quantitative studies reporting data relating to referral, uptake, attendance and/or completion in pulmonary rehabilitation. PARTICIPANTS: People aged >18years with a diagnosis of COPD and/or their healthcare professionals. DATA EXTRACTION AND ANALYSIS: Data were extracted regarding the nature of barriers and enablers of pulmonary rehabilitation referral and participation. Extracted data items were mapped to the Theoretical Domains Framework (TDF). RESULTS: A total of 6969 references were screened, with 48 studies included and 369 relevant items mapped to the TDF. The most frequently represented domain was 'Environment' (33/48 included studies, 37% of mapped items), which included items such as waiting time, burden of illness, travel, transport and health system resources. Other frequently represented domains were 'Knowledge' (18/48 studies, including items such as clinician knowledge of referral processes, patient understanding of rehabilitation content) and 'Beliefs about consequences' (15/48 studies, including items such as beliefs regarding role and safety of exercise, expectations of rehabilitation outcomes). Barriers to referral, uptake, attendance or completion represented 71% (n=183) of items mapped to the TDF. All domains of the TDF were represented; however, items were least frequently coded to the domains of 'Optimism' and 'Memory'. The methodological quality of included studies was fair (mean quality score 9/12, SD 2). CONCLUSION: Many factors - particularly those related to environment, knowledge, attitudes and behaviours - interact to influence referral, uptake, attendance and completion of pulmonary rehabilitation. Overcoming the challenges associated with the personal and/or healthcare system environment will be imperative to improving access and uptake of pulmonary rehabilitation. TRIAL REGISTRATION: PROSPERO CRD42015015976. [Cox NS, Oliveira CC, Lahham A, Holland AE (2017) Pulmonary rehabilitation referral and participation are commonly influenced by environment, knowledge, and beliefs about consequences: a systematic review using the Theoretical Domains Framework. Journal of Physiotherapy 63: 84-93].

Crim, C., M. L. Watkins, et al. (2019). **"Randomized dose-finding study of batefenterol via dry powder inhaler in patients with COPD."** Int J Chron Obstruct Pulmon Dis **14**: 615-629.

Background: Batefenterol is a novel bifunctional muscarinic antagonist beta2-agonist in development for COPD. The primary objective of this randomized, double-blind, placebo-controlled, active comparator, Phase IIb study was to model the dose-response of batefenterol and select a dose for Phase III development. Patients and methods: Patients aged >/=40 years with COPD and FEV1 >/=30% and </=70% predicted normal were randomized equally to batefenterol 37.5, 75, 150, 300, or 600 microg, placebo, or umeclidinium/vilanterol (UMEC/VI) 62.5/25 microg once daily. The primary and secondary endpoints were weighted-mean FEV1 over 0-6 hours post-dose and trough FEV1, analyzed by Bayesian and maximum likelihood estimation Emax of dose-response modeling, respectively, on day 42. Results: In the intent-to-treat population (N=323), all batefenterol doses demonstrated statistically and clinically significant improvements from baseline vs placebo in the primary and secondary endpoints (191.1-292.8 and 182.2-244.8 mL, respectively), with a relatively flat dose-response. In the subgroup reversible to salbutamol, there were greater differences between batefenterol doses. Lung function improvements with batefenterol >/=150 microg were comparable with those with UMEC/VI. Batefenterol was well tolerated and no new safety signals were observed. Conclusion: Batefenterol 300 microg may represent the optimal dose for Phase III studies.

Criner, G. J., B. R. Celli, et al. (2019). **"Benralizumab for the Prevention of COPD Exacerbations."** N Engl J Med **381**(11): 1023-1034.

BACKGROUND: The efficacy and safety of benralizumab, an interleukin-5 receptor alpha-directed cytolytic monoclonal antibody, for the prevention of exacerbations in patients with moderate to very severe

chronic obstructive pulmonary disease (COPD) are not known. METHODS: In the GALATHEA and TERRANOVA trials, we enrolled patients with COPD (at a ratio of approximately 2:1 on the basis of eosinophil count [>/=220 per cubic millimeter vs. <220 per cubic millimeter]) who had frequent exacerbations despite receiving guideline-based inhaled treatment. Patients were randomly assigned to receive benralizumab (30 or 100 mg in GALATHEA; 10, 30, or 100 mg in TERRANOVA) every 8 weeks (every 4 weeks for the first three doses) or placebo. The primary end point was the treatment effect of benralizumab, measured as the annualized COPD exacerbation rate ratio (benralizumab vs. placebo) at week 56 in patients with baseline blood eosinophil counts of 220 per cubic millimeter or greater. Safety was also assessed. RESULTS: In GALATHEA, the estimates of the annualized exacerbation rate were 1.19 per year (95% confidence interval [CI], 1.04 to 1.36) in the 30-mg benralizumab group, 1.03 per year (95% CI, 0.90 to 1.19) in the 100-mg benralizumab group, and 1.24 per year (95% CI, 1.08 to 1.42) in the placebo group; the rate ratio as compared with placebo was 0.96 for 30 mg of benralizumab (P = 0.65) and 0.83 for 100 mg of benralizumab (P = 0.05). In TERRANOVA, the estimates of the annualized exacerbation rate for 10 mg, 30 mg, and 100 mg of benralizumab and for placebo were 0.99 per year (95% CI, 0.87 to 1.13), 1.21 per year (95% CI, 1.08 to 1.37), 1.09 per year (95% CI, 0.96 to 1.23), and 1.17 per year (95% CI, 1.04 to 1.32), respectively; the corresponding rate ratios were 0.85 (P = 0.06), 1.04 (P = 0.66), and 0.93 (P = 0.40). At 56 weeks, none of the annualized COPD exacerbation rate ratios for any dose of benralizumab as compared with placebo reached significance in either trial. Types and frequencies of adverse events were similar with benralizumab and placebo. CONCLUSIONS: Add-on benralizumab was not associated with a lower annualized rate of COPD exacerbations than placebo among patients with moderate to very severe COPD, a history of frequent moderate or severe exacerbations, and blood eosinophil counts of 220 per cubic millimeter or greater (Funded by AstraZeneca [GALATHEA and TERRANOVA] and Kyowa Hakko Kirin [GALATHEA]; GALATHEA and TERRANOVA ClinicalTrials.gov numbers, NCT02138916 and NCT02155660.).

https://www.nejm.org/doi/full/10.1056/NEJMoa1905248?url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Acrossref.org&rfr_dat=cr_pub%3Dpubmed

Criner, G. J., R. Sue, et al. (2018). **"A Multicenter Randomized Controlled Trial of Zephyr Endobronchial Valve Treatment in Heterogeneous Emphysema (LIBERATE)."** Am J Respir Crit Care Med **198**(9): 1151-1164.

RATIONALE: This is the first multicenter randomized controlled trial to evaluate the effectiveness and safety of Zephyr Endobronchial Valve (EBV) in patients with little to no collateral ventilation out to 12 months. OBJECTIVES: To evaluate the effectiveness and safety of Zephyr EBV in heterogeneous emphysema with little to no collateral ventilation in the treated lobe. METHODS: Subjects were enrolled with a 2:1 randomization (EBV/standard of care [SoC]) at 24 sites. Primary outcome at 12 months was the DeltaEBV-SoC of subjects with a post-bronchodilator FEV1 improvement from baseline of greater than or equal to 15%. Secondary endpoints included absolute changes in post-bronchodilator FEV1, 6-minute-walk distance, and St. George's Respiratory Questionnaire scores. MEASUREMENTS AND MAIN RESULTS: A total of 190 subjects (128 EBV and 62 SoC) were randomized. At 12 months, 47.7% EBV and 16.8% SoC subjects had a DeltaFEV1 greater than or equal to 15% (P < 0.001). DeltaEBV-SoC at 12 months was statistically and clinically significant: for FEV1, 0.106 L (P < 0.001); 6-minute-walk distance, +39.31 m (P = 0.002); and St. George's Respiratory Questionnaire, -7.05 points (P = 0.004). Significant DeltaEBV-SoC were also observed in hyperinflation (residual volume, -522 ml; P < 0.001), modified Medical Research Council Dyspnea Scale (-0.8 points; P < 0.001), and the BODE (body mass index, airflow obstruction, dyspnea, and exercise capacity) index (-1.2 points). Pneumothorax was the most common serious adverse event in the treatment period (procedure to 45 d), in 34/128 (26.6%) of EBV subjects. Four deaths occurred in the EBV group during this phase, and one each in the EBV and SoC groups between 46 days and 12 months. CONCLUSIONS: Zephyr EBV provides clinically meaningful benefits in lung function, exercise tolerance, dyspnea, and quality of life out to at least 12 months, with an acceptable safety profile in patients with little or no collateral ventilation in the target lobe. Clinical trial registered with www.clinicaltrials.gov (NCT 01796392).

Evans, R., M. Brutsche, et al. (2018). **"Quantifying patient centered outcomes associated with the use of bilateral endobronchial coil treatment in patients with severe emphysema."** Curr Med Res Opin **34**(11): 1927-1932.

OBJECTIVE: To determine the impact of endobronchial coils on health-related quality-of-life (HRQoL). This paper utilizes trial data to identify the predictors of HRQoL in patients with severe emphysema, and subsequently estimates the impact of a new treatment on HRQoL (measured by utilities). These utility estimates are used to generate indicative long-term QALY estimates for a range of clinically plausible scenarios as a precursor to cost-effectiveness analyses. METHODS: Patient level HRQoL data from RENEW and the National Emphysema Treatment Trial (NETT) were combined and mapped to generic EuroQol 5-dimension health utility questionnaire (EQ-5D) values using a published algorithm. Multilevel statistical models were developed using treatment, time, response, and baseline characteristics (EQ-5D, age, gender, FEV1, lung RV) to predict EQ-5D over time. Lifetime QALY estimates were generated using published survival data from NETT (assuming no impact of treatment on mortality) and four clinically plausible response profiles. Each response profile was combined with assumptions around treatment impact (constant or time varying). RESULTS: After controlling for baseline characteristics, both treatment and response had a statistically significant impact ($p < .001$) on utility (+0.101 and +0.061, respectively). When combined with selected baseline characteristics and time, Coils and Standard of Care (SoC) generated more QALYs than SoC alone in all scenarios, with incremental lifetime benefit ranging from 0.29-0.55 QALYs. CONCLUSIONS: Coils and SoC resulted in statistically significant improvements in HRQoL compared to SoC alone in patients with severe emphysema.

Fouda, S., M. Kelany, et al. (2018). **"Tobacco smoking in Egypt: a scoping literature review of its epidemiology and control measures."** East Mediterr Health J **24**(2): 198-215.

Background: According to World Health Organization (WHO) reports, the prevalence of smoking is increasing in many developing countries, including Egypt. The aim of this study is to summarize the published data in the literature about tobacco smoking in Egypt. Methods: A computerized literature search of PubMed and relevant Egyptian journals was conducted using the relevant keywords. The findings of retrieved studies were extracted and discussed in a narrative approach. Results: Our search retrieved 44 relevant studies. The most updated prevalence of tobacco smoking in Egypt is 22% in 2010 and is increasing. Highly significant odds ratios were reported for sibling, parent, and peer smoking as risk factors for smoking. Cardiovascular disorders, malignant tumors, and erectile dysfunction are common complications of smoking in the Egyptian population. Efforts to control tobacco smoking are available, but inadequate. Conclusions: Tobacco smoking is a prevalent health problem in Egypt, associated with cardiovascular disorders and malignant tumors. Health education programmes should be delivered through mass media and school-based programmes to reach a large section of the Egyptian population.

Frent, S. M., K. R. Chapman, et al. (2019). **"Capturing Exacerbations of Chronic Obstructive Pulmonary Disease with EXACT. A Subanalysis of FLAME."** Am J Respir Crit Care Med **199**(1): 43-51.

RATIONALE: Chronic obstructive pulmonary disease exacerbations accelerate lung function decline, reduce quality of life, and increase mortality. A subset of patients (n = 457) from the FLAME (Effect of Indacaterol Glycopyrronium vs. Fluticasone Salmeterol on COPD Exacerbations) study used the Exacerbations of COPD Tool (EXACT) to capture symptom-defined exacerbations. OBJECTIVES: To evaluate the effect of indacaterol/glycopyrronium versus salmeterol/fluticasone on symptom-defined exacerbations measured using EXACT, and to assess differences between these events and exacerbations requiring healthcare resource use (HCRU). METHODS: All patients in FLAME used an electronic diary to record and detect symptom deteriorations; HCRU-related exacerbations were confirmed by investigators. In patients using

the EXACT questionnaire, the onset, recovery, and magnitude of symptom-defined exacerbations were identified by changes in total scores relative to baseline. We analyzed the annualized rate and time to first symptom-defined (EXACT) exacerbation and assessed differences between symptom-defined and HCRU events in terms of number, severity, and concordance. MEASUREMENTS AND MAIN RESULTS: A nonsignificant 17% reduction in the annualized rate of symptom-defined (EXACT) exacerbations (rate ratio, 0.83; 95% confidence interval [CI], 0.60-1.14; P = 0.242) and a numerically longer time to first symptom-defined exacerbation were observed with indacaterol/glycopyrronium versus salmeterol/fluticasone (hazard ratio, 0.76; 95% CI, 0.56-1.03; P = 0.075). These results were consistent with data from the overall FLAME population. Of the symptom-defined (EXACT) events, 23.5% corresponded to HCRU events, and 22.2% of HRCU events were captured by EXACT (kappa index, 0.24; 95% CI, 0.15-0.33). CONCLUSIONS: Regardless of the exacerbation definition used, our findings support the use of long-acting beta2 agonists/long-acting muscarinic receptor antagonists as the preferred treatment option for patients at risk of future exacerbations. Clinical trial registered with www.clinicaltrials.gov (NCT01782326).

Furian, M., M. Lichtblau, et al. (2018). **"Efficacy of Dexamethasone in Preventing Acute Mountain Sickness in COPD Patients: Randomized Trial."** Chest **154**(4): 788-797.

BACKGROUND: Patients with COPD may experience acute mountain sickness (AMS) and other altitude-related adverse health effects (ARAHE) when traveling to high altitudes. This study evaluated whether dexamethasone, a drug used for the prevention of AMS in healthy individuals, would prevent AMS/ARAHE in patients with COPD. METHODS: This placebo-controlled, double-blind, parallel-design trial included patients with COPD and Global Initiative for Obstructive Lung Disease grade 1 to 2 who were living below 800 m. Patients were randomized to receive dexamethasone (8 mg/d) or placebo starting on the day before ascent and while staying in a high-altitude clinic at 3,100 m for 2 days. The primary outcome assessed during the altitude sojourn was the combined incidence of AMS/ARAHE, defined as an Environmental Symptoms Questionnaire cerebral score evaluating AMS >/= 0.7 or ARAHE requiring descent or an intervention. RESULTS: In 60 patients randomized to receive dexamethasone (median [quartiles] age: 57 years [50; 60], FEV1 86% predicted [70; 104]; PaO2 at 760 m: 9.6 kPa [9.2; 10.0]), the incidence of AMS/ARAHE was 22% (13 of 60). In 58 patients randomized to receive placebo (age: 60 y [53; 64]; FEV1 94% predicted [76; 103]; PaO2: 10.0 kPa [9.1; 10.5]), the incidence of AMS/ARAHE was 24% (14 of 58) (chi(2) statistic vs dexamethasone, P = .749). Dexamethasone mitigated the altitude-induced PaO2 reduction compared with placebo (mean between-group difference [95% CI], 0.4 kPa [0.0-0.8]; P = .028). CONCLUSIONS: In lowlanders with mild to moderate COPD, the incidence of AMS/ARAHE at 3,100 m was moderate and not reduced by dexamethasone treatment. Based on these findings, dexamethasone cannot be recommended for the prevention of AMS/ARAHE in patients with COPD undertaking high-altitude travel, although the drug mitigated the altitude-induced hypoxemia. TRIAL REGISTRY: ClinicalTrials.gov; No.: NCT02450968; URL: www.clinicaltrials.gov.

Fusi-Schmidhauser, T., A. Riglietti, et al. (2018). **"Palliative Care Provision for Patients with Advanced Chronic Obstructive Pulmonary Disease: A Systematic Integrative Literature Review."** Copd **15**(6): 600-611.

Although chronic obstructive pulmonary disease (COPD) is recognized as being a life-limiting condition with palliative care needs, palliative care provision is seldom implemented. The disease unpredictability, the misconceptions about palliative care being only for people with cancer, and only relevant in the last days of life, prevent a timely integrated care plan. This systematic review aimed to explore how palliative care is provided in advanced COPD and to identify elements defining integrated palliative care. Eight databases, including MEDLINE, EMBASE and CINAHL, were searched using a comprehensive search strategy to identify studies on palliative care provision in advanced COPD, published from January 1, 1960 to November 30, 2017. Citation tracking and evaluation of trial registers were also performed.

Study quality was assessed with a critical appraisal tool for both qualitative and quantitative data. Of the 458 titles, 24 were eligible for inclusion. Experiences about advanced COPD, palliative care timing, service delivery and palliative care integration emerged as main themes, defining a developing taxonomy for palliative care provision in advanced COPD. This taxonomy involves different levels of care provision and integrated care is the last step of this dynamic process. Furthermore, palliative care involvement, holistic needs' assessment and management and advance care planning have been identified as elements of integrated care. This literature review identified elements that could be used to develop a taxonomy of palliative care delivery in advanced COPD. Further research is needed to improve our understanding on palliative care provision in advanced COPD.

Gao, H., Y. Gao, et al. (2019). **"Effect of physical therapy for chronic obstructive pulmonary disease: A protocol for an updated systematic review of randomized controlled trial."** Medicine (Baltimore) **98**(38): e17241.

BACKGROUND: Previous studies have reported that physical therapy (PT) can be used for the treatment of chronic obstructive pulmonary disease (COPD). However, its effectiveness is still inconclusive. This systematic review will aim to assess its effectiveness and safety for the treatment of patients with COPD. METHODS: All randomized controlled trials (RCTs) literatures of PT for COPD will be searched from the databases of Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE, MEDILINE, Web of Science, Cumulative Index to Nursing and Allied Health Literature, Allied and Complementary Medicine Database, Chinese Biomedical Literature Database, China National Knowledge Infrastructure, VIP Information, and Wanfang Data from inception to the present without any language restrictions. Two reviewers will independently perform the study selection, data extraction, and methodological quality assessment. A third reviewer will be invited to resolve any disagreements occurred between 2 reviewers. RESULTS: The primary outcome is lung function. The secondary outcomes include symptoms, health-related quality of life, mortality, and adverse events. The outcome data will be pooled by using the models of random-effects or fixed-effects according to the detected heterogeneity. CONCLUSION: The findings of this study will provide up-todated summary evidence for assessing the effectiveness and safety of PT for COPD.

Greulich, T., J. Chlumsky, et al. (2018). **"Safety of biweekly alpha1-antitrypsin treatment in the RAPID programme."** Eur Respir J **52**(5)

Haider, S. H., A. Oskuei, et al. (2019). **"Receptor for advanced glycation end-products and environmental exposure related obstructive airways disease: a systematic review."** Eur Respir Rev **28**(151)BACKGROUND: Our group has identified the receptor for advanced glycation end-products (RAGE) as a predictor of World Trade Center particulate matter associated lung injury. The aim of this systematic review is to assess the relationship between RAGE and obstructive airways disease secondary to environmental exposure. METHODS: A comprehensive search using PubMed and Embase was performed on January 5, 2018 utilising keywords focusing on environmental exposure, obstructive airways disease and RAGE and was registered with PROSPERO (CRD42018093834). We included original human research studies in English, focusing on pulmonary end-points associated with RAGE and environmental exposure. RESULTS: A total of 213 studies were identified by the initial search. After removing the duplicates and applying inclusion and exclusion criteria, we screened the titles and abstracts of 61 studies. Finally, 19 full-text articles were included. The exposures discussed in these

articles include particulate matter (n=2) and cigarette smoke (n=17). CONCLUSION: RAGE is a mediator of inflammation associated end-organ dysfunction such as obstructive airways disease. Soluble RAGE, a decoy receptor, may have a protective effect in some pulmonary processes. Overall, RAGE is biologically relevant in environmental exposure associated lung disease. Future investigations should focus on further understanding the role and therapeutic potential of RAGE in particulate matter exposure associated lung disease.

Han, M. K., N. Tayob, et al. (2018). **"Association between Emphysema and Chronic Obstructive Pulmonary Disease Outcomes in the COPDGene and SPIROMICS Cohorts: A Post Hoc Analysis of Two Clinical Trials."** Am J Respir Crit Care Med **198**(2): 265-267.

Hanania, N. A., S. Sethi, et al. (2019). **"Long-term safety and efficacy of formoterol fumarate inhalation solution in patients with moderate-to-severe COPD."** Int J Chron Obstruct Pulmon Dis **14**: 117-127.

Background: Formoterol fumarate inhalation solution (FFIS; Perforomist((R))) is a long-acting beta2-agonist (LABA) marketed in the US as a nebulized COPD maintenance treatment. Because long-term LABA use was associated with a potential increased risk of exacerbation or death in asthma patients, the US Food and Drug Administration (FDA) requested a postmarketing commitment study to evaluate long-term safety in COPD patients. Methods: This was a multicenter, randomized, double-blind, placebo-controlled, noninferiority study. Patients (N=1,071; mean age, 62.6 years; 48.5% male; 89.7% white) with moderate-to-severe COPD on stable COPD therapy received FFIS (20 microg; n=541) or placebo (n=530) twice daily. The primary end point was the combined incidence of respiratory death, first COPD-related ER visit, or first COPD exacerbation-related hospitalization during 1 year post randomization. Noninferiority to placebo was concluded if the two-sided 90% CI of the HR of FFIS to placebo was <1.5. Secondary end points included spirometry. Results: The planned 1-year treatment period was completed by 520 patients; 551 discontinued prematurely (FFIS: 45.7%; placebo: 57.4%). The median treatment duration was approximately 10 and 7 months for FFIS and placebo, respectively. Among 1,071 randomized patients, 121 had >/=1 primary event (FFIS: 11.8%; placebo: 10.8%). The estimated HR of a primary event with FFIS vs placebo was 0.965 (90% CI: 0.711, 1.308), demonstrating that FFIS was noninferior to placebo. No respiratory deaths were observed in the FFIS group. Adverse events were similar for FFIS vs placebo (patients with >/=1 treatment-emergent adverse events: 374 [69.1%] vs 369 [69.6%], respectively). Compared with placebo, FFIS demonstrated statistically greater improvements from baseline in trough FEV1, FVC, percent predicted FEV1, and patient-reported outcomes (Transition Dyspnea Index). Conclusions: Nebulized FFIS was noninferior to placebo with respect to safety in patients with moderate-to-severe COPD. Additionally, fewer treatment withdrawals and larger lung function improvements were observed with FFIS compared with placebo when added to other maintenance COPD therapies.

Harb, H. S., A. A. Elberry, et al. (2018). **"Performance of Large Spacer Versus Nebulizer T-Piece in Single-Limb Noninvasive Ventilation."** Respir Care **63**(11): 1360-1369.

