

Systematic reviews and clinical trials

Al Sallakh, M. A., S. E. Rodgers, et al. (2018). **"Identifying patients with asthma-chronic obstructive pulmonary disease overlap syndrome using latent class analysis of electronic health record data: a study protocol."** NPJ Prim Care Respir Med **28**(1): 22.

Asthma and chronic obstructive pulmonary disease (COPD) are two common different clinical diagnoses with overlapping clinical features. Both conditions have been increasingly studied using electronic health records (EHR). Asthma-COPD overlap syndrome (ACOS) is an emerging concept where clinical features from both conditions co-exist, and for which, however, there is no consensus definition. Nonetheless, we expect EHR data of people with ACOS to be systematically different from those with "asthma only" or "COPD only". We aim to develop a latent class model to understand the overlap between asthma and COPD in EHR data. From the Secure Anonymised Information Linkage (SAIL) databank, we will use routinely collected primary care data recorded in or before 2014 in Wales for people who aged 40 years or more on 1st Jan 2014. Based on this latent class model, we will train a classification algorithm and compare its performance with commonly used objective and self-reported case definitions for asthma and COPD. The resulting classification algorithm is intended to be used to identify people with ACOS, 'asthma only', and 'COPD only' in primary care datasets.

Altman, P., L. Wehbe, et al. (2018). **"Comparison of peak inspiratory flow rate via the Breezhaler(R), Ellipta(R) and HandiHaler(R) dry powder inhalers in patients with moderate to very severe COPD: a randomized cross-over trial."** BMC Pulm Med **18**(1): 100.

**BACKGROUND:** The chronic and progressive nature of chronic obstructive pulmonary disease (COPD) requires self-administration of inhaled medication. Dry powder inhalers (DPIs) are increasingly being used for inhalation therapy in COPD. Important considerations when selecting DPIs include inhalation effort required and flow rates achieved by patients. Here, we present the comparison of the peak inspiratory flow rate (PIF) values achieved by COPD patients, with moderate to very severe airflow limitation, through the Breezhaler(R), the Ellipta(R) and the HandiHaler(R) inhalers. The effects of disease severity, age and gender on PIF rate were also evaluated. **METHODS:** This randomized, open-label, multicenter, cross-over, Phase IV study recruited patients with moderate to very severe airflow limitation (Global Initiative for Obstructive Lung Disease 2014 strategy), aged  $\geq 40$  years and having a smoking history of  $\geq 10$  pack years. No active drug or placebo was administered during the study. The

inhalation profiles were recorded using inhalers fitted with a pressure tap and transducer at the wall of the mouthpiece. For each patient, the inhalation with the highest PIF value, out of three replicate inhalations per device, was selected for analysis. A paired t-test was performed to compare mean PIFs between each combination of devices. RESULTS: In total, 97 COPD patients were enrolled and completed the study. The highest mean PIF value (L/min +/- SE) was observed with the Breezhaler(R) (108 +/- 23), followed by the Ellipta(R) (78 +/- 15) and the HandiHaler(R) (49 +/- 9) inhalers and the lowest mean pressure drop values were recorded with the Breezhaler(R) inhaler, followed by the Ellipta(R) inhaler and the HandiHaler(R) inhaler, in the overall patient population. A similar trend was consistently observed in patients across all subgroups of COPD severity, within all age groups and for both genders. CONCLUSIONS: Patients with COPD were able to inhale with the least inspiratory effort and generate the highest mean PIF value through the Breezhaler(R) inhaler when compared with the Ellipta(R) and the HandiHaler(R) inhalers. These results were similar irrespective of patients' COPD severity, age or gender. TRIAL REGISTRATION: The trial was registered with ClinicalTrials.gov NCT02596009 on 4 November 2015.

Axson, E. L., V. Sundaram, et al. (2018). **"Hospitalisation and mortality outcomes of patients with comorbid COPD and heart failure: a systematic review protocol."** *BMJ Open* 8(6): e023058.

INTRODUCTION: Chronic obstructive pulmonary disease (COPD) and heart failure (HF) often coexist in patients. Many studies have explored the short-term and long-term outcomes of patients with comorbid COPD and HF; however, there have been discrepancies in their findings. METHODS AND ANALYSIS: In this systematic review, MEDLINE and Embase will be searched using a prespecified search strategy. Randomised controlled trials and studies conducted in the general population that employ analytical or descriptive (longitudinal or case-control) study designs that report odds ratios (ORs), hazard ratios (HRs), or risk ratios (RRs) of mortality or hospitalisation, comparing patients with comorbid COPD and HF with patients with just COPD, will be selected. Screening by title and abstract, then full-text screening will be conducted by two reviewers. The Population, Exposure, Comparator, Outcomes, Study (PECOS) characteristics framework will be used to systemise the data extraction from selected studies. Study quality will be assessed using an adapted version of the Newcastle-Ottawa risk of bias tool. Data extraction and the risk of bias will also be conducted by two reviewers. Given sufficient homogeneity of selected studies, a meta-analysis will be conducted. Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) criteria will be used to assess the quality of cumulative evidence. DISSEMINATION: With this review, we hope to improve the understanding of clinical outcomes of patients with comorbid COPD and HF. We intend to publish the results of our review in a peer-reviewed journal and to present our findings at national and international meetings and conferences. PROSPERO REGISTRATION NUMBER: CRD42018089534.

Balaban, R. B., F. Zhang, et al. (2017). **"Impact of a Patient Navigator Program on Hospital-Based and Outpatient Utilization Over 180 Days in a Safety-Net Health System."** *J Gen Intern Med* **32**(9): 981-989.

**BACKGROUND:** With emerging global payment structures, medical systems need to understand longer-term impacts of care transition strategies. **OBJECTIVE:** To determine the effect of a care transition program using patient navigators (PNs) on health service utilization among high-risk safety-net patients over a 180-day period. **DESIGN:** Randomized controlled trial conducted October 2011 through April 2013. **PARTICIPANTS:** Patients admitted to the general medicine service with  $\geq 1$  readmission risk factor: (1) age  $\geq 60$ ; (2) in-network inpatient admission within prior 6 months; (3) index length of stay  $\geq 3$  days; or (4) admission diagnosis of heart failure or (5) chronic obstructive pulmonary disease. The analytic sample included 739 intervention patients, 1182 controls. **INTERVENTIONS:** Through hospital visits and 30 days of post-discharge telephone outreach, PNs provided coaching and assistance with medications, appointments, transportation, communication with primary care, and self-care. **MAIN MEASURES:** Primary outcomes: (1) hospital-based utilization, a composite of ED visits and hospital admissions; (2) hospital admissions; (3) ED visits; and (4) outpatient visits. We evaluated outcomes following an index discharge, stratified by patient age ( $\geq 60$  and  $< 60$  years), using a 180-day time frame divided into six 30-day periods. **KEY RESULTS:** The PN program produced starkly different outcomes by patient age. Among older PN patients, hospital-based utilization was consistently lower than controls, producing an 18.7% cumulative decrease at 180 days ( $p = 0.038$ ); outpatient visits increased in the critical first 30-day period ( $p = 0.006$ ). Among younger PN patients, hospital-based utilization was 31.7% ( $p = 0.038$ ) higher at 180 days, largely reflecting sharply higher utilization in the initial 30 days ( $p = 0.002$ ), with non-significant changes thereafter; outpatient visits experienced no significant changes. **CONCLUSIONS:** A PN program serving high-risk safety-net patients differentially impacted patients based on age, and among younger patients, outcomes varied over time. Our findings highlight the importance for future research to evaluate care transition programs among different subpopulations and over longer time periods.

Barker, A. F., M. A. Campos, et al. (2017). **"Bioequivalence of a Liquid Formulation of Alpha1-Proteinase Inhibitor Compared with Prolastin(R)-C (Lyophilized Alpha1-PI) in Alpha1-Antitrypsin Deficiency."** *Copd* **14**(6): 590-596.

This study evaluated the bioequivalence, safety, and immunogenicity of a new liquid formulation of human plasma-derived alpha1-proteinase inhibitor, Liquid Alpha1-PI, compared with the Lyophilized Alpha1-PI formulation (Prolastin(R)-C), for augmentation therapy in patients with alpha1-antitrypsin deficiency (AATD). In this double-blind, randomized, 20-week crossover study, 32 subjects with AATD were randomized to receive 8 weekly infusions of 60 mg/kg of Liquid Alpha1-PI or Lyophilized Alpha1-PI. Serial blood samples were drawn for 7 days after the

last dose followed by 8 weeks of the alternative treatment. The primary endpoint was bioequivalence at steady state, as measured by area under the concentration versus time curve from 0 to 7 days (AUC<sub>0-7</sub> days) postdose using an antigenic content assay. Bioequivalence was defined as 90% confidence interval (CI) for the ratio of the geometric least squares (LS) mean of AUC<sub>0-7</sub> days for both products within the limits of 0.80 and 1.25. Safety and immunogenicity were assessed. Mean alpha1-PI concentration versus time curves for both formulations were superimposable. Mean AUC<sub>0-7</sub> days was 20 320 versus 19 838 mg x h/dl for Liquid Alpha1-PI and Lyophilized Alpha1-PI, respectively. The LS mean ratio of AUC<sub>0-7</sub> days (90% CI) for Liquid Alpha1-PI versus Lyophilized Alpha1-PI was 1.05 (1.03-1.08), indicating bioequivalence. Liquid Alpha1-PI was well tolerated and adverse events were consistent with Lyophilized Alpha1-PI. Immunogenicity to either product was not detected. In conclusion, Liquid Alpha1-PI is bioequivalent to Lyophilized Alpha1-PI, with a similar safety profile. The liquid formulation would eliminate the need for reconstitution and shorten preparation time for patients receiving augmentation therapy for AATD.

Baroi, S., R. J. McNamara, et al. (2018). **"Advances in Remote Respiratory Assessments for People with Chronic Obstructive Pulmonary Disease: A Systematic Review."** *Telemed J E Health* **24**(6): 415-424.

**BACKGROUND:** Chronic obstructive pulmonary disease (COPD) is a leading cause of mortality. Advances in remote technologies and telemedicine provide new ways to monitor respiratory function and improve chronic disease management. However, telemedicine does not always include remote respiratory assessments, and the current state of knowledge for people with COPD has not been evaluated. **OBJECTIVE:** Systematically review the use of remote respiratory assessments in people with COPD, including the following questions: What devices have been used? Can acute exacerbations of chronic obstructive pulmonary disease (AECOPD) be predicted by using remote devices? Do remote respiratory assessments improve health-related outcomes? **MATERIALS AND METHODS:** The review protocol was registered (PROSPERO 2016:CRD42016049333). MEDLINE, EMBASE, and COMPENDEX databases were searched for studies that included remote respiratory assessments in people with COPD. A narrative synthesis was then conducted by two reviewers according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. **RESULTS:** Fifteen studies met the inclusion criteria. Forced expiratory volume assessed daily by using a spirometer was the most common modality. Other measurements included resting respiratory rate, respiratory sounds, and end-tidal carbon dioxide level. Remote assessments had high user satisfaction. Benefits included early detection of AECOPD, improved health-related outcomes, and the ability to replace hospital care with a virtual ward. **CONCLUSION:** Remote respiratory assessments are feasible and when combined with sufficient organizational backup can improve health-related outcomes in some but not all cohorts. Future research should focus on the early detection, intervention, and rehabilitation for AECOPD in high-risk people who

have limited access to best care and investigate continuous as well as intermittent monitoring.

Bell, D., L. Mansfield, et al. (2017). **"A Randomized, Crossover Trial Evaluating Patient Handling, Preference, and Ease of Use of the Fluticasone Propionate/Formoterol Breath-Triggered Inhaler."** J Aerosol Med Pulm Drug Deliv **30**(6): 425-434.

**BACKGROUND:** Appropriate inhaler selection is of fundamental importance in obstructive lung disease management. Key factors in device selection include a patient's capacity to operate a particular device and their preference for it. **METHODS:** This randomized, open-label, two-period, crossover study (NCT01739387) compared the ability of adolescent and adult patients with obstructive lung disease to correctly handle the fluticasone propionate/formoterol fumarate (FP/FORM; Flutiform((R))) pressurized metered-dose inhaler (pMDI) and FP/FORM K-haler((R)), a novel breath-triggered inhaler (BTI), following a simple, standardized training regimen. The primary endpoint was the ability to perform all steps correctly at the first attempt. Secondary endpoints included the ability to perform all critical steps correctly at the first attempt, the requisite number of attempts to successfully use the inhaler, the ability to be trained within 15 minutes, and the ability to trigger the K-haler BTI to actuate at the first attempt. Ease of device use and device preference versus patients' usual maintenance inhalers were also assessed. **RESULTS AND CONCLUSIONS:** At the first attempt, an identical proportion (77.2% [95% confidence interval [CI]: 72.1, 81.8]) of 307 patients performed all pMDI and K-haler BTI handling steps correctly, whereas the corresponding proportions performing all critical steps correctly were 82.4% (95% CIs: 77.7, 86.5) and 87.0% (95% CI: 82.7, 90.5), respectively. For both devices, >90% of patients required only two attempts to master device usage; >99% of patients could be trained to correctly use each device within 15 minutes. Virtually all patients (99.0% [95% CIs: 97.2, 99.8]) were able to successfully trigger the K-haler BTI's dose-release mechanism at first attempt. Ease of use and preference data for FP/FORM pMDI challenged the perceived wisdom that dry powder inhalers are necessarily simpler to use, whereas the corresponding data for FP/FORM K-haler strongly favored this novel BTI over the Turbuhaler((R)), Accuhaler((R)), and other pMDIs.

Bigna, J. J., J. J. Noubiap, et al. (2017). **"Prevalence and etiologies of pulmonary hypertension in Africa: a systematic review and meta-analysis."** BMC Pulm Med **17**(1): 183.

**BACKGROUND:** Despite the recent increasing worldwide attention towards pulmonary hypertension (PH), its epidemiology remains poorly described in Africa. Accordingly, we performed a systematic review and meta-analysis of PH prevalence, incidence and etiologies in Africa. **METHODS:** We searched

PubMed, EMBASE, African Journals Online, and Africa Index Medicus. Published observational studies until September 20, 2017, including adult participants residing in Africa were considered. Two review authors independently selected studies, assessed included studies for methodological quality, and extracted data. A random-effects model was used for meta-analysis. Heterogeneity was evaluated by the chi (2) test on Cochrane's Q statistic which is quantified by I(2) values. Using Newcastle-Ottawa Scale, we considered a score of 0-4, 5-7, and 8-10 as indicative of high, moderate, and low risk of bias in included studies, respectively. RESULTS: Of 1611 entries, 25 studies were retained. Twelve (48%), seven (28%), and six (24%) papers had respectively a low, moderate and high risk of bias. The prevalence of PH widely varied across different populations: 9.8% (95% confidence interval: 3.2-19.3; I(2) = 99.4%; 6 studies) in 11,163 people presenting with cardiac complaints; 10.6% (4.3-19.1; I(2) = 90.3%; 4 studies) in 937 HIV-infected people; 32.9% (17.6-50.4; I(2) = 97.2%; 3 studies) in 2077 patients with heart failure; 23.2% (15.2-32.2; I(2) = 59.4%; 3 studies) in 248 patients on hemodialysis; 12.9% (11.8-14.0; I(2) = 79.7%; 2 studies) in 3750 patients with rheumatic heart disease; 36.9% (29.7-44.3; I(2) = 79.7%; 2 studies) in 79 patients with sickle cell disease; 62.7% (49.0-74.7; 1 study) in 51 patients with chronic obstructive pulmonary disease; 25.4% (16.3-37.3; 1 study) in 63 patients with systemic lupus erythematosus; 68.7% (62.8-74.1; 1 study) in 259 patients with cardiac surgery; and 7.4% (4.6-11.9; 1 study) in 202 patients with systemic sclerosis. No study reported PH incidence. From one international study (n = 209), PH etiologies were: left heart disease (68.9%), pulmonary arterial hypertension (15.8%), lung disease and/or hypoxia (12.0%), chronic thromboembolic PH (1.9%) and unclear/multifactorial PH (15.8%). CONCLUSION: The prevalence of PH is relatively high in some populations in Africa, perhaps mainly driven by left heart diseases, highlighting the need for context-specific interventions.

Bradford, E., S. Jacobson, et al. (2017). **"The value of blood cytokines and chemokines in assessing COPD."** *Respir Res* 18(1): 180.

BACKGROUND: Blood biomarkers are increasingly used to stratify high risk chronic obstructive pulmonary disease (COPD) patients; however, there are fewer studies that have investigated multiple biomarkers and replicated in multiple large well-characterized cohorts of susceptible current and former smokers.

METHODS: We used two MSD multiplex panels to measure 9 cytokines and chemokines in 2123 subjects from COPDGene and 1117 subjects from SPIROMICS. These biomarkers included: interleukin (IL)-2, IL-6, IL-8, IL-10, tumor necrosis factor (TNF)-alpha, interferon (IFN)-gamma, eotaxin/CCL-11, eotaxin-3/CCL-26, and thymus and activation-regulated chemokine (TARC)/CCL-17. Regression models adjusted for clinical covariates were used to determine which biomarkers were associated with the following COPD phenotypes: airflow obstruction (forced expiratory flow at 1 s (FEV1%) and FEV1/forced vital capacity (FEV1/FVC), chronic bronchitis, COPD exacerbations, and emphysema. Biomarker-genotype associations were assessed by genome-wide association of single nucleotide polymorphisms (SNPs). RESULTS: Eotaxin and IL-6 were strongly associated with airflow obstruction and accounted for 3-5% of the

measurement variance on top of clinical variables. IL-6 was associated with progressive airflow obstruction over 5 years and both IL-6 and IL-8 were associated with progressive emphysema over 5 years. None of the biomarkers were consistently associated with chronic bronchitis or COPD exacerbations. We identified one novel SNP (rs9302690 SNP) that was associated with CCL17 plasma measurements. **CONCLUSION:** When assessing smoking related pulmonary disease, biomarkers of inflammation such as IL-2, IL-6, IL-8, and eotaxin may add additional modest predictive value on top of clinical variables alone. **TRIAL REGISTRATION:** COPDGene (ClinicalTrials.gov Identifier: NCT02445183 ). Subpopulations and Intermediate Outcomes Measures in COPD Study (SPIROMICS) ( ClinicalTrials.gov Identifier: NCT 01969344 ).

Broendum, E., C. S. Ulrik, et al. (2018). "**Barriers for recruitment of patients with chronic obstructive pulmonary disease to a controlled telemedicine trial.**" Health Informatics J **24**(2): 216-224.

The aim of this analysis is to investigate reasons why patients with chronic obstructive pulmonary disease decline to participate in a controlled trial of telemedicine. Patients with previous chronic obstructive pulmonary disease exacerbations were invited to participate in a 6-month randomized telemedicine trial. For eligible patients, reasons for refusal were registered. Of 560 eligible patients, 279 (50%) declined to participate in the trial, 257 (92%) reported a reason: 53 (20.6%) technical concerns, 164 (63.8%) personal reasons, 17 (6.6%) preferred outpatient clinic visits, and 23 (8.9%) did not want to participate in clinical research. Compared to consenting patients, subjects declining participation were significantly older, more often female, had higher lung function (%predicted), lower body mass index, higher admission-rate for chronic obstructive pulmonary disease in the previous year, and were more often diagnosed with osteoporosis. Many eligible patients decline participating in a controlled tele-healthcare trial and, furthermore, a tailored approach for recruiting females and elderly patients appears appropriate.

Brown, K. E., D. D. Sin, et al. (2017). "**Serum bilirubin and the risk of chronic obstructive pulmonary disease exacerbations.**" Respir Res **18**(1): 179.

**BACKGROUND:** Bilirubin is a potent anti-oxidant and higher serum concentrations of bilirubin have been associated with better lung function, slower lung function decline, and lower incidence of chronic obstructive pulmonary disease (COPD). We sought to determine whether elevated bilirubin blood concentrations are associated with lower risk for acute exacerbations of COPD (AECOPD). **METHODS:** We performed a secondary analyses of data in the Simvastatin for Prevention of Exacerbations in Moderate-to-Severe COPD (STATCOPE) and the Azithromycin for Prevention of Exacerbations of COPD (MACRO) studies. We used time-dependent multivariable Cox proportional hazards analyses, using

bilirubin concentrations prior to first AECOPD as the exposure variable and time to first AECOPD as the outcome variable. STATCOPE was used for model development, with validation in MACRO. RESULTS: In STATCOPE (n = 853), higher bilirubin was associated with a lower but statistically insignificant hazard for AECOPD, (adjusted hazard ratio [aHR] 0.89 per log<sub>10</sub> increase [95%CI: 0.74 to 1.09; p = 0.26]). In the validation MACRO study (n = 1018), higher bilirubin was associated with a significantly lower hazard for AECOPD (aHR 0.80 per log<sub>10</sub> increase [95%CI: 0.67 to 0.94; p = 0.008]). CONCLUSIONS: Bilirubin may be a biomarker of AECOPD risk and may be a novel therapeutic target to reduce AECOPD risk. TRIAL REGISTRATIONS: ClinicalTrials.gov NCT01061671 (registered 02 February 2010) and ClinicalTrials.gov NCT00325897 (registered 12 May 2006).

Burkes, R. M. and J. F. Donohue (2018). **"An Update on the Global Initiative for Chronic Obstructive Lung Disease 2017 Guidelines With a Focus on Classification and Management of Stable COPD."** Respir Care **63**(6): 749-758.

The 2017 Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines offer important changes to the assessment and management of stable COPD of importance to practitioners, respiratory therapists, pharmacists, and nurses who care for patients with COPD. Therapies are now chosen based on the burden of symptoms and the history of COPD exacerbations, and inhaler regimens are modifiable based on continual clinical reassessment. Although identifying the degree of airway obstruction remains important for informing the clinical status of the patient with COPD, FEV<sub>1</sub> is no longer used to direct the therapeutic approach. Therapies and modes of inhaled medication delivery for each GOLD grouping have been modified and reflect the need for reevaluation of patient symptoms and COPD exacerbation history as an indicator to add or withdraw therapies. As the knowledge of this important disease continues to expand, exacerbation and symptom prevention in patients with stable COPD will remain as an important target of COPD therapies and research. Novel drug combinations and delivery devices are sure to positively affect the practitioner's approach to patients with stable COPD. The new 2017 GOLD guidelines represent a step toward personalized care of the patient with COPD.

Caliskan, S. G., M. D. Bilgin, et al. (2018). **"Nonlinear analysis of electrodermal activity signals for healthy subjects and patients with chronic obstructive pulmonary disease."** Australas Phys Eng Sci Med **41**(2): 487-494.

It is known that signals recorded from physiological systems represent nonlinear features. Several recent studies report that quantitative information about signal complexity is obtained by using nonlinear analysis algorithms. Chronic obstructive pulmonary disease (COPD) is one of the causes of mortality



worldwide with an increasing prevalence. This study aims to investigate nonlinear parameters such as largest Lyapunov exponent (LLE) and correlation dimension of electrodermal activity signals recorded from healthy subjects and patients with COPD. Electrodermal activity signals recorded from 14 healthy subjects and 24 patients with COPD were analysed. Auditory and tactile stimuli were applied at different time intervals during the recording process. Signals were reconstructed in the phase space compatible with theory and LLE and correlation dimension values were calculated. Statistical analysis was performed by using Shapiro-Wilk normality test, one-way analysis of variance (ANOVA) with Bonferroni post-test and Kruskal-Wallis non-parametric test. It was determined that the chaoticity and the complexity of the system increased in the presence of COPD. The systematic auditory stimuli increases chaoticity more than random auditory stimuli. Furthermore it was observed that participants develop habituation to the same auditory stimuli in time. There is no significant difference between COPD groups. Different results were found for the tactile stimuli applied to right or left ear. The results revealed that the nonlinear analysis of physiological data can be used for the development of new strategies for the diagnosis of chronic diseases.

Campman, C., D. van Ranst, et al. (2017). **"Computerized screening for cognitive impairment in patients with COPD."** Int J Chron Obstruct Pulmon Dis **12**: 3075-3083.

**PURPOSE:** COPD is associated with cognitive impairment. These impairments should be diagnosed, but due to time- and budget-reasons, they are often not investigated. The aim of this study is to examine the viability of a brief computerized cognitive test battery, Central Nervous System Vital Signs (CNSVS), in COPD patients. **PATIENTS AND METHODS:** Patients with COPD referred to tertiary pulmonary rehabilitation were included. Cognitive functioning of patients was assessed with CNSVS before pulmonary rehabilitation and compared with age-corrected CNSVS norms. CNSVS is a 30 minute computerized test battery that includes tests of verbal and visual memory, psychomotor speed, processing speed, cognitive flexibility, complex attention, executive functioning, and reaction time. **RESULTS:** CNSVS was fully completed by 205 (93.2%, 105 females, 100 males) of the total group of patients (n=220, 116 females, 104 males). Z-tests showed that COPD patients performed significantly worse than the norms on all CNSVS cognitive domains. Slightly more than half of the patients (51.8%) had impaired functioning on 1 or more cognitive domains. Patients without computer experience performed significantly worse on CNSVS than patients using the computer frequently. **CONCLUSION:** The completion rate of CNSVS was high and cognitive dysfunctions measured with this screening were similar to the results found in prior research, including paper and pen cognitive tests. These results support the viability of this brief computerized cognitive screening in COPD patients, that may lead to better care for these patients. Cognitive performance of patients with little computer experience should be interpreted carefully. Future research on this issue is needed.

Capel, M., M. Mareque, et al. (2018). **"Cost-Effectiveness of Fixed-Dose Combinations Therapies for Chronic Obstructive Pulmonary Disease Treatment."** Clin Drug Investig **38**(7): 611-620.

**BACKGROUND AND OBJECTIVE:** Chronic obstructive pulmonary disease (COPD), a progressive lung disorder associated with decline of respiratory function, affects 10.2% of Spanish adults (40-80 years of age). This study aimed to assess the cost-effectiveness of two fixed-dose combinations of long-acting muscarinic antagonist and long-acting beta2-agonist therapies for COPD, with Spanish National Health System perspective. **METHODS:** A Markov model with five health states based on severity levels defined by GOLD 2010 criteria was used to simulate in monthly cycles the evolution along a 5-year period of a cohort of moderate-to-severe COPD patients, treated with aclidinium-formoterol (ACL/FF) 400/12 microg or tiotropium-olodaterol (TIO/OLO) 5/5 microg fixed-dose combinations. Clinical data on lung-function improvement were obtained from a network meta-analysis and applied to mean baseline forced-expiratory-volume in 1 s (FEV1) for the first 24-weeks period. Natural history for lung-function decline (41 ml/year) was applied until the end of simulation. Risk of exacerbation and pneumonia occurrence were considered. Pharmaceutical costs were calculated with dosages according to indication and public ex-factory prices. The health state-specific disease management and event costs, and utilities were derived from the literature. Total costs (euro 2016) and benefits [life-year-gained (LYG) and quality-adjusted-life-year (QALY)] were discounted (3.0% yearly). Sensitivity analyses were performed. **RESULTS:** Both therapies provided the same outcomes (4.073 LYG and 2.928 QALY) at 5-year period. ACL/FF 400/12 microg provided marginally lower costs (euro - 332) compared to TIO/OLO 5/5 microg. **CONCLUSION:** ACL/FF 400/12 microg was a cost-saving therapy in patients with moderate-to-severe COPD in Spain, and provided equivalent effects compared to TIO/OLO 5/5 microg.

