COPD/Emphysema PubMed search results covering the period 19/01/2019- 26/04/2019

Systematic reviews and clinical trials

Search strategy: (("pulmonary disease, chronic obstructive"[MeSH Terms] OR "emphysema"[MeSH Terms]) AND ((systematic[sb] OR Clinical Trial[ptyp]) AND English[lang]) AND ("2019/01/19"[CDAT] : "3000"[CDAT])) AND ((systematic[sb] OR Clinical Trial[ptyp]) AND English[lang]) AND ((systematic[sb] OR Clinical Trial[ptyp]) AND English[lang])

Braunlich, J., F. Mauersberger, et al. (2018). **"Effectiveness of nasal highflow in hypercapnic COPD patients is flow and leakage dependent."** BMC Pulm Med **18**(1): 14.

BACKGROUND: Nasal Highflow (NHF) delivers a humidified and heated airflow via nasal prongs. Current data provide evidence for efficacy of NHF in patients with hypoxemic respiratory failure. Preliminary data suggest that NHF may decrease hypercapnia in hypercapnic respiratory failure. The aim of this study was to evaluate the mechanism of NHF mediated PCO2 reduction in patients with chronic obstructive pulmonary disease (COPD). METHODS: In 36 hypercapnic COPD patients (PCO2 > 45 mmHg), hypercapnia was evaluated by capillary gas sampling 1 h after NHF breathing under four conditions A to D with different flow rates and different degrees of leakage (A = 20 L/min, low leakage, two prongs, both inside; B = 40 L/min, low leakage, two prongs, both inside; C = 40 L/min, high leakage, two prongs, one outside and open; D = 40 L/min, high leakage, two prongs, one outside and closed). Under identical conditions, mean airway pressure was measured in the hypopharynx of 10 COPD patients. RESULTS: Hypercapnia significantly decreased in all patients. In patients with capillary PCO2 > 55 mmHg (n = 26), PCO2 additionally decreased significantly by increased leakage and/or flow rate in comparison to lower leakage/ flow rate conditions (A = 94.2 +/- 8.2%; B = 93.5 +/- 4.4%; C = 90.5 +/- 7.2%; D = 86.8 +/- 3.8%). The highest mean airway pressure was observed in patients breathing under condition B (2.3 +/- 1.6 mbar; $p < 0.05$). CONCLUSIONS: This study demonstrates effective PCO2 reduction with NHF therapy in stable hypercapnic COPD patients. This effect does not correlate with an increase in mean airway pressure but with increased leakage and airflow, indicating airway wash out and reduction of functional dead space as important mechanisms of NHF therapy. These results may be useful when considering NHF treatment in hypercapnic COPD patients. TRIAL REGISTRATION: Clinical Trials: NCT02504814; First posted July 22, 2015.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5784698/pdf/12890_2018_Article_576.pdf

Bringsvor, H. B., E. Langeland, et al. (2018). **"Effects of a COPD self-management support intervention: a randomized controlled trial."** Int J Chron Obstruct Pulmon Dis **13**: 3677-3688.

Background: This study examines the effects of the COPD-specific health promoting self-management intervention "Better living with COPD" on different self-management-related domains, self-efficacy, and sense of coherence (SOC). Methods: In a randomized controlled design, 182 people with COPD were allocated to either an intervention group (offered Better living with COPD in addition to usual care) or a control group (usual care). Self-management-related domains were measured by the Health Education Impact Questionnaire (heiQ) before and after intervention. Self-efficacy was measured by the General Self-Efficacy Scale (GSE) and SOC was measured by the 13-item Sense of Coherence Scale (SOC-13). Effects were assessed by ANCOVA, using intention-to-treat (ITT) analysis and per-protocol analysis (PPA). Results: The PPA and the ITT analysis showed significant positive changes on Constructive attitudes and approaches (heiQ) (ITT: P=0.0069; PPA: P=0.0021) and Skill and technique acquisition (heiQ) (ITT: P=0.0405; PPA: P=0.0356). Self-monitoring and insight (heiQ) showed significant positive change in the PPA (P=0.0494). No significant changes were found on the other self-management domains (heiQ), self-efficacy (GSE), or SOC (SOC-13). Conclusion: Better living with COPD had a significant positive short-term effect on some self-management-related domains, and could be an intervention contributing to the support of self-management in people with COPD. However, further work is needed to establish the clinical relevance of the findings and to evaluate the long-term effects.

https://www.dovepress.com/getfile.php?fileID=46010

Dainty, K. N., M. B. Seaton, et al. (2018). **"Home Visit-Based Community Paramedicine and Its Potential Role in Improving Patient-Centered Primary Care: A Grounded Theory Study and Framework."** Health Serv Res **53**(5): 3455-3470.

OBJECTIVE: Community paramedicine (CP) is a model of community-based health care being used around the world. Our objective was to study the patient perspective and valuation of this type of program to understand its potential value for primary care innovation in the future. STUDY SETTING: The EPIC community paramedicine program is a partnership between primary care physicians and specially trained community paramedics, designed to provide in-home support for complex chronic disease patients in Ontario, Canada. STUDY DESIGN: As part of an ongoing clinical trial we designed an embedded qualitative evaluation using constructionist grounded theory methodology. DATA COLLECTION METHODS: Data collection included in-depth interviews with 30 patients and/or family members and 60 hours of observation. PRINCIPAL FINDINGS: The health care needs of this complex population are largely attributes that impact a patient's quality of life-including recognition of their vulnerability, providing a safety-net in times of exacerbation and health education and accountability. This seems to be facilitated by a relationship with a dedicated provider that increases continuity of care. CONCLUSIONS: Home-based community paramedicine programs like EPIC appear to be able to create a patient-centered, safe, responsive therapeutic relationship that is often not possible within the standard primary health care system.

https://onlinelibrary.wiley.com/doi/abs/10.1111/1475-6773.12855

Darken, P., P. DePetrillo, et al. (2018). **"The pharmacokinetics of three doses of budesonide/glycopyrronium/formoterol fumarate dihydrate metered dose inhaler compared with active controls: A Phase I randomized, single-dose, crossover study in healthy adults."** Pulm Pharmacol Ther **50**: 11-18.

The budesonide/glycopyrronium/formoterol fumarate dihydrate metered dose inhaler (BGF MDI) is an inhaled corticosteroid/long-acting muscarinic antagonist/long-acting beta2-agonist fixed-dose combination formulated with innovative co-suspension delivery technology that is in clinical development for the treatment of chronic obstructive pulmonary disease (COPD). This randomized, Phase I, single-dose, six-treatment, four-period, crossover study (NCT01980615) examined the pharmacokinetic (PK) and safety profile of three doses of BGF MDI (320/14.4/10 mug [equivalent to budesonide/glycopyrrolate/formoterol fumarate 320/18/9.6 mug], 160/14.4/10 mug and 80/14.4/10 mug), two doses of a budesonide/formoterol fumarate dihydrate fixed-dose combination (BUD/FORM MDI 320/9 mug and 160/9 mug; not using co-suspension delivery technology) and a glycopyrronium/formoterol fumarate dihydrate co-suspension delivery technology MDI (GFF MDI 14.4/10 mug) in healthy volunteers (18-45 years of age). PK parameters included area under the plasma concentration-time curve from 0 to 12 h (AUC0-12), AUC up to the last measurable concentration (AUC0-t), maximum plasma concentration (Cmax) and time to maximum plasma concentration (tmax). Safety was monitored throughout the study. Of 84 subjects randomized, 76 completed the study. BGF MDI 320/14.4/10 mug was bioequivalent to BUD/FORM MDI 320/9 mug for budesonide for Cmax, AUC0-12 and AUC0-t (primary objective). Dose proportionality was observed for the budesonide component between BGF MDI 80/14.4/10 mug and BGF MDI 160/14.4/10 mug, and between BGF MDI 160/14.4/10 mug and BGF MDI 320/14.4/10 mug. Systemic exposure to glycopyrronium and formoterol after BGF MDI 320/14.4/10 mug treatment was similar to GFF MDI 14.4/10 mug. The rate of adverse events was 3.7-17.9% across treatments without any serious adverse events. In conclusion, BGF MDI 320/14.4/10 mug had a similar budesonide PK profile to BUD/FORM MDI 320/9 mug. No PK drug-drug interactions were observed when budesonide was added to glycopyrronium and formoterol fumarate dihydrate. These data support the use of budesonide 320 mug and 160 mug in future clinical trials of BGF MDI in COPD.

https://www.sciencedirect.com/science/article/pii/S1094553917302547?via%3Dihub

De Backer, W., J. De Backer, et al. (2018). **"A randomized study using functional respiratory imaging to characterize bronchodilator effects of glycopyrrolate/formoterol fumarate delivered by a metered dose inhaler using co-suspension delivery technology in patients with COPD."** Int J Chron Obstruct Pulmon Dis **13**: 2673-2684.

Background: Functional respiratory imaging (FRI) uses high-resolution computed tomography (HRCT) scans to assess changes in airway volume and resistance. Patients and methods: In this randomized, double-blind, 2-week, crossover, Phase IIIB study, patients with moderate-to-severe COPD received twice-daily glycopyrrolate/formoterol fumarate delivered by a metered dose inhaler (GFF MDI, 18/9.6 mug) and placebo MDI, formulated using innovative co-suspension delivery technology. Co-primary endpoints included the following: specific image-based airway volume (siVaw) and specific image-based airway resistance (siRaw) at Day 15, measured using FRI. Secondary and other endpoints included the following: change from baseline in post-dose forced expiratory volume in 1 second (FEV1) and inspiratory capacity (IC; spirometry) and ratio to baseline in post-dose functional residual capacity (FRC) and residual volume (RV; body plethysmography). Results: Twenty patients (46-78 years of age) were randomized and treated; of whom 19 completed the study. GFF MDI treatment increased siVaw by 75% and reduced siRaw by 71% vs placebo MDI (both P<0.0001). Image-based airway volume (iVaw) and image-based airway resistance (iRaw), without adjusting for lobe volume, demonstrated corresponding findings to the co-primary endpoint, as lobe volumes did not change with either treatment. Approximately 48% of the delivered dose of glycopyrronium and formoterol fumarate was estimated to be deposited in the lungs. Compared with placebo, GFF MDI treatment improved post-dose FEV1 and IC (443 mL and 454 mL, respectively; both P<0.001) and reduced FRC and RV (13% and 22%, respectively; both P<0.0001). There were no significant safety findings. Conclusion: GFF MDI demonstrated significant, clinically meaningful benefits on FRI-based airway volume and resistance in patients with moderate-to-severe COPD. Benefits were associated with improvements in FEV1, IC, and hyperinflation. Clinical trial registration: ClinicalTrials.gov: NCT02643082.

https://www.dovepress.com/getfile.php?fileID=44028

De Benedetto, F., R. Pastorelli, et al. (2018). **"Supplementation with Qter((R)) and Creatine improves functional performance in COPD patients on long term oxygen therapy."** Respir Med **142**: 86-93.

BACKGROUND: Skeletal muscle dysfunction and poor functional capacity are important extra-pulmonary manifestations of chronic obstructive pulmonary disease (COPD), especially in COPD patients on long-term O2 therapy (LTOT). Beside the role of pulmonary rehabilitation, the effect of nutritional interventions is still controversial, and there are knowledge gaps on the effective role of nutraceutical supplementation on hard endpoints. The aim of this study was to investigate the effects of nutritional supplementation with Coenzyme Q10 (QTer((R))) - a powerful antioxidant with the potential to reduce oxidative stress and improve mitochondrial function-and Creatine on functional, nutritional, and metabolomic profile in COPD patients on long-term O2 therapy. METHODS: One-hundred and eight patients with COPD from 9 Italian hospitals were enrolled in this double-blinded randomized placebo-controlled clinical study. At baseline and after 2 months of therapy, the patients underwent spirometry, 6-minute walk test (6MWT), bioelectrical impedance analysis, and activities of daily living questionnaire (ADL). Also, dyspnea scores and BODE index were calculated. At both time points, plasma concentration of CoQ10 and metabolomic profiling were measured. FINDINGS: Ninety patients, who randomly received supplementation with QTer((R)) and Creatine or placebo, completed the study. Compared with placebo, supplemented patients showed improvements in 6MWT (51+/-69 versus 15+/-91m, p<0.05), body cell mass and phase angle, sodium/potassium ratio, dyspnea indices and ADL score. The CoQ10 plasma concentration increased in the supplementation group whereas it did not change in the placebo group. The metabolomics profile also differed between groups. Adverse events were similar in both groups. INTERPRETATION: These results show that in patients with COPD, dietary supplementation with CoQ10 and Creatine improves functional performance, body composition and perception of dyspnea. A systemic increase in some anti-inflammatory metabolites supports a pathobiological mechanism as a

reason for these benefits. Further trials should help clarifying the role of QTer((R)) and Creatine supplementation in patients with COPD.

https://www.resmedjournal.com/article/S0954-6111(18)30259-2/fulltext

Driessen, M. T., J. Whalen, et al. (2018). **"Cost-effectiveness analysis of umeclidinium bromide/vilanterol 62.5/25 mcg versus tiotropium/olodaterol 5/5 mcg in symptomatic patients with chronic obstructive pulmonary disease: a Spanish National Healthcare System perspective."** Respir Res **19**(1): 224.

BACKGROUND: A head-to-head study demonstrated the superiority of once-daily umeclidinium bromide/vilanterol (UMEC/VI) 62.5/25 mcg on trough forced expiratory volume in 1 s (FEV1) versus once-daily tiotropium/olodaterol (TIO/OLO) 5/5 mcg in symptomatic patients with chronic obstructive pulmonary disease (COPD). This analysis evaluated the cost effectiveness of UMEC/VI versus TIO/OLO from a Spanish National Healthcare System perspective, using data from this study and Spanish literature. METHODS: This analysis was conducted from the perspective of the Spanish National Healthcare System with a 3-year horizon as base case. A disease progression model using a linked risk equation approach was used to estimate disease progression and associated healthcare costs, and quality-adjusted life years (QALYs). The Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) study was used to develop the statistical risk equations for clinical endpoints, and costs were calculated using a health state approach (by dyspnea severity). Utilities for QALY calculation were estimated using patient baseline characteristics within a regression fit to Spanish observational data. Treatment effect, expressed as change from baseline in FEV1 was obtained from the head-to-head study and used in the model (UMEC/VI minus TIO/OLO difference: + 52 mL [95% confidence interval: 28, 77]). Baseline patient characteristics were sourced from Spanish literature or the head-to-head study if unavailable. A scenario analysis using only the intent-to-treat (ITT) population from the head-to-head study, and sensitivity analyses (including probabilistic sensitivity analyses), were conducted. Direct healthcare costs (2017 Euro) were obtained from Spanish sources and costs and benefits were discounted at 3% per annum. RESULTS: UMEC/VI was associated with small improvements in QALYs (+ 0.029) over a 3-year time horizon, compared with TIO/OLO, alongside cost savings of euro393/patient. The ITT scenario analysis and sensitivity analyses had similar results. All probabilistic simulations resulted in UMEC/VI being less costly and more effective than TIO/OLO. CONCLUSION: UMEC/VI dominated TIO/OLO (more effective and less expensive). These results may aid payers and decision-makers in Spain when making judgements on which long-acting muscarinic antagonist/long-acting beta2-agonist (LAMA/LABA) treatments can be considered cost effective in Spain.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6245710/pdf/12931_2018_Article_916.pdf

Ferguson, G. T., C. Reisner, et al. (2018). **"Cardiovascular safety profile of a fixed-dose combination of glycopyrrolate and formoterol fumarate delivered via metered dose inhaler using co-suspension delivery technology."** Pulm Pharmacol Ther **49**: 67-74.

BACKGROUND: Glycopyrrolate/formoterol fumarate (GFF) metered dose inhaler (MDI) is a fixed-dose combination of the long-acting muscarinic antagonist (LAMA), glycopyrrolate (GP), and the long-acting beta2-agonist (LABA), formoterol fumarate (FF), delivered via metered dose inhaler using innovative co-suspension delivery technology. Here we report the results of two studies that examined the cardiovascular safety of GFF MDI. METHODS: The thorough QT (TQT) study was a Phase I, randomized, double-blind, single-dose, crossover study to assess GFF MDI 18/9.6 (Bevespi Aerosphere((R))), GFF MDI 144/38.4 and GP MDI 144mug, compared with placebo MDI and open-label moxifloxacin 400mg (active control) in healthy volunteers (PT003009). The cardiovascular safety study in patients with chronic obstructive pulmonary disease (COPD) was a Phase IIb, randomized, multicenter, double-blind, 14-day dosing, parallel-group study to evaluate GFF MDI 36/9.6, GP MDI 36 and FF MDI 9.6mug compared with open-label FF dry powder inhaler (DPI; Foradil((R)) Aerolizer((R))) 12mug, in patients with moderate-to-severe COPD (PT003003 [NCT01349803]). RESULTS: Seventy healthy volunteers were randomized in the

TQT study. GFF MDI 144/38.4, GFF MDI 18/9.6 and GP MDI 144mug all met the confidence interval-based criteria for negative QT prolongation potential. In the study in patients with COPD, 237 subjects were randomized and treated. GFF MDI 36/9.6, GP MDI 36, and FF MDI 9.6mug did not result in clinically meaningful changes from baseline in 24-h mean heart rate at Day 14 (primary endpoint) or in any of the other Holter monitoring endpoints at Day 14, compared with FF DPI 12mug. CONCLUSIONS: No clinically significant effects on cardiovascular safety occurred at therapeutic or supratherapeutic doses of GFF MDI, apart from a small and transient increase in heart rate following supratherapeutic dose of GFF MDI 144/38.4mug. Furthermore, there were no unexpected safety findings reported in either healthy volunteers or patients with COPD.

https://www.sciencedirect.com/science/article/pii/S1094553917302481?via%3Dihub

Foil, K. E., M. G. Blanton, et al. (2018). **"Sequencing Alpha-1 MZ Individuals Shows Frequent Biallelic Mutations."** Pulm Med **2018**: 2836389.

Rationale: Individuals with a single Z mutation in the SERPINA1 gene that codes for alpha-1 antitrypsin (AAT) are at increased risk for COPD if they have ever-smoked. Whether additional variants alter the risk for COPD in this population remains unknown. Objectives: To determine whether additional SERPINA1 variants impact COPD development in a previously identified MZ (carrier) cohort. Methods: Individuals with prior MZ results and AAT serum level <16uM were recruited from the Alpha-1 Coded Testing study and Alpha-1 Foundation Research Registry. Participants completed smoking history, demographics, and COPD Severity Score (Range 0-33) using REDCap data capture. At-home finger-stick tests were performed for next generation sequencing (NGS) at the Biocerna LLC laboratory. A genetic counselor reviewed records and interviewed participants with additional variants by NGS. A Wilcoxon Rank Sum test was used to assess correlation between variants and the COPD severity score. Results: A second SERPINA1 variant of known or possible significance was identified in 6 (5.8%) participants. One each of ZZ, SZ, FZ, ZSmunich, ZM2obernburg, and Z/c.922G>T genotypes were identified. ZZ, SZ, and FZ are known pathogenic genotypes. Smunich is a likely pathogenic variant. M2obernburg and c.922G>T are variants of uncertain significance. The ZZ individual was on augmentation therapy when determined MZ by protease inhibitor (Pi) phenotyping; the others had limited targeted genotyping with MZ results. These six participants with biallelic variants had positive COPD severity scores >1. Presence of additional variants was not significantly associated with COPD symptoms in this small sample size. Conclusions: Some diagnosed MZ individuals instead have biallelic variants. Larger studies are needed to determine COPD-risk liability of variants. Accurate diagnosis impacts medical management and familial risk assessment. Pi phenotyping can be confounded by augmentation therapy and liver transplantation. Because a normal M allele may be reported in the absence of tested mutation(s) in AATD genotyping, clinicians should consider clinical circumstances and laboratory methods when selecting and interpreting AATD tests. Advanced testing, including NGS, may be beneficial for select individuals with prior MZ results. Clinical Trial Registration: This study was registered with clinicaltrials.gov (NCT NCT02810327).

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6145046/pdf/PM2018-2836389.pdf

Furian, M., D. Flueck, et al. (2018). **"Exercise performance and symptoms in lowlanders with COPD ascending to moderate altitude: randomized trial."** Int J Chron Obstruct Pulmon Dis **13**: 3529-3538.

Objective: To evaluate the effects of altitude travel on exercise performance and symptoms in lowlanders with COPD. Design: Randomized crossover trial. Setting: University Hospital Zurich (490 m), research facility in mountain villages, Davos Clavadel (1,650 m) and Davos Jakobshorn (2,590 m). Participants: Forty COPD patients, Global Initiative for Obstructive Lung Disease (GOLD) grade 2-3, living below 800 m, median (quartiles) age 67 y (60; 69), forced expiratory volume in 1 second 57% predicted (49; 70). Intervention: Two-day sojourns at 490 m, 1,650 m, and 2,590 m in randomized order. Outcome measures: Six-minute walk distance (6MWD), cardiopulmonary exercise tests, symptoms, and other health effects. Results: At 490 m, days 1 and 2, median (quartiles) 6MWD were 558 m (477; 587) and 577 m (531; 629). At 2,590 m, days 1 and 2, mean changes in 6MWD from corresponding day at 490 m were -41 m (95% CI -51 to -31)

and -40 m (-53 to -27), n=40, P<0.05, both changes. At 1,650 m, day 1, 6MWD had changed by -22 m (-32 to -13), maximal oxygen uptake during bicycle exercise by -7% (-13 to 0) vs 490 m, P<0.05, both changes. At 490 m, 1,650 m, and 2,590 m, day 1, resting PaO2 were 9.0 (8.4; 9.4), 8.1 (7.5; 8.6), and 6.8 (6.3; 7.4) kPa, respectively, P<0.05 higher altitudes vs 490 m. While staying at higher altitudes, nine patients (24%) experienced symptoms or adverse health effects requiring oxygen therapy or relocation to lower altitude. Conclusion: During sojourns at 1,650 m and 2,590 m, lowlanders with moderate to severe COPD experienced a mild reduction in exercise performance and nearly one quarter required oxygen therapy or descent to lower altitude because of adverse health effects. The findings may help to counsel COPD patients planning altitude travel. Registration: ClinicalTrials.gov: NCT01875133.

https://www.dovepress.com/getfile.php?fileID=45659

Gascho, D., J. Heimer, et al. (2019). **"Relevant findings on postmortem CT and postmortem MRI in hanging, ligature strangulation and manual strangulation and their additional value compared to autopsy - a systematic review."** Forensic Sci Med Pathol **15**(1): 84-92.

Several articles have described the use of postmortem computed tomography (CT) and postmortem magnetic resonance imaging (MRI) in forensic medicine. Although access to CT scanners and, particularly, access to MRI scanners, is still limited for several institutes, both modalities are being applied with increasing frequency in the forensic setting. Certainly, postmortem imaging can provide crucial information prior to autopsy, and this method has even been considered a replacement to autopsy in selected cases by some forensic institutes. However, the role of postmortem imaging has to be assessed individually according to various injury categories and causes of death. Therefore, this systematic review focuses on the role of postmortem CT and MRI in cases of hanging and ligature and manual strangulation. We assessed the most common and relevant findings on CT and MRI in cases of strangulation and compared the detectability of these findings among CT, MRI and autopsy. According to the available literature, mainly fractures of the hyoid bone or thyroid cartilage were investigated using postmortem CT. Compared to autopsy, CT demonstrated equivalent results concerning the detection of these fractures. A currently described "gas bubble sign" may even facilitate the detection of laryngeal fractures on CT. Regarding the detection of hemorrhages in the soft tissue of the neck, postmortem MRI is more suitable for the detection of this "vital sign" in strangulation. Compared to autopsy, postmortem MRI is almost equally accurate for the detection of hemorrhages in the neck. Another "vital sign", gas within the soft tissue in hanging, which is hardly detectable by conventional autopsy, can be clearly depicted by CT and MRI. The number of cases of manual and ligature strangulation that were investigated by means of postmortem CT and MRI is much smaller than the number of cases of hanging that were investigated by CT and MRI. Likewise, judicial hanging and the hangman's fracture on postmortem imaging were described in only a few cases. Based on the results of this systematic review, we discuss the additional value of CT and MRI in fatal strangulation compared to autopsy, and we reflect on where the literature is currently lacking.

https://link.springer.com/article/10.1007%2Fs12024-018-0070-z

Gingo, M. R., M. Nouraie, et al. (2018). **"Decreased Lung Function and All-Cause Mortality in HIV-infected Individuals."** Ann Am Thorac Soc **15**(2): 192-199.

RATIONALE: Human immunodeficiency virus (HIV) infection is associated with pulmonary disease and worse lung function, but the relationship of lung function with survival in HIV is unknown. OBJECTIVES: To determine whether lung function is associated with all-cause mortality in HIV-infected individuals. METHODS: HIV-infected participants from cohorts in three locations underwent pre- and post-bronchodilator spirometry and determination of single-breath diffusing capacity of the lung for carbon monoxide (DlCO) in 2008-2009, computed tomographic (CT) scanning of the chest for quantitative emphysema and airway measures, and echocardiography for estimated left ventricular systolic and diastolic function and tricuspid regurgitant velocity. Bivariate analysis and multivariable Cox proportional hazards models were used to determine whether decreased lung function was independently associated with increased all-cause mortality. Models were adjusted for covariates including age, sex, body mass

index, smoking status, self-reported hepatitis C status, HIV viral levels, CD4(+) T-cell counts, hemoglobin, antiretroviral therapy, and illicit drug use. RESULTS: Overall, 396 HIV-infected participants underwent pulmonary function testing. Thirty-two participants (8%) died during a median follow-up period of 69 months. A post-bronchodilator FEV1-to-FVC ratio less than 0.7 (hazard ratio [HR], 2.47; 95% confidence interval [CI], 1.10-5.58) and a DlCO less than 60% (HR, 2.28; 95% CI, 1.08-4.82) were independently associated with worse mortality. Also, hepatitis C (HR, 2.68; 95% CI, 1.22-5.89) and baseline plasma HIV RNA level (HR per ln RNA copies/ml, 1.50; 95% CI, 1.22-1.86) were associated with mortality in HIV-infected participants. The only CT or echocardiographic measure associated with greater mortality in univariate analysis was greater wall thickness of medium-sized airways (HR for wall area percent, 1.08; 95% CI, 1.00-1.18; P = 0.051), but none of the CT or echocardiogram measures were associated with mortality in multivariable analysis. CONCLUSIONS: Airflow obstruction and impaired diffusing capacity appear to be associated with all-cause mortality in HIV-infected persons over an average of 6 years of follow-up. These data highlight the importance of lung dysfunction in HIV-infected persons and should be confirmed in larger cohorts and with extended follow-up periods. Clinical trial registered with www.clinicaltrials.gov (NCT00869544, NCT01326572).

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5822404/pdf/AnnalsATS.201606-492OC.pdf

Greulich, T., F. Rodriguez-Frias, et al. (2018). **"Real world evaluation of a novel lateral flow assay (AlphaKit(R) QuickScreen) for the detection of alpha-1-antitrypsin deficiency."** Respir Res **19**(1): 151.

BACKGROUND: Alpha-1-Antitrypsin (AAT) deficiency (AATD) is a hereditary disorder that manifests primarily as pulmonary emphysema and liver cirrhosis. The clinically most relevant mutation causing AATD is a single nucleotide polymorphism Glu342Lys (Z-mutation). Despite the recommendation to test every COPD patient, the condition remains severely underdiagnosed with a delay of several years between first symptoms and diagnosis. The Grifols' AlphaKit(R) QuickScreen is a novel qualitative point-of-care (POC) in vitro screening test developed for the detection of the Z AAT protein in capillary whole blood. The objective of this prospective, international, multi-center, diagnostic, interventional real-world study was to assess the performance of this device for the detection of AATD in test-naive COPD patients. METHODS: 1044 test-naive COPD patients were recruited from 9 centers in Spain and 10 centers in Germany, ranging from primary to tertiary care. To evaluate the performance of the test, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated compared with the gold standard (genotyping). RESULTS: Genotyping and phenotyping of all 1019 evaluable samples revealed 4.12% of patients as carriers of at least one Z-allele, while 0.29% carried the homozygous genotype Pi*ZZ. The evaluation of the test's ability to detect the PiZ protein yielded the following results: specificity 97.8%, sensitivity 73.8%, negative predictive value 98.9%, and positive predictive value 58.5%. All false negatives (n = 11) were heterozygote Pi*MZ samples. CONCLUSIONS: The tested device can be used as an appropriate tool to exclude AATD in primary care and in the overall COPD population, except in patients with a high a-priori- probability of AATD.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6090649/pdf/12931_2018_Article_826.pdf

Hashemian, S. M., E. Mortaz, et al. (2018). **"Budesonide facilitates weaning from mechanical ventilation in difficult-to-wean very severe COPD patients: Association with inflammatory mediators and cells."** J Crit Care **44**: 161-167.