BACKGROUND: Predosing patients with COPD with salbutamol by using a pressurized metered-dose-inhaler (pMDI) as a bronchodilator was hypothesized to improve the distribution of the subsequent nebulized dose. This study determined the effect of a pMDI preliminary bronchodilator dose on the aerosol delivered by a mesh nebulizer during single-limb noninvasive ventilation. METHODS: Twelve subjects

with COPD who received noninvasive ventilation were enrolled in a randomized, open-label, urinary pharmacokinetic study. A bi-level ventilator with a dry single-limb circuit and the fixed expiratory port was set in the spontaneous mode, with initial inspiratory and expiratory pressures of 20 and 5 cm H2O respectively, a 1:3 inspiratory-expiratory ratio, and 15 breaths/min. Salbutamol was administered via a mesh nebulizer with a large spacer or T-piece placed between the fixed-orifice expiratory valve and the oronasal mask. In vivo dosing methods were randomized for days 1, 3, and 5 of the study. On each day, a 1-mL respirable solution that contained 5,000 mug salbutamol was nebulized by using a mesh nebulizer with 3 setting: (1) T-piece, (2) large spacer, and (3) large spacer plus pMDI. Only with the large spacer plus pMDI setting, 2 pMDI doses, which contained 100 mug salbutamol each, were actuated before nebulization. Urine samples were collected at 0.5 h (as an index of pulmonary bioavailability) and pooled up to 24 h after dosing (as an index of systemic absorption). On day 2, ex vivo studies were performed for the 3 setting with salbutamol collected onto filters placed before the mask. The drug was eluted from the filters and analyzed to determine the inhaled dose. RESULTS: A large spacer plus pMDI showed a trend to deliver a higher fraction (percentage of nominal dose) of both ex vivo filters and 0.5-h urinary salbutamol. The 0.5-h urinary salbutamol excreted with a large spacer plus pMDI (1.99%) was larger than with the T-piece (1.73%) and large spacer (1.78%). This trend did not extend to the 24-h levels, in which bioavailability with the large spacer plus pMDI (49.9%) was lower than with the T-piece (52.8%) and with the large spacer (54.3%). However, no differences were significant. CONCLUSIONS: The T-piece and large spacer were equally efficient for salbutamol delivery from the mesh nebulizer in patients with COPD and on single-limb noninvasive ventilation. Adding a preliminary bronchodilator dose by pMDI prenebulization showed a trend toward greater pulmonary bioavailability of nebulized salbutamol and may be worth considering to maximize delivery of salbutamol to patients who are severely ill.

Hartman, J. E., K. Klooster, et al. (2018). **"Patient-specific goals significantly improve after endobronchial coil treatment in patients with severe emphysema."** Clin Respir J **12**(6): 2157-2158.

Hong, H., C. Huang, et al. (2019). **"Efficacy and safety of acupoint autohemotherapy in treating stable chronic obstructive pulmonary disease: Protocol for a systematic review and meta-analysis."** Medicine (Baltimore) **98**(38): e17291.

BACKGROUND: Chronic Obstructive Pulmonary Disease (COPD) is a clinically common chronic disease with the characteristic of recurrent attacks, difficulty of cure and high morbidity, disability, death rates. COPD exerts a great burden on patients, families and society. Acupoint Autohemotherapy (AA) is a traditional Chinese medicine (TCM) treatment by taking the patient's own venous blood and injecting them at acupoints, combined with the continuous stimulation of blood and the specific efficacy of the acupoint itself. It has been proved to be useful in pulmonary treatment and rehabilitation of COPD patients. However, the efficacy of AA on COPD patients has not been fully statistically evaluated. In this study, we aim to systematically examine the efficacy and safety of AA for COPD patients. METHODS: Data from all English and Chinese databases, including Medline, Cochrane Library, Embase, China National Knowledge Infrastructure Database, Wanfang Database, China Biomedical Literature Database and Chongqing VIP information, will be used to conduct a systematic and comprehensive literature search. The range of date is from inception to July 2019. Randomized controlled trials (RCTs) related to AA and western medicine in the treatment of COPD will be included. Quality of included trials will be assessed according to the risk of bias tool of Cochrane Handbook 5.1.0. The GRADE approach will be used to rate the certainty of the evidence of estimates derived from meta-analysis. RevMan 5.3 will be used for data synthesis, sensitivity analysis, meta-regression analysis, subgroup analysis and risk of bias assessment. A funnel plot will be developed to evaluate reporting bias, and Begg and Egger tests will be used to assess funnel plot symmetries. Grading of recommendations assessment, development and evaluation system will be

utilized to assess the quality of evidence. RESULTS: This systematic review and meta-analysis aims to summarize the direct and indirect outcomes for AA and western medicine on COPD patients and evaluate its efficacy and safety. The results will be submitted to a peer-reviewed journal once completed. CONCLUSION: The systematic review will provide evidence to assess the efficacy and safety of AA and western medicine in the treatment of COPD patients. PROSPERO REGISTRATION NUMBER: PROSPERO CRD42019137189.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6756693/pdf/medi-98-e17291.pdf

Ishiura, Y., M. Fujimura, et al. (2019). **"Effect of triple therapy in patients with asthma-COPD overlap."** Int J Clin Pharmacol Ther **57**(8): 384-392.

OBJECTIVE: Asthma-chronic obstructive pulmonary disease (COPD) overlap (ACO) is of increasing interest because ACO patients have significantly worse outcomes, leading to greater social and economic burdens compared with asthma or COPD alone. Some guidelines for ACO recommend triple therapy with inhaled corticosteroids, long-acting beta2 agonists, and long-acting muscarinic antagonists. However, this approach is based on extrapolating data from patients with asthma or COPD alone. Therapeutic studies for ACO have not previously been conducted. MATERIALS AND METHODS: A 12-week, randomized, open-label cross-over pilot study was conducted in 17 ACO patients to evaluate the effect of umeclidinium (UMEC) 62.5 microg once-daily added to fluticasone furoate/vilanterol (FF/VI) 200/25 microg once-daily. A 4-week run-in, a first and a second 4-week treatment period were included. Respiratory function, respiratory impedance, fractional exhaled nitric oxide, COPD assessment test, and asthma control test scores were evaluated 0, 4, and 8 weeks after randomization. RESULTS: Mean values of post-bronchodilator forced expiratory volume in 1 second as a percentage of the predicted value (%FEV1), after UMEC was added to FF/VI, were significantly higher than after the run-in ($p < 0.01$). Mean values of resonant frequency during inspiration (Fres), after UMEC was added to FF/VI, were significantly lower than after the run-in ($p < 0.01$). CONCLUSION: Adding UMEC to FF/VI provides greater improvement in lung function, indicating that triple therapy is a suitable regular treatment for ACO.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6637394/pdf/intjclinpharmacol-57-384.pdf

Jiang, G. Y., Q. Li, et al. (2019). **"Short-term treatment of irbesartan and hydrochlorothiazide decreases plasma N-terminal pro-brain natriuretic peptide levels in subjects with acute exacerbations of COPD."** Int J Chron Obstruct Pulmon Dis **14**: 73-80.

Background: Plasma levels of N-terminal pro-brain natriuretic peptide (NT-proBNP) are elevated in subjects with COPD, and high plasma NT-proBNP levels are correlated with a poor prognosis. Thus, it is crucial to decrease the plasma NT-proBNP levels at the early stage of disease. We aimed to assess the effects of short-term treatment of irbesartan and hydrochlorothiazide on plasma NT-proBNP levels and health-related quality of life (HRQOL) in subjects with acute exacerbations of COPD (AECOPD). Subjects and methods: Eighty subjects with AECOPD and high plasma NT-proBNP levels, without any clinical evidence of cor pulmonale, were enrolled. The subjects were randomly allocated into two groups of 40 subjects. In addition to standard treatment for AECOPD, the subjects in group I were treated with irbesartan alone, and those in group II were treated with irbesartan and hydrochlorothiazide for a week. Forty subjects with stable COPD were enrolled as a control group. Plasma NT-proBNP concentrations were measured on admission and on the first, fourth, and seventh days. The subjects' health-related quality of life was evaluated applying the 36-item short-form questionnaire on the first day before treatment and on the seventh day after treatment. Results: Treatment of irbesartan and hydrochlorothiazide significantly decreased plasma NT-proBNP levels in subjects with AECOPD, and this reduction was more significant in group II than that in group I. There were no significant differences in 36-item short-form domain scores between subjects with stable COPD and those with AECOPD who were treated with irbesartan and hydrochlorothiazide. Conclusion: Treatment of irbesartan and hydrochlorothiazide rapidly decreased plasma NT-proBNP levels in subjects with AECOPD, and the treatment did not impair their physical status.

Kostrzon, M., A. Sliwka, et al. (2019). **"Subterranean Pulmonary Rehabilitation in Chronic Obstructive Pulmonary Disease."** Adv Exp Med Biol **1176**: 35-46.

Pulmonary rehabilitation (PR) has been recommended as an integral part of treatment for patients with chronic obstructive pulmonary disease (COPD). Climate therapy in salt mine chambers has been found of benefit in chronic respiratory diseases. The study compares long-term effects of underground PR in the Wieliczka Salt Mine with that conducted on the surface. There were 42 COPD patients enrolled in the study, with FEV1/FVC <0.7 predicted and post-bronchodilator reversibility <12%, randomized into pulmonary rehabilitation in the mine (Group I, n = 23) and PR on the surface (Group II, n = 19). The outcomes consisted of lung function variables, exercise performance (6-min walk test - 6MWT), dyspnea (mMRC), and compliance with the disease and quality of life (COPD Assessment Test - CAT) and BODE index, compared at baseline (P0), end (P1), and 6 months after pulmonary rehabilitation (P2). The findings were that subterranean pulmonary rehabilitation significantly reduced CAT score ($p < 0.001$), BODE index ($p = 0.004$), and dyspnea (mMRC) ($p = 0.001$) and increased distance in 6MWT ($p < 0.001$), compared with its equivalent conducted on the surface. Further, beneficial effect of subterranean treatment was sustained during the following half a year as opposed to the effect noticed on patients treated on the surface. We conclude that subterranean pulmonary rehabilitative treatment reduces symptoms and improves exercise tolerance to a greater and sustained extent, compared to a similar treatment on the surface, in patients suffering from COPD.

Lazaar, A. L., B. E. Miller, et al. (2018). **"Effect of the CXCR2 antagonist danirixin on symptoms and health status in COPD."** Eur Respir J **52**(4)

Lee, A. L., T. E. Dolmage, et al. (2018). **"The Impact of Listening to Music During a High-Intensity Exercise Endurance Test in People With COPD."** Chest **153**(5): 1134-1141.

BACKGROUND: In people with COPD, dyspnea is the primary symptom limiting exercise tolerance. One approach to reducing dyspnea during exercise is through music listening. A constant speed endurance test reflects a high-intensity aerobic exercise training session, but whether listening to music affects endurance time is unknown. This study aimed to determine the effects of listening to music during a constant speed endurance test in COPD. METHODS: Participants with COPD completed two endurance walk tests, one with and one without listening to self-selected music throughout the test. The primary outcome was the difference in endurance time between the two conditions. Heart rate, percutaneous oxygen saturation, dyspnea, and rate of perceived exertion were measured before and after each test. RESULTS: Nineteen participants (mean [SD]: age, 71 [8] years; FEV1, 47 [19] % predicted) completed the study. Endurance time was greater (1.10 [95% CI, 0.41-1.78] min) while listening to music (7.0 [3.1] min) than without (5.9 [2.6] min), and reduced end-test dyspnea (1.0 [95% CI, -2.80 to -1.80] units) (with music, 4.6 [1.7] units; vs without music, 5.6 [1.4] units, respectively). There was not a significant difference in heart rate, percutaneous oxygen saturation, or leg fatigue. There were no adverse events under either condition. CONCLUSIONS: In COPD, dyspnea was less while listening to music and was accompanied by an increased tolerance of high-intensity exercise demonstrated by greater endurance time. Practically, the effect was modest but may represent an aid for exercise training of these patients. TRIAL REGISTRY: Australian New Zealand Clinical Trials Registry; No. ACTRN12617001217392.

Lehmann, S., T. Ringbaek, et al. (2019). **"A randomized trial to determine the impact of indacaterol/glycopyrronium on nighttime oxygenation and symptoms in patients with moderate-to-severe COPD: the DuoSleep study."** Int J Chron Obstruct Pulmon Dis **14**: 199-210.

Purpose: This study investigated the effect of dual bronchodilation with the long-acting beta-receptor agonist/long-acting muscarinic antagonist combination, indacaterol/glycopyrronium (IND/GLY), on nighttime oxygenation, lung function, sleep quality, and symptoms in patients with moderate-to-severe COPD. Patients and methods: This was a 4-week, double-blind, multicenter, placebo-controlled, two-period crossover study. Patients were randomized in a 1:1 ratio to receive IND/GLY 110/50 microg once daily or matching placebo. The primary objective was to evaluate the effect of treatment with IND/GLY on mean nighttime oxygenation, compared with placebo. The secondary objective was to determine the time spent <90% in blood oxygen saturation (SpO2) compared with placebo. Exploratory objectives were to assess the effect of IND/GLY, compared with placebo, on sleep quality measured by the Medical Outcomes Study (MOS) Sleep Scale and the COPD and Asthma Sleep Impact Scale (CASIS) questionnaires and on symptoms assessed by COPD Assessment Test (CAT) questionnaire. Results: In total, 38 patients were randomized (n=22, IND/GLY; n=16, placebo). The change in nighttime oxygenation (SpO2) was similar, and there was a comparable difference in time spent <90% SpO2 between IND/GLY and placebo. Increases from baseline for the difference between IND/GLY and placebo for trough FEV1, FVC, and inspiratory capacity (P<0.05) were seen, with a corresponding reduction in residual volume and functional residual capacity (P<0.05). IND/GLY treatment showed an improvement in scores for CAT (P=0.0208), CASIS, and the MOS Sleep Scale measures, Sleep Problems Index I, Sleep Problems Index II (P=0.0315), Sleep Adequacy, Sleep Disturbance Scale, Somnolence Scale, and Short of Breath Scale (P=0.0031). Conclusion: In this study, IND/GLY 110/50 microg once daily improved symptoms, sleep quality, and lung function, but showed no effect on nighttime oxygenation in patients with moderate-to-severe COPD.

Li, Z., X. Yuan, et al. (2019). **"Procalcitonin-guided antibiotic therapy in acute exacerbation of chronic obstructive pulmonary disease: An updated meta-analysis."** Medicine (Baltimore) **98**(32): e16775.

BACKGROUND: The benefit of a procalcitonin (PCT)-guided antibiotic strategy in acute exacerbation of chronic obstructive pulmonary disease (AECOPD) remains uncertain. OBJECTIVES: This updated meta-analysis was performed to reevaluate the therapeutic potential of PCT-guided antibiotic therapy in AECOPD. DATA SOURCES: We searched PubMed, Embase, Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov up to February 2019 to identify randomized controlled trials (RCTs) investigating the role of PCT-guided antibiotic strategies in treating adult patients with AECOPD. Relative risk (RR) or mean differences (MD) with accompanying 95% confidence intervals (CIs) were calculated with a random-effects model. RESULTS: Eight RCTs with a total of 1376 participants were included. The results suggested that a PCT-guided antibiotic strategy reduced antibiotic prescriptions (RR: 0.55; 95% CI: 0.39-0.76; P = .0003). However, antibiotic exposure duration (MD: -1.34; 95% CI: -2.83-0.16; P = .08), antibiotic use after discharge (RR: 1.61; 95% CI: 0.61-4.23; P = .34), clinical success (RR: 1.02; 95% CI: 0.96-1.08; P = .47), all-cause mortality (RR: 1.05; 95% CI: 0.72-1.55; P = .79), exacerbation at follow-up (RR: 0.97; 95% CI: 0.80-1.18; P = .78), readmission at follow-up (RR: 1.12; 95% CI: 0.82-1.53; P = .49), length of hospital stay (MD: -0.36; 95% CI: -1.36-0.64; P = .48), and adverse events (RR: 1.33; 95% CI: 0.79-2.23; P = .28) were similar in both groups. IMPLICATIONS OF KEY FINDINGS: A PCT-guided antibiotic strategy is associated with fewer antibiotic prescriptions, and has similar efficacy and safety compared with standard antibiotic therapy in AECOPD patients.

Malik, P. R. A., C. Fahim, et al. (2018). **"Incentive Spirometry After Lung Resection: A Randomized Controlled Trial."** Ann Thorac Surg **106**(2): 340-345.

BACKGROUND: Incentive spirometry (IS) is thought to reduce the incidence of postoperative pulmonary complications (PPC) after lung resection. We sought to determine whether the addition of IS to routine physiotherapy following lung resection results in a lower rate of PPC, as compared with physiotherapy alone. METHODS: A single-blind prospective randomized controlled trial was conducted in adults undergoing lung resection. Individuals with previous lung surgery or home oxygen were excluded. Participants randomized to the control arm (PHY) received routine physiotherapy alone (deep breathing, ambulation and shoulder exercises). Those randomized to the intervention arm (PHY/IS) received IS in addition to routine physiotherapy. The trial was powered to detect a 10% difference in the rate of PPC (beta = 80%). Student's t test and chi-square were utilized for continuous and categorical variables, respectively, with a significance level of p = 0.05. RESULTS: A total of 387 participants (n = 195 PHY/IS; n = 192 PHY) were randomized between 2014 and 2017. Baseline characteristics were comparable for both arms. The majority of patients underwent a pulmonary lobectomy (PHY/IS = 59.5%, PHY = 61.0%; p = 0.84), with no difference in the rates of minimally invasive and open procedures. There were no differences in the incidence of PPC at 30 days postoperatively (PHY/IS = 12.3%, PHY = 13.0%; p = 0.88). There were no differences in rates of pneumonia (PHY/IS = 4.6%, PHY = 7.8%; p = 0.21), mechanical ventilation (PHY/IS = 2.1%, PHY = 1.0%; p = 0.41), home oxygen (PHY/IS = 13.8%, PHY = 14.6%; p = 0.89), hospital length of stay (PHY/IS = 4 days, PHY = 4 days; p = 0.34), or rate of readmission to hospital (PHY/IS = 10.3%, PHY = 9.9%; p = 1.00). CONCLUSIONS: The addition of IS to routine postoperative physiotherapy does not reduce the incidence of PPC after lung resection.

Mandelzweig, K., A. Leligdowicz, et al. (2018). **"Non-invasive ventilation in children and adults in low- and low-middle income countries: A systematic review and meta-analysis."** J Crit Care **47**: 310-319.

PURPOSE: We systematically reviewed the effects of NIV for acute respiratory failure (ARF) in low- and low-middle income countries. MATERIALS AND METHODS: We searched MEDLINE, CENTRAL, and EMBASE (to January 2016) for observational studies and trials of NIV for ARF or in the peri-extubation period in adults and post-neonatal children. We abstracted outcomes data and assessed quality. Meta-analyses used random-effect models. RESULTS: Fifty-four studies (ten pediatric/n=1099; 44 adult/n=2904), mostly South Asian, were included. Common diagnoses were pneumonia and chronic obstructive pulmonary disease (COPD). Considering observational studies and the NIV arm of trials, NIV was associated with moderate risks of mortality (pooled risk 9.5%, 95% confidence interval (CI) 4.6-14.5% in children; 16.2% [11.2-21.2%] in adults); NIV failure (10.5% [4.6-16.5%] in children; 28.5% [22.4-34.6%] in adults); and intubation (5.3% [0.8-9.7%] in children; 28.8% [21.9-35.8%] in adults). The risk of mortality was greater (p=0.035) in adults with hypoxemic (25.7% [15.2-36.1%]) vs. hypercapneic (12.8% [7.0-18.6%]) ARF. NIV reduced mortality in COPD (relative risk [RR] 0.47 [0.27-0.79]) and in patients weaning from ventilation (RR 0.48 [0.28-0.80]). The pooled pneumothorax risk was 2.4% (0.8-3.9%) in children and 5.2% (1.0-9.4%) in adults. Meta-analyses had high heterogeneity. CONCLUSIONS: NIV for ARF in these settings appears to be effective.

Marrara, K. T., V. A. P. Di Lorenzo, et al. (2018). **"Noninvasive Ventilation as an Important Adjunct to an Exercise Training Program in Subjects With Moderate to Severe COPD."** Respir Care **63**(11): 1388-1398.

BACKGROUND: The primary objective of this study was to investigate whether noninvasive ventilation (NIV) can positively affect exercise capacity, maximum oxygen uptake (VO2), and symptoms after a 6-week physical training program for subjects with moderate to very severe COPD. METHODS: 47 subjects with COPD who were enrolled in a physical training program were randomized to either physical training

alone or NIV + physical training (NIV-Physical training). Physical training consisted of dynamic aerobic exercises on a treadmill 3 times/week for 6 weeks, for a total of 18 sessions. NIV was titrated according to the subject's tolerance at rest and during exercise. Assessments included physiological responses and symptoms at the incremental cardiopulmonary exercise test peak and during submaximal exercise on a treadmill, 6-min walk distance, maximum inspiratory (PImax) and expiratory pressure (PEmax), BODE index, and health-related quality of life. RESULTS: 43 subjects completed the 6-week physical training program. Both groups improved 6-min walk distance, PImax, BODE index, and quality of life, and no differences were found between groups. However, significant improvements were observed for subjects in the NIV-Physical training group with regard to PEmax, maximum VO2 , maximum metabolic equivalents, circulatory power, and maximum SpO2 . CONCLUSIONS: A 6-week physical training program alone can improve tolerance for exercise and quality of life, in addition to reducing the risk of mortality. However, NIV associated with a physical training program was shown to have an additive beneficial effect on powerful prognostic markers (maximum VO2 and circulatory power) and to reduce symptoms and improve oxygen saturation in subjects with moderate to very severe COPD.

Martinez, F. J., K. F. Rabe, et al. (2018). **"Determinants of Response to Roflumilast in Severe Chronic Obstructive Pulmonary Disease. Pooled Analysis of Two Randomized Trials."** Am J Respir Crit Care Med **198**(10): 1268-1278.

RATIONALE: Roflumilast reduces exacerbations in patients with severe chronic obstructive pulmonary disease associated with chronic bronchitis and a history of exacerbations. Further characterization of patients most likely to benefit is warranted. OBJECTIVES: Define characteristics that most robustly identify patients who derive greatest exacerbation risk reduction with roflumilast. METHODS: Predefined, pooled analyses of REACT (Roflumilast in the Prevention of COPD Exacerbations While Taking Appropriate Combination Treatment; NCT01329029) and RE(2)SPOND (Roflumilast Effect on Exacerbations in Patients on Dual [LABA/ICS] Therapy; NCT01443845) multicenter, randomized, double-blind, placebo-controlled studies. The primary endpoint was rate of moderate or severe exacerbations per patient per year. MEASUREMENTS AND MAIN RESULTS: In the overall intention-to-treat population (n = 4,287), roflumilast reduced moderate or severe exacerbations by 12.3% (rate ratio, 0.88, 95% confidence interval, 0.80-0.97; P = 0.0086) and severe exacerbations by 16.1% (0.84; 0.71-0.99; P = 0.0409) versus placebo. The reduction in moderate or severe exacerbations with roflumilast was most pronounced in patients who had been hospitalized for an exacerbation in the prior year (0.74; 0.63-0.88; P = 0.0005); had more than two exacerbations in the prior year (0.79; 0.65-0.96; P = 0.0160); or had baseline eosinophils >/=150 cells/mul (0.81; 0.71-0.93; P = 0.0020), >/=150 to <300 cells/mul (0.84; 0.71-0.98; P = 0.0282), or >/=300 cells/mul (0.77; 0.61-0.97; P = 0.0264). Similar subgroup results were noted for severe exacerbations. In patients with prior hospitalization and higher baseline blood eosinophil concentrations, roflumilast reduced moderate or severe exacerbations by 34.5% at >/=150 cells/mul (0.65; 0.52-0.82; P = 0.0003) and 42.7% at >/=300 cells/mul (0.57; 0.37-0.88; P = 0.0111) versus placebo. CONCLUSIONS: This prespecified, pooled analysis confirms the benefit of roflumilast in decreasing exacerbations in patients with prior hospitalization for exacerbation, greater exacerbation frequency, and higher (>/=150 cells/mul, >/=150 to <300 cells/mul, or >/=300 cells/mul) baseline blood eosinophil count.