Cataldo, D., E. Derom, et al. (2018). **"Overuse of inhaled corticosteroids in COPD: five questions for withdrawal in daily practice."** Int J Chron Obstruct Pulmon Dis **13**: 2089-2099.

Evidence and guidelines are becoming increasingly clear about imbalance between the risks and benefits of inhaled corticosteroids (ICSs) in patients with COPD. While selected patients may benefit from ICS-containing regimens, ICSs are often inappropriately prescribed with - according to Belgian market research data - up to 70% of patients in current practice receiving ICSs, usually as a fixed combination with a long-acting beta2-adrenoreceptor agonist. Studies and recommendations support withdrawal of ICSs in a large group of patients with COPD. However, historical habits appear difficult to change even in the light of recent scientific evidence. We have built a collaborative educational platform with chest physicians and primary care physicians to increase awareness and provide guidance and support in this matter.

Cavalcante, R., Y. Sotomi, et al. (2017). **"Impact of the SYNTAX scores I and II in patients with diabetes and multivessel coronary disease: a pooled analysis of patient level data from the SYNTAX, PRECOMBAT, and BEST trials."** Eur Heart J **38**(25): 1969-1977.

**Aims:** To assess the impact of the SYNTAX scores I and II in outcomes after percutaneous coronary intervention (PCI) and coronary artery bypass graft (CABG) for patients with diabetes and multivessel disease (MVD). **Methods and results:** We performed a patient-level pooled analysis of three large randomized trials of patients with MVD. The impact of coronary anatomic complexity as measured by the SYNTAX score in the differences in outcomes following PCI and CABG was assessed at a median follow-up of 5 years. We also assessed the performance of the SYNTAX II score model in patients with and without diabetes. From the 3280 patients enrolled in the three trials, a total of 1068 (32.6%) had diabetes. The rate of the composite of death, myocardial infarction (MI), or stroke was similar in the PCI and CABG arms in patients with low-intermediate ( $\leq 32$ ) SYNTAX scores (15.1% vs. 14.9%, respectively;  $P = 0.93$ ) while it was significantly higher in the PCI arm in patients with high ( $\geq 33$ ) SYNTAX scores (24.5% vs. 13.2%, respectively;  $P = 0.018$ ). The SYNTAX score II showed good calibration and moderate discrimination ability in patients with diabetes (c-index = 0.68) as well as in those without (c-index = 0.67). **Conclusions:** Differences in 5 years outcomes following PCI and CABG for patients with MVD and diabetes were influenced by anatomic complexity as measured by the SYNTAX score. The SYNTAX score II mortality prediction model showed similar performance regardless of the diabetes status.

Cazzola, M., L. Calzetta, et al. (2018). **"Impact of doxofylline in COPD: A pairwise meta-analysis."** Pulm Pharmacol Ther **51**: 1-9.

Doxofylline is an effective bronchodilator for relieving airway obstruction in patients with asthma or chronic obstructive pulmonary disease (COPD), and displays a better safety profile with respect to theophylline. Herein, we performed a pairwise meta-analysis of the currently available data to provide consistent and homogeneous findings on the impact of this xanthine in COPD patients. Results obtained from 820 patients were selected from 20 clinical trials. Meta-regression was performed to examine the source of heterogeneity between-studies and identify potential confounder covariates. The quality of the evidence was assessed by the GRADE system. Doxofylline induced a significant ( $P < 0.001$ ) increase in forced expiratory volume in 1s (FEV1) of 8.20% (95%CI 4.00-12.41; I(2) 93%) and 317ml (95%CI 19-439; I(2) 87%) compared with baseline. The total administered dose of doxofylline significantly ( $P < 0.001$ ) interacted with the size of the effect estimates detected for FEV1. Doxofylline induced a significant ( $P < 0.001$ ), although moderate, increase in adverse events (AEs) frequency (proportion 0.03, 95%CI

0.02-0.04; I(2) 88%), but only epigastralgia, nausea, dyspepsia and headache were statistically significant ( $P < 0.05$ ). The GRADE analysis indicated high quality of evidence (+++++) for the impact of doxofylline on FEV1, and moderate quality of evidence (++++) for the safety profile in COPD patients. Doxofylline is an effective and safe medicine when administered to patients with COPD and can be considered as an alternative to theophylline.

Chambliss, J. M., S. Sur, et al. (2018). **"Asthma versus chronic obstructive pulmonary disease, the Dutch versus British hypothesis, and role of interleukin-5."** Curr Opin Allergy Clin Immunol **18**(1): 26-31.

PURPOSE OF REVIEW: Asthma and COPD represent heterogeneous disorders with broad ranging impact on patients and health systems. This review focuses on evidence for early attempts at understanding their pathogenesis by the British and Dutch hypotheses. It also addresses the role of eosinophils, IL-5, and biologics targeting these pathways in asthma and COPD. RECENT FINDINGS: Among asthma and COPD patients, clusters exist based on phenotypic and biologic markers allowing for further understanding of endotypes. Recent studies suggest the role of eosinophils and optimal therapies for each condition may be different. SUMMARY: Although patients with ACOS or overlap symptoms may be an exception, overall there appears to be more evidence supporting that asthma and COPD are distinct processes. Targeting eosinophils with anti-IL-5 therapy appears to be an exciting pathway in the properly selected patient with asthma and recent data also supports its use in COPD.

Chan, H. S., F. W. S. Ko, et al. (2018). **"Comorbidities, mortality, and management of chronic obstructive pulmonary disease patients who required admissions to public hospitals in Hong Kong - computerized data collection and analysis."** Int J Chron Obstruct Pulmon Dis **13**: 1913-1925.

Background: COPD is a common cause for hospital admission. Conventional studies of the epidemiology of COPD involved large patient number and immense resources and were difficult to be repeated. The present study aimed at assessing the utilization of a computerized data management system in the collection and analysis of the epidemiological and clinical data of a large COPD cohort in Hong Kong (HK). Patients and methods: It was a computerized, multicenter, retrospective review of the characteristics of patients discharged from medical departments of the 16 participating hospitals with the primary discharge diagnosis of COPD in 1 year (2012). Comparison was made between the different subgroups in the use of medications, ventilatory support, and other health care resources. The mortality of the subjects in different subgroups was traced up to December 31, 2014. The top 10 causes of death were analyzed. Results: In total, 9,776 subjects (82.6% men, mean age = 78 years) were identified. Of the 1,918 subjects with lung function coding, 85 (4.4%), 488

(25.5%), 808 (42.1%), and 537 (28.0%) subjects had the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 1, 2, 3, and 4 classes, respectively. Patients with higher GOLD classes had higher number of hospital admissions, longer hospital stay, increased usage of noninvasive mechanical ventilation (NIV), combinations of long-acting bronchodilators, and higher mortality. Of the 9,776 subjects, 2,278 (23.3%) received NIV, but invasive mechanical ventilation was uncommon (134 of 9,776 subjects [1.4%]); 4,427 (45.3%) subjects had died by the end of 2014. The top causes of death were COPD, pneumonia, lung cancer, and other malignancies. Conclusion: Patients admitted to hospitals for COPD in HK had significant comorbidities, mortality, and imposed heavy burden on health care resources. It is possible to collect and analyze data of a large COPD cohort through a computerized system. Suboptimal coding of lung function results was observed, and underutilization of long-acting bronchodilators was common.

Charron, C. E., P. Russell, et al. (2017). **"RV568, a narrow-spectrum kinase inhibitor with p38 MAPK-alpha and -gamma selectivity, suppresses COPD inflammation."** *Eur Respir J* **50**(4) Novel anti-inflammatory approaches targeting chronically activated kinase pathways in chronic obstructive pulmonary disease (COPD) are needed. We evaluated RV568, a p38 mitogen-activated protein kinase-alpha and -gamma and SRC family kinase inhibitor, in cellular and in vivo models relevant to COPD and examined its safety and efficacy in COPD patients. The anti-inflammatory activities of RV568 were tested in primary cultured monocytes, macrophages and bronchial epithelial cells and in vivo in lipopolysaccharide and cigarette smoke-exposed murine models. RV568 was evaluated in a 14-day trial in COPD patients. RV568 showed potent anti-inflammatory effects in monocytes and macrophages, which were often greater than those of corticosteroids or the p38 inhibitor Birb796. RV568 combined with corticosteroid had anti-inflammatory effects suggestive of a synergistic interaction in poly I:C-stimulated BEAS-2B cells and in the cigarette smoke model. In COPD patients, inhaled RV568 (50 microg and 100 microg) improved pre-bronchodilator forced expiratory volume in 1 s (69 mL and 48 mL respectively) and significantly reduced sputum malondialdehyde ( $p < 0.05$ ) compared to placebo, although there were no changes in sputum cell counts. Adverse events during RV568 and placebo treatment were similar. RV568 shows potent anti-inflammatory effects on cell and animal models relevant to COPD. RV568 was well-tolerated and demonstrated a modest clinical benefit in a 14-day COPD clinical trial.

Chen, H., Q. S. Zeng, et al. (2017). **"Quantitative Low-Dose Computed Tomography of the Lung Parenchyma and Airways for the Differentiation between Chronic Obstructive Pulmonary Disease and Asthma Patients."** *Respiration* **94**(4): 366-374.

**BACKGROUND:** It is difficult to differentiate between chronic obstructive pulmonary disease (COPD) and asthma in clinics; therefore, for diagnostic purposes, imaging-based measurements could be beneficial to differentiate between the two diseases. **OBJECTIVES:** We aim to analyze quantitative measurements of the lung and bronchial parameters that are provided by low-dose computed tomography (CT) to differentiate COPD and asthma from an imaging perspective. **MATERIALS AND METHODS:** 69 COPD patients, 52 asthma patients, and 20 healthy subjects were recruited to participate in CT imaging and pulmonary function tests (PFTs). Comparative analysis was performed to identify differences between COPD and asthma in CT measurements. PFT measurements enabled validation of the differentiation between COPD and asthma patients. **RESULTS:** There were significant differences among the COPD, asthma, and healthy control groups. The differences were more significant among the following: inspiratory emphysema index (EI)-950 (%), expiratory lung volume, expiratory mean lung density (MLD), and expiratory EI-950 (%) and EI-850 (%). The COPD group had a significantly higher EI-950 (%) than the asthma group ( $p = 0.008$ ). There were significant differences among the three groups in lumen area (LA), wall area (WA), total area, and Pi10WA. The asthma group had significantly higher WA%/WV% than both the COPD ( $p = 0.002$ ) and the control group ( $p = 0.012$ ). There was high sensitivity in EI-950 (%), EI-850 (%) and expiratory MLD in the parenchyma and high sensitivity in LA and Pi10WA in small airways in the differential diagnosis of COPD and asthma. **CONCLUSION:** To aid the diagnosis, CT can provide quantitative measurements to differentiate between COPD and asthma patients.

Clari, M., M. Matarese, et al. (2017). **"Self-Care of People with Chronic Obstructive Pulmonary Disease: A Meta-Synthesis."** *Patient* 10(4): 407-427.

**BACKGROUND:** Self-care in people with chronic obstructive pulmonary disease (COPD) can improve health-related quality of life, reduce hospital admissions and decrease dyspnoea. **OBJECTIVE:** This review aimed to systematically identify, evaluate and synthesise the qualitative literature on the self-care behaviours and strategies used by people with COPD. **METHODS:** The Joanna Briggs Institute (JBI) meta-aggregative method was followed. An electronic search of six relevant databases was conducted. The search was limited to articles published from January 1996 to January 2016. Reference lists of all identified articles were searched to find additional literature. Two independent reviewers analysed the studies against the inclusion criteria, extracted the data and assessed the methodological quality of the 14 identified papers using the JBI qualitative assessment and review critical appraisal instrument. Findings were synthesised using a meta-aggregation process. **RESULTS:** Four synthesised findings emerged from the aggregation of 114 findings: self-care is directed towards the prevention, control and management of the physical consequences of COPD; self-care focuses on the management of the psychological effects of COPD; self-care is aimed at reducing the impact of COPD on social life; and self-care is influenced by contact with healthcare services and requires the acquisition of knowledge and skills. **CONCLUSIONS:** This meta-synthesis provides evidence on the self-care behaviours and strategies that people with

COPD perform to prevent, control and manage the physical, psychological and social consequences of the disease. The findings of this meta-synthesis could help healthcare professionals to tailor self-care educational programmes to the experiences, preferences and priorities of people with COPD.

Contoli, M., A. G. Corsico, et al. (2017). **"Use of ICS in COPD: From Blockbuster Medicine to Precision Medicine."** *Copd* 14(6): 641-647.

Chronic obstructive pulmonary disease (COPD) is a major cause of mortality worldwide, whose burden is expected to increase in the next decades, because of numerous risk factors, including the aging of the population. COPD is both preventable and treatable by an effective management including risk factor reduction, prevention, assessment, and treatment of acute exacerbations and co-morbidities. The available agents approved for COPD treatment are long-acting or ultra-long-acting beta2-agonists (LABAs) and long-acting muscarinic antagonists (LAMAs) bronchodilators, as well as inhaled corticosteroids (ICS) in combination with LABAs. ICS use has been restricted only to selected COPD patients by the most recent documents, mainly based on the risk of exacerbations. However, several observational studies showed a high rate of prescription of ICS in COPD, irrespective of clinical recommendations, questioning the efficacy of these compounds in unselected patients with COPD and leading to possible increase risk of side effects related to ICS use. After examining the low levels of adherence in primary care and in the clinical settings to national and international recommendations for the treatment of COPD in different countries, the most common drivers of the prevailing use of ICS are critically reviewed here by examining their pros and cons, aimed at identifying evidence-based drivers for a proper selection of patients who may benefit from the proper use of ICS.

Cully, J. A., M. A. Stanley, et al. (2017). **"Delivery of Brief Cognitive Behavioral Therapy for Medically Ill Patients in Primary Care: A Pragmatic Randomized Clinical Trial."** *J Gen Intern Med* 32(9): 1014-1024.

**BACKGROUND:** Few studies have examined the practical effectiveness and implementation potential of brief psychotherapies that integrate mental and physical health. **OBJECTIVE:** To determine whether an integrated brief cognitive behavioral therapy (bCBT), delivered by mental health providers in primary care, would improve depression, anxiety and quality of life for medically ill veterans. **DESIGN:** Pragmatic patient-randomized trial comparing bCBT to enhanced usual care (EUC). **PARTICIPANTS:** A total of 302 participants with heart failure and/or chronic obstructive pulmonary disease (COPD) with elevated symptoms of depression and/or anxiety were enrolled from two Veterans Health Administration primary care clinics. **INTERVENTION:** bCBT was delivered to 180 participants by staff mental health providers (n = 19). bCBT addressed physical and emotional health using a modular, skill-based approach. bCBT was delivered in person or

by telephone over 4 months. Participants randomized to EUC (n = 122) received a mental health assessment documented in their medical record. MAIN MEASURES: Primary outcomes included depression (Patient Health Questionnaire) and anxiety (Beck Anxiety Inventory). Secondary outcomes included health-related quality of life. Assessments occurred at baseline, posttreatment (4 months), and 8- and 12-month follow-up. KEY RESULTS: Participants received, on average, 3.9 bCBT sessions with 63.3% completing treatment (4+ sessions). bCBT improved symptoms of depression ( $p = 0.004$ ; effect size,  $d = 0.33$ ) and anxiety ( $p < 0.001$ ;  $d = 0.37$ ) relative to EUC at posttreatment, with effects maintained at 8 and 12 months. Health-related quality of life improved posttreatment for bCBT participants with COPD but not for heart failure. Health-related quality of life outcomes were not maintained at 12 months. CONCLUSIONS: Integrated bCBT is acceptable to participants and providers, appears feasible for delivery in primary care settings and is effective for medically ill veterans with depression and anxiety. Improvements for both depression and anxiety were modest but persistent, and the impact on physical health outcomes was limited to shorter-term effects and COPD participants. Clinical trials.Gov identifier: NCT01149772.

D'Urzo, A., G. Bader, et al. (2018). **"Comparison of glycopyrronium versus tiotropium on the time to clinically important deteriorations in patients with COPD: a post-hoc analysis of randomized trials."** NPJ Prim Care Respir Med 28(1): 18.

Glycopyrronium is a once-daily, inhaled long-acting muscarinic antagonist (LAMA) demonstrating similar efficacy to inhaled tiotropium in patients with moderate-to-severe COPD; however, the benefit of LAMAs on COPD symptoms has been variable. COPD is a progressive disease in which many patients develop an acute or sustained deterioration. Data on the prevention of clinically important deteriorations (CID) using LAMAs are limited. A pooled analysis was performed on four Phase III trials (n = 2936) that compared the efficacy of glycopyrronium (n = 1859) with tiotropium (n = 1077). The primary endpoint was significant delay and/or reduction in the occurrence of CID. CID was defined as any of the following:  $\geq 100$  mL decrease from baseline in pre-dose forced expiratory volume in 1 second (FEV1),  $\geq 4$  point increase in St George's Respiratory Questionnaire score or a moderate-to-severe COPD exacerbation occurring after the first dose of study medication. A sustained CID was a CID occurring on  $\geq 2$  consecutive visits 4 weeks apart or for  $\geq 50\%$  of all available subsequent visits. Baseline characteristics for the overall population were similar. Patients had moderate (62%) or severe (38%) COPD. Mean post-bronchodilator FEV1 was approximately 55% predicted, and mean FEV1 reversibility was 16.7 and 18.6% in the glycopyrronium and tiotropium groups, respectively. Both glycopyrronium and tiotropium significantly reduced time to CID and sustained CID versus placebo ( $p < 0.001$ ). No statistically significant differences were found between the glycopyrronium and tiotropium treatment groups in time to CID or sustained CID. Glycopyrronium is effective in delaying time to clinically important deteriorations, with similar efficacy to tiotropium.



Daitx, R. B., K. Dos Santos, et al. (2018). **"Limited utility of Kinesio Taping(R) in the physiotherapy treatment for patients with chronic obstructive pulmonary disease exacerbation."** Physiother Theory Pract **34**(10): 741-746.

BACKGROUND: Kinesio Taping(R) has been used as a physiotherapy treatment in musculoskeletal disorders. However, few studies have evaluated its effectiveness in patients with chronic obstructive pulmonary disease (COPD). OBJECTIVES: To analyze the effects of Kinesio Taping(R) associated with conventional physiotherapy, on the maximal inspiratory and expiratory pressures (MIP and MEP), forced expiratory volume in 1 second (FEV1), peak expiratory flow (PEF), and pulse oxygen saturation (SpO2) of patients hospitalized for COPD exacerbation. METHODS: Prospective, randomized, single-blinded study. Sixty-two participants who were randomized into two groups: 1) control (medication and standard physiotherapy treatment); and 2) Kinesio Taping(R) (standard treatment plus application of Kinesio Taping(R) on the respiratory muscles). The outcomes were assessed 24 hours after the treatment. RESULTS: After the intervention, the Kinesio Taping(R) group showed a statistically significant increase in all outcomes assessed. However, when the mean differences between groups were analyzed, there were no statistically significant differences in MIP, MEP, FEV1, and PEF. Differences were found only in SpO2 that was improved in the Kinesio Taping(R) group. CONCLUSIONS: The application of Kinesio Taping(R) associated with physiotherapy improved SpO2 of non-hypoxemic patients with COPD exacerbation. Further studies should be conducted to evaluate the method in the long run and in another outcome.

De Brandt, J., M. A. Spruit, et al. (2018). **"Changes in lower limb muscle function and muscle mass following exercise-based interventions in patients with chronic obstructive pulmonary disease: A review of the English-language literature."** Chron Respir Dis **15**(2): 182-219.

Chronic obstructive pulmonary disease (COPD) patients often experience lower limb muscle dysfunction and wasting. Exercise-based training has potential to improve muscle function and mass, but literature on this topic is extensive and heterogeneous including numerous interventions and outcome measures. This review uses a detailed systematic approach to investigate the effect of this wide range of exercise-based interventions on muscle function and mass. PUBMED and PEDro databases were searched. In all, 70 studies ( n = 2504 COPD patients) that implemented an exercise-based intervention and reported muscle strength, endurance, or mass in clinically stable COPD patients were critically appraised. Aerobic and/or resistance training, high-intensity interval training, electrical or magnetic muscle stimulation, whole-body vibration, and water-based training were investigated. Muscle strength increased in 78%, muscle endurance in 92%, and muscle mass in 88% of the cases where that specific outcome was measured. Despite large heterogeneity in exercise-based interventions and

outcome measures used, most exercise-based trials showed improvements in muscle strength, endurance, and mass in COPD patients. Which intervention(s) is (are) best for which subgroup of patients remains currently unknown. Furthermore, this literature review identifies gaps in the current knowledge and generates recommendations for future research to enhance our knowledge on exercise-based interventions in COPD patients.

Deng, N., T. Gu, et al. (2018). **"Effects of telephone support on exercise capacity and quality of life in patients with chronic obstructive pulmonary disease: a meta-analysis."** Psychol Health Med **23**(8): 917-933.

The aim of this meta-analysis was to evaluate the effects of disease education or pulmonary rehabilitation programs assisted with telephone support on physical capacity and quality of life (QOL) in chronic obstructive pulmonary disease (COPD) patients. A systematic search of PubMed, Embase, Web of Science and The Cochrane Library was conducted until May 2017. Randomized controlled trials (RCTs) examining the effects of telephone-assisted intervention versus a control group on exercise tolerance and QOL in patients with COPD were included. Two independent authors assessed the methodological quality of the trials using the Cochrane risk of bias tool. A meta-analysis was conducted with the Revman5.3 to quantify the effects of telephone-assisted interventions on walking capacity and QOL. In total, 10 studies involving 1037 participants were included. Due to the effect of telephone-assisted interventions, statistically significant results were found on Saint-George's Respiratory Questionnaire (SGRQ) symptom scores [standard mean difference (SMD) -.18, 95% confidence interval (CI) -.33, -.03, p-value .02], SGRQ impact scores [SMD -.35, 95% CI -.60, -.10, p-value .006], SGRQ activity scores [SMD -.30, 95% CI -.45, -.15, p-value < .0001], SGRQ total score [SMD -.36, 95% CI -.51, -.21, p-value < .00001]. The effects on 6-min walk test (6MWT) and all Chronic Respiratory Questionnaire (CRQ) subscales were not significant ( $p > .05$ ) based on the insufficient evidence. In conclusion, the role of telephone-assisted interventions in the management of COPD remains equivocal. Some encouraging results were seen with regard to SGRQ symptom, SGRQ impact, SGRQ activity and SGRQ total score. We believe that more methodologically rigorous large-scale randomized controlled trials are necessary to answer this study question.

Dennis, S., H. K. Reddel, et al. (2017). **"Barriers and outcomes of an evidence-based approach to diagnosis and management of chronic obstructive pulmonary disease (COPD) in Australia: a qualitative study."** Fam Pract **34**(4): 485-490.

Background: Chronic obstructive pulmonary disease (COPD) is commonly managed in primary care but there is poor awareness of evidence-based guidelines and the quality and interpretation of spirometry is suboptimal. Objectives: The aims of this

qualitative study were to explore how an intervention involving case finding and management of COPD was implemented, and the extent to which the GPs and practice nurses (PNs) worked in partnership to diagnose and manage COPD. Methods: Semi-structured interviews with PNs (n = 7), GPs (n = 4) and patients (n = 26) who had participated in the Primary care EarLy Intervention for Copd mANagement (PELICAN) study. The Theoretical Domains Framework was used to guide the coding and analysis of the interviews with PN and GPs. The patient interviews were analysed thematically. Results: PNs developed technical skills and understood the requirements for good-quality spirometry. However, many lacked confidence in its interpretation and felt this was not part of their professional role. This was reflected in responses from the GPs. Once COPD was diagnosed, the GPs tended to manage the patients with the PNs less involved. This was in contrast with PNs' active role in managing patients with other chronic diseases such as diabetes. The extent to which the GPs and PNs worked in partnership to manage COPD varied. Conclusions: PNs improved their skills and confidence in performing spirometry. Beliefs about their professional role, identity and confidence influenced the extent to which PNs were involved in interpretation of the spirometry results and managing the patient in partnership with the GP.

Desveaux, L., S. L. Harrison, et al. (2018). **"Effects of exercise training on cognition in chronic obstructive pulmonary disease: A systematic review."** Respir Med **139**: 110-116.

**BACKGROUND:** As exercise may mitigate cognitive decline in individuals with chronic obstructive pulmonary disease (COPD), its effect has been evaluated in a number of clinical trials. The objective of the present systematic review was to describe the impact of exercise training on cognition in COPD. **METHODS:** Electronic searches of four databases were performed from inception until March 24, 2015 and last updated 23rd October 2017. Included studies reported on at least one cognitive outcome before and after a formal exercise-training program in individuals with COPD. Two reviewers independently rated study quality using the Downs and Black checklist. The protocol was registered on PROSPERO (CRD42015017884). **RESULTS:** Seven articles, representing six exercise interventions in 293 individuals with COPD (55% males, mean age 67+/-2 year) were included. Although each study documented a significant pre-post training improvement in at least one cognitive domain, the heterogeneity in study design, exercise intervention and cognitive outcome measures among studies precluded a meta-analysis. The only randomized controlled trial available reported an improvement on a letter verbal fluency task in the exercise group only. **CONCLUSIONS:** Exercise training may positively impact cognition in COPD patients, but current evidence is limited by the heterogeneity of study design, exercise intervention and cognitive outcome measures. Future studies should emphasize comprehensive reporting of intervention parameters, including program length, type(s) of exercise, and duration of individual sessions, in order to facilitate applied insights to inform replication and/or program development.

Diez-Manglano, J., J. Recio Iglesias, et al. (2017). **"Effectiveness of a simple intervention on management of acute exacerbations of chronic obstructive pulmonary disease and its cardiovascular comorbidities: COREPOC study."** Med Clin (Barc) **149**(6): 240-247.

**BACKGROUND AND OBJECTIVE:** To determine the effectiveness of a simple educational intervention to improve the management of cardiovascular comorbidities in patients hospitalized with an acute exacerbation of chronic obstructive pulmonary disease (COPD). **MATERIAL AND METHODS:** Multicenter study participated in by 26 hospital centers. A panel of experts elaborated a set of recommendations about diagnostic and therapeutic management of acute exacerbation of COPD and cardiovascular comorbidities (coronary artery disease, atrial fibrillation, heart failure and diabetes). The recommendations were graduated as indispensable, advisable and outstanding. Compliance with recommendations were assessed in the discharge letter for COPD patients hospitalized with acute exacerbation in Internal Medicine departments. The protocols to treat the comorbidities in COPD were explained in a clinical session. After 6 months' compliance with recommendations they were reassessed. **RESULTS:** A total of 390 cases before and after the intervention were assessed. There was significant progress in 53% of cases. The improvement was greater in cases referred to general management and COPD management (66.7 and 76.9%, respectively), and lower in cases referred to ischemic heart disease (11.1%) and none in those referred to coronary artery disease. After the intervention, the adherence to overall and indispensable recommendations was higher ( $P=.020$  and  $P=.017$ , respectively) and a trend to improve was observed in advisable ( $P=.058$ ) and outstanding recommendations ( $P=.063$ ). **CONCLUSIONS:** A simple intervention can improve the management of lung disease in COPD patients with an acute exacerbation, but has less effect on the management of comorbidities.

