Welcome to the latest issue of COPD Research Review.

Highlights include evidence of the safety of cardioselective beta-blockers during acute exacerbations of COPD, a report of the benefits of tiotropium in early-stage COPD, and Canadian findings that statins may decrease lung-related and all-cause mortality in patients with COPD. Japanese investigators report that plasma levels of growth differentiation factor 11 (an anti-ageing factor) are decreased in COPD patients, and researchers in England report that neither bupropion nor varenicline cause adverse cardiovascular or neuropsychiatric events in smokers with COPD.

We hope you find these and the other selected studies interesting and welcome any feedback you may have.

Kind Regards,
Dr Philip Lee
philip.lee@researchreview.com.au

In this issue:

> Cardioselective beta-blockers are safe during acute exacerbations
> Tiotropium in early-stage COPD
> Statins and mortality in COPD
> COPD patients have lower growth differentiation factor 11 levels
> Cardiovascular and neuropsychiatric safety of varenicline and bupropion
> Seasonal dynamics of airway pathogens
> Treating breathlessness via the brain
> Why is triple therapy used in newly diagnosed patients?
> Self-management behaviours that reduce exacerbation impact
> Obesity and acute exacerbations

Abbreviations used in this issue:

COPD = chronic obstructive pulmonary disease
FEV₁ = forced expiratory volume in 1s
GOLD = Global Initiative for Chronic Obstructive Lung Disease
HR = hazard ratio
ICS = inhaled corticosteroid
LABA = long-acting beta-agonist
LAMA = long-acting muscarinic antagonist

Abstract

Commencement of cardioselective beta-blockers during hospitalisation for acute exacerbations of chronic obstructive pulmonary disease

Authors: Neef P et al.

Summary: This retrospective Australian study determined the safety of starting cardioselective beta-blocker therapy in patients hospitalised with acute exacerbation of COPD. Outcomes were reviewed for 1071 COPD patients with acute exacerbation; 36 of whom started beta-blocker therapy upon admission. The most common indications for starting beta-blockers were atrial fibrillation (53%) and acute coronary syndrome (36%). Metoprolol was the most commonly prescribed beta-blocker (75%). None of the patients had significant declines in respiratory function after starting a beta-blocker. One patient (2.8%) had symptomatic hypotension after 48h of therapy.

Comment: Previous studies showed that cardioselective beta-blockers are safe to use in COPD. Meta-analysis has also demonstrated that cardioselective beta-blockers do not result in a significant change in FEV₁, or respiratory symptoms when compared to placebo in COPD. This Australian retrospective analysis found no significant adverse respiratory events in association with the introduction of cardioselective beta-blockers in acute COPD exacerbations. Beta-blockers have a proven mortality benefit in various cardiovascular diseases including hypertension, heart failure and coronary artery disease. They should not be withheld during hospital admission for acute COPD exacerbation.

Abstract

Tiotropium in early-stage chronic obstructive pulmonary disease

Authors: Zhou Y et al.

Summary: This study in China investigated the effects of tiotropium on lung function in patients with mild to moderate COPD. 841 patients with GOLD stage 1 (mild) or 2 (moderate) COPD were randomised in a double-blind design to receive a once-daily inhaled dose of tiotropium 18µg or matching placebo for 2 years. The primary end-point was the between-group difference in the change from baseline to 24 months in FEV₁, before bronchodilator use. FEV₁ in the tiotropium group was higher than that in the placebo group throughout the trial (ranges of mean differences: 127–169ml before bronchodilator use and 71–133ml after bronchodilator use; all p<0.001). There was no significant amelioration in the mean annual decline in FEV₁ before bronchodilator use, but the annual decline in FEV₁ after bronchodilator use was 22ml per year lower in the tiotropium group than in the placebo group (p=0.006).

Comment: COPD pharmacotherapy is guided by GOLD stage and symptom burden. Whilst short-acting bronchodilators are commonly prescribed in mild to moderate COPD, most symptomatic patients could benefit from maintenance therapy in the form of LAMA/LABA. Previous small studies/subgroup