Matthys, H. and P. Funk (2018). **"Pelargonium sidoides preparation EPs 7630 in COPD: health-related quality-of-life and other patient-reported outcomes in adults receiving add-on therapy."** Curr Med Res Opin **34**(7): 1245-1251.

OBJECTIVE: Patient-reported outcomes (PRO) such as health-related quality-of-life (HRQoL) belong to the most important criteria for the evaluation of medical therapies in clinical trials or practice-based benefit assessments. This study, therefore, revisited results of an earlier published clinical trial investigating the

effects of the herbal drug preparation from the roots of Pelargonium sidoides EPs 7630, administered as add-on therapy in patients suffering from chronic obstructive pulmonary disease (COPD), with respect to HRQoL and other PRO. METHODS: A total of 199 adults diagnosed with COPD stages II/III and receiving standard treatment according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) were randomly assigned to add-on therapy with EPs 7630 or placebo for 24 weeks. HRQoL (disease-specific St. George's Respiratory Questionnaire, SGRQ; current HRQoL state according to the EuroQuol visual analog scale, EQ VAS) and PRO (Integrative Medicine Outcomes Scale, IMOS; Integrative Medicine Patient Satisfaction Scale, IMPSS; symptom severity score of cough, sputum production and sternal pain while coughing; duration of inability to work) were assessed at each study visit or documented daily by the patient in a patient diary, respectively. RESULTS: At week 24, all HRQoL and PRO measures showed a more pronounced improvement under EPs 7630 than under placebo (EQ VAS, $p < .001$; SGRQ total score, $p < .001$; symptom severity score of cough, sputum production, and sternal pain while coughing, $p = .021$; duration of inability to work, $p = .004$; two-sided t-test each; IMOS, $p < .001$, IMPSS, $p < .001$, two-sided Mantel-Haenszel test each). Moreover, the difference seen for the SGRQ exceeded the SGRQ minimal clinically important difference (MCID) threshold of 4 points. CONCLUSIONS: Add-on therapy with EPs 7630 led to an improvement in HRQoL and other PRO in adult patients with COPD compared to placebo while showing a good long-term tolerability.

Oliveira, M. V. C., E. Pizzichini, et al. (2018). **"Evaluation of the preference, satisfaction and correct use of Breezhaler((R)) and Respimat((R)) inhalers in patients with chronic obstructive pulmonary disease - INHALATOR study."** Respir Med **144**: 61-67.

The INHALATOR study was a randomized, multicentre, open label, two-period of 7 days each, crossover study, with 7 days of washout in-between, aiming to evaluate the correct use, satisfaction and preference between Breezhaler((R)) and Respimat((R)) devices in patients under daily use of open Spiriva((R)) or open Onbrize((R)), as monotherapy for treatment of mild or moderate COPD. Patients aged >/=40 years with a smoking history of at least 10 pack-year were included in the study. Primary endpoint was the rate of correct use of each device at the first day of treatment after reading the drug leaflet information and was evaluated under the supervision of a trained evaluator. At the end of each treatment phase, the inhaler use was re-evaluated and a satisfaction questionnaire was completed. The patients' preference for the inhaler devices was assessed at the end of the study. After exclusions due to screening failures, 140 patients were randomized: 136 received at least one dose of Breezhaler((R)) and 135 of Respimat((R)). At treatment start, the rate of correct inhaler use was 40.4% (95%CI: 32.2%-48.7%) for Breezhaler((R)) and 36.3% (95%CI: 28.2%-44.4%) for Respimat((R)) (p=0.451). After 7 days, the rates were 68.9% (95%CI: 61.1%-76.7%) and 60.4% (95%CI: 52.2%-68.7%), respectively (p=0.077). According to the Feeling of Satisfaction with Inhaler Questionnaire - FSI 10 patients were more satisfied using Breezhaler((R)) than Respimat((R)) and 57.1% preferred using Breezhaler((R)) (p=0.001) while 30.1% preferred Respimat((R)) (p<0.001).

Paneroni, M., C. Simonelli, et al. (2018). **"Short-Term Effects of Normocapnic Hyperpnea and Exercise Training in Patients With Chronic Obstructive Pulmonary Disease: A Pilot Study."** Am J Phys Med Rehabil **97**(12): 866-872.

OBJECTIVE: The aim of the study was to evaluate the short-term physiologic effects of respiratory muscle training with normocapnic hyperpnea added to standard exercise training on respiratory muscle endurance/strength and exercise tolerance in patients with chronic obstructive pulmonary disease. DESIGN: The study used a randomized controlled trial. Patients referred for rehabilitation were randomly assigned to 20 sessions (twice daily 5 d/wk) of either normocapnic hyperpnea (group 1, n = 12) or sham maneuvers (group 2, n = 10) in addition to individualized cycle training and abdominal, upper, and lower limb muscle exercise. At baseline and end of study, patients underwent evaluation of respiratory muscle

endurance, maximum voluntary ventilation, maximal inspiratory, and expiratory pressures, and 6-min walking distance. RESULTS: After training, a significant improvement was found only for group 1 in respiratory muscle endurance time (by 654 [481] secs versus 149 [216] secs for group 2, P = 0.0108) and maximal inspiratory (group 1: from 81.2 [21.9] cmH2O to 107.6 [23.0] cmH2O, P = 0.018 versus group 2: from 75.4 [13.8] cmH2O to 81.3 [18.9] cmH2O, P = 0.139). The difference between groups for 6-min walking distance, maximum voluntary ventilation, and expiratory pressures was not significant. CONCLUSIONS: Short-term normocapnic hyperpnea training added to standard exercise, compared with exercise training alone, improves respiratory muscle endurance and strength but not exercise tolerance in patients with chronic obstructive pulmonary disease.

Perkins-Porras, L., M. Riaz, et al. (2018). **"Feasibility study to assess the effect of a brief mindfulness intervention for patients with chronic obstructive pulmonary disease: A randomized controlled trial."** Chron Respir Dis **15**(4): 400-410.

Psychological distress is common among patients with chronic obstructive pulmonary disease (COPD). This study aimed to assess whether a 10-minute mindfulness intervention reduces distress and breathlessness, improves mood and increases mindfulness among hospital inpatients following acute exacerbation of COPD.Fifty patients were recruited following an acute admission. The immediate effects of a 10-minute mindfulness-based body scan were compared with a control intervention. Participants were randomized to receive either a mindfulness-based body scan (n = 24) or a control condition (n = 26) via a 10-minute audio recording. Participants completed a self-assessment survey, including the Borg scale for breathlessness, Philadelphia Mindfulness Scale and Hospital Anxiety and Depression Scale. They then completed six brief single item measures of dyspnoea, anxiety, depression, happiness, stress and mindfulness before and after the intervention daily for three consecutive days. Acceptability was rated according to 'usefulness' and whether they would recommend the intervention to other patients. Results showed that there was a tendency for change in most outcomes, but no significant differences between the groups. Most participants rated the intervention as useful and would recommend it. Existing knowledge of mindfulness interventions among these patients is very limited and this study may be helpful in the development of other brief interventions.

Pirina, P., M. P. Foschino Barbaro, et al. (2018). **"Small airway inflammation and extrafine inhaled corticosteroids plus long-acting beta2-agonists formulations in chronic obstructive pulmonary disease."** Respir Med **143**: 74-81.

OBJECTIVES: To summarize the evidence of small airways involvement in chronic obstructive pulmonary disease (COPD) pathophysiology, and to evaluate the efficacy of extrafine formulations of inhaled corticosteroids (ICS) in combination with long-acting beta2-agonists (LABAs) in the treatment of COPD. DATA SOURCE: A search of the PubMed database was conducted using the keywords "COPD", "small airways", "inflammation" and "extrafine formulation." The search was limited to entries published in English before August 2016. Only studies conducted in humans were considered. STUDY SELECTION: Publications were included on the basis of relevance. RESULTS: COPD is a common preventable and treatable disease, characterized by persistent and progressive airflow limitation. With improved understanding of COPD pathophysiology, small airways (internal diameter <2mm), a well-known major site of COPD-associated inflammation and remodeling, have emerged as a potential target for COPD pharmacologic therapies. The ability of extrafine formulations of ICS in combination with LABAs to achieve central and peripheral lung deposition, and the implications of the enhanced efficacy that this may bring, are discussed by examining findings from the development trials plan of the extrafine formulation of beclometasone dipropionate/formoterol fumarate (Foster((R)), Chiesi Farmaceutici, Italy) in patients with COPD. CONCLUSION: There is an urgent need for improved and reliable techniques for small airways assessment in order to detect early damage, disease progression and response to treatment. Evidence

from randomized clinical trials supports the benefits of extrafine ICS/LABA formulations in COPD, real world studies are necessary to confirm this.

Quanqing, M. (2017). **"The study of long term curative effect of chronic obstructive pulmonary disease in remission stage treated with TCM."** Pak J Pharm Sci **30**(3(Special)): 1121-1124.

In this study of long term curative effect of chronic obstructive pulmonary disease in remission stage treated with TCM, we have selected 79 patients from January 2013 to January 2015 in our hospital with chronic obstructive pulmonary disease as the research object, we have divided into observation group (40 cases) and control group (39 cases) randomly, the control group received routine treatment, observation group received TCM pulmonary rehabilitation therapy, compare pulmonary function and clinical curative effect of 2 groups of patients, and dyspnea index (Brog index), blood oxygen saturation after 6 and 12 months' treatment. The lung function of the observation group was better than that of control group, the difference was significant (P<0.05). The effective rate of observation group was 97.50%, which was better than that of control group (84.62%), the difference was significant (P<0.05). Brog score, blood oxygen saturation of 2 groups of patients before treatment was not statistically significant (P>0.05); observation group's Brog scores after 6 and12 months' treatment were (2.96 + 0.87), (1.61 + 0.49), oxygen saturation were 94%, 99%, the control group's Brog scores were (4.65 + 0.54), (2.97 + 0.91), oxygen saturation were 86%, 93%, the observation group's indicators were better than that of control group after treatment, the difference was significant (P<0.05). TCM lung rehabilitation treatment of chronic obstructive pulmonary disease has obvious curative effect, it can improve the function of lung, reduce the occurrence of dyspnea, improve patients' tolerance and have obvious long-term curative effect.

Roberts, N. J., L. Kidd, et al. (2018). **"A systematic review of the content and delivery of education in pulmonary rehabilitation programmes."** Respir Med **145**: 161-181.

INTRODUCTION: Pulmonary rehabilitation (PR) is a core component of Chronic Obstructive Pulmonary Disease (COPD) management with well recognized benefits. While suggestions for educational content within pulmonary rehabilitation have been detailed in clinical guidance, it is unclear what educational content is delivered as part of pulmonary rehabilitation, who delivers it, and how it is delivered. METHODS: A systematic review was conducted to identify what educational content is delivered as part of pulmonary rehabilitation, how is this delivered and who delivers it. Databases were searched from 1981 to 2017 using multiple search terms related to "pulmonary rehabilitation" and "education". RESULTS: Fourteen studies were identified. This included 6 survey studies, 5 quasi-experimental studies and 3 RCTs. Five key topics that were consistently included within PR programmes were identified as: 1) Anxiety/depression and stress management. 2) Early recognition of signs of infection. 3) Dyspnea and symptom management. 4) Nutrition. 5) Techniques using inhalers and nebulizers. Broader topics such as welfare/benefits, sexuality, and advance care directives did not frequently feature. Only four studies used tools to measure knowledge or learning pre and post rehabilitation in an attempt to evaluate the effectiveness of the education delivered as part of PR. CONCLUSIONS: The delivery of education in PR programmes is variable and does not follow suggested educational topics. Education needs to take a patient centered motivational approach to ensure effective delivery. Further research into appropriate educational outcome measures are needed, in order to evaluate the changes in behaviour associated with education.

Rottier, S. J., J. de Jonge, et al. (2019). **"Prevalence of alpha-1-antitrypsin deficiency carriers in a population with and without colonic diverticula. A multicentre prospective case-control study: the ALADDIN study."** Int J Colorectal Dis **34**(5): 933-938.

PURPOSE: The underling pathophysiological mechanisms that cause the formation of colonic diverticula (diverticulosis) remain unclear. Connective tissue changes due to ageing that cause changes in collagen structure of the colonic wall is one theory. Alpha-1-antitrypsin (A1AT) is a protease inhibitor known to protect connective tissue in other organs. Associations between (carriers of) A1AT deficiency and the development of colonic diverticula will be the main focus of this study. METHODS: A multicentre prospective case-controlled study. In total, 230 patients >/= 60 years with acute abdominal pain undergoing an abdominal computed tomography (CT) will be included. The research group consists of patients with diverticulosis and/or diverticulitis; controls are patients without diverticula (0 to </= 5 diverticula). Genotype analysis for A1AT deficiency will be performed. RATIONALE: Hypothetically, connective tissue changes, in particular related to (carriers of) A1AT deficiency, can contribute to the development of diverticula and diverticulitis. We expect to find a higher prevalence of A1AT carriers in patients with diverticulosis compared to patients without diverticulosis. Having diverticulosis does not affect the general health of these individuals per se, when asymptomatic. Once an association is found, present findings can be the basis for a second study to assess the risk of developing acute diverticulitis and its disease course in carriers of A1AT deficiency. Because a large cohort is needed in the latter, we shall first perform a pilot study to investigate the likelihood of the primary hypothesis. TRIAL REGISTRATION: Netherlands Trial register, NTR6251, NL55016.094.15.

https://link.springer.com/content/pdf/10.1007%2Fs00384-019-03248-8.pdf

Sandberg, J., M. J. Johnson, et al. (2018). **"Validation of the Dyspnea Exertion Scale of Breathlessness in People With Life-Limiting Illness."** J Pain Symptom Manage **56**(3): 430-435.e2.

BACKGROUND: Although chronic breathlessness is common in life-limiting illnesses, validated feasible instruments to measure functional impact of the symptom in this population are scarce. We aimed to validate the Dyspnea Exertion Scale (DES) compared with the modified Medical Research Council (mMRC) breathlessness scale for test-retest reliability, concurrent validity, and responsiveness in people with life-limiting illness. METHODS: A total of 188 participants, 66% males, with chronic breathlessness, mostly (70%) because of chronic pulmonary disease (chronic obstructive pulmonary disease) self-reported evening scores of mMRC, DES, Numerical Rating Scale (NRS), and Eastern Cooperative Oncology Group during nine days. RESULTS: About 44% (n = 81) scored the highest score on mMRC indicating a ceiling effect not seen with DES. Both scales had moderate-to-good test-retest agreement (89% DES; 84% mMRC; P < 0.001 for both). Analyses for concurrent validity showed that higher DES and mMRC scores were correlated with higher NRS breathlessness intensity scores and Eastern Cooperative Oncology Group scores throughout the nine days. In longitudinal analyses, DES (r = 0.30; P < 0.001) was more responsive to change in NRS score during nine days than the mMRC (r = 0.16; P = 0.03). CONCLUSION: Compared with mMRC, DES had comparable or better measurement properties in terms of test-retest reliability and concurrent validity and could be used as a discriminative tool in this population, but both scales are too insensitive to change to be used as an outcome in clinical trials.

Singh, D., K. Abbott-Banner, et al. (2018). **"The short-term bronchodilator effects of the dual phosphodiesterase 3 and 4 inhibitor RPL554 in COPD."** Eur Respir J **52**(5)We investigated the short-term bronchodilator effects of RPL554 (an inhaled dual phosphodiesterase 3 and 4 inhibitor) combined with other bronchodilators in chronic obstructive pulmonary disease patients with reversibility (>150 mL to short-acting bronchodilators).Study 1 was a six-way, placebo-controlled crossover study (n=36) with single doses of RPL554 (6 mg), salbutamol (200 microg), ipratropium (40 microg), RPL554 (6 mg)+salbutamol (200 microg), RPL554 (6 mg)+ipratropium (40 microg) or placebo. Study 2 was a three-way crossover study (n=30) of tiotropium (18 microg) combined with RPL554 (1.5 or 6 mg) or placebo

for 3 days. Forced expiratory volume in 1 s (FEV1), lung volumes and specific airway conductance (sG aw) were measured.In study 1, peak FEV1 change compared with placebo was similar with RPL554, ipratropium and salbutamol (mean 223, 199 and 187 mL, respectively). The peak FEV1 was higher for RPL554+ipratropium versus ipratropium (mean difference 94 mL; p<0.0001) and RPL554+salbutamol versus salbutamol (mean difference 108 mL; p<0.0001). In study 2 (day 3), both RPL554 doses caused greater peak FEV1 effects than placebo. The average FEV1 (0-12 h) increase was greater with RPL554 6 mg only versus placebo (mean difference 65 mL; p=0.0009). In both studies, lung volumes and sG aw showed greater RPL554 combination treatment effects versus monotherapy.RPL554 combined with standard bronchodilators caused additional bronchodilation and hyperinflation reduction.

Singh, D., A. Ravi, et al. (2018). **"The pharmacokinetics, pharmacodynamics and tolerability of PUR0200, a novel tiotropium formulation, in chronic obstructive pulmonary disease."** Br J Clin Pharmacol **84**(9): 2097-2105.

AIMS: PUR0200 is a tiotropium bromide formulation engineered with the iSPERSE dry powder delivery technology. PUR0200 is being developed as a bioequivalent alternative to tiotropium bromide, delivered using Spiriva(R) HandiHaler(R) (HH). We investigated the bronchodilator effects, pharmacokinetics and safety of PUR0200 in patients with chronic obstructive pulmonary disease (COPD). METHODS: This was a randomized, placebo-controlled, crossover study using different PUR0200 doses and the comparator tiotropium HH. In vitro aerodynamic particle size distribution (aPSD) characterization of PUR0200 and tiotropium HH are presented. The main endpoints included forced expiratory volume in 1 s (FEV1) trough and (0-24 h) and pharmacokinetic parameters. RESULTS: The increased fine-particle fraction of PUR0200 demonstrated by testing using the next-generation impactor increased the proportion of drug available for lung deposition compared with the tiotropium HH. There was a numerical dose-response effect for PUR0200 on FEV1 , with 3 mug demonstrating a lower effect than higher doses. The placebo-adjusted mean (95% confidence interval) increases from baseline at 24 h postdose were 150 ml (100-200), 210 ml (160-270) and 200 ml (140-250) for 3 mug, 6 mug and 9 mug doses of PUR0200, respectively. Tiotropium HH (18 mug) caused a mean 169 ml (standard deviation 157ml) improvement in trough FEV1 , which was not significantly different to the PUR0200 effects at any of the tested doses. CONCLUSIONS: PUR0200 treatment caused bronchodilation in COPD patients that was similar in magnitude to that caused by tiotropium HH. This enabled a similar clinical effect on lung function to be achieved with PUR0200 using a lower metered dose of tiotropium compared with tiotropium HH.

Streicher, K., S. Sridhar, et al. (2018). **"Baseline Plasma Cell Gene Signature Predicts Improvement in Systemic Sclerosis Skin Scores Following Treatment With Inebilizumab (MEDI-551) and Correlates With Disease Activity in Systemic Lupus Erythematosus and Chronic Obstructive Pulmonary Disease."** Arthritis Rheumatol **70**(12): 2087-2095.

OBJECTIVE: B cells impact the progression of systemic sclerosis (SSc; scleroderma) through multiple pathogenic mechanisms. CD19 inhibition in mice reduced skin thickness, collagen production, and autoantibody levels, consistent with CD19 expression on plasma cells (PCs), the source of antibody production. PC depletion could effectively reduce collagen deposition and inflammation in SSc; therefore, we investigated the effects of PC depletion on SSc disease activity. METHODS: A PC gene signature was evaluated in SSc skin biopsy samples in 2 phase I clinical trials. We assessed microarray data from tissue from public studies of chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis (IPF), dermatomyositis (DM), systemic lupus erythematosus (SLE), and atopic dermatitis, as well as blood from a phase IIb clinical trial in SLE. RESULTS: The PC signature was elevated in SSc skin specimens compared to healthy donor skin (P = 2.28 x 10(-6)) and correlated with the baseline modified Rodnan skin thickness score (MRSS) (r = 0.64, P = 0.0004). Patients with a high PC signature at baseline showed greater improvement in the MRSS (mean +/- SD change 35 +/- 16%; P = 6.30 x 10(-4)) following anti-

CD19 treatment with inebilizumab (MEDI-551) than did patients with a low PC signature at baseline (mean +/- SD change 8 +/- 12%; P = 0.104). The PC signature was overexpressed in tissue from patients with SLE, DM, COPD, interstitial lung disease, and IPF relative to controls (all fold change >2; P < 0.001). The PC signature also differed significantly between SLE patients with mild-to-moderate disease and those with severe disease (SLE Disease Activity Index cutoff at 10) (fold change 1.44; P = 3.90 x 10(-3)) and correlated significantly with the degree of emphysema in COPD (r = 0.53, P = 7.55 x 10(-8)). CONCLUSION: Our results support the notion that PCs have a role in the pathogenesis of SSc and other autoimmune or pulmonary indications. An elevated pretreatment PC signature was associated with increased benefit from MEDI-551 in SSc.

Taccone, F. S., M. V. Malfertheiner, et al. (2017). **"Extracorporeal CO2 removal in critically ill patients: a systematic review."** Minerva Anestesiol **83**(7): 762-772.

INTRODUCTION: The use of extracorporeal CO2 removal (ECCO2R) is increasingly employed in critically ill patients. However, the clinical evidence supporting its efficacy remains currently poor. EVIDENCE ACQUISITION: A systematic review using MEDLINE via PubMed was performed to identify eligible studies (until 30th September 2016). The amount of CO2 reduction, the effect on the duration of mechanical ventilation and weaning, the impact on patients' outcome and the occurrence of complications were evaluated. The quality of evidence was evaluated according to the GRADE (Grading of Recommendations Assessment, Development and Evaluation) criteria. EVIDENCE SYNTHESIS: Six studies were included (three evaluating patients with chronic obstructive pulmonary disease [COPD]; three evaluating patients with acute respiratory distress syndrome [ARDS]), involving 279 adult patients; 142 treated with ECCO2R and 137 controls. No study on pediatric population met the inclusion criteria for analysis. The overall quality of evidence of the two randomized trials and four case-control studies varied from moderate to very low. PaCO2 was generally reduced by 25-33% within a few hours following ECCO2R initiation. One ARDS study showed a significant decrease in the duration of mechanical ventilation, although this result was only found by post-hoc analysis. The three studies on COPD demonstrated that some patients supported by ECCO2R devices could avoid endotracheal intubation, however the ICU-LOS and survival was not influenced by ECCO2R when compared to controls. CONCLUSIONS: In COPD patients, a significantly reduced need for endotracheal intubation was reported. However, the use of ECCO2R has not shown significant improvement on the outcome of critically ill patients in the reviewed studies. Therefore appropriately powered, randomized, controlled studies are urgently needed.

Troosters, T., F. Maltais, et al. (2018). **"Effect of Bronchodilation, Exercise Training, and Behavior Modification on Symptoms and Physical Activity in Chronic Obstructive Pulmonary Disease."** Am J Respir Crit Care Med **198**(8): 1021-1032.