Duenk, R. G., C. Verhagen, et al. (2017). **"Proactive palliative care for patients with COPD (PROLONG): a pragmatic cluster controlled trial."** Int J Chron Obstruct Pulmon Dis **12**: 2795-2806.

**BACKGROUND AND AIM:** Patients with advanced chronic obstructive pulmonary disease (COPD) have poor quality of life. The aim of this study was to assess the effects of proactive palliative care on the well-being of these patients. **TRIAL REGISTRATION:** This trial is registered with the Netherlands Trial Register, NTR4037. **PATIENTS AND METHODS:** A pragmatic cluster controlled trial (quasi-experimental design) was performed with hospitals as cluster (three intervention and three control) and a pretrial assessment was performed. Hospitals were selected for the intervention group based on the presence of a specialized palliative care team (SPCT). To control for confounders, a pretrial assessment was performed in which hospitals were compared on baseline characteristics. Patients with COPD with poor prognosis were recruited during

hospitalization for acute exacerbation. All patients received usual care while patients in the intervention group received additional proactive palliative care in monthly meetings with an SPCT. Our primary outcome was change in quality of life score after 3 months, which was measured using the St George Respiratory Questionnaire (SGRQ). Secondary outcomes were, among others, quality of life at 6, 9 and 12 months; readmissions; survival; and having made advance care planning (ACP) choices. All analyses were performed following the principle of intention to treat. RESULTS: During the year 2014, 228 patients (90 intervention and 138 control) were recruited and at 3 months, 163 patients (67 intervention and 96 control) completed the SGRQ. There was no significant difference in change scores of the SGRQ total at 3 months between groups (-0.79 [95% CI, -4.61 to 3.34],  $p=0.70$ ). However, patients who received proactive palliative care experienced less impact of their COPD (SGRQ impact subscale) at 6 months (-6.22 [-11.73 to -0.71],  $p=0.04$ ) and had more often made ACP choices (adjusted odds ratio 3.26 [1.49-7.14],  $p=0.003$ ). Other secondary outcomes were not significantly different. CONCLUSION: Proactive palliative care did not improve the overall quality of life of patients with COPD. However, patients more often made ACP choices which may lead to better quality of care toward the end of life.

Echevarria, C., J. Gray, et al. (2018). **"Home treatment of COPD exacerbation selected by DECAF score: a non-inferiority, randomised controlled trial and economic evaluation."** *Thorax* 73(8): 713-722.

BACKGROUND: Previous models of Hospital at Home (HAH) for COPD exacerbation (ECOPD) were limited by the lack of a reliable prognostic score to guide patient selection. Approximately 50% of hospitalised patients have a low mortality risk by DECAF, thus are potentially suitable. METHODS: In a non-inferiority randomised controlled trial, 118 patients admitted with a low-risk ECOPD (DECAF 0 or 1) were recruited to HAH or usual care (UC). The primary outcome was health and social costs at 90 days. RESULTS: Mean 90-day costs were pound1016 lower in HAH, but the one-sided 95% CI crossed the non-inferiority limit of pound150 (CI -2343 to 312). Savings were primarily due to reduced hospital bed days: HAH=1 (IQR 1-7), UC=5 (IQR 2-12) ( $P=0.001$ ). Length of stay during the index admission in UC was only 3 days, which was 2 days shorter than expected. Based on quality-adjusted life years, the probability of HAH being cost-effective was 90%. There was one death within 90 days in each arm, readmission rates were similar and 90% of patients preferred HAH for subsequent ECOPD. CONCLUSION: HAH selected by low-risk DECAF score was safe, clinically effective, cost-effective, and preferred by most patients. Compared with earlier models, selection is simpler and approximately twice as many patients are eligible. The introduction of DECAF was associated with a fall in UC length of stay without adverse outcome, supporting use of DECAF to direct early discharge. TRIAL REGISTRATION NUMBER: Registered prospectively ISRCTN29082260.

Elbehairy, A. F., K. A. Webb, et al. (2018). **"Acute bronchodilator therapy does not reduce wasted ventilation during exercise in COPD."** Respir Physiol Neurobiol **252-253**: 64-71.

This randomized, double-blind, crossover study aimed to determine if acute treatment with inhaled bronchodilators, by improving regional lung hyperinflation and ventilation distribution, would reduce dead space-to-tidal volume ratio (VD/VT); thus contributing to improved exertional dyspnea in COPD. Twenty COPD patients (FEV1=50+/-15% predicted; mean+/-SD) performed pulmonary function tests and symptom-limited constant-work rate exercise at 75% peak-work rate (with arterialized capillary blood gases) after nebulized bronchodilator (BD; ipratropium 0.5mg+salbutamol 2.5mg) or placebo (PL; normal saline). After BD versus PL: Functional residual capacity decreased by 0.4L (p=.0001). Isotime during exercise after BD versus PL (p<.05): dyspnea decreased: 1.2+/-1.9 Borg-units; minute ventilation increased: 3.8+/-5.5L/min; IC increased: 0.24+/-0.28L and VT increased 0.19+/-0.16L. There was no significant difference in arterial CO2 tension or VD/VT, but alveolar ventilation increased by 3.8+/-5.5L/min (p=.02). Post-BD improvements in respiratory mechanics explained 51% of dyspnea reduction at a standardized exercise time. Bronchodilator-induced improvements in respiratory mechanics were not associated with reduced wasted ventilation - a residual contributory factor to exertional dyspnea during exercise in COPD.

Facius, A., E. Marostica, et al. (2018). **"Pharmacokinetic and Pharmacodynamic Modelling to Characterize the Tolerability of Alternative Up-Titration Regimens of Roflumilast in Patients with Chronic Obstructive Pulmonary Disease."** Clin Pharmacokinet **57**(8): 1029-1038.

BACKGROUND: In the OPTIMIZE study, 4 weeks of roflumilast 250 microg once daily before escalation to the approved 500 microg once daily maintenance dose reduced treatment discontinuations and improved tolerability to roflumilast among patients with chronic obstructive pulmonary disease (COPD). In this study, we present the pharmacokinetic (PK) results and PK/pharmacodynamic (PD) modelling data from OPTIMIZE. METHODS: OPTIMIZE was a multicentre, double-blind, phase III study in which patients with severe COPD were randomized 1:1:1 to receive oral roflumilast 250 mug once daily, 500 mug every other day, or 500 mug once daily for 4 weeks, followed by 500 mug once daily for 8 weeks. A population PK (popPK) model characterized roflumilast exposure levels (total phosphodiesterase-4 inhibition [tPDE4i]). Furthermore, models characterized the percentage of patients with adverse events (AEs) of interest (PK/AE model), and time to discontinuation due to such AEs (PK/time-to-event model). RESULTS: The popPK model adequately described average plasma concentrations and variability from 1238 patients. The percentage of patients with AEs of interest increased with predicted tPDE4i exposure (logit scale slope 0.484; confidence interval 0.262-0.706; p = 2 x 10<sup>-5</sup>). PK/time-to-event model analysis predicted that patients receiving the 250 mug up-titration regimen had significantly lower discontinuation rates and longer time to discontinuation

compared with roflumilast 500 mug every other day or 500 mug once daily ( $p = 0.0014$ ). **CONCLUSIONS:** In this PK/PD model, a 4-week up-titration regimen with roflumilast 250 microg once daily was found to reduce discontinuations and improve tolerability, confirming the main clinical findings of the OPTIMIZE study. However, use of this lower dose as long-term maintenance therapy may not induce sufficient phosphodiesterase-4 inhibition to exert clinical efficacy, supporting the approval of 500 microg as maintenance dose. **TRIAL REGISTRATION:** OPTIMIZE: NCT02165826; REACT: NCT01329029.

Farquhar, M. (2017). "**Carers and breathlessness.**" Curr Opin Support Palliat Care **11**(3): 165-173.

**PURPOSE OF REVIEW:** Informal carers play a key role in supporting patients living with breathlessness in advanced disease, but with considerable impacts on their own well being. The purpose was to review recent advances in our understanding of the caring role in refractory breathlessness, its impacts on carers, and interventions to support them. **RECENT FINDINGS:** A systematic literature search resulted in 28 included articles that could be mapped to four broad areas of carer enquiry: the carer role ( $n = 6$ ), role impact ( $n = 7$ ), carer support ( $n = 11$ ) and carer views ( $n = 4$ ). Search terms focused on breathlessness, but few of the included articles were exclusively on breathlessness: most were disease-related, predominantly chronic obstructive pulmonary disease (COPD). There were a range of methodologies, including four systematic reviews; UK studies were most common. **SUMMARY:** Carers of patients with breathlessness take on a role characterized by uncertainty, largely unsupported by healthcare professionals (HCPs). HCP acknowledgement of these carers, their contribution and the impact of the caring role, is lacking. The patient-carer dyad should be considered the unit of care. Carer intervention should be individualized, supporting carers as clients and coworkers. There was a dearth of studies recruiting via primary care, focusing on conditions other than COPD and longitudinal work.

Ferrari, R., L. M. O. Caram, et al. (2018). "**The relationship between Vitamin D status and exacerbation in COPD patients- a literature review.**" Respir Med **139**: 34-38.

**OBJECTIVE:** To investigate the relationship between Vitamin D and exacerbation in COPD patients. **METHODS:** The PubMed database was searched for articles published from 2012 onwards using search terms related to Vitamin D and exacerbation in COPD patients. Meta-analysis, clinical trials, observational studies, and human studies were included. Non-English articles or articles with full text unavailable were excluded; a total of 15 articles were selected. **RESULTS:** The association between exacerbation frequency and Vitamin D levels in observational studies remains controversial, however, meta-analysis

revealed a negative association between serum Vitamin D and exacerbation. Also, two clinical trials showed that Vitamin D3 supplementation in COPD patients reduced the risk of moderate and severe exacerbation. Vitamin D binding protein (VDBP) polymorphisms seem to affect patient exacerbation susceptibility. **CONCLUSIONS:** Few studies in literature have data related to diet, 25-hydroxyVitamin D [25(OH)D] and polymorphism in COPD exacerbation. One clinical trial indicates Vitamin D supplementation plays a role in COPD patients with hypovitaminosis D in preventing exacerbations. Further studies are needed to elucidate the role of Vitamin D in this population and to establish the best marker for Vitamin D, which patient subgroups will benefit, and the best supplement dosage without leading to toxicity.

Finamore, P., C. Pedone, et al. (2018). **"Validation of exhaled volatile organic compounds analysis using electronic nose as index of COPD severity."** Int J Chron Obstruct Pulmon Dis **13**: 1441-1448.

**Aim:** Six-minute walking test distance (6MWD) and body mass index, obstruction, dyspnea and exercise (BODE) index are measures of functional status in COPD patients, but require space, time and patient's compliance. Exhaled volatile organic compounds (VOCs) analysis via electronic nose is a quick and easy method that has already been used to discriminate COPD phenotypes. The aim of this study is to evaluate whether VOCs analysis can predict functional status and its variation over time in COPD patients. **Methods:** A monocentric prospective study with 1 year of follow-up was carried out. All patients underwent pulmonary function tests, arterial gas analysis, bioimpedance analysis, 6-minute walking test, and VOCs collection. Exhaled breath was collected with Pneumopipe((R)) and analyzed using BIONOTE electronic nose. Outcomes prediction was performed by k-fold cross-validated partial least square discriminant analysis: accuracy, sensitivity and specificity as well as Cohen's kappa for agreement were calculated. **Results:** We enrolled 63 patients, 60.3% men, with a mean age of 71 (SD: 8) years, median BODE index of 1 (interquartile range: 0-3) and mean 6MWD normalized by squared height (n6MWD) of 133.5 (SD: 42) m/m(2). The BIONOTE predicted baseline BODE score (dichotomized as BODE score <3 or ≥3) with an accuracy of 86% and quartiles of n6MWD with an accuracy of 79%. n6MWD decline more than the median value after 1 year was predicted with an accuracy of 86% by BIONOTE, 52% by Global Initiative for Chronic Obstructive Lung Disease (GOLD) class and 78% by combined BIONOTE and GOLD class. **Conclusion:** Exhaled VOCs analysis identifies classes of BODE and n6MWD quartiles, and outperforms GOLD classification in predicting n6MWD variation.

Fujimoto, K., H. Yamazaki, et al. (2017). **"Efficacy of tiotropium and indacaterol monotherapy and their combination on dynamic lung hyperinflation in**



**COPD: a random open-label crossover study." Int J Chron Obstruct Pulmon Dis 12: 3195-3201.**

Background and objective: The difference in efficacy of long-acting muscarinic antagonists (LAMAs) and long-acting beta2-agonists (LABAs) for dynamic lung hyperinflation (DLH) in COPD is unclear. The purpose of this study was to elucidate the difference in efficacy of LAMA and LABA alone and the combination thereof for DLH. Subjects and methods: Thirty stable patients were enrolled and randomly divided into two groups following baseline measurements. One group was treated with 5 mug tiotropium (Respimat inhaler) for 4 weeks following a 4-week treatment with 150 mug indacaterol, while the other group was treated with indacaterol for 4 weeks following a 4-week treatment with tiotropium. For both groups, these treatments were followed by a combination of the two drugs for 4 weeks. Pulmonary function tests, including DLH evaluated by metronome-paced incremental hyperventilation and exercise tolerance evaluated by the shuttle-walk test, were performed at the end of each treatment period. Results: In total, 23 patients completed this study. Both tiotropium and indacaterol alone significantly increased forced expiratory volume in 1 second, exercise tolerance, and improved health status. Tiotropium significantly improved DLH, but indacaterol did not. The combination therapy resulted in further improvements in lung function and exercise tolerance, but not in DLH. Conclusion: The efficacy of tiotropium in inhibiting DLH following metronome-paced incremental hyperventilation may be superior to that of 150 mug indacaterol, although the effects on airflow obstruction were the same, and the combination therapy showed further improvement in airflow obstruction, but not in DLH.

Furian, M., S. E. Hartmann, et al. (2018). "**Exercise Performance of Lowlanders with COPD at 2,590 m: Data from a Randomized Trial.**" Respiration 95(6): 422-432.

BACKGROUND: Effects of hypobaric hypoxia at altitude on exercise performance of lowlanders with chronic obstructive pulmonary disease (COPD) have not been studied in detail. OBJECTIVES: To quantify changes in exercise performance and associated physiologic responses in lowlanders with COPD travelling to moderate altitude. METHODS: A total of 31 COPD patients with a median age (quartiles) of 66 years (59; 69) and FEV1 of 56% predicted (49; 69) living below 800 m performed a constant-load bicycle exercise to exhaustion at 60% of the maximal work rate at 490 m (Zurich) and at an identical work rate at 2,590 m (Davos) in randomized order. Pulmonary gas exchange, pulse oximetry (SpO2), cerebral tissue oxygenation (CTO; near-infrared spectroscopy), and middle cerebral artery peak blood flow velocity (MCAv) by Doppler ultrasound during 30 s at end exercise were compared between altitudes. RESULTS: With ascent from 490 to 2,590 m, the median endurance time (quartiles) was reduced from 500 s (256; 795) to 205 s (139; 297) by a median (95% CI) of 303 s (150-420) ( $p < 0.001$ ). End exercise SpO2 decreased from 92% (89; 94) to 81% (77; 84) and CTO from 62% (56; 66) to 55% (50; 60); end exercise minute ventilation increased from 40.6 L/min (35.5; 47.8) to 47.2 L/min (39.6; 58.7) ( $p < 0.05$ ; all comparisons 2,590 vs. 490 m). MCAv increased similarly from rest to end exercise at 490 m (+25% [17; 36]) and at 2,590 m (+21% [14; 30]). However, the ratio of MCAv increase to SpO2 drop during exercise decreased from +6%/ % (3;

12) at 490 m to +3%/ % (2; 5) at 2,590 m ( $p < 0.05$ ). **CONCLUSIONS:** In lowlanders with COPD travelling to 2,590 m, exercise endurance is reduced by more than half compared to 490 m in association with reductions in systemic and cerebral oxygen availability.

Gagne, M., J. Moisan, et al. (2018). **"Comparative impact of two continuing education activities targeted at COPD educators on educational outcomes: protocol for a non-randomized controlled study using mixed methods."** BMC Health Serv Res **18**(1): 460.

**BACKGROUND:** Therapeutic patient education (TPE) improves quality of life and reduces health care utilization among patients with chronic obstructive pulmonary disease (COPD). However, benefits from TPE might depend on the performance of the educators and training is needed to ensure the effective delivery of TPE interventions. Based on the framework by Moore et al. (J Contin Educ Health Prof 29:1-15, 2009), we will compare the impact of two continuing education (CE) activities on TPE in regard to the following educational outcomes: (1) learning, (2) self-report of competence, (3) performance of the educators, and (4) outcomes of COPD patients who will meet the newly trained educators for TPE. **METHODS:** We will conduct a non-randomized controlled study using mixed methods. Educators will first participate in a CE activity on TPE that will include a role-playing simulation (experimental group) or in a lecture on TPE (comparison group) and then will perform TPE in COPD patients. Among educators, we will assess: (1) learning, by measuring knowledge about TPE, and (2) self-report of competence using self-administered questionnaires before and after the activity. Then, after the CE activity, we will assess (3) educators' performance levels in delivering TPE by rating a videotaped TPE intervention. In COPD patients who will meet the newly trained educators for TPE after either CE activity, we will assess (4) quality of life and resource utilization using interviewer-administered questionnaires, before and after TPE. Statistical analyses will compare the experimental group against the comparison group using multivariate models. Using a semi-structured interview guide, we will conduct interviews with educators and perform content analysis. Results will be integrated in order that qualitative results further explain the quantitative ones. **DISCUSSION:** To the best of our knowledge, this is the first controlled mixed methods study to compare the impact of two CE activities on TPE in regard to four educational outcomes. We believe this study will serve as a model for evaluating CE activities on TPE. Results from this study could increase educators' performance levels in delivering effective TPE interventions, and, in turn, COPD patient outcomes. **TRIAL REGISTRATION:** The study was registered on <https://clinicaltrials.gov/> ( NCT02870998 ) on March 15, 2016.

Galletti, J., G. McHeileh, et al. (2018). **"The Clinical Effects of Manipulative Therapy in People with Chronic Obstructive Pulmonary Disease."** J Altern Complement Med **24**(7): 677-683.

**OBJECTIVES:** This study aimed to determine the effects of manipulative therapies (MT), including spinal manipulation, and diaphragmatic release techniques on lung function, exercise capacity, symptoms, and health-related quality of life (HRQOL) in people with chronic obstructive pulmonary disease (COPD). **DESIGN:** Systematic review. **PARTICIPANTS:** People diagnosed with COPD. **INTERVENTION:** Randomized controlled trials of MT (either with or without pulmonary rehabilitation [PR]) compared to other treatments (soft tissue [ST] therapy or sham therapy) applied in people with COPD were identified following the search of seven databases. Two reviewers independently assessed study quality and extracted data. **OUTCOME MEASURES:** Lung function, exercise capacity, symptoms, and HRQOL. **RESULTS:** Four studies were included, with a total of 68 participants. The heterogeneity between treatments prevented meta-analysis. There was no beneficial effect on spirometry measures of lung function with MT. MT combined with PR improved exercise capacity by 48-49 m more than ST therapy plus PR. Less dyspnea was reported with MT and ST therapy compared to ST therapy alone ( $p = 0.01$ ), but there was no effect on HRQOL, or symptoms of anxiety or depression. **CONCLUSIONS:** In people with COPD, MT (either with or without PR) improved functional exercise capacity, but had no effect on lung function, or HRQOL. Further research is required to determine the underlying mechanism of this treatment approach and its relationship to exercise capacity.

Garcia-Rio, F., J. J. Soler-Cataluna, et al. (2017). **"Requirements, Strengths and Weaknesses of Inhaler Devices for COPD Patients from the Expert Prescribers' Point of View: Results of the EPOCA Delphi Consensus."** Copd **14**(6): 573-580.

The study aimed to assess the preferences of expert physicians about the requirements for inhalation devices for patients with chronic obstructive pulmonary disease (COPD) and to identify the most relevant advantages and disadvantages to their prescription. In a two-round Delphi survey, 96 Spanish COPD-expert pulmonologists completed an internet-based questionnaire to evaluate the degree of importance of the characteristics of the inhaler devices in their choice for COPD. The requirements needed for use in COPD were that the device permits a high pulmonary deposit of the drug, allowed its dispensation at low inspiratory flows, did not require hand-mouth coordination, generated an exact and reproducible dose, its operation was easy to teach, provided the perception of a correct inhalation, had an intuitive use mechanism and security mechanisms to prevent overdosing and generates a reduced oropharyngeal deposit (very good consensus). Modulite(R), Respimat(R) and NEXThaler(R) were associated with high pulmonary deposit, and Respimat(R) showed correct dispensation at low inspiratory flows. All dry-powder inhaler devices were associated with the advantage of not requiring coordination, and Respimat(R) was the only device considered as difficult to teach by more than 50% of the experts. Breezhaler(R) and Genuair(R) were positively associated with patients' awareness of correct

inhalation, whereas Spiromax(R) stood out for its intuitive use mechanism. In conclusion, our study contributes to defining the inhaler device properties required for their use in patients with COPD, and to identify the devices that, in the opinion of experts, best meet each requirement.

Gelinas, J. C., N. C. Lewis, et al. (2017). **"Aerobic exercise training does not alter vascular structure and function in chronic obstructive pulmonary disease."** *Exp Physiol* **102**(11): 1548-1560.

**NEW FINDINGS:** What is the central question of this study? Chronic obstructive pulmonary disease (COPD) is associated with endothelial dysfunction, arterial stiffness and systemic inflammation, which are linked to increased cardiovascular disease risk. We asked whether periodized aerobic exercise training could improve vascular structure and function in patients with COPD. What is the main finding and its importance? Eight weeks of periodized aerobic training did not improve endothelial function, arterial stiffness or systemic inflammation in COPD, despite improvements in aerobic capacity, blood pressure and dyspnoea. Short-term training programmes may not be long enough to improve vascular-related cardiovascular risk in COPD. Chronic obstructive pulmonary disease (COPD) has been associated with endothelial dysfunction and arterial stiffening, which are predictive of future cardiovascular events. Although aerobic exercise improves vascular function in healthy individuals and those with chronic disease, it is unknown whether aerobic exercise can positively modify the vasculature in COPD. We examined the effects of 8 weeks of periodized aerobic training on vascular structure and function and inflammation in 24 patients with COPD (age, 69 +/- 7 years; forced expiratory volume in 1 second as a percentage of predicted (FEV1 %pred), 68 +/- 19%) and 20 matched control subjects (age, 64 +/- 5 years; FEV1 %pred, 113 +/- 16%) for comparison. Endothelial function was measured using brachial artery flow-mediated dilatation, whereas central and peripheral pulse wave velocity, carotid artery intima-media thickness, carotid compliance, distensibility and beta-stiffness index were measured using applanation tonometry and ultrasound. Peak aerobic power (VO<sub>2</sub> peak) was measured using an incremental cycling test. Upper and lower body cycling training was performed three times per week for 8 weeks, and designed to optimize vascular adaptation by increasing and sustaining vascular shear stress. Flow-mediated dilatation was not increased in COPD patients (+0.15 +/- 2.27%, P = 0.82) or control subjects (+0.34 +/- 3.20%, P = 0.64) and was not different between groups (P = 0.68). No significant improvements in central pulse wave velocity (COPD, +0.30 +/- 1.79 m s<sup>-1</sup>) versus control subjects, -0.34 +/- 1.47 m s<sup>-1</sup>) or other markers of vascular structure or function were found within or between groups. The VO<sub>2</sub> peak increased significantly in COPD and control subjects, and was greater in control subjects (1.6 +/- 1.4 versus 4.1 +/- 3.7 ml kg min<sup>-1</sup>, P = 0.003), while blood pressure and dyspnoea were reduced in COPD patients (P < 0.05). These findings demonstrate that 8 weeks of aerobic training improved cardiorespiratory fitness and blood pressure in COPD but had little effect on other established markers of cardiovascular disease risk.

Golpe, R., M. Suarez-Valor, et al. (2018). **"Mortality in COPD patients according to clinical phenotypes."** *Int J Chron Obstruct Pulmon Dis* **13**: 1433-1439.

Purpose: Grouping COPD subjects into clinical phenotypes might be useful for the management of the disease, but the clinical implications of such classification are still not totally clear, especially regarding prognosis. The primary objective of this study was to assess whether the mortality rates were different between four predefined clinical phenotypes. Patients and methods: This is a retrospective, observational study carried out at the COPD clinic of a University Hospital. A total of 891 COPD patients were classified, according to the Spanish COPD guidelines, into the following four phenotypes: asthma-COPD overlap (ACO; 75 subjects), nonexacerbator (NONEX; 531 subjects), exacerbator with chronic bronchitis (EXCB; 194 subjects), and exacerbator with emphysema (EXEMPH; 91 subjects). We compared the mortality outcomes between the phenotypes. Results: After a follow-up of 48.4+/-25.2 months, there were 194 deaths (21.8%). There were significant differences in all-cause mortality between phenotypes. The ACO phenotype had the best long-term prognosis, whereas EXEMPH had the highest risk of death. NONEX and EXCB mortality figures were in between the other two groups. We also found some differences in the causes of death, and patients with EXEMPH were at a higher risk of dying because of COPD itself. The differences in mortality did not seem related to the classification into phenotypes in itself but to disparities in COPD severity and comorbidity load between groups. Conclusion: Classifying COPD patients according to several predefined clinical phenotypes can identify clusters of subjects with different mortality outcomes. Some phenotypes are associated with a specific cause of death. The mechanisms that underlie these differences seem to be related to COPD severity and comorbidities.

Goossens, L. M. A., M. Rutten-van Molken, et al. (2017). **"ABC Index: quantifying experienced burden of COPD in a discrete choice experiment and predicting costs."** *BMJ Open* **7**(12): e017831.

OBJECTIVE: The Assessment of Burden of COPD (ABC) tool supports shared decision making between patient and caregiver. It includes a coloured balloon diagram to visualise patients' scores on burden indicators. We aim to determine the importance of each indicator from a patient perspective, in order to calculate a weighted index score and investigate whether that score is predictive of costs. DESIGN: Discrete choice experiment. SETTING AND PARTICIPANTS: Primary care and secondary care in the Netherlands. 282 patients with chronic obstructive pulmonary disease (COPD) and 252 members of the general public participated. METHODS: Respondents received 14 choice questions and indicated which of two health states was more severe. Health states were described in terms of specific symptoms, limitations in physical, daily and social activities, mental problems, fatigue and exacerbations, most of which had three levels of severity. Weights for each item-level combination were derived from a

Bayesian mixed logit model. Weights were rescaled to construct an index score from 0 (best) to 100 (worst). Regression models were used to find a classification of this index score in mild, moderate and severe that was discriminative in terms of healthcare costs. RESULTS: Fatigue, limitations in moderate physical activities, number of exacerbations, dyspnoea at rest and fear of breathing getting worse contributed most to the burden of disease. Patients assigned less weight to dyspnoea during exercise, listlessness and limitations with regard to strenuous activities. Respondents from the general public mostly agreed. Mild, moderate and severe burden of disease were defined as scores <20, 20-39 and ≥40. This categorisation was most predictive of healthcare utilisation and annual costs: euro1368, euro2510 and euro9885, respectively. CONCLUSIONS: The ABC Index is a new index score for the burden of COPD, which is based on patients' preferences. The classification of the index score into mild, moderate and severe is predictive of future healthcare costs. TRIAL REGISTRATION NUMBER: NTR3788; Post-results.