INTRODUCTION: Mechanical ventilatory support is life-saving therapy for patients with respiratory failure in intensive care units (ICU) but is linked to ventilator-associated pneumonia and other nosocomial infections. Interventions that improve the efficiency of weaning from mechanical ventilation may improve patient outcomes. OBJECTIVE: To determine whether inhaled budesonide decreases time-to-weaning in COPD stage 4 difficult-to-wean patients and reduces the release of pro-inflammatory cytokines in ICU patients. MATERIALS AND METHODS: We recruited 55 difficult-to-wean COPD patients (Stage 4) within the ICU of the Masih Daneshvari Hospital. Subjects were randomly assigned to receive inhaled budesonide (0.5mg/day) or placebo (normal saline). Dynamic compliance and BAL cytokines

were measured. RESULTS: Budesonide significantly reduced the number of days on MV (days-to-weaning=4.6+/-1.6days) compared to that seen in the control group (7.2+/-2.7days, p=0.014). Dynamic compliance was significantly improved in the budesonide group on days 3 (p=0.018) and 5 (p=0.011) The levels of CXCL-8 and IL-6 diminished on days 3-5 after start of budesonide (p<0.05). CONCLUSION: In COPD patients on MV, nebulized budesonide was associated with reduced BAL CXCL8 and IL-6 levels and neutrophil numbers as well as an improvement in ventilatory mechanics and facilitated weaning.

https://spiral.imperial.ac.uk:8443/handle/10044/1/60287

Honeyford, K., E. Cecil, et al. (2018). **"The weekend effect: does hospital mortality differ by day of the week? A systematic review and meta-analysis."** BMC Health Serv Res **18**(1): 870.

BACKGROUND: The concept of a weekend effect, poorer outcomes for patients admitted to hospitals at the weekend is not new, but is the focus of debate in England. Many studies have been published which consider outcomes for patients on admitted at the weekend. This systematic review and meta-analysis aims to estimate the effect of weekend admission on mortality in UK hospitals. METHODS: This is a systematic review and meta-analysis of published studies on the weekend effect in UK hospitals. We used EMBASE, MEDLINE, HMIC, Cochrane, Web of Science and Scopus to search for relevant papers. We included systematic reviews, randomised controlled trials and observational studies) on patients admitted to hospital in the UK and published after 2001. Our outcome was death; studies reporting mortality were included. Reviewers identified studies, extracted data and assessed the quality of the evidence, independently and in duplicate. Discrepancy in assessment was considered by a third reviewer. All meta-analyses were performed using a random-effects meta-regression to incorporate the heterogeneity into the weighting. RESULTS: Forty five articles were included in the qualitative synthesis. 53% of the articles concluded that outcomes for patients either undergoing surgery or admitted at the weekend were worse. We included 39 in the meta-analysis which contributed 50 separate analyses. We found an overall effect of 1.07 [odds ratio (OR)] (95%CI:1.03-1.12), suggesting that patients admitted at the weekend had higher odds of mortality than those admitted during the week. Sub-group analyses suggest that the weekend effect remained when measures of case mix severity were included in the models (OR:1.06 95%CI:1.02-1.10), but that the weekend effect was not significant when clinical registry data was used (OR:1.03 95%CI: 0.98-1.09). Heterogeneity was high, which may affect generalisability. CONCLUSIONS: Despite high levels of heterogeneity, we found evidence of a weekend effect in the UK, even after accounting for severity of disease. Further work is required to examine other potential explanations for the "weekend effect" such as staffing levels and other organisational factors. TRIAL REGISTRATION: PROSPERO International Prospective Register of Systematic Reviews -registration number: CRD42016041225 .

http://spiral.imperial.ac.uk/bitstream/10044/1/66151/7/Honeyford_The%20weekend%20effect_BMC.pdf

Jung, C. Y., Y. H. Choe, et al. (2018). **"Use of serology and polymerase chain reaction to detect atypical respiratory pathogens during acute exacerbation of chronic obstructive pulmonary disease."** Korean J Intern Med **33**(5): 941-951.

BACKGROUND/AIMS: To use serological and multiplex polymerase chain reaction (PCR) assays to examine sputum samples from patients experiencing acute exacerbation of chronic obstructive pulmonary disease (AECOPD) for the presence of atypical pathogens, including Mycoplasma pneumoniae, Chlamydia pneumoniae, and Legionella pneumophila. METHODS: From September 2012 to February 2014, 341 patients with AECOPD attending outpatient clinics were enrolled as part of a randomized, double-blind, multicenter study. A commercial enzyme-linked immunosorbent assay was used to measure serum immunoglobulin M (IgM) and IgG antibody titers on the first day of the study and at 36 days post-enrollment. Multiplex PCR was used to test sputum samples for the presence of atypical pathogens. A urinary antigen test for L. pneumophila was performed on the first day. RESULTS: Nineteen patients (5.6%) showed serological evidence of acute infection with M. pneumoniae. Also, one and seven patients (2%) showed serological evidence of acute infection with C. pneumoniae and L. pneumophila,

respectively. All DNA samples were negative for M. pneumoniae, C. pneumoniae, and L. pneumophila according to PCR. Only one urine sample was positive for L. pneumophila antigen, but serologic evidence was lacking. CONCLUSION: Serological testing suggested that infection by atypical pathogens during AECOPD was relatively uncommon. In addition, PCR provided no direct evidence of infection by atypical pathogens. Thus, atypical pathogens may not be a major cause of AECOPD in South Korea.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6129643/pdf/kjim-2017-279.pdf

Kerwin, E. M., R. Tosiello, et al. (2018). **"Effect of background long-acting beta2-agonist therapy on the efficacy and safety of a novel, nebulized glycopyrrolate in subjects with moderate-to-very-severe COPD."** Int J Chron Obstruct Pulmon Dis **13**: 2917-2929.

Background: Phase III studies demonstrated efficacy and safety of nebulized glycopyrrolate inhalation solution (GLY) in subjects with COPD. Secondary analyses were performed to examine the effect of background long-acting beta2-agonist (LABA) use on the efficacy and safety of nebulized GLY. Methods: In two 12-week placebo-controlled studies (GOLDEN 3 and GOLDEN 4) and one 48-week, open-label active-controlled study (GOLDEN 5), a total of 2,379 subjects were stratified by background LABA use (LABA-yes: n=861; LABA-no: n=1,518) and randomized to placebo vs GLY 25 or 50 microg twice daily, or GLY 50 microg twice daily vs tiotropium (TIO) 18 microg once daily. Lung function, patient-reported outcomes, exacerbations, and safety were assessed. Results: Compared with placebo, pooled data from the 12-week studies showed significant improvements from baseline with GLY 25 and 50 microg across LABA subgroups in trough FEV1 (LABA-yes: 0.101 and 0.110 L; LABA-no: 0.092 and 0.101 L, respectively; P<0.001) and St George's Respiratory Questionnaire total score (SGRQ; LABA-yes: -2.957 and -3.888; LABA-no: -3.301 and -2.073, respectively; P<0.05). Incidence of treatment-emergent adverse events (TEAEs) was similar in LABA subgroups, and lower in GLY 25 microg vs placebo. In the 48-week active-controlled study, GLY and TIO both showed improvement from baseline across LABA subgroups in FEV1 (LABA-yes: 0.106 and 0.092 L; LABA-no: 0.096 and 0.096 L, respectively) and in SGRQ total score (LABA-yes: -5.190 and -3.094; LABA-no: -4.368 and -4.821, respectively). Incidence of TEAEs was similar between GLY and TIO, and across LABA subgroups. Exacerbation rates were similar across treatments and LABA subgroups, and cardiovascular events of special interest were more frequent in the LABA-no subgroup. Nebulized GLY, combined with LABA, did not generate any additional safety signals. Conclusion: Nebulized GLY demonstrated efficacy and was well tolerated up to 48 weeks in subjects with COPD with/without background LABA.

https://www.dovepress.com/getfile.php?fileID=44554

Kobylecki, C. J., S. Vedel-Krogh, et al. (2018). **"Plasma urate, lung function and chronic obstructive pulmonary disease: a Mendelian randomisation study in 114 979 individuals from the general population."** Thorax **73**(8): 748-757.

BACKGROUND: Urate is a strong antioxidant in plasma and may protect against lung function impairment. We tested the hypothesis that high plasma urate is causally associated with better lung function and low risk of respiratory symptoms and COPD. METHODS: We measured lung function and plasma urate in 114 979 individuals from the Copenhagen City Heart Study and the Copenhagen General Population Study and genotyped for SLC2A9 rs7442295 and ABCG2 rs2231142 variants, previously associated with high plasma urate, in 110 152 individuals. RESULTS: In the two studies combined, multivariable-adjusted 100 micromol/L higher plasma urate was associated with -1.54% (95% CI -1.67 to -1.40) lower FEV1 % predicted and -1.57% (95% CI -1.69 to -1.44) lower FVC % predicted observationally; the corresponding estimates for genetically determined 100 micromol/L higher plasma urate were -0.46% (95% CI -1.17 to 0.25) and -0.40% (95% CI -1.03 to 0.23). High plasma urate was also associated with higher risk of respiratory symptoms; however, genetically determined high plasma urate was not associated with respiratory symptoms. Finally, we identified 14 151 individuals with COPD and found ORs of 1.08 (95% CI 1.06 to 1.11) for COPD observationally and 1.01 (95% CI 0.88 to 1.15) genetically per 100 micromol/L higher plasma urate. CONCLUSION: High plasma urate was associated with worse lung function and

higher risk of respiratory symptoms and COPD in observational analyses; however, genetically high plasma urate was not associated with any of these outcomes. Thus, our data do not support a direct causal relationship.

https://thorax.bmj.com/content/thoraxjnl/73/8/748.full.pdf

Lin, H., Y. Lu, et al. (2019). **"Does chronic obstructive pulmonary disease relate to poor prognosis in patients with lung cancer?: A meta-analysis."** Medicine (Baltimore) **98**(11): e14837.

BACKGROUND: Nowadays, there is growing recognition that chronic obstructive pulmonary disease (COPD) may have influence on lung cancer. However, coexisted COPD related to prognosis of lung cancer is still elusive. We conducted this meta-analysis to examine the association between COPD and 5-year overall survival (OS) and postoperative pulmonary complications of patients with lung cancer. METHODS: A comprehensive computer-based online search was conducted using PubMed, Embase, Medline, and the Cochrane Library for articles published before September 30, 2017. We identified 29 eligible studies, which included 70,111 patients in the related literature. RESULTS: Twenty-two of the 29 studies provided hazard ratio for OS (1.18, 95% confidence interval: 1.11-1.25; P < .001), it suggested that the presence of COPD indicated poor survival for the patients with lung cancer. In subgroup analysis, the relationship between COPD and OS occurrence remained statistically prominent in the subgroups stratified by study designs, COPD diagnosis timing, lung cancer surgery, cancer stage, and origins of patients. The presence of COPD increased the risk of bronchopleural fistula, pneumonia, prolonged air leakage, and prolonged mechanical ventilation. CONCLUSIONS: The present meta-analysis suggested that coexisting COPD is associated with poor survival outcomes in patients with lung cancer and higher rates of postoperative pulmonary complications.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6426564/pdf/medi-98-e14837.pdf

Lipworth, B. J., D. J. Collier, et al. (2018). **"Improved lung function and patient-reported outcomes with co-suspension delivery technology glycopyrrolate/formoterol fumarate metered dose inhaler in COPD: a randomized Phase III study conducted in Asia, Europe, and the USA."** Int J Chron Obstruct Pulmon Dis **13**: 2969-2984.

Background: COPD is a major global cause of mortality and morbidity. PINNACLE-4 evaluated the efficacy and safety of GFF MDI (glycopyrrolate/formoterol fumarate metered dose inhaler) in patients from Asia, Europe, and the USA with moderate-to-very severe COPD. Methods: In this double-blind, placebo-controlled, Phase III study, patients were randomized to treatment with GFF MDI 18/9.6 mug, glycopyrrolate (GP) MDI 18 mug, formoterol fumarate (FF) MDI 9.6 mug, or placebo MDI (all twice daily) for 24 weeks. Lung function, patient-reported outcomes (symptoms and health-related quality of life), and safety were assessed. Results: Of the 1,756 patients randomized, 1,740 patients were included in the intent-to-treat population (mean age 64.2 years, 74.1% male, and 40.2% Asian). GFF MDI significantly improved morning predose trough FEV1 at Week 24 (primary endpoint) vs placebo MDI, GP MDI, and FF MDI (least squares mean differences: 165, 59, and 72 mL, respectively; all P<0.0001). GFF MDI also significantly improved other lung function endpoints vs placebo MDI, GP MDI, and FF MDI and patient-reported outcomes vs placebo MDI and GP MDI. A larger proportion of patients treated with GFF MDI achieved the minimum clinically important difference in Transition Dyspnea Index score vs GP MDI and placebo MDI and in St George's Respiratory Questionnaire score vs placebo MDI. Adverse event rates were similar across treatment groups. Conclusion: These results demonstrated the efficacy of GFF MDI in patients with moderate-to-very severe COPD. GFF MDI was well tolerated, with a safety profile commensurate with long-acting bronchodilators.

https://www.dovepress.com/getfile.php?fileID=44753

Liu, H., M. Song, et al. (2019). **"Group singing improves depression and life quality in patients with stable COPD: a randomized community-based trial in China."** Qual Life Res **28**(3): 725-735.
PURPOSE: To explore the effects of group singing therapy on depression symptoms and quality of life of patients with stable chronic obstructive pulmonary disease (COPD). METHODS: Patients with COPD were randomly allocated to intervention (n = 30) and control groups (n = 30). The intervention group received group singing therapy once a week for 24 sessions along with routine health education, whereas the control group only received the routine health education. All patients were administered the Hospital Anxiety and Depression Scale depression subscale (HADS-D) and the Clinical COPD Questionnaire (CCQ). Data were collected at baseline and at 1, 3, and 6 months. RESULTS: Fifty-six participants completed this trial. Significant between-group differences were observed with respect to the main effect of group and time as well as the effect of group x time interaction on HADS-D score. The HADS-D score was significantly improved 1, 3, 6 months after group singing therapy. The CCQ total scores were significantly different between the two groups with respect to the main effect of group and time and the group x time interaction effect. Significantly better CCQ was detected in the intervention group at 3 months and 6 months after intervention. CONCLUSIONS: Group singing therapy reduces depressive symptoms and improves the quality of life of patients with stable COPD.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6394522/pdf/11136_2018_Article_2063.pdf

Ma, J., J. Zheng, et al. (2018). **"Effects of YuPingFeng granules on acute exacerbations of COPD: a randomized, placebo-controlled study."** Int J Chron Obstruct Pulmon Dis **13**: 3107-3114.
Purpose: Recurrence of acute exacerbations has a major impact on patients with COPD. Therefore, effective prevention and treatment of exacerbation is crucial in the management of COPD, especially for patients with moderate to severe disease. This study evaluated the effectiveness of YuPingFeng granule administration in preventing exacerbation and improving symptom score, as well as its long-term (1 year) safety profile, in patients with COPD. Patients and methods: This was a randomized, double-blind, parallel, placebo-controlled study of 240 patients from eight centers in China. Participants were eligible if they had mild to severe COPD as defined by Global Initiative for Chronic Obstructive Lung Disease, had a history of at least two COPD exacerbations or one hospitalization within the previous year, and had remained clinically stable for over 4 weeks before the study. They were randomly assigned to receive 5 g of YuPingFeng or placebo, three times per day, for 1 year. The primary end point was the exacerbation rate over 1 year, and the analysis was by intention to treat. Secondary end points included symptom score, which was assessed by COPD assessment test (CAT) score and safety profiles. This trial was registered in the Chinese Clinical Trial Registry (http://www.chictr.org.cn; registration number: ChiCTR-IPR-15007023). Results: The YuPingFeng group had a significantly lower exacerbation rate than the placebo group (1.15 vs 1.55; risk ratio=0.677 [95% CI 0.531-0.863]; P=0.002) and a significantly reduced risk of second exacerbation (95% CI 0.326-0.772; P=0.002). After treatment, the mean change in the CAT score in the YuPingFeng group (-4.41+/-7.01) differed significantly from that in the placebo group (-2.49+/-5.31; P=0.001). YuPingFeng was well tolerated. Conclusion: YuPingFeng granules can be considered as a treatment option for COPD; this treatment prevents acute exacerbations of COPD and has a good safety profile.

https://www.dovepress.com/getfile.php?fileID=44942

Maqsood, U., T. N. Ho, et al. (2019). **"Once daily long-acting beta2-agonists and long-acting muscarinic antagonists in a combined inhaler versus placebo for chronic obstructive pulmonary disease."** Cochrane Database Syst Rev **3**: Cd012930.
BACKGROUND: Chronic obstructive pulmonary disease (COPD) is a respiratory condition causing accumulation of mucus in the airways, cough, and breathlessness; the disease is progressive and is the fourth most common cause of death worldwide. Current treatment strategies for COPD are multi-modal and aim to reduce morbidity and mortality and increase patients' quality of life by slowing disease progression and

preventing exacerbations. Fixed-dose combinations (FDCs) of a long-acting beta2-agonist (LABA) plus a long-acting muscarinic antagonist (LAMA) delivered via a single inhaler are approved by regulatory authorities in the USA, Europe, and Japan for the treatment of COPD. Several LABA/LAMA FDCs are available and recent meta-analyses have clarified their utility versus their mono-components in COPD. Evaluation of the efficacy and safety of once-daily LABA/LAMA FDCs versus placebo will facilitate the comparison of different FDCs in future network meta-analyses. OBJECTIVES: We assessed the evidence for once-daily LABA/LAMA combinations (delivered in a single inhaler) versus placebo on clinically meaningful outcomes in patients with stable COPD. SEARCH METHODS: We identified trials from Cochrane Airways' Specialised Register (CASR) and also conducted a search of the US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov) and the World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch). We searched CASR and trial registries from their inception to 3 December 2018; we imposed no restriction on language of publication. SELECTION CRITERIA: We included parallel-group and cross-over randomised controlled trials (RCTs) comparing once-daily LABA/LAMA FDC versus placebo. We included studies reported as full-text, those published as abstract only, and unpublished data. We excluded very short-term trials with a duration of less than 3 weeks. We included adults (>/= 40 years old) with a diagnosis of stable COPD. We included studies that allowed participants to continue using their ICS during the trial as long as the ICS was not part of the randomised treatment. DATA COLLECTION AND ANALYSIS: Two review authors independently screened the search results to determine included studies, extracted data on prespecified outcomes of interest, and assessed the risk of bias of included studies; we resolved disagreements by discussion with a third review author. Where possible, we used a random-effects model to meta-analyse extracted data. We rated all outcomes using the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) system and presented results in 'Summary of findings' tables. MAIN RESULTS: We identified and included 22 RCTs randomly assigning 8641 people with COPD to either once-daily LABA/LAMA FDC (6252 participants) or placebo (3819 participants); nine studies had a cross-over design. Studies had a duration of between three and 52 weeks (median 12 weeks). The mean age of participants across the included studies ranged from 59 to 65 years and in 21 of 22 studies, participants had GOLD stage II or III COPD. Concomitant inhaled corticosteroid (ICS) use was permitted in all of the included studies (where stated); across the included studies, between 28% to 58% of participants were using ICS at baseline. Six studies evaluated the once-daily combination of IND/GLY (110/50 mug), seven studies evaluated TIO/OLO (2.5/5 or 5/5 mug), eight studies evaluated UMEC/VI (62.5/5, 125/25 or 500/25 mug) and one study evaluated ACD/FOR (200/6, 200/12 or 200/18 mug); all LABA/LAMA combinations were compared with placebo.The risk of bias was generally considered to be low or unknown (insufficient detail provided), with only one study per domain considered to have a high risk of bias except for the domain 'other bias' which was determined to be at high risk of bias in four studies (in three studies, disease severity was greater at baseline in participants receiving LABA/LAMA compared with participants receiving placebo, which would be expected to shift the treatment effect in favour of placebo).Compared to the placebo, the pooled results for the primary outcomes for the once-daily LABA/LAMA arm were as follows: all-cause mortality, OR 1.88 (95% CI 0.81 to 4.36, low-certainty evidence); all-cause serious adverse events (SAEs), OR 1.06 (95% CI 0.88 to 1.28, high-certainty evidence); acute exacerbations of COPD (AECOPD), OR 0.53 (95% CI 0.36 to 0.78, moderate-certainty evidence); adjusted St George's Respiratory Questionnaire (SGRQ) score, MD -4.08 (95% CI -4.80 to -3.36, high-certainty evidence); proportion of SGRQ responders, OR 1.75 (95% CI 1.54 to 1.99). Compared with placebo, the pooled results for the secondary outcomes for the once-daily LABA/LAMA arm were as follows: adjusted trough forced expiratory volume in one second (FEV1), MD 0.20 L (95% CI 0.19 to 0.21, moderate-certainty evidence); adjusted peak FEV1, MD 0.31 L (95% CI 0.29 to 0.32, moderate-certainty evidence); and all-cause AEs, OR 0.95 (95% CI 0.86 to 1.04; high-certainty evidence). No studies reported data for the 6-minute walk test. The results were generally consistent across subgroups for different LABA/LAMA combinations and doses. AUTHORS' CONCLUSIONS: Compared with placebo, once-daily LABA/LAMA (either IND/GLY, UMEC/VI or TIO/OLO) via a combination inhaler is associated with a clinically significant improvement in lung function and health-related quality of life in patients with mild-to-moderate COPD; UMEC/VI appears to reduce the rate of exacerbations in this population. These conclusions are supported by moderate or high certainty evidence based on studies with an observation period of up to one year.

Mariotti, F., M. Govoni, et al. (2018). **"Safety, tolerability, and pharmacokinetics of single and repeat ascending doses of CHF6001, a novel inhaled phosphodiesterase-4 inhibitor: two randomized trials in healthy volunteers."** Int J Chron Obstruct Pulmon Dis **13**: 3399-3410.

Purpose: The purpose of this study was to evaluate safety, tolerability, and pharmacokinetics (PK) of CHF6001, an inhaled phosphodiesterase-4 inhibitor. Materials and methods: Two healthy volunteer, randomized, double-blind, placebo-controlled studies were conducted. In each, Part 1 evaluated single ascending doses, with PK sampling up to 48 hours post-dose; Part 2 evaluated multiple ascending doses (Study 1, 7 days; Study 2, 14 days), with PK sampling up to 24 hours post-dose on first and last day of each period. In Study 1, treatments were administered via single-dose dry-powder inhaler (SDDPI; Aerolizer): Part 1, 20, 100, 200, 400, 800, 1,600, and 2,000 microg or placebo; Part 2, 100, 300, 600, 1,200, and 1,600 microg or placebo once daily (OD). In Study 2, treatments were administered via multi-dose dry-powder inhaler (MDDPI; NEXThaler): Part 1, 2,400, 4,000, and 4,800 microg or placebo; Part 2, 1,200, 2,000, or 2,400 microg twice daily (BID) or placebo. Modeling and simulation then compared OD and BID dosing via MDDPI. Results: There was a clear correlation between CHF6001 dose and plasma concentration, following single and multiple doses and using SDDPI and MDDPI. CHF6001 plasma concentration area under the curve (AUC) was dose proportional, with steady state slopes of the fitted line of 0.95 (90% CI: 0.86, 1.04) for AUC0-24 h in Study 1, and 0.85 (90% CI: 0.38, 1.32) for AUC0-12 h in Study 2. Bioavailability was30% higher with MDDPI than SDDPI. The PK simulation confirmed dose proportionality; the same total daily dose OD or BID via MDDPI resulted in similar 24 hours exposure, with BID dosing providing smaller fluctuation and lower maximum concentration. CHF6001 was well tolerated with no relationship between dose and adverse events. Conclusion: CHF6001 demonstrated a good safety profile. There was a clear dose proportionality for systemic exposure, with higher bioavailability via MDDPI, suggesting that the MDDPI provides better pulmonary drug deposition. BID dosing was associated with a better exposure profile.

https://www.dovepress.com/getfile.php?fileID=45458

Nair, A., G. K. Alaparthi, et al. (2019). **"Comparison of Diaphragmatic Stretch Technique and Manual Diaphragm Release Technique on Diaphragmatic Excursion in Chronic Obstructive Pulmonary Disease: A Randomized Crossover Trial."** Pulm Med **2019**: 6364376.

Background: Chronic Obstructive Pulmonary Disease (COPD) impairs the function of the diaphragm by placing it at a mechanical disadvantage, shortening its operating length and changing the mechanical linkage between its various parts. This makes the diaphragm's contraction less effective in raising and expanding the lower rib cage, thereby increasing the work of breathing and reducing the functional capacity. Aim of the Study: To compare the effects of diaphragmatic stretch and manual diaphragm release technique on diaphragmatic excursion in patients with COPD. Materials and Methods: This randomised crossover trial included 20 clinically stable patients with mild and moderate COPD classified according to the GOLD criteria. The patients were allocated to group A or group B by block randomization done by primary investigator. The information about the technique was concealed in a sealed opaque envelope and revealed to the patients only after allocation of groups. After taking the demographic data and baseline values of the outcome measures (diaphragm mobility by ultrasonography performed by an experienced radiologist and chest expansion by inch tape performed by the therapist), group A subjects underwent the diaphragmatic stretch technique and the group B subjects underwent the manual diaphragm release technique. Both the interventions were performed in 2 sets of 10 deep breaths with 1-minute interval between the sets. The two outcome variables were recorded immediately after the intervention. A wash-out period of 3 hours was maintained to neutralize the effect of given intervention. Later the patients of group A and group B were crossed over to the other group. Results: In the diaphragmatic stretch technique, there was a statistically significant improvement in the diaphragmatic excursion before and after the treatment. On the right side, p=0.00 and p=0.003 in the midclavicular line and midaxillary line. On the left side, p=0.004 and p=0.312 in the midclavicular and midaxillary line. In manual diaphragm release technique, there was a statistically significant improvement before and after the treatment. On the right side, p=0.000 and p=0.000 in the midclavicular line and midaxillary line. On the left side, p=0.002 and p=0.000 in the midclavicular line and midaxillary line. There was no statistically significant

difference in diaphragmatic excursion in the comparison of the postintervention values of both techniques. Conclusion: The diaphragmatic stretch technique and manual diaphragm release technique can be safely recommended for patients with clinically stable COPD to improve diaphragmatic excursion.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6335861/pdf/PM2019-6364376.pdf

Nilsen, K., K. Gove, et al. (2018). **"Comparison of two methods of determining lung de-recruitment, using the forced oscillation technique."** Eur J Appl Physiol **118**(10): 2213-2224.

Airway closure has proved to be important in a number of respiratory diseases and may be the primary functional defect in asthma. A surrogate measure of closing volume can be identified using the forced oscillation technique (FOT), by performing a deflation maneuver and examining the resultant reactance (Xrs) lung volume relationship. This study aims to determine if a slow vital capacity maneuver can be used instead of this deflation maneuver and compare it to existing more complex techniques. Three subject groups were included in the study; healthy (n = 29), asthmatic (n = 18), and COPD (n = 10) for a total of 57 subjects. Reactance lung volume curves were generated via FOT recordings during two different breathing manoeuvres (both pre and post bronchodilator). The correlation and agreement between surrogate closing volume (Volcrit) and reactance (Xrscrit) at this volume was analysed. The changes in Volcrit and Xrscrit pre and post bronchodilator were also analysed. Across all three subject groups, the two different measures of Volcrit were shown to be statistically equivalent ($p > 0.05$) and demonstrated a strong fit to the data ($R(2) = 0.49, 0.78, 0.59$, for asthmatic, COPD and healthy subject groups, respectively). A bias was evident between the two measurements of Xrscrit with statistically different means ($p < 0.05$). However, the two measurements of Xrscrit displayed the same trends. In conclusion, we have developed an alternative technique for measuring airway closure from FOT recordings. The technique delivers equivalent and possibly more sensitive results to previous methods while being simple and easily performed by the patient.

https://link.springer.com/article/10.1007%2Fs00421-018-3949-1

Pascual-Gonzalez, Y., M. Lopez-Sanchez, et al. (2018). **"Defining the role of neutrophil-to-lymphocyte ratio in COPD: a systematic literature review."** Int J Chron Obstruct Pulmon Dis **13**: 3651-3662.