RATIONALE: Bronchodilation and exercise training (ExT) improve exercise tolerance in patients with chronic obstructive pulmonary disease (COPD); however, behavior modification is required to impact daily physical activity (PA). OBJECTIVES: To assess whether tiotropium/olodaterol, with or without ExT, would improve exercise endurance time (EET) and PA compared with placebo in patients participating in a self-management behavior-modification (SMBM) program. METHODS: This was a 12-week, randomized, partially double-blind, placebo-controlled, parallel-group trial in patients with COPD (PHYSACTO; NCT02085161). All patients were enrolled into SMBM and randomized 1:1:1:1 to once-daily placebo, tiotropium 5 mug, tiotropium/olodaterol 5/5 mug, or tiotropium/olodaterol 5/5 mug plus 8 weeks ExT. EET, measured by endurance shuttle walk test after 8 weeks, was the primary endpoint. Additional endpoints assessed downstream effects on PA (measured via accelerometry), and activity-related dyspnea and difficulty (using validated patient-reported questionnaires). MEASUREMENTS AND MAIN RESULTS: SMBM plus tiotropium/olodaterol, with or without ExT, significantly improved EET at Week 8

versus SMBM plus placebo (treatment ratio vs. placebo: with ExT, 1.46; 95% confidence interval, 1.20-1.78; P = 0.0002; without ExT, 1.29; 95% confidence interval, 1.06-1.57; P = 0.0109). No significant increases in steps per day from baseline were observed over SMBM plus placebo at Week 12 (increase of 1,098) when other therapies were added. Adding tiotropium/olodaterol, with or without ExT, to SMBM reduced activity-related dyspnea versus placebo, whereas adding tiotropium/olodaterol plus ExT reduced activity-related difficulty. CONCLUSIONS: Tiotropium/olodaterol, with or without ExT, improved EET in patients with COPD taking part in an SMBM program. Combination bronchodilation, with or without ExT, did not provide additional increases in objective PA compared with SMBM alone but did reduce PA-related dyspnea and difficulty. Clinical trial registered with www.clinicaltrials.gov (NCT02085161).

Turner, A. M., J. Stolk, et al. (2018). **"Hepatic-targeted RNA interference provides robust and persistent knockdown of alpha-1 antitrypsin levels in ZZ patients."** J Hepatol **69**(2): 378-384.

BACKGROUND & AIMS: Alpha-1 antitrypsin deficiency (AATD) is a genetic disorder causing pulmonary and liver disease. The PiZ mutation in AAT (SERPINA1) results in mis-folded AAT protein (Z-AAT) accumulating in hepatocytes, leading to fibrosis and cirrhosis. RNAi-based therapeutics silencing production of hepatic Z-AAT might benefit patients with AATD-associated liver disease. This study evaluated an RNAi therapeutic to silence production of AAT. METHODS: Part A of this double-blind first-in-human study randomized 54 healthy volunteers (HVs) into single dose cohorts (two placebo: four active), receiving escalating doses of the investigational agent ARC-AAT from 0.38 to 8.0mg/kg or placebo. Part B randomized 11 patients with PiZZ (homozygous for Z-AAT) genotype AATD, who received up to 4.0mg/kg of ARC-AAT or placebo. Patients with baseline FibroScan(R) >11kPa or forced expiratory volume in one second (FEV1) <60% were excluded. Assessments included safety, pharmacokinetics, and change in serum AAT concentrations. RESULTS: A total of 36 HVs received ARC-AAT and 18 received placebo (part A). Seven PiZZ individuals received ARC-AAT and four received placebo (part B). A dose response in serum AAT reduction was observed at doses >/=4mg/kg with similar relative reductions in PiZZ patients and HVs at 4mg/kg and a maximum reduction of 76.1% (HVs) vs. 78.8% (PiZZ) at this dose. The time it took for serum AAT to return to baseline was similar for HV and PiZZ. There were no notable differences between HV and PiZZ safety parameters. The study was terminated early because of toxicity findings related to the delivery vehicle (ARC-EX1) seen in a non-human primate study. CONCLUSION: PiZZ patients and HVs responded similarly to ARC-AAT. Deep and durable knockdown of hepatic AAT production based on observed reduction in serum AAT concentrations was demonstrated. LAY SUMMARY: Accumulation of abnormal proteins in the livers of patients with alpha-1 antitrypsin deficiency may lead to decreased liver function and potentially liver failure. Therapeutics targeting the production of these abnormal proteins may be used to prevent or treat liver disease in patients with alpha-1 antitrypsin deficiency. CLINICAL TRIAL REGISTRATION NUMBER: NCT02363946.

Villela, M. A., S. Dunworth, et al. (2018). **"Can my patient dive after a first episode of primary spontaneous pneumothorax? A systematic review of the literature."** Undersea Hyperb Med **45**(2): 199-208.

Introduction: Patients with prior primary spontaneous pneumothorax (PSP) frequently seek clearance to dive. Despite wide consensus in precluding compressed-air diving in this population, there is a paucity of data to support this decision. We reviewed the literature reporting the risk of PSP recurrence. Methods: A literature search was performed in PubMed and Web of Science using predefined terms. Studies published in English reporting the recurrence rate after a first PSP were included. Results: Forty studies (n=3,904) were included. Risk of PSP recurrence ranged 0-67% (22 +/- 15.5%; mean +/- SD). Mean follow-up was 36 months, and 63 +/- 39% of recurrences occurred during the first year of follow-up. Elevated height/weight ratio and emphysema-like changes (ELCs) are associated with PSP recurrence. ELCs are present in 59%-89% (vs. 0-15%) of patients with recurrence and can be detected effectively with

high-resolution CT scan (sensitivity of 84-88%). Surgical pleurodesis reduces the risk of recurrence substantially (4.0 +/- 4% vs. 22 +/- 15.5%). Conclusion2: Risk of PSP recurrence seems to decline over time and is associated to certain radiological and clinical risk factors. This could be incremented by the stresses of compressed-air diving. A basis for informed patient-physician discussions regarding future diving is provided in this review.

Walker, P. P., P. P. Pompilio, et al. (2018). **"Telemonitoring in Chronic Obstructive Pulmonary Disease (CHROMED). A Randomized Clinical Trial."** Am J Respir Crit Care Med **198**(5): 620-628.

RATIONALE: Early detection of chronic obstructive pulmonary disease (COPD) exacerbations using telemonitoring of physiological variables might reduce the frequency of hospitalization. OBJECTIVES: To evaluate the efficacy of home monitoring of lung mechanics by the forced oscillation technique and cardiac parameters in older patients with COPD and comorbidities. METHODS: This multicenter, randomized clinical trial recruited 312 patients with Global Initiative for Chronic Obstructive Lung Disease grades II to IV COPD (median age, 71 yr [interquartile range, 66-76 yr]; 49.6% grade II, 50.4% grades III-IV), with a history of exacerbation in the previous year and at least one nonpulmonary comorbidity. Patients were randomized to usual care (n = 158) or telemonitoring (n = 154) and followed for 9 months. All telemonitoring patients self-assessed lung mechanics daily, and in a subgroup with congestive heart failure (n = 37) cardiac parameters were also monitored. An algorithm identified deterioration, triggering a telephone contact to determine appropriate interventions. MEASUREMENTS AND MAIN RESULTS: Primary outcomes were time to first hospitalization (TTFH) and change in the EuroQoL EQ-5D utility index score. Secondary outcomes included: rate of antibiotic/corticosteroid prescription; hospitalization; the COPD Assessment Tool, Patient Health Questionnaire-9, and Minnesota Living with Heart Failure questionnaire scores; quality-adjusted life years; and healthcare costs. Telemonitoring did not affect TTFH, EQ-5D utility index score, antibiotic prescriptions, hospitalization rate, or questionnaire scores. In an exploratory analysis, telemedicine was associated with fewer repeat hospitalizations (-54%; P = 0.017). CONCLUSIONS: In older patients with COPD and comorbidities, remote monitoring of lung function by forced oscillation technique and cardiac parameters did not change TTFH and EQ-5D. Clinical trial registered with www.clinicaltrials.gov (NCT 01960907).

Walker, R. C., A. Tong, et al. (2019). **"Patient expectations and experiences of remote monitoring for chronic diseases: Systematic review and thematic synthesis of qualitative studies."** Int J Med Inform **124**: 78-85.

OBJECTIVES: To describe the range of patients' beliefs, attitudes, expectations, and experiences of remote monitoring for chronic conditions across different healthcare contexts and populations. DESIGN: We searched MEDLINE, Embase, PsychINFO, and CINAHL, Google Scholar, and reference lists of related studies through to July 2017. Thematic synthesis was used to analyse the findings of the primary studies. Study characteristics were examined to explain differences in findings. SETTING: All healthcare settings PARTICIPANTS: Adults with chronic diseases OUTCOMES: Patient beliefs, attitudes, expectations and experiences of remote monitoring RESULTS: We included 16 studies involving 307 participants with chronic obstructive pulmonary disease, heart failure, diabetes, hypertension, and end stage kidney disease. The studies were conducted in 8 countries. We identified four themes: gaining knowledge and triggering actions (tracking and responding to change, prompting timely and accessible care, supporting self-management and shared decision-making); reassurance and security (safety in being alone, peace of mind); concern about additional burden (reluctance to learn something new, lack of trust in technology, avoiding additional out-of-pocket costs), and jeopardising interpersonal connections (fear of being lost in data, losing face to face contact). CONCLUSIONS: For patients with chronic disease, remote monitoring increased their disease-specific knowledge, triggered earlier clinical assessment and treatment, improved self-management and shared decision-making. However, these potential benefits

were balanced against concerns about losing interpersonal contact, and the additional personal responsibility of remote monitoring.

White, P., G. Gilworth, et al. (2019). **"Improving uptake and completion of pulmonary rehabilitation in COPD with lay health workers: feasibility of a clinical trial."** Int J Chron Obstruct Pulmon Dis **14**: 631-643.

Purpose: This study was designed to evaluate the feasibility of a cluster randomized controlled trial to test the efficacy of lay health workers (LHWs) in improving the uptake and completion of pulmonary rehabilitation (PR) in the treatment of COPD. Materials and methods: LHWs, trained in confidentiality, role boundaries, and behavior change techniques, supported patients newly referred for PR. Interactions between LHWs and participants were recorded with smartphones. Outcomes were recruitment and retention rates of LHWs, questionnaire and interview-evaluated acceptability and analysis of intervention fidelity. Results: Forty (36%) of 110 PR-experienced COPD patients applied to become LHWs. Twenty (18%) were selected for training. Twelve (11%) supported patients. Sixty-six COPD patients referred for PR received the intervention (5.5 participants per LHW). Ten LHWs were retained to the end of the study. Seventy-three percent of supported patients were satisfied or very satisfied with the intervention. LHWs delivered the intervention with appropriate style and variable fidelity. LHWs would welcome more intensive training. Based on this proof of concept, a cluster randomized controlled trial of an LHW intervention to improve uptake and completion of PR is feasible. Conclusion: PR-experienced COPD patients can be recruited, trained, and retained as LHWs to support participation in PR, and can deliver the intervention. Participant COPD patients found the intervention acceptable. A cluster randomized controlled clinical trial is feasible.

Woo, L., H. E. Smith, et al. (2019). **"The Economic Burden of Chronic Obstructive Pulmonary Disease in the Asia-Pacific Region: A Systematic Review."** Value Health Reg Issues **18**: 121-131.

BACKGROUND: Chronic obstructive pulmonary disease (COPD) is a significant and disabling condition that entails high economic burden for society. OBJECTIVE: The aim of this article is to assess cost studies of COPD and analyze cross-country cost comparisons in Asia-Pacific. METHODS: A systematic literature search from October 2000 to October 2018 was conducted using PubMed, MEDLINE, and EMBASE to identify relevant studies. Costs reported by the different studies were converted to 2017 US dollars using the consumer price index for medical care. The quality of the studies was assessed using the Consolidated Health Economic Evaluation Reporting Standards. RESULTS: Ten studies (6 countries and 11 estimates) were identified and included for full review after consideration of the inclusion and exclusion criteria. Annual total societal costs of COPD ranged from $4398 to $23 049 per capita in Japan and $453 to $12 167 in South Korea. There were no intracountry comparison estimates for the remaining countries (Singapore: $2700; Taiwan: $4000; China: $3942; and Thailand: $1105). In addition, there were estimates of partial costs in Singapore and Taiwan. CONCLUSIONS: Results of this review showed high cost variations between countries, with estimates in 2 countries (Japan and South Korea) exceeding those in UK and USA. Wide variation in disease cost estimates will continue to exist as long as there are differences in cost methodologies, disease severities included, and data limitation. We propose that researchers conducting burden-of-illness studies use standard methods and reporting formats to support cross-country comparisons.

https://www.sciencedirect.com/science/article/abs/pii/S2212109919300469?via%3Dihub

Xiong, C., Y. Li, et al. (2019). **"Chinese Herbal Medicine Versus Placebo for the Treatment Of Chronic Obstructive Pulmonary Disease: A Protocol of Systematic Review and Meta-analysis."** Medicine (Baltimore) **98**(35): e17002.

BACKGROUND: Chinese herbal medicine (CHM) has been shown to be effective in the treatment of stable chronic obstructive pulmonary disease (COPD) by published meta-analyses. However, disease outcomes were inconsistent and heterogeneity was observed attributed to placebo-controlled studies. We present a protocol for a systematic review aiming to evaluate the clinical efficacy and safety of CHM comparing to placebo in the treatment of stable COPD, to provide robust evidence for the use of CHM in COPD. METHODS: We will comprehensively search the following 9 databases from inception to March 2019: Web of Science, PubMed, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), Chinese National Knowledge Infrastructure (CNKI), WANFANG Database, Chinese Scientific and Technological Periodical Database (VIP) and Chinese Biomedical Database (CBM), and the Cochrane Library database. All clinical randomized controlled trials comparing CHM to placebo for the treatment of stable COPD in English or Chinese will be included. The primary outcome will be quality of life, symptom score and exacerbation frequency, and the secondary outcomes include traditional Chinese medicine syndrome score and effective rate, lung function, 6-minute walk distance, and adverse events. Data extraction and quality assessment will be performed independently by 2 reviewers. Data synthesis and risk of bias will be assessed using the Review Manager software. This protocol will be conducted according to the Preferred Reporting Item for Systematic Review and Meta-analysis Protocols (PRISMA-P) guidance. RESULTS: This systematic review and meta-analysis will provide a high-quality comprehensive evaluation of the efficacy and safety based on current literature evidence of CHM intervention for stable COPD. CONCLUSION: The conclusion of this study will present the evidence of whether CHM is an effective and safe intervention for stable COPD patients.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6736470/pdf/medi-98-e17002.pdf

Yu, F., M. Xin, et al. (2019). **"The Qigong Wuqinxi for chronic obstructive pulmonary disease: Protocol for a systematic review and meta-analysis."** Medicine (Baltimore) **98**(30): e16633.

BACKGROUND: Chronic obstructive pulmonary disease (COPD) is a chronic and progressive disease that represents an important public health challenge nowadays. Despite the growing number of studies assessing the rehabilitation outcome of Wuqinxi for COPD, their many variables and observations are often explored with a relatively small sample size, accordingly maybe lead to potential false-positive results. The aim of this systematic review and meta-analysis is to evaluate the rehabilitation efficacy of Wuqinxi for COPD. METHODS: A detailed search for articles up to June 2019 will be performed to identify randomized controlled trials for Wuqinxi in COPD. The following database will be used: PUBMED, Embase, Scopus, Web of Science, Google Scholar, Cochrane Library, Sino Med, Chinese National Knowledge Infrastructure, Chinese Science and Technology Periodicals Database, and Wanfang Database. Grey literature will be explored and the selection of studies, data extraction and validation will performed independently by 2 reviewers using predefined selection criteria and quality indicators. Stata V.13.0 and Review manager 5.3 software will be used for data synthesis, sensitivity analysis, subgroup analysis, and risk of bias assessment. We will use the grading of recommendations assessment, development, and evaluation system to assess the quality of evidence. RESULTS: This research will update previous evidence summaries and provide a quantitative and standardized assessment of the rehabilitation efficacy of Wuqinxi for COPD. CONCLUSION: This systematic review will generate the latest evidence for determining whether Wuqinxi has a positive rehabilitation effect for COPD.PROSPERO registration number: PROSPERO CRD 42019120960.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6708999/pdf/medi-98-e16633.pdf

Yu, M., L. Gao, et al. (2019). **"Safety and efficacy of acupuncture for the treatment of chronic obstructive pulmonary disease: A systematic review protocol."** Medicine (Baltimore) **98**(37): e17112.

BACKGROUND: Chronic obstructive pulmonary disease (COPD) is a common chronic respiratory disease with increasing morbidity and mortality that cause huge social and economic loss. Although recommended by guidelines, pulmonary rehabilitation has not been widely applied in clinics because of its inherent limitations. Acupuncture therapy (AT) as one of the most popular treatments in traditional Chinese medicine has been used to treat COPD. We aim to evaluate the safety and efficacy of acupuncture in the treatment of COPD. METHODS: Web of science, PubMed, Springer, Medline, Cochrane Library, EBASE, WHO International Clinical Trials Registry Platform (ICTRP), China National Knowledge Infrastructure Database (CNKI), Wan Fang Database, Chinese Scientific Journal Database (VIP), and Chinese Biomedical Literature Database will be searched from their inception to May 10, 2019. Randomized controlled trials that evaluated the safety and efficacy of acupuncture for the treatment on patients with COPD will be included. The primary outcome measures will include Dyspnea scores, lung function and blood eosinophils. The secondary outcome measures will include St George's Respiratory Questionnaire and 6-minute walk distance. Study selection, data extraction, and risk of bias assessment will be independently undertaken, respectively. Statistical analysis will be conducted by RevMan software (version 5.3). RESULTS: This study will provide high-quality synthesis based on current evidence of acupuncture treatment for COPD in several aspects, including symptom score, quality of life score, side effects and laboratory examination, such as lung function text, blood eosinophils (EOS) etc. CONCLUSION:: The results of this study will provide updated evidence for weather acupuncture is an effective and safe intervention for COPD. ETHICS AND DISSEMINATION: It is not necessary for this systematic review to acquire an ethical approval. This review will be disseminated in a peer-reviewed journal or conference presentation. PROSPERO REGISTRATION NUMBER: PROSPERO CRD42019136087.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6750299/pdf/medi-98-e17112.pdf

Zareifopoulos, N., A. Bellou, et al. (2018). **"Prevalence of Comorbid Chronic Obstructive Pulmonary Disease in Individuals Suffering from Schizophrenia and Bipolar Disorder: A Systematic Review."** Copd **15**(6): 612-620.

The disease burden associated with schizophrenia and bipolar disorder is substantial, with affected individuals having a shorter life expectancy and a high risk of severe physical comorbid conditions. These individuals are more likely to smoke and have a longer smoking history compared to the general population. Furthermore, use of antipsychotic drugs has also been linked to active smoking. Chronic obstructive pulmonary disease (COPD) is a respiratory condition affecting elderly individuals with a long smoking history, so it would be expected that individuals suffering from major mental disorders may exhibit a higher prevalence of COPD compared to the general population. We searched the databases Pubmed and Scopus for observational studies of at least 200 patients including at least one group suffering from schizophrenia or bipolar disorder and a comparison group of individuals at risk of COPD. The initial search, along with the data extraction process and the risk of bias assessment were carried out independently by the two reviewers. Eight studies were included. The risk of bias was substantial as most studies did not adequately address confounding variables. A pooled analysis showed a greater likelihood of suffering from comorbid COPD compared with the general population both for schizophrenic (OR 1.573, 1.439-1.720) and bipolar individuals (OR 1.551, 1.452-1.658). Based on these findings, COPD is more common in individuals suffering from major mental illness compared to the general population. Further research is required to ascertain whether smoking is the only cause and develop strategies for the prevention of COPD in these high-risk groups.

Zheng, J., N. Zhong, et al. (2018). **"The Efficacy and Safety of Once-daily Fluticasone Furoate/Umeclidinium/Vilanterol Versus Twice-daily Budesonide/Formoterol in a Subgroup of Patients from China with Symptomatic COPD at Risk of Exacerbations (FULFIL Trial)."** Copd **15**(4): 334-340.

The FULFIL study evaluated once-daily fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) 100 microg/62.5 microg/25 microg versus twice-daily budesonide/formoterol (BUD/FOR) 400 microg/12 microg in patients with symptomatic COPD at risk of exacerbations. FULFIL demonstrated clinically meaningful and statistically significant improvements at Week 24 in trough forced expiratory volume in 1 second (FEV1), St George's Respiratory Questionnaire (SGRQ) Total scores and reduced exacerbation frequency. Predefined analyses were performed to evaluate treatment effects in a subgroup of patients recruited in China (China subgroup; FF/UMEC/VI, n = 32; BUD/FOR, n = 29). Analyses included treatment by region (China versus non-China) to allow estimated treatment effects in patients from China to be compared with those of the non-China subgroup and the overall FULFIL intent-to-treat (ITT) population. In the China subgroup at Week 24: the mean change from baseline in trough FEV1 was 125 mL (95% confidence interval [CI] 36, 214) for FF/UMEC/VI and -70 mL (95% CI -163, 23) BUD/FOR (between-treatment difference: 195 mL [95% CI 67, 323]; p = 0.003) and in SGRQ Total score was -5.6 units (95% CI -10.5, -0.7) and -0.3 units (95% CI -5.4, 4.7), respectively (between-treatment difference: -5.3 [95% CI -12.3, 1.7]; p = 0.140). Fewer moderate/severe exacerbations occurred with FF/UMEC/VI than BUD/FOR (16% and 28%, respectively). The overall incidence of adverse events was similar between arms (FF/UMEC/VI: 38%; BUD/FOR: 31%). This prespecified subgroup analysis of patients recruited in China to FULFIL demonstrated comparable efficacy and safety to that observed in the non-China and in the overall ITT populations, for FF/UMEC/VI versus BUD/FOR.

COPD/Emphysema PubMed search results covering the period 20/07/2019 to 25/10/19
Systematic reviews and clinical trials – In Process

(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]

Abdulsalim, S., M. K. Unnikrishnan, et al. (2019). **"Impact of a Clinical Pharmacist Intervention on Medicine Costs in Patients with Chronic Obstructive Pulmonary Disease in India."** Pharmacoecon OpenBACKGROUND: Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality, especially in low- and middle-income countries (LMICs) such as India. Medicine costs are a key issue in LMICs, with typically high patient co-payments. In addition, pharmacists are underutilised in LMICs, including India. However, pharmacist-led educational interventions may improve the care of patients with COPD, as well as reduce medicine costs. Consequently, the objective of this study was to assess the effectiveness of a pharmacist-led intervention in reducing medicine costs. METHODOLOGY: We assessed the impact of a pharmacist intervention on direct medicine costs in COPD patients (medicine costs and pharmacist time) in a randomised controlled study involving an intervention and control group, conducted at a tertiary care teaching hospital in India. RESULTS: The 6-monthly cost of medicines at baseline increased with disease severity, from a maximum of US$29.46 for those with mild COPD to US$63.28 for those with very severe COPD. Substantial savings in medical costs were achieved with the pharmacist-led programme, to a maximum of US$20.49 over 6 months for very severe patients. This equates to a reduction of 30.6% in medicine costs ($p < 0.001$), reduced to 26.1% when pharmacists' time (US$3.00/patient) was included. CONCLUSION: There could be a key role for pharmacists as educators for COPD patients in LMICs, to improve care and reduce costs, including patient co-payments.

https://link.springer.com/content/pdf/10.1007%2Fs41669-019-0172-x.pdf

Adolfo, J. R., W. Dhein, et al. (2019). **"Intensity of physical exercise and its effect on functional capacity in COPD: systematic review and meta-analysis."** J Bras Pneumol **45**(6): e20180011.