Gove, K., T. Wilkinson, et al. (2018). **"Systematic review of evidence for relationships between physiological and CT indices of small airways and clinical outcomes in COPD."** *Respir Med* 139: 117-125.

BACKGROUND: Small airways disease (SAD) is considered pivotal in the pathology of COPD. There are numerous publications describing physiological and Computed Tomography (CT) imaging markers to detect SAD. However, there is no agreed gold standard and limited understanding of the clinical associations of these measures to disease outcomes. METHODS: We conducted a systematic review using Embase, Medline and Pubmed to explore the relationship between physiological and CT SAD measures in COPD (GOLD Stages 1-4). Furthermore, evidence linking these physiological measures with defined clinical outcomes such as health status, functional assessment and exacerbation frequency were summarised. RESULTS: The search yielded 1160 abstracts of which 19 met the search criteria. Six studies examined physiological and CT measures while 13 publications identified physiological measures and clinical outcomes. Strong correlations were seen between CT and physiological measures of SAD. Varying associations between physiological measures and defined clinical outcomes were noted. CONCLUSIONS: Physiological and CT measures of SAD correlate and infer similar information. Physiological measures of SAD may offer valuable insight into clinical expression of the disease. A consensus on the standardisation and recommendation of tests to measure SAD is needed in order to better understand any clinical benefits of targeted drug therapy to the small airways.

Halpin, D. M., M. Miravittles, et al. (2017). **"Impact and prevention of severe exacerbations of COPD: a review of the evidence."** Int J Chron Obstruct Pulmon Dis **12**: 2891-2908.

Severe exacerbations of COPD, ie, those leading to hospitalization, have profound clinical implications for patients and significant economic consequences for society. The prevalence and burden of severe COPD exacerbations remain high, despite recognition of the importance of exacerbation prevention and the availability of new treatment options. Severe COPD exacerbations are associated with high mortality, have negative impact on quality of life, are linked to cardiovascular complications, and are a significant burden on the health-care system. This review identified risk factors that contribute to the development of severe exacerbations, treatment options (bronchodilators, antibiotics, corticosteroids [CSs], oxygen therapy, and ventilator support) to manage severe exacerbations, and strategies to prevent readmission to hospital. Risk factors that are amenable to change have been highlighted. A number of bronchodilators have demonstrated successful reduction in risk of severe exacerbations, including long-acting muscarinic antagonist or long-acting beta2-agonist mono- or combination therapies, in addition to vaccination, mucolytic and antibiotic therapy, and nonpharmacological interventions, such as pulmonary rehabilitation. Recognition of the importance of severe exacerbations is an essential step in improving outcomes for patients with COPD. Evidence-based approaches to prevent and manage severe exacerbations should be implemented as part of targeted strategies for disease management.

Heidari, M., S. Fayazi, et al. (2018). **"Effect of the 5A Model on Clinical Status Indexes of COPD Patients."** Rehabil Nurs **43**(3): 158-166.

**PURPOSE:** This RCT study investigates the effects of a self-management program on clinical status indexes of COPD patients. **DESIGN:** In this study, 50 COPD patients referred to the respiratory clinic participated. **METHODS:** Patients were randomly assigned to control and intervention groups. The control group received standard care, and the intervention group received standard care plus the self-management program. Patients were assessed by spirometry, Modified Borg scale, and 6-minute walking test at the baseline and the end of 12-weeks. Paired t-test, independent t-test, and chi-square were used to analyze variables. **FINDINGS:** No significant difference was noted in the spirometry indexes mean in the two groups; however, significant differences were noted in dyspnea and exercise tolerance at the end. **CONCLUSION/CLINICAL RELEVANCE:** Using the 5A model can lead to increased exercise tolerance and decreased dyspnea in COPD patients. Therefore, this self-management program is recommended as an effective way to improve their functional status.

Herth, F. J. F., D. J. Slebos, et al. (2017). **"Endoscopic Lung Volume Reduction: An Expert Panel Recommendation - Update 2017."** *Respiration* **94**(4): 380-388.

Interest in endoscopic lung volume reduction (ELVR) technologies for emphysema is consistently growing. In the last couple of months, several endoscopic options (e.g., endo- or intrabronchial valves, coil implants, and thermal vapor ablation) that have been evaluated in randomized controlled trials have been reported with the ultimate goal of improving respiratory mechanics and alleviating chronic dyspnea. Patients presenting with severe air trapping and thoracic hyperinflation have the greatest potential to derive benefit from ELVR procedures. Baseline assessment should ideally include cardiological evaluation, high-resolution computed tomography scan and perfusion scintigraphy, full pulmonary function tests, and cardiopulmonary exercise testing. This expert statement updates best practice recommendations regarding patient selection and utilization of these various techniques for the treatment of patients with advanced emphysema.

Hill, K., V. Cavalheri, et al. (2018). **"Neuromuscular electrostimulation for adults with chronic obstructive pulmonary disease."** *Cochrane Database Syst Rev* **5**: Cd010821.

**BACKGROUND:** In people with chronic obstructive pulmonary disease (COPD), the use of neuromuscular electrostimulation (NMES) either alone, or together with conventional exercise training, might improve the condition of the peripheral muscles, increase exercise capacity and functional performance, reduce symptoms and improve health-related quality of life (HRQoL). **OBJECTIVES:** To determine the effects of NMES, applied in isolation or concurrently with conventional exercise training to one or more peripheral muscles, on peripheral muscle force and endurance, muscle size, exercise capacity, functional performance, symptoms, HRQoL and adverse events in people with COPD. **SEARCH METHODS:** We searched the Cochrane Airways Group Specialised Register, the Physiotherapy Evidence Database, clinical trial registries and conference abstracts on 14 March 2018. **SELECTION CRITERIA:** Randomised controlled trials that recruited adults with COPD if they had compared outcomes between a group that received NMES and a group that received usual care or compared outcomes between a group that received NMES plus conventional exercise training and a group that participated in conventional exercise training alone. **DATA COLLECTION AND ANALYSIS:** Two review authors independently extracted data and assessed risk of bias using the Cochrane 'Risk of bias' tool. We expressed continuous data as either the standardised mean difference (SMD) or mean difference (MD) with the corresponding 95% confidence interval (CI). We assessed the quality of evidence using the GRADE approach. **MAIN RESULTS:** Nineteen studies met the inclusion criteria of which 16 contributed data on 267 participants with COPD (mean age 56 to 76 years and 67% were men). Of these 16 studies, seven explored the effect of NMES versus usual care and nine explored the effect of NMES plus conventional exercise training versus conventional exercise training alone. Six studies utilised sham stimulation in the control group. When applied in isolation, NMES produced an increase in peripheral muscle force (SMD 0.34, 95% CI 0.02 to 0.65; low-quality evidence) and quadriceps endurance (SMD 1.36, 95% CI 0.59 to 2.12; low-quality



evidence) but the effect on thigh muscle size was unclear (MD 0.25, 95% CI -0.11 to 0.61; low-quality evidence). There were increases in six-minute walk distance (6MWD) (MD 39.26 m, 95% CI 16.31 to 62.22; low-quality evidence) and time to symptom limitation exercising at a submaximal intensity (MD 3.62 minutes, 95% CI 2.33 to 4.91). There was a reduction in the severity of leg fatigue on completion of an exercise test (MD -1.12 units, 95% CI -1.81 to -0.43). The increase in peak rate of oxygen uptake (VO<sub>2</sub>peak) was of borderline significance (MD 0.10 L/minute, 95% CI 0.00 to 0.19). For NMES with conventional exercise training, there was an uncertain effect on peripheral muscle force (SMD 0.47, 95% CI -0.10 to 1.04; very low-quality evidence) and there were insufficient studies to undertake a meta-analysis on the effect on quadriceps endurance or thigh muscle size. However, there was an increase in 6MWD in favour of NMES combined with conventional exercise training (MD 25.87 m, 95% CI 1.06 to 50.69; very low-quality evidence). In people admitted to either in an intensive care unit or a respiratory high dependency centre, NMES combined with conventional exercise reduced the time taken for participants to first sit out of bed by 4.98 days (95% CI -8.55 to -1.41; very low-quality evidence), although the statistical heterogeneity for this analysis was high ( $I^2 = 60\%$ ). For both types of studies (i.e. NMES versus usual care and NMES with conventional exercise training versus conventional exercise training alone), there was no risk difference for mortality or minor adverse events in participants who received NMES. **AUTHORS' CONCLUSIONS:** NMES, when applied in isolation, increased quadriceps force and endurance, 6MWD and time to symptom limitation exercising at a submaximal intensity, and reduced the severity of leg fatigue on completion of exercise testing. It may increase VO<sub>2</sub>peak, but the true effect on this outcome measure could be trivial. However, the quality of evidence was low or very low due to risk of bias within the studies, imprecision of the estimates, small number of studies and inconsistency between the studies. Although there were no additional gains in quadriceps force with NMES plus conventional exercise training, there was evidence of an increase in 6MWD. Further, in people who were the most debilitated, the addition of NMES may have accelerated the achievement of a functional milestone, that is, the first time someone sits out of bed.

Hitchings, A. W., E. H. Baker, et al. (2016). **"Handling missing items in the Exacerbations of Chronic Pulmonary Disease Tool."** Eur Respir J **48**(2): 564-6.

Hua, L., H. Xia, et al. (2018). **"Prediction of microRNA and gene target from an integrated network in chronic obstructive pulmonary disease based on canonical correlation analysis."** Technol Health Care **26**(S1): 121-134.

**BACKGROUND:** Chronic obstructive pulmonary disease (COPD) is a complex disorder with a high mortality. The pathophysiology of COPD has not been characterized till date. **OBJECTIVE:** To identify COPD-related biomarkers by a bioinformatics analysis. **METHODS:** Here, we conducted the canonical correlation analysis to extract the potential COPD-related miRNAs and mRNAs based on the miRNA-mRNA dual expression profiling data. After identifying miRNAs and mRNAs related to COPD, we constructed an interaction network by integrating three validated miRNA-target sources. Then we expanded the network by adding miRNA-mRNA pairs, which were identified by Spearman rank correlation test. For miRNAs involved in the network, we further performed the Gene Ontology (GO) functional enrichment analysis of their targets. To validate COPD-related mRNAs involved in the network, we performed receiver operating characteristic (ROC) curve analysis and Support Vector Machine (SVM) classification on only those mRNAs that overlapped with COPD-related mRNAs of Online Mendelian Inheritance in Man (OMIM) database. **RESULTS:** The results indicate that some identified miRNAs and their targets in the constructed network might be potential biomarkers of COPD. **CONCLUSIONS:** Our study helps us to predict the potential risk biomarkers of COPD, and it can certainly help in further elucidating the genetic etiology of COPD.

Ichinose, M., M. Nishimura, et al. (2018). "**Tiotropium/olodaterol versus tiotropium in Japanese patients with COPD: results from the DYNAGITO study.**" Int J Chron Obstruct Pulmon Dis **13**: 2147-2156.

**Background:** The DYNAGITO study was a Phase IIIb, randomized, double-blind, multicenter, active-controlled, parallel-group, 52-week study designed to determine the efficacy and safety of tiotropium and olodaterol combination therapy (TIO+OLO 5/5 mug) versus tiotropium monotherapy (TIO 5 mug) for reducing moderate-to-severe exacerbations of COPD. This is a prespecified analysis of the DYNAGITO data in Japanese patients. **Patients and methods:** Enrolled patients had a diagnosis of COPD with at least one moderate-to-severe exacerbation in the previous 12 months. Of the total 7,880 treated patients in the DYNAGITO study, 461 (TIO+OLO 5/5 mug: n=226, TIO 5 mug: n=235) were Japanese. The primary endpoint was the annualized rate of moderate-to-severe COPD exacerbations. The key secondary endpoint was the time to first moderate-to-severe COPD exacerbation, and other secondary endpoints included the annualized rate of exacerbations leading to hospitalization, time to first COPD exacerbation leading to hospitalization, and all-cause mortality. Safety data were analyzed descriptively. **Results:** Combination therapy with TIO+OLO resulted in a 29% lower rate of moderate-to-severe COPD exacerbations relative to TIO monotherapy (rate ratio 0.71; 99% CI: 0.46, 1.10; p=0.0434). The risk of a first moderate-to-severe COPD exacerbation was 19% lower with TIO+OLO combination therapy than with TIO monotherapy (HR 0.81; 99% CI: 0.57, 1.17; p=0.1379), although this difference was not statistically significant. The annualized rate of COPD exacerbations requiring hospitalization was 14% lower in the TIO+OLO arm than in the TIO arm (rate ratio 0.86; 95% CI: 0.52, 1.42; p=0.5654). The adverse event incidence was balanced between treatment arms. **Conclusion:** In a prespecified subgroup analysis of Japanese patients in the

DYNAGITO study, combination therapy with TIO+OLO was more effective than TIO in reducing exacerbations. Both treatments were well tolerated.

Iepsen, U. W., G. W. Munch, et al. (2017). "**Leg blood flow is impaired during small muscle mass exercise in patients with COPD.**" J Appl Physiol (1985) **123**(3): 624-631.

Skeletal muscle blood flow is regulated to match the oxygen demand and dysregulation could contribute to exercise intolerance in patients with chronic obstructive pulmonary disease (COPD). We measured leg hemodynamics and metabolites from vasoactive compounds in muscle interstitial fluid and plasma at rest, during one-legged knee-extensor exercise, and during arterial infusions of sodium nitroprusside (SNP) and acetylcholine (ACh), respectively. Ten patients with moderate to severe COPD and eight age- and sex-matched healthy controls were studied. During knee-extensor exercise (10 W), leg blood flow was lower in the patients compared with the controls (1.82  $\pm$  0.11 vs. 2.36  $\pm$  0.14 l/min, respectively;  $P < 0.05$ ), which compromised leg oxygen delivery (372  $\pm$  26 vs. 453  $\pm$  32 ml O<sub>2</sub>/min, respectively;  $P < 0.05$ ). At rest, plasma endothelin-1 (vasoconstrictor) was higher in the patients with COPD ( $P < 0.05$ ) and also tended to be higher during exercise ( $P = 0.07$ ), whereas the formation of interstitial prostacyclin (vasodilator) was only increased in the controls. There was no difference between groups in the nitrite/nitrate levels (vasodilator) in plasma or interstitial fluid during exercise. Moreover, patients and controls showed similar vasodilatory capacity in response to both endothelium-independent (SNP) and endothelium-dependent (ACh) stimulation. The results suggest that leg muscle blood flow is impaired during small muscle mass exercise in patients with COPD possibly due to impaired formation of prostacyclin and increased levels of endothelin-1. **NEW & NOTEWORTHY** This study demonstrates that chronic obstructive pulmonary disease (COPD) is associated with a reduced blood flow to skeletal muscle during small muscle mass exercise. In contrast to healthy individuals, interstitial prostacyclin levels did not increase during exercise and plasma endothelin-1 levels were higher in the patients with COPD.

Izaaryene, J., J. Mancini, et al. (2017). "**Embolisation of pulmonary radio frequency pathway - a randomised trial.**" Int J Hyperthermia **33**(7): 814-819.

**PURPOSE:** Pneumothorax is the most common complication following a pulmonary percutaneous radiofrequency ablation (RFA), and thoracic drainages are the most frequent causes of an extended hospital stay. Our main objective was to show that the use of gelatin torpedoes may significantly decrease the number of chest tube placement. **MATERIALS AND METHODS:** Seventy-three patients were prospectively included in this study and then randomised into two groups: 34 with embolisation and without 39 without embolisation. Each group was

comparable for different pneumothorax risk factors. **RESULTS:** There were 16 (47%) pneumothorax in Group A ("with embolisation"), which was significantly lower ( $p < .0001$ ) than the 35 pneumothorax (90%) in Group B ("without embolisation"). The pneumothorax volume ( $p = .02$ ) was significantly lower in Group A (22.7% average, standard deviation 15.6%) than in Group B (average 34.1%, standard deviation 17.1%). The number of drainages was significantly smaller in those with embolisation (3 drainages or 8%) than those without embolisation (25 drainages or 64%) ( $p < .001$ ). **CONCLUSION:** When using absorbable gelatin torpedoes, pulmonary RFA pathways embolisation significantly decreased the number of pneumothorax and thoracic drainages to the advantage of therapeutic abstention and exsufflation, non-invasive and functional operational techniques.

Jafarinejad, H., M. Moghoofei, et al. (2017). **"Worldwide prevalence of viral infection in AECOPD patients: A meta-analysis."** *Microb Pathog* **113**: 190-196.

**BACKGROUND AND OBJECTIVE:** Chronic obstructive pulmonary disease (COPD) is a chronic progressive lung disease. On the other hand, viral infections of the airway are associated with the acute exacerbations of COPD. A systematic review and meta-analysis were performed to determine the prevalence rate of viral infections in acute exacerbations of COPD patients. **METHODS:** PubMed database was systematically searched for population-based prevalence studies (1930-2017). Fixed and random effects models were used for estimation of summary effect-sizes. Between-study heterogeneity and publication bias were also calculated. "Viral infections" and "COPD patients with exacerbations" were the two critical inclusion criteria. **RESULTS:** Twenty-eight studies were selected out of 26078 articles for the present review. The overall estimation of the prevalence of viral infection was 0.374 (95% C.I: 0.359-0.388). Also, the evident heterogeneity of viral infection was observed among the studies (Cochran Q test,  $p$  value  $< 0.001$  and I-squared = 97.5%). The highest and lowest prevalence rate was related to rhinovirus and echovirus, respectively. Also, the results of this study showed that the prevalence of viral infection in exacerbated COPD patients has fluctuation during the years with a slight increase and decrease. **CONCLUSIONS:** The results of this systematic review demonstrated that respiratory viral infections have an important role in the acute exacerbation of COPD (AECOPD). In addition, determining the exact geographic epidemiology of these viruses is very important to manage the treatment of these infections.

Jolly, K., M. S. Sidhu, et al. (2018). **"Self management of patients with mild COPD in primary care: randomised controlled trial."** *Bmj* **361**: k2241.

**OBJECTIVE:** To evaluate the effectiveness of telephone health coaching delivered by a nurse to support self management in a primary care population with mild symptoms of chronic obstructive pulmonary disease (COPD). **DESIGN:**

Multicentre randomised controlled trial. **SETTING:** 71 general practices in four areas of England. **PARTICIPANTS:** 577 patients with Medical Research Council dyspnoea scale scores of 1 or 2, recruited from primary care COPD registers with spirometry confirmed diagnosis. Patients were randomised to telephone health coaching (n=289) or usual care (n=288). **INTERVENTIONS:** Telephone health coaching intervention delivered by nurses, underpinned by Social Cognitive Theory. The coaching promoted accessing smoking cessation services, increasing physical activity, medication management, and action planning (4 sessions over 11 weeks; postal information at weeks 16 and 24). The nurses received two days of training. The usual care group received a leaflet about COPD. **MAIN OUTCOME MEASURES:** The primary outcome was health related quality of life at 12 months using the short version of the St George's Respiratory Questionnaire (SGRQ-C). **RESULTS:** The intervention was delivered with good fidelity: 86% of scheduled calls were delivered; 75% of patients received all four calls. 92% of patients were followed-up at six months and 89% at 12 months. There was no difference in SGRQ-C total score at 12 months (mean difference -1.3, 95% confidence interval -3.6 to 0.9, P=0.23). Compared with patients in the usual care group, at six months follow-up, the intervention group reported greater physical activity, more had received a care plan (44% v 30%), rescue packs of antibiotics (37% v 29%), and inhaler use technique check (68% v 55%). **CONCLUSIONS:** A new telephone health coaching intervention to promote behaviour change in primary care patients with mild symptoms of dyspnoea did lead to changes in self management activities, but did not improve health related quality of life. **TRIAL REGISTRATION:** Current controlled trials ISRCTN 06710391.

Kaireit, T. F., M. Gutberlet, et al. (2018). **"Comparison of quantitative regional ventilation-weighted fourier decomposition MRI with dynamic fluorinated gas washout MRI and lung function testing in COPD patients."** J Magn Reson Imaging **47**(6): 1534-1541.

**BACKGROUND:** Ventilation-weighted Fourier decomposition-MRI (FD-MRI) has matured as a reliable technique for quantitative measures of regional lung ventilation in recent years, but has yet not been validated in COPD patients. **PURPOSE/HYPOTHESIS:** To compare regional fractional lung ventilation obtained by ventilation-weighted FD-MRI with dynamic fluorinated gas washout MRI ((19) F-MRI) and lung function test parameters. **STUDY TYPE:** Prospective study. **POPULATION:** Twenty-seven patients with chronic obstructive pulmonary disease (COPD, median age 61 [54-67] years) were included. **FIELD STRENGTH/SEQUENCE:** For FD-MRI and for (19) F-MRI a spoiled gradient echo sequence was used at 1.5T. **ASSESSMENT:** FD-MRI coronal slices were acquired in free breathing. Dynamic (19) F-MRI was performed after inhalation of 25-30 L of a mixture of 79% fluorinated gas (C3 F8 ) and 21% oxygen via a closed face mask tubing using a dedicated coil tuned to 59.9 MHz. (19) F washout times in numbers of breaths ((19) F-nbreaths ) as well as fractional ventilation maps for both methods (FD-FV, (19) F-FV) were calculated. Slices were matched using a landmark driven algorithm, and only corresponding slices with an overlap of >90% were coregistered for evaluation. **STATISTICAL TESTS:**

The obtained parameters were correlated with each other using Spearman's correlation coefficient (r). RESULTS: FD-FV strongly correlated with (19) F-nbreaths on a global ( $r = -0.72$ ,  $P < 0.0001$ ) as well as on a lobar level and with lung function test parameters (FD-FV vs. FEV1,  $r = 0.76$ ,  $P < 0.0001$ ). There was a small systematic overestimation of FD-FV compared to (19) F-FV (mean difference  $-0.03$  (95% confidence interval [CI]:  $-0.097$ ;  $-0.045$ ). DATA CONCLUSION: Regional ventilation-weighted Fourier decomposition-MRI is a promising noninvasive, radiation-free tool for quantification of regional ventilation in COPD patients. LEVEL OF EVIDENCE: 2 Technical Efficacy: Stage 2 J. Magn. Reson. Imaging 2018;47:1534-1541.

Kang, Y., B. G. Steele, et al. (2018). "**Mortality in Advanced Chronic Obstructive Pulmonary Disease and Heart Failure Following Cardiopulmonary Rehabilitation.**" *Biol Res Nurs* **20**(4): 429-439.

Cardiopulmonary rehabilitation (CR) improves physical function and quality of life (QoL) in chronic obstructive pulmonary disease (COPD) and heart failure (HF), but it is unknown if CR improves outcomes in very severe disease. This study's purpose was to describe functional capacity (6-min walk distance [6MWD], steps/day), symptoms (dyspnea, depression), QoL (Short-Form Health Survey-Veterans [SF-36 V]) and cardiopulmonary function ( N-terminal pro-brain natriuretic peptide [NT-proBNP], forced expiratory volume in 1 s [FEV1]), and derive predictors of mortality among patients with severe COPD and HF who participated in CR. METHODS AND RESULTS: In this secondary analysis of a randomized controlled trial comparing two CR methods in severe COPD and HF, 90 (COPD = 63, HF = 27) male veterans, mean age  $66 \pm 9.24$  years, 79% Caucasian, and body mass index  $31 \text{ kg/m}^2$ , were followed for 12 months after CR. The COPD group had greater functional decline than the HF group (6MWD,  $p = .006$ ). Dyspnea was lower ( $p = .001$ ) and QoL higher ( $p = .006$ ) in the HF group. Mean NT-proBNP was higher in the HF group at all time points. FEV1 improved over 12 months in both groups ( $p = .01$ ). Mortality was 8.9%, 16.7%, and 37.8% at 12, 24, and 60 months, respectively. One-year predictors of mortality were baseline total steps ( $<3,000/\text{day}$ ), 6MWD ( $<229$  meters), and NT-proBNP level ( $>2,000 \text{ mg/pg}$ ). CONCLUSIONS: In very severe COPD and HF, risks of mortality over 12 months can predict patients unlikely to benefit from CR and should be considered at initial referral.

Karlsson, S. L., V. Backer, et al. (2018). "**Oral prednisolone for 4 days does not increase exercise tolerance in men with COPD.**" *Chron Respir Dis* **15**(2): 220-222.

One of the primary objectives in management of chronic obstructive pulmonary disease (COPD) is preventing decrease in lung function and reducing the annual number of acute exacerbations of COPD (AECOPD). An oral course of systemic

corticosteroids is a commonly used treatment in AECOPD. We hypothesize that this treatment also increases exercise performance and decreases muscle fatigue. In a randomized double-blinded, parallel, placebo-controlled trial, we investigated 14 men (8 on prednisolone 37.5 mg vs. 6 on placebo) with severe and very severe COPD. For 5 consecutive days, the patients performed a submaximal endurance test measuring time to exhaustion (TTE, primary endpoint), spirometry, maximal inspiratory and expiratory pressure and maximal isometric contraction of the quadriceps femoris muscle (maximum voluntary contraction (MVC)). At visits 2, 3 and 4, a fatigue protocol was carried out after 40 minutes of cycling at 40% of maximal effort. No differences between groups were found for TTE, lung function or maximal inspiratory or expiratory pressure, however, patients on prednisolone showed significant increased MVC: median 5.15 [3.35; 9.15] against placebo: -2 [-5.57; 3.95] (  $p = 0.03$ ). This finding indicates an impact of corticosteroids on muscle groups being exposed to submaximal endurance.

Kerwin, E. M., T. M. Siler, et al. (2018). **"Efficacy, safety, and pharmacokinetics of budesonide/formoterol fumarate delivered via metered dose inhaler using innovative co-suspension delivery technology in patients with moderate-to-severe COPD."** Int J Chron Obstruct Pulmon Dis **13**: 1483-1494.

Purpose: This study investigated the efficacy, safety, and pharmacokinetics of the inhaled corticosteroid/long-acting beta2-agonist fixed-dose combination budesonide/formoterol fumarate (BFF) metered dose inhaler (MDI), compared with the monocomponents budesonide (BD) MDI and formoterol fumarate (FF) MDI, in patients with moderate-to-severe COPD. Materials and methods: In this Phase IIb, randomized, double-blind, four-period, five-treatment, incomplete-block, crossover study (NCT02196077), all patients received BFF MDI 320/9.6 mug and FF MDI 9.6 mug, and two of either BFF MDI 160/9.6 mug, BFF MDI 80/9.6 mug, or BD MDI 320 mug twice daily for 28 days. The primary efficacy endpoint was forced expiratory volume in 1 second area under the curve from 0 to 12 hours on Day 29. Secondary efficacy endpoints included additional lung function assessments, and evaluation of dyspnea and rescue medication use. Safety was monitored throughout. The systemic exposure to budesonide and formoterol was assessed on Day 29. Results: Overall, 180 patients were randomized. For forced expiratory volume in 1 second area under the curve from 0 to 12 hours on Day 29, all BFF MDI doses showed significant improvements versus BD MDI 320 mug (least squares mean differences 186-221 mL; all  $p < 0.0001$ ), and BFF MDI 320/9.6 mug demonstrated a significant improvement versus FF MDI 9.6 mug (least squares mean difference 56 mL;  $p = 0.0013$ ). Furthermore, all BFF MDI doses showed significant improvements versus BD MDI 320 mug for all lung function, dyspnea, and rescue medication use secondary efficacy endpoints. All BFF MDI doses were well tolerated, and the safety profile was not substantially different from the monocomponents. There was no evidence of clinically meaningful pharmacokinetic interactions when budesonide and formoterol were formulated together in BFF MDI. Conclusion: The findings presented here confirm that BFF MDI 320/9.6 mug is an appropriate dose to take forward into Phase III studies in patients with COPD.