COPD is characterized by a pulmonary and systemic inflammatory process. Several authors have reported the elevation of multiple inflammatory markers in patients with COPD; however, their use in routine clinical practice has limitations. The neutrophil-to-lymphocyte ratio (NLR) is a useful and cost-effective inflammatory marker derived from routine complete blood count. We performed a systematic literature review using the PRISMA statement. Twenty-two articles were included, recruiting 7,601 COPD patients and 784 healthy controls. Compared with controls, COPD patients had significantly higher NLR values. We found a significant correlation between the NLR and clinical/functional parameters (FEV1, mMRC, and BODE index) in COPD patients. Elevation of the NLR is associated with the diagnosis of acute exacerbation of COPD (pooled data propose a cut-off value of 3.34 with a median sensitivity, specificity, and area under the curve of 80%, 86%, and 0.86, respectively). Additionally, increased NLR is also associated with the diagnosis of a bacterial infection in exacerbated patients, with a cut-off value of 7.30, although with a low sensitivity and specificity. The NLR is an independent predictor of in-hospital and late mortality after exacerbation. In conclusion, the NLR could be a useful marker in COPD patients; however, further studies are needed to better identify the clinical value of the NLR.

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Patout, M., G. Arbane, et al. (2019). **"Polysomnography versus limited respiratory monitoring and nurse-led titration to optimise non-invasive ventilation set-up: a pilot randomised clinical trial."** Thorax **74**(1): 83-86.

Polysomnography (PSG) is recommended for non-invasive ventilation (NIV) set-up in patients with chronic respiratory failure. In this pilot randomised clinical trial, we compared the physiological effectiveness of NIV set-up guided by PSG to limited respiratory monitoring (LRM) and nurse-led titration in patients with COPD-obstructive sleep apnoea (OSA) overlap. The principal outcome of interest was change in daytime arterial partial pressure of carbon dioxide (PaCO2) at 3 months. Fourteen patients with daytime PaCO2 >6 kPa and body mass index >30 kg/m(2) were recruited. At 3 months, PaCO2 was reduced by -0.88 kPa (95% CI -1.52 to -0.24 kPa) in the LRM group and by -0.36 kPa (95% CI -0.96 to 0.24 kPa) in the PSG group. These pilot data provide support to undertake a clinical trial investigating the clinical effectiveness of attended limited respiratory monitoring and PSG to establish NIV in patients with COPD-OSA overlap. TRIAL NUMBER: Results, NCT02444806.

https://thorax.bmj.com/content/74/1/83.long

Pavasini, R., F. Vieceli Dalla Sega, et al. (2017). **"Endothelial dysfunction and increased platelet reactivity in patients with acute coronary syndrome and undiagnosed COPD: insights into the SCAP trial."** Eur Respir J **50**(4)

https://erj.ersjournals.com/content/erj/50/4/1701183.full.pdf

Perotin, J. M., S. Leroy, et al. (2018). **"Endobronchial coil treatment in severe emphysema patients with alpha-1 antitrypsin deficiency."** Int J Chron Obstruct Pulmon Dis **13**: 3645-3649.

Endobronchial coil treatment (ECT) is a minimally invasive procedure developed for palliative care of patients with severe emphysema. ECT has demonstrated a decrease in hyperinflation, an improvement in quality of life, and an acceptable safety profile in randomized controlled trials (RCTs). Because alpha-1 antitrypsin deficiency (AATD) is a classical exclusion criterion in RCTs, there is no available data for ECT in AATD. In this post hoc analysis of the REVOLENS study (Reduction volumique endobronchique par spirales; ClinicalTrials.gov Identifier: NCT01822795), a multicenter 1:1 RCT which compared bilateral ECT with usual care in severe emphysema, we analyzed the efficacy and safety results at 1 year in six patients with AATD (five males, one female; mean age: 52+/-9 years) who underwent ECT. A significant decrease in hyperinflation (0.35 L decrease in residual volume [RV]) was observed in four out of six patients at 6 months and three out of six patients at 12 months, and an improvement in quality of life (improvement of 4 points in the St George's Respiratory Questionnaire [SGRQ]) was observed in four out of six patients at both 6 and 12 months. Efficacy results at 6 and 12 months from the six AATD patients were compared with 84 non-AATD patients who underwent ECT, and no statistically significant differences were found for FEV1, RV, 6MWT score and SGRQ score. Respiratory-related serious adverse event was limited to pneumonia in one AATD patient at 1 year post-ECT. This post hoc study suggests that AATD patients may have similar efficacy and safety outcomes at 1 year as non-AATD patients. Because of the paucity of available data, appropriately powered studies are needed to determine the effects of ECT in AATD.

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Pollok, J., J. E. van Agteren, et al. (2019). **"Psychological therapies for the treatment of depression in chronic obstructive pulmonary disease."** Cochrane Database Syst Rev **3**: Cd012347.

BACKGROUND: Chronic obstructive pulmonary disease (COPD) has been recognised as a global health concern, and one of the leading causes of morbidity and mortality worldwide. Projections of the World Health Organization (WHO) indicate that prevalence rates of COPD continue to increase, and by 2030, it will become the world's third leading cause of death. Depression is a major comorbidity amongst patients

with COPD, with an estimate prevalence of up to 80% in severe stages of COPD. Prevalence studies show that patients who have COPD are four times as likely to develop depression compared to those without COPD. Regrettably, they rarely receive appropriate treatment for COPD-related depression. Available findings from trials indicate that untreated depression is associated with worse compliance with medical treatment, poor quality of life, increased mortality rates, increased hospital admissions and readmissions, prolonged length of hospital stay, and subsequently, increased costs to the healthcare system. Given the burden and high prevalence of untreated depression, it is important to evaluate and update existing experimental evidence using rigorous methodology, and to identify effective psychological therapies for patients with COPD-related depression. OBJECTIVES: To assess the effectiveness of psychological therapies for the treatment of depression in patients with chronic obstructive pulmonary disease. SEARCH METHODS: We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (2018, Issue 11), and Ovid MEDLINE, Embase and PsycINFO from June 2016 to 26 November 2018. Previously these databases were searched via the Cochrane Airways and Common Mental Disorders Groups' Specialised Trials Registers (all years to June 2016). We searched ClinicalTrials.gov, the ISRCTN registry, and the World Health Organization International Clinical Trials Registry Platform (ICTRP) to 26 November 2018 to identify unpublished or ongoing trials. Additionally, the grey literature databases and the reference lists of studies initially identified for full-text screening were also searched. SELECTION CRITERIA: Eligible for inclusion were randomised controlled trials that compared the use of psychological therapies with either no intervention, education, or combined with a co-intervention and compared with the same co-intervention in a population of patients with COPD whose depressive symptoms were measured before or at baseline assessment. DATA COLLECTION AND ANALYSIS: Two review authors independently assessed the titles and abstracts identified by the search to determine which studies satisfied the inclusion criteria. We assessed two primary outcomes: depressive symptoms and adverse events; and the following secondary outcomes: quality of life, dyspnoea, forced expiratory volume in one second (FEV1), exercise tolerance, hospital length of stay or readmission rate, and cost-effectiveness. Potentially eligible full-text articles were also independently assessed by two review authors. A PRISMA flow diagram was prepared to demonstrate the decision process in detail. We used the Cochrane 'Risk of bias' evaluation tool to examine the risk of bias, and assessed the quality of evidence using the GRADE framework. All outcomes were continuous, therefore, we calculated the pooled standardised mean difference (SMD) or mean difference (MD) with a corresponding 95% confidence interval (CI). We used a random-effects model to calculate treatment effects. MAIN RESULTS: The findings are based on 13 randomised controlled trials (RCTs), with a total of 1500 participants. In some of the included studies, the investigators did not recruit participants with clinically confirmed depression but applied screening criteria after randomisation. Hence, across the studies, baseline scores for depressive symptoms varied from no symptoms to severe depression. The severity of COPD across the studies was moderate to severe.Primary outcomesThere was a small effect showing the effectiveness of psychological therapies in improving depressive symptoms when compared to no intervention (SMD 0.19, 95% CI 0.05 to 0.33; P = 0.009; 6 studies, 764 participants), or to education (SMD 0.23, 95% CI 0.06 to 0.41; P = 0.010; 3 studies, 507 participants).Two studies compared psychological therapies plus a co-intervention versus the co-intervention alone (i.e. pulmonary rehabilitation (PR)). The results suggest that a psychological therapy combined with a PR programme can reduce depressive symptoms more than a PR programme alone (SMD 0.37, 95% CI -0.00 to 0.74; P = 0.05; 2 studies, 112 participants).We rated the quality of evidence as very low. Owing to the nature of psychological therapies, blinding of participants, personnel, and outcome assessment was a concern.None of the included studies measured adverse events.Secondary outcomesQuality of life was measured in four studies in the comparison with no intervention, and in three studies in the comparison with education. We found inconclusive results for improving quality of life. However, when we pooled data from two studies using the same measure, the result suggested that psychological therapy improved quality of life better than no intervention. One study measured hospital admission rates and cost-effectiveness and showed significant reductions in the intervention group compared to the education group. We rated the quality of evidence as very low for the secondary outcomes. AUTHORS' CONCLUSIONS: The findings from this review indicate that psychological therapies (using a CBT-based approach) may be effective for treating COPD-related depression, but the evidence is limited. Depressive symptoms improved more in the intervention groups compared to: 1) no intervention (attention placebo or standard care), 2) educational interventions, and 3) a co-intervention (pulmonary rehabilitation). However, the effect sizes were small and quality of the evidence very low due to clinical heterogeneity and risk of bias. This means that more experimental studies with larger numbers of participants are needed, to confirm the potential beneficial effects of therapies with a CBT approach for COPD-related depression.New trials should also address the gap in knowledge related to limited

data on adverse effects, and the secondary outcomes of quality of life, dyspnoea, forced expiratory volume in one second (FEV1), exercise tolerance, hospital length of stay and frequency of readmissions, and cost-effectiveness. Also, new research studies need to adhere to robust methodology to produce higher quality evidence.

Rogliani, P., L. Calzetta, et al. (2018). **"LABA/LAMA fixed-dose combinations in patients with COPD: a systematic review."** Int J Chron Obstruct Pulmon Dis **13**: 3115-3130.

Objectives: The aim of this study was to assess the current evidence for long-acting beta2-agonist (LABA)/long-acting muscarinic antagonist (LAMA) fixed-dose combinations (FDCs) in the treatment of COPD. Materials and methods: A systematic literature search of randomized controlled trials published in English up to September 2017 of LABA/LAMA FDCs vs LABA or LAMA or LABA/inhaled corticosteroid (ICS) FDCs in COPD patients was performed using PubMed, Embase, Scopus, and Google Scholar. Outcomes including forced expiratory volume in 1 second (FEV1), Transition Dyspnea Index (TDI) scores, St George's Respiratory Questionnaire (SGRQ) scores, exacerbations, exercise tolerance (endurance time [ET]), inspiratory capacity (IC), and rescue medication use were evaluated. Results: In total, 27 studies were included in the review. LABA/LAMA FDCs significantly improved lung function (FEV1) at 12 weeks compared with LABA or LAMA or LABA/ICS. These effects were maintained over time. Significant improvements with LABA/LAMA FDCs vs each evaluated comparator were also observed in TDI and SGRQ scores, even if significant differences between different LABA/LAMA FDCs were detected. Only the LABA/LAMA FDC indacaterol/glycopyrronium has shown superiority vs LAMA and LABA/ICS for reducing exacerbation rates, while olodaterol/tiotropium and indacaterol/glycopyrronium have been shown to improve ET and IC vs the active comparators. Rescue medication use was significantly reduced by LABA/LAMA FDCs vs the evaluated comparators. LABA/LAMA FDCs were safe, with no increase in the risk of adverse events with LABA/LAMA FDCs vs the monocomponents. Conclusion: Evidence supporting the efficacy of LABA/LAMA FDCs for COPD is heterogeneous, particularly for TDI and SGRQ scores, exacerbation rates, ET, and IC. So far, indacaterol/glycopyrronium is the LABA/LAMA FDC that has the strongest evidence for superiority vs LABA, LAMA, and LABA/ICS FDCs across the evaluated outcomes. LABA/LAMA FDCs were safe; however, more data should be collected in a real-world setting to confirm their safety.

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Santos Pellegrini, J. A., M. M. Boniatti, et al. (2018). **"Pressure-support ventilation or T-piece spontaneous breathing trials for patients with chronic obstructive pulmonary disease - A randomized controlled trial."** PLoS One **13**(8): e0202404.

BACKGROUND: Little is known about the best strategy for weaning patients with chronic obstructive pulmonary disease (COPD) from mechanical ventilation. Spontaneous breathing trials (SBT) using a T-piece or pressure-support ventilation (PSV) have a central role in this process. Our aim was to compare T-piece and PSV SBTs according to the duration of mechanical ventilation (MV) in patients with COPD. METHODS: Patients with COPD who had at least 48 hours of invasive MV support were randomized to 30 minutes of T-piece or PSV at 10 cm H2O after being considered able to undergo a SBT. All patients were preemptively connected to non-invasive ventilation after extubation. Tracheostomized patients were excluded. The primary outcome was total invasive MV duration. Time to liberation from MV was assessed as secondary outcome. RESULTS: Between 2012 and 2016, 190 patients were randomized to T-piece (99) or PSV (91) groups. Extubation at first SBT was achieved in 78% of patients. The mean total MV duration was 10.82 +/- 9.1 days for the T-piece group and 7.31 +/- 4.9 days for the PSV group ($p < 0.001$); however, the pre-SBT duration also differed (7.35 +/- 3.9 and 5.84 +/- 3.3, respectively; $p = 0.002$). The time to liberation was 8.36 +/- 11.04 days for the T-piece group and 4.06 +/- 4.94 for the PSV group (univariate mean ratio = 2.06 [1.29-3.27], $p = 0.003$) for the subgroup of patients with difficult or prolonged weaning. The study group was independently associated with the time to liberation in this

subgroup. CONCLUSIONS: The SBT technique did not influence MV duration for patients with COPD. For the difficult/prolonged weaning subgroup, the T-piece may be associated with a longer time to liberation, although this should be clarified by further studies. TRIAL REGISTRATION: ClinicalTrials.gov NCT01464567, at November 3, 2011.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6107186/pdf/pone.0202404.pdf

Schuler, M., M. Wittmann, et al. (2018). **"The interrelations among aspects of dyspnea and symptoms of depression in COPD patients - a network analysis."** J Affect Disord **240**: 33-40.

BACKGROUND: Depression is a frequent comorbidity in COPD. COPD symptoms such as dyspnea may play an important role in the causal relationship between COPD and depression. We investigated the interrelations among different aspects of dyspnea and other COPD parameters and symptoms of depression in COPD patients. METHODS: This is a secondary analysis of N=590 COPD patients. At the beginning (T0) and the end (T1) of a 3-week inpatient pulmonary rehabilitation, dyspnea aspects intensity (BORG scale), frequency (2 CCQ items), functioning (CCQ-function) and cognitive/emotional response (2 SGRQ items) as well as cough (2 CCQ items), functional capacity (6MWD), lung function (FEV1) and symptoms of depression (PHQ-9) were assessed. Regression analyses with PHQ-9 sum score as dependent variable as well as network analysis using PHQ-9 single items were performed. Structural invariance over time was examined. RESULTS: Dyspnea frequency, function, and cognitive/emotional response showed conditional independent relationships with PHQ-9 sum score. Network analysis showed that dyspnea frequency and dyspnea functioning were primarily associated with somatic depression symptoms (for example, sleep problems, loss of energy), while cognitive/emotional response was primarily related to cognitive-affective depression symptoms (for example, feeling down/depressed/hopeless). Regression parameters, network structure and network global strength did not differ between T0 and T1. LIMITATIONS: Models are based on between-person relationships. Results should be confirmed using time-series data. CONCLUSIONS: Dyspnea and depression seem to be interrelated through a variety of different and complex pathways in COPD patients. Results may be used to explain intervention effects and develop new intervention strategies to reduce depression in COPD.

Seyama, K., T. Nukiwa, et al. (2019). **"Safety and pharmacokinetics of Alpha-1 MP (Prolastin((R))-C) in Japanese patients with alpha1-antitrypsin (AAT) deficiency."** Respir Investig **57**(1): 89-96.

BACKGROUND: Alpha1-Proteinase Inhibitor, Modified Process (Alpha-1 MP) is used for augmentation therapy in alpha1-antitrypsin deficiency (AATD), an extremely rare disease in Japan. Weekly doses of 60mg/kg Alpha-1 MP have been shown to be safe and well tolerated in non-Japanese subjects, but the safety and pharmacokinetics (PK) have not been evaluated in Japanese subjects. The objectives of this study were to evaluate the safety and PK of 60mg/kg Alpha-1 MP administered by weekly IV infusions over 8 weeks in Japanese subjects with AATD. METHODS: This was a multicenter, open-label trial in Japanese adults aged >/=20 years with AATD. Samples for evaluation of serum alpha1-PI concentration and PK parameters were collected at 10 time points until the seventh day after the last dose at Week 8: immediately before dosing, immediately after dosing (time 0), and 0.25, 2, 4, 8, 24, 48, 120, and 168hours after dosing. RESULTS: Four subjects were analyzed. The median tmax was 0.534h. Mean +/- SD values for t(1/2), Cmax, and AUC0-7days were 150.4 +/- 36.18h, 174.2 +/- 30.51mg/dL, and 14,913.2 +/- 1633.45mg*h/dL, respectively. Mean trough concentration at week 8 was 55.4 +/- 7.23mg/dL. Alpha-1 MP therapy was safe, with no serious adverse events or deaths reported. Two treatment-emergent adverse events of fatigue in one subject were considered to be possibly related. CONCLUSIONS: The PK and safety of Alpha-1 MP in Japanese subjects with AATD were consistent with the Alpha-1 MP profile in non-Japanese subjects (ClinicalTrials.gov: NCT02870309; JAPIC CTI: JapicCTI-163160).

https://www.sciencedirect.com/science/article/pii/S2212534518301096?via%3Dihub

Shrestha, S. K., B. Srivastava, et al. (2017). **"Effect of Sildenafil Citrate on Pulmonary Arterial Systolic Pressure and Sub-maximal Exercise Capacity in Chronic Obstructive Pulmonary Disease."** Kathmandu Univ Med J (KUMJ) **15**(60): 271-278.

Background Pulmonary hypertension (PH) often complicates Chronic Obstructive Pulmonary Disease (COPD). Sildenafil reduces pulmonary arterial pressure associated with multitude of diseases. Objective To evaluate the use of Sildenafil in Pulmonary Hypertension associated with COPD. Method This randomized control study enrolled 72 patients: 61 completed the study. Thirtypatients with COPD received Sildenafil 25 mg thrice daily and 31 patients with COPD received optimal medical therapy for four weeks. Symptom assessment and dyspnoea grading was done with modified Borg scale and Modified Medical Research Council (MMRC) grade. The functional assessment was done with WHO functional classification. The estimation of pulmonary arterial systolic pressure and six minute walking distance was done before and after four weeks of the administration of therapy in both groups. Adverse reaction profiling was done for Sildenafil. The primary outcomes were the changes in pulmonary arterial systolic pressure and six minute walk test. The secondary outcomes were change in modified Borg scale for dyspnoea, MMRC grading and WHO functional class. Result The mean decrease in pulmonary arterial systolic pressure in Sildenafil group was significant as compared to controls (9.87+7.84 mmHg Vs 5.93+7.44 mmHg, P=0.048). The mean increase in six minute walk distance was significantly more in cases as compared to controls (48.13+25.79 m Vs 32.59+32.96 m,P=0.047). The changes in modified Borg scale was not significant (1.20+1.92 to 1.55+1.23; P=0.401). There was significant changes in MMRC grade (p=0.037). There was no significant change in WHO functional class after four weeks (p=0.071). Conclusion Sildenafil marginally decreased pulmonary arterial systolic pressure and increased six minute walk distance in COPD patients. It improved MMRC grading without affecting modified Borg's Scale and WHO functional class.

Shum, J., I. Poureslami, et al. (2018). **"Airway diseases and health literacy (HL) measurement tools: A systematic review to inform respiratory research and practice."** Patient Educ Couns **101**(4): 596-618.

OBJECTIVE: To identify and evaluate asthma/COPD measurement tools that assess any of the five health literacy (HL) domains: (1) access, (2) understand, (3) evaluate, (4) communicate, and (5) use, as well as numeracy. METHODS: MEDLINE/Embase (via Ovid) databases from 1974 to 2016 were searched and complimented by grey literature. Study selection and data extraction were conducted by two reviewers independently. RESULTS: We identified 65 tools including 40 asthma, 22 COPD, and 3 asthma/COPD focused tools. Thirty tools had been validated and two assessed all five domains. The 'understand' domain was captured in 49 tools, followed by 'access' in 29 tools, 'use' in 24 tools, 'evaluate' in 20 tools, and 'communicate' in 10 tools. Two tools assessed 'numeracy'. Tool content comprised disease physiology, triggers, symptoms, inhaler technique, self-management practices, and rehab programs. CONCLUSIONS: This review highlights paucity of HL tools that have been validated and/or assess the 'communicate' domain and makes a valuable contribution to filling an existing research gap in the field of HL by determining the deficiencies of such tools. PRACTICE IMPLICATIONS: Our review uncovers which HL domains are under-measured, justifying the need to develop an airways HL measurement tool which applies the 5-domain model for asthma/COPD management.

Silva, C., M. Gomes Neto, et al. (2018). **"Effects of upper limb resistance exercise on aerobic capacity, muscle strength, and quality of life in COPD patients: a randomized controlled trial."** Clin Rehabil **32**(12): 1636-1644.

OBJECTIVE:: To evaluate the effects of upper limb resistance exercise on the functional capacity, muscle function, and quality of life in patients with chronic obstructive pulmonary disease. SETTING:: Clinical School of Physiotherapy in a Public University of Brazil. SUBJECTS:: 58 patients were recruited; of these, 7 were excluded and 51 individuals were enrolled. INTERVENTION:: Control group performed warm-up, aerobic exercise, inspiratory muscle training, and session stretching, followed by massage therapy. The treatment group performed warm-up, aerobic exercise, inspiratory muscle training, three sets of upper limb resistance exercise, and session stretching, followed by massage therapy. Total three sessions per week for eight weeks. PRIMARY OUTCOME MEASURES:: 6-minute walk test, respiratory and peripheral muscle strength, dyspnea, and quality of life. Normality of the data was tested using the Shapiro-Wilk test; paired analysis of variance was used for intergroup analyses. RESULTS:: 51 patients (25 in the control group and 26 in the treatment group); 41% of the subjects were men. Mean forced expiratory volume was 2.6 +/- 0.6 L, and mean body mass index was 27.3 +/- 7.0 kg/m(2). The upper limb resistance exercise resulted in significantly greater benefit in terms of exercise capacity (88.5 +/- 81.9 m, P = 0.043), inspiratory muscle strength (22.9 +/- 24.2 cm H2O, P = 0.001), upper limb muscle strength (2.3 +/- 3.1 kg, P = 0.027), and quality of life scores (-15.3 +/- 10.9 points, P = 0.000). CONCLUSION:: Upper limb resistance exercise improved the exercise capacity, respiratory muscle strength, and quality of life.

Sridhar, S., H. Liu, et al. (2019). **"Modulation of blood inflammatory markers by benralizumab in patients with eosinophilic airway diseases."** Respir Res **20**(1): 14.

BACKGROUND: Benralizumab, a humanized, afucosylated, monoclonal antibody that targets interleukin-5 receptor alpha, depletes eosinophils and basophils by enhanced antibody-dependent cell-mediated cytotoxicity. It demonstrated efficacy for patients with moderate to severe asthma and, in a Phase IIa trial, for chronic obstructive pulmonary disease (COPD) with eosinophilic inflammation. We investigated effects of benralizumab 100 mg every 8 weeks (first three doses every 4 weeks) subcutaneous on blood inflammatory markers through proteomic and gene-expression analyses collected during two Phase II studies of patients with eosinophilic asthma and eosinophilic COPD. METHODS: Serum samples for proteomic analysis and whole blood for gene expression analysis were collected at baseline and 52 weeks (asthma study) or 32 weeks (COPD study) post-treatment. Proteomic analyses were conducted on a custom set of 90 and 147 Rules-Based Medicine analytes for asthma and COPD, respectively. Gene expression was profiled by Affymetrix Human Genome U133 plus 2 arrays (~ 54 K probes). Gene set variation analysis (GSVA) was used to determine transcriptomic activity of immune signatures. Treatment-related differences between analytes, genes, and gene signatures were analyzed for the overall population and for patient subgroups stratified by baseline blood eosinophil count (eosinophil-high [>/=300 cells/muL] and eosinophil-low [< 300 cells/muL]) via t-test and repeated measures analysis of variance. RESULTS: Eosinophil chemokines eotaxin-1 and eotaxin-2 were significantly upregulated (false discovery rate [FDR] < 0.05) by approximately 2.1- and 1.4-fold in the asthma study and by 2.3- and 1.7-fold in the COPD study following benralizumab treatment. Magnitude of upregulation of these two chemokines was greater for eosinophil-high patients than eosinophil-low patients in both studies. Benralizumab was associated with significant reductions (FDR < 0.05) in expression of genes associated with eosinophils and basophils, such as CLC, IL-5Ralpha, and PRSS33; immune-signaling complex genes (FCER1A); G-protein-coupled receptor genes (HRH4, ADORA3, P2RY14); and further immune-related genes (ALOX15 and OLIG2). The magnitude of downregulation of gene expression was greater for eosinophil-high than eosinophil-low patients. GSVA on immune signatures indicated significant treatment reductions (FDR < 0.05) in eosinophil-associated signatures. CONCLUSIONS: Benralizumab is highly selective, modulating blood proteins or genes associated with eosinophils or basophils. Modulated protein and gene expression patterns are most prominently altered in eosinophil-high vs. eosinophil-low patients. TRIAL REGISTRATION: NCT01227278 and NCT01238861 .

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6339432/pdf/12931_2018_Article_968.pdf

Toyama, T., T. Kawayama, et al. (2019). **"Differences in Adherence Barriers to Inhaled Medicines between Japanese Patients with Chronic Obstructive Pulmonary Disease and Asthma Evaluated using the "Adherence Starts with Knowledge 20" (ASK-20) Questionnaire."** Intern Med **58**(2): 175-185.

Objective This multicenter, cross-sectional, non-interventional trial aimed to investigate adherence barriers to inhaled medicines when compared with oral medicines in Japanese patients with chronic obstructive pulmonary disease (COPD) and asthma. Methods The self-reporting "Adherence Starts with Knowledge 20" (ASK-20) questionnaire was administered for adherence barriers of inhaled and oral medicines to outpatients with regular clinic attendance. Results Patients with COPD and asthma reported different adherence barriers to inhaled medicines. Independent adherence barriers [odds ratio (95% confidence interval)] to inhaled medicines relative to those for oral medicines among patients with COPD and asthma were those related to item Q8 ["I know if I am reaching my health goals"; 2.49 (1.39-4.47); p=0.0022] and item Q2 ["I run out of my medicine because I do not get refills on time"; 2.69 (1.26-5.75); p=0.0127], respectively. Among patients with poor adherence to only inhaled medicines, those with COPD and asthma recognized item Q3 ["consuming alcohol and taking medicines"; 6.63 (1.27-34.7); p<0.05] and item Q1 ["forget to take medicines only sometimes"; 4.29 (1.83-10.0); p<0.05], respectively, were recognized as independent adherence barriers to inhaled medicines. The total ASK-20 scores and total barrier counts in patients with poor adherence to inhaled medicines were significantly higher than in those without poor adherence among patients with asthma (p=0.0057) but not those with COPD (p>0.05). Conclusion These results will aid in personalizing education on adherence to inhaled medicines among patients with COPD and asthma.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6378151/pdf/1349-7235-58-0175.pdf

Tupper, O. D., T. L. Gregersen, et al. (2018). **"Effect of tele-health care on quality of life in patients with severe COPD: a randomized clinical trial."** Int J Chron Obstruct Pulmon Dis **13**: 2657-2662.