OBJECTIVE: To evaluate the effects of high-intensity interval training (HIIT), in comparison with those of continuous exercise, on functional capacity and cardiovascular variables in patients with COPD, through a systematic review and meta-analysis of randomized controlled trials. METHODS: We searched PubMed, the Physiotherapy Evidence Database, the Cochrane Central Register of Controlled Trials, and EMBASE, as well as performing hand searches, for articles published up through January of 2017. We included studies comparing exercise regimens of different intensities, in terms of their effects on functional capacity and cardiovascular variables in patients with COPD. RESULTS: Of the 78 articles identified, 6 were included in the systematic review and meta-analysis. Maximal oxygen consumption (VO2max) did not differ significantly between HIIT and control interventions. That was true for relative VO2max (0.03 mL/kg/min; 95% CI: -3.05 to 3.10) and absolute VO2max (0.03 L/min, 95% CI: -0.02 to 0.08). CONCLUSIONS: The effects of HIIT appear to be comparable to those of continuous exercise in relation to functional and cardiovascular responses. However, our findings should be interpreted with caution because the studies evaluated present a high risk of bias, which could have a direct influence on the results.

Andreas, S., C. Rover, et al. (2019). **"Decline of COPD exacerbations in clinical trials over two decades - a systematic review and meta-regression."** Respir Res **20**(1): 186.

BACKGROUND: An important goal of chronic obstructive pulmonary disease (COPD) treatment is to reduce the frequency of exacerbations. Some observations suggest a decline in exacerbation rates in clinical trials over time. A more systematic understanding would help to improve the design and interpretation of COPD trials. METHODS: We performed a systematic review and meta-regression of the placebo groups in published randomized controlled trials reporting exacerbations as an outcome. A Bayesian negative binomial model was developed to accommodate results that are reported in different formats; results are reported with credible intervals (CI) and posterior tail probabilities (pB). RESULTS: Of 1114 studies identified by our search, 55 were ultimately included. Exacerbation rates decreased by 6.7% (95% CI (4.4, 9.0); pB < 0.001) per year, or 50% (95% CI (36, 61)) per decade. Adjusting for available study and baseline characteristics such as forced expiratory volume in 1 s (FEV1) did not alter the observed trend considerably. Two subsets of studies, one using a true placebo group and the other allowing inhaled corticosteroids in the "placebo" group, also yielded consistent results. CONCLUSIONS: In conclusion, this meta-regression indicates that the rate of COPD exacerbations decreased over the past two decades to a clinically relevant extent independent of important prognostic factors. This suggests that care is needed in the design of new trials or when comparing results from older trials with more recent ones. Also a considerable effect of adjunct therapy on COPD exacerbations can be assumed. REGISTRATION: PROSPERO 2018 CRD4218118823.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6697937/pdf/12931_2019_Article_1163.pdf

Barrett, N. A., E. Kostakou, et al. (2019). **"Extracorporeal carbon dioxide removal for acute hypercapnic exacerbations of chronic obstructive pulmonary disease: study protocol for a randomised controlled trial."** Trials **20**(1): 465.

BACKGROUND: Chronic obstructive pulmonary disease (COPD) is a common cause of chronic respiratory failure and its course is punctuated by a series of acute exacerbations which commonly lead to hospital admission. Exacerbations are managed through the application of non-invasive ventilation and, when this fails, tracheal intubation and mechanical ventilation. The need for mechanical ventilation significantly increases the risk of death. An alternative therapy, extracorporeal carbon dioxide removal (ECCO2R), has been shown to be efficacious in removing carbon dioxide from the blood; however, its impact on respiratory physiology and patient outcomes has not been explored. METHODS/DESIGN: A randomised controlled open label trial of patients (12 in each arm) with acute exacerbations of COPD at risk of failing conventional therapy (NIV) randomised to either remaining on NIV or having ECCO2R added to NIV with a primary endpoint of time to cessation of NIV. The change in respiratory physiology following the application of ECCO2R and/or NIV will be measured using electrical impedance tomography, oesophageal pressure and parasternal electromyography. Additional outcomes, including patient tolerance, outcomes, need for readmission, changes in blood gases and biochemistry and procedural complications, will be measured. Physiological changes will be compared within one patient over time and between the two groups. Healthcare costs in the UK system will also be compared between the two groups. DISCUSSION: COPD is a common disease and exacerbations are a leading cause of hospital admission in the UK and worldwide, with a sizeable mortality. The management of patients with COPD consumes significant hospital and financial resources. This study seeks to understand the feasibility of a novel approach to the management of patients with acute exacerbations of COPD as well as to understand the underlying physiological changes to explain why the approach does or does not assist this patient cohort. Detailed respiratory physiology has not been previously undertaken using this technique and there are no other randomised controlled trials currently in the literature. TRIAL REGISTRATION: ClinicalTrials.gov, NCT02086084.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6664508/pdf/13063_2019_Article_3548.pdf

Baxter, D. A., J. L. Shergis, et al. (2019). **"Muscle energy technique for chronic obstructive pulmonary disease: a systematic review."** Chiropr Man Therap **27**: 37.

Background: Chronic Obstructive Pulmonary Disease (COPD) is an increasingly prevalent respiratory disease that impacts on daily living. In addition to difficulty breathing, many people experience extrapulmonary comorbidities such as musculoskeletal disorders. Pulmonary rehabilitation can improve fitness and strength but may be difficult for patients with musculoskeletal disorders. Recent research indicates promising benefits of adding manual therapy to standard care to improve clinical outcomes. Objectives: To evaluate the efficacy and safety of Muscle Energy Technique (MET) for people with COPD. Methods: Ten databases were searched from inceptions to May 2018. Eligible studies were randomised controlled trials assessing MET compared to any control for COPD. Outcomes included lung function, exercise capacity, health-related quality of life, and adverse events. Results: Three randomised controlled trials assessing 90 participants were included. The quality of the research was limited by reporting of outcome measures and results, varying treatment protocols, and small sample sizes. Results from one study showed that pulmonary function was not statistically different between groups at end of treatment (FEV1% MD 4.87%; 95% CI - 0.79 to 10.53). Exercise capacity and perceived dyspnoea ratings were improved in single studies. Adverse events were unrelated to the MET intervention. Conclusions: The use of MET for COPD is an emerging field of research, with few studies evaluating its efficacy and safety. Currently, there is insufficient evidence to support the use of MET in the management of COPD. Rigorously designed studies with larger sample sizes are needed to better understand the role of MET for COPD.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6700764/pdf/12998_2019_Article_256.pdf

Buhr, R. G., N. J. Jackson, et al. (2019). **"Comorbidity and thirty-day hospital readmission odds in chronic obstructive pulmonary disease: a comparison of the Charlson and Elixhauser comorbidity indices."** BMC Health Serv Res **19**(1): 701.

BACKGROUND: Readmissions following exacerbations of chronic obstructive pulmonary disease (COPD) are prevalent and costly. Multimorbidity is common in COPD and understanding how comorbidity influences readmission risk will enable health systems to manage these complex patients. OBJECTIVES: We compared two commonly used comorbidity indices published by Charlson and Elixhauser regarding their ability to estimate readmission odds in COPD and determine which one provided a superior model. METHODS: We analyzed discharge records for COPD from the Nationwide Readmissions Database spanning 2010 to 2016. Inclusion and readmission criteria from the Hospital Readmissions Reduction Program were utilized. Elixhauser and Charlson Comorbidity Index scores were calculated from published methodology. A mixed-effects logistic regression model with random intercepts for hospital clusters was fit for each comorbidity index, including year, patient-level, and hospital-level covariates to estimate odds of thirty-day readmissions. Sensitivity analyses included testing age inclusion thresholds and model stability across time. RESULTS: In analysis of 1.6 million COPD discharges, readmission odds increased by 9% for each half standard deviation increase of Charlson Index scores and 13% per half standard deviation increase of Elixhauser Index scores. Model fit was slightly better for the Elixhauser Index using information criteria. Model parameters were stable in our sensitivity analyses. CONCLUSIONS: Both comorbidity indices provide meaningful information in prediction readmission odds in COPD with slightly better model fit in the Elixhauser model. Incorporation of comorbidity information into risk prediction models and hospital discharge planning may be informative to mitigate readmissions.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6794890/pdf/12913_2019_Article_4549.pdf

Calzetta, L., F. Di Marco, et al. (2019). **"Impact of ICS/LABA and LABA/LAMA FDCs on functional and clinical outcomes in COPD: A network meta-analysis."** Pulm Pharmacol Ther: 101855.

BACKGROUND: Inhaled corticosteroid (ICS)/long-acting beta2 agonist (LABA) fixed-dose combinations (FDCs) and LABA/long-acting muscarinic antagonist (LAMA) FDCs are extensively used to treat chronic obstructive pulmonary disease (COPD). The aim of the present network meta-analysis was to assess the comparative efficacy of all the currently available dual therapies in patients with moderate-to-severe

COPD. METHODS: A network meta-analysis (>/=3 nodes, Bayesian method) was performed by searching for randomized clinical trials (RCTs) that compared the impact of different LABA/LAMA FDCs vs. ICS/LABA FDCs on both primary and secondary endpoints. The primary endpoints were: the change from baseline in trough forced expiratory volume in 1s (FEV1) and the risk of exacerbation of COPD (AECOPD). The secondary endpoints were: peak FEV1, St' George's Respiratory Questionnaire (SGRQ), Transition Dyspnea Index (TDI), and rescue medication use. RESULTS: Data of 17,734 COPD patients were extracted from 16 RCTs. The length of treatment ranged from 6 weeks to 52 weeks. All LABA/LAMA FDCs, except aclidinium/formoterol, produced a statistically significant improvement compared to ICS/LABAs in trough FEV1. The surface under the cumulative ranking curve (SUCRA) analysis indicated that umeclidinium/vilanterol, glycopyrronium/indacaterol and glycopyrrolate/formoterol fumarate were the most effective FDCs in improving trough FEV1. Across the FDCs analyzed for the risk of AECOPD, glycopyrronium/indacaterol significantly reduced the exacerbation risk compared to fluticasone propionate/salmeterol and resulted the most effective combination in the SUCRA analysis. Similar trend were also observed for the peak FEV1. No significant differences were detected across the investigated FDCs regarding SGRQ, TDI, and use of rescue medication. CONCLUSIONS: The results of this meta-analysis show that LABA/LAMA combinations are consistently more effective than ICS/LABA FDCs for most of the evaluated outcomes. However, differences have also been observed between FDCs belonging to the same class. Across the investigated LABA/LAMA FDCs, glycopyrronium/indacaterol revealed a consistent and robust efficacy profile.

https://www.sciencedirect.com/science/article/pii/S1094553919301622?via%3Dihub

Cao, Y., S. Xuan, et al. (2019). **"Effects of long-term macrolide therapy at low doses in stable COPD."** Int J Chron Obstruct Pulmon Dis **14**: 1289-1298.

Background: Chronic obstructive pulmonary disease (COPD) is currently the fourth largest fatal disease in the world, and is expected to rise to third place by 2020. Frequent acute exacerbations lead to increased mortality. Some suggestions for prophylactic use of macrolides in preventing COPD exacerbations have been raised, but there are still several issues that need to be addressed, such as target population, the course of treatment, therapeutic dose, and so on. Objective: To evaluate, via exploratory meta-analysis, the efficacy of long-term macrolide therapy at low doses in stable COPD. Methods: A systematic literature search was performed in PubMed, Embase, and Cochrane database from inception to March 28, 2019. Randomized controlled trials (RCT) which reported long-term use of macrolides in prevention of COPD were eligible. Results: A total of 10 articles were included in this study. It was found that there was a 23% relative risk reduction in COPD exacerbations among patients taking macrolides compared to placebo (P<0.01). The median time to first exacerbation was effectively prolonged among patients taking macrolides vs placebo (P<0.01). Sub-group analysis showed erythromycin was advantageous and older patients were less responsive to macrolides. Conclusions: Long-term low dose usage of macrolides could significantly reduce the frequency of the acute exacerbation of COPD. The treatment was well tolerated, with few adverse reactions, but it was not suitable for the elderly. It is recommended that this treatment regimen could be used in patients with GOLD grading C or D, because they have a higher risk of acute exacerbation and mortality. It needs to be further discussed whether this treatment should last for 12 months or longer.

https://www.dovepress.com/getfile.php?fileID=50490

Chen, Y. W., A. H. Ramsook, et al. (2019). **"Prevalence and Risk Factors for Osteoporosis in Individuals With COPD: A Systematic Review and Meta-analysis."** ChestBACKGROUND: Osteoporosis is prevalent in individuals with COPD. Updated evidence is required to complement the previous systematic review on this topic to provide best practice. The aim of this systematic review and meta-analysis was to quantitatively synthesize data from studies with respect to the prevalence and risk factors for osteoporosis among individuals with COPD. METHODS: EMBASE, CINAHL, MEDLINE, and PubMed databases were searched for articles containing the key words "COPD," "osteoporosis," "prevalence," and

"risk factor." Eligibility screening, data extraction, and quality assessment of the retrieved articles were conducted independently by two reviewers. Meta-analyses were performed to determine osteoporosis prevalence and risk factors in individuals with COPD. Meta-regression analyses were conducted to explore the sources of heterogeneity. RESULTS: The pooled global prevalence from 58 studies was 38% (95% CI, 34-43). The presence of COPD increased the likelihood of having osteoporosis (OR, 2.83). Other significant risk factors for osteoporosis in COPD patients were BMI < 18.5 kg/m(2) (OR, 4.26) and the presence of sarcopenia (OR, 3.65). CONCLUSIONS: Osteoporosis is prevalent in individuals with COPD, and the prevalence seems to be high and similar in many countries. Patients with COPD should be screened for osteoporosis and contributing risk factors.

https://journal.chestnet.org/article/S0012-3692(19)31379-0/fulltext

Cramer, H., H. Haller, et al. (2019). **"The risks and benefits of yoga for patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis."** Clin Rehabil: 269215519860551.

OBJECTIVES: To determine the effectiveness and safety of yoga interventions on disease symptoms, quality of life and function in patients diagnosed with chronic obstructive pulmonary disease (COPD). DATA SOURCES: Medline/PubMed, Scopus, and CENTRAL (Cochrane Central Register of Controlled Trials) were searched through 6 June 2019. REVIEW METHODS: Randomized controlled trials assessing the effects of yoga on quality of life, dyspnea, exercise capacity, and pulmonary function (FEV1) in patients with COPD were included. Safety was defined as secondary outcome. Mean differences (MD) and standardized mean differences (SMD) with 95% confidence intervals (CIs) were computed. Risk of bias was assessed using the Cochrane tool. RESULTS: Eleven randomized controlled trials with a total of 586 patients were included. Meta-analysis revealed evidence for effects of yoga compared to no treatment on quality of life on the COPD Assessment Test (MD = 3.81; 95% CI = 0.97 to 6.65; P = 0.009, I(2) = 70%), exercise capacity assessed by the 6-minute walk test (MD = 25.53 m; 95% CI = 12.16 m to 38.90 m; P = 0.001, I(2) = 0%), and pulmonary function assessed by FEV1 predicted (MD = 3.95%; 95% CI = 2.74% to 5.17%; P < 0.001, I(2) = 0%). Only the effects on exercise capacity and pulmonary function were robust against methodological bias. Effects were only present in breathing-focused yoga interventions but not in interventions including yoga postures. Adverse events were reported infrequently. CONCLUSION: This meta-analysis found robust effects of yoga on exercise capacity and pulmonary function in patients with COPD. Yoga, specifically yoga breathing techniques, can be an effective adjunct intervention for patients with COPD. Yoga's safety needs to be assessed in more depth in future studies.

https://journals.sagepub.com/doi/10.1177/0269215519860551

Devereux, G., S. Cotton, et al. (2019). **"Low-dose oral theophylline combined with inhaled corticosteroids for people with chronic obstructive pulmonary disease and high risk of exacerbations: a RCT."** Health Technol Assess **23**(37): 1-146.

BACKGROUND: Despite widespread use of therapies such as inhaled corticosteroids (ICSs), people with chronic obstructive pulmonary disease (COPD) continue to suffer, have reduced life expectancy and utilise considerable NHS resources. Laboratory investigations have demonstrated that at low plasma concentrations (1-5 mg/l) theophylline markedly enhances the anti-inflammatory effects of corticosteroids in COPD. OBJECTIVE: To determine the clinical effectiveness and cost-effectiveness of adding low-dose theophylline to a drug regimen containing ICSs in people with COPD at high risk of exacerbation. DESIGN: A multicentre, pragmatic, double-blind, randomised, placebo-controlled clinical trial. SETTING: The trial was conducted in 121 UK primary and secondary care sites. PARTICIPANTS: People with COPD [i.e. who have a forced expiratory volume in 1 second (FEV1)/forced vital capacity (FVC) of < 0.7] currently on a drug regimen including ICSs with a history of two or more exacerbations treated with antibiotics and/or oral corticosteroids (OCSs) in the previous year. INTERVENTIONS: Participants were randomised (1 : 1) to receive either low-dose theophylline or placebo for 1 year. The dose of theophylline (200 mg once or twice a day) was determined by ideal body weight and smoking status. PRIMARY OUTCOME: The number of participant-reported exacerbations in the 1-year treatment

period that were treated with antibiotics and/or OCSs. RESULTS: A total of 1578 people were randomised (60% from primary care): 791 to theophylline and 787 to placebo. There were 11 post-randomisation exclusions. Trial medication was prescribed to 1567 participants: 788 in the theophylline arm and 779 in the placebo arm. Participants in the trial arms were well balanced in terms of characteristics. The mean age was 68.4 [standard deviation (SD) 8.4] years, 54% were male, 32% smoked and mean FEV1 was 51.7% (SD 20.0%) predicted. Primary outcome data were available for 98% of participants: 772 in the theophylline arm and 764 in the placebo arm. There were 1489 person-years of follow-up data. The mean number of exacerbations was 2.24 (SD 1.99) for participants allocated to theophylline and 2.23 (SD 1.97) for participants allocated to placebo [adjusted incidence rate ratio (IRR) 0.99, 95% confidence interval (CI) 0.91 to 1.08]. Low-dose theophylline had no significant effects on lung function (i.e. FEV1), incidence of pneumonia, mortality, breathlessness or measures of quality of life or disease impact. Hospital admissions due to COPD exacerbation were less frequent with low-dose theophylline (adjusted IRR 0.72, 95% CI 0.55 to 0.94). However, 39 of the 51 excess hospital admissions in the placebo group were accounted for by 10 participants having three or more exacerbations. There were no differences in the reporting of theophylline side effects between the theophylline and placebo arms. LIMITATIONS: A higher than expected percentage of participants (26%) ceased trial medication; this was balanced between the theophylline and placebo arms and mitigated by over-recruitment (n = 154 additional participants were recruited) and the high rate of follow-up. The limitation of not using documented exacerbations is addressed by evidence that patient recall is highly reliable and the results of a small within-trial validation study. CONCLUSION: For people with COPD at high risk of exacerbation, the addition of low-dose oral theophylline to a drug regimen that includes ICSs confers no overall clinical or health economic benefit. This result was evident from the intention-to-treat and per-protocol analyses. FUTURE WORK: To promote consideration of the findings of this trial in national and international COPD guidelines. TRIAL REGISTRATION: Current Controlled Trials ISRCTN27066620. FUNDING: This project was funded by the National Institute for Health Research (NIHR) Health Technology Assessment programme and will be published in full in Health Technology Assessment; Vol. 23, No. 37. See the NIHR Journals Library website for further project information.

Chronic obstructive pulmonary disease (COPD) is a long-term lung disease that cannot be cured. The main symptom is shortness of breath on exertion. In the UK, about 1.2 million people have COPD. It is a major cause of death and costs the NHS > pound1B a year. Sudden 'flare-ups' of symptoms often need emergency treatment, shorten life expectancy and reduce people's ability to get on with their lives. Theophylline is a drug that has been around for decades. In the past, it was used in high doses to treat COPD by opening up airways. However, its benefits were limited and it often caused unpleasant side effects. High-dose theophylline has been replaced by drugs administered by inhalers, such as inhaled corticosteroids (ICSs). Recent work in the laboratory and in animal models suggests that, at low dose, theophylline could make ICSs work better in COPD with none of the side effects of high-dose theophylline. The Theophylline With Inhaled CorticoSteroid (TWICS) trial tested whether or not adding low-dose theophylline reduces flare-ups in people with COPD taking ICSs. A total of 1578 people with COPD from 121 centres all over the UK took part. Participants were randomly divided into two groups: one group took low-dose theophylline and the other took dummy placebo pills. Participants were asked to attend visits at 6 and 12 months. A total of 791 participants were prescribed low-dose theophylline and 787 were prescribed dummy placebo pills. Although not everyone took the tablets for a whole year, it was possible to count the number of flare-ups in 98% of those taking part. In total, there were 3430 flare-ups. On average, the people taking low-dose theophylline had 2.24 flare-ups and the people taking placebo had 2.23 flare-ups. Overall, the trial showed that, for people with COPD, taking low-dose theophylline on top of steroid inhalers makes no real difference.

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Duiverman, M. L., J. M. Vonk, et al. (2019). **"Home initiation of chronic non-invasive ventilation in COPD patients with chronic hypercapnic respiratory failure: a randomised controlled trial."** ThoraxINTRODUCTION: Chronic non-invasive ventilation (NIV) has become evidence-based care for stable hypercapnic COPD patients. While the number of patients increases, home initiation of NIV would greatly alleviate the healthcare burden. We hypothesise that home initiation of NIV with the use of

telemedicine in stable hypercapnic COPD is non-inferior to in-hospital NIV initiation. METHODS: Sixty-seven stable hypercapnic COPD patients were randomised to initiation of NIV in the hospital or at home using telemedicine. Primary outcome was daytime arterial carbon dioxide pressure (PaCO2) reduction after 6 months NIV, with a non-inferiority margin of 0.4 kPa. Secondary outcomes were health-related quality of life (HRQoL) and costs. RESULTS: Home NIV initiation was non-inferior to in-hospital initiation (adjusted mean difference in PaCO2 change home vs in-hospital: 0.04 kPa (95% CI -0.31 to 0.38 kPa), with both groups showing a PaCO2 reduction at 6 months compared with baseline (home: from 7.3+/-0.9 to 6.4+/-0.8 kPa (p<0.001) and in-hospital: from 7.4+/-1.0 to 6.4+/-0.6 kPa (p<0.001)). In both groups, HRQoL improved without a difference in change between groups (Clinical COPD Questionnaire total score-adjusted mean difference 0.0 (95% CI -0.4 to 0.5)). Furthermore, home NIV initiation was significantly cheaper (home: median euro3768 (IQR euro3546-euro4163) vs in-hospital: median euro8537 (IQR euro7540-euro9175); p<0.001). DISCUSSION: This is the first study showing that home initiation of chronic NIV in stable hypercapnic COPD patients, with the use of telemedicine, is non-inferior to in-hospital initiation, safe and reduces costs by over 50%. TRIAL REGISTRATION NUMBER: NCT02652559.

https://thorax.bmj.com/content/thoraxjnl/early/2019/09/03/thoraxjnl-2019-213303.full.pdf

Farver-Vestergaard, I., M. O'Connor, et al. (2019). **"Tele-delivered mindfulness-based cognitive therapy in chronic obstructive pulmonary disease: A mixed-methods feasibility study."** J Telemed Telecare **25**(8): 468-475.