Kopsaftis, Z., R. Wood-Baker, et al. (2018). **"Influenza vaccine for chronic obstructive pulmonary disease (COPD)."** Cochrane Database Syst Rev 6: Cd002733.

**BACKGROUND:** Influenza vaccinations are currently recommended in the care of people with COPD, but these recommendations are based largely on evidence from observational studies, with very few randomised controlled trials (RCTs) reported. Influenza infection causes excess morbidity and mortality in people with COPD, but there is also the potential for influenza vaccination to cause adverse effects, or not to be cost effective. **OBJECTIVES:** To determine whether influenza vaccination in people with COPD reduces respiratory illness, reduces mortality, is associated with excess adverse events, and is cost effective. **SEARCH METHODS:** We searched the Cochrane Airways Trials Register, two clinical trials registries, and reference lists of articles. A number of drug companies we contacted also provided references. The latest search was carried out in December 2017. **SELECTION CRITERIA:** RCTs that compared live or inactivated virus vaccines with placebo, either alone or with another vaccine, in people with COPD. **DATA COLLECTION AND ANALYSIS:** Two review authors independently extracted data. All entries were double-checked. We contacted study authors and drug companies for missing information. We used standard methods expected by Cochrane. **MAIN RESULTS:** We included 11 RCTs with 6750 participants, but only six of these included people with COPD (2469 participants). The others were conducted on elderly and high-risk individuals, some of whom had chronic lung disease. Interventions compared with placebo were inactivated virus injections and live attenuated intranasal virus vaccines. Some studies compared intra-muscular inactivated vaccine and intranasal live attenuated vaccine with intra-muscular inactivated vaccine and intranasal placebo. Studies were conducted in the UK, USA and Thailand. Inactivated vaccine reduced the total number of exacerbations per vaccinated participant compared with those who received placebo (mean difference (MD) -0.37, 95% confidence interval (CI) -0.64 to -0.11;  $P = 0.006$ ; two RCTs, 180 participants; low quality evidence). This was due to the reduction in 'late' exacerbations, occurring after three or four weeks (MD -0.39, 95% CI -0.61 to -0.18;  $P = 0.0004$ ; two RCTs, 180 participants; low quality evidence). Both in people with COPD, and in older people (only a minority of whom had COPD), there were significantly more local adverse reactions in people who had received the vaccine, but the effects were generally mild and transient. There was no evidence of an effect of intranasal live attenuated virus when this was added to inactivated intramuscular vaccination. Two studies evaluating mortality for influenza vaccine versus placebo were too small to have detected any effect on mortality. However, a large study ( $N=2215$ ) noted that there was no difference in mortality when adding live attenuated virus to inactivated virus vaccination. **AUTHORS' CONCLUSIONS:** It appeared, from the limited number of RCTs we were able to include, all of which were more than a decade old, that inactivated vaccine reduced exacerbations in people with COPD. The size of effect was similar to that seen in large observational studies, and was due to a reduction in exacerbations occurring three or more weeks after vaccination, and due to influenza. There was a mild



increase in transient local adverse effects with vaccination, but no evidence of an increase in early exacerbations. Addition of live attenuated virus to the inactivated vaccine was not shown to confer additional benefit.

Kunadian, V., D. Chan, et al. (2018). **"Antiplatelet therapy in the primary prevention of cardiovascular disease in patients with chronic obstructive pulmonary disease: protocol of a randomised controlled proof-of-concept trial (APPLE COPD-ICON 2)."** *BMJ Open* 8(5): e020713.

INTRODUCTION: The antiplatelet therapy in the primary prevention of cardiovascular disease in patients with chronic obstructive pulmonary disease (APPLE COPD-ICON2) trial is a prospective 2x2 factorial, double-blinded proof-of-concept randomised controlled trial targeting patients with chronic obstructive pulmonary disease (COPD) at high risk of cardiovascular disease. The primary goal of this trial is to investigate if treatment with antiplatelet therapy will produce the required response in platelet function measured using the Multiplate test in patients with COPD. METHODS AND ANALYSIS: Patients with COPD are screened for eligibility using inclusion and exclusion criteria. Eligible patients are randomised and allocated into one of four groups to receive aspirin plus placebo, ticagrelor plus placebo, aspirin plus ticagrelor or placebo only. Markers of systemic inflammation, platelet reactivity, arterial stiffness, carotid intima-media thickness (CMT), lung function and quality of life questionnaires are assessed. The primary outcome consists of inhibition (binary response) of aspirin and ADP-induced platelet function at 6 months. Secondary outcomes include changes in inflammatory markers, CMT, non-invasive measures of vascular stiffness, quality of life using questionnaires (EuroQol-five dimensions-five levels of perceived problems (EQ5D-5L), St. George's COPD questionnaire) and to record occurrence of repeat hospitalisation, angina, myocardial infarction or death from baseline to 6 months. Safety outcomes will be rates of major and minor bleeding, forced expiratory volume in 1 s, forced vital capacity and Medical Research Council dyspnoea scale. ETHICS AND DISSEMINATION: The study was approved by the North East-Tyne and Wear South Research Ethics Committee (15/NE/0155). Findings of the study will be presented in scientific sessions and published in peer-reviewed journals. TRIAL REGISTRATION NUMBER: ISRCTN43245574; Pre-results.

Kunisaki, K. M., M. T. Dransfield, et al. (2018). **"Exacerbations of Chronic Obstructive Pulmonary Disease and Cardiac Events. A Post Hoc Cohort Analysis from the SUMMIT Randomized Clinical Trial."** *Am J Respir Crit Care Med* 198(1): 51-57.

RATIONALE: Acute exacerbations of chronic obstructive pulmonary disease (AECOPD) are common, associated with acute inflammation, and may increase subsequent cardiovascular disease (CVD) risk. OBJECTIVES: Determine whether AECOPD

events are associated with increased risk of subsequent CVD. **METHODS:** We performed a secondary cohort analysis of the SUMMIT (Study to Understand Mortality and Morbidity) trial, a convenience sample of current/former smokers with moderate COPD from 1,368 centers in 43 countries. All had CVD or increased CVD risk. AECOPD was defined as an increase in respiratory symptoms requiring treatment with antibiotics, systemic corticosteroids, and/or hospitalization. CVD events were a composite outcome of cardiovascular death, myocardial infarction, stroke, unstable angina, and transient ischemic attack. All CVD events were adjudicated. Cox proportional hazards models compared the hazard for a CVD event before AECOPD versus after AECOPD.

**MEASUREMENTS AND MAIN RESULTS:** Among 16,485 participants in SUMMIT, 4,704 participants had at least one AECOPD and 688 had at least one CVD event. The hazard ratio (HR) for CVD events after AECOPD was increased, particularly in the first 30 days after AECOPD (HR, 3.8; 95% confidence interval, 2.7-5.5) and was elevated up to 1 year after AECOPD. The 30-day HR after hospitalized AECOPD was more than twofold greater (HR, 9.9; 95% confidence interval, 6.6-14.9). **CONCLUSIONS:** In patients with COPD with CVD or risk factors for CVD, exacerbations confer an increased risk of subsequent CVD events, especially in hospitalized patients and within the first 30 days after exacerbation. Patients and clinicians should have heightened vigilance for early CVD events after AECOPD. Clinical trial registered with [www.clinicaltrials.gov](http://www.clinicaltrials.gov) (NCT 01313676).

Lacasse, Y., A. M. Tan, et al. (2018). **"Home Oxygen in Chronic Obstructive Pulmonary Disease."** *Am J Respir Crit Care Med* **197**(10): 1254-1264.

Two landmark trials conducted more than 35 years ago provided scientific evidence that, under very specific circumstances, long-term oxygen therapy (LTOT) may prolong life. These two trials enrolled 290 patients with chronic obstructive pulmonary disease and severe daytime hypoxemia documented by direct arterial blood gas measurement. From that time, LTOT became a standard of care, and the indications for oxygen therapy expanded to include nocturnal oxygen therapy for isolated nocturnal oxygen desaturation, ambulatory oxygen to correct exercise-induced desaturation, and short-burst oxygen to relieve dyspnea. In most cases, the rationale for broadening the indications for oxygen therapy is that, if hypoxemia exists, correcting it by increasing the FiO<sub>2</sub> should help. However, with the exception of LTOT in severely hypoxemic patients with chronic obstructive pulmonary disease, randomized controlled trials of oxygen therapy have failed to demonstrate clinically significant benefits. Also, adherence to LTOT is usually suboptimal. Important areas for future research include improving understanding of the mechanisms of action of supplemental oxygen, the clinical and biochemical predictors of responsiveness to LTOT, the methods for measuring and enhancing adherence to LTOT, and the cost-effectiveness of oxygen therapy. A standardization of terminology to describe the use of supplemental oxygen at home is provided.

LaForce, C., E. Derom, et al. (2018). **"Long-term safety of tiotropium/olodaterol Respimat((R)) in patients with moderate-to-very severe COPD and renal impairment in the TONADO((R)) studies."** Int J Chron Obstruct Pulmon Dis **13**: 1819-1831.

**Introduction:** The safety, lung function efficacy, and symptomatic benefits of combined tiotropium and olodaterol in patients with COPD were established in the 1-year TONADO((R)) studies (NCT01431274; NCT01431287). As tiotropium is predominantly excreted by the kidneys, the long-term safety profile of tiotropium/olodaterol was investigated in patients with renal impairment in a prespecified safety analysis of the TONADO studies. **Methods:** These were 2 replicate, randomized, double-blind, parallel-group, 52-week Phase III studies that assessed tiotropium/olodaterol compared with tiotropium or olodaterol alone (all via Respimat((R))) in patients with moderate-to-very severe COPD. In this analysis, renal impairment was defined as mild (creatinine clearance [CLcr] 60-89 mL/min), moderate (CLcr 30-59 mL/min) or severe (CLcr 15-29 mL/min). Adverse events (AEs) were pooled from both studies. **Results:** Of 3,041 patients included in this analysis, 1,333 (43.8%) had mild, 404 (13.3%) had moderate, and 5 (0.2%) had severe renal impairment; these were distributed equally between treatment groups. Almost one-quarter of all treated patients (23.4%) had a history of cardiac disorder, 45.6% had hypertension, and 13.3% had glucose metabolism disorders, including diabetes. AEs with olodaterol, tiotropium, and tiotropium/olodaterol occurred in 75.1%, 70.8%, and 72.0% of patients with no renal impairment, 75.7%, 74.0%, and 73.3% with mild renal impairment, and 84.3%, 79.5%, and 79.7% with moderate renal impairment, respectively. There was no notable effect of renal impairment on the proportion of patients with an AE, and no differences were observed between tiotropium/olodaterol versus the monocomponents. There was no difference in the incidence of major adverse cardiac events, renal and urinary tract AEs, or potential anticholinergic effects with increasing severity of renal impairment. **Conclusion:** Over half the patients enrolled in the TONADO studies had renal impairment, and there was a high level of pre-existing cardiovascular comorbidity. The safety and tolerability of tiotropium/olodaterol is comparable to the monocomponents, irrespective of the level of renal impairment.

Lee, L., E. Kerwin, et al. (2017). **"The effect of umecclidinium on lung function and symptoms in patients with fixed airflow obstruction and reversibility to salbutamol: A randomised, 3-phase study."** Respir Med **131**: 148-157.

**INTRODUCTION:** The long-acting muscarinic antagonist, umecclidinium (UMEC), combined with the inhaled corticosteroid, fluticasone furoate (FF), improves lung function in symptomatic patients with asthma. We assessed FF/UMEC in patients with a primary diagnosis of asthma or chronic obstructive pulmonary disease (COPD), but physiological characteristics of both (fixed airflow obstruction and reversibility to salbutamol). **METHODS:** This double-blind, parallel-arm, 3-phase study randomised 338 patients (1:1:1:1:2:2) to FF 100 mcg alone or combined

with UMEC (15.6, 62.5, 125, or 250 mcg) or vilanterol 25 mcg (Phase A, 4 weeks). Primary endpoint: change from baseline in clinic trough forced expiratory volume in 1 s (FEV1) (end of Phase A). Secondary endpoints: morning peak expiratory flow (PEF), rescue medication use and Evaluating Respiratory Symptoms in COPD (E-RS: COPD) scores. Safety was assessed. RESULTS: In the intent-to-treat population, the increase in trough FEV1 over FF was significant for FF/UMEC 62.5 (0.140 L [p = 0.019]) and 125 mcg (0.120 L [p = 0.039]), with similar changes for patients with a primary diagnosis of asthma or COPD. Changes from baseline in morning PEF and E-RS total score were greater for all FF/UMEC doses vs FF (p ≤ 0.05). Change from baseline in rescue medication use was statistically or clinically significant for all FF/UMEC doses vs FF. The incidence of on-treatment adverse events was 15%-32% (Phase A), with no dose-related effects. CONCLUSIONS: FF/UMEC 62.5 mcg produced clinically meaningful improvements in FEV1, morning PEF, E-RS total score and rescue medication use. FF/UMEC may benefit patients with features of both asthma and COPD. CLINICALTRIALS.GOV: NCT02164539; GSK: 200699.

Li, C. X., C. E. Wheelock, et al. (2018). **"Integration of multi-omics datasets enables molecular classification of COPD."** *Eur Respir J* **51**(5) Chronic obstructive pulmonary disease (COPD) is an umbrella diagnosis caused by a multitude of underlying mechanisms, and molecular sub-phenotyping is needed to develop molecular diagnostic/prognostic tools and efficacious treatments. The objective of these studies was to investigate whether multi-omics integration improves the accuracy of molecular classification of COPD in small cohorts. Nine omics data blocks (comprising mRNA, micro RNA, proteomes and metabolomes) collected from several anatomical locations from 52 female subjects were integrated by similarity network fusion (SNF). Multi-omics integration significantly improved the accuracy of group classification of COPD patients from healthy never-smokers and from smokers with normal spirometry, reducing required group sizes from n=30 to n=6 at 95% power. Seven different combinations of four to seven omics platforms achieved >95% accuracy. For the first time, a quantitative relationship between multi-omics data integration and accuracy of data-driven classification power has been demonstrated across nine omics data blocks. Integrating five to seven omics data blocks enabled 100% correct classification of COPD diagnosis with groups as small as n=6 individuals, despite strong confounding effects of current smoking. These results can serve as guidelines for the design of future systems-based multi-omics investigations, with indications that integrating five to six data blocks from several molecular levels and anatomical locations suffices to facilitate unsupervised molecular classification in small cohorts.

Liang, M., Z. Jiang, et al. (2016). **"Clinical Association of Chemokine (C-X-C motif) Ligand 1 (CXCL1) with Interstitial Pneumonia with Autoimmune Features (IPAF)."** *Sci Rep* 6: 38949.

The term "interstitial pneumonia with autoimmune features" (IPAF) has been recently proposed. We here investigate the clinical characteristics of IPAF and evaluate the clinical implications of CXCL1-CXCR2 axis in IPAF. An increased plasma level of CXCL1 was exhibited in IPAF compared to idiopathic interstitial pneumonia (IIP), chronic obstructive pulmonary disease (COPD), and healthy controls. Additionally, plasma CXCL1 levels were clinically associated with diffusing capacity of the lungs for carbon monoxide (DLCO), erythrocyte sedimentation rate (ESR), and involved parenchyma extension in IPAF. Furthermore, circulating CXCL1 levels were highest in IPAF patients with acute exacerbations. CXCR2, the chemokine receptor for CXCL1, was readily observed in inflammatory aggregates and endothelial cells in IPAF lungs, but was lower in IIP lungs and healthy lungs. Interestingly, increased CXCL1 concentrations in BALF paralleled neutrophil counts in IPAF. Overall, the plasma concentrations of CXCL1 indicated the disease activity and prognosis in IPAF. Thus, the CXCL1/CXCR2 axis appears to be involved in the progression of IPAF.

Louvaris, Z., S. Spetsioti, et al. (2016). **"Interval training induces clinically meaningful effects in daily activity levels in COPD."** *Eur Respir J* 48(2): 567-70.

Lu, M. C., M. D. Yang, et al. (2018). **"Effect of Oligomeric Proanthocyanidin on the Antioxidant Status and Lung Function of Patients with Chronic Obstructive Pulmonary Disease."** *In Vivo* 32(4): 753-758.

BACKGROUND/AIM: Evidence exists that oxidative stress and oxidative damage play a pivotal role in chronic obstructive pulmonary disease (COPD). Oligomeric proanthocyanidins (OPCs) extracted from grape seeds have been shown to exhibit antioxidant capabilities greater than those of vitamin C and E. The objective of this study was to evaluate the effects of OPCs on antioxidant status and lung function in patients with COPD. PATIENTS AND METHODS: Patients were supplemented with 150 mg/day OPC (n=13) orally or with a placebo (n=14) for 8 weeks in a randomized double-blind clinical design. Changes in anthropometric values, lung function, oxidative state, and lipid profiles were assessed after OPC or placebo treatment for 8 weeks. RESULTS: The results showed that OPC supplementation significantly reduced the concentration of malondialdehyde, superoxide dismutase, and total cholesterol (TC)/high-density lipoprotein cholesterol (HDL-C) ratio. The concentration of HDL-C significantly increased in the OPC-treated group. The plasma triglyceride, TC and low-density lipoprotein cholesterol values and the activities of catalase and glutathione peroxidase also decreased, but did not significantly differ between the OPC- and

placebo-treated groups. Lung function was not significantly different between the two groups after 8 weeks. **CONCLUSION:** OPC supplementation was effective in increasing the antioxidant capacity, in addition to improving the lipid profiles in patients with COPD.

Luckett, T., J. Phillips, et al. (2017). **"Contributions of a hand-held fan to self-management of chronic breathlessness."** Eur Respir J **50**(2) This study explored the benefits of a hand-held fan as perceived by patients with chronic breathlessness and their carers. A secondary multimethod analysis was conducted of interview data collected in three clinical trials. Two researchers independently coded level of benefit qualitatively reported by each patient. Univariate and multivariate statistics were used to explore perceived benefit as a factor of sex, age and diagnosis. Qualitative analysis used an integrative method. 133 patients commented on the fan, of whom 72 had a carer. Diagnoses included nonmalignant (n=91, 68.4%) and malignant (n=21, 15.8%) conditions. Of 111 patients who provided codable data, four (3.6%) perceived no benefit, 16 (14.4%) were uncertain, 80 (72.0%) perceived some benefit and 11 (10.0%) perceived very substantial benefit. Multivariate analysis was inconclusive. Benefit was described in terms of shorter recovery time, especially after activity. 10 (7.5%) patients said the fan reduced their need for home oxygen or inhaled beta-agonist medications. Negative perceptions of a few included dislike of the cooling sensation and embarrassment in public. Findings suggest that a hand-held fan is a portable intervention with few disadvantages from which most patients with chronic breathlessness will derive benefit alongside other nonpharmacological and pharmacological strategies. Research is needed to optimise guidance on fan administration.

Lyon, C., R. Radi, et al. (2018). **"Clinical Inquiries: Does prophylactic azithromycin reduce the number of COPD exacerbations or hospitalizations?"** J Fam Pract **67**(6): 384-385.

Yes for exacerbations, no for hospitalizations. Prophylactic azithromycin reduces the number of exacerbations by about 25%. It also extends the time between exacerbations by approximately 90 days for patients with moderate-to-severe chronic obstructive pulmonary disease (COPD). Azithromycin benefits patients who are >65 years, patients with Global Initiative for Obstructive Lung Disease (GOLD) stage II or III COPD, former smokers, and patients using long-term oxygen; it doesn't benefit patients ≤65 years, patients with GOLD stage IV COPD, current smokers, or patients not using oxygen (strength of recommendation [SOR]: B, randomized controlled trials [RCTs]). Prophylactic azithromycin doesn't reduce hospitalizations overall (SOR: B, single small RCT).

Magnet, F. S., D. S. Majorski, et al. (2017). **"Capillary PO<sub>2</sub> does not adequately reflect arterial PO<sub>2</sub> in hypoxemic COPD patients."** Int J Chron Obstruct Pulmon Dis **12**: 2647-2653.

**PURPOSE:** To compare arterial (PaO<sub>2</sub>) with capillary (PcO<sub>2</sub>) partial pressure of oxygen in hypoxemic COPD patients because capillary blood gas analysis (CBG) is increasingly being used as an alternative to arterial blood gas analysis (ABG) in a non-intensive care unit setting, although the agreement between PcO<sub>2</sub> and PaO<sub>2</sub> has not been evaluated in hypoxemic COPD patients. **PATIENTS AND METHODS:** Bland-Altman comparison of PaO<sub>2</sub> and PcO<sub>2</sub> served as the primary outcome parameter if PcO<sub>2</sub> values were  $\leq 60$  mmHg and the secondary outcome parameter if PcO<sub>2</sub> values were  $\leq 55$  mmHg. Pain associated with the measurements was assessed using a 100-mm visual analog scale. **RESULTS:** One hundred and two PaO<sub>2</sub>/PcO<sub>2</sub> measurement pairs were obtained. For PcO<sub>2</sub> values  $\leq 60$  mmHg, the mean difference between PaO<sub>2</sub> and PcO<sub>2</sub> was  $5.99 \pm 6.05$  mmHg (limits of agreement: -5.88 to 17.85 mmHg). For PcO<sub>2</sub> values  $\leq 55$  mmHg (n=73), the mean difference was  $5.33 \pm 5.52$  mmHg (limits of agreement: -5.48 to 16.15 mmHg). If PaO<sub>2</sub>  $\leq 55$  ( $\leq 60$ ) mmHg was set as the cut-off value, in 20.6% (30.4%) of all patients, long-term oxygen therapy have been unnecessarily prescribed if only PcO<sub>2</sub> would have been assessed. ABG was rated as more painful compared with CBG. **CONCLUSIONS:** PcO<sub>2</sub> does not adequately reflect PaO<sub>2</sub> in hypoxemic COPD patients, which can lead to a relevant number of unnecessary long-term oxygen therapy prescriptions.

Mahboub, B. H., M. G. Vats, et al. (2017). **"Joint statement for the diagnosis, management, and prevention of chronic obstructive pulmonary disease for Gulf Cooperation Council countries and Middle East-North Africa region, 2017."** Int J Chron Obstruct Pulmon Dis **12**: 2869-2890.

Smoking and subsequent development of COPD is an ever-increasing epidemic in Arabian Gulf and Middle East countries, with no signs of decline. The important fact to be highlighted is that this COPD epidemic of increasing incidence and prevalence is mostly unrecognized by patients, due to the common attribution of symptoms to "smoker's cough", and the underdiagnosis and undertreatment by physicians because the common signs and symptoms masquerade as asthma. Consequently, there are long-term adverse effects of missing the diagnosis. The purpose of this review article is to focus upon the status of COPD in Arabian Gulf and Middle East countries, stressing the increasing burden of smoking and COPD, to emphasize the specific factors leading to rise in prevalence of COPD, to bring to light the underdiagnosis and undermanagement of COPD, and to treat COPD in conformity with standard guidelines with local and regional modifications. This review ends with suggestions and recommendations to the health department to formulate policies and to generate awareness among the general public about the side effects of smoking and consequences of COPD.

Malerba, M., A. Radaeli, et al. (2018). **"The discovery and development of acclidinium bromide for the treatment of chronic obstructive pulmonary disease."** Expert Opin Drug Discov **13**(6): 563-577.

INTRODUCTION: Bronchodilators, including long-acting muscarinic receptor antagonists (LAMAs), are a mainstay of the pharmacological treatment of chronic obstructive pulmonary disease (COPD). LAMAs act as bronchodilators principally by antagonizing airway smooth muscle cells M3 muscarinic receptors. Acclidinium bromide is a twice-daily LAMA which was developed to improve on the efficacy and/or safety of previous LAMAs. Area covered: Herein, the authors present the pharmacotherapeutic role of acclidinium in COPD and point out unmet need in this research area. The following aspects are covered: a) the discovery and medicinal chemistry of acclidinium bromide; b) an overview of the market; c) its mechanism of action; d) its pharmacokinetic/pharmacodynamic profile derived from pre-clinical studies; e) the clinical studies which led to its licensing; f) the evidence from meta-analyses; g) the acclidinium/formoterol fixed dose combination for COPD and h) priorities in this area of research. Expert opinion: Acclidinium bromide has the pharmacological properties, safety and efficacy profile and inhaler characteristics which makes it a valuable therapeutic option for pharmacological management of patients with COPD. Due to its rapid biotransformation into inactive metabolites, acclidinium is potentially one of the safest LAMAs. Further head-to-head randomized clinical trials are required to define efficacy and safety of acclidinium when compared to once-daily LAMAs. The clinical relevance of airway anti-remodeling effects of acclidinium has to be defined.

Mannino, D. M., E. M. Clerisme-Beaty, et al. (2018). **"Exacerbation recovery patterns in newly diagnosed or maintenance treatment-naïve patients with COPD: secondary analyses of TICARI 1 trial data."** Int J Chron Obstruct Pulmon Dis **13**: 1515-1525.

Background: Little is known about the recovery patterns from acute exacerbations of chronic obstructive pulmonary disease (AECOPD) in newly diagnosed or maintenance treatment-naïve patients with COPD. This study describes the course of AECOPD in these patients at the time of treatment for the symptoms of acute respiratory tract infection (RTI). Methods: This study was a secondary analysis of data from a 12-week, randomized clinical trial (TICARI 1) testing the efficacy and safety of once-daily tiotropium 18 microg maintenance therapy versus placebo in newly diagnosed or maintenance treatment-naïve COPD patients with acute RTI symptoms for  $\leq 7$  days. Patients received standard care for AECOPD and RTI. Due to under-recruitment, the trial ended early and hence was underpowered to detect treatment differences. Data were pooled and exacerbation recovery patterns examined by using the EXacerbation of Chronic Pulmonary Disease Tool (EXACT), forced expiratory volume in 1 second, rescue



medication use, COPD Assessment Test, Functional Assessment of Chronic Illness Therapy-Short Form, and Work Productivity and Activity Impairment Questionnaire: Respiratory Symptoms. Results: Of 140 patients, 73.6% had a prior COPD diagnosis without maintenance therapy; 80.0% had moderate-to-severe airflow obstruction. In addition to study drug, 40.0% were prescribed pharmacologic therapy (corticosteroids [34.3%], antibiotics [16.4%], and short-acting beta2-adrenergic agonists [5.0%]) within +/-7 days of randomization. Over 12 weeks, 78.6% exhibited symptomatic recovery (EXACT score) in a median of 5.0 days. Across all patients, 49.3% recovered without relapse, 29.3% recovered and then relapsed, and 21.4% had persistent symptoms (recovery criteria unmet). Conclusion: A substantial portion of newly diagnosed or maintenance treatment-naïve patients with COPD experience relapse or persistent symptoms following a clinic visit for AECOPD with symptoms of RTI. Whether initiating maintenance therapy could improve outcomes and reduce exacerbation risk requires further study.