Background and objective: Telemonitoring (TM) of patients with COPD has gained much interest, but studies have produced conflicting results. We aimed to investigate the effect of TM with the option of video consultations on quality of life (QoL) in patients with severe COPD. Patients and methods: COPD patients at high risk of exacerbations were eligible for the 6-month study and a total of 281 patients were equally randomized to either TM (n=141) or usual care (n=140). TM comprised recording of symptoms, oxygen saturation, spirometry, and video consultations. Algorithms generated alerts if readings breached thresholds. Both groups filled in a health-related QoL questionnaire (15D((c))) and the COPD Assessment Test (CAT) at baseline and at 6 months. Within-group differences were analyzed by paired t-test. Results: Most of the enrolled patients had severe COPD (86% with Global Initiative for Chronic Obstructive Lung Disease stage 3 or 4 and 45% with admission for COPD within the last year, respectively). No difference in drop-out rate and mortality was found between the groups, and likewise there was no difference in 15D or CAT at baseline. At 6 months, a significant improvement of 0.016 in 15D score (p=0.03; minimal clinically important difference 0.015) was observed in the TM group (compared to baseline), while there was no improvement in the control group -0.003 (p=0.68). After stratifying 15D score at baseline to <0.75 or >/=0.75, respectively, there was a significant difference in the <0.75 TM group of 0.037 (p=0.001), which is a substantial improvement. No statistically significant changes were found in CAT score. Conclusion: Compared to the nonintervention group, TM as an add-on to usual care over a 6-month period improved QoL, as assessed by the 15D questionnaire, in patients with severe COPD, whereas no difference between groups was observed in CAT score.

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van der Palen, J., W. Moeskops-van Beurden, et al. (2018). **"A randomized, open-label, single-visit, crossover study simulating triple-drug delivery with Ellipta compared with dual inhaler combinations in patients with COPD."** Int J Chron Obstruct Pulmon Dis **13**: 2515-2523.

Background: Administering maintenance COPD therapy with a combination of multiple inhalers may increase inhaler errors. This study evaluated the potential benefits of using a single Ellipta dry powder inhaler

(DPI) compared with two combinations of DPIs commonly used to deliver triple maintenance therapy. Methods: Patients receiving inhaled COPD medication were enrolled in this multicenter, randomized, open-label, placebo-device, crossover study with a 2x2 complete block design (NCT0298218), which comprised two substudies: Ellipta vs Diskus + HandiHaler (substudy 1) or Turbuhaler + HandiHaler (substudy 2). Patients demonstrated inhaler use after reading the relevant patient information leaflet (PIL). A trained investigator assessed user errors (critical errors [errors likely to result in no or significantly reduced medication being inhaled] and overall errors). The primary endpoint was the proportion of patients making >/=1 critical error after reading the PIL. The secondary endpoints included error rates during </=2 reassessments following investigator instruction (if required), instruction time, and patient preference. Results: After reading the PIL, significantly fewer patients made critical errors with Ellipta compared with Diskus + HandiHaler (9% [7/80] vs 75% [60/80], respectively; P<0.001) or Turbuhaler + HandiHaler (9% [7/79] vs 73% [58/79], respectively; P<0.001). The number of patients making overall errors was also lower with Ellipta vs tested inhaler combinations (P<0.001 for each substudy). The median instruction time needed for error-free use was shorter with Ellipta in substudies 1 and 2 (2.7 and 2.6 minutes, respectively) vs either combination (10.6 [Diskus + HandiHaler] and 11.3 minutes [Turbuhaler + HandiHaler], respectively). Significantly more patients preferred Ellipta over Diskus + HandiHaler or Turbuhaler + HandiHaler overall for taking their COPD medication (81% vs 9% and 84% vs 4%, respectively) and per the number of steps for taking their COPD medication (89% vs 8% and 91% vs 5%, respectively). Conclusion: Fewer patients with COPD made critical errors with the single DPI, and patients required less instruction time, compared with each dual DPI combination.

https://www.dovepress.com/getfile.php?fileID=43797

Wang, J., S. Guo, et al. (2019). **"Observation of the curative effect of device-guided rehabilitation on respiratory function in stable patients with chronic obstructive pulmonary disease."** Medicine (Baltimore) **98**(8): e14034.

BACKGROUND: Chronic obstructive pulmonary disease (COPD) is a serious lung disease for individuals in middle age and especially in old people. The study was aimed to observe the curative effect of device-guided rehabilitation on respiratory functions in stable COPD patients. METHODS: Sixty-seven stable COPD patients were enrolled and assigned to the experiment group (n = 36) and the control group (n = 31). The conventional pulmonary rehabilitation treatments, including pursed lips breathing (PLB) and abdominal breathing training, were applied in the control group. Respiratory muscle training of the experiment group was performed using the respiratory endurance training device combined with traditional techniques. Both groups were assessed by 6-minute walk test (6MWT), COPD assessment test (CAT), body mass index, airflow obstruction, dyspnea, and exercise capacity (BODE) index. Besides, the pulmonary function (FVC%, FEVl%) were measured at 6 months before and after treatment. RESULTS: After treatment, the 6MWT, CAT, BODE index were significantly increased compared with pre-treatment in both groups (P < .01), but not FVC% and FEVl%. Compared with the control group, the combination therapy in the experiment group could significantly improve the 6MWT (P = .0094), CAT (P = .0071) and BODE index (P = .0064) as well as the changes of 6MWT (P < .01), CAT (P < .01), and BODE index (P < .01) before and after treatment. CONCLUSIONS: The traditional respiratory training combined with device-guided pulmonary rehabilitation can improve the respiratory muscle function and athletic ability in stable COPD patients.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6408035/pdf/medi-98-e14034.pdf

Wedzicha, J. A., D. Singh, et al. (2019). **"Treatment response to indacaterol/glycopyrronium versus salmeterol/fluticasone in exacerbating COPD patients by gender: a post-hoc analysis in the FLAME study."** Respir Res **20**(1): 4.

BACKGROUND: The burden of chronic obstructive lung disease (COPD) is increasing in women, with recent evidence suggesting gender differences in disease characteristics and potentially in treatment outcomes. METHODS: FLAME was a 52-week randomized controlled trial in patients with severe-to-very-severe

COPD and a history of exacerbations. In this post-hoc analysis, gender-based baseline differences and treatment outcomes between indacaterol/glycopyrronium 110/50 mug once daily (IND/GLY) and salmeterol/fluticasone 50/500 twice daily (SFC) were assessed in terms of rate of exacerbations, time-to-first exacerbation, lung function, health status, and rescue medication use. RESULTS: This post-hoc analysis included 2557 men and 805 women. Baseline characteristics differed between genders, with women being younger, having better lung function and more often experiencing >/=2 exacerbations in the previous year. Compared with SFC, IND/GLY treatment was associated with reductions in the annualized rates of moderate/severe exacerbations (rate ratio [95% CI]: 0.81 [0.73-0.91], 0.89 [0.74-1.07] in men and women, respectively). Similarly, time-to-first moderate/severe exacerbation was also delayed (hazard ratio [95% CI]: 0.79 [0.70-0.89] and 0.76 [0.63-0.91] in men and women, respectively). Results were similar for all (mild/moderate/severe) exacerbations. Improvements in lung function, health status and rescue medication use with IND/GLY vs SFC were comparable between men and women. The smaller sample size for women may account for some observed discrepancies in treatment responses. CONCLUSIONS: Although there were gender differences in baseline characteristics, IND/GLY demonstrated similar trends for exacerbation prevention and lung function improvement in men and women with moderate-to-very-severe COPD and a history of exacerbations compared with SFC. Small differences in the effects seen between genders may be attributed to the different sizes of the two groups and need to be further evaluated in randomized trials that are appropriately powered for gender analysis. TRIAL REGISTRATION: Post hoc analysis of the FLAME study. ClinicalTrials.gov number: NCT01782326 . Registered 1 February 2013.

http://spiral.imperial.ac.uk/bitstream/10044/1/67847/2/Treatment%20response%20to%20indacaterol/glycopyrronium%20versus%20salmeterol/fluticasone%20in%20exacerbating%20COPD%20patients%20by%20gender%3a%20a%20post-hoc%20analysis%20in%20the%20FLAME%20study.pdf

Windisch, W., S. B. Schwarz, et al. (2018). **"Using web-based videos to improve inhalation technique in COPD patients requiring hospitalization: A randomized controlled trial."** PLoS One **13**(10): e0201188.

BACKGROUND: Inhalation errors frequently occur in patients receiving inhalation treatment, which can significantly impair treatment success. While this underscores the importance of inhalation training, the role of modern web-based instructional videos has not yet been investigated. METHODS: A randomized controlled trial using standardized checklists (10 items: preparation, N = 3, inhalation routine, N = 6, and closure of inhalation, N = 1) was carried out to determine the relative effects of web-based, device-specific videos versus standard personal instruction on reducing multiple (>/=2) inhalation errors in severe COPD patients requiring hospitalisation. Investigators assessing inhalation errors were blinded to the intervention. RESULTS: Multiple handling errors were recorded at baseline in 152 out of 159 patients (95.6%). Each teaching method led to a similar reduction in errors (videos: from 4.2+/-1.6 to 1.5+/-1.5 errors; personal instruction: from 3.8+/-1.5 to 1.3+/-1.6; p<0.0001), although non-inferiority of web-based video teaching could not be confirmed statistically due to an unpredictably high number of patients in both groups still making multiple handling errors (44.0% versus 40.3%, mean difference 3.7%; 95%CI [-12.0-19.4%]). CONCLUSION: Multiple inhalation errors regularly occur in severe COPD patients requiring hospitalisation. Web-based video teaching is capable of reducing inhalation errors. However, compared to personal instruction non-inferiority could not be established. This was due to an unexpectedly high number of patients with persisting inhalation errors despite training. TRIAL REGISTRATION: Clinical trial Registration: German Clinical Trial Register, DRKS 00004320.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6191087/pdf/pone.0201188.pdf

Xu, W., R. Li, et al. (2018). **"Combination of inspiratory and expiratory muscle training in same respiratory cycle versus different cycles in COPD patients: a randomized trial."** Respir Res **19**(1): 225.

BACKGROUND: Difference between combined inspiratory and expiratory muscle training in same respiratory cycle or different cycles remained unclarified. We explored the difference between both patterns of combined trainings in patients with COPD. METHODS: In this randomized, open-label, controlled trial, stable COPD

subjects trained for 48 minutes daily, for 8 weeks, using a monitoring device for quality control. Ninety-two subjects were randomly and equally assigned for sham training, inspiratory muscle training(IMT), combined inspiratory and expiratory muscle training in same cycle(CTSC) or combined inspiratory and expiratory muscle training in different cycles(CTDC). Respiratory muscle strength, as the primary endpoint, was measured before and after training. Registry: ClinicalTrials.gov (identifier: NCT02326181). RESULTS: Respiratory muscle training improved maximal inspiratory pressure(PImax), while no significant difference was found in PImax among IMT, CTSC and CTDC. Maximal expiratory pressure(PEmax) in CTSC and CTDC was greater than IMT($P = 0.026$, and $P=0.04$, respectively) and sham training ($P = 0.001$). IMT, CTSC, and CTDC shortened inhalation and prolonged exhalation($P < 0.01$). Subjects with respiratory muscle weakness in IMT and CTDC exhibited greater increase in PImax than those without. IMT, CTSC and CTDC showed no difference in symptoms and quality of life scales among themselves($P > 0.05$). CONCLUSION: Both patterns of CTSC and CTDC improved inspiratory and expiratory muscle strength, while IMT alone only raised PImax. Respiratory muscle training might change the respiratory cycles, and be more beneficial for COPD patients with inspiratory muscle weakness.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6245535/pdf/12931_2018_Article_917.pdf

Systematic reviews and clinical trials – in process

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

Ahmadi, A., H. Ghaedi, et al. (2019). **"Association between chronic obstructive pulmonary disease and interleukins gene variants: A systematic review and meta-analysis."** Cytokine **117**: 65-71.

Interleukins are cytokines involved in systemic inflammation and immune system regulation. Many studies have investigated the association between common genetic variations in interleukin-coding genes and COPD susceptibility. In this study, a systematic review and meta-analysis was performed to evaluate the association between interleukin gene variations and COPD pathogenesis. Association studies were retrieved from PubMed and Google Scholar databases using the standard systematic search strategy. A total of 26 different studies evaluating eight polymorphisms in four interleukin genes were included in this study. In overall comparisons, IL1beta-rs16944, -rs1143627, -rs1143634, IL13-rs20541 polymorphisms were found not to be associated with the increased risk for developing COPD. However, IL1RN-rs2234663 and IL13-rs1800925 showed a strong association with COPD. We showed that the CC genotype carriers of the IL6-rs1800795 are at significantly higher risk of developing COPD (OR=1.31, 95% CI: 1.04-1.64, P=0.01) compared to GG carriers. In case of IL6-rs1800796, individuals with CC and CG genotypes showed a lower risk to develop COPD (OR=0.46, 95%CI: 0.32-0.66, P>0.00). This updated meta-analysis strongly supports the association of IL1RN-rs2234663, IL6-rs1800795, -rs1800795 and IL13-rs1800925 variants with COPD.

Bakerly, N. D., A. Woodcock, et al. (2019). **"Benefit and safety of fluticasone furoate/vilanterol in the Salford Lung Study in chronic obstructive pulmonary disease (SLS COPD) according to baseline patient characteristics and treatment subgroups."** Respir Med **147**: 58-65.

BACKGROUND: SLS COPD was the first open-label randomised controlled trial demonstrating a reduction in moderate/severe COPD exacerbations with once-daily inhaled fluticasone furoate/vilanterol (FF/VI) in everyday clinical practice. Here we report FF/VI effectiveness and safety in predefined patient subgroups. METHODS: Patients with COPD, exacerbation history, and receiving maintenance inhaler therapy, were randomised to initiate FF/VI 100/25mug or continue usual care (UC) with 12 months' follow-up. Annual rates of moderate/severe exacerbations (primary outcome), selected secondary outcomes, and incidence of pneumonia serious adverse events of special interest (SAESI) were compared between randomisation groups across various patient subgroups/baseline treatment strata. SAESI rates by actual treatment were also assessed. RESULTS: Lower exacerbation rates were observed for FF/VI versus UC across all subgroups/strata, including ICS + LABA therapy subset (8.0% [0.1, 15.4]), except in patients without baseline airflow limitation (-0.5% [-29.8, 22.1]). Larger reductions compared to the overall analysis were observed for patients on ICS-containing regimens (excluding LAMA) before the study (15.6% [3.4, 26.3]), and with baseline CAT score <10 (25.3% [-0.4, 44.4]). Pneumonia SAESI rates were similar for FF/VI versus UC across all subgroups/strata, except the LABA, LAMA or LABA + LAMA stratum (incidence ratio 2.8 [0.9, 8.5]). SAESI rates were not increased for FF/VI versus other ICS + LABA. CONCLUSIONS: Initiating FF/VI versus continuing UC reduced exacerbation rates without increased pneumonia SAESI risk compared to other ICS-containing regimens and in various patient subgroups, consistent with primary study findings. FF/VI may be a therapeutic option for a broad population of COPD patients, including those with more severe disease.

https://www.resmedjournal.com/article/S0954-6111(19)30008-3/pdf

Bellou, V., L. Belbasis, et al. (2019). **"Elucidating the risk factors for chronic obstructive pulmonary disease: an umbrella review of meta-analyses."** Int J Tuberc Lung Dis **23**(1): 58-66.

Chronic obstructive pulmonary disease (COPD) is commonly attributed to smoking, and other potential risk factors are ignored. We aimed to critically appraise the epidemiological credibility of the risk factors for COPD that have been examined in published meta-analyses. We performed a systematic search to capture systematic reviews and meta-analyses of observational studies on environmental factors and biomarkers for risk of COPD. We applied a set of standardised methodological criteria based on the level of statistical significance, sample size, between-study heterogeneity and statistical biases. Our search yielded 11 eligible papers, including 18 meta-analyses on environmental factors or biomarkers for COPD risk, and eight eligible papers with systematic reviews only. Eleven associations achieved statistical significance at P < 0.001 and six associations at P < 1 x 10(-6). Thirteen associations presented an I(2) >/= 50%, while six associations had evidence of small-study effects and/or excess significance bias. History of tuberculosis or rheumatoid arthritis, exposure to biomass fuels, tobacco smoking and second hand smoking were supported by high epidemiological credibility for an increased risk of COPD. Furthermore, highly suggestive evidence was found for increased levels of serum C-reactive protein, and serum fibrinogen in COPD patients compared with healthy controls. To summarise, our approach suggests that, while a proportion of COPD patients are non-smokers, only a narrow range of risk factors not related to smoking have been studied for an association with COPD. There is also a need to decipher possible protective factors in COPD pathogenesis given that more than a half of ever-smokers do not develop COPD.

Bloom, C. I., F. Ricciardi, et al. (2019). **"Predicting COPD 1-year mortality using prognostic predictors routinely measured in primary care."** BMC Med **17**(1): 73.

BACKGROUND: Chronic obstructive pulmonary disease (COPD) is a major cause of mortality. Patients with advanced disease often have a poor quality of life, such that guidelines recommend providing palliative care in their last year of life. Uptake and use of palliative care in advanced COPD is low; difficulty in predicting 1-year mortality is thought to be a major contributing factor. METHODS: We identified two primary care COPD cohorts using UK electronic healthcare records (Clinical Practice Research Datalink). The first cohort was randomised equally into training and test sets. An external dataset was drawn from a second cohort. A risk model to predict mortality within 12 months was derived from the training set using backwards elimination Cox regression. The model was given the acronym BARC based on putative prognostic factors including body mass index and blood results (B), age (A), respiratory variables (airflow obstruction, exacerbations, smoking) (R) and comorbidities (C). The BARC index predictive performance was validated in the test set and external dataset by assessing calibration and discrimination. The observed and expected probabilities of death were assessed for increasing quartiles of mortality risk (very low risk, low risk, moderate risk, high risk). The BARC index was compared to the established index scores body mass index, obstructive, dyspnoea and exacerbations (BODEx), dyspnoea, obstruction, smoking and exacerbations (DOSE) and age, dyspnoea and obstruction (ADO). RESULTS: Fifty-four thousand nine hundred ninety patients were eligible from the first cohort and 4931 from the second cohort. Eighteen variables were included in the BARC, including age, airflow obstruction, body mass index, smoking, exacerbations and comorbidities. The risk model had acceptable predictive performance (test set: C-index = 0.79, 95% CI 0.78-0.81, D-statistic = 1.87, 95% CI 1.77-1.96, calibration slope = 0.95, 95% CI 0.9-0.99; external dataset: C-index = 0.67, 95% CI 0.65-0.7, D-statistic = 0.98, 95% CI 0.8-1.2, calibration slope = 0.54, 95% CI 0.45-0.64) and acceptable accuracy predicting the probability of death (probability of death in 1 year, n high-risk group, test set: expected = 0.31, observed = 0.30; external dataset: expected = 0.22, observed = 0.27). The BARC compared favourably to existing index scores that can also be applied without specialist respiratory variables (area under the curve: BARC = 0.78, 95% CI 0.76-0.79; BODEx = 0.48, 95% CI 0.45-0.51; DOSE = 0.60, 95% CI 0.57-0.61; ADO = 0.68, 95% CI 0.66-0.69, external dataset: BARC = 0.70, 95% CI 0.67-0.72; BODEx = 0.41, 95% CI 0.38-0.45; DOSE = 0.52, 95% CI 0.49-0.55; ADO = 0.57, 95% CI 0.54-0.60). CONCLUSION: The BARC index performed better than existing tools in predicting 1-year mortality. Critically, the risk score only requires routinely collected non-specialist information which, therefore, could help identify patients seen in primary care that may benefit from palliative care.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6449897/pdf/12916_2019_Article_1310.pdf

Boueiz, A., B. Pham, et al. (2019). **"Integrative Genomics Analysis Identifies ACVR1B as a Candidate Causal Gene of Emphysema Distribution."** Am J Respir Cell Mol Biol **60**(4): 388-398.

Genome-wide association studies (GWAS) have identified multiple associations with emphysema apicobasal distribution (EABD), but the biological functions of these variants are unknown. To characterize the functions of EABD-associated variants, we integrated GWAS results with 1) expression quantitative trait loci (eQTL) from the Genotype Tissue Expression (GTEx) project and subjects in the COPDGene (Genetic Epidemiology of COPD) study and 2) cell type epigenomic marks from the Roadmap Epigenomics project. On the basis of these analyses, we selected a variant near ACVR1B (activin A receptor type 1B) for functional validation. SNPs from 168 loci with P values less than 5 x 10(-5) in the largest GWAS meta-analysis of EABD were analyzed. Eighty-four loci overlapped eQTL, with 12 of these loci showing greater than 80% likelihood of harboring a single, shared GWAS and eQTL causal variant. Seventeen cell types were enriched for overlap between EABD loci and Roadmap Epigenomics marks (permutation P < 0.05), with the strongest enrichment observed in CD4(+), CD8(+), and regulatory T cells. We selected a putative causal variant, rs7962469, associated with ACVR1B expression in lung tissue for additional functional investigation, and reporter assays confirmed allele-specific regulatory activity for this variant in human bronchial epithelial and Jurkat immune cell lines. ACVR1B expression levels exhibit a nominally significant association with emphysema distribution. EABD-associated loci are preferentially enriched in regulatory elements of multiple cell types, most notably T-cell subsets. Multiple EABD loci colocalize to regulatory elements that are active across multiple tissues and cell types, and functional analyses confirm the presence of an EABD-associated functional variant that regulates ACVR1B expression, indicating that transforming growth factor-beta signaling plays a role in the EABD phenotype. Clinical trial registered with www.clinicaltrials.gov (NCT00608764).

Calzetta, L., M. Cazzola, et al. (2019). **"Adding a LAMA to ICS/LABA Therapy: A Meta-analysis of Triple Combination Therapy in COPD."** Chest **155**(4): 758-770.

BACKGROUND: Inhaled corticosteroid (ICS)/long-acting beta2-agonist (LABA) combination is commonly prescribed to treat COPD; therefore, we performed a meta-analysis on the effect of adding a long-acting muscarinic receptor antagonist (LAMA) to ICS/LABA combination in COPD. METHODS: Studies were identified by searching in different databases the randomized controlled trials that investigated the effect of ICS/LABA/LAMA combination in COPD. The primary end points were the effect of triple therapy on trough FEV1, risk of acute exacerbation of COPD (AECOPD), and risk of cardiovascular serious adverse events (SAEs), compared with ICS/LABA combination. The Grading of Recommendations Assessment, Development, and Evaluation system was used to assess the quality of evidence. RESULTS: Thirteen randomized controlled trials including 15,519 patients with COPD (ICS/LABA/LAMA combination, 53.1%; ICS/LABA combination, 46.9%) were meta-analyzed. ICS/LABA/LAMA combination improved trough FEV1 (mean difference, +104.86 mL; 95% CI, 86.74-122.99; high quality of evidence) and protected against AECOPD (relative risk, 0.78; 95% CI, 0.71-0.85; high quality of evidence) vs ICS/LABA combination. For every approximately four patients treated with triple therapy, one increased FEV1 > 100 mL, and approximately 26 patients had to be treated for 1 year with ICS/LABA/LAMA combination to prevent one AECOPD, compared with ICS/LABA combination. Adding a LAMA to ICS/LABA therapy did not modulate the risk of cardiovascular SAEs (moderate quality of evidence). CONCLUSIONS: Triple therapy provides significant clinical benefit in patients with COPD on ICS/LABA combination. ICS/LABA therapy can be escalated to triple therapy without a real risk to increase cardiovascular SAEs when a LAMA is added to the combination. TRIAL REGISTRY: ClinicalTrials.gov; No.: CRD42018095300; URL: www.clinicaltrials.gov.

https://journal.chestnet.org/article/S0012-3692(19)30014-5/fulltext

Chang, Y. P., C. H. Lai, et al. (2019). **"Mortality and vertebral fracture risk associated with long-term oral steroid use in patients with chronic obstructive pulmonary disease: A systemic review and meta-analysis."** Chron Respir Dis **16**: 1479973119838280.

Short-term oral steroid use may improve lung function and respiratory symptoms in patients with stable chronic obstructive pulmonary disease (COPD). However, long-term oral steroid (LTOS) use is not recommended owing to its potential adverse effects. Our study aimed to investigate whether chronic use of oral steroids for more than 4 months would increase mortality and vertebral fracture risk in patients with stable COPD. A systemic search of the PubMed database was conducted, and meta-analysis was performed using Review Manager 5.3. Five studies with a total of 1795 patients showed there was an increased risk of mortality in patients using LTOS (relative risk, 1.63; 95% confidence interval (CI), 1.19-2.23; $p < 0.0001$; $I(2) = 86\%$). In addition, four studies with a total of 17,764 patients showed there was an increased risk of vertebral fracture in patients using LTOS (odds ratio, 2.31; 95% CI, 1.52-3.50; $p = 0.03$; $I(2) = 65\%$). Our meta-analysis showed LTOS was associated with increased mortality and vertebral fracture risk in patients with COPD, and this risk may be due to the adverse effects of LTOS and progression COPD.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6448104/pdf/10.1177_1479973119838280.pdf

Cherbuin, N., E. I. Walsh, et al. (2019). **"Chronic Obstructive Pulmonary Disease and Risk of Dementia and Mortality in Lower to Middle Income Countries."** J Alzheimers DisBACKGROUND: Chronic obstructive pulmonary disease (COPD) is a major disease burden which accounts for 5% of all deaths globally, with most of those (>90%) occurring in lower to middle income countries (LMIC). It is also emerging as an important modifiable dementia risk factor. OBJECTIVE: To address the knowledge gap surrounding the nature of the associations between COPD, dementia, and mortality, and the geographical variation of those associations in LMIC. METHODS: Data from the 10/66 study surveying 15,394 participants (mean age 74 years, 62% female) across 8 countries was used to estimate the prevalence of self-reported COPD and its association with incident dementia and premature death. Proportional sub-hazards models using a cumulative incidence function were applied to identify the probability of incident dementia onset given the risk of premature death, with estimates pooled across countries via random effect meta-analysis. RESULTS: Over the 3-year follow-up, almost 10% of participants developed dementia and 14% were deceased. COPD was not significantly associated with dementia incidence except in Cuba. However, fully adjusted models indicated that individuals with COPD were at a 28% increased risk of premature death, a trend present across most countries when analyzed individually. CONCLUSION: The link between COPD and dementia is currently somewhat different and weaker in LMIC than in developed countries. This may be because premature death in the populations studied mask the development of clinical dementia. Given the global trend toward increased life expectancy, it is critical that the disease burden associated with COPD be addressed without delay if a further rise in dementia prevalence associated with COPD is to be avoided in LMIC.

https://content.iospress.com:443/download/journal-of-alzheimers-disease/jad180562?id=journal-of-alzheimers-disease%2Fjad180562

Chouaid, C., N. Germain, et al. (2019). **"Patient preference for chronic obstructive pulmonary disease (COPD) treatment inhalers: a discrete choice experiment in France."** Curr Med Res Opin **35**(5): 785-792.