INTRODUCTION: Mindfulness-based cognitive therapy has been shown to reduce psychological distress in chronic obstructive pulmonary disease, but uptake and attendance rates of hospital-based, face-to-face mindfulness-based cognitive therapy are low. The present mixed-methods study evaluates the clinical feasibility of home-based, tele-delivered mindfulness-based cognitive therapy in chronic obstructive pulmonary disease. METHODS: Eight patients with chronic obstructive pulmonary disease (mean age: 72.6 years; 50% female) received a standardised eight-week mindfulness-based cognitive therapy programme delivered via home-based video-conferences in groups of four. Feasibility in relation to (a) clinical change, (b) attendance and (c) instructor-patient working alliance were evaluated with questionnaires and semi-structured interviews. RESULTS: Statistically non-significant reductions in psychological distress (Cohen's d = 0.504; p = 0.399) and physical health status impairment (d = 0.743; p = 0.156) were observed from pre- to post-intervention. Participant narratives about clinical outcomes focused on changes in how to relate to unpleasant sensations, i.e. through attentional flexibility, taking a pause and acceptance. The average attendance rate was 7.5 (standard deviation = 0.8) out of eight sessions and no participants dropped out. The tele-based format appeared to accommodate participants' planning difficulties and promoted their ability and wish to participate. Although participant narratives suggested the tele-based format to be a barrier to developing a trusting and safe therapeutic environment, working alliance questionnaire scores were comparable to those found for face-to-face mindfulness-based cognitive therapy. DISCUSSION: The preliminary results indicate that tele-delivered mindfulness-based cognitive therapy is a clinically feasible intervention in chronic obstructive pulmonary disease. Future large-scale, randomised controlled trials testing its efficacy on the outcomes of psychological distress and physical health status should include analyses of potential mediators and moderators of the effect as well as and careful monitoring of attendance and adverse events.

https://journals.sagepub.com/doi/full/10.1177/1357633X18780563?url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Acrossref.org&rfr_dat=cr_pub%3Dpubmed

Fernandes-James, C., C. D. Graham, et al. (2019). **"Association of psychological flexibility with engagement in pulmonary rehabilitation following an acute exacerbation of chronic obstructive pulmonary disease."** Chron Respir Dis **16**: 1479973119880893.

This study aimed to investigate (a) the association between psychological flexibility and engagement in pulmonary rehabilitation within 8 weeks following hospitalisation for an acute exacerbation of chronic

obstructive pulmonary disease (AECOPD) and (b) how psychological (in)flexibility presents in this context. A mixed-methods study was conducted. Psychological flexibility during an AECOPD was assessed using The Acceptance and Action Questionnaire-II (AAQ-II) (n = 41) and the Engaged Living Scale (ELS) (n = 40). Engagement in post-AECOPD pulmonary rehabilitation was then recorded. Twenty-three patients also participated in cognitive interviews. Psychological flexibility was associated with a greater chance of accepting a pulmonary rehabilitation referral following an AECOPD. Small numbers prohibited analysis on attendance or completion. An AAQ-II score of 11 translated to a 60 (37-82)% probability of accepting a referral to pulmonary rehabilitation and an ELS score of 73 was associated with a 68 (46-91)% probability of accepting. Four themes were extracted from interviews: (1) family values, (2) self as abnormal, (3) 'can't do anything' versus 'I do what I can' and (4) disability, and related emotions, as barriers to action. Randomised clinical trials are needed to evaluate interventions designed to increase psychological flexibility (i.e. acceptance and commitment therapy) to support acceptance of pulmonary rehabilitation post-AECOPD.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6769226/pdf/10.1177_1479973119880893.pdf

Frykholm, E., V. P. Lima, et al. (2019). **"Physiological and Symptomatic Responses to Arm versus Leg Activities in People with Chronic Obstructive Pulmonary Disease: A Systematic Review and Meta-Analysis."** Copd: 1-16.

While the mechanisms underlying exercise limitations and symptoms during leg activities have been investigated in detail, knowledge of potential differences between leg and arm activities are not well understood and results from individual studies are contradictory. Thus, the aim of the present study was to synthesize physiological and symptomatic responses during activities involving the arms relative to activities involving the legs in people with Chronic Obstructive Pulmonary Disease (COPD). Any study with a cross-sectional comparison of acute physiological (cardiorespiratory, metabolic) and symptomatic responses to activities performed with the arms versus the legs were included. Studies were sub-grouped based on the type of activity performed (cycle ergometer, resistance exercises, or functional test/activities). Eighteen studies with 423 individuals with COPD were included. Leg cycle ergometer resulted in greater tidal volume (137 mL), minute ventilation (4.8 L/min), and oxygen consumption (164 mL/min) than arm cycle ergometer, while symptomatic responses were similar. Resistance exercises resulted in similar physiological and symptomatic responses irrespective of whether the legs or the arms were involved while studies on functional activities report different results depending on the type and intensity of the activity performed. With the exception of cycle ergometer activities, physiological and symptomatic responses do not seem to depend on whether the arms or the legs are used, but rather seem to be task and intensity dependent. These novel findings suggest, for example, that strategies used to increase exercise tolerance should not be dependent on whether the arms or the legs are used, but rather the intensity of specific activity performed.

https://www.tandfonline.com/doi/pdf/10.1080/15412555.2019.1674269?needAccess=true

Gaveikaite, V., C. Grundstrom, et al. (2019). **"A systematic map and in-depth review of European telehealth interventions efficacy for chronic obstructive pulmonary disease."** Respir Med **158**: 78-88.

BACKGROUND: Evidence to support the implementation of telehealth (TH) interventions in the management of chronic obstructive pulmonary disease (COPD) varies throughout Europe. Despite more than ten years of TH research in COPD management, it is still not possible to define which TH interventions are beneficial to which patient group. Therefore, informing policymakers on TH implementation is complicated. We aimed to examine the provision and efficacy of TH for COPD management to guide future decision-making. METHODS: A mapping study of twelve systematic reviews of TH interventions for COPD management was conducted. This was followed by an in-depth review of fourteen clinical trials performed in Europe extracted from the systematic reviews. Efficacy outcomes for COPD management were synthesized. RESULTS: The mapping study revealed that systematic reviews with a meta-analysis often report positive clinical outcomes. Despite this, we identified a lack of pragmatic trial design

affecting the synthesis of reported outcomes. The in-depth review visualized outcomes for three TH categories, which revealed a plethora of heterogeneous outcomes. Suggestions for reporting within these three outcomes are synthesized as targets for future empirical research reporting. CONCLUSION: The present study indicates the need for more standardized and updated systematic reviews. Policymakers should advocate for improved TH trial designs, focusing on the entire intervention's adoption process evaluation. One of the policymakers' priorities should be the harmonization of the outcome sets, which would be considered suitable for deciding about subsequent reimbursement. We propose possible outcome sets in three TH categories which could be used for discussion with stakeholders.

https://www.resmedjournal.com/article/S0954-6111(19)30285-9/fulltext

Gloeckl, R., I. Jarosch, et al. (2019). **"Comparison of supplemental oxygen delivery by continuous versus demand based flow systems in hypoxemic COPD patients - A randomized, single-blinded cross-over study."** Respir Med **156**: 26-32.

BACKGROUND: Supplemental oxygen is a recommended therapy option in stable hypoxemic COPD patients. Often, supplemental oxygen is provided by continuous flow (CF). However, demand oxygen delivery systems (DODS) that provide an oxygen bolus only during inspiration have gained increasing use as they prolong oxygen cylinder life (beside battery life). However, there is a lack of evidence if different DODS and CF devices are equivalent. METHODS: Seventy hypoxemic COPD patients (FEV1 32+/-9% predicted, PaO2 56+/-7mmHg) on long-term oxygen therapy were included in this prospective single-blinded, randomized cross-over trial. Following an initial incremental shuttle walk test, patients performed 3 endurance shuttle walk tests (ESWT) at 85% of their maximum walking speed in random order with: (A) CF (ESWT-CF), (B) a DODS based on liquid oxygen (ESWT-DL) and (C) an DODS oxygen concentrator (ESWT-DC). The primary outcome was oxygen saturation (SpO2) at ESWT isotime. Secondary outcomes were total ESWT duration, heart rate (HR) and breathing frequency (BF) at isotime and dyspnea at end-exercise. RESULTS: SpO2 at ESWT isotime was not clinically different between devices: 90+/-4% (CF), 89+/-5% (DL) and 90+/-5% (DC). However, 20% of the patients showed a >/=4% lower oxygen desaturation while using a DODS device. Secondary outcomes were similar under the three conditions. CONCLUSION: Oxygen supplementation via DODS (based on liquid oxygen or as a concentrator) yielded comparable physiological effects during standardized walking in stable hypoxemic COPD patients like CF. However, 20% of patients showed a clinically relevant lower oxygen saturation while using a DODS device. Therefore, we suggest individual testing of oxygen saturation of DODS suitability.

https://www.resmedjournal.com/article/S0954-6111(19)30258-6/fulltext

Han, F., X. Yang, et al. (2019). **"Association between outdoor PM2.5 and prevalence of COPD: a systematic review and meta-analysis."** Postgrad Med J **95**(1129): 612-618.

There were conflictions and differences among the results of cross-sectional studies association between PM2.5 and COPD prevalence. We aimed to explore the real association between outdoor PM2.5 and COPD prevalence, analyze the possible cause to the differences and conflictions in previous cross-sectional studies. Cross-sectional literatures about the association between outdoor PM2.5 and COPD prevalence were selected up to 12 September 2018. Subgroup analysis was performed to explore the source of the heterogeneity. Publication bias was tested via funnel plot. Leave-one-out method was used to conduct influential analysis. Variance analysis was used to analyze the influence of concentration, literature quality and age (over 60 or not) on the ln (aOR) values. The initial search revealed 230 studies, of which 8 were selected. The heterogeneity in this study was significant (I(2)=62, P<0.01), and random effects model was used. The pooled OR for the association between PM2.5 and COPD prevalence is 2.32(95%CI, 1.91-2.82). There was no evidence of publication bias. Subgroup analysis showed the subgroup of age seemed to be the source of heterogeneity (P=0.0143, residual I(2)=0%). Variance analysis showed that the differences of ln (aOR) among each concentration group(p=0.0075) were statistically significant, the same as age groups(P=0.0234). This meta-analysis study demonstrated a conclusive association between

PM2.5 and prevalence of COPD (OR: 2.32, 95%CI 1.91-2.82). The significant heterogeneity among selected studies was mainly caused by age (over 60 or not). High PM2.5 concentration should be needed in further research of the relationship between PM2.5 and chronic diseases.

https://pmj.bmj.com/content/95/1129/612

Huang, J. D., T. J. Gu, et al. (2019). **"Invasive-noninvasive Sequential Ventilation for the Treatment of Acute Exacerbation of Chronic Obstructive Pulmonary Disease."** Comb Chem High Throughput Screen **22**(3): 160-168.

BACKGROUND: The study aimed to evaluate the efficacy and safety of invasivenoninvasive sequential ventilation versus invasive ventilation in the treatment of Acute Exacerbation of Chronic Obstructive Pulmonary Disease (AECOPD). METHODS: PubMed, Cochrane, Embase, Wanfang, CNKI, VIP database were searched by the index words to identify the qualified RCTs, and relevant literature sources were also searched. The latest research was conducted in June 2017. Relative Risks (RR), and Mean Difference (MD) along with 95% confidence interval (95% CI) were used to analyze the main outcomes. RESULTS: Twenty-nine RCTs were involved in this analysis of 1061 patients in the invasivenoninvasive sequential ventilation group (In-non group) and 1074 patients in the invasive ventilation group (In group). The results indicated that compared with the invasive ventilation, invasive-noninvasive sequential ventilation would significantly decrease the incidence of VAP (RR:0.20, 95%CI: 0.16-0.26), mortality (RR:0.38, 95%CI: 0.26-0.55), reintubation (RR:0.39, 95%CI: 0.27-0.55); and statistically reduced the duration of invasive ventilation (MD:-9.23, 95%CI: -10.65, -7.82), the total duration of mechanical ventilation (MD:-4.91, 95%CI: -5.99, -3.83), and the length of stay in the ICU (MD:-5.10, 95%CI: -5.43, -4.76). CONCLUSION: The results demonstrated that the application of noninvasive sequential ventilation after invasive ventilation at the pulmonary infection control window has a significant influence on VAP incidence, mortality, and the length of stay in the ICU, but further well-designed, adequately powered RCTs are required to validate the conclusion.

http://www.eurekaselect.com/171605/article

Jolly, K., M. Sidhu, et al. (2019). **"Improving recruitment to a study of telehealth management for COPD: a cluster randomised controlled 'study within a trial' (SWAT) of a multimedia information resource."** Trials **20**(1): 453.

BACKGROUND: Good quality information is critical for valid informed consent to trials, but current paper-based consent procedures are potentially unwieldy and can be difficult to comprehend, which may deter people from participating. Multimedia resources may be able to provide more accessible and user-friendly information. We aimed to test whether offering access to a multimedia information resource alongside standard, printed patient information impacted on recruitment rates by conducting a pragmatic 'study within a trial' (SWAT) embedding a trial of a multimedia resource within an existing trial. METHODS: The PSM COPD study involved people with mild symptoms of chronic obstructive pulmonary disease (COPD) recruited from primary care being randomised to a nurse-delivered telephone health coaching intervention, or usual primary care. For the SWAT of recruitment procedures, practices recruiting participants were cluster randomised to use either the standard printed patient information materials or standard printed patient information materials with access to a multimedia information resource. The multimedia resource was developed by patient and public involvement (PPI) contributors and researchers, and included study-specific information (e.g. study purpose, risks), and generic information about trials (e.g. confidentiality, randomisation). We developed a list of components and used animations as well as video clips of patients discussing their experiences of participation, matched to these components. The primary outcome was the proportion of participants randomised. RESULTS: Nine point six percent of those receiving standard printed patient information materials and access to the multimedia information resource were recruited, compared to 10.8% in those receiving standard printed materials alone (odds ratio (OR) = 0.844, 95% confidence interval (CI) 0.58 to 1.22). We also found no effects on the proportion of people responding to the invitation (OR = 1.02, 95% CI 0.79

to 1.33) or retention in the trial at 6 (ORs 0.84, 95% CI 0.57 to 1.22) and 12 months after randomisation (ORs 0.80, 95% CI 0.54 to 1.18), respectively. CONCLUSIONS: The study suggests no benefits of access to a multimedia information resource alongside patient information materials on recruitment. This may reflect the limited engagement of patients with the multimedia resource. Further uses of multimedia resources will need to explore how content can be explicitly matched to user needs and preferences and methods to encourage engagement to see if effects can be enhanced. More SWATs of multimedia into ongoing trials will provide a more precise estimate of effect, and explore further how effects vary by trial context and recruitment process, intervention, and patient population. TRIAL REGISTRATION: Current controlled trials ISRCTN 06710391 . Registered on 21 November 2013. SWAT REGISTRATION: SWAT 23: Systematic Techniques for Assisting Recruitment to Trials (MRC START). Registered on 11 January 2012.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6657092/pdf/13063_2019_Article_3496.pdf

Kamei, T., H. D. Nakamura, et al. (2019). **"Clinical benefit of two-times-per-day aclidinium bromide compared with once-a-day tiotropium bromide hydrate in COPD: a multicentre, open-label, randomised study."** BMJ Open **9**(7): e024114.

OBJECTIVE: Chronic obstructive pulmonary disease (COPD) is mainly treated pharmaceutically with bronchodilators. The purpose of this study was to evaluate the clinical benefits of two-times-per-day aclidinium bromide (Acli-BID) compared with once-a-day tiotropium bromide hydrate (Tio-QD) in patients with COPD. DESIGN: This study was a multicentre, open-label, randomised study. SETTING: Fourcentres in Kagawa prefecture, Japan. PARTICIPANT: Patients who were diagnosed to have COPD Grade 2-3 according to the Global Initiative for Chronic Obstructive Lung Disease 2015 criteria were enrolled. INTERVENTIONS: Patients were randomly assigned to receive Acli-BID or Tio-QD at a 1:1 ratio, and followed for 8 weeks. Acli-BID was administered in the morning and night, and Tio-QD was administered in the night. PRIMARY AND SECONDARY OUTCOME MEASURES: Primary outcome was forced expiratory volume in one second area under the curve (FEV1AUC0-3), and secondary outcomes were pulmonary function, physical activity, St George's Respiratory Questionnaire (SGRQ), modified Medical Research Council (mMRC), the 8-item Short-Form Health Survey (SF-8) and COPD exacerbations. Adverse events were evaluated during the study. RESULTS: 44 patients were included in this study. FEV1AUC0-3 at week 8 was 4.62+/-1.43 L.hour in Acli-BID and 4.73+/-1.60 L.hour in Tio-QD (mean difference (MD) -0.11 L.hour; 95% CI), -1.04 to 0.83). Significant improvement was observed in activity-related subscales of SGRQ (MD -7.78; 95% CI -14.61 to -0.94) and SF-8 (MD 4.01; 95% CI 0.37 to 7.65), mMRC (MD -0.66; 95% CI -1.19 to -0.13) and rate ratio (0.52, 95% CI 0.27 to 0.99) of exacerbations in the Acli-BID compared with the Tio-QD. Acli-BID and Tio-QD significantly improved sedentary behaviour (MD -35.20 min; 95% CI -67.41 to -2.94 and MD -55.40 min; 95% CI -98.15 to -12.77) within each group, but there was no significant difference between the two groups. CONCLUSION: Acli-BID as with Tio-QD could be one of the therapeutic options for patients with COPD to improve pulmonary function. Also, our results suggest that intervention with bronchodilators enhanced physical activity in patients with COPD. TRIAL REGISTRATION NUMBER: UMIN 000020020.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6661652/pdf/bmjopen-2018-024114.pdf

Lai, C. C., C. H. Chen, et al. (2019). **"The effects of single inhaler triple therapy vs single inhaler dual therapy or separate triple therapy for the management of chronic obstructive pulmonary disease: a systematic review and meta-analysis of randomized controlled trials."** Int J Chron Obstruct Pulmon Dis **14**: 1539-1548.

Background: This study aims to compare the effects of single inhaler triple therapy comprised of inhaled corticosteroids (ICSs), long-acting beta2-agonists (LABAs), and long-acting muscarinic receptor antagonists (LAMAs) with dual therapies comprised of either LABA/LAMA, ICS/LABA or separate ICS/LABA plus LAMA triple therapy. Methods: The Pubmed, Embase, and Cochrane databases were searched up to October 31st 2018. Only randomized controlled trials were included in the meta-analysis. The primary outcome was the rate of moderate-to-severe chronic obstructive pulmonary disease (COPD)

exacerbations. Results: Seven studies fulfilling the inclusion criteria were included in the meta-analysis. Single inhaler triple therapy was associated with a significantly lower risk of COPD exacerbation compared with LABA/LAMA (rate ratio, 0.69; 95% confidence interval [CI] 0.55 to 0.87, I(2) =85%), and ICS/LABA (rate ratio, 0.81; 95% CI 0.73 to 0.89, I(2) =29%) dual therapy. Single inhaler triple therapy led to a more significant improvement in lung function and quality of life compared with LABA/LAMA and ICS/LABA dual therapy. Single inhaler triple therapy was associated with a higher risk of pneumonia compared with LABA/LAMA (risk ratio, 1.38, 95% CI 1.14 to 1.67, I(2) =0) dual therapy. Conclusions: The use of single inhaler triple therapy for COPD patients can result in lower rates of moderate or severe exacerbations of COPD as well as improved lung function and quality of life compared with dual therapy with LABA/LAMA or ICS/LABA.

https://www.dovepress.com/getfile.php?fileID=51141

Lenferink, A., J. van der Palen, et al. (2019). **"Exacerbation action plans for patients with COPD and comorbidities: a randomised controlled trial."** Eur Respir JThis international randomised controlled trial evaluated whether COPD patients with comorbidities, trained in using patient-tailored multi-disease exacerbation action plans, had fewer COPD exacerbation days than usual care (UC).COPD patients (GOLD II-IV) with >/=1 comorbidity (ischaemic heart disease, heart failure, diabetes, anxiety, depression) were randomised to a patient-tailored self-management intervention (n=102) or UC (n=99). Daily symptom diaries were completed for 12 months. The primary outcome "COPD exacerbation days/patient/year" was assessed using intention-to-treat analyses.No significant difference was observed in the number of COPD exacerbation days/patient/year (self-management: median 9.6 (IQR 0.7-31.1); UC: median 15.6 (IQR 3.0-40.3); Incidence Rate Ratio (IRR) 0.87 (95% CI 0.54; 1.39); p=0.546). There was a significantly shorter duration per COPD exacerbation for self-management (self-management: median 8.1 (IQR 4.8-10.1) days; UC: median 9.5 (IQR 7.0-15.1) days; p=0.021), with no between-group differences in the total number of respiratory hospitalisations (IRR 0.76 (95% CI 0.42;1.35); p=0.348), but a lower probability of >/=1 respiratory-related hospitalisation compared to UC (Relative Risk (RR) 0.55 (95% CI 0.35; 0.87); p=0.008). No between-group differences were observed in all-cause hospitalisations (IRR 1.07 (95% CI 0.66; 1.72)) or mortality (self-management: n=4 (3.9%); UC: n=7 (7.1%); RR 0.55 (95% CI 0.17; 1.84)).Patient-tailored exacerbation action plans for COPD patients with comorbidities did not significantly reduce exacerbation days, but reduced the duration per COPD exacerbation and the risk of having at least one respiratory-related hospitalisation during follow-up, without excess all-cause mortality.

https://erj.ersjournals.com/content/early/2019/07/24/13993003.02134-2018

Li, N., P. Li, et al. (2019). **"Effects of resistance training on exercise capacity in elderly patients with chronic obstructive pulmonary disease: a meta-analysis and systematic review."** Aging Clin Exp ResOBJECTIVE: The objective of this study was to summarize and determine the effectiveness of resistance training on exercise capacity in patients with chronic obstructive pulmonary disease (COPD). METHODS: We searched PubMed, EMBASE, Cochrane Library, and two Chinese databases (China National Knowledge Infrastructure and Wanfang Data) to identify articles written in English or Chinese and published from January 2000 to January 2019. Randomized controlled trials were included if they evaluated the effects of resistance training on exercise capacity in COPD patients. We assessed the quality of the trials using the Physiotherapy Evidence Database Scale. Data from these studies were pooled to calculate weighted mean difference (WMD) or standardized mean difference (SMD) with 95% confidence intervals (CI). RESULTS: Eleven studies with a total of 405 participants met the inclusion criteria. Compared with the non-exercise control group, resistance training significantly improved 6-min walking distance (WMD, 54.52; 95% CI 25.47-83.56; I(2) = 43%; P = 0.14), transfer numbers for the 6-min pegboard and ring test (WMD, 25.17; 95% CI 10.17-40.16; I(2) = 0%; P = 0.55), and tolerance time for the unsupported upper-limb exercise test (SMD, 0.41; 95% CI 0.03-0.79; I(2) = 0%; P = 0.83). There were no significant differences in constant work rate endurance test results or in peak oxygen uptake between

the two groups. CONCLUSIONS: Resistance training was an effective approach to improve functional exercise capacity, endurance exercise capacity, and peak exercise capacity in COPD patients.

https://link.springer.com/article/10.1007%2Fs40520-019-01339-8

Lin, Q., L. Zhuo, et al. (2019). **"Effects of breathing exercises using home-based positive pressure in the expiratory phase in patients with COPD."** Postgrad Med J **95**(1127): 476-481.