Marengoni, A., D. L. Vetrano, et al. (2018). **"The Relationship Between COPD and Frailty: A Systematic Review and Meta-Analysis of Observational Studies."** *Chest* **154**(1): 21-40.

**BACKGROUND:** Frailty is common in seniors and is characterized by diminished physiological reserves and increased vulnerability to stressors. Frailty can change the prognosis and treatment approach of several chronic diseases, including COPD. The association between frailty and COPD has never been systematically reviewed. **OBJECTIVES:** The goal of this study was to conduct a systematic review and meta-analysis assessing the association of COPD with frailty and pre-frailty. **METHODS:** Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were used when reporting this review. We searched PubMed, Web of Science, and Embase from January 1, 2002, to October 6, 2017. The quality of the studies was evaluated by using the Newcastle Ottawa Scale. Two assessors independently rated each study: scores > 7 were considered a low risk of bias; 5 to 7, a moderate risk of bias; and < 5, a high risk of bias. Pooled estimates were obtained through random effect models and Mantel-Haenszel weighting. Homogeneity ( $I^2$ ) and publication bias were assessed. **RESULTS:** A total of 27 studies were selected: 23 cross-sectional, three longitudinal, and one both. The pooled prevalence of pre-frailty in individuals with COPD was 56% (95% CI, 52-60;  $I^2$  = 80.8%); it was 19% (95% CI, 14-24;  $I^2$  = 94.4%) for frailty. Patients with COPD had a two-fold increased odds of frailty (pooled OR, 1.97 [95% CI, 1.53-2.53];  $I^2$  = 0.0%). Three longitudinal studies, presenting heterogeneous aims and methods, suggested a bidirectional association between COPD and frailty. **CONCLUSIONS:** Frailty and pre-frailty are common in individuals with COPD. Older subjects with COPD have a two-fold increased odds of frailty. These results may have clinical implications, as they identify the need to assess frailty in individuals with COPD and to further investigate any potential negative effects associated with the co-occurrence of these conditions. Longitudinal research that examines temporal associations between COPD and frailty are needed to further clarify this relationship and to

assess if treatment of COPD may prevent the onset of frailty. TRIAL REGISTRY: PROSPERO registration No.: 58302; URL: <https://www.crd.york.ac.uk/prospero/>.

Matera, M. G., L. Calzetta, et al. (2018). **"A safety comparison of LABA+LAMA vs LABA+ICS combination therapy for COPD."** Expert Opin Drug Saf **17**(5): 509-517.

INTRODUCTION: LABA+LAMA and LABA+ICS combinations are key pharmacological approaches to the treatment of COPD. However, both combination types can induce adverse events (AEs). Areas covered: Current literature on LABA+LAMA and LABA+ICS combinations has been reviewed with a specific focus on their safety profile in the treatment of COPD. Expert opinion: Several meta-analyses have compared the pooled safety data from randomized clinical trials (RCTs) of LABA+LAMA combinations with LABA+ICS combinations. LABA+LAMA caused significantly less AEs and SAEs. However, this evidence in real life is less solid because of the lack of appropriate studies. A statistically significant reduction in the risk for pneumonia with LABA+LAMA compared with LABA+ICS has been repeatedly documented by various meta-analyses. The meta-analytic signal indicates that an equal number of patients would die or have cardiac SAEs on LABA+LAMA or LABA+ICS, and in an observational, real-life study the LABA+LAMA combination had similar or lower risk of these events in comparison to LABA+ICS. Nonetheless, since RCTs are conducted under widely varying conditions and, consequently, AE rates of a drug observed in a RCT cannot be directly compared with rates in the RCTs of another drug and may not reflect the rates observed in practice, we need more specific data.

Matheson, M. C., G. Bowatte, et al. (2018). **"Prediction models for the development of COPD: a systematic review."** Int J Chron Obstruct Pulmon Dis **13**: 1927-1935.

Early identification of people at risk of developing COPD is crucial for implementing preventive strategies. We aimed to systematically review and assess the performance of all published models that predicted development of COPD. A search was conducted to identify studies that developed a prediction model for COPD development. The Checklist for Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modelling Studies was followed when extracting data and appraising the selected studies. Of the 4,481 records identified, 30 articles were selected for full-text review, and only four of these were eligible to be included in the review. The only consistent predictor across all four models was a measure of smoking. Sex and age were used in most models; however, other factors varied widely. Two of the models had good ability to discriminate between people who were correctly or incorrectly classified as at risk of developing COPD. Overall none of the models were particularly useful in accurately predicting future risk of COPD, nor were they good at ruling out future

risk of COPD. Further studies are needed to develop new prediction models and robustly validate them in external cohorts.

Mathews, G. and B. Johnston (2017). **"Palliative and end-of-life care for adults with advanced chronic obstructive pulmonary disease: a rapid review focusing on patient and family caregiver perspectives."** Curr Opin Support Palliat Care 11(4): 315-327.

**PURPOSE OF REVIEW:** The aim of the review was to explore patient and family caregiver perspectives on key issues for ensuring quality of end-of-life care for people with chronic obstructive pulmonary disease (COPD). The growing evidence on the value of specialist palliative care services demonstrates significant improvements in treatments and provisions; however, much of the literature is generic in nature or centred on people with a cancer diagnosis. In this review, we examine the literature to ascertain the views and needs of patients and carers affected by advanced COPD, a highly debilitating condition that can have a profoundly negative impact on the quality of end-of-life experience.

**RECENT FINDINGS:** A total of 19 papers were included in the review. The main themes in the literature were Holistic Care, Illness Trajectory and Technology.

**SUMMARY:** Areas of unmet need emphasized across physical, psychosocial and spiritual domains were identified, particularly in relation to appropriate and timely conversations. Positive developments in the care and treatment of advanced COPD include the use of the STIOLTO Respimat inhaler, a brief educative and psychosocial intervention based on cognitive-behavioural therapy, and high-intensity exercise training. There is some evidence regarding the use of technology in end-stage COPD.

McKeough, Z., R. Leung, et al. (2018). **"Shuttle walk tests in people with COPD who demonstrate exercise-induced oxygen desaturation: An analysis of test repeatability and cardiorespiratory responses."** Chron Respir Dis 15(2): 131-137.

Exercise-induced oxygen desaturation (EID) is prevalent in people with chronic obstructive pulmonary disease (COPD). This article reports a sub-analysis from a randomized controlled trial (RCT) in people with COPD and EID (COPD/EID). The primary aim, in people with COPD/ EID, was to determine the repeatability of the distance and time walked in the incremental shuttle walk test (ISWT) and endurance shuttle walk test (ESWT), respectively. A secondary aim was to determine whether any participant characteristics predicted those who did not demonstrate improvements on a repeat ISWT or ESWT. Participants with nadir oxygen saturation (SpO<sub>2</sub>) < 90% on the 6-minute walk test were recruited to the RCT. Two ISWTs and two ESWTs were then performed as part of the baseline assessments, and participants were included in this sub-analysis if their nadir SpO<sub>2</sub> was <90% during the better of two ISWTs. Repeatability of the tests was

analysed using Bland-Altman plots and paired t-tests. Participant characteristics of age, lung function, level of nadir SpO<sub>2</sub> and end-test dyspnoea were used to predict those who were not likely to demonstrate improvements on a repeat test using receiver operating curves. Eighty-seven participants (mean age (standard deviation, SD) 70 (7) years; forced expiratory volume in one second (FEV<sub>1</sub>) 47 (17)% predicted) were included. The mean differences (coefficient of repeatability) for the ISWTs and ESWTs were 9 m (55 m) and 19 seconds (142 seconds) respectively (  $p < 0.05$ ). No participant characteristic predicted the absence of improvement on the second ISWT (area under the curve (AUC) ranged from 0.49 to 0.58, all  $p > 0.2$ ) or the second ESWT (AUC ranged from 0.43 to 0.52, all  $p > 0.3$ ). Although repeating the tests showed only small improvements in distance (ISWT) and time (ESWT) walked in people with COPD/EID, the variability was large making definite conclusions about test repeatability in these individuals difficult.

Mehta, A. B., I. S. Douglas, et al. (2017). **"Evidence-based Utilization of Noninvasive Ventilation and Patient Outcomes."** *Ann Am Thorac Soc* **14**(11): 1667-1673.

**RATIONALE:** Strong evidence supports use of noninvasive ventilation (NIV) for patients with respiratory distress from chronic obstructive pulmonary disease and heart failure (strong evidence conditions [SECs]). Despite unclear benefits of NIV for other causes of acute respiratory failure, utilization for conditions with weaker evidence is increasing, despite evidence demonstrating higher mortality for patients who suffer NIV failure (progression from NIV to invasive mechanical ventilation [IMV])) compared with being treated initially with IMV. **OBJECTIVES:** To determine the association of hospital variation in evidence-based utilization of NIV with patient outcomes. **METHODS:** Using the California State Inpatient Database 2011, we identified adult patients who received NIV. Patients were considered to have an SEC for NIV if they had an acute exacerbation of chronic obstructive pulmonary disease or heart failure. We used multivariable hierarchical logistic regression to determine the association between hospital rates of NIV use for SECs and patient risk of NIV failure (need for IMV after NIV). **RESULTS:** Among 22,706 hospitalizations with NIV as the initial ventilatory strategy, 6,820 (30.0%) had SECs. Patients with SECs had lower risk of NIV failure than patients with weak evidence conditions (8.1 vs. 18.2%,  $P < 0.0001$ ). Regardless of underlying diagnosis, patients admitted to hospitals with greater use of NIV for SECs had lower risk of NIV failure (Quartile 4 vs. Quartile 1 adjusted odds ratio = 0.62; 95% CI = 0.49-0.80). Even patients without an SEC benefited from admission to hospitals that used NIV more often for patients with SECs (Quartile 4 vs. Quartile 1 adjusted odds ratio for NIV failure = 0.68; 95% CI = 0.52-0.88). **CONCLUSIONS:** Most patients who received NIV did not have conditions with strong supporting evidence for its use with wide institutional variation in patient selection for NIV. Surprisingly, we found that all patients, even those without an SEC, benefited from admission to hospitals with greater evidence-based utilization of NIV, suggesting a "hospital effect" that is synergistic with patient selection.

Melro, H., J. Gomes, et al. (2018). **"Genetic profile and patient-reported outcomes in chronic obstructive pulmonary disease: A systematic review."** PLoS One **13**(6): e0198920.

**BACKGROUND:** Chronic Obstructive Pulmonary Disease (COPD) impacts differently on patients at similar grades, suggesting that factors other than lung function may influence patients' experience of the disease. Recent studies have found associations between genetic variations and patient-reported outcomes (PROs). Identifying these associations might be fundamental to predict the disease progression and develop tailored interventions. This systematic review aimed to identify the genetic variations associated with PROs in COPD. **METHODS AND FINDINGS:** Databases were searched until July 2017 (PROSPERO: CRD42016041639) and additional searches were conducted scanning the reference list of the articles. Two independent reviewers assessed the quality of studies using the Q-Genie checklist. This instrument is composed of 11 questions, each subdivided in 7 options from 1 poor-7 excellent. Thirteen studies reporting 5 PROs in association with genes were reviewed. Studies were rated between "good quality" (n = 8) and "moderate" (n = 5). The most reported PRO was frequency of exacerbations (n = 7/13), which was mainly associated with MBL2 gene variants. Other PRO's were health-related quality of life (HRQOL) (n = 4/13), depressive symptoms (n = 1/13), exacerbation severity (n = 1/13) and breathlessness, cough and sputum (n = 1/13), which were commonly associated with other genetic variants. **CONCLUSIONS:** Although a limited number of PRO's have been related to genetic variations, findings suggest that there is a significant association between specific gene variants and the number/severity of exacerbations, depressive symptoms and HRQOL. Further research is needed to confirm these findings and assess the genetic influence on other dimensions of patients' lives, since it may enhance our understanding and management of COPD.

Miller, M. R., S. Haroon, et al. (2018). **"Clinical characteristics of patients newly diagnosed with COPD by the fixed ratio and lower limit of normal criteria: a cross-sectional analysis of the TargetCOPD trial."** Int J Chron Obstruct Pulmon Dis **13**: 1979-1986.

**Background:** Consensus on the definition of airflow obstruction to diagnose COPD remains unresolved. **Methods:** We undertook systematic case finding for COPD in primary care using the fixed ratio (FR) criterion (forced expiratory volume in 1 s/forced vital capacity [FEV1/FVC] <0.7) for defining airflow obstruction and also using the lower limit of normal (LLN). We then compared the clinical characteristics of those identified by the 2 criteria. **Results:** A total of 3,721 individuals reporting respiratory symptoms were invited for spirometry. A total of 2,607 attended (mean age 60.4 years, 52.8% male, 29.8% current smokers) and 32.6% had airflow obstruction by FR ("FR+") and 20.2% by LLN ("LLN+"). Compared with the LLN+/FR+ group, the LLN-/FR+ group (12.4%) was

significantly older, had higher FEV1 and FEV1/FVC, lower COPD assessment test scores, and less cough, sputum, and wheeze, but was significantly more likely to report a diagnosis of heart disease (14.2% versus 6.9%,  $p < 0.001$ ). Compared with the LLN+/FR+ group, the LLN-/FR- group was younger, had a higher body mass index, fewer pack-years, a lower prevalence of respiratory symptoms except for dyspnea, and lower FVC and higher FEV1. The probability of known heart disease was significantly lower in the LLN+/FR+ group compared with those with preserved lung function (LLN-/FR-) (adjusted odds ratio 0.62, 95% CI: 0.43-0.90) but this was not seen in the LLN-/FR+ group (adjusted odds ratio 0.90, 95% CI: 0.63-1.29). Conclusion: In symptomatic individuals, defining airflow obstruction by FR instead of LLN identifies a significant number of individuals who have less respiratory and more cardiac clinical characteristics.

Morath, B., T. Mayer, et al. (2017). **"Risk factors of adverse health outcomes after hospital discharge modifiable by clinical pharmacist interventions: a review with a systematic approach."** *Br J Clin Pharmacol* **83**(10): 2163-2178.

The present review assessed the evidence on risk factors for the occurrence of adverse health outcomes after discharge (i.e. unplanned readmission or adverse drug event after discharge) that are potentially modifiable by clinical pharmacist interventions. The findings were compared with patient characteristics reported in guidelines that supposedly indicate a high risk of drug-related problems. First, guidelines and risk assessment tools were searched for patient characteristics indicating a high risk of drug-related problems. Second, a systematic PubMed search was conducted to identify risk factors significantly associated with adverse health outcomes after discharge that are potentially modifiable by a clinical pharmacist intervention. After the PubMed search, 37 studies were included, reporting 16 risk factors. Only seven of 34 patient characteristics mentioned in pertinent guidelines corresponded to one of these risk factors. Diabetes mellitus ( $n = 11$ ), chronic obstructive lung disease ( $n = 9$ ), obesity ( $n = 7$ ), smoking ( $n = 5$ ) and polypharmacy ( $n = 5$ ) were the risk factors reported most frequently in the studies. Additionally, single studies also found associations of adverse health outcomes with different drug classes {e.g. warfarin [hazard ratio 1.50; odds ratio (OR) 3.52], furosemide [OR 2.25] or high beta-blocker starting doses [OR 3.10]}. Although several modifiable risk factors were found, many patient characteristics supposedly indicating a high risk of drug-related problems were not part of the assessed risk factors in the context of an increased risk of adverse health outcomes after discharge. Therefore, an obligatory set of modifiable patient characteristics should be created and implemented in future studies investigating the risk for adverse health outcomes after discharge.

Morlino, P., B. Balbi, et al. (2017). **"Gait abnormalities of COPD are not directly related to respiratory function."** *Gait Posture* **58**: 352-357.

**STUDY OBJECTIVE:** To assess whether gait abnormalities in COPD depend on mere impairment of respiratory function. **METHODS:** In 40 patients with COPD at different GOLD stages and 28 controls, we evaluated: forced expiratory volume in 1s (FEV1); partial pressure of oxygen; Mini-Mental State Examination (MMSE); dynamic balance through the Mini-BESTest (MBT); Timed Up and Go (TUG) test without and with dual task counting aloud back by three; 6-min walk test (6MWT); body sway during quiet stance (stabilometry); spatial-temporal variables of gait by a 4-m long sensorized walkway (baropodometry). Lower-limb muscle strength, tendon reflexes, and sensation were also clinically evaluated. **RESULTS:** Muscle strength of proximal but not distal muscles was slightly reduced in patients, whereas reflexes and sensation were unaffected. FEV1, partial pressure of oxygen, MMSE, MBT, stabilometry, as well as baropodometry, were abnormal and unrelated to muscle weakness. The time taken to perform the TUG test was increased, and to a larger extent with than without dual task. At baropodometry, variability of step length was increased; abnormalities of gait variables were associated with larger body sway but not with FEV1 or hypoxemia. Gait speed at 6MWT was correlated with MBT score and with FEV1 as well as hypoxemia. **CONCLUSIONS:** 6MWT findings give a measure of gait disability linked to endurance-related respiratory failure. Gait at baropodometry is associated with impairment of balance, cognitive status and abnormal dual task performance. We suggest that central nervous lesions, presumably of vascular origin, are detrimental to balance and gait in COPD.

Noonan, M. C., J. Wingham, et al. (2018). **"Who Cares?' The experiences of caregivers of adults living with heart failure, chronic obstructive pulmonary disease and coronary artery disease: a mixed methods systematic review."** *BMJ Open* 8(7): e020927.

**OBJECTIVE:** To assess the experiences of unpaid caregivers providing care to people with heart failure (HF) or chronic obstructive pulmonary disease (COPD) or coronary artery disease (CAD). Design Mixed methods systematic review including qualitative and quantitative studies. Data sources Databases searched: Medline Ebsco, PsycInfo, CINAHL Plus with Full Text, Embase, Web of Science, Ethos: The British Library and ProQuest. Grey literature identified using: Global Dissertations and Theses and Applied Sciences Index and hand searches and citation checking of included references. Search time frame: 1 January 1990 to 30 August 2017. **ELIGIBILITY CRITERIA FOR SELECTING STUDIES:** Inclusion was limited to English language studies in unpaid adult caregivers (>18 years), providing care for patients with HF, COPD or CAD. Studies that considered caregivers for any other diagnoses and studies undertaken in low-income and middle-income countries were excluded. Quality assessment of included studies was conducted by two authors. **DATA ANALYSIS/SYNTHESIS:** A results-based convergent synthesis was conducted. **RESULTS:** Searches returned 8026 titles and abstracts. 54 studies-21 qualitative, 32 quantitative and 1 mixed method were included. This totalled 26 453 caregivers who were primarily female (63%), with median age of 62 years. Narrative synthesis yielded six concepts related to caregiver experience: (1) mental health, (2) caregiver role, (3) lifestyle change, (4) support for caregivers, (5) knowledge and (6) relationships. There was a

discordance between paradigms regarding emerging concepts. Four concepts emerged from qualitative papers which were not present in quantitative papers: (1) expert by experience, (2) vigilance, (3) shared care and (4) time.

**CONCLUSION:** Caregiving is life altering and complex with significant health implications. Health professionals should support caregivers who in turn can facilitate the recipient to manage their long-term condition. Further longitudinal research exploring the evolution of caregiver experiences over time of patients with chronic cardiopulmonary conditions is required. **TRIAL REGISTRATION NUMBER:** CRD42016053412.

Ntritsos, G., J. Franek, et al. (2018). **"Gender-specific estimates of COPD prevalence: a systematic review and meta-analysis."** Int J Chron Obstruct Pulmon Dis **13**: 1507-1514.

**Rationale:** COPD has been perceived as being a disease of older men. However, >7 million women are estimated to live with COPD in the USA alone. Despite a growing body of literature suggesting an increasing burden of COPD in women, the evidence is limited. **Objectives:** To assess and synthesize the available evidence among population-based epidemiologic studies and calculate the global prevalence of COPD in men and women. **Materials and methods:** A systematic review and meta-analysis reporting gender-specific prevalence of COPD was undertaken. Gender-specific prevalence estimates were abstracted from relevant studies. Associated patient characteristics as well as custom variables pertaining to the diagnostic method and other important epidemiologic covariates were also collected. A Bayesian random-effects meta-analysis was performed investigating gender-specific prevalence of COPD stratified by age, geography, calendar time, study setting, diagnostic method, and disease severity. **Measurements and main results:** Among 194 eligible studies, summary prevalence was 9.23% (95% credible interval [CrI]: 8.16%-10.36%) in men and 6.16% (95% CrI: 5.41%-6.95%) in women. Gender prevalences varied widely by the World Health Organization Global Burden of Disease subregions, with the highest female prevalence found in North America (8.07% vs 7.30%) and in participants in urban settings (13.03% vs 8.34%). Meta-regression indicated that age  $\geq 40$  and bronchodilator testing contributed most significantly to heterogeneity of prevalence estimates across studies. **Conclusion:** We conducted the largest ever systematic review and meta-analysis of global prevalence of COPD and the first large gender-specific review. These results will increase awareness of COPD as a critical woman's health issue.

Oliveira, A., C. Pinho, et al. (2017). **"Effects of a respiratory physiotherapy session in patients with LRTI: a pre/post-test study."** Clin Respir J **11**(6): 703-712.

**INTRODUCTION:** The role of respiratory physiotherapy (RP) in lower respiratory tract infections (LRTI) has been questioned. However, studies have focused on



hospitalised patients, and the presence/absence of an underlying disease has been neglected. **OBJECTIVES:** To assess the effects of a RP session in community patients with LRTI and to explore the differences between patients with pneumonia (restrictive disease - AR) and those with exacerbations of an obstructive disease (AO). **METHODS:** A pre/post-test study was conducted. A RP session was applied to patients with LRTI and crackles, wheezes, dyspnoea, perception of sputum and oxygen saturation were collected pre/post session. Comparisons were performed using paired t-tests or Wilcoxon tests. **RESULTS:** Thirty patients (14 males, 55.23 +/- 17.78 years) with pneumonia (AR, n = 12), exacerbations of chronic obstructive pulmonary disease, acute bronchitis and asthma (AO, n = 18) were enrolled. After treatment, the total sample presented lower wheeze rates at trachea ( $P = 0.02$ ;  $r = -0.54$ ) and less sputum ( $P = 0.01$ ;  $r = -0.47$ ). AR patients presented a decrease in the number of crackles ( $P < 0.05$ ;  $0.30 < dz < 0.26$ ) and number and rate of wheezes at chest locations ( $P < 0.05$ ;  $-0.56 < r < -0.48$ ). AO patients showed an increase in the number of crackles ( $P < 0.05$ ;  $0.20 < dz < 0.31$ ), wheeze frequency ( $P = 0.03$ ;  $r = -0.27$ ) and dyspnoea ( $P = 0.04$ ;  $r = -0.55$ ); and a decrease in the number of wheezes at trachea ( $P = 0.02$ ;  $r = -0.54$ ). **CONCLUSIONS:** RP seems effective in reducing wheezes and perception of sputum in patients with LRTI. However, when considering AR and AO diseases separately, further changes in respiratory sounds and dyspnoea emerged. This highlights the importance of considering subgroups of patients with LRTI to develop RP evidence-base practice.

Ottiger, M., M. Nickler, et al. (2018). **"Gut, microbiota-dependent trimethylamine-N-oxide is associated with long-term all-cause mortality in patients with exacerbated chronic obstructive pulmonary disease."** *Nutrition* **45**: 135-141.e1.

**OBJECTIVES:** The gut, microflora-dependent metabolite trimethylamine-N-oxide (TMAO) has emerged as a dietary-associated risk factor for incident cardiovascular events. Chronic obstructive pulmonary disease (COPD) is a prevalent disease worldwide with a high associated risk for cardiovascular disease and death due to an infectious cause. **AIMS:** To study whether TMAO is predictive for adverse clinical outcomes in patients with exacerbated COPD. **METHODS:** A total of 189 patients with COPD exacerbation were prospectively followed for a median of 6.1 y. TMAO plasma levels at the time of emergency department admission were measured by liquid chromatography coupled with tandem mass spectrometry. Cox and linear regression models were used to investigate associations of TMAO with all-cause mortality and different comorbidities. **RESULTS:** All-cause mortality was 55.6% after 6 y. The deceased patients showed significantly higher median admission TMAO (μmol/L) levels compared with survivors (3.9 [interquartile range: 2.3-7.1] versus 2.9 [interquartile range: 1.8-4.7];  $P = 0.01$ ), which resulted in an unadjusted hazard ratio of 1.8 ([95% confidence interval: 1.2-3.0],  $P = 0.01$ ). This association was no longer significant after multivariate adjustment. Median TMAO levels were similar in nonpneumonic and pneumonic COPD exacerbation. Higher age, higher body mass index, diabetes mellitus, and chronic kidney disease were predictors for increased plasma TMAO levels in linear regression analysis. **CONCLUSIONS:**

Increased circulating TMAO levels per se were associated with long-term all-cause mortality in patients with COPD independent of type of exacerbation. However, this association was largely explained by comorbidities and age. Whether TMAO levels can additionally be influenced by nutritional interventions should be addressed in future studies.

Paliogiannis, P., A. G. Fois, et al. (2018). **"Circulating malondialdehyde concentrations in patients with stable chronic obstructive pulmonary disease: a systematic review and meta-analysis."** Biomark Med **12**(7): 771-781.

The aim of this meta-analysis was to review the available evidence regarding the blood concentrations of the oxidative stress marker malondialdehyde (MDA) in chronic obstructive pulmonary disease (COPD) patients in comparison to healthy individuals. 14 studies were included in the meta-analysis (from inception to October 2017) with a total of 817 COPD patients and 530 healthy controls. Pooled MDA concentrations were significantly higher in patients with COPD than controls (standardized mean differences = 2.39  $\mu\text{mol/l}$ , 95% CI: 1.50-3.28  $\mu\text{mol/l}$ ;  $p < 0.001$ ). Our meta-analysis showed that the blood concentrations of MDA are consistently higher in patients with COPD when compared with healthy controls, suggesting an important role of lipid peroxidation, and thus oxidative stress, in the pathogenesis of COPD.

Qiu, S., X. Cai, et al. (2018). **"Using step counters to promote physical activity and exercise capacity in patients with chronic obstructive pulmonary disease: a meta-analysis."** Ther Adv Respir Dis **12**: 1753466618787386.

**BACKGROUND:** Although step counters are popularly employed for physical rehabilitation in chronic obstructive pulmonary disease (COPD) patients, their effectiveness is inconsistent and even questioned. This meta-analysis aimed to investigate whether step counter use increases physical activity or improves exercise capacity in COPD patients. **METHODS:** Electronic databases were searched for randomized controlled trials that assessed the efficacy of step counter use in increasing physical activity or in improving exercise capacity. Data were aggregated using a random-effects model to get the overall effect sizes [standard mean difference (SMD) with 95% confidence interval (CI)], and subgroup analyses were performed. **RESULTS:** A total of 15 trials enrolling 1316 patients with moderate to severe COPD were included. Step counter use increased physical activity compared with controls (SMD = 0.57, 95% CI 0.31-0.84), which is equal to a magnitude of 1026 steps/day in daily steps. It also enhanced exercise capacity with an effect size of 0.30 (95% CI 0.16-0.45), approximating to a magnitude of 11.6 m in the 6-min walking distance. Step counter use could augment physical activity (SMD = 0.64, 95% CI 0.19-1.08) and exercise capacity (SMD = 0.32, 95% CI 0.01-0.62) for patients receiving

pulmonary rehabilitation. Yet it cannot enhance physical activity or exercise capacity in patients with severe COPD or among studies with intervention durations 6 months (both  $p > 0.50$ ). **CONCLUSIONS:** Step counter use increases physical activity and improves exercise capacity in COPD patients, at least in the short term, which supports the notion of recommending step counter use in COPD management.

Ray, R., L. Tombs, et al. (2018). **"Efficacy of Umeclidinium/Vilanterol in Elderly Patients with COPD: A Pooled Analysis of Randomized Controlled Trials."** Drugs Aging **35**(7): 637-647.

**OBJECTIVE:** The aim of this pooled analysis was to assess the efficacy and safety of umeclidinium/vilanterol (UMEC/VI) 62.5/25 microg dual bronchodilation versus placebo in elderly symptomatic patients with chronic obstructive pulmonary disease (COPD). **METHODS:** We conducted a post hoc pooled analysis of data from 10 randomized controlled trials (RCTs). Change from baseline (CFB) in trough forced expiratory volume in 1 s (FEV1), proportion of FEV1 responders ( $\geq 100$ -mL increase from baseline), and safety were analyzed in patients aged  $< 65$ ,  $\geq 65$ , and  $\geq 75$  years on Days 28, 56, and 84 (12-week analysis of parallel-group design studies), Days 28, 56, 84, 112, 140, 168, and 169 (24-week analysis of parallel-group design studies), and Days 2, 42, and 84 (12-week analysis of crossover design studies). **RESULTS:** The UMEC/VI intent-to-treat (ITT) populations comprised 2246, 1296, and 472 patients in the 12-week parallel-group, 24-week parallel-group, and 12-week crossover analysis, respectively ( $\geq 65$  years: 36-44%;  $\geq 75$  years: 7-11%). The placebo ITT populations comprised 528, 280, and 505 patients, respectively ( $\geq 65$  years: 37-41%;  $\geq 75$  years: 5-11%). Significant improvements in trough FEV1 and significantly greater proportions of FEV1 responders were seen with UMEC/VI compared with placebo in all analyses regardless of patient age or timepoint considered ( $p \leq 0.023$ ), except Day 84 trough FEV1 CFB in the 12-week crossover analysis in patients aged  $\geq 75$  years ( $p = 0.064$ ). UMEC/VI safety profile was similar to placebo in all age groups. **CONCLUSIONS:** In this pooled analysis of RCT data, once-daily UMEC/VI was well tolerated and provided clinically significant lung function benefits compared with placebo in younger and older patients with COPD. **FUNDING:** GlaxoSmithKline (study 208125).

Reisner, C., G. Gottschlich, et al. (2017). **"24-h bronchodilation and inspiratory capacity improvements with glycopyrrolate/formoterol fumarate via co-suspension delivery technology in COPD."** Respir Res **18**(1): 157.

**BACKGROUND:** Symptoms of chronic obstructive pulmonary disease may vary throughout the day and it is important that therapeutic approaches provide 24-h symptom control. We report the results of two phase IIIb crossover studies, PT003011 and PT003012, investigating the 24-h lung function profile of GFF MDI

(glycopyrrolate/formoterol fumarate 18/9.6 µg delivered using innovative co-suspension delivery technology) administered twice daily. **METHODS:** Patients with moderate-to-very severe chronic obstructive pulmonary disease received 4 weeks' treatment with each of GFF MDI, placebo MDI, and open-label tiotropium (PT003011 only). Lung function was assessed over 24 h on day 29 of each treatment period. The primary outcome was forced expiratory volume in 1 second area under the curve from 0 to 24 h (FEV1AUC0-24). Other outcomes included change from baseline in average daily rescue medication use over the treatment period. In addition, we conducted a post-hoc analysis of data pooled from both studies to further characterize the effect of GFF MDI on inspiratory capacity. **RESULTS:** GFF MDI treatment significantly increased FEV1AUC0-24 versus placebo in studies PT003011 (n = 75) and PT003012 (n = 35) on day 29 (both studies  $p < 0.0001$ ), with similar improvements in FEV1AUC versus placebo for hours 0-12 and 12-24. In PT003011, improvements with GFF MDI versus tiotropium in FEV1AUC were greater during hours 12-24 compared to 0-12 h. GFF MDI treatment also resulted in a significant reduction in rescue medication use versus placebo (-0.84 [ $p < 0.0001$ ] and -1.11 [ $p = 0.0054$ ] puffs/day in PT003011 and PT003012, respectively), and versus tiotropium in PT003011 (-0.44 [ $p = 0.017$ ] puffs/day). A post-hoc pooled analysis showed patients treated with GFF MDI were more likely to achieve a >15% increase from baseline in inspiratory capacity than patients treated with placebo or tiotropium (72.1%, 19.0% and 47.0% of patients, respectively after the evening dose on day 29). There were no significant safety/tolerability findings. **CONCLUSIONS:** GFF MDI significantly improved 24-h lung function versus placebo in patients with moderate-to-very severe chronic obstructive pulmonary disease, with similar benefits in the second 12-h period compared to the first, supporting twice-daily dosing of GFF MDI. **TRIAL REGISTRATION:** Pearl Therapeutics, Inc.; [www.clinicaltrials.gov](http://www.clinicaltrials.gov) ; NCT02347072 and NCT02347085 . Registered 21 January 2015.

Reisner, C., J. Pearle, et al. (2018). **"Efficacy and safety of four doses of glycopyrrolate/formoterol fumarate delivered via a metered dose inhaler compared with the monocomponents in patients with moderate-to-severe COPD."** *Int J Chron Obstruct Pulmon Dis* **13**: 1965-1977.

**Purpose:** To determine the efficacy and safety of glycopyrrolate/formoterol fumarate metered dose inhaler (GFF MDI 36/9.6, 36/7.2, 18/9.6, 9/9.6 microg) using innovative co-suspension delivery technology, compared with glycopyrrolate (GP) MDI 36 microg and formoterol fumarate (FF) MDI 9.6 microg, in patients with moderate-to-severe COPD. **Methods:** In this Phase IIb, randomized, double-blind, balanced incomplete-block, two-period, cross-over study (NCT01349816), patients received treatment twice-daily for 7 days. The primary efficacy endpoint was forced expiratory volume in 1 second (FEV1) area under the curve from 0 to 12 hours (AUC0-12) on Day 7. Secondary efficacy endpoints were peak change from baseline in FEV1 through 2 hours; time to onset of action ( $\geq 10\%$  improvement in mean FEV1); proportion of patients achieving  $\geq 12\%$  improvement in FEV1 on Day 1; peak change from baseline in inspiratory capacity (IC) on Days 1 and 7; change from baseline in morning pre-dose FEV1;

peak change from baseline in FEV1 through 6 hours; and change from baseline in mean evening 12-hour post-dose trough FEV1 on Day 7. Safety was assessed. Results: All 185 randomized patients received treatment. All doses of GFF MDI significantly improved the primary endpoint compared with GP MDI 36 microg (all  $P \leq 0.0137$ ). For peak change in FEV1 and IC and time to onset of action secondary endpoints,  $\geq 2$  doses of GFF MDI demonstrated superiority to GP MDI 36 microg. No significant differences were observed between GFF MDI and FF MDI 9.6 microg for primary and secondary endpoints. The incidence of adverse events was similar between treatments. Conclusion: While all doses of GFF MDI were superior to GP MDI 36 microg for the primary end-point, in this study neither superiority of GFF MDI to FF MDI 9.6 microg nor a clear dose-response was observed. All treatments were well tolerated with no unexpected safety findings.

Renn, B. N., N. E. Hundt, et al. (2018). **"Integrated Brief Cognitive Behavioral Therapy Improves Illness Intrusiveness in Veterans With Chronic Obstructive Pulmonary Disease."** *Ann Behav Med* 52(8): 686-696.

Background: Progressive illnesses such as chronic obstructive pulmonary disease (COPD) impart a high level of physical and psychological burden. Evidence-based psychotherapies hold the potential to improve perceptions of physical health impairment, yet few studies have documented these effects. Purpose: To evaluate the effect of brief cognitive behavioral therapy (bCBT) on disease-related illness intrusiveness. Methods: Participants were 175 Veterans with COPD and clinically elevated symptoms of depression and/or anxiety enrolled in a larger randomized trial ( $n = 99$  randomized to bCBT,  $n = 76$  to enhanced usual care; EUC). bCBT included up to six treatment sessions and optional booster sessions over a 4-month period. EUC entailed an assessment with documentation in the medical record. Primary outcomes focused on posttreatment changes on the Illness Intrusiveness Rating Scale (IIRS), an established measure of perceived impairment from a chronic health condition. Results: Illness intrusiveness improved for bCBT participants relative to EUC, after controlling for baseline IIRS scores, depression, and anxiety ( $p = .03$ , partial  $\eta^2 = .03$ ). Specific improvement was observed in the Instrumental subscale ( $p = .02$ ), encompassing improved intrusiveness of COPD on daily activities and daily functioning. IIRS scores improved in the absence of changes in physical functioning. Conclusions: Illness intrusiveness was high among Veterans with COPD but improved over the course of bCBT. Integrated behavioral health interventions hold the potential to reduce disease intrusiveness. The IIRS may be a valuable tool to augment traditional assessment and measurement-based care approaches of behavioral health interventions for medically ill patients.

Robinson, H., V. Williams, et al. (2018). **"Facilitators and barriers to physical activity following pulmonary rehabilitation in COPD: a systematic review of qualitative studies."** *NPJ Prim Care Respir Med* **28**(1): 19.

Pulmonary rehabilitation has short-term benefits on dyspnea, exercise capacity and quality of life in COPD, but evidence suggests these do not always translate to increased daily physical activity on a patient level. This is attributed to a limited understanding of the determinants of physical activity maintenance following pulmonary rehabilitation. This systematic review of qualitative research was conducted to understand COPD patients' perceived facilitators and barriers to physical activity following pulmonary rehabilitation. Electronic databases of published data, non-published data, and trial registers were searched to identify qualitative studies (interviews, focus groups) reporting the facilitators and barriers to physical activity following pulmonary rehabilitation for people with COPD. Thematic synthesis of qualitative data was adopted involving line-by-line coding of the findings of the included studies, development of descriptive themes, and generation of analytical themes. Fourteen studies including 167 COPD patients met the inclusion criteria. Seven sub-themes were identified as influential to physical activity following pulmonary rehabilitation. These included: intentions, self-efficacy, feedback of capabilities and improvements, relationship with health care professionals, peer interaction, opportunities following pulmonary rehabilitation and routine. These encapsulated the facilitators and barriers to physical activity following pulmonary rehabilitation and were identified as sub-themes within the three analytical themes, which were beliefs, social support, and the environment. The findings highlight the challenge of promoting physical activity following pulmonary rehabilitation in COPD and provide complementary evidence to aid evaluations of interventions already attempted in this area, but also adds insight into future development of interventions targeting physical activity maintenance in COPD.

Rogliani, P., M. G. Matera, et al. (2018). **"Emerging biological therapies for treating chronic obstructive pulmonary disease: A pairwise and network meta-analysis."** *Pulm Pharmacol Ther* **50**: 28-37.

Inflammation in chronic obstructive pulmonary disease (COPD) is often corticosteroid resistant and, thus, alternative anti-inflammatory approaches are needed. Since it is still not clear whether blocking specific pro-inflammatory factors may provide clinical benefit in COPD, we have performed a meta-analysis to quantify the impact of monoclonal antibodies (mABs) targeting the cytokine/chemokine-mediated inflammation in COPD. A pairwise and network meta-analyses were performed by extracting data from randomized clinical trials on COPD concerning the impact of mABs vs. placebo on the risk of exacerbation, forced expiratory volume in 1s (FEV1), and St. George's Respiratory Questionnaire (SGRQ). Data on the interleukin (IL)-1 $\beta$  antagonist canakinumab, IL-1R1 antagonist MEDI8986, IL-5 antagonist mepolizumab, IL-5R antagonist benralizumab, IL-8 antagonist ABX-IL8, and TNF- $\alpha$  antagonist infliximab were found. Overall, mAB therapy had a moderate impact on the risk exacerbation, but not on FEV1 and SGRQ. The pairwise meta-analysis performed in eosinophilic patients, and the network approach, indicated that mepolizumab elicited a beneficial effect

against the risk of exacerbation, whereas benralizumab was more effective in improving both FEV1 and SGRQ. This study demonstrates that targeting the pathway activated by IL-5 may have a beneficial impact in eosinophilic COPD patients.

Rogliani, P., J. Ora, et al. (2018). **"Pleiotropic effects of hypoglycemic agents: implications in asthma and COPD."** *Curr Opin Pharmacol* **40**: 34-38.

Diabetes mellitus (DM) is a complex multifactorial disease due to the interaction between environmental noxae and genetic predisposition. Furthermore, an increased association between DM, especially Type 2 diabetes mellitus (T2DM), and the onset of pulmonary function impairment with a bronchial hyperresponsiveness has been documented. DM is a risk factor for accelerated decline in FEV1 and the development of asthma and COPD. The increased blood glucose concentrations along with higher levels of oxidative stress and inflammation can influence the pulmonary function and, since hypoglycemic drugs can act on these different defects we can hypothesize their direct effect on obstructive pulmonary diseases. Metformin, a biguanide, is the molecule having several evidences of its action on asthma and COPD in patients with T2DM. In this population, Metformin can ameliorate pulmonary outcomes reducing high glucose concentrations, inflammation through the activation of the AMP-activated protein kinase, leading to the decreased production of pro-inflammatory cytokines and blunting allergic eosinophilic airway inflammation. There are evidences of Pioglitazone role on asthma, since the activation of PPARgamma Pioglitazone might inhibit the synthesis and release of pro-inflammatory cytokines. Indeed, Pioglitazone can improve symptoms associated with asthma reducing episodes of exacerbation and oral steroid prescription. Finally, randomized clinical trials using hypoglycemic agents on patients with asthma and COPD with and without DM should be proposed as well as the implementation of a new formulation of hypoglycemic agents to make it possible to administer it via aerosol.

Rose, S., C. Paul, et al. (2017). **"Stigma-related experiences in non-communicable respiratory diseases: A systematic review."** *Chron Respir Dis* **14**(3): 199-216.

The stigma of non-communicable respiratory diseases (NCRDs), whether perceived or otherwise, can be an important element of a patient's experience of his/her illness and a contributing factor to poor psychosocial, treatment and clinical outcomes. This systematic review examines the evidence regarding the associations between stigma-related experiences and patient outcomes, comparing findings across a range of common NCRDs. Electronic databases and manual searches were conducted to identify original quantitative research published to December 2015. Articles focussing on adult patient samples diagnosed with asthma, chronic obstructive pulmonary disease (COPD), cystic

fibrosis, lung cancer or mesothelioma, and included a measurement of stigma-related experience (i.e. perceived stigma, shame, blame or guilt), were eligible for inclusion. Included articles were described for study characteristics, outcome scores, correlates between stigma-related experiences and patient outcomes and methodological rigor. Twenty-five articles were eligible for this review, with most (n = 20) related to lung cancer. No articles for cystic fibrosis were identified. Twenty unique scales were used, with low to moderate stigma-related experiences reported overall. The stigma-related experiences significantly correlated with all six patient-related domains explored (psychosocial, quality of life, behavioral, physical, treatment and work), which were investigated more widely in COPD and lung cancer samples. No studies adequately met all criteria for methodological rigor. The inter-connectedness of stigma-related experiences to other aspects of patient experiences highlight that an integrated approach is needed to address this important issue. Future studies should adopt more rigorous methodology, including streamlining measures, to provide robust evidence.

Rozenberg, D., V. Martelli, et al. (2017). **"Utilization of non-invasive imaging tools for assessment of peripheral skeletal muscle size and composition in chronic lung disease: A systematic review."** *Respir Med* **131**: 125-134.

**OBJECTIVES:** Non-invasive imaging modalities allow for detailed assessment of peripheral skeletal muscle wasting, which is associated with increased morbidity and mortality in chronic lung disease. Given the increased utilization of imaging tools, a systematic review was conducted using PRISMA guidelines to describe the modalities and acquisition techniques used to evaluate skeletal muscle in chronic lung disease and assess the relationships of muscle size and composition with strength, physical performance, structural alterations and clinical outcomes. **METHODS:** Six electronic databases were searched (inception-May 2017) to identify prospective studies measuring peripheral skeletal muscle size or composition using computed tomography (CT), magnetic resonance imaging/spectroscopy (MRI/MRS), or ultrasound (US) in adult chronic lung disease patients. **RESULTS:** Fifty-eight articles were included, which utilized: CT (n = 26), MRI/MRS (n = 16) and US (n = 16) in 2254 participants. All studies measured muscle size, predominantly of the lower extremity (n = 53), and only nine assessed muscle composition (i.e. fat infiltration) mainly with CT or MRI/MRS (n = 7). Thigh muscle size had a significant association with strength (r = 0.43-0.83, n = 13/14 studies), 6-min walk distance (r = 0.60-0.62, n = 3/6) and physical activity (r = 0.30-0.82, n = 3). Thigh muscle atrophy was independently associated with increased re-hospitalization (n = 1) and mortality (n = 3). Increased muscle fat infiltration had a moderate association with reduced physical performance partly related to increased anaerobic metabolism, but its prognostic utility was not assessed. **CONCLUSION:** Imaging modalities are valuable tools for the characterization of skeletal muscle dysfunction in chronic lung disease in clinical and research settings. The use of muscle imaging as a prognostic marker is promising and requires further study.



Santus, P., D. Radovanovic, et al. (2018). **"Effects of bronchodilation on biomarkers of peripheral airway inflammation in COPD."** *Pharmacol Res* **133**: 160-169.

Peripheral airway inflammation and dysfunction are key elements in the pathogenesis of COPD. The exhaled alveolar fraction of nitric oxide (CANO) is an indirect biomarker of lung peripheral inflammation. We tested whether inhaled long-acting bronchodilators (LABA) can affect CANO and we evaluated correlations with lung mechanics in patients with COPD. Two-centre, randomised, double blind, crossover study including COPD patients with moderate-to-severe airflow obstruction. Following a pharmacological washout, multi-flow exhaled fraction of NO (FENO), plethysmography, lung diffusion (DLCO), single breath nitrogen washout test and dyspnoea were measured in a crossover manner at baseline and 30, 60 and 180min following administration of salmeterol (Sal) or formoterol fumarate (FF). (ClinicalTrials.gov, number NCT01853787). Forty-five patients were enrolled (median age: 71.8 years; 84.4% males). At baseline, CANO correlated with airway resistances ( $r=0.422$ ), residual volume/total lung capacity (RV/TLC;  $r=0.375$ ), transfer factor ( $r=-0.463$ ) and forced expiratory volume in 1s (FEV1;  $r=-0.375$ , all  $P<0.01$ ). After LABA administration, we found a significant reduction of FENO that reached statistical significance at 180'; no difference was found between FF and S. Consistently, a significant reduction of CANO was documented at 60' and 180' compared to baseline for both FF and S ( $P<0.01$  and  $P<0.05$ , respectively). Changes in CANO were correlated with changes in vital capacity ( $r=-0.44$ ;  $P<0.001$ ) and RV/TLC ( $r=0.56$ ;  $P<0.001$ ), but not FEV1. In COPD, direct correlations were found between the levels of CANO and the magnitude of peripheral airway dysfunction. LABA reduced CANO levels. The reduction was associated with improvement in functional parameters reflecting air trapping.

Schermer, T. R., M. Vatsolaki, et al. (2018). **"Point of care microspirometry to facilitate the COPD diagnostic process in primary care: a clustered randomised trial."** *NPJ Prim Care Respir Med* **28**(1): 17.

We studied if pre-bronchodilator FEV1/FEV6 determinations with microspirometers by GPs improve the diagnostic process for COPD in a 6-8 month clustered randomised controlled trial in Dutch general practices (<http://www.trialregister.nl> : NTR4041). GPs allocated to microspirometry (MI) used COPD-6((R)) microspirometers in patients  $\geq 50$  years old with a smoking history and respiratory complaints that could indicate undiagnosed COPD and ask to refer patients for full spirometry if MI was positive (FEV1/FEV6  $<0.73$ ). Introduction of the COPD-6((R)) was postponed in the usual care (UC) group. GPs of both study arms were asked to list all patients that fulfilled study criteria and at the end of the study we screened the electronic medical record system for number of patients that fulfilled study criteria and visited their GP within the study period. Main end point was a documented diagnostic conclusion of COPD within 3 months after the patient's visit. We used multilevel logistic regression with

correction for relevant covariates. Next, we described the process of care. 21 practices (88 GPs) participated and 416 possible undiagnosed COPD patient visited these practices in the study period. 78 (of 192 visiting) subjects were listed by MI GPs and diagnostic conclusions were documented in 77%, compared to 61 listed (of 224 visiting) subjects and 44% with documented diagnostic conclusions by UC GPs (Odds Ratio: OR: 4.3, 95%CI: 1.6-11.5). Microspirometry improved the diagnostic process for possible underlying COPD in patients who consulted their GP with respiratory symptoms, but the majority of possible undiagnosed COPD patients remained unrecognised by GPs.

Sehl, J., J. O'Doherty, et al. (2018). **"Adherence to COPD management guidelines in general practice? A review of the literature."** *Ir J Med Sci* **187**(2): 403-407.

**BACKGROUND:** Chronic obstructive pulmonary disease (COPD) is a progressive illness that is mostly managed in the general practice setting. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines are the international gold standard, and it is important to understand how these are being applied in general practice. **AIMS:** This review aimed to assess the current level of adherence to international best practice guidelines among general practitioners in relation to COPD. **METHODS:** PubMed and EMBASE searches (from 2012 to 2016) were performed and used the search terms guidelines, COPD, general practitioners, and primary care. Papers were excluded if they were not primary sources, were published before 2012, or did not pertain to a general practice setting. **RESULTS:** After applying set inclusion and exclusion criteria, 11 studies were retrieved. These papers were grouped under three categories: diagnosis, pharmacological, and non-pharmacological management, based on the GOLD guidelines. **CONCLUSIONS:** Current studies show significant variability in adherence to the GOLD guidelines. Barriers identified include lack of clarity, unfamiliarity with recommendations, and lack of familiarity with the guidelines. If general practice is expected to manage COPD and other chronic diseases, health service investment is needed to provide appropriate focused guidelines, to support their dissemination and resources to implement them in practice.

Sergio, L. P. S., L. M. F. Lucinda, et al. (2018). **"Emphysema induced by elastase alters the mRNA relative levels from DNA repair genes in acute lung injury in response to sepsis induced by lipopolysaccharide administration in Wistar rats."** *Exp Lung Res* **44**(2): 79-88.

**Purpose/Aim of the study:** Patients suffering from chronic obstructive pulmonary disease (COPD) in association with acute respiratory distress syndrome (ARDS) present oxidative stress in lung cells, with production of free radicals and DNA lesions in pulmonary and adjacent cells. Once the DNA molecule is damaged, a set of enzymatic mechanisms are triggered to preserve genetic code integrity and

cellular homeostasis. These enzymatic mechanisms include the base and the nucleotide excision repair pathways, as well as telomere regulation. Thus, the aim of this work was to evaluate the mRNA levels from APEX1, ERCC2, TP53, and TRF2 genes in lung tissue from Wistar rats affected by acute lung injury in response to sepsis and emphysema. **MATERIALS AND METHODS:** Adult male Wistar rats were randomized into 4 groups (n = 6, for each group): control, emphysema, sepsis, and emphysema with sepsis. Pulmonary emphysema was induced by intratracheal instillation of elastase (12 IU/animal) and sepsis induced by intraperitoneal *Escherichia coli* lipopolysaccharide (LPS) injection (10 mg/kg). Lungs were removed, and samples were withdrawn for histological analysis and total RNA extraction, cDNA synthesis, and mRNA level evaluation by real time quantitative polymerase chain reaction. **RESULTS:** Data show acute lung injury by LPS and emphysema by elastase and that APEX1, ERCC2, TP53, and TRF2 mRNA levels are increased significantly ( $p < 0.01$ ) in emphysema with sepsis group. **CONCLUSION:** Our results suggest that alteration in mRNA levels from DNA repair and genomic stability could be part of cell response to acute lung injury in response to emphysema and sepsis.

Singh, D., M. Corradi, et al. (2017). **"Triple therapy in COPD: new evidence with the extrafine fixed combination of beclomethasone dipropionate, formoterol fumarate, and glycopyrronium bromide."** *Int J Chron Obstruct Pulmon Dis* **12**: 2917-2928.

The goals of COPD therapy are to prevent and control symptoms, reduce the frequency and severity of exacerbations, and improve exercise tolerance. The triple combination therapy of inhaled corticosteroids (ICSs), long-acting beta2 agonists (LABAs), and long-acting muscarinic antagonists (LAMAs) has become an option for maintenance treatment of COPD and as a "step-up" therapy from single or double combination treatments. There is evidence that triple combination ICS/LABA/LAMA with different inhalers improves lung function, symptoms, and health status and reduces exacerbations. A new triple fixed-dose combination of extrafine beclomethasone dipropionate (100 microg/puff)/formoterol fumarate (6 microg/puff)/glycopyrronium bromide (12.5 microg/puff) has been developed as a hydrofluoroalkane pressurized metered dose inhaler. Two large pivotal studies showed that this extrafine fixed ICS/LABA/LAMA triple combination is superior to fixed ICS/LABA combined therapy and also superior to the LAMA tiotropium in terms of lung function and exacerbation prevention in COPD patients at risk of exacerbation. This review considers the new information provided by these clinical trials of extrafine triple therapy and the implications for the clinical management of COPD patients.

Torres-Sanchez, I., M. C. Valenza, et al. (2018). **"Effects of different physical therapy programs on perceived health status in acute exacerbation of chronic**

**obstructive pulmonary disease patients: a randomized clinical trial." Disabil Rehabil 40(17): 2025-2031.**

**PURPOSE:** To evaluate the repercussion of different physical therapy interventions on the perceived health status of chronic obstructive pulmonary disease (COPD) patients during acute exacerbation. **MATERIALS AND METHODS:** Randomized controlled trial. Patients were assigned to: control group (standard medical treatment), controlled breathing + range of motion exercises group or Resistance exercises group. Perceived health status was assessed at baseline and discharge using the EuroQol-5D (EQ-5D) questionnaire. Clinical profile of patients was evaluated at baseline for descriptive purposes. **RESULTS:** Ninety patients were randomized into the groups. Perceived health status improved significantly in all groups. Significant differences were found in mobility, self-care and usual activities subscales of EQ-5D and Visual Analogue Scale between control and controlled breathing + range of motion exercises group. Significant differences were found in all variables except pain between control group and Resistance exercises group. Finally, usual care and anxiety/depression subscales of EQ-5D showed significant differences between controlled breathing + range of motion exercises group and Resistance exercises group, the improvements being greater in Resistance exercises group. **CONCLUSIONS:** Physical therapy added to standard medical treatment of acute exacerbated COPD patients achieves a higher improvement in perceived health status than the prescription of standard medical treatment alone. Implications for Rehabilitation Physical therapy added to standard medical treatment in patients hospitalized due to acute exacerbation of chronic obstructive pulmonary disease achieves a higher improvement in the perceived health status than the prescription of standard medical treatment alone. Short duration physical therapy programs added to the standard care appear to be helpful in the management of acute exacerbations of chronic obstructive pulmonary disease patients.

Valenza, M. C., I. Torres-Sanchez, et al. (2018). **"Effects of home-based neuromuscular electrical stimulation in severe chronic obstructive pulmonary disease patients: a randomized controlled clinical trial." Eur J Phys Rehabil Med 54(3): 323-332.**

**BACKGROUND:** Chronic obstructive pulmonary disease (COPD) patients experience a sustained deterioration of several capacities. Those with severe COPD undergo a considerable decline in their physical and functional capacities, but pulmonary rehabilitation (PR) is used to reduce the weakness of such patients. To date, neuromuscular electrical stimulation (NMES) has been used in acute COPD patients but NMES superimposed onto voluntary muscular contraction has not been tested in COPD patients. **AIM:** The aim of this study was to evaluate the effects of superimposed NMES on the cardiorespiratory performance and functionality of severe COPD patients undergoing a home-based rehabilitation program. **DESIGN:** This was a randomized controlled clinical trial. **POPULATION:** A total of 36 stable severe COPD patients were included in this study and were randomly divided into two groups: an intervention group and a control group. **SETTING:** The study was conducted as a home-based program. **METHODS:** The control group received standard medical treatment. The

intervention group additionally underwent an individualized physical therapy program. The intervention consisted of a pulmonary rehabilitation (PR) protocol for 8 weeks (2 h/week). The protocol was carried out as follows: 10 minutes of controlled breathing training; 30 minutes of NMES superimposed onto voluntary muscular contraction; and 5 minutes of relaxation/cool-down. The outcome measures were cardiorespiratory performance measured using the 6-Minute Walk Test in the treadmill and functionality assessed with the functional independence measure. RESULTS: In the intervention group, significant improvements were observed after the treatment in cardiorespiratory performance and functionality ( $P < 0.05$ ), while the control group did not show any significant changes ( $P > 0.05$ ). The between-group analysis showed significant differences in cardiorespiratory performance and functionality ( $P < 0.05$ ). CONCLUSIONS: An 8-week individualized home-based PR program including controlled breathing training, aerobic exercise with elastic bands, and NMES superimposed onto voluntary muscle contraction significantly improves cardiorespiratory performance and functionality in stable COPD patients. CLINICAL REHABILITATION IMPACT: A home-based pulmonary rehabilitation program including controlled breathing training, and NMES superimposed onto voluntary muscle contraction significantly improves cardiorespiratory performance and functionality in stable COPD patients.

van Eerd, E. A. M., M. Bech Risor, et al. (2017). **"Why do physicians lack engagement with smoking cessation treatment in their COPD patients? A multinational qualitative study."** *NPJ Prim Care Respir Med* 27(1): 41.

Smoking cessation is the only effective intervention to slow down the accelerated decline in lung function in smokers with chronic obstructive pulmonary disease. Nevertheless, physicians often do not routinely provide evidence-based smoking cessation treatment to their patients. To understand underlying reasons, we explored how physicians engage in smoking cessation treatment in their chronic obstructive pulmonary disease patients. In total, 21 focus group discussions were held with general practitioners and pulmonologists in seven different countries in Europe and Asia. We generated three themes, whereby some of the issues concerned smokers in general: first, 'physicians' frustration with chronic obstructive pulmonary disease patients who smoke'. These frustrations interfered with the provision of evidence-based treatment and could result in this group of patients being treated unequally. Second: 'physicians' limited knowledge of, and negative beliefs about, smoking cessation treatment'. This hindered treating smokers effectively. Third: 'healthcare organisational factors that influence the use of smoking cessation treatments'. Money and time issues, as well as the failure to regard smoking as a disease, influenced how physicians engaged in smoking cessation treatment. Our results indicate that there is a number of barriers to the provision of effective smoking cessation treatment in patients with chronic obstructive pulmonary disease and smokers in general. Introducing an informative smoking cessation programme, including communication skills and ethical issues, in the vocational and postgraduate medical training may help to address these barriers. This is important in order to increase engagement with smoking cessation treatment and to improve quality of chronic obstructive

pulmonary disease care. **CHRONIC LUNG DISEASE: CHANGING ATTITUDES TO HELP PATIENTS STOP SMOKING:** Doctors should be given careful, ethically-informed guidance during medical training to help them to support patients to quit smoking. The most important part of treatment for patients with chronic obstructive pulmonary disease (COPD) is help to stop smoking. However, there is evidence to suggest that doctors don't always motivate COPD patients to quit. Eva Anne Marije van Eerd at Maastricht University, The Netherlands, together with an international team of scientists, conducted focus group interviews with doctors in seven different countries to assess barriers to smoking cessation. They found that doctors' frustration with and negative attitudes towards patients who continued to smoke contributed to poor cessation management and treatment inequalities in some cases. Many doctors also cited a lack of experience with smoking cessation techniques alongside time and money issues as barriers to effective treatment.

Wang, J., J. Li, et al. (2018). **"Acupuncture Therapy for Functional Effects and Quality of Life in COPD Patients: A Systematic Review and Meta-Analysis."** Biomed Res Int **2018**: 3026726.

**Objective:** This study aimed to evaluate the efficacy and safety of acupuncture therapy (AT) for improving functional effects and quality of life in COPD patients. **Methods:** PubMed, Embase, Cochrane Library, Web of Science, Chinese Biomedical Literature Database (CBM), China National Knowledge Infrastructure (CNKI), Chongqing VIP (CQVIP), and Wanfang Data were searched. The randomized controlled trials (RCTs) evaluating the effect of AT on COPD patients were included. Primary outcome measures included six-minute walk distance (6MWD) and St. George's Respiratory Questionnaire (SGRQ). Study selection, data extraction, and risk of bias assessment were independently conducted, respectively. Statistical analysis was conducted by RevMan software (version 5.3) and Stata software (version 12.0). **Results:** Nineteen studies (1298 participants) were included. 6MWD improved more (MD: 47.84; 95% CI: 23.33 to 72.35;  $Z = 3.83$ ,  $P = 0.0001$ ) and effective rate was higher (OR: 2.26; 95% CI: 1.43 to 3.58;  $Z = 3.48$ ,  $P = 0.0005$ ) in the experimental group compared to the control group. Symptom domain scores (MD: -24.86; 95% CI: -32.17 to -17.55;  $Z = 6.66$ ,  $P < 0.00001$ ), activity domain scores (MD: -16.52; 95% CI: -22.57 to -10.47;  $Z = 5.36$ ,  $P < 0.00001$ ) and impact domain scores (MD: -13.07; 95% CI: -17.23 to -8.92;  $Z = 6.16$ ,  $P < 0.00001$ ) of SGRQ in the experimental group improved more compared to the control group. There was no significant improvement in SGRQ total scores between two groups. The improvement of FEV1 was not significant between two groups, yet subgroup analysis showed that patients treated with AT adjunctive to other treatments improved more in FEV1 (MD: 0.41; 95% CI: 0.28 to 0.54;  $Z = 6.01$ ,  $P < 0.00001$ ) compared to those treated with other treatments alone. **Conclusion:** AT may be effective in improving functional effects and quality of life in COPD patients. Besides, AT may also improve pulmonary function of patients with COPD. However, further high-quality RCTs are needed to confirm the efficacy and safety of AT for COPD patients.

Wang, J. J., Y. Xie, et al. (2018). **"Transcutaneous electric nerve stimulation over acupoints for chronic obstructive pulmonary disease: Protocol for a systematic review and meta-analysis."** *Medicine (Baltimore)* **97**(25): e11199.

**BACKGROUND:** There is a limited evidence concerning the efficacy of transcutaneous electric nerve stimulation over acupoints (Acu-TENS) for chronic obstructive pulmonary disease (COPD). Thus, this review aims to systematically determine the effect of Acu-TENS on COPD. **METHODS:** PubMed, Embase, The Cochrane Library, Web of Science, Chinese Biomedical Literature Database, China National Knowledge Infrastructure, Chongqing VIP, and Wanfang Data will be searched from their inception to May 10, 2018. Randomized controlled trials that evaluated the effect of Acu-TENS on patients with COPD will be included. The primary outcome measures will include 6-minute walk distance and dyspnea visual analog scale scores. The secondary outcome measures will include lung function and St George's Respiratory Questionnaire. Study selection, data extraction, and risk of bias assessment will be independently undertaken, respectively. Statistical analysis will be conducted by RevMan software (version 5.3). **RESULTS:** This systematic review will provide a detailed summary of current evidences related to the efficacy of Acu-TENS in improving exercise capacity, breathlessness, quality of life, and lung function of patients with COPD. **CONCLUSION:** This evidence may be useful to clinicians, patients, and health policy makers with regard to the use of Acu-TENS in the treatment of COPD. **ETHICS AND DISSEMINATION:** This review will not gather original data; hence, ethical approval is not required. The results will be disseminated through a peer-reviewed publication or conference presentations.

Wang, K., G. Q. Zeng, et al. (2017). **"Cycle ergometer and inspiratory muscle training offer modest benefit compared with cycle ergometer alone: a comprehensive assessment in stable COPD patients."** *Int J Chron Obstruct Pulmon Dis* **12**: 2655-2668.

**BACKGROUND:** Cycle ergometer training (CET) has been shown to improve exercise performance of the quadriceps muscles in patients with COPD, and inspiratory muscle training (IMT) may improve the pressure-generating capacity of the inspiratory muscles. However, the effects of combined CET and IMT remain unclear and there is a lack of comprehensive assessment. **MATERIALS AND METHODS:** Eighty-one patients with COPD were randomly allocated to three groups: 28 received 8 weeks of CET + IMT (combined training group), 27 received 8 weeks of CET alone (CET group), and 26 only received 8 weeks of free walking (control group). Comprehensive assessment including respiratory muscle strength, exercise capacity, pulmonary function, dyspnea, quality of life, emotional status, nutritional status, and body mass index, airflow obstruction, and exercise capacity index were measured before and after the pulmonary rehabilitation program. **RESULTS:** Respiratory muscle strength, exercise

capacity, inspiratory capacity, dyspnea, quality of life, depression and anxiety, and nutritional status were all improved in the combined training and CET groups when compared with that in the control group ( $P < 0.05$ ) after pulmonary rehabilitation program. Inspiratory muscle strength increased significantly in the combined training group when compared with that in the CET group (Delta PImax [maximal inspiratory pressure]  $5.20 \pm 0.89$  cmH<sub>2</sub>O vs  $1.32 \pm 0.91$  cmH<sub>2</sub>O;  $P < 0.05$ ). However, there were no significant differences in the other indices between the two groups ( $P > 0.05$ ). Patients with weakened respiratory muscles in the combined training group derived no greater benefit than those without respiratory muscle weakness ( $P > 0.05$ ). There were no significant differences in these indices between the patients with malnutrition and normal nutrition after pulmonary rehabilitation program ( $P > 0.05$ ). **CONCLUSION:** Combined training is more effective than CET alone for increasing inspiratory muscle strength. IMT may not be useful when combined with CET in patients with weakened inspiratory muscles. Nutritional status had slight impact on the effects of pulmonary rehabilitation. A comprehensive assessment approach can be more objective to evaluate the effects of combined CET and IMT.

Wang, L., K. Hao, et al. (2017). **"Role of the Lung Microbiome in the Pathogenesis of Chronic Obstructive Pulmonary Disease."** *Chin Med J (Engl)* **130**(17): 2107-2111.

**OBJECTIVE:** The development of culture-independent techniques for microbiological analysis shows that bronchial tree is not sterile in either healthy or chronic obstructive pulmonary disease (COPD) individuals. With the advance of sequencing technologies, lung microbiome has become a new frontier for pulmonary disease research, and such advance has led to better understanding of the lung microbiome in COPD. This review aimed to summarize the recent advances in lung microbiome, its relationships with COPD, and the possible mechanisms that microbiome contributed to COPD pathogenesis. **DATA SOURCES:** Literature search was conducted using PubMed to collect all available studies concerning lung microbiome in COPD. The search terms were "microbiome" and "chronic obstructive pulmonary disease", or "microbiome" and "lung/pulmonary". **STUDY SELECTION:** The papers in English about lung microbiome or lung microbiome in COPD were selected, and the type of articles was not limited. **RESULTS:** The lung is a complex microbial ecosystem; the microbiome in lung is a collection of viable and nonviable microbiota (bacteria, viruses, and fungi) residing in the bronchial tree and parenchymal tissues, which is important for health. The following types of respiratory samples are often used to detect the lung microbiome: sputum, bronchial aspirate, bronchoalveolar lavage, and bronchial mucosa. Disordered bacterial microbiome is participated in pathogenesis of COPD; there are also dynamic changes in microbiota during COPD exacerbations. Lung microbiome may contribute to the pathogenesis of COPD by manipulating inflammatory and/or immune process. **CONCLUSIONS:** Normal lung microbiome could be useful for prophylactic or therapeutic management in COPD, and the changes of lung microbiome could also serve as biomarkers for the evaluation of COPD.



Wang, L., Y. Z. Jin, et al. (2017). **"Hemodynamic and gas exchange effects of inhaled iloprost in patients with COPD and pulmonary hypertension."** Int J Chron Obstruct Pulmon Dis **12**: 3353-3360.

Studies have shown that vasodilators such as iloprost can be useful for treating pulmonary hypertension (PH). However, in patients with COPD, vasodilators may inhibit hypoxic pulmonary vasoconstriction and impair gas exchange. The efficacy and safety of iloprost inhalation was assessed in 67 patients with PH associated with COPD (COPD-PH), diagnosed by right heart catheterization. Of these, 37 patients had severe PH (mean pulmonary arterial pressure [mPAP] >35 mmHg or mPAP 25-35 mmHg with low cardiac index [ $<2.0 \text{ Lmin}^{-1}\text{m}^{-2}$ ]). All patients received a single 20 microg dose of iloprost via a nebulizer (4.4 microg delivered at the mouthpiece). No serious adverse events were reported. Hemodynamic and gas exchange parameters (arterial blood gas and shunt fraction [Qs/Qt]) were measured or calculated at baseline and 10 min after iloprost inhalation. mPAP decreased by 2.1 mmHg (95% CI, -3.3 to -1.0), pulmonary vascular resistance (PVR) decreased by 62.4 dynscm<sup>-5</sup> (95% CI, -92.9 to -31.8), and cardiac output increased by 0.4 Lmin<sup>-1</sup> (95% CI, 0.2-0.5). There was a more significant decline in PVR in patients with severe COPD-PH than in those with nonsevere COPD-PH. Hypoxemia and intrapulmonary shunt were more extreme in patients with severe COPD-PH. However, there were no significant differences in arterial blood gas and Qs/Qt between patients with nonsevere and severe forms of COPD-PH. In conclusion, iloprost improved pulmonary hemodynamics without detrimental effects on arterial oxygenation in patients with COPD-PH, even in those with severe PH. These findings suggest that the short-term use of iloprost in patients with COPD-PH is effective and well tolerated.

Wedzicha, J. A., P. M. A. Calverley, et al. (2017). **"Prevention of COPD exacerbations: a European Respiratory Society/American Thoracic Society guideline."** Eur Respir J **50**(3) This document provides clinical recommendations for the prevention of chronic obstructive pulmonary disease (COPD) exacerbations. It represents a collaborative effort between the European Respiratory Society and the American Thoracic Society. Comprehensive evidence syntheses were performed to summarise all available evidence relevant to the Task Force's questions. The evidence was appraised using the Grading of Recommendations, Assessment, Development and Evaluation approach and the results were summarised in evidence profiles. The evidence syntheses were discussed and recommendations formulated by a multidisciplinary Task Force of COPD experts. After considering the balance of desirable (benefits) and undesirable consequences (burden in the form of adverse effects and cost), quality of evidence, feasibility, and acceptability of various interventions, the Task Force made recommendations for mucolytic, long-acting muscarinic antagonist,

phosphodiesterase-4 inhibitor (roflumilast) and macrolide therapy, as well as a conditional recommendation against fluoroquinolone therapy. All of the recommendations were conditional, except for a strong recommendation for the use of a long-acting antimuscarinic agent versus a long-acting beta2-adrenergic, indicating that there was uncertainty about the balance of desirable and undesirable consequences of the intervention, and that well-informed patients may make different choices regarding whether to have or not have the specific intervention. The guideline summarises the evidence and provides recommendations for pharmacological therapy for the prevention of COPD exacerbations.

Widyastuti, K., D. N. Makhabah, et al. (2018). **"Benefits and costs of home pedometer assisted physical activity in patients with COPD. A preliminary randomized controlled trial."** *Pulmonology* **24**(4): 211-218.

**BACKGROUND AND OBJECTIVE:** There are barriers to providing pulmonary rehabilitation for chronic obstructive pulmonary disease (COPD) such as the high number of patients, difficult access to health facilities and high costs of programs. Pedometers can monitor and improve physical activity (PA). The aim of this study was to evaluate benefits and costs of home pedometer assisted PA, as compared to a standard outpatient supervised exercise training program in patients with COPD. **METHODS:** Patients were randomly assigned either to home pedometer assisted PA (Group 1), or to a six-week outpatient standard supervised exercise training program (Group 2). Patients of Group 1 had to walk at home for 6 weeks, at least 30min daily at the fastest step pace as possible, to achieve a weekly 10% increase in their average daily steps up to more than 6500. Pre and post programs we assessed: the six minute walking distance (6MWT: primary outcome), daily steps count, the Medical Research Council scale (MRC), the COPD assessment test score, and the BODE index (body-mass index, airflow obstruction, dyspnea, exercise capacity). Costs of programs were also evaluated. **RESULTS:** Out of 40 patients, 18 in both groups (mean (standard deviation)) age: 68.3 (6.7) and 61.2 (6.7) years; FEV1: 1.1 (0.5) and 0.9 (0.4) liters in Group 1 and 2 respectively completed the study. At the end of the program 44.5% patients of Group 1 had reached the target daily steps, in 26.6 (9.5) days. Following the programs, both groups showed significant improvements in all outcome measures, except BODE. The home program was cheaper ( $p=0.0001$ ), with a mean 76.3 euros saving per patient. **CONCLUSION:** Home pedometer assisted PA may be a useful and cheaper alternative to outpatient supervised exercise training programs in patients with COPD.

Xaubet, A., M. Molina-Molina, et al. (2017). **"Guidelines for the medical treatment of idiopathic pulmonary fibrosis."** *Arch Bronconeumol* **53**(5): 263-269.

Idiopathic pulmonary fibrosis is defined as chronic fibrosing interstitial pneumonia limited to the lung, with poor prognosis. The incidence has been rising in recent years probably due to improved diagnostic methods and increased life expectancy. In 2013, the SEPAR guidelines for the diagnosis and treatment for idiopathic pulmonary fibrosis were published. Since then, clinical trials and meta-analyses have shown strong scientific evidence for the use of pirfenidone and nintedanib in the treatment of idiopathic pulmonary fibrosis. In 2015, the international consensus of 2011 was updated and new therapeutic recommendations were established, prompting us to update our recommendation for the medical treatment of idiopathic pulmonary fibrosis accordingly. Diagnostic aspects and non-pharmacological treatment will not be discussed as no relevant developments have emerged since the 2013 guidelines.

Zeiger, R. S., T. N. Tran, et al. (2018). **"Relationship of Blood Eosinophil Count to Exacerbations in Chronic Obstructive Pulmonary Disease."** J Allergy Clin Immunol Pract 6(3): 944-954.e5.

**BACKGROUND:** Eosinophilic airway inflammation characterizes a chronic obstructive pulmonary disease (COPD) phenotype that requires more study. **OBJECTIVE:** To investigate the relationship of blood eosinophil count to exacerbations in COPD. **METHODS:** Using administrative pharmacy and health care utilization data from 2009 to 2012, we retrospectively identified patients 40 years or older with a COPD diagnosis, postbronchodilator FEV1/forced vital capacity ratio of less than 0.7, and a blood eosinophil count (N = 7,245). COPD exacerbations were defined as hospitalizations or emergency department visits with a primary diagnosis of COPD, or outpatient visits with systemic corticosteroid dispensing within +/-14 days associated with an encounter code consistent with a COPD exacerbation. The relationship between the index blood eosinophil count and the rate of COPD exacerbations in the follow-up year was determined by multivariable analyses. **RESULTS:** Patients with COPD were predominantly male (57.1%), white (71.8%), often current or past smokers (75.4%), and had frequent comorbidities; 19.0% had eosinophil counts of greater than or equal to 300 cells/mm<sup>3</sup>, 76.1% were classified as moderate to very severe by lung function, and the COPD exacerbation rate was 0.38 per year (95% CI, 0.37-0.40). After adjustment for potential confounders, COPD exacerbations during 1-year follow-up were significantly greater for patients with blood eosinophil counts of greater than or equal to 300 cells/mm<sup>3</sup> (rate ratio [RR], 1.25; 95% CI, 1.10-1.43), greater than or equal to 400 cells/mm<sup>3</sup> (RR, 1.48; 95% CI, 1.26-1.75), and greater than or equal to 500 cells/mm<sup>3</sup> (RR, 1.76; 95% CI, 1.45-2.14), respectively, compared with patients with eosinophils lower than the cutoffs. **CONCLUSIONS:** In this study, high blood eosinophil counts were an independent risk factor for future exacerbations in patients with COPD, a phenotype that might benefit from therapy directed at eosinophilic-driven disease and inflammation.

Zhang, Y., R. L. Morgan, et al. (2018). "**A systematic review of how patients value COPD outcomes.**" *Eur Respir J* **52**(1) Our objective was to summarise systematically all research evidence related to how patients value outcomes in chronic obstructive pulmonary disease (COPD). We conducted a systematic review (systematic review registration number CRD42015015206) by searching PubMed, Embase, PsycInfo and CINAHL, and included reports that assessed the relative importance of outcomes from COPD patients' perspective. Two authors independently determined the eligibility of studies, abstracted the eligible studies and assessed risk of bias. We narratively summarised eligible studies, meta-analysed utilities for individual outcomes and assessed the certainty of evidence using the Grading of Recommendations, Assessment, Development and Evaluations approach. We included 217 quantitative studies. Investigators most commonly used utility measurements of outcomes (n=136), discrete choice exercises (n=13), probability trade-off (n=4) and forced choice techniques (n=46). Patients rated adverse events as important but on average, less so than symptom relief. Exacerbation and hospitalisation due to exacerbation are the outcomes that COPD patients rate as most important. This systematic review provides a comprehensive registry of related studies.

Zhang, Z., J. Wang, et al. (2018). "**Exposure to nitrogen dioxide and chronic obstructive pulmonary disease (COPD) in adults: a systematic review and meta-analysis.**" *Environ Sci Pollut Res Int* **25**(15): 15133-15145.

Exposure to nitrogen dioxide (NO<sub>2</sub>) has long been linked to elevated mortality and morbidity from epidemiological evidences. However, questions remain unclear whether NO<sub>2</sub> acts directly on human health or being an indicator of other ambient pollutants. In this study, random-effect meta-analyses were performed on examining exposure to nitrogen oxide (NO<sub>x</sub>) and its association with chronic obstructive pulmonary disease (COPD). The overall relative risk (RR) of COPD risk related to a 10 µg/m<sup>3</sup> increase in NO<sub>2</sub> exposure increased by 2.0%. The pooled effect on prevalence was 17% with an increase of 10 µg/m<sup>3</sup> in NO<sub>2</sub> concentration, and 1.3% on hospital admissions, and 2.6% on mortality. The RR of COPD cases related to NO<sub>2</sub> long-term exposure was 2.5 and 1.4% in short-term exposure. The COPD effect related with a 10 µg/m<sup>3</sup> increase in exposure to a general outdoor-sourced NO<sub>2</sub> was 1.7 and 17.8% to exposure to an exclusively traffic-sourced NO<sub>2</sub>; importantly, we did observe the effect of NO<sub>2</sub> on COPD mortality with a large majority in lag0. Long-term traffic exerted more severe impairments on COPD prevalence than long-term or short-term outdoor effect; long-term mortality effect on COPD was serious in single model from this meta-analysis. Overall, our study reported consistent evidence of the potential positive association between NO<sub>2</sub> and COPD risk.

Zhu, S., K. Shi, et al. (2018). **"A modified 6-form Tai Chi for patients with COPD."**  
Complement Ther Med **39**: 36-42.

**BACKGROUND AND OBJECTIVE:** 24-form Tai Chi is a traditional exercise popular among old people in China, but it has some complex movements beyond of capabilities of patients with COPD. This study was to modify and simplify 24-form Tai Chi and evaluate effects of the modified Tai Chi on lung function, exercise capacity, dyspnea symptom and health status in patients with COPD.

**METHODS:** A two-step procedure was applied: an initial qualitative research module consisting of focus group discussion, expert consultation and patient interviews was conducted to simplified and modified 24-form Tai Chi for patients with COPD. Then, a randomized controlled trial consisting of 60 patients with II to IV COPD was conducted to evaluate effects of the modified Tai Chi on lung function (FEV1%), exercise capacity (Six minutes walking distance, 6MWD), dyspnea symptom (Modified Medical Research Council Scale, mMRC) and health status (COPD Assessment Test, CAT). All measures were obtained at baseline, 3-month follow-up and 9-month follow-up. **RESULTS:** A new simpler 6-form Tai Chi that combining characteristics of COPD, the experts' wisdom and patients' needs was developed. Patients with COPD can grasp it in about 3h and participants showed 86.0% adherence to the Tai Chi training and no negative accidents occurred. Generalized estimating equations (GEE) showed that there were significant differences in FEV1%, 6MWD and CAT scores between modified Tai Chi (MTC) group and the control group over time (model group $\times$ time interaction  $\chi^2=13.68$ ,  $P<0.001$ ;  $\chi^2=192.39$ ,  $P<0.001$ ;  $\chi^2=6.05$ ,  $P=0.014$ , respectively), however, no statistical significance in mMRC scores was found between the 2 groups over time (model group $\times$ time interaction  $\chi^2=3.54$ ,  $P=0.06$ ). The baseline of FEV1%, 6MWD, mMRC scores and CAT scores are significant covariates for lung function, exercise capacity, dyspnea symptom and health status, respectively ( $\chi^2=149.43$ ,  $P<0.001$ ;  $\chi^2=5.78$ ,  $P=0.016$ ;  $\chi^2=66.71$ ,  $P<0.001$ ;  $\chi^2=81.83$ ,  $P<0.001$ , respectively). **CONCLUSIONS:** This modified 6-form Tai Chi routine is easy to grasp, easy to adhere to, safe to practice and effective to improve lung function, exercise capacity, health status and to prevent dyspnea symptom from getting worse for patients with COPD and it can be recommended as a suitable exercise therapy for them.