OBJECTIVES: Understanding inhaler preferences may contribute to improving adherence in COPD patients and improving long-term outcomes. This study aims to identify and quantify preferences for convenience-related inhaler attributes in French moderate-to-severe COPD patients, with discrete choice experiment (DCE) methodology. METHODS: Attributes were defined from a literature search, clinician and patient

interviews: shape, dose insertion, dose preparation, dose release, dose confirmation, dose counter and reusability. An online DCE was conducted in respondents with self-reported COPD stage 2-4 recruited through a panel. The study questionnaire included twelve choice scenarios per respondent and questions on patient characteristics, treatment and disease severity. Statistical analyses used a mixed logit regression model with random effects. Utility scores were estimated for four types of inhalers: Inhaler A - soft mist inhaler; Inhaler B - reusable soft mist inhaler; Inhaler C - multi-dose dry powder inhaler; and Inhaler D - single dose dry powder inhaler. RESULTS: The study was completed by 153 patients (50 females); respondents were 50.4 years old on average; 13 different inhaler devices were reported. The most preferred inhaler is L-shaped, has dose preparation with capsule insertion and a dose counter, and is reusable. Inhaler profiles A and B had the highest utilities (mean of 1.2533 and 0.9578 respectively) compared to inhaler C (0.6315) and D (0.2200). CONCLUSIONS: This study showed statistically significant results that the strongest drivers of preference in French users of inhalation devices for COPD are shape, dose counter and reusability. Convenience-related characteristics are important to patients and should be taken into account by clinicians prescribing these devices.

https://www.tandfonline.com/doi/pdf/10.1080/03007995.2019.1574507?needAccess=true

Cook, R., V. Thomas, et al. (2019). **"People with chronic obstructive pulmonary disease exacerbations prefer early discharge, then treatment at home."** Bmj **364**: k5339.

The studyHome treatment of COPD exacerbation selected by DECAF score: a non-inferiority, randomised controlled trial and economic evaluationEchevarria C, Gray J, Hartley T, Miller J, Simpson AJ, Gibson GJ, Bourke SCPublished on 24 April 2018 Thorax 2018;73:713-22This project was funded by the National Institute for Health Research-Research for Patient Benefit Programme (project number PB-PG-0213-30105).To read the full NIHR Signal, go to: https://discover.dc.nihr.ac.uk/content/signal-000691/hospital-at-home-treatment-f or-copd-flare-ups.

https://www.bmj.com/content/364/bmj.k5339.long

Farver-Vestergaard, I., M. O'Connor, et al. (2018). **"Tele-delivered mindfulness-based cognitive therapy in chronic obstructive pulmonary disease: A mixed-methods feasibility study."** J Telemed Telecare: 1357633x18780563.

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.

Fermont, J. M., K. L. Masconi, et al. (2019). **"Biomarkers and clinical outcomes in COPD: a systematic review and meta-analysis."** Thorax **74**(5): 439-446.

BACKGROUND: Conventional measures to evaluate COPD may fail to capture systemic problems, particularly musculoskeletal weakness and cardiovascular disease. Identifying these manifestations and assessing their association with clinical outcomes (ie, mortality, exacerbation and COPD hospital admission) is of increasing clinical importance. OBJECTIVE: To assess associations between 6 min walk distance (6MWD), heart rate, fibrinogen, C reactive protein (CRP), white cell count (WCC), interleukins 6 and 8 (IL-6 and IL-8), tumour necrosis factor-alpha, quadriceps maximum voluntary contraction, sniff nasal inspiratory pressure, short physical performance battery, pulse wave velocity, carotid intima-media thickness and augmentation index and clinical outcomes in patients with stable COPD. METHODS: We systematically searched electronic databases (August 2018) and identified 61 studies, which were synthesised, including meta-analyses to estimate pooled HRs, following Meta-analysis of Observational Studies in Epidemiology (MOOSE) and Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. RESULTS: Shorter 6MWD and elevated heart rate, fibrinogen, CRP and WCC were associated with higher risk of mortality. Pooled HRs were 0.80 (95% CI 0.73 to 0.89) per 50 m longer 6MWD, 1.10 (95% CI 1.02 to 1.18) per 10 bpm higher heart rate, 3.13 (95% CI 2.14 to 4.57) per twofold increase in fibrinogen, 1.17 (95% CI 1.06 to 1.28) per twofold increase in CRP and 2.07 (95% CI 1.29 to 3.31) per twofold increase in WCC. Shorter 6MWD and elevated fibrinogen and CRP were associated with exacerbation, and shorter 6MWD, higher heart rate, CRP and IL-6 were associated with hospitalisation. Few studies examined associations with musculoskeletal measures. CONCLUSION: Findings suggest 6MWD, heart rate, CRP, fibrinogen and WCC are associated with clinical outcomes in patients with stable COPD. Use of musculoskeletal measures to assess outcomes in patients with COPD requires further investigation. TRIAL REGISTRATION NUMBER: CRD42016052075.

https://thorax.bmj.com/content/thoraxjnl/74/5/439.full.pdf

Finch, A. P., P. van Velzen, et al. (2019). **"Doxycycline Added to Prednisolone in Outpatient-Treated Acute Exacerbations of COPD: A Cost-Effectiveness Analysis Alongside a Randomised Controlled Trial."** Pharmacoeconomics **37**(5): 689-699.

BACKGROUND: Most patients with mild to severe chronic obstructive pulmonary disease (COPD) experience exacerbations, which are also associated with increased healthcare costs. Despite limited evidence of antibiotics' benefits for exacerbations in outpatients, antibiotics are frequently prescribed. The aim of this study was to investigate whether doxycycline added to prednisolone is cost-effective compared to placebo plus prednisolone for the treatment of COPD acute exacerbations. METHODS: An economic evaluation from the societal perspective was performed alongside a 2-year randomised trial in 301 COPD patients in the Netherlands. The primary outcome was cost per quality-adjusted life year (QALY). The secondary outcome was cost per exacerbation prevented. Healthcare utilisation and loss of productivity were measured using retrospective questionnaires and clinical report forms. Missing data were imputed using multiple imputations by chained equations. Bootstrapping was employed to estimate statistical uncertainty surrounding cost-effectiveness outcomes. A sensitivity analysis from the healthcare perspective was performed. RESULTS: On average, costs in the doxycycline group were euro898 higher than in the placebo group [95% confidence interval (CI) - 2617 to 4409] for the 2 years of follow-up. QALY values were higher in the doxycycline group (0.03; 95% CI - 0.00 to 0.06), but patients in this group suffered 0.01 more exacerbations than patients in the placebo group (95% CI - 0.14 to 0.11). Cost-effectiveness acceptability curves showed that the probability of doxycycline being cost-effective compared to placebo was 61% and 43% at a willingness-to-pay threshold of euro34,000 per QALY and per exacerbation avoided, respectively. The sensitivity analysis showed similar results from the

healthcare system perspective. CONCLUSIONS: In patients with mild to severe COPD treated for exacerbations in an outpatient setting, doxycycline added to prednisolone is not cost-effective compared to prednisolone plus placebo over a 2-year period.

https://link.springer.com/content/pdf/10.1007%2Fs40273-018-0756-9.pdf

Frei, A., T. Radtke, et al. (2019). **"Effects of a long-term home-based exercise training programme using minimal equipment vs. usual care in COPD patients: a study protocol for two multicentre randomised controlled trials (HOMEX-1 and HOMEX-2 trials)."** BMC Pulm Med **19**(1): 57.

BACKGROUND: Exercise training is an important component of pulmonary rehabilitation (PR) programmes in chronic obstructive pulmonary disease (COPD), but the great majority of COPD patients who would benefit from PR never follow such programmes or fail to maintain exercise training after PR completion. Against this background, we developed an exercise training programme that requires minimal equipment and can be implemented long-term in the patient's home-setting. The aims of the HOMEX-1 and HOMEX-2 trials are to assess the effectiveness of this home-based exercise training programme in two groups of COPD patients over the course of one year: patients who have completed PR (HOMEX-1 trial) and patients who did not enrol in existing PR programmes within the last two years (HOMEX-2 trial). METHODS: HOMEX-1 and HOMEX-2 are multicentre, parallel group, randomised controlled trials. For both trials each, it is planned to include 120 study participants with a diagnosis of COPD. Participants will be randomised with a 1:1 ratio into the intervention group or the control group (usual care/no intervention). The intervention consists of minimal-equipment exercise training elements with progressive level of intensity, conducted by the participant during six days per week and instructed and coached by a trained health care professional during three home visits and regular telephone calls during one year. Primary outcome is change in dyspnoea (domain of Chronic Respiratory Questionnaire) from baseline to 12-months follow-up. Secondary outcomes are change in dyspnoea over the course of the year (assessed at 3, 6 and 12 month) and change in functional exercise capacity, physical activity, health-related quality of life, health status, exacerbations and symptoms from baseline to 12 months follow-up. In addition, explanatory, safety and cost-effectiveness outcomes will be assessed. We will conduct intention-to-treat analyses separately per trial and per protocol analyses as sensitivity analyses. DISCUSSION: The HOMEX-1 and HOMEX-2 trials assess a novel intervention that provides an innovative way of making exercise training as accessible as possible for COPD patients. If the intervention proves to be effective long-term, it will fill the gap of providing an easily accessible and feasible intervention so that more COPD patients can follow an exercise programme. TRIAL REGISTRATION: ClinicalTrials.gov Identifier: HOMEX-1 NCT03461887 (registration date: March 12, 2018; retrospectively registered); HOMEX-2 NCT03654092 (registration date: August 31, 2018).

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6397487/pdf/12890_2019_Article_817.pdf

Gloeckl, R., C. Osadnik, et al. (2019). **"Comparison of continuous flow versus demand oxygen delivery systems in patients with COPD: A systematic review and meta-analysis."** Respirology **24**(4): 329-337.

Demand oxygen delivery systems (DODS) enable prolongation of liquid oxygen cylinder life compared to continuous oxygen flow (CONT) use. Evidence is lacking, however, regarding their efficacy. This study investigated the literature comparing liquid-based CONT to DODS in patients with chronic obstructive pulmonary disease (COPD). Four electronic databases were searched from 1980 until January 2018. Primary outcomes were oxyhaemoglobin saturation (SpO2 %) at rest and during exercise and exercise performance. Risk of bias was evaluated using the Cochrane tool. Data were analysed via meta-analysis where possible using the generic inverse variance method in Revman 5.3 or narrative synthesis. Ten crossover trials involving 152 patients with moderate to severe COPD (forced expiratory volume in 1 s (FEV1) range: 27-42% predicted) were included. There was a large degree of uncertainty regarding potential bias related to allocation concealment and blinding for all studies. Data from three studies (n = 44) showed no significant differences between DODS and CONT in terms of SpO2 % at rest -0.2% (95% CI: -0.5% to 0.1%) or during exercise -0.3% (95% CI: -2.1% to 1.5%). The pooled mean difference of two

studies (n = 56) in 6-min walk distance was 5.7 m (95% CI: -14.4 to 25.8 m). Findings were consistent between the meta-analysis and narrative synthesis. These findings from a limited number of studies suggest oxygen delivery via DODS or CONT confers similar effects in terms of SpO2 % or exercise performance in patients with COPD. However, as DODS devices use various specifications that may yield large intra-individual differences, individual SpO2 % testing appears advisable for those considering DODS use.

https://onlinelibrary.wiley.com/doi/pdf/10.1111/resp.13457

Gloeckl, R., S. Teschler, et al. (2016). **"Comparison of two- and six-minute walk tests in detecting oxygen desaturation in patients with severe chronic obstructive pulmonary disease - A randomized crossover trial."** Chron Respir DisThe two-minute walk test (2MWT) is less well validated than the well-known six-minute walk test (6MWT) as a field walking test in patients with chronic obstructive pulmonary disease (COPD). The primary objective of this study was to compare the accuracy of the 2MWT to the 6MWT in detecting exercise-induced oxygen desaturation in patients with severe COPD. Twenty-six patients with COPD (age: 61 +/- 10 years, forced expired volume in one second: 37 +/- 10%) that were normoxemic at rest performed a 2MWT and a 6MWT under normal ambient conditions on two consecutive days in random order. Oxygen saturation, total walking distance, heart rate, breathing frequency, dyspnea, and leg fatigue were evaluated. Average walking distances were 150 m (95% confidence interval (95% CI): 134-165 m) and 397 m (95% CI: 347-447 m) for the 2MWT and 6MWT, respectively ($r = 0.80$, $p < 0.0001$). The difference in minimum oxygen saturation during the 2MWT (83%, 95% CI: 81-86%) and 6MWT (mean 82%, 95% CI: 80-84%) was not statistically different and the data strongly correlated between the groups ($r = 0.81$, $p < 0.0001$). Other measurements from the 6MWT, including heart rate, breathing rate, and levels of perceived exertion were also comparable in 2MWT. The 2MWT showed comparable validity in detecting exercise-induced oxygen desaturation in patients with severe COPD compared to the 6MWT.

Grischott, T., L. Falcato, et al. (2019). **"Chronic obstructive pulmonary disease (COPD) among opioid-dependent patients in agonist treatment. A diagnostic study."** AddictionAIMS: To estimate the prevalence of chronic obstructive pulmonary disease (COPD) and related risk factors in people in opioid agonist treatment (OAT), to compare airflow limitation severity and age-specific COPD prevalence rates with those in the general population, and to assess the OAT patients' willingness to adopt life-style changes and to use therapeutic offers for COPD management. DESIGN: Cross-sectional study in a random sample of OAT patients. SETTING: Out-patient centres for substance addiction medicine in Zurich, Switzerland. PARTICIPANTS: A total of 125 participants, recruited from November 2016 to April 2017 through invitation letters followed by phone or personal contact. MEASUREMENTS: Standardized questionnaires about drug use, smoking habits and medical history, completed during face-to-face interviews or from medical records. Spirometry without and-depending on the result-with bronchodilation. FINDINGS: Almost one-third [30.3%; 95% confidence interval (CI) = 22.6-39.0%] of the 119 participants with valid spirometry tests were diagnosed with COPD. Among males aged 30-59 years, the age-adjusted prevalence of at least moderate airflow limitation (GOLD grade >/= 2) was 2.4 (95% CI = 1.3-4.4) times as high as in the ever-smoking Swiss population in the same age group. Smoking tobacco (92.0%) and substance inhalation (cannabis = 97.6%, cocaine = 69.6%, heroin = 68.0%) were highly prevalent among all participants. The participants expressed considerable interest in life-style changes and use of therapeutic offers for COPD management, with smoking cessation being least (20.2% of tobacco smokers interested) and pharmacological treatment to alleviate COPD symptoms most popular. CONCLUSIONS: In Switzerland, COPD prevalence and multiple risk factors for COPD appear to be high among people in OAT compared with the general population. Individuals in OAT appear to develop COPD at a younger average age compared with the general population and are open to life-style changes and other COPD management approaches.

https://onlinelibrary.wiley.com/doi/abs/10.1111/add.14559

Guo, Y., F. Cao, et al. (2019). **"Laparoscopic Major Gastrointestinal Surgery Is Safe for Properly Selected Patient with COPD: A Meta-Analysis."** Biomed Res Int **2019**: 8280358.

Background: Laparoscopy has been widely applied in gastrointestinal surgery, with benefits such as less intraoperative blood loss, faster recovery, and shorter length of hospital stay. However, it remains controversial if laparoscopic major gastrointestinal surgery could be conducted for patients with chronic obstructive pulmonary disease (COPD) which was traditionally considered as an important risk factor for postoperative pulmonary complications. The present study was conducted to review and assess the safety and feasibility of laparoscopic major abdominal surgery for patient with COPD. Materials and Methods: Databases including PubMed, EmBase, Cochrane Library, and Wan-fang were searched for all years up to Jul 1, 2018. Studies comparing perioperative results for COPD patients undergoing major gastrointestinal surgery between laparoscopic and open approaches were enrolled. Results: Laparoscopic approach was associated with less intraoperative blood loss (MD = -174.03; 95% CI: -232.16 to -115.91, P < 0.00001; P < 0.00001, I(2)=93% for heterogeneity) and shorter length of hospital stay (MD = -3.30; 95% CI: -3.75 to -2.86, P < 0.00001; P = 0.99, I(2)=0% for heterogeneity). As for pulmonary complications, laparoscopic approach was associated with lower overall pulmonary complications rate (OR = 0.58; 95% CI: 0.48 to 0.71, P < 0.00001; P = 0.42, I(2)=0% for heterogeneity) and lower postoperative pneumonia rate (OR = 0.53; 95% CI: 0.41 to 0.67, P < 0.00001; P = 0.57, I(2)=0% for heterogeneity). Moreover, laparoscopic approach was associated with lower wound infection (OR = 0.51; 95% CI: 0.42 to 0.63, P < 0.00001; P = 0.99, I(2)=0% for heterogeneity) and abdominal abscess rates (OR = 0.59; 95% CI: 0.44 to 0.79, P < 0.0004; P = 0.24, I(2)=30% for heterogeneity). Conclusions: Laparoscopic major gastrointestinal surgery for properly selected COPD patient was safe and feasible, with shorter term benefits.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6420973/pdf/BMRI2019-8280358.pdf

Hartman, J. E., L. Vanfleteren, et al. (2019). **"Endobronchial valves for severe emphysema."** Eur Respir Rev **28**(152)The results of the randomised controlled trials investigating the bronchoscopic lung volume reduction treatment using endobronchial valves (EBV) are promising, and have led to their inclusion in treatment guidelines, US Food and Drug Administration approval and inclusion in routine care in an increasing number of countries. The one-way valve treatment has advanced and is now a regular treatment option. However, this new phase will lead to new challenges in terms of implementation. We believe that key issues in future research concern advanced patient selection, improved methods for target lobe selection, increased knowledge on the predictive risk of a pneumothorax, positioning of pulmonary rehabilitation in conjunction with the EBV treatment, the positioning of lung volume reduction surgery versus EBV treatment, and the long-term efficacy, adverse events, impact on exacerbations and hospitalisations, costs and survival. Hopefully, the increasing number of patients treated, the setup of (inter)national registries and future research efforts will further optimise all aspects of this treatment.

https://err.ersjournals.com/content/errev/28/152/180121.full.pdf

Hill, K., C. Ng, et al. (2019). **"The minimal detectable difference for endurance shuttle walk test performance in people with COPD on completion of a program of high-intensity ground-based walking."** Respir Med **146**: 18-22.

BACKGROUND: In people with moderate-to-severe chronic obstructive pulmonary disease (COPD), the minimal detectable difference (MDD) in endurance shuttle walk test (ESWT) performance following exercise

training is unclear. We sought to determine the MDD for ESWT performance following supervised ground-based walking training using anchor- and distribution-based approaches and report whether these values exceeded random variation in test performance. METHODS: Participants with COPD trained for 30-45min, 2-3 times weekly for 8-10 weeks. The ESWT was performed before and after the training period. Immediately after training, participants rated their change in walking ability using a Global Rating of Change scale. Receiver Operating Characteristic curves were used to derive the value that best separated those who perceived their improvement in walking ability to be at least 'a little' better from 'almost the same, hardly any change'. These values were compared with those calculated using a distribution-based method. Random variation in test performance was defined as the minimal detectable change (MDC), calculated using the standard error of measurement. RESULTS: 78 participants (aged 70+/-8yr and FEV1 43+/-15% predicted) completed the ESWT before and after training. The value that best separated those who perceived their walking ability as 'a little' better was 70s. The 95% confidence intervals around this estimate traversed zero. The distribution-based estimate was 156s. The MDC was 227s. CONCLUSIONS: The MDD established using the anchor- and distribution-based approaches differed considerably. Large variation in test performance cautions against using the MDD to interpret changes in an individual. CLINICAL TRIALS REGISTRATION: Australian New Zealand Clinical Trials Registry (ACTRN12609000472279).

https://www.resmedjournal.com/article/S0954-6111(18)30373-1/pdf

Holte, T. O., J. Asmervik, et al. (2008). **NIPH Systematic Reviews: Executive Summaries**. Effect of Intermittent Oxygen Therapy Among COPD Patients without Severe Hypoxemia. Oslo, Norway, Knowledge Centre for the Health Services at The Norwegian Institute of Public Health (NIPH)

Background Long-term oxygen therapy (LTOT) is prescribed to increase the survival of patients with chronic obstructive pulmonary disease (COPD) and severe resting hypoxemia. Over the last years the question has been raised whether patients without indication for LTOT might have an effect of intermittent oxygen therapy. Intermittent oxygen therapy refers to the not continuous oxygen therapy; ambulant oxygen during activity and short-burst oxygen (SBOT) before or after activity or at rest. The objective of intermittent oxygen therapy is not increased survival, but symptom relief, better function and increased quality of life. The pulmonary units in Norwegian hospitals have no standardised guidelines for the use of intermittent oxygen for this patient group. Mandate The main objective of this project is to give contribution to the discussion on specialist guidelines. The Norwegian Respiratory Society asked the Norwegian Knowledge Centre for the Health Services to summarize the documentation of the effect of intermittent oxygen therapy among COPD patients without severe hypoxemia. Methods We performed a search for systematic reviews in the Cochrane database, and a systematic search for new literature in the databases MEDLINE and EMBASE. Results We included three systematic reviews and six new randomised controlled trials, which were not included in the reviews. Acute effect of ambulatory oxygen during exercise tests COPD patients without hypoxemia have a small effect of oxygen therapy on exercise capacity during exercise tests in a laboratory. The documentation consists of 34 small randomised crossover studies (606 patients) summarized in a systematic review, and of three newer studies. Long term effect of ambulatory oxygen COPD patients without hypoxemia do not have documented long-term effect of ambulant oxygen therapy during regularly exercise over time, compared to placebo. The documentation consists of five studies (159 patients). The review showed that oxygen did not give better exercise capacity, health-related quality of life or oxygen saturation. A new randomized controlled trial of ambulant oxygen during daily activities did not show an effect on quality of life. Acute effect of short-burst oxygen A systematic review with eight randomised controlled trials indicates that SBOT does not reduce dyspnea among COPD patients compared to placebo, neither before nor after activity. We identified no studies that examined the effect of SBOT at rest. Long-term effect of short-burst oxygen We identified only one randomised controlled trial with follow-up of COPD patients given SBOT over time. The availability of SBOT over 6 months among patients with COPD and no hypoxemia at rest did not improve health-related quality of life or reduce acute health care utilisation among the included patients. Conclusion COPD patients without hypoxemia have a small effect of oxygen therapy during exercise tests in a laboratory compared with placebo. SBOT given before or after activity has no documented effect on dyspnea. The results from the tests carried out in laboratories give limited information on the usefulness of the intermittent oxygen therapy in the regular daily life of the patients or the effects on quality of life. The documentation indicates that COPD patients without severe

hypoxemia undergoing oxygen therapy during exercise training over time do not achieve better exercise capacity or health-related quality of life compared with placebo. There is limited documentation concerning the long term effect of intermittent oxygen therapy in the home setting. Further research There is a need for further research focusing on: the long term effect on quality of life of ambulatory oxygen in the home setting, the subgroups of COPD patients with a possible benefit of ambulatory oxygen, and the effect of various doses of oxygen.

Hong, Y. and S. H. Lee (2019). **"Effectiveness of tele-monitoring by patient severity and intervention type in chronic obstructive pulmonary disease patients: A systematic review and meta-analysis."** Int J Nurs Stud **92**: 1-15.

BACKGROUND: Chronic obstructive pulmonary disease is a major burden on healthcare systems worldwide. Tele-monitoring has recently been used for management of chronic obstructive pulmonary disease patients. OBJECTIVES: We analyzed the effect of tele-monitoring on chronic obstructive pulmonary disease patients and performed subgroup analysis by patient severity and intervention type. DESIGN: Systematic review. DATA SOURCE: Electronic databases including Ovid-Medline, Ovid-Embase, and the Cochrane Library. REVIEW METHODS: We conducted a meta-analysis of randomized controlled trials published up to April 2017. Three databases were searched, two investigators independently extracted data and assessed study quality using risk of bias. RESULTS: Out of 1,185 studies, 27articles were identified to be relevant for this study. The included studies were divided by intervention: 15studies used tele-monitoring only, 4studies used integrated tele-monitoring (pure control), and 8studies used integrated tele-monitoring (not pure control). We also divided the studies by patient severity: 16studies included severely ill patients, 8studies included moderately ill patients, and 3studies did not discuss the severity of the patients' illness. Meta-analysis showed that tele-monitoring reduced the emergency room visits (risk ratio 0.63, 95% confidence interval 0.55-0.72) and hospitalizations (risk ratio 0.88, 95% confidence interval 0.80-0.97). The subgroup analysis of patient severity showed that tele-monitoring more effectively reduced emergency room visits in patients with severe vs. moderate disease (risk ratio 0.48, 95% confidence interval 0.31-0.74; risk ratio 1.28, 95% confidence interval 0.61-2.69, retrospectively) and hospitalizations (risk ratio 0.92, 95% confidence interval 0.82-1.02; risk ratio 1.24, 95% confidence interval 0.57-2.70, retrospectively). The mental health quality of life score (mean difference 3.06, 95% confidence interval 2.15-3.98) showed more improved quality of life than the physical health quality of life score (mean difference -0.11, 95% confidence interval -0.83-0.61). CONCLUSIONS: Tele-monitoring reduced rates of emergency room visits and hospitalizations and improved the mental health quality of life score. Integrated tele-monitoring including the delivery of coping skills or education by online methods including pulmonary rehabilitation is recommended to produce significant improvement. This application of integrated tele-monitoring (the delivery of education, exercise etc. in addition to tele-monitoring) is more useful for patients with (very) severe chronic obstructive pulmonary disease than those with moderate disease. Tele-monitoring might be a useful application of information and communication technologies, if the intervention includes the appropriate intervention components for eligible patients. Further studies such as large size randomized controlled trials with sub-group by patient severity and intervention type is needed to confirm these finding.

Houben, C. H. M., M. A. Spruit, et al. (2019). **"Cluster-randomised trial of a nurse-led advance care planning session in patients with COPD and their loved ones."** Thorax **74**(4): 328-336.

RATIONALE: Advance care planning (ACP) is uncommon in patients with chronic obstructive pulmonary disease (COPD). OBJECTIVES: To assess whether a nurse-led ACP-intervention can improve quality of patient-physician end-of-life care communication in patients with COPD. Furthermore, the influence of an ACP-intervention on symptoms of anxiety and depression in patients and loved ones was studied. Finally, quality of death and dying was assessed in patients who died during 2-year follow-up. METHODS: A multicentre cluster randomised-controlled trial in patients with advanced COPD was performed. The intervention group received an 1.5 hours structured nurse-led ACP-session. Outcomes were: quality of

patient-physician end-of-life care communication, prevalence of ACP-discussions 6 months after baseline, symptoms of anxiety and depression in patients and loved ones and quality of death and dying. RESULTS: 165 patients were enrolled (89 intervention; 76 control). The improvement of quality of patient-physician end-of-life care communication was significantly higher in the intervention group compared with the control group ($p<0.001$). The ACP-intervention was significantly associated with the occurrence of an ACP-discussion with physicians within 6 months ($p=0.003$). At follow-up, symptoms of anxiety were significantly lower in loved ones in the intervention group compared with the control group ($p=0.02$). Symptoms of anxiety in patients and symptoms of depression in both patients and loved ones were comparable at follow-up ($p>0.05$). The quality of death and dying was comparable between both groups ($p=0.17$). CONCLUSION: One nurse-led ACP-intervention session improves patient-physician end-of-life care communication without causing psychosocial distress in both patients and loved ones.

https://thorax.bmj.com/content/thoraxjnl/74/4/328.full.pdf

Hsieh, P. C., M. C. Yang, et al. (2019). **"Acupuncture therapy improves health-related quality of life in patients with chronic obstructive pulmonary disease: A systematic review and meta-analysis."** Complement Ther Clin Pract **35**: 208-218.

BACKGROUND: Chronic obstructive pulmonary disease (COPD) is highly prevalent around the world and has a large impact on its patients, leading to a poor health-related quality of life (HRQL) and exercise capacity. Even under optimal medications, there are still many patients with poor HRQL. Body acupuncture therapy (BAT) is a non-invasive and a popular therapy. Therefore, we aimed to comprehensively analyze the effects of BAT in COPD. MATERIALS AND METHODS: Eight electronic databases were searched. We included randomized controlled trials (RCTs) that evaluated the effect of BAT, medication (M), and pulmonary rehabilitation (PR). The primary outcome was HRQL evaluated by St. George's respiratory questionnaire (SGRQ) or COPD assessment test (CAT). RESULTS: Of the 922 articles, 12 studies were included with attesting a total of 798 participants. The result obtained indicated a significant improvement that favored the BAT + M group over the M group in CAT scores (MD: -4.77; 95% CI: -6.53 to -3.01; $p < 0.00001$). CONCLUSIONS: BAT is an effective adjunctive non-pharmacological treatment to improve HRQL in patients under medical treatment for COPD. We suggested that BAT should be considered as one of the methods of management in patients with COPD.

Huang, X., X. Duan, et al. (2019). **"Shengmai injection as an adjunctive therapy for the treatment of chronic obstructive pulmonary disease: A systematic review and meta-analysis."** Complement Ther Med **43**: 140-147.

OBJECTIVE: To evaluate the clinical efficacy of Shengmai injection for the treatment of chronic obstructive pulmonary disease (COPD) through an evidence-based approach. METHODS: Randomized controlled trials (RCTs) investigating the effect of Shengmai injection on COPD were included in this study. Seven electronic databases were searched to obtain eligible studies. The quality of the included RCTs was evaluated according to the Cochrane Risk of Bias Assessment Tool. When appropriate, meta-analysis of the data was conducted by RevMan 5.3 software and Stata 13.0 software. The relative risk (RR) or mean difference (MD) and 95% confidence interval (CIs) were reported for dichotomous or continuous outcomes, respectively. Sensitivity analysis was performed to verify the independence of the results. Funnel plots and the Begg and Egger tests were implemented to determine the potential publication bias. RESULTS: Ultimately, 23 RCTs were included, involving 1804 participants. Meta-analysis showed that the combination of Shengmai injection and western medicine (WM) could achieve a better effect than WM alone in terms of improving the clinical total effective rate (RR = 1.20, 95% CIs: 1.15-1.24), pulmonary function (FEV1(L): MD = 0.41, 95% CIs 0.32 to 0.49; FEV1(%): MD = 6.21, 95% CIs: 2.72-9.71), blood gas index (PaO2: MD = 6.13, 95% CIs: 2.93-9.32; PaCO2: MD=-6.2, 95% CIs: -11.63 to -0.77), immunoglobulin levels (IgG: MD = 3.55, 95% CIs: 3.10-3.99; IgA: MD = 0.34, 95% CIs: 0.31to 0.38; IgM: MD = 0.35, 95% CIs: 0.27 to 0.42), C-reactive protein levels (MD = -8.05, 95% CIs: -10.11 to -6.00) and

the lung rale disappearance time (MD = -2.57, 95% CIs: -3.19 to -1.95). Additionally, the CAT score, mMRC and average hospitalization time were also reduced significantly by Shengmai injection plus WM. Among 11 RCTs that mentioned safety issues, 6 RCTs found no adverse events, and the other 5 RCTs reported the details of adverse events. CONCLUSION: Shengmai injection may positively influence COPD in combination with WM. However, firm conclusions could not be draw due to the low quality of the evidence. Further high-quality studies are still required to test the efficacy of Shengmai injection for this condition.

https://www.sciencedirect.com/science/article/pii/S096522991830877X?via%3Dihub

Jacobs, D. M., U. Pandit, et al. (2019). **"Acute exacerbations in chronic obstructive pulmonary disease: should we use antibiotics and if so, which ones?"** Curr Opin Infect Dis **32**(2): 143-151.

PURPOSE OF REVIEW: Acute exacerbations are a major cause of morbidity and mortality in chronic obstructive pulmonary disease (COPD) with evidence suggesting at least 50% of exacerbations involve bacteria that benefit from antibiotic treatment. Here, we review the most relevant data regarding the use of antibiotics in exacerbations of COPD and provide insights on the selection of initial antibiotic therapy for their treatment. RECENT FINDINGS: Identification of bacterial exacerbations still relies on clinical assessment rather than laboratory biomarkers. Several recent studies, including a meta-analysis and placebo-controlled trials, demonstrate improved outcomes with antibiotics in all but mild exacerbations of COPD, including both inpatient and outpatient. A broader antibiotic regimen should be used for patients who have risk factors for poor outcomes. A risk-stratification approach can guide antibiotic choice, although the stratification algorithm still needs to be validated in a randomized controlled trial. SUMMARY: The use of antibiotics for the treatment of moderate-to-severe suspected bacterial exacerbations in COPD is supported by published trials and evidence-based systematic reviews. Recent trials also show differences in outcomes based on antibiotic choice. More research is necessary to evaluate risk stratification approaches when selecting initial antibiotic therapy.

Jain, S. S., I. N. Sarkar, et al. (2018). **"Using Demographic Factors and Comorbidities to Develop a Predictive Model for ICU Mortality in Patients with Acute Exacerbation COPD."** AMIA Annu Symp Proc **2018**: 1319-1328.

Recognizing factors associated with mortality in patients admitted to the ICU with acute exacerbation of chronic obstructive pulmonary disease could reduce healthcare costs and improve end-of-life care. Previous studies have identified possible predictive variables, but analysis is lacking on the combined effect of demographic factors and comorbidities. Using the MIMIC-III database, this study examined factors associated with mortality in a model incorporating comorbidities, comorbidity indices, and demographic factors. After determining associations between predictive variables and mortality through univariate and multivariate binomial logistic regression, three predictive models were developed: (1) univariate GLM-derived logistic, (2) Mean Gini-derived logistic (MGDL), and (3) random forest. The MGDL model best predicted mortality with an AUROC of 0.778. Variables with the greatest relative importance in determining mortality included the Charlson Comorbidity Index, Elixhauser Index, male, and arrhythmia. The results support the potential of using the MGDL model and need for further work in exploring demographic factors.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6371239/pdf/2963258.pdf

Jolliffe, D. A., L. Greenberg, et al. (2019). **"Vitamin D to prevent exacerbations of COPD: systematic review and meta-analysis of individual participant data from randomised controlled trials."** Thorax **74**(4): 337-345.

BACKGROUND: Randomised controlled trials (RCTs) of vitamin D to prevent COPD exacerbations have yielded conflicting results.Individual participant data meta-analysis could identify factors that explain this variation. METHODS: PubMed, Embase, the Cochrane Central Register of Controlled Trials and Web of Science were searched from inception up to and including 5 October 2017 to identify RCTs of vitamin D supplementation in patients with COPD that reported incidence of acute exacerbations. Individual participant data meta-analysis was performed using fixed effects models adjusting for age, sex, Global Initiative for Chronic Obstructive Lung Disease spirometric grade and trial. RESULTS: Four eligible RCTs (total 560 participants) were identified; individual participant data were obtained for 469/472 (99.4%) participants in three RCTs. Supplementation did not influence overall rate of moderate/severe COPD exacerbations (adjusted incidence rate ratio (aIRR) 0.94, 95% CI 0.78 to 1.13). Prespecified subgroup analysis revealed that protective effects were seen in participants with baseline 25-hydroxyvitamin D levels <25 nmol/L (aIRR 0.55, 95% CI 0.36 to 0.84) but not in those with baseline 25-hydroxyvitamin D levels >/=25 nmol/L (aIRR 1.04, 95% CI 0.85 to 1.27; p for interaction=0.015). Vitamin D did not influence the proportion of participants experiencing at least one serious adverse event (adjusted OR 1.16, 95% CI 0.76 to 1.75). CONCLUSIONS: Vitamin D supplementation safely and substantially reduced the rate of moderate/severe COPD exacerbations in patients with baseline 25-hydroxyvitamin D levels <25 nmol/L but not in those with higher levels. TRIAL REGISTRATION NUMBER: CRD42014013953.

https://thorax.bmj.com/content/74/4/337.long

Kerley, C. P., P. E. James, et al. (2019). **"Dietary nitrate improved exercise capacity in COPD but not blood pressure or pulmonary function: a 2 week, double-blind randomised, placebo-controlled crossover trial."** Int J Food Sci Nutr **70**(2): 222-231.

Dietary nitrate may improve exercise tolerance in some healthy and clinical populations. Existing data regarding dietary nitrate in COPD is inconsistent. We conducted a 14d double-blind, randomised, placebo-controlled, crossover trial of daily nitrate-rich beetroot juice (BRJ; 12.9 mmol) versus nitrate-depleted BRJ (PL; 0.5 mmol). At baseline and after each condition, we assessed functional capacity (incremental shuttle walk test; ISWT), ambulatory blood pressure, pulmonary function, quality of life as well as exhaled nitric oxide (eNO), and plasma nitrate/nitrite (NOx). Eight subjects with COPD completed the trial. BRJ supplementation was associated with significantly increased NOx ($p < .05$) and a 14.6% increase in ISWT distance (+56 m, $p = .00004$) as well as a trend towards increased eNO compared to PL. There was no other differences. Dietary nitrate appears to have ergogenic effect in subjects with mild-moderate COPD. This effect does not appear to be related to altering blood pressure or pulmonary function.

https://www.tandfonline.com/doi/full/10.1080/09637486.2018.1492521

Kourlaba, G., G. Hillas, et al. (2019). **"The Economic Burden of Chronic Obstructive Pulmonary Disease in Greece."** Appl Health Econ Health Policy **17**(1): 111-121.

BACKGROUND: Chronic obstructive pulmonary disease (COPD) is a leading cause of disability and death worldwide, imposing a substantial socioeconomic burden on societies and patients due to the long-term management required. OBJECTIVE: To assess the economic burden of COPD in Greece and its potential determinants. METHODS: A population-based, random-digit dialled, telephone nationwide survey was conducted to recruit patients with COPD in Greece (N = 351). A structured questionnaire was used to collect data. The total annual cost per patient from a societal perspective was calculated. RESULTS: The mean (95% CI) annual total cost per patient for the management of COPD from a societal perspective was euro2150 (euro1879-euro2443). The total annual cost was mainly driven by the medication cost (36.1%), followed by the cost of hospitalizations (26.7%) and long-term oxygen therapy (13.8%). Multiple generalized linear model revealed that age, COPD Assessment Test (CAT) score and exacerbations were independently associated with the total annual cost. CONCLUSION: Investment in interventions aiming

at delaying progression of disease, preventing acute exacerbations, and managing chronic symptoms are required to reduce the overall economic burden of COPD in Greece.

https://link.springer.com/article/10.1007%2Fs40258-018-0431-5

Latshang, T. D., R. P. M. Tardent, et al. (2019). **"Sleep and breathing disturbances in patients with chronic obstructive pulmonary disease traveling to altitude: a randomized trial."** Sleep **42**(1)Study Objectives: Patients with chronic obstructive pulmonary disease (COPD) have impaired pulmonary gas exchange near sea level. The purpose of the current study was to investigate whether exposure to hypobaric hypoxia during a stay at altitude affects nocturnal oxygen saturation, breathing pattern, and sleep in patients with moderate to severe COPD. Methods: Thirty-two patients with COPD, median age 67 years, FEV1 59% predicted, PaO2 68 mmHg, living below 800 m, underwent polysomnography and questionnaire evaluations in Zurich (490 m), and in Swiss Alpine villages at 1650 and 2590 m, for two nights each, in random order. Mean nocturnal oxygen saturation (SpO2), the apnea-hypopnea index (AHI), and sleep structure were compared between altitudes. Results: Polysomnography during the first night at each altitude revealed a reduced SpO2 at 1650 and 2590 m (medians 89% and 85%) compared with 490 m (92%, p <0.05 vs. higher altitudes) and a higher AHI (medians 26.8/hr and 55.7/hr) vs. 490 m (15.4/hr, p <0.05 vs. higher altitudes) due to emergence of frequent central apneas/hypopneas. At 2590 m, sleep efficiency (median 59%) and slow-wave sleep (median 17% of total sleep time) were reduced compared with 490 m (72% and 20%, respectively, p <0.05). In the morning after one night at 2590 m, patients estimated to have spent more time awake (median 110 min) than at 490 m (43 min, p <0.05) and felt slightly less alert. Conclusions: During a stay at moderate altitude, lowlanders with moderate to severe COPD experience nocturnal hypoxemia that induces central sleep apneas, altered sleep structure, and insomnia. These novel findings help us to counsel patients with COPD planning altitude travel. Trial Registration: ClinicalTrials.gov: NCT01870830.

https://academic.oup.com/sleep/article-abstract/42/1/zsy203/5229280?redirectedFrom=fulltext

Lee, E. N. and M. J. Kim (2019). **"Meta-analysis of the Effect of a Pulmonary Rehabilitation Program on Respiratory Muscle Strength in Patients with Chronic Obstructive Pulmonary Disease."** Asian Nurs Res (Korean Soc Nurs Sci) **13**(1): 1-10.

PURPOSE: Pulmonary rehabilitation (PR) programs are important in the treatment of patients with chronic obstructive pulmonary disease (COPD) but vary widely in type, duration, and efficacy. This meta-analysis investigated the effect of PR programs on respiratory muscle strength in patients with COPD. METHODS: PubMed, Embase, and CINAHL were searched. The primary outcome variables were maximal expiratory pressure (MEP) and maximal inspiratory pressure (MIP). The secondary outcome variables were the modified Borg score after the 6-min walking test, percent predicted forced expiratory volume in 1 second (FEV1%pred), and percent FEV1/forced volume capacity (FVC). Comprehensive Meta-Analysis, version 3.0, was used to analyze the data. The effect size was calculated using the standardized mean difference (SMD) and 95% confidence interval (CI). RESULTS: Twenty randomized controlled trials (with 992 participants) were included in the analysis. The PR programs had a significant effect on the MEP (SMD, 0.87; 95% CI, 0.42-1.32; p < .001), MIP (SMD, 0.53; 95% CI, 0.13-0.93; p = .009), and modified Borg score (SMD, -0.37; 95% CI, -0.52 to -0.22; p < .001) in patients with COPD. There was no effect on FEV1%pred (SMD, 0.09; 95% CI, -0.12 to 0.30; p = .406) or FEV1/FVC% (SMD, 0.04; 95% CI, -0.17 to 0.26; p = .702). CONCLUSION: PR programs improve respiratory muscle strength in patients with COPD. Strategies for selecting a suitable PR program need to be developed, and future studies should evaluate the long-term effects of such programs on pulmonary function.

https://www.asian-nursingresearch.com/article/S1976-1317(18)30245-7/pdf

Lee, P. N., B. A. Forey, et al. (2018). **"The relationship of cigarette smoking in Japan to lung cancer, COPD, ischemic heart disease and stroke: A systematic review."** F1000Res **7**: 204.

Background: To present up-to-date meta-analyses of evidence from Japan relating smoking to major smoking-related diseases. Methods: We restricted attention to lung cancer, chronic obstructive pulmonary disease (COPD), ischemic heart disease (IHD) and stroke, considering relative risks (RRs) for current and ex-smokers relative to never smokers. Evidence by amount smoked and time quit was also considered. For IHD and stroke only, studies had to provide age-adjusted RRs, with age-specific results considered. For each disease we extended earlier published databases to include more recent studies. Meta-analyses were conducted, with random-effects RRs and tests of heterogeneity presented. Results: Of 40 studies, 26 reported results for lung cancer and 7 to 9 for each other disease. For current smoking, RRs (95%CIs) were lung cancer 3.59 (3.25-3.96), COPD 3.57 (2.72-4.70), IHD 2.21 (1.96-2.50) and stroke 1.40 (1.25-1.57). Ex-smoking RRs were lower. Data for lung cancer and IHD showed a clear tendency for RRs to rise with increasing amount smoked and decrease with increasing time quit. Dose-response data were unavailable for COPD and unclear for stroke, where the association was weaker. Conclusions: Compared to studies in other Asian and Western countries, current smoking RRs were quite similar for IHD and stroke. The comparison is not clear for COPD, where the Japanese data, mainly from cross-sectional studies, is limited. For lung cancer, the RRs are similar to those in other Asian countries, but substantially lower than in Western countries. Explanations for this are unclear, but less accurate reporting of smoking by Japanese may contribute to the difference.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6367657/pdf/f1000research-7-15218.pdf

Lewis, A., E. L. Axson, et al. (2019). **"Protocol for a systematic literature review and network meta-analysis of the clinical benefit of inhaled maintenance therapies in chronic obstructive pulmonary disease."** BMJ Open **9**(2): e025048.

INTRODUCTION: Chronic obstructive pulmonary disease (COPD) exacerbations progress the course of disease and impair lung function. Inhaled maintenance therapy reduces exacerbations. It is not yet established which inhaled therapy combination is best to reduce exacerbations, lung function decline and symptom burden. METHODS AND ANALYSIS: MEDLINE, EMBASE and the Cochrane Library will be searched for articles between January 2011 and May 2018 using a pre-specified search strategy. Conference proceedings will be searched. Systematic reviews (with or without meta-analysis), randomised controlled trials (RCTs), cohort studies and case controlled studies comparing six interventions comprising different combinations of long-acting bronchodilators and inhaled corticosteroids in unison or on their own. The primary outcome is the reduction in moderate-to-severe exacerbations. Secondary outcomes include: lung function, quality of life, mortality and other adverse events. Titles and abstracts will screened by the primary researcher. A second reviewer will repeat this on a proportion of records. The Population, Intervention, Comparator, Outcomes and Study framework will be used for data extraction. A network meta-analyses of outcomes from RCTs and real-world evidence will be integrated if feasible. The 95% credible interval will be used to assess the statistical significance of each summary effect. Ranking of interventions will be based on their surface under cumulative ranking area. ETHICS AND DISSEMINATION: COPD exacerbations are burdensome to patients. We aim to report results that provide clinicians with a more informed choice of which inhaled therapy combinations are best to reduce exacerbations, improve disease burden and reduce lung function and exercise capacity decline, compared with the potential harms, in certain populations with COPD. PROSPERO REGISTRATION NUMBER: CRD42018088013.

http://spiral.imperial.ac.uk/bitstream/10044/1/67306/7/e025048.full.pdf

Lewis, A., D. Dullaghan, et al. (2019). **"An observational cohort study of exercise and education for people with chronic obstructive pulmonary disease not meeting criteria for formal pulmonary rehabilitation programmes."** Chron Respir Dis **16**: 1479973119838283.

Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality. Pulmonary rehabilitation (PR) is offered to patients with functional breathlessness. However, access to PR is limited. The objective of this study was to evaluate whether a 4-week education and exercise programme offered to COPD patients with Medical Research Council (MRC) dyspnoea 1-2 improves disease self-management. Patients were recruited by their GP to attend four weekly 2-h sessions provided by a multidisciplinary team. Patients completed outcome measures before and after the program. Forty-two patients entered the programme and 26 out of 42 (61.9%) completed all sessions. The Bristol COPD Knowledge Questionnaire and Patient Activation Measure improved (both p </= 0.001). Disease burden was not reduced according to the COPD assessment test. All patients accepted a referral for ongoing exercise. Fourteen current smokers (81.3%) accepted a referral for smoking cessation, three patients with anxiety or depression (37.5%) accepted a psychological therapies referral. The programme improved COPD disease knowledge, patient activation and stimulated referrals to further services supporting disease management. Randomised controlled trials are warranted for similar interventions for COPD patients with early stage disease.

Lewthwaite, H., T. Olds, et al. (2019). **"Use of time in chronic obstructive pulmonary disease: Longitudinal associations with symptoms and quality of life using a compositional analysis approach."** PLoS One **14**(3): e0214058.

BACKGROUND AND OBJECTIVES: This study explored whether, for people with chronic obstructive pulmonary disease (COPD), changes to the 24-hour composition of physical activity (PA), sedentary behaviour (SB) and sleep were associated with changes in symptoms and health-related quality of life (HRQoL); and how time re-allocations between these behaviours were associated with changes in outcomes. METHODS: This study pools data on people with COPD drawn from two previous studies: a randomised controlled trial of cognitive behavioural therapy and pulmonary rehabilitation and a usual care cohort. Participants recalled behaviours and completed symptom and HRQoL assessments at baseline (T0) and four months (T1). Linear mixed-effects models (pooled control/intervention samples) predicted changes in outcomes from T0 to T1 with a change to the 24-hour behaviour composition; compositional isotemporal substitution predicted change in outcomes when re-allocating time between behaviours. RESULTS: Valid data were obtained for 95 participants (forced expiratory volume in one second %predicted = 49.6+/-15.3) at T0 and T1. A change in the 24-hour behaviour composition was associated with a change in anxiety ($p<0.01$) and mastery ($p<0.01$), but not breathlessness, depression or fatigue. When modelling time re-allocation with compositional isotemporal substitution, more time re-allocated to higher intensity PA or sleep was associated with favourable changes in outcomes; re-allocating time to SB or light PA was associated with unfavourable changes in outcomes. The direction of association, however, could not be determined. CONCLUSION: To improve the overall health and wellbeing of people with COPD, intervention approaches that optimise the composition of PA, SB and sleep may be beneficial.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6428329/pdf/pone.0214058.pdf

Li, H., W. P. Fu, et al. (2013). **"Microsomal epoxide hydrolase gene polymorphisms and risk of chronic obstructive pulmonary disease: A comprehensive meta-analysis."** Oncol Lett **5**(3): 1022-1030.

Microsomal epoxide hydrolase (EPHX1) is an enzyme involved in the detoxification the products of smoking and is proposed to be a genetic factor for the development of chronic obstructive pulmonary disease (COPD). Two functional polymorphisms of EPHX1, T113C and A139G, have been analyzed in numerous studies to assess the COPD risk attributed to these variants. However, the conclusions were controversial. We performed a comprehensive meta-analysis to clarify these findings. A total of 24 studies comprising 8,259 COPD patients and 42,883 controls were included. The overall results showed that the EPHX1 113 mutant homozygote was significantly associated with an increased risk of COPD (OR, 1.33; 95% CI, 1.06-1.69). The subgroup analyses demonstrated this association in Caucasian individuals (OR, 1.61; 95% CI,

1.12-2.31) but not in Asian individuals. The 139 mutant heterozygote was significantly associated with a decreased risk of COPD in Asian populations (OR, 0.82; 95% CI, 0.68-0.99) but not in Caucasian populations. Pooled analyses revealed that the extremely slow (OR, 1.77; 95% CI, 1.23-2.55) and slow EPHX1 enzyme activity (OR, 1.44; 95% CI, 1.13-1.85) were associated with an increased risk of COPD, while the fast enzyme activity was not associated with a decreased risk of COPD. The stratified analysis demonstrated this association in Caucasian but not in Asian individuals. Furthermore, a modest difference in the risk of COPD was observed between the subgroups by using the cigarette smokers or the non-smokers as controls. A significant correlation between the two functional polymorphisms, T113C and A139G, of the EPHX1 gene and the enzyme activity and the individual's susceptibility to COPD was noted. In addition, the results supported a contribution of EPHX1 to the aetiology of COPD.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3576314/pdf/ol-05-03-1022.pdf

Liang, J., M. J. Abramson, et al. (2019). **"Interdisciplinary COPD intervention in primary care: a cluster randomised controlled trial."** Eur Respir JWe evaluated the effectiveness of an interdisciplinary, primary care-based model of care for COPD.A cluster randomised controlled trial was conducted in 43 general practices in Australia. Adults with a history of smoking and/or COPD, aged >/=40 years with >/=2 clinic visits in the previous year were enrolled following spirometric confirmation of COPD. The model of care comprised smoking cessation support, home medicines review (HMR), and home-based pulmonary rehabilitation (HomeBase). Main outcomes included changes in St George's Respiratory Questionnaire (SGRQ) score, COPD Assessment Test (CAT), dyspnoea, smoking abstinence and lung function at six and 12 months.We identified 272 participants with COPD (157 intervention, 115 usual care); 49/157 (31%) completed both HMR and HomeBase. Intention-to-treat analysis showed no statistically significant difference in change in SGRQ at six months (adjusted between group difference 2.45 favouring intervention, 95%CI - 0.89 to 5.79). Per protocol analyses showed clinically and statistically significant improvements in SGRQ in those receiving the full intervention compared to usual care (difference 5.22, 0.19 to 10.25). No statistically significant differences were observed in change in CAT, dyspnoea, smoking abstinence or lung function.No significant evidence was found for the effectiveness of this interdisciplinary model of care for COPD in primary care over usual care. Low uptake was a limitation.

https://erj.ersjournals.com/content/53/4/1801530

Liu, C., Y. Li, et al. (2019). **"Adjuvant therapy efficacy of Chinese drugs pharmaceutics for COPD patients with respiratory failure: a meta-analysis."** Biosci Rep **39**(4)We performed a meta-analysis to evaluate the efficacy and safety of Western medicine combined with Tanreqing for patients with chronic obstructive pulmonary disease (COPD) and respiratory failure. We comprehensively searched several online databases from the times of their inception to November 2018. The trial quality was assessed using the bias risk tool recommended by the Cochrane library. Relative risks (RRs) and their 95% confidence intervals (CIs) for binary outcomes and weighted mean differences (MDs) with 95% CIs for continuous data were calculated. A fixed effect model indicated that integrated Tanreqing group experienced higher overall treatment effectiveness (RR = 1.23, 95% CI: 1.17-1.30, P=0.000). Pooled results from random effects models indicated the oxygen partial pressure of the test group was significantly higher than that of the control groups (MD = 9.55, 95% CI: 4.57-14.52, P<0.000). The carbon dioxide pressure of the test group was significantly lower than that of the control groups (MD = -6.06, 95% CI: -8.19 to -3.93, P=0.000). The lung function score of the test group was significantly higher than that of the control group (MD = 7.87, 95% CI: 4.45-11.29). Sensitivity analysis indicated that the data were statistically robust. Clinical effects of Western medicine combined with Tanreqing used to treat combined COPD/respiratory failure were better than those afforded by Western medicine; no serious adverse reactions were noted. However, publication bias was evident, and further trials with larger sample sizes are required.

http://www.bioscirep.org/content/ppbioscirep/39/4/BSR20182279.full.pdf

Low, S. W., J. Z. Lee, et al. (2019). **"Endobronchial Valves Therapy for Advanced Emphysema: A Meta-Analysis of Randomized Trials."** J Bronchology Interv Pulmonol **26**(2): 81-89.

BACKGROUND: Trials suggest that bronchoscopic lung volume reduction (BLVR) with endobronchial valve (EBV) implantation may produce similar effects as lung volume reduction surgery, by inducing atelectasis and reducing hyperinflation through a minimally invasive procedure. This study sought to investigate the efficacy and safety of BLVR with EBV for advanced emphysema. METHODS: We searched PubMed, EMBASE, Web of Science, CINAHL, ClinicalTrials.gov, and Cochrane Library databases for randomized controlled trials comparing EBV implantation versus standard medical treatment or sham bronchoscopy. The main outcome of interest was the percentage change of forced expiratory volume in 1 second. RESULTS: Data analyzed from 5 randomized controlled trials with 703 patients revealed improvement in percentage change of forced expiratory volume in 1 second in EBV group compared with control group [weighted mean difference (WMD)=11.43; 95% confidence interval (CI), 6.05-16.80; P<0.0001] and improvement in the St. George's Respiratory Questionnaire score (WMD=-5.69; 95% CI, -8.67 to -2.70; P=0.0002). There is no difference shown in the 6-minute walking test (WMD=14.12; 95% CI, -4.71 to 32.95; P=0.14). The overall complication rate of EBV was not significantly different except for an increased rate of pneumothorax [relative risk (RR)=8.16; 95% CI, 2.21-30.11; P=0.002), any hemoptysis (RR=5.01; 95% CI, 1.12-22.49; P=0.04)] and valve migration (RR=8.64; 95% CI, 2.01-37.13; P=0.004). CONCLUSION: BLVR using EBV shows short-term improvement in lung function and quality of life, but with increased risk of minor hemoptysis, pneumothorax, and valve migration. Follow-up data on the studies are needed to determine its long-term efficacy.

Maltais, F., J. L. Aumann, et al. (2019). **"Dual bronchodilation with tiotropium/olodaterol further reduces activity-related breathlessness versus tiotropium alone in COPD."** Eur Respir J **53**(3)The 3-min constant speed shuttle test (CSST) was used to examine the effect of tiotropium/olodaterol compared with tiotropium at reducing activity-related breathlessness in patients with chronic obstructive pulmonary disease (COPD).This was a randomised, double-blind, two-period crossover study including COPD patients with moderate to severe pulmonary impairment, lung hyperinflation at rest and a Mahler Baseline Dyspnoea Index <8. Patients received 6 weeks of tiotropium/olodaterol 5/5 microg and tiotropium 5 microg in a randomised order with a 3-week washout period. The speed for the 3-min CSST was determined for each patient such that an intensity of breathing discomfort >/=4 ("somewhat severe") on the modified Borg scale was reached at the end of a completed 3-min CSST.After 6 weeks, there was a decrease in the intensity of breathlessness (Borg dyspnoea score) at the end of the 3-min CSST from baseline with both tiotropium (mean -0.968, 95% CI -1.238- -0.698; n=100) and tiotropium/olodaterol (mean -1.325, 95% CI -1.594- -1.056; n=101). The decrease in breathlessness was statistically significantly greater with tiotropium/olodaterol versus tiotropium (treatment difference -0.357, 95% CI -0.661- -0.053; p=0.0217).Tiotropium/olodaterol reduced activity-related breathlessness more than tiotropium in dyspnoeic patients with moderate to severe COPD exhibiting lung hyperinflation.

https://erj.ersjournals.com/content/erj/53/3/1802049.full.pdf

Maricoto, T., J. Correia-de-Sousa, et al. (2019). **"Inhaler technique education in elderly patients with asthma or COPD: impact on disease exacerbations-a protocol for a single-blinded randomised controlled trial."** BMJ Open **9**(1): e022685.

INTRODUCTION: Chronic Obstructive Pulmonary Disease (COPD)and asthma affect more than 10% of the population. Most patients use their inhaler incorrectly, mainly the elderly, thereby becoming more susceptible to poor clinical control and exacerbations. Placebo device training is regarded as one of the best teaching methods, but there is scarce evidence to support it as the most effective one to improve major clinical outcomes. Our objective is to perform a single-blinded RCT to assess the impact of this education tool in these patients. METHODS AND ANALYSIS: A multicentre single-blinded Randomised Controlled Trial (RCT) will be set up, comparing an inhaler education programme with a teach-to-goal placebo-device training versus usual care, with a 1-year follow-up, in patients above 65 years of age with asthma or COPD. Intervention will be provided at baseline, and after 3 and 6 months, with interim analysis at an intermediate time point. Exacerbation rates were set as primary outcomes, and quality of life, adherence rates, clinical control and respiratory function were chosen as secondary outcomes. A sample size of 146 participants (73 in each arm) was estimated as adequate to detect a 50% reduction in event rates. Two-sample proportions chi(2) test will be used to study primary outcome and subgroup analysis will be carried out according to major baseline characteristics. ETHICS AND DISSEMINATION: Every participant will sign a written consent form. A Data Safety Monitoring Board will be set up to evaluate data throughout the study and to monitor early stopping criteria. Identity of all participants will be protected. This protocol was approved on 22 November 2017 by the local Ethics Committee of University of Beira Interior, with the reference number CE-UBI-Pj-2017-025. Results will be presented in scientific meetings and published in peer-reviewed journals. TRIAL REGISTRATION NUMBER: NCT03449316; Pre-Results.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6352786/pdf/bmjopen-2018-022685.pdf

Maricoto, T., J. Marques-Gomes, et al. (2019). **"Inhaler Review in Older Adults with Asthma or COPD: A Cost-Effectiveness Study and a Perspective in Portugal."** J Am Geriatr SocOBJECTIVES: Older patients with asthma or chronic obstructive pulmonary disease are particularly susceptible to exacerbations that may be associated with incorrect use of inhalers. Educational programs with inhaler technique review seem to be effective, but no studies have addressed their cost-effectiveness in older adult patients. The objective was to perform a cost-effectiveness analysis of education programs in older patients and estimate the cost benefit of applying such a program in Portugal. DESIGN: We developed a decision tree analysis from a healthcare perspective, according to intervention costs and the exacerbation rates and costs described in a previous meta-analysis. A sensitivity analysis of worst and best case scenarios was performed to estimate thresholds for intervention affordable limits, as well as cost-saving estimations and incremental cost-effectiveness ratios (ICERs) for a Portuguese scenario. SETTING AND PARTICIPANTS: We estimated cost-effectiveness thresholds applicable in all settings and performed a sensitivity analysis of a theoretical intervention model in all patients including an inhaler technique review at an annual appointment with a doctor and a nurse. RESULTS: In the best case scenario, the intervention affordable budget could be up to almost 1800euro (US $1585.24) per patient per year. Mean intervention-associated savings in Portugal would be 311.88euro (US $274.68) per patient per year, representing annual savings up to euro131 million (US $150 million) for the whole health system, already including intervention costs. ICERs for Portugal vary between 93.73euro (US $82.55) and 437.43euro (US $385.25) per exacerbation avoided. CONCLUSION: A model of an intervention program with an inhaler technique review in older adult patients suggests that this intervention is cost-effective and can generate significant savings. J Am Geriatr Soc 1-7, 2019.

https://onlinelibrary.wiley.com/doi/abs/10.1111/jgs.15834

Obeidat, M., M. Sadatsafavi, et al. (2019). **"Precision health: treating the individual patient with chronic obstructive pulmonary disease."** Med J AustChronic obstructive pulmonary disease (COPD) is defined based on a reduced ratio of forced expiratory volume in one second (FEV1) to forced vital capacity (FVC) on spirometry. However, within this definition, there is significant heterogeneity of pathophysiological processes that lead to airflow obstruction and variation in phenotypic manifestations across patients.

Current pharmacological treatments are based on large randomised clinical trials that apply to an "average" patient. Precision health enables tailoring of treatment for each individual patient by taking into account their unique characteristics. The number needed to treat (NNT) metric is often used to define implementation of precision health for specific interventions, with common endpoints requiring an NNT </= 5 to achieve precision therapy. Higher NNTs may be acceptable for rare but important endpoints such as mortality. Long-acting muscarinic antagonists and inhaled corticosteroids, which are commonly used in COPD, have 1-year treatment NNTs between 15 and 20 for exacerbation prevention in unselected patients with COPD. Subgroup identification using biomarkers or clinical traits may enable precision health. For example, NNT for inhaled corticosteroids is 9 in patients with a blood eosinophil count >/= 300 cells/muL and 8 for long-acting muscarinic antagonists in patients with a body mass index </= 20 kg/m(2) . Lung volume reduction surgery is associated with an NNT of 6 for survival over 5 years in patients with upper lobe-predominant disease and low exercise capacity (whereas the NNT is 245 when no bioimaging or exercise markers are used). Continuous domiciliary oxygen therapy (for at least 15 hours/day) has an NNT of 5 for survival over 5 years in patients with resting hypoxemia (PaO2 < 60 mmHg on room air). Emerging areas of precision health in COPD with potential for low NNTs in specific circumstances include anti-interleukin-5 therapy for eosinophilic COPD, and immunoglobulin replacement therapy for patients with severe immunoglobulin deficiency.

https://onlinelibrary.wiley.com/doi/abs/10.5694/mja2.50138

Pathak, U., N. C. Gupta, et al. (2019). **"Risk of COPD due to indoor air pollution from biomass cooking fuel: a systematic review and meta-analysis."** Int J Environ Health Res: 1-14.

Chronic obstructive pulmonary disease (COPD) is one of the leading causes of mortality in developing nations. In this meta-analysis, we aimed to determine the association between indoor air pollution and risk of COPD. Database searches were conducted using indoor air pollution, biomass and COPD related terms to identify relevant articles. The eligible studies were case-control, retrospective cohort, cross-sectional studies and conducted in adults that assessed COPD using any diagnostic criteria. A total of 35 studies with 73,122 participants were included. The pooled analysis showed that exposure to indoor air pollution due to solid biomass fuels increased risk of COPD by 2.65 (95% confidence interval [CI] 2.13-3.31; n = 73,122) and chronic bronchitis by 2.89 (95% CI 2.18-3.82) times more compared to non-biomass fuels. The risk of COPD was higher in Africa region (odds ratio [OR] 3.19), Asia (OR 2.88), South America (OR 2.15), Europe (OR 2.30) and North America (OR 2.14). The results of our meta-analysis indicated that exposure to indoor air pollution due to biomass smoke is strongly associated with COPD. Abbreviations: CS: cross-sectional; CC: case-control; NR: not reported; ATS: American Thoracic Society; BMRC: British Medical Research Council; GOLD: Global Initiative for Obstructive Lung Disease; IAP: indoor air pollution; BMF: biomass fuel; CB: chronic bronchitis; OR: odds ratio; UCI; upper confidence interval; LCI: lower confidence interval; COPD: chronic obstructive pulmonary disease.

https://www.tandfonline.com/doi/full/10.1080/09603123.2019.1575951

Prins, H. J., R. Duijkers, et al. (2019). **"CRP-guided Antibiotic Treatment in acute exacerbations of COPD admitted to Hospital."** Eur Respir JINTRODUCTION: the role of antibiotics in acute exacerbations of COPD (AECOPD) is controversial, a biomarker identifying patients who benefit from antibiotics is mandatory. We performed a RCT in patients with AECOPD comparing CRP-guided antibiotic treatment to patient reported symptoms according to GOLD strategy in order to show a reduction of antibiotic prescription METHODS: patients hospitalised with AECOPD were randomised to receive antibiotics based according the GOLD strategy or according to the CRP (>/=50 mg.L(-1)) strategy. RESULTS: 101 patients were randomised to the CRP-group and 119 to GOLD-group. Fewer patients in the CRP-group were treated with antibiotics 31.7% versus 46.2% in the GOLD-group (p=0.028) (adjusted OR, 0.178 95%CI 0.077-0.411, p=0.029). Thirty-day treatment failure rate was equal (CRP-group 44.5% versus GOLD-group 45.5%; (p=0.881) (adjusted OR 1.146 95%CI 0.649-1.187 p=0.630) as was time to next exacerbation (CRP-group 32 days, versus GOLD-group 28 days (p=0.713) (adjusted HR0.878 (95%CI

0.649-1.187 p=0.398). Length of stay was similar in both groups (CRP-group 7 days versus GOLD-group 6 days (p=0.206). On day 30 no difference in symptoms score, quality of life or serious adverse events was detected. CONCLUSION: CRP as a biomarker to guide antibiotic treatment in severe AECOPD leads to a significant reduction of antibiotic treatment. In the present study no differences between both groups in adverse events were found. Further research is needed for the generalisability of these findings TRIAL REGISTRATION: clinicaltrials.gov (NCT01232140).

https://erj.ersjournals.com/content/early/2019/03/06/13993003.02014-2018

Rasmussen, S. M., J. Brok, et al. (2018). **"Association Between Chronic Obstructive Pulmonary Disease and Type 2 Diabetes: A Systematic Review and Meta-Analysis."** Copd **15**(5): 526-535.

BACKGROUND: Chronic obstructive pulmonary disease (COPD) has been associated with an increased risk of type 2 diabetes (T2D). However, the mechanisms linking COPD and T2D is not fully understood and contradicting results are reported in the literature. AIM: The aim of this study is to investigate whether COPD is associated with an increased risk of T2D. METHODS: A systematic review and meta-analysis of cohort and case-control studies were performed. Search for studies and data extraction was carried out by two authors independently. Study quality was assessed by NOS. Adjusted data were pooled using the random effects model to calculate summary odds ratios (ORs) with corresponding 95% confidence intervals (CIs). RESULTS: We identified four cohort studies and three case-control studies with a total of 1,369,560 participants of whom 42,716 were COPD patients. The quality of the studies was acceptable, with an average on 7.7 indicating overall good study quality. The meta-analysis on adjusted data from all seven studies showed that the COPD group had a higher risk of T2D compared with the non-COPD group: random effect OR = 1.17 (1.01-1.35), p = 0.03. No heterogeneity was found I(2) = 0%. When including only studies diagnosing both COPD and T2D according to recommended guidelines the association did not remain statistically significant, OR =1.17 (0.96-1.42), p = 0.12. CONCLUSION: This systemic review and meta-analyses showed that the association between COPD and T2D might be influenced by the diagnostic method and should be further investigated in studies using diagnostic definition according to guidelines. Nevertheless, physicians should be aware of comorbidities in COPD patients.

https://www.tandfonline.com/doi/full/10.1080/15412555.2018.1532495

Salari-Moghaddam, A., A. Milajerdi, et al. (2018). **"Processed red meat intake and risk of COPD: A systematic review and dose-response meta-analysis of prospective cohort studies."** Clin NutrBACKGROUND & AIMS: No earlier study has summarized findings from previous publications on processed red meat intake and risk of Chronic Obstructive Pulmonary Disease (COPD). This systematic review and meta-analysis was conducted to examine the association between processed red meat intake and COPD risk. METHODS: We searched in PubMed/Medline, ISI Web of Knowledge, Scopus, EMBASE and Google Scholar up to April 2018 to identify relevant studies. Prospective cohort studies that considered processed red meat as the exposure variable and COPD as the main outcome variable or as one of the outcomes were included in the systematic review. Publications in which hazard ratios (HRs) were reported as effect size were included in the meta-analysis. Finally, five cohort studies were considered in this systematic review and meta-analysis. RESULTS: In total, 289,952 participants, including 8338 subjects with COPD, aged >/=27 years were included in the meta-analysis. These studies were from Sweden and the US. Linear dose response meta-analysis revealed that each 50 gr/week increase in processed red meat intake was associated with 8% higher risk of COPD (HR: 1.08; 95% CI: 1.03, 1.13). There was an evidence of non-linear association between processed red meat intake and risk of COPD (P < 0.001). CONCLUSIONS: In this systematic review and meta-analysis, we found a significant positive association between processed red meat intake and risk of COPD. PROSPERO REGISTRATION NUMBER: CRD42017077971.

https://www.clinicalnutritionjournal.com/article/S0261-5614(18)30205-X/fulltext

Shergis, J. L., F. Thien, et al. (2019). **"12-month randomised controlled trial of ginseng extract for moderate COPD."** ThoraxBACKGROUND: Panax ginseng (ginseng) is a therapeutic herb which might be beneficial in COPD. The study investigated if ginseng, compared with placebo, is effective and safe for people with moderate COPD. METHODS: This multicentre, randomised, double-blind, placebo-controlled trial compared 24 weeks of ginseng capsules (100 mg twice daily) with placebo. Participants were followed up for a further 24 weeks. Participants were aged 40 years and over and had airflow limitation in the moderate (Global Initiative for Chronic Obstructive Lung Disease 2) COPD range. The coprimary endpoints were the St George's Respiratory Questionnaire, the COPD Assessment Test and the Short Form Health Survey. Secondary outcomes included lung function, exacerbation rate and use of relief medication. FINDINGS: 168 participants were randomised 1:1 from five centres in Australia and China. Baseline characteristics were balanced between groups. There were no significant differences between ginseng and placebo, with overall results improving in both groups. Ginseng seemed safe for, and well tolerated by, people with COPD. INTERPRETATION: There was no significant difference in improvement in health-related quality of life (primary outcome) between the ginseng and placebo groups. TRIAL REGISTRATION NUMBER: ACTRN12610000768099.

https://thorax.bmj.com/content/early/2019/04/01/thoraxjnl-2018-212665

Simonelli, C., M. Vitacca, et al. (2019). **"Effectiveness of manual therapy in COPD: A systematic review of randomised controlled trials."** PulmonologyPURPOSE: Manual therapy (MT) has been proposed in pulmonary rehabilitation programmes for patients with chronic obstructive pulmonary disease (COPD), but an updated systematic review of the evidence is lacking. We aimed to systematically review the effectiveness of MT interventions, alone or added to exercise, on lung function, exercise capacity and quality of life in COPD patients, compared to other therapies (e.g. exercise alone) or no treatment. MATERIALS AND METHODS: We searched MEDLINE, EMBASE, Physiotherapy Evidence Database, and Cochrane Central Register of Controlled Trials databases, using the terms: COPD, manual therapy, manipulation, joint mobilisation, osteopathic manipulation. Only randomised controlled trials (RCT) were considered. RESULTS: Out of 555 articles screened, 6 fulfilled the inclusion criteria. The study designs were heterogeneous (with different intervention schedules) and there was a high risk of bias. No effect on lung function was found, while results on exercise capacity were contrasting. MT had no effect on quality of life, although valid measures were available only in one study. Only mild adverse events were reported. CONCLUSIONS: Few RCTs of poor methodological quality are available on the effects of MT in COPD. More and better quality RCTs are needed before this technique can be included in rehabilitation programmes for these patients.

https://www.sciencedirect.com/science/article/pii/S2531043719300078?via%3Dihub

Sink, E., K. Patel, et al. (2018). **"Effectiveness of a novel, automated telephone intervention on time to hospitalisation in patients with COPD: A randomised controlled trial."** J Telemed Telecare: 1357633x18800211.

Introduction Owing to its capacity to perform remote assessments, telemedicine is rising as a new force in chronic obstructive pulmonary disease (COPD) management. We conducted an eight month randomised-controlled-trial to study the effect of an automated telemedicine intervention on patients' time-to-hospitalisation. Methods A total of 168 patients with a diagnosis of COPD in the past 24 months were enrolled to receive the intervention at a primary care clinic. The treatment group received daily phone messages from an automated system asking them to report if they were breathing better than, worse than, or the same as the day prior. Patients reported their breathing status by responding to the text message or call. If a patient reported breathing worse, an alert was sent directly to that patient's

provider within the clinic. The control group received the same daily phone messages as the treatment group. However, no proactive breathing alerts were ever generated to the provider for these subjects. The primary outcome was the subjects' time-to-first-COPD-related hospitalisation following the start of messages. Results The treatment group's time-to-hospitalisation was significantly different than the control group's with a hazard ratio of 2.36 (95% confidence interval 1.02-5.45, p = 0.0443). The number needed-to-treat ratio was 8.62. Subject engagement consistently ranged between 60% and 75%. The treatment group received both proactive monitoring and follow-up care from the providers. Discussion Active monitoring with provider feedback enables the detection of exacerbation events early enough for subjects to avoid admissions. The use of non-smartphone interventions reduces barriers to care presented by more complicated and expensive technologies. This intervention represents a simple, innovative, and inexpensive tool for improved COPD management.

Spathis, D. and P. Vlamos (2017). **"Diagnosing asthma and chronic obstructive pulmonary disease with machine learning."** Health Informatics J: 1460458217723169.

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.

Staub, L. J., R. R. Mazzali Biscaro, et al. (2019). **"Lung Ultrasound for the Emergency Diagnosis of Pneumonia, Acute Heart Failure, and Exacerbations of Chronic Obstructive Pulmonary Disease/Asthma in Adults: A Systematic Review and Meta-analysis."** J Emerg Med **56**(1): 53-69.

BACKGROUND: Lung ultrasound can accelerate the diagnosis of life-threatening diseases in adults with respiratory symptoms. OBJECTIVE: Systematically review the accuracy of lung ultrasonography (LUS) for emergency diagnosis of pneumonia, acute heart failure, and exacerbation of chronic obstructive pulmonary disease (COPD)/asthma in adults. METHODS: PubMed, Embase, Scopus, Web of Science, and LILACS (Literatura Latino Americana e do Caribe em Ciencias da Saude; until 2016) were searched for prospective diagnostic accuracy studies. Rutter-Gatsonis hierarchical summary receiver operating characteristic method was used to measure the overall accuracy of LUS and Reitsma bivariate model to measure the accuracy of the different sonographic signs. This review was previously registered in PROSPERO (Centre for Reviews and Dissemination, University of York, York, UK; CRD42016048085). RESULTS: Twenty-five studies were included: 14 assessing pneumonia, 14 assessing acute heart failure, and four assessing exacerbations of COPD/asthma. The area under the summary receiver operating characteristic curve of LUS was 0.948 for pneumonia, 0.914 for acute heart failure, and 0.906 for exacerbations of COPD/asthma. In patients suspected to have pneumonia, consolidation had sensitivity of 0.82 (95% confidence interval [CI] 0.74-0.88) and specificity of 0.94 (95% CI 0.85-0.98) for this disease. In acutely dyspneic patients, modified diffuse interstitial syndrome had sensitivity of 0.90 (95% CI 0.87-0.93) and specificity of 0.93 (95% CI 0.91-0.95) for acute heart failure, whereas B-profile had sensitivity of 0.93 (95% CI 0.72-0.98) and specificity of 0.92 (95% CI 0.79-0.97) for this disease in patients with respiratory failure. In patients with acute dyspnea or respiratory failure, the A-profile without PLAPS (posterior-lateral alveolar pleural syndrome) had sensitivity of 0.78 (95% CI 0.67-0.86) and specificity of 0.94 (95% CI 0.89-0.97) for exacerbations of COPD/asthma. CONCLUSION: Lung ultrasound is an accurate tool for the emergency diagnosis of pneumonia, acute heart failure, and exacerbations of COPD/asthma.

https://www.jem-journal.com/article/S0736-4679(18)30925-9/fulltext

Steindal, S. A., H. Torheim, et al. (2019). **"Effectiveness of nursing interventions for breathlessness in people with chronic obstructive pulmonary disease: A systematic review and meta-analysis."** J Adv Nurs **75**(5): 927-945.

AIM: To critically review and synthesize the findings of studies that evaluated the effectiveness of nursing interventions for improving breathlessness in adults with chronic obstructive pulmonary disease. BACKGROUND: Systematic reviews of nursing interventions for breathlessness in people with chronic obstructive pulmonary disease have not been specifically addressed. DESIGN: Systematic review with meta-analysis. DATA SOURCES: A systematic search of Medline, CINAHL, PsycINFO and Embase was performed for studies published between January 2000 and June 2017. REVIEW METHODS: Risk of bias, data extraction and meta-analysis were conducted using Cochrane methodology. The quality of evidence was assessed using the GRADE approach. RESULTS: Twenty papers were included. A meta-analysis of interventions performed at home, including two trials, showed a significant effect in favour of experimental groups for the symptom score of the St. George Respiratory Questionnaire compared with controls. A meta-analysis of interventions performed in clinics with home follow-up showed a significant effect in favour of experimental groups for the mastery and fatigue scores of the Chronic Respiratory Questionnaire compared with controls. In this category of intervention, an additional meta-analysis showed a significant effect in favour of experimental groups for the symptom, activity and total scores of the St. George Respiratory Questionnaire compared with controls. The quality of evidence was assessed to be very low to moderate. CONCLUSION: The results are equivocal as to whether nursing interventions performed at home and nursing interventions performed in hospital with follow-up improve breathlessness in people with chronic obstructive pulmonary disease.

https://onlinelibrary.wiley.com/doi/abs/10.1111/jan.13902

Sul, A. R., D. H. Lyu, et al. (2018). **"Effectiveness of telemonitoring versus usual care for chronic obstructive pulmonary disease: A systematic review and meta-analysis."** J Telemed Telecare: 1357633x18811757.

AIMS: The purpose of this research was to investigate the effectiveness of telemonitoring for chronic obstructive pulmonary disease. METHODS: We searched MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials and CINAHL up to September 2018. We selected randomised controlled trials comparing telemonitoring and control groups for chronic obstructive pulmonary disease management. Two reviewers independently examined articles based on eligibility, extracted data and evaluated the risk of bias. The Cochrane tool was applied for assessing the risk of bias. The 95% confidence interval was calculated. RESULTS: A total of 28 randomised controlled trials were included. Meta-analysis revealed that there were no variables showing a statistically significant difference between telemonitoring and control groups. Chronic obstructive pulmonary disease exacerbation rate (six studies) was not different between two groups (risk ratio 0.67, 95% confidence interval 0.31-1.42). Subgroup analysis showed that telemonitoring reduced exacerbation rates when the intervention continued for longer than six months or pulmonary function was monitored. No differences between groups were noticed for mortality (seven studies, risk ratio 0.89, 95% confidence interval 0.60-1.34). Similarly, no differences between groups were observed in the patient-reported outcomes (St George's Respiratory Questionnaire, Chronic Respiratory Disease Questionnaire-Dyspnea score) and for health service utilization (length of hospital stay, number of hospital admissions, number of emergency room visits). CONCLUSIONS: Telemonitoring for chronic obstructive pulmonary disease was unlikely to result in statistically significant improvements in health outcomes. However, our novel finding was that at least six months of intervention duration and monitoring of pulmonary function play roles in activating the effects of telemonitoring.

Tang, B., J. Wang, et al. (2019). **"Risks of budesonide/formoterol for the treatment of stable COPD: a meta-analysis."** Int J Chron Obstruct Pulmon Dis **14**: 757-766.

Purpose: The aim of this study was to investigate the comparative risks of budesonide/formoterol, versus placebo or monotherapies, for the treatment of patients with stable COPD. Materials and methods: We undertook a systematic search of the literature in PubMed, Embase, and the Cochrane Central Register of Controlled Trials, for randomized controlled trials (RCTs) comparing budesonide/formoterol with control regimens for the treatment of patients with stable COPD and at least 12 weeks of follow-up, meeting the inclusion criteria. Studies were reviewed, and OR with corresponding 95% CI was used to pool the results. Results: A total of eight studies involving 9,254 patients met the inclusion criteria of this meta-analysis. Compared with placebo, combination therapy with budesonide/formoterol was associated with a significantly higher risk of adverse effects including oral candidiasis (OR: 3.09, 95% CI: 1.95-4.91) and dysphonia (OR: 2.76, 95% CI: 1.40-5.44), but not pneumonia (OR: 0.94, 95% CI: 0.64-1.37) or bronchitis (OR: 1.36, 95% CI: 0.95-1.95). A similar pattern was also evident for the comparison of formoterol with budesonide/formoterol, with increased occurrence of oral candidiasis (OR: 2.72, 95% CI: 1.33-5.58) and dysphonia (OR: 4.13, 95% CI: 1.95-8.76); however, there were no significant differences in pneumonia (OR: 1.31, 95% CI: 0.98-1.74) or bronchitis (OR: 1.05, 95% CI: 0.83-1.31). In contrast, compared with budesonide, combined budesonide/formoterol was associated with similar risks of adverse effects, including pneumonia (OR: 1.20, 95% CI: 0.60-2.39), bronchitis (OR: 0.95, 95% CI: 0.41-2.20), oral candidiasis (OR: 0.79, 95% CI: 0.41-1.53), and dysphonia (OR: 1.00, 95% CI: 0.40-2.47). Conclusion: Combination therapy does not cause more adverse events, including pneumonia and bronchitis, than control (placebo, formoterol, or budesonide) treatment in patients with stable COPD, while there were higher risks of oral candidiasis and dysphonia compared with the non-inhaled corticosteroid group (placebo, formoterol).

https://www.dovepress.com/getfile.php?fileID=48840

Tang, B., J. Wang, et al. (2019). **"Comparative Ef fi cacy of Budesonide/Formoterol with Budesonide, Formoterol or Placebo for Stable Chronic Obstructive Pulmonary Disease: A Meta-Analysis."** Med Sci Monit **25**: 1155-1163.

BACKGROUND The 2018 Global Initiative for Chronic Obstructive Lung Disease publication suggested that the combination of bronchodilator therapy of inhaled glucocorticoid/long-acting beta(2) adrenoceptor agonist is more effective in improving pulmonary function and health status in the treatment of patients with acute exacerbations than the individual components; however, it is not known whether this also the case for stable chronic obstructive pulmonary disease (COPD). The purpose of this meta-analysis was to evaluate the effectiveness of budesonide/formoterol in the maintenance and relief therapy of patients with stable COPD. MATERIAL AND METHODS An electronic search of the literature in MEDLINE, Embase, and Cochrane Central Register of Controlled Trials was undertaken to identify published randomized controlled trials (RCTs) of >/=12 weeks duration comparing the budesonide/formoterol, with budesonide, formoterol, or placebo in the treatment of patients with stable COPD. The identified RCTs were reviewed. The mean difference (MD) with corresponding 95% confidence interval (CI) was used to pool the results. RESULTS Seven high quality studies with RCTs met the inclusion criteria for meta-analysis. Compared with budesonide alone, the combination therapy of budesonide/formoterol showed significant improvement in the following spirometric indices: pre-dose forced expiratory volume in 1 second (FEV(1)) (SMD: 0.26, 95% CI: 0.18, 0.34; P=0.000). In addition, versus formoterol alone, budesonide/formoterol was associated with a significant increase in pre-dose FEV(1) (SMD: 0.12, 95% CI: 0.07, 0.17; P=0.000). A similar pattern was also evident in the comparison to placebo, where budesonide/formoterol yielded greater increase in pre-dose FEV(1) (SMD: 0.24, 95% CI: 0.18, 0.30; P=0.000). Moreover, compared with other controls, the combination of budesonide-formoterol signi fi cantly improved morning peak expiratory flow and evening peak expiratory flow, signi fi cantly reduced the total score of St. George's Respiratory Questionnaire. CONCLUSIONS For stable COPD patients, compared with controls (monocomponents or placebo), budesonide/formoterol improved pulmonary function and health status. Future larger long-term RCTs are warranted to assess the beneficial clinical efficacy of budesonide/formoterol in COPD patients.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6380161/pdf/medscimonit-25-1155.pdf

Udsen, F. W., O. Hejlesen, et al. (2014). **"A systematic review of the cost and cost-effectiveness of telehealth for patients suffering from chronic obstructive pulmonary disease."** J Telemed Telecare **20**(4): 212-220.

We conducted a systematic review of the evidence on the costs and cost-effectiveness of telehealth for patients with chronic obstructive pulmonary disease (COPD). A literature search identified six relevant economic evaluations that were assessed according to the Consensus Health Economic Criteria list (CHEC list). Three studies were from North America and three studies were from Europe. All studies reported the use of home monitoring devices that measured and transmitted different physical indicators to nurses who provided personalised feedback to patients during weekdays. The six studies involved a total of 559 COPD patients of whom 281 were randomised to telehealth. The review demonstrated a potential for cost savings. All six studies reported a lower average cost per patient with telehealth plus usual care compared with usual care alone. However, the quality of the economic evidence was poor. Five studies were evaluated as low quality and one study was evaluated as moderate quality, with CHEC list scores of 21-68%. Caution is advised for healthcare decision-makers seeking large-scale implementation of telehealth in routine clinical practice. The clinical effectiveness of such implementations with follow-up exceeding 12 months has not yet been demonstrated.

van Geffen, W. H., D. J. Slebos, et al. (2019). **"Surgical and endoscopic interventions that reduce lung volume for emphysema: a systemic review and meta-analysis."** Lancet Respir Med **7**(4): 313-324.

BACKGROUND: Severe emphysema is a debilitating condition with few treatment options. Lung volume reduction procedures in the treatment of severe emphysema have shown excellent results in selected patients but their exact role remains unclear with studies reporting a wide variation in outcomes. We therefore aimed to evaluate the effects of volume reduction. METHODS: We did a systematic review and meta-analysis. We searched MEDLINE on Sept 29, 2016, for trials of lung volume reduction in patients with emphysema, and we did an updated search on Embase and PubMed on June 18, 2018. We only included randomised controlled studies published in English evaluating the intervention with either sham or standard of care. Inclusion was limited to trials of techniques in which there was sustainable volume reduction. Primary outcomes were residual volume, FEV1, St George's Respiratory Questionnaire (SGRQ), and 6-min walk distance (6MWT). Secondary outcomes were severe adverse events (including mortality), short-term mortality, and overall mortality. We extracted summary level data from the trial publications and where necessary we obtained unpublished data. A random-effects model with the I(2) statistic was used to determine heterogeneity and trial weight in each analysis. The study is registered with the PROSPERO database, number CRD42016045705. FINDINGS: We identified 4747 references in the search, and included 20 randomised controlled trials of lung volume reduction involving 2794 participants with emphysema. Following lung volume reduction from any of the interventions in pooled analyses (ie, surgery, endobronchial valve, endobronchial coil, or sclerosing agents), the mean differences compared with the control were reduction in residual volume of 0.58 L (95% CI -0.80 to -0.37), increase in FEV1 of 15.87% (95% CI 12.27 to 19.47), improvement in 6MWT of 43.28 m (31.36 to 55.21), and reduction in the SGRQ of 9.39 points (-10.92 to -7.86). The odds ratio for a severe adverse event, which included mortality, was 6.21 (95% CI 4.02 to 9.58) following intervention. Regression analysis showed improvements relative to the degree of volume reduction: FEV1 ($r(2)=0.86$; $p<0.0001$), 6MWT ($r(2)=0.77$; $p<0.0001$), and SGRQ ($r(2)=0.70$; $p<0.0001$). Most studies were at high risk of bias for lack of blinding, and heterogeneity was high for some outcomes when pooled across all interventions, but was generally lower in the subgroups by intervention type. INTERPRETATION: Despite limitations of high risk of bias and heterogeneity for some analyses, our results provide support that lung volume reduction in patients with severe emphysema on maximal medical treatment has clinically meaningful benefits. These benefits should be considered alongside potential adverse events. FUNDING: None.

https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(18)30431-4/fulltext

Varmaghani, M., M. Dehghani, et al. (2019). **"Global prevalence of chronic obstructive pulmonary disease: systematic review and meta-analysis."** East Mediterr Health J **25**(1): 47-57.

Background: Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality worldwide. Aims: To synthesize data on the worldwide prevalence and severity of COPD by geographical region, age groups, and smoking status in a systematic review. Methods: A systematic search was performed following Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines. International databases including PubMed, Scopus and Web of Science were searched for population-based studies published between January 2004 and May 2015 that reported the prevalence of COPD anywhere in the world. The prevalence of COPD was calculated based on World Health Organization (WHO) regions and sex and severity stages using metaprop. Meta-regression and subgroup analysis were applied to determine the sources of heterogeneity. Results: Sixty papers were screened with a combined subject sample size of 127 598. The prevalence of post-bronchodilator COPD was 12.16% (10.91-13.40%). The pooled prevalence of COPD was 15.70% (13.80-18.59%) in men and 9.93% (8.73-11.13%) in women. Among all WHO regions, the highest prevalence was recorded in the Region of the Americas (14.53%), and the lowest was recorded in the South-East Asia Region/Western Pacific Region (8.80%). Meta-regression model variables were: sample size, WHO region, study quality score, level of gathering data, publication year, and sampling methods that justified 29.82% of heterogeneity detected among COPD prevalence rates worldwide. Conclusions: Global prevalence of COPD among men is about 5% higher than among women. The most prevalent stage of COPD is stage 1.

Vivodtzev, I., E. L'Her, et al. (2019). **"Automated O2 titration improves exercise capacity in patients with hypercapnic chronic obstructive pulmonary disease: a randomised controlled cross-over trial."** Thorax **74**(3): 298-301.

Automatically titrated O2 flows (FreeO2) was compared with constant O2 flow on exercise capacity, O2 saturation and risk of hyperoxia-related hypercapnia in patients with severe COPD with baseline hypercapnia and long-term oxygen therapy (LTOT). Twelve patients were enrolled in a randomised double-blind cross-over study to perform exercise with either FreeO2 or constant flow. Endurance time (primary outcome) and SpO2 were both significantly improved with FreeO2compared with constant flow ($p<0.04$), although pCO2 was similar in both conditions. Automated titration of O2 significantly and clinically improved endurance walking time in patients with severe COPD receiving LTOT, without worsening of pCO2 TRIAL REGISTRATION NUMBER: Results , NCT01575327.

https://thorax.bmj.com/content/74/3/298.long

Vogel-Claussen, J., C. O. Schonfeld, et al. (2019). **"Effect of Indacaterol/Glycopyrronium on Pulmonary Perfusion and Ventilation in Hyperinflated COPD Patients (CLAIM): A Double-Blind, Randomised, Crossover Trial."** Am J Respir Crit Care MedRATIONALE: In the CLAIM study, dual bronchodilation with indacaterol/glycopyrronium (IND/GLY) significantly reduced hyperinflation, which translated into improved cardiac function, measured by left ventricular end-diastolic volume and cardiac output. Pulmonary microvascular blood flow (PMBF) is reduced in COPD; however, the effect of reduced lung hyperinflation on PMBF remains unknown. OBJECTIVES: To determine the effect of lung deflation with IND/GLY on PMBF and regional pulmonary ventilation using magnetic resonance imaging (MRI) in hyperinflated patients with COPD. METHODS: In this double-blind, randomized, two-period crossover study [https://clinicaltrials.gov/ NCT02442206], gadolinium-enhanced MRI and phase-resolved

functional lung MRI were used to measure PMBF and regional ventilation, respectively, in COPD patients receiving IND/GLY versus placebo. MEASUREMENTS AND MAIN RESULTS: Sixty-two (62) patients were randomized to receive once-daily IND/GLY (110/50 mug) for 14 days, followed by 14 days of placebo, or vice versa. Treatment periods were separated by a 14-day washout. Sixty patients were included in the per-protocol analysis. MRI measurements showed significant improvements in total PMBF (P=0.006) and regional PMBF (P values for individual lobes were between 0.004-0.022) in response to IND/GLY versus placebo. Regional ventilation was also significantly improved with IND/GLY, as evidenced by a 12.4% increase versus placebo (P=0.011), a 14.3% relative decrease in ventilation defect percentage (VDP) of non-/hypo-ventilated lung tissue (cut-off was defined as 0.075 regional ventilation, P=0.0002), and a 15.7% reduction in the coefficient of variation of regional ventilation compared with placebo (P<0.0001). CONCLUSIONS: Pharmacological intervention with IND/GLY improves pulmonary microvascular blood flow and regional ventilation in COPD patients with hyperinflation. Clinical trial registration available at www.clinicaltrials.gov, ID NCT02442206.

Wang, K., Y. Hao, et al. (2019). **"A Systematic Review and Meta-Analysis on Short-Term Particulate Matter Exposure and Chronic Obstructive Pulmonary Disease Hospitalizations in China."** J Occup Environ Med **61**(4): e112-e124.

OBJECTIVE: We conducted a meta-analysis of short-term particulate matter (PM) exposure and chronic obstructive pulmonary disease (COPD) hospitalizations in China, including data from two-pollutant model. METHODS: From PubMed and Web of Science, we selected case-crossover or time-series studies conducted in Mainland China, Hong Kong, Macao, or Taiwan to investigate the association between PM exposure and COPD hospitalizations. The meta-analysis was performed using data from both single-pollutant and two-pollutant models for PM2.5 and PM10. RESULTS: A total of 16 studies were included in our analysis. Short-term exposure to PM2.5 and PM10 were both significantly associated with COPD hospitalizations. The results remained robust in two-pollutant model, whereas subgroup analyses demonstrated a modest heterogeneity. CONCLUSIONS: Our review shows a small but obvious exposure-hospitalization effect in China. More studies are needed to generate the needed evidence, and advocacy is needed to stimulate initiation of solutions to the problem.

Wang, L., K. Wu, et al. (2018). **"The Effects of Tai Chi on Lung Function, Exercise Capacity and Health Related Quality of Life for Patients With Chronic Obstructive Pulmonary Disease: A Pilot Study."** Heart Lung CircBACKGROUND: Although several studies have assessed the effect of Tai Chi in management of chronic obstructive pulmonary disease (COPD), these studies have a wide sample variation and convey inconclusive results. This study aims to determine if a 3-month Tai Chi program improves lung function, exercise capacity, and health related quality of life (HRQoL) in people with COPD. METHODS: A randomised controlled, single blind trial was undertaken. Patients were randomly allocated to either Tai Chi group (n=26) or control group (n=24). Participants in the Tai Chi group received a Tai Chi exercise program three times weekly for 3-months while participants in the control group were advised to maintain their routine activities. Outcome measures included lung function, 6-minute walk distance (6WMD) and COPD Assessment Test (CAT). The measurements took place at baseline and immediately after the 3-month intervention period. RESULTS: Of 50 participants, 46 completed the intervention. Compared to control, Tai Chi significantly increased 6WMD (mean difference 60.5m, 95% CI 30.27-78.69), and reduced score of CAT (mean difference 14 points, 95% CI 11-24). An 86% compliance to the Tai Chi training was noted and no adverse events were observed in Tai Chi group. CONCLUSIONS: The Tai Chi program is a safe, effective and feasible method to improve exercise capacity and health-related quality of life in people with COPD.

https://www.heartlungcirc.org/article/S1443-9506(18)31833-X/fulltext

Westra, B., S. de Wolf, et al. (2019). **"Quality of resistance training description in COPD trials: study protocol for a systematic review."** BMJ Open **9**(1): e025030.

INTRODUCTION: Limb muscle dysfunction is a common manifestation in patients with chronic obstructive pulmonary disease (COPD). Optimising of limb muscle function is therefore an important goal during pulmonary rehabilitation of patients with COPD. Resistance training (RT) is the best available intervention to achieve this goal. Previous systematic reviews on RT primarily focused on methodological quality. However, the intervention holds the essence of each experimental study. Replication of RT interventions requires clear, complete and accessible reporting of the essential components. The American College of Sports Medicine (ACSM) provides evidence-based guidelines for RT prescription and recommends RT models specific to desired outcomes, that is, improvements in strength, muscular hypertrophy, power or local muscle endurance. The aim of this review is to investigate if the application of the RT principles and key training variables is described sufficiently in current evidence on the effects of RT interventions in patients with COPD. METHODS AND ANALYSIS: Any research study (randomised, non-randomised controlled, controlled pre-post studies and observational studies) with an RT intervention in patients with COPD will be considered for this systematic review. Potentially relevant studies published in English from inception to 1 October 2017 will be identified from Embase, Cochrane Library, Cumulative Index of Nursing and Allied Health Literature (CINAHL) and Physiotherapy Evidence Database (PEDro). Studies exploring the effects of RT following a single session and RT interventions limited to other respiratory chronic diseases will not be included. Additionally, studies including non-COPD participants will be excluded, if the COPD data are not separated. Pairs of reviewers will independently extract data using data collecting sheets. Quality appraisal of RT description will be performed in timeframes according to the latest published ACSM position statement on exercise or RT. ETHICS AND DISSEMINATION: This protocol is a systematic review and therefore ethical approval is not required. The results of this review will be disseminated through peer-reviewed publication and presented at scientific conferences. PROSPERO REGISTRATION NUMBER: CRD42017067403.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6347903/pdf/bmjopen-2018-025030.pdf

Windmon, A., M. Minakshi, et al. (2018). **"TussisWatch: A Smartphone System to Identify Cough Episodes as Early Symptoms of Chronic Obstructive Pulmonary Disease and Congestive Heart Failure."** IEEE J Biomed Health InformChronic Obstructive Pulmonary Disease (COPD) and Congestive Heart Failure (CHF) are leading chronic health concerns among the aging population today. They are both typically characterized by episodes of cough that share similarities. In this paper, we design TussisWatch, a smart-phone based system to record and process cough episodes for early identification of COPD or CHF. In our technique, for each cough episode, we do the following: (1) filter noise; (2) use domain expertise to partition each cough episode into multiple segments, indicative of disease or otherwise; (3) identify a limited number of audio features for each cough segment; (4) remove inherent biases as a result of sample size differences; and finally, (5) design a two-level classification scheme, based on the idea of Random Forests, to process a recorded cough segment. Our classifier, at the first-level, identifies whether or not a given cough segment indicates a disease. If yes, the second level classifier identifies the cough segment as symptomatic of COPD or CHF. Testing with a cohort of 9 COPD, 9 CHF and 18 CONTROLS subjects spread across both genders, races and ages, our system achieves good performance in terms of Sensitivity, Specificity, Accuracy and Area under ROC curve. The proposed system has the potential to aid early access to healthcare, and may be also used to educate patients on self-care at home.

https://ieeexplore.ieee.org/document/8471168/

Wootton, S. L., K. Hill, et al. (2019). **"Effects of Ongoing Feedback During a 12-Month Maintenance Walking Program on Daily Physical Activity in People with COPD."** LungThis multi-centred, randomised controlled trial explored the effects of adding ongoing feedback to a 12-month unsupervised maintenance walking program, on daily physical activity (PA) in people with chronic obstructive pulmonary disease. Participants were randomised to either an intervention group (IG) or a usual care group (UCG). During the maintenance program, the IG received ongoing feedback (telephone calls, biofeedback provided via pedometer and progressive goal setting) and the UCG received no feedback. The SenseWear(R) Pro3 Armband was used to measure PA. Of the 86 participants {IG = 42, (mean [SD]: age 70 [7] years; FEV1 43 [16] % predicted); UCG = 44, (age 69 [9] years; FEV1 44 [15] % predicted)} included at baseline, 43 had sufficient data to be included in the final analysis. There were no between-group differences in any of the PA variables from baseline to completion of the program (all p > 0.05). Ongoing feedback was no more effective than no feedback in improving PA during a 12-month unsupervised walking program.Trial Registration: The trial was registered in the Australia and New Zealand Clinical Trials Registry (ACTRN12609000472279).

https://link.springer.com/article/10.1007%2Fs00408-019-00216-5

Xie, X., Y. Zhang, et al. (2015). **"Vitamin D-binding protein gene polymorphisms and chronic obstructive pulmonary disease susceptibility: A meta-analysis."** Biomed Rep **3**(2): 183-188.

The vitamin D-binding protein (VDBP) genetic polymorphisms have been associated with chronic obstructive pulmonary disease (COPD). A number of studies have been conducted to investigate the combined effects of the VDBP gene (GC) rs7041 and rs4588 polymorphisms on the COPD risk. However, the results obtained are inconclusive. The present meta-analysis aimed to investigate whether GC polymorphisms may be a potential risk factor for COPD. The Web of Science, PubMed, Google Scholar, Embase, Cochrane Library, China National Knowledge Infrastructure and Wanfang Database were searched from inception until June 1, 2014. The meta-analysis was performed using the STATA 12.0 software. Twelve case-control studies, including 2,937 subjects, met the inclusion criteria. Overall, a significantly increased risk was detected in populations of GC*1F homozygotes, whereas no associations between other GC polymorphisms and COPD risk were detected. According to ethnicity, the results demonstrated that the GC*1F homozygotes may be a risk factor for COPD and the GC*2 homozygotes may be a protective factor against COPD in the Asian population. However, similar associations were not observed among the Caucasian population. In conclusion, the current meta-analysis indicates that the GC*1F homozygotes may be a risk factor for COPD and the GC*2 homozygotes may be a protective factors against COPD in the Asian population.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4360878/pdf/br-03-02-0183.pdf

Zayed, Y., M. Barbarawi, et al. (2019). **"Triple versus Dual Inhaler therapy in moderate-to-severe COPD: A systematic review and meta-analysis of randomized controlled trials."** Clin Respir JINTRODUCTION: Treatment of COPD is evolving specially with triple inhaler therapy. OBJECTIVES: To perform a meta-analysis to ascertain the safety and efficacy of triple inhaler therapy consisting of an inhaled-glucocorticoid (ICS), long-acting muscarinic-antagonist (LAMA), and long-acting beta2-agonist (LABA) when compared with dual therapy (ICS-LABA or LAMA-LABA). METHODS: We performed an electronic database search to include randomized controlled trials (RCTs) comparing between triple and dual inhalers. Pooled rate-ratio (RR) or odds-ratio (OR) for dichotomous data and weighted mean difference (MD) for continuous data were calculated with their corresponding 95% confidence interval (CI). RESULTS: Our study included 12 RCTs totaling 19,322, mean age of 65+/-8.2 years and 68.2% were male. Pooled analysis demonstrated a significant reduction in moderate-to-severe COPD exacerbations with triple therapy (RR 0.75; 95% CI 0.69-0.83; P< 0.01). Additionally, triple therapy caused significant increase in trough FEV1 (MD 0.09 L; 95% CI 0.07-0.12; P<0.01), significant reduction in the mean St. George's Respiratory Questionnaire (SGRQ) score (MD -1.67; 95% CI -2.02- -1.31; P<0.01), and more patients experienced >/=4 points reduction of SGRQ score (OR 1.27; 95% CI 1.19-1.35; P<0.01). Triple therapy

was associated with an increased risk of pneumonia when compared to LABA/LAMA (OR 1.25; 95% 1.03-1.97; P=0.03) but there were no significant differences in other adverse events between triple and dual inhalers. CONCLUSIONS: Among patients with moderate-to-severe COPD, triple inhaler therapy was associated with a reduction of moderate-to-severe COPD exacerbations, improved lung function, and improved quality of life when compared to dual inhaler therapy but with an increased pneumonia risk. This article is protected by copyright. All rights reserved. KEY WORDS: COPD, triple inhaler, dual inhaler, meta-analysis.

https://onlinelibrary.wiley.com/doi/pdf/10.1111/crj.13026

Zeng, S., A. Tham, et al. (2018). **"Back to the Box: Using Lung Volumes to Predict Susceptibility to Develop Chronic Obstructive Pulmonary Disease among Smokers."** Ann Am Thorac Soc **15**(Supplement_4): S286-s287.

BACKGROUND: Abnormal lung volumes that represent air trapping are common in chronic obstructive pulmonary disease (COPD). However, their clinical significance in those without spirometrically defined COPD (normal forced expiratory volume in 1 s [FEV1] to forced vital capacity [FVC] ratio) is unclear. METHODS: Using the Veterans Administration Informatics and Computing Infrastructure (VINCI) database, we identified 7,479 patients at risk for COPD (smokers > 40 years of age without restrictive lung disease) who had preserved spirometry (FEV1/FVC and FEV1 >/= lower limit of normal) and also had concomitant lung volume measurements by plethysmography across 37 Veterans Affairs Medical Centers in the United States between 1985 and 2017, and examined their subsequent health records for clinical diagnoses of COPD, respiratory exacerbations, healthcare utilization, spirometry, and mortality. We then estimated the association of lung volumes representing air trapping (residual volume [RV], functional residual capacity [FRC], inspiratory capacity [IC], and their ratios to total lung capacity [TLC]) with health outcomes and changes in spirometry using mixed-effect linear (and logistic) regression modeling with inclusion of follow-up time as random effects, and Cox proportional hazards and Poisson regression modeling as indicated (1). Predicted values and ranges for lung function measurements were calculated using Crapo predicted formulas (2 - 4), except for FRC/TLC, IC, and IC/TLC, for which data from Francisco and colleagues (5) and Quanjer and colleagues (6) were used. Data from other VA Medical Centers were not used because of lack of availability of coded pulmonary function testing data that were obtainable through VINCI (1). RESULTS: Air trapping was prevalent, with 30.8% of patients having RV/TLC greater than the upper limit of normal. RV/TLC varied widely, spanning 46% +/- 13% and 38% +/- 11% across the increments of FEV1/FVC and FEV1, respectively. Patients with RV/TLC greater than the upper limit of normal were more likely to receive subsequent clinical diagnoses of COPD (odds ratio [OR], 1.47 +/- 0.08; P < 0.001) and had higher all-cause mortality (hazard ratio [HR], 1.41 +/- 0.06; P < 0.001). They had higher numbers of respiratory medication prescriptions and hospital and intensive care unit admissions. Other air-trapping indices showed similar associations with health outcomes (1). Inclusion of baseline airflow indices (FEV1/FVC, FEV1, FEV1 reversibility, and forced expiratory flow, midexpiratory phase) in the multivariate analysis did not significantly affect the observed associations (1). In addition, high-normal RV/TLC was associated with intermediate adverse health outcomes compared with low-normal and abnormal RV/TLC. Abnormal RV/TLC predicted higher likelihood of progression to spirometric COPD (OR, 1.27 +/- 0.15; P = 0.044). CONCLUSIONS: These findings indicate the predictive usefulness of lung volume measurements in those at risk for COPD and argue for their use as an additional dimension for COPD risk stratification. Smokers with abnormal lung volumes representing air trapping are at higher risk to develop adverse respiratory outcomes and COPD. Understanding physiological and biological mechanisms underlying this susceptibility could lead to discovery of novel therapeutic strategies.

Zhu, Z., X. Wang, et al. (2019). **"Genetic overlap of chronic obstructive pulmonary disease and cardiovascular disease-related traits: a large-scale genome-wide cross-trait analysis."** Respir Res **20**(1): 64.

BACKGROUND: A growing number of studies clearly demonstrate a substantial association between chronic obstructive pulmonary disease (COPD) and cardiovascular diseases (CVD), although little is known about the shared genetics that contribute to this association. METHODS: We conducted a large-scale cross-trait genome-wide association study to investigate genetic overlap between COPD (Ncase = 12,550, Ncontrol = 46,368) from the International COPD Genetics Consortium and four primary cardiac traits: resting heart rate (RHR) (N = 458,969), high blood pressure (HBP) (Ncase = 144,793, Ncontrol = 313,761), coronary artery disease (CAD)(Ncase = 60,801, Ncontrol = 123,504), and stroke (Ncase = 40,585, Ncontrol = 406,111) from UK Biobank, CARDIoGRAMplusC4D Consortium, and International Stroke Genetics Consortium data. RESULTS: RHR and HBP had modest genetic correlation, and CAD had borderline evidence with COPD at a genome-wide level. We found evidence of local genetic correlation with particular regions of the genome. Cross-trait meta-analysis of COPD identified 21 loci jointly associated with RHR, 22 loci with HBP, and 3 loci with CAD. Functional analysis revealed that shared genes were enriched in smoking-related pathways and in cardiovascular, nervous, and immune system tissues. An examination of smoking-related genetic variants identified SNPs located in 15q25.1 region associated with cigarettes per day, with effects on RHR and CAD. A Mendelian randomization analysis showed a significant positive causal effect of COPD on RHR (causal estimate = 0.1374, P = 0.008). CONCLUSION: In a set of large-scale GWAS, we identify evidence of shared genetics between COPD and cardiac traits.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6444755/pdf/12931_2019_Article_1036.pdf

Zoumot, Z., C. Davey, et al. (2015). **Efficacy and Mechanism Evaluation**. A randomised controlled study of Bronchoscopic Lung Volume Reduction with endobronchial valves for patients with Heterogeneous emphysema and Intact interlobar Fissures: the BeLieVeR-HIFi study. Southampton (UK), NIHR Journals Library

BACKGROUND: Despite optimal therapy many patients with emphysema remain significantly breathless and limited. Bronchoscopic lung volume reduction (BLVR), using valves placed to allow air to leave but not enter the worst-affected areas of the lung, has been proposed as a way to improve lung function in these patients, but response is variable because interlobar collateral ventilation prevents the devices from working. Based on retrospective analysis of clinical trials, patients with heterogeneous emphysema and intact interlobar fissures are most likely to benefit. OBJECTIVES: To establish whether or not it is possible to identify patients prospectively who will reliably benefit from endobronchial valve placement. DESIGN: Prospective, randomised, parallel-group, double-blind, sham-controlled trial. SETTING: The study was performed at a single specialist centre. PARTICIPANTS: Adult patients with heterogeneous emphysema and a target lobe with intact interlobar fissures were eligible if they had significant gas trapping (total lung capacity > 100% predicted, residual volume > 150% predicted), breathlessness [Medical Research Council (MRC) dyspnoea score of >/= 3] and exercise limitation (6-minute walk distance of < 450 m). Participants were on optimised pharmacotherapy and were non-smokers. INTERVENTIONS: Study participants were randomised to either unilateral lobar endobronchial valve placement aiming to achieve lobar atelectasis or bronchoscopy and 'sham' valve placement. MAIN OUTCOME MEASURES: The primary end point was improvement in forced expiratory volume in 1 second (FEV1) in the treatment arm compared with the control arm measured 90 days post procedure. Secondary end points were change in lung volumes, gas transfer, exercise capacity (both walking and endurance cycle ergometry) and health-related quality of life. RESULTS: In total, 50 patients were recruited, 25 to each arm; 62% were male and mean (standard deviation) FEV1% predicted was 31.7% (10.2%). The primary end point of the study was met as FEV1 increased by 24.8% [95% confidence interval (CI) 8.0% to 41.5%] in the treatment arm and by 3.9% (95% CI 0.7% to 7.1%) in the control arm [between-group difference 20.9% (95% CI 4.3% to 37.5%); p = 0.033]. There were both statistically and clinically significant improvements in lung volumes and carbon monoxide gas transfer as well as endurance time and dynamic hyperinflation during cycle ergometry. Two deaths occurred in the

treatment arm and one control patient was unable to attend for follow-up assessment because of a prolonged pneumothorax. Two pneumothoraces occurred in the treatment arm. CONCLUSIONS: With appropriate selection of patients through a multidisciplinary team it is possible to produce a significant improvement in lung function through lobar occlusion with endobronchial valves in heterogeneous emphysema. Prospective trials are needed to compare the effect of BLVR with surgical approaches in terms of magnitude and duration of benefit. TRIAL REGISTRATION: Current Controlled Trials ISRCTN04761234. FUNDING: This project was funded by the Efficacy and Mechanism Evaluation (EME) programme, a MRC and NIHR partnership.