BACKGROUND: Patients with chronic obstructive pulmonary disease (COPD) commonly have higher intrinsic positive end-expiratory pressure (PEEPi). A breathing exercise programme strategy employing an appropriate PEEP may improve their pulmonary functional capacity, exercise tolerance and health-related quality of life. Breathing with an expiratory resistive load, which is a method of modulating spontaneous breathing against PEEPi, has not been fully studied in patients with COPD. The objective of this study was to investigate the role of changing spontaneous breathing in home-based conditions and regulating spontaneous breathing with breathing exercises in patients with COPD. METHODS: This was a prospective randomised trial including 64 patients with a diagnosis of stage III or IV COPD. Patients were randomised into two groups: standard treatment and standard treatment combined with breathing exercise rehabilitation. The effects of the treatments on the COPD assessment test (CAT) score, 6-minute walk test (6MWT) results and pulmonary function were compared at 0, 6, 12 and 18 months within and between the two groups. RESULTS: All outcomes showed no significant differences between the two groups at the beginning of the study, while the 6MWT and CAT scores exhibited clinically and statistically significant improvements ($p<0.001$) by the end of the study. At month 18, the change in the predicted percentage of forced expiratory volume in 1 s (FEV1%pred) differed between the two groups ($p<0.05$). In addition, there were statistically significant differences in the 6MWT results, CAT scores and FEV1%pred values between the baseline and month 18 ($p<0.0001$) in the intervention group. CONCLUSIONS: Improvements in 6MWT results, pulmonary function and CAT scores are associated with a successful response to breathing against PEEPi in patients with COPD. TRIAL REGISTRATION: This trial was registered at research registry.com (identifier research registry 4816).

https://pmj.bmj.com/content/95/1127/476.long

Liu, S., J. Chen, et al. (2019). **"Comparative effectiveness of six Chinese herb formulas for acute exacerbation of chronic obstructive pulmonary disease: a systematic review and network meta-analysis."** BMC Complement Altern Med **19**(1): 226.

BACKGROUND: Six Chinese herb formulas, namely, the Weijing decoction (WJ), the Maxingshigan decoction (MXSG), the Yuebijiabanxia decoction (YBBX), the Qingqihuatan decoction (QQHT), the Dingchuan decoction (DC) and the Sangbaipi decoction (SBP), are commonly used, along with routine pharmacotherapy, to manage the acute exacerbation of chronic obstructive pulmonary disease (AECOPD). In this study, we conducted a systematic review to summarize the efficacy of these six formulas, and we also conducted a network meta-analysis (NMA) to rank these formulas. METHODS: We searched five English databases and four Chinese databases, with dates ranging from the starting dates of these databases to December 2016. Randomized controlled trials that evaluated any of the six Chinese herb formulas combined with the use of pharmacotherapy for AECOPD were identified. RESULTS: Fifty-five studies involving 4560 participants were included. The pairwise meta-analyses showed that WJ and QQHT had superior effects on the improvement of lung function (forced expiratory volume in 1 seconds; FEV1) (mean difference (MD): 0.25, 95% confidence interval (CI): 0.19-0.30 and 0.34, 95%CI: 0.10-0.58). MXSG, WJ and QQHT were found to be more effective for improving arterial blood gases (PaO_2 and $PaCO_2$). In terms of effective rates, all of these formulas had additional favourable effects compared to routine pharmacotherapy. The results of the NMA analyses indicated that only MXSG showed superior add-on effects for the improvement of FEV1 (MD: 0.37, 95% credible interval (CrI): 0.03-0.72). Most of the formulas combined with routine pharmacotherapy were superior to pharmacotherapy alone for the improvement of arterial blood gases and effective rates. The ranking tests suggested that QQHT and MXSG combined with routine pharmacotherapy might be optimal

options for the treatment of AECOPD. CONCLUSIONS: This NMA indicated that QQHT and MXSG might be more effective treatment regimens for AECOPD. Further well-designed studies that specifically examine the direct comparisons of these formulas are needed to support our conclusions.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6704718/pdf/12906_2019_Article_2633.pdf

Moghoofei, M., S. Azimzadeh Jamalkandi, et al. (2019). **"Bacterial infections in acute exacerbation of chronic obstructive pulmonary disease: a systematic review and meta-analysis."** InfectionOBJECTIVE: Due to the importance of Chronic obstructive pulmonary disease (COPD) as the fourth cause of mortality worldwide and the lack of studies evaluating the prevalence of bacterial infections in disease exacerbation, this systematic review and meta-analysis was performed to determine the prevalence rate of bacterial infections in COPD patients. METHODS: PubMed, ISI Web of Science, and Scopus databases were systematically searched for population-based prevalence studies (1980-2018). MeSH terms for "Bacterial infections" and "AECOPD" were used as search keywords. The selected studies were filtered according to the inclusion and exclusion criteria. Fixed and random-effects models were used for estimation of summary effect sizes. Between-study heterogeneity, as well as publication bias, were calculated. RESULTS: Finally, 118 out of 31,440 studies were selected. The overall estimation of the prevalence of bacterial infection was 49.59% [95% confidence interval (CI) 0.4418-0.55]. The heterogeneity in estimating the pooled prevalence of bacterial infections was shown in the studies (Cochran Q test: 6615, P < 0.0001, I(2) = 98.23%). In addition, S. pneumoniae, H. influenzae, M. catarrhalis, A. baumannii, P. aeruginosa, and S. aureus were the most prevalent reported bacteria. CONCLUSIONS: Our results as the first meta-analysis for the issue demonstrated that bacterial infections are an important risk factor for AECOPD. Further studies must be performed for understanding the exact role of bacterial agents in AECOPD and help physicians for more applicable preventive and therapeutic measurements.

https://link.springer.com/article/10.1007%2Fs15010-019-01350-1

Ni, W., J. Bao, et al. (2019). **"Potential of serum procalcitonin in predicting bacterial exacerbation and guiding antibiotic administration in severe COPD exacerbations: a systematic review and meta-analysis."** Infect Dis (Lond) **51**(9): 639-650.

Background: The value of procalcitonin (PCT) in the diagnosis of bacterial infections and for determining antibiotic usage among patients with acute exacerbations of chronic obstructive pulmonary disease (AECOPD) is currently unclear. Methods: We systematically reviewed the literature and selected studies that evaluated PCT as a biomarker for predicting bacterial infection and compared PCT-based protocols to determine its application in the initiation or discontinuation of antibiotics. Guidance for systematic reviews from Cochrane and the GRADE were followed to perform this study. Data were pooled and analyzed by using a random-effects or a fixed-effects model based on the heterogeneity. Results: The pooled sensitivity and specificity of PCT in diagnosing respiratory bacterial infections were 0.60 and 0.76, respectively, with the area under the summary receiver operating characteristic curve of 0.77. Subgroup analysis showed that the sensitivity and specificity of PCT for patients in ICU were 0.48 and 0.69, respectively. PCT-based protocols decreased antibiotic prescription (relative risk = 0.66, 95% CI: 0.62-0.71) and total antibiotic exposure (mean difference = -2.60, 95% CI: -4.48-0.72), without affecting clinical outcomes such as treatment failure, length of hospitalization and rates of re-exacerbation or overall mortality. Conclusions: PCT has a moderate ability to distinguish bacterial respiratory infection in patients with AECOPD. PCT-guided algorithm can reduce unnecessary administration of antibiotics without increasing adverse outcomes. However, for patients requiring admission in the ICU, PCT may have a poor diagnostic value, and the PCT-guided algorithm may not effectively and safely reduce the antibiotic exposure.

https://www.tandfonline.com/doi/abs/10.1080/23744235.2019.1644456

Noonan, M. C., J. Wingham, et al. (2019). **"Involving caregivers in self-management interventions for patients with heart failure and chronic obstructive pulmonary disease. A systematic review and meta-analysis."** J Adv NursAIM: To quantify the impact of involving caregivers in self-management interventions on health-related quality of life of patients with heart failure or chronic obstructive pulmonary disease. DESIGN: Systematic review, meta-analysis. DATA SOURCES: Searched: Medline Ebsco, PsycINFO, CINAHL, Embase, Web of Science, The British Library and ProQuest. Search time frame; January 1990-March 2018. REVIEW METHODS: Randomized controlled trials involving caregivers in self-management interventions (>/=2 components) compared with usual care for patients with heart failure or chronic obstructive pulmonary disease. A matched sample based on publication year, geographic location and inclusion of an exercise intervention of studies not involving caregivers were identified. Primary outcome of analysis was patient health-related quality of life. RESULTS: Thirteen randomized controlled trials (1,701 participants: 1,439 heart failure; 262 chronic obstructive pulmonary disease) involving caregivers (mean age 59; 58% female) were identified. Reported patient health-related quality of life measures included; Minnesota Living with Heart Failure questionnaire, St. George's respiratory questionnaire and Short-Form-36. Compared with usual care, there was similar magnitude in mean improvement in patient health-related quality of life with self-management interventions in trials involving caregivers (SMD: 0.23, 95% confidence interval: -0.15-0.61) compared with trials without caregivers (SMD: 0.27, 0.08-0.46). CONCLUSION: Within the methodological constraints of this study, our results indicate that involving caregivers in self-management interventions does not result in additional improvement in patient health-related quality of life in heart failure or chronic obstructive pulmonary disease. However, involvement of caregivers in intervention delivery remains an important consideration and key area of research. IMPACT: Greater understanding and awareness is needed of the methodology of caregiver engagement in intervention development and delivery and its impact on patient outcomes.

https://onlinelibrary.wiley.com/doi/abs/10.1111/jan.14172

Obeidat, M., A. Faiz, et al. (2019). **"The Pharmacogenomics of Inhaled Corticosteroids and Lung Function Decline in COPD."** Eur Respir JInhaled corticosteroids (ICS) are widely prescribed for patients with chronic obstructive pulmonary disease (COPD), yet with variable outcomes and adverse reactions which may be genetically determined. The primary aim of the study was to identify the genetic determinants for FEV1 changes related to ICS therapy. In the Lung Health Study 2 (LHS-2), 1116 COPD patients were randomised to the ICS, triamcinolone acetonide (n=559), or placebo (n=557) with spirometry performed every 6 months for 3 years. We performed a pharmacogenomic genome-wide association study (GWAS) for the genotype-by-ICS treatment effect on 3 years of forced expiratory volume in 1 s (FEV1) changes (estimated as slope) in 802 genotyped LHS-2 participants. Replication was performed in 199 COPD patients randomised to the ICS, fluticasone or placebo. A total of five loci showed genotype-by-ICS interaction at p<5x10(-6); of these, SNP rs111720447 on chromosome 7 was replicated (discovery p=4.8x10(-6), replication p=5.9x10(-5)) with the same direction of interaction effect. ENCODE data revealed that in glucocorticoid treated (dexamethasone) A549 alveolar cell line, glucocorticoid receptor binding sites were located near SNP rs111720447. In stratified analyses of LHS-2, genotype at SNP rs111720447 was significantly associated with rate of FEV1 decline in patients taking ICS (C allele beta=56.35 mL.year(-1), 95% confidence interval (CI)=29.96, 82.76 mL.yr(-1)) and also in patients who were assigned to placebo, though the relationship was weaker and in the opposite direction than that in the ICS group (C allele beta=-27.57 mL.year(-1), 95% CI=-53.27, -1.87 mL.yr(-1)). The study uncovered genetic factors associated with FEV1 changes related to ICS in COPD patients, which may provide new insight on the potential biology of steroid responsiveness in COPD.

https://erj.ersjournals.com/content/erj/early/2019/08/21/13993003.00521-2019.full.pdf

O'Connor, C., R. Lawson, et al. (2019). **"Is inspiratory muscle training (IMT) an acceptable treatment option for people with chronic obstructive pulmonary disease (COPD) who have declined pulmonary rehabilitation (PR) and can IMT enhance PR uptake? A single-group prepost feasibility study in a home-based setting."** BMJ Open **9**(8): e028507.

OBJECTIVES: This feasibility study aimed to assess the acceptability of inspiratory muscle training (IMT) in people with chronic obstructive pulmonary disease (COPD) who declined pulmonary rehabilitation (PR) as a potential treatment option or precursor to PR. Objectives were to assess attitudes to IMT, PR and alternatives to PR; factors influencing adherence with IMT and acceptability of outcome measures, research tools and study protocol. DESIGN: A pragmatic, mixed methods, prepost feasibility study was conducted. Recruitment took place over a 4-month period. Participants were followed up for a period of 6 months. SETTINGS: IMT sessions and assessments were conducted in the domiciliary setting. PARTICIPANTS: Inclusion criteria: people over the age of 35, stable COPD, Medical Research Council Dyspnoea scale of 3 or above, declined PR. EXCLUSION CRITERIA: history of spontaneous pneumothorax, incomplete recovery from a traumatic pneumothorax, asthma, known recently perforated eardrum, unstable angina, ventricular dysrhythmias, cerebrovascular event or myocardial infarction within the last 2 months. Participants were selected from a purposive sample. Of the 22 potential participants screened, 11 were recruited and interviewed. Ten participants commenced IMT. Seven participants completed the follow-up assessment. INTERVENTION: Eight weeks of IMT twice a day, 5 days a week with visits once weekly by a physiotherapist. Unsupervised IMT twice a day three times a week until follow-up at 6 months. OUTCOMES: Acceptability of IMT and the study process was explored via semi-structured interviews. Adherence with IMT was assessed by the Powerbreathe K3 device and participant diaries. Uptake of PR was identified. RESULTS: IMT was found to be acceptable. Adherence was explored. Four people went on to participate in PR. CONCLUSIONS: Feasibility was established. A randomised controlled trial is warranted to establish efficacy and cost-effectiveness of IMT in those who decline PR and IMT as an intervention to promote uptake of PR. TRIAL REGISTRATION NUMBER: NCT01956565; Post-results.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6701573/pdf/bmjopen-2018-028507.pdf

Oshagbemi, O. A., J. O. Odiba, et al. (2019). **"Absolute Blood Eosinophil Counts to Guide Inhaled Corticosteroids Therapy Among Patients with COPD: Systematic Review and Meta-analysis."** Curr Drug TargetsINTRODUCTION: The Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2019 recommends the use of absolute blood eosinophil count as a guide for the escalation and de-escalation of inhaled corticosteroids (ICS) in the pharmacological management of patients with chronic obstructive pulmonary disease (COPD). We evaluated the risk of moderate or severe exacerbations among patients escalating and de-escalating ICS therapy by absolute blood eosinophil thresholds in this systematic review. METHODS: Through a comprehensive literature search of Pubmed/MEDLINE, EMBASE, and clinical trial sites up to April 2019, we identified relevant studies. We used generic inverse variance method with fixed-effects estimates to compare the risk of moderate or severe exacerbations among COPD patients with elevated blood eosinophil counts exposed to inhaled corticosteroids (ICS) versus non-ICS treatments groups expressed as risk ratios. RESULTS: Ten studies (8 randomised control trials and 2 observational studies) were included, with a total of 85,059 COPD patients. In our pooled analysis, we found an overall reduction in risk of moderate or severe exacerbations in patients with absolute blood eosinophil thresholds ranging from >/= 100 to >/= 340 cells/muL among patients escalating ICS (RR, 0.77, 95% CI, 0.73-0.81). For studies evaluating the effects of de-escalation of ICS on moderate to severe exacerbations using blood eosinophil thresholds of >/= 300 to >/= 340 cells/muL had an increased risk of moderate or severe exacerbations following the de-escalation of ICS (RR, 1.66, 95% CI, 1.31-2.10). CONCLUSION: This study confirms the validity of the recommended absolute blood eosinophil count thresholds for the escalation and de-escalation of ICS among COPD patients. However, this recommendation is for COPD patients with prior exacerbations rather than among newly diagnosed COPD patients as observed in this study. COPD patients with current or past history of asthma represent a unique phenotypic group which should be further evaluated.

http://www.eurekaselect.com/174199/article

Pascoe, S. J., A. Papi, et al. (2019). **"Circulating neutrophils levels are a predictor of pneumonia risk in chronic obstructive pulmonary disease."** Respir Res **20**(1): 195.

BACKGROUND: Patients with chronic obstructive pulmonary disease (COPD) have excess risk of developing pneumonia; however, no definitive biomarkers of risk have been established. We hypothesized that blood neutrophils would help predict pneumonia risk in COPD. METHODS: A meta-analysis of randomized, double-blind clinical trials of COPD patients meeting the following criteria were selected from the GlaxoSmithKline trial registry: >/=1 inhaled corticosteroid-containing (ICS) arm (fluticasone propionate/salmeterol or fluticasone furoate/vilanterol), a control arm (non-ICS), pre-randomization blood neutrophil counts, >/=24-week duration. The number of patients with pneumonia events and time to first event (Kaplan-Meier analysis) were evaluated (post-hoc), stratified by baseline blood neutrophil count and ICS use. A Cox proportional hazards model was used to calculate hazard ratios (HR), split by median baseline blood neutrophils. RESULTS: Ten studies (1998 to 2011) with 11,131 patients were identified. The ICS (n = 6735) and non-ICS (n = 4396) cohorts were well matched in neutrophil distributions and demographics. Increasing neutrophil count was associated with an increased proportion of patients with pneumonia events; patients below the median neutrophil count were at less risk of a pneumonia event (HR, 0.75 [95% confidence interval 0.61-0.92]), and had longer time to a first event, compared with those at/above the median. The increase in pneumonia risk by neutrophil count was similar between the two cohorts. CONCLUSIONS: Increased blood neutrophils in COPD were associated with increased pneumonia risk, independent of ICS use. These data suggest blood neutrophils may be a useful marker in defining treatment pathways in COPD.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6708190/pdf/12931_2019_Article_1157.pdf

Pericleous, P. and T. P. van Staa (2019). **"The use of wearable technology to monitor physical activity in patients with COPD: a literature review."** Int J Chron Obstruct Pulmon Dis **14**: 1317-1322.

Background: Physical activity is an important predictor for survival in patients with COPD. Wearable technology, such as pedometer or accelerometer, may offer an opportunity to quantify physical activity and evaluate related health benefits in these patients. Objectives: To assess the performance of wearable technology in monitoring and improving physical activity in COPD patients from published studies. Methods: Literature search of Medline, Cochrane, Dare, Embase and PubMed databases was made to find relevant articles that used wearable technology to monitor physical activity in COPD patients. Results: We identified 13 studies that used wearable technology, a pedometer or an accelerator, to monitor physical activity in COPD patients. Of these, six studies were randomized controlled trials (RCTs) which used the monitors as part of the intervention. Two studies reported the same outcomes and comparable units. They had measured the difference that the intervention makes on the number of steps taken daily by the patients. The results were highly heterogeneous with I(2)=92%. The random-effects model gave an effect outcome on the number of steps taken daily of 1,821.01 [-282.71; 3,924.74] in favor of the wearable technology. Four of the 13 studies have reported technical issues with the use of the wearable technology, including high signal-to-noise ratio, memory storage problems and inaccuracy of counts. While other studies did not mention any technical issues, it is not clear whether these did not experience them or chose not to report them. Conclusions: Our literature search has shown that data on the use of wearable technology to monitor physical activity in COPD patients are limited by the small number of studies and their heterogeneous study design. Further research and better-designed RCTs are needed to provide reliable results before physical activity monitors can be implemented routinely for COPD patients.

https://www.dovepress.com/getfile.php?fileID=50594

Pinto-Plata, V., C. Casanova, et al. (2019). **"Plasma metabolomics and clinical predictors of survival differences in COPD patients."** Respir Res **20**(1): 219.

BACKGROUND: Plasma metabolomics profile (PMP) in COPD has been associated with clinical characteristics, but PMP's relationship to survival has not been reported. We determined PMP differences between patients with COPD who died an average of 2 years after enrollment (Non-survivors, NS) compared to those who survived (S) and also with age matched controls (C). METHODS: We studied prospectively 90 patients with severe COPD and 30 controls. NS were divided in discovery and validation cohorts (30 patients each) and the results compared to the PMP of 30 S and C. All participants completed lung function tests, dyspnea scores, quality of life, exercise capacity, BODE index, and plasma metabolomics by liquid and gas chromatography / mass spectometry (LC/MS, LC/MS(2), GC/MS). Statistically, we used Random Forest Analysis (RFA) and Support Vector Machine (SVM) to determine metabolites that differentiated the 3 groups and compared the ability of metabolites vs. clinical characteristics to classify patients into survivors and non-survivors. RESULTS: There were 79 metabolites statistically different between S and NS [$p < 0.05$ and false discovery rate (q value) < 0.1]. RFA and SVM classification of COPD survivors and non-survivors had a predicted accuracy of 74 and 85% respectively. Elevation of tricyclic acid cycle intermediates branched amino acids depletion and increase in lactate, fructose and xylonate showed the most relevant differences between S vs. NS suggesting alteration in mitochondrial oxidative energy generation. PMP had similar predictive power for risk of death as information provided by clinical characteristics. CONCLUSIONS: A plasma metabolomic profile characterized by an oxidative energy production difference between survivors and non-survivors was observed in COPD patients 2 years before death.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6794856/pdf/12931_2019_Article_1167.pdf

Ridwan, E. S., H. Hadi, et al. (2019). **"Effects of Transitional Care on Hospital Readmission and Mortality Rate in Subjects With COPD: A Systematic Review and Meta-Analysis."** Respir Care **64**(9): 1146-1156.

BACKGROUND: Studies on the effect of transitional care on hospital readmissions have reported inconsistent findings, and the effect on mortality has not been reviewed systematically. This systematic review and meta-analysis of randomized controlled trials aims to examine the effect of transitional care interventions on COPD-related readmissions, all-cause hospital readmissions, and all-cause mortality rates in subjects with COPD. METHODS: Electronic databases (CINAHL, Embase, Scopus, MEDLINE, Cochrane, PubMed, Web of Science, Airity, BMJ Respiratory Research Journal, and National Digital Library of Theses and Dissertations) were searched from inception to April 26, 2017. Online searches were conducted using key words and MeSH terms for COPD and transitional care. Entry terms for searching included chronic obstructive pulmonary disease, COPD, COPD transitional care or care transition, continuity of patient care, patient discharge, and patient transfer. The quality of the included trials was assessed using the Cochrane Collaboration tool. RESULTS: 13 randomized controlled trials met the inclusion criteria. Transitional care significantly reduced the risk of COPD-related readmissions (odds ratio = 0.599, 95% CI 0.421-0.852) and all-cause hospital readmissions (odds ratio = 0.720, 95% CI 0.531-0.978), but not that of all-cause mortality (odds ratio = 0.863, 95% CI 0.576-1.294) in subjects with COPD. The effects of transitional care on hospital readmissions were moderated by the duration of interventions, type of care providers, and use of telephone follow-up as an element of the intervention. CONCLUSIONS: There was a significant effect of transitional care on both COPD-related and all-cause hospital readmissions in subjects with COPD. Duration of interventions, type of care providers, and use of telephone follow-up appeared to moderate the beneficial effects of transitional care.

http://rc.rcjournal.com/content/64/9/1146.short

Rogliani, P., M. G. Matera, et al. (2019). **"Efficacy and cardiovascular safety profile of dual bronchodilation therapy in chronic obstructive pulmonary disease: A bidimensional comparative analysis across fixed-dose combinations."** Pulm Pharmacol Ther **59**: 101841.

Despite several long-acting beta2-adrenoceptor agonist (LABA)/long-acting muscarinic antagonist (LAMA) fixed-dose combinations (FDCs) are currently approved for the treatment of chronic obstructive pulmonary disease (COPD), there are limited findings concerning the direct comparison across the different LABA/LAMA FDCs. The aim of this study was to compare the efficacy/safety profile of approved LABA/LAMA FDCs in COPD. A network meta-analysis was performed by linking the efficacy (forced expiratory volume in 1s, St' George Respiratory Questionnaire, transitional dyspnea index) and safety (cardiovascular serious adverse events) outcomes resulting from randomized controlled trials that directly compared LABA/LAMA FDCs with placebo and/or each other. The Surface Under the Cumulative Ranking Curve Analysis (SUCRA) was performed for each single outcome (SUCRA: 1=best, 0=worst). The combined efficacy/safety profile was reported via the novel Improved Bidimensional SUCRA score (IBiS: the higher the value the better the treatment). Data obtained from 12,136 COPD patients (79.50% LABA/LAMA FDCs vs. placebo; 20.50% direct comparison between different LABA/LAMA FDCs) were extracted from 22 studies published between 2013 and 2019. The IBiS score showed the following rank of efficacy/safety profile: tiotropium/olodaterol 5/5mug (area 66.83%) >> glycopyrronium/indacaterol 15.6/27.5mug (area 40.43%) > umeclidinium/vilanterol 62.5/25mug (area 30.48%) approximately aclidinium/formoterol 400/12mug (area 28.44%) > glycopyrronium/indacaterol 50/110mug (area 19.95%) > glycopyrronium/formoterol 14.4/9.6mug (area 11.50%). Each available LABA/LAMA FDC has a specific efficacy/safety profile that needs to be considered for personalized therapy in COPD. Head-to-head studies aimed to assess the impact of different LABA/LAMA FDCs on the risk of COPD exacerbation are needed to further improve the information provided by this quantitative synthesis.

https://www.sciencedirect.com/science/article/pii/S1094553919301634?via%3Dihub

Shi, C. and H. Zhao (2019). **"Association between Tumor Necrosis Factor-308 G/A Polymorphism and Chronic Obstructive Pulmonary Disease Risk in Chinese Population: Evidence from a Meta-Analysis."** Clin Lab **65**(10)BACKGROUND: Association studies of tumor necrosis factor (TNF)-308 G/A (rs1800629) polymorphism and chronic obstructive pulmonary disease (COPD) have shown inconsistent and contradictory results among different populations. In the present study, a meta-analysis was performed to evaluate the association between TNF-308 G/A polymorphism and COPD susceptibility in Chinese population. MATERIALS AND METHODS: Systemic assessment was performed for the published studies from PubMed, Embase, Web of Science, the Cochrane Library, Wanfang Data, and CNKI prior to July 2018. Odds ratios (ORs) with their 95% confidence intervals (CIs) were pooled using STATA software. RESULTS: A total of eighteen studies comprising 1,817 COPD cases and 2,056 controls were included in this meta-analysis. Overall, significant results were obtained between TNF-308 G/A polymorphism and COPD risk in Chinese population (A vs. G, OR = 2.45, 95% CI: 1.93 - 3.11; AA vs. GG, OR = 4.53, 95% CI: 2.67 - 7.68; AA vs. GA + GG, OR = 3.74, 95% CI: 2.21 - 6.33; AA + GA vs. GG, OR = 2.53, 95% CI: 1.97 - 3.26) under allele and homozygote models as well as recessive and dominant models. In the subgroup analyses, TNF-308 G/A polymorphism was significantly associated with increased COPD risk both in North China and South China, as well as in population-based studies. CONCLUSIONS: This meta-analysis indicates that TNF-308A/G polymorphism may contribute to individual suscepti-bility to COPD in Chinese population.

Singh, D., K. M. Beeh, et al. (2019). **"Effect of the inhaled PDE4 inhibitor CHF6001 on biomarkers of inflammation in COPD."** Respir Res **20**(1): 180.

BACKGROUND: CHF6001 is a novel inhaled phosphodiesterase-4 inhibitor. This Phase IIa study assessed the effects of CHF6001 on markers of inflammation in induced sputum and blood in patients with chronic obstructive pulmonary disease (COPD). METHODS: This was a multicentre, three-period (each 32 days), three-way, placebo-controlled, double-blind, complete-block crossover study. Eligible patients had COPD, chronic bronchitis, and were receiving inhaled triple therapy for >/=2 months. Patients received CHF6001 800 or 1600 mug, or matching placebo twice daily via multi-dose dry-powder inhaler

(NEXThaler). Induced sputum was collected pre-dose on Day 1, and post-dose on Days 20, 26 and 32. Blood was sampled pre-dose on Day 1, and pre- and post-dose on Day 32. RESULTS: Of 61 randomised patients, 54 (88.5%) completed the study. There were no significant differences between groups for overall sputum cell count, or absolute numbers of neutrophils, eosinophils or lymphocytes. CHF6001 800 mug significantly decreased the absolute number and percentage of macrophages vs placebo. In sputum, compared with placebo both CHF6001 doses significantly decreased leukotriene B4, C-X-C motif chemokine ligand 8, macrophage inflammatory protein 1beta, matrix metalloproteinase 9, and tumour necrosis factor alpha (TNFalpha). In blood, both CHF6001 doses significantly decreased serum surfactant protein D vs placebo. CHF6001 1600 mug significantly decreased TNFalpha ex-vivo (after incubation with lipopolysaccharide). CONCLUSION: The data from this study show that CHF6001 inhaled twice daily has anti-inflammatory effects in the lungs of patients with COPD already treated with triple inhaled therapy. TRIAL REGISTRATION: The study is registered on ClinicalTrials.gov (NCT03004417).

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6688371/pdf/12931_2019_Article_1142.pdf

Solidoro, P., F. Patrucco, et al. (2019). **"Comparing a fixed combination of budesonide/formoterol with other inhaled corticosteroid plus long-acting beta-agonist combinations in patients with chronic obstructive pulmonary disease: a review."** Expert Rev Respir Med **13**(11): 1087-1094.

Introduction: Inhaled corticosteroid (ICS) plus long-acting beta2-agonist (LABA) combinations are commonly used in the treatment of patients with chronic obstructive pulmonary disease (COPD). At least four fixed-dose ICS/LABA combinations are available, including budesonide/formoterol, beclomethasone/formoterol, fluticasone/vilanterol and fluticasone/salmeterol, but there is little guidance for clinicians on which of these combinations to prescribe. Areas covered: The aim of this in-depth review was to identify studies that compared budesonide/formoterol with the other ICS/LABA combinations and assess the data on exacerbations, safety, and patient quality of life. PubMed and Ovid databases were searched, and 14 studies were identified. Our findings highlight the lack of prospective, randomized, controlled trials comparing LABA/ICS combinations in the treatment of COPD as only two such studies were identified. However, current evidence suggests that the effects of budesonide/formoterol on reducing exacerbations and improving quality of life may be similar to, or more marked than, those of other LABA/ICS combinations in COPD and, compared with the other LABA/ICS combinations, budesonide/formoterol may be associated with a lower incidence of serious pneumonia events and oral candidiasis. Expert opinion: To better guide clinicians in selecting between the available ICS/LABA, robust meta-analyses and well-designed head-to-head clinical trials are urgently needed.

https://www.tandfonline.com/doi/full/10.1080/17476348.2019.1665514

Spathis, D. and P. Vlamos (2019). **"Diagnosing asthma and chronic obstructive pulmonary disease with machine learning."** Health Informatics J **25**(3): 811-827.

This study examines the clinical decision support systems in healthcare, in particular about the prevention, diagnosis and treatment of respiratory diseases, such as Asthma and chronic obstructive pulmonary disease. The empirical pulmonology study of a representative sample (n = 132) attempts to identify the major factors that contribute to the diagnosis of these diseases. Machine learning results show that in chronic obstructive pulmonary disease's case, Random Forest classifier outperforms other techniques with 97.7 per cent precision, while the most prominent attributes for diagnosis are smoking, forced expiratory volume 1, age and forced vital capacity. In asthma's case, the best precision, 80.3 per cent, is achieved again with the Random Forest classifier, while the most prominent attribute is MEF2575.

https://journals.sagepub.com/doi/full/10.1177/1460458217723169?url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Acrossref.org&rfr_dat=cr_pub%3Dpubmed

Stenlund, T., A. Nyberg, et al. (2019). **"Web-based support for self-management strategies versus usual care for people with COPD in primary healthcare: a protocol for a randomised, 12-month, parallel-group pragmatic trial."** BMJ Open **9**(10): e030788.

INTRODUCTION: The use of adequate self-management strategies for people with chronic obstructive pulmonary disease (COPD) may increase the level of physical activity (PA), improve health-related quality of life (HRQoL) and reduce healthcare use. Whether web-based support in addition to prompts (email and SMS) could be used to promote self-management strategies to facilitate behaviour change in people with COPD is not clear. This clinical trial aims to generate evidence on the effect of a web-based solution, the COPD Web, in a cohort of people with COPD in a primary healthcare context. METHODS AND ANALYSIS: The overall design is a pragmatic randomised controlled trial with preassessments and postassessments (3 and 12 months) and an implementation and user experience evaluation. People with a diagnosis of COPD, treated in primary healthcare will be eligible for the study. A total of 144 participants will be enrolled by healthcare professionals at included primary healthcare units and, after fulfilled baseline assessments, randomised to either control or intervention group. All participants will receive usual care, a pedometer and a leaflet about the importance of PA. Participants in the intervention will, in addition, get access to the COPD Web, an interactive self-managed website that aims to support people with COPD in self-management strategies. They will also continuously get support from prompts with a focus on behaviour change.The effect on participants' PA, dyspnoea, COPD-related symptoms, HRQoL and health economics will be assessed using accelerometer and questionnaires. To identify enablers and barriers for the use of web-based support to change behaviour, semistructured interviews will be conducted in a subgroup of participants at the 3 months follow-up. ETHICS AND DISSEMINATION: Ethical approval has been received from the Regional Ethical Review Board in Umea, Sweden. Dnr 2018-274-31. Findings will be presented at conferences, submitted for publication in peer-reviewed journals and presented to the involved healthcare professionals, participants and patient organisations. TRIAL REGISTRATION NUMBER: NCT03746873.

https://bmjopen.bmj.com/content/bmjopen/9/10/e030788.full.pdf

Tong, H., Y. Liu, et al. (2019). **"The therapeutic effects of qigong in patients with chronic obstructive pulmonary disease in the stable stage: a meta-analysis."** BMC Complement Altern Med **19**(1): 239.

OBJECTIVES: Chronic obstructive pulmonary disease (COPD) is one global disease. Lung function gradually declines. Medication does not fully reverse the airflow limitation. Qigong's role in COPD rehabilitation has been assessed. We aimed to assess the effects of Qigong practised by COPD patients. METHODS: Eligible articles were obtained through a systematic search. The databased were search on October 8, 2017, and the date range of the searches in the electronic databases had no upper limit. The Cochrane risk-of-bias tool was used to evaluate the quality of the eligible studies. Mean differences with 95% confidence intervals were utilized to analyse the results. RESULTS: Ten included studies contained 993 participants. Statistical improvements occurred in the 6-min walk distance (6MWD) (MD, 30.57 m; 95% CI, 19.61-41.53 m; P < 0.00001); forced expiratory volume in 1 s (FEV1) (MD, 0.32 L; 95% CI, 0.09-0.56 L; P < 0.001); forced vital capacity rate of 1 s (FEV1/FVC) (MD, 2.66%; 95% CI, 1.32-2.26%; P = 0.0001); forced expiratory volume in 1 s/predicted (FEV1/pre) (MD, 6.04; CI, 2.58-9.5; P = 0.006); Monitored Functional Task Evaluation (MD, 0.88; 95% CI, 0.78-0.99; P < 0.00001); COPD Assessment Test for exercise (MD, - 5.54; 95% CI, - 9.49 to - 1.59; P = 0.006); Short Form-36 Health Quality Survey (SF-36)-General Health (MD, 5.22; 95% CI, 3.65-6.80; P < 0.00001); and Short Form-36 Health Quality Survey (SF-36)-Mental Health (MD, - 1.21; 95% CI, - 2.75 to 0.33; P = 0.12). CONCLUSIONS: In this meta-analysis of RCTs between ten included studies, we found that Qigong can improve COPD patients in lung function, exercise capacity and quality of life who were in the stable stage.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6727520/pdf/12906_2019_Article_2639.pdf

Walsh, A., L. Perrem, et al. (2019). **"Statins versus placebo for people with chronic obstructive pulmonary disease."** Cochrane Database Syst Rev **7**: Cd011959.

BACKGROUND: Chronic obstructive pulmonary disease (COPD) is a common, preventable, and treatable respiratory disease. COPD exacerbations are associated with worse quality of life, increased hospitalisations, and increased mortality. Currently available pharmacological interventions have variable impact on exacerbation frequency. The anti-inflammatory effects of statins may lead to decreased pulmonary and systemic inflammation, resulting in fewer exacerbations of COPD. Several observational studies have shown potential benefits of statins for patients with COPD. OBJECTIVES: This review aims to evaluate available evidence on benefits and harms associated with statin therapy compared with placebo as adjunct therapy for patients with COPD. Primary objectives include the following.* To determine whether statins reduce mortality rates in COPD.* To determine whether statins reduce exacerbation frequency, improve quality of life, or improve lung function in COPD.* To determine whether statins are associated with adverse effects. SEARCH METHODS: We identified trials from the Cochrane Airways Trials Register, which contains studies identified through multiple electronic searches and handsearches of other sources. We also searched trial registries and reference lists of primary studies. We conducted the most recent search on 20 May 2019. SELECTION CRITERIA: Parallel, randomised controlled trials recruiting adults with COPD. DATA COLLECTION AND ANALYSIS: We used standard methods as expected by Cochrane. Prespecified primary outcomes were number of exacerbations, all-cause mortality, and COPD-specific mortality. MAIN RESULTS: Eight studies including 1323 participants with COPD were included in the review. Participants had a mean age of 61.4 to 72 years, and most were male (median 73.4%). Mean baseline forced expiratory volume in one second (FEV(1)) ranged from 41% to 90% predicted. All studies compared moderate- or high-intensity statin therapy versus placebo. The duration of treatment ranged from 12 weeks to 36 months.We found no statistically significant difference between statins and placebo in our primary outcome of number of exacerbations per person-year (mean difference (MD) -0.03, 95% confidence interval (CI) -0.25 to 0.19, 1 trial, 877 participants), including number of exacerbations requiring hospitalisation per person-year (MD 0.00, 95% CI -0.10 to 0.10, 1 trial, 877 exacerbations). This evidence was of moderate quality after downgrading for unclear risk of bias. Our primary outcomes of all-cause mortality (odds ratio (OR) 1.03, 95% CI 0.61 to 1.74, 2 trials, 952 participants) and COPD-specific mortality (OR 1.25, 95% CI 0.38 to 4.13, 1 trial, 877 participants) showed no significant difference between statins and placebo, with wide confidence intervals suggesting uncertainty about the precision of the results. This evidence was of low quality after downgrading for unclear risk of bias and imprecision.Results of the secondary outcomes analysis showed no clear differences between statins and placebo for FEV(1) (% predicted) (MD 1.18, 95% CI -2.6 to 4.97, 6 trials, 325 participants) but did show a statistically significant improvement in FEV(1)/forced vital capacity (FVC) (MD 2.66, 95% CI 0.12 to 5.2; P = 0.04; 6 trials, 325 participants). A sensitivity analysis excluding two trials at high risk of bias showed no statistically significant difference in FEV(1)/FVC (MD 2.05, 95% CI -0.87 to -4.97; P = 0.17; 4 trials, 255 participants). We also found no significant differences between the two groups in functional capacity measured by six-minute walk distance in metres (MD 1.79, 95% CI -52.51 to 56.09, 3 trials, 71 participants), with wide confidence intervals suggesting uncertainty about the precision of the results. Results show no clear difference in quality of life, which was reported in three trials, and a slight reduction in C-reactive protein (CRP) in the intervention group, which was statistically significant (MD -1.03, 95% CI -1.95 to -0.11; I(2) = 0%, P = 0.03; 3 trials, 142 participants). We noted a significant reduction in interleukin (IL)-6 in the intervention group (MD -2.11, 95% CI -2.65 to -1.56; I(2) = 0%, P </= 0.00001; 2 trials, 125 participants). All trials mentioned adverse events and indicated that statins were generally well tolerated. One study reported adverse events in detail and indicated that rates of all non-fatal adverse events (the number of serious adverse events per person-year) were similar in both groups (0.63 +/- 1.56 events (intervention group) and 0.62 +/- 1.48 events (control group); P > 0.20) for all comparisons, except for non-fatal serious adverse events involving the gastrointestinal tract, which were more frequent in the intervention group (in 30 patients (0.05 events per person-year) vs 17 patients (0.02 events per person-year); P = 0.02). Another trial lists the total numbers and percentages of adverse events in the intervention group (12 (26%)) and in the control group (21 (43%)) and of serious adverse events in the intervention group (4 (9%)) and in the control group (3 (6%)).The other trials stated that researchers found no significant adverse effects of statins but did not report adverse events in detail. AUTHORS' CONCLUSIONS: A small number of trials providing low- or moderate-quality evidence were suitable for inclusion in this review. They showed that use of statins resulted in a reduction in CRP and IL-6, but that this did not translate into clear clinical benefit for people with COPD. Further randomised controlled trials are needed to explore this topic.

Wei, J., C. S. Pang, et al. (2019). **"Effect of Orally Administered N-Acetylcysteine on Chronic Bronchitis: A Meta-analysis."** Adv TherINTRODUCTION: The effect of N-acetylcysteine (NAC) treatment for patients with chronic bronchitis (CB) is controversial. To better understand the role of NAC in CB treatment, we performed a meta-analysis to provide a more accurate estimation of the importance of NAC treatment. METHODS: PubMed, Embase, and CNKI were systematically searched. The pooled relative risk (RR) and 95% confidence intervals (CI) were calculated using either fixed-effect model or random-effect model based on heterogeneity examination. Statistical analyses were performed using the STATA 12.0 and RevMan 5.2. RESULTS: A total of 11 publications with 775 patients who were taking NAC and 789 controls who were taking placebo were judged eligible regarding inclusion criteria. The pooled analysis demonstrated significant evidence that NAC reduced the frequency of CB exacerbations (RR = 0.81, 95% CI 0.69-0.93, P = 0.004). Patients treated with NAC had significant symptom improvement compared with controls (RR = 1.68, 95% CI 1.13-2.52, P = 0.01). NAC did not significantly increase the risk of adverse effects compared with placebo (RR 0.86, 95% CI 0.67-1.09, P = 0.22). Subgroup analysis was carried out to assess the stability of results. No publication bias was detected during analyses. CONCLUSION: There is a role for NAC treatment in the management of CB by reducing symptoms and exacerbations compared with placebo, without increasing the risk of adverse effects. A regular treatment of low dosage (< 1200 mg per day) and a duration of at least 3 months seems to be effective.

https://link.springer.com/article/10.1007%2Fs12325-019-01111-4

Yang, M., Y. Du, et al. (2019). **"Inhaled corticosteroids and risk of pneumonia in patients with chronic obstructive pulmonary disease: A meta-analysis of randomized controlled trials."** Int Immunopharmacol **77**: 105950.

OBJECTIVE: Inhaled corticosteroids (ICS) are generally used to treat patients with chronic obstructive pulmonary disease (COPD) who suffer from repeated exacerbations. Recently, it was reported that ICS treatment increased the risk of pneumonia in COPD patients. But it is controversial.The objective of this paper is to clarify the associations between ICS treatment and the risk of pneumonia in COPD patients. METHODS: PubMed, Cochrane Library, Clinical Trials.gov, and Embase were searched from February 2019 to June 2019. Randomized clinical trials (RCTs) were incorporatedthat compared ICS with non-ICS treatment on the risk of pneumonia in COPD patients. Meta-analyses were conducted by the Peto and Mantel-Haenszel approaches with corresponding 95% CIs. RESULTS: Twenty-five trials (N=49,982 subjects) were included. Pooled results demonstrated a significantly increased risk of pneumonia with ICS use in COPD patients (RR, 1.59, 95% CI, 1.33-1.90; I(2)=51%). ICS treatment also increased the risk of severe pneumonia (RR, 2.17, 95% CI, 1.47-3.22; I(2)=29%). The results of subgroup analysis based on doses of ICS were consistent with the above. However, subgroup analyses based on types of ICS revealed that fluticasone therapy was associated with an increased risk of pneumonia but not budesonide. In addition, medium- and low-doses of budesonide treatment also did not increase the risk of pneumonia. CONCLUSIONS: Use of ICS increases the risk of pneumonia in patients with COPD. The above is prominent for fluticasone-containing ICSs but not for budesonide-containing ICSs.

https://www.sciencedirect.com/science/article/pii/S1567576919317370?via%3Dihub

Yao, Y., J. Zhou, et al. (2019). **"Association between tumor necrosis factor-alpha and chronic obstructive pulmonary disease: a systematic review and meta-analysis."** Ther Adv Respir Dis **13**: 1753466619866096.

BACKGROUND: Patients diagnosed with chronic obstructive pulmonary disease (COPD) have increased risks for a series of physical and mental illnesses. Tumor necrosis factor-alpha (TNF-alpha) has been reported to

participate in the development of COPD and its complications. However, the values of blood TNF-alpha level used in the diagnosis of COPD remains controversial. In view of this, we performed a systematic review and meta-analysis to evaluate the correlation between TNF-alpha level and COPD. METHODS: We searched PubMed, Web of Science, Embase and CNKI up to May 2018. The selection criteria were set according to the PICOS framework. A random-effects model was then applied to evaluate the overall effect sizes by calculating standard mean difference (SMD) and its 95% confidence intervals (CIs). RESULTS: A total of 40 articles containing 4189 COPD patients and 1676 healthy controls were included in this meta-analysis. The results indicated a significant increase in TNF-alpha level in the COPD group compared with the control group (SMD: 1.24, 95% CI: 0.78-1.71, p < 0.00001). According to the subgroup analyses, we noted that TNF-alpha level was associated with predicted first second of forced expiration (FEV1) (%) and study region. However, no association between TNF-alpha level and COPD was found when the participants were nonsmokers, and the mean age was less than 60 years. CONCLUSIONS: Our results indicated that TNF-alpha level was increased in COPD patients when compared with healthy controls. Illness progression and a diagnosis of COPD might contribute to higher TNF-alpha levels. However, the underlying mechanism still remains unknown and needs further investigation. The reviews of this paper are available via the supplemental material section.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6688146/pdf/10.1177_1753466619866096.pdf

Zhao, Q., S. Li, et al. (2019). **"Ambient heat and hospitalisation for COPD in Brazil: a nationwide case-crossover study."** Thorax **74**(11): 1031-1036.

BACKGROUND: Heat exposure has been related to increased morbidity and mortality for several health outcomes. There is little evidence whether this is also true for COPD. This study quantified the relationship between ambient heat and hospitalisation for COPD in the Brazilian population. METHODS: Data on hospitalisations for COPD and weather conditions were collected from 1642 cities during the 2000-2015 hot seasons. A time-stratified, case-crossover design was used for city-specific analyses, which were then pooled at the regional and national levels using random-effect meta-analyses. Stratified analyses were performed by sex, age group and early/late hot season. Annual change in the association was examined using a random-effect meta-regression model. RESULTS: The OR of hospitalisation was 1.05 (95% CI 1.04 to 1.06) for every 5 increase in daily mean temperature at the national level, with the effect estimate stronger in the late hot season compared with the early hot season. The effect was similar in women and in men but was greatest for those aged >/=75 years. The association was stronger in the central west and southeast regions and minimal in the northeast. Assuming a causal relationship, 7.2% of admissions were attributable to heat exposure. There was no significant temporal decline in the impact of ambient heat over the 16-year study period. CONCLUSION: In Brazil, exposure to ambient heat was positively associated with hospitalisation for COPD, particularly during the late hot season. These data add to the growing evidence base implicating global warming as being an important contributor to the future healthcare burden.

https://thorax.bmj.com/content/74/11/1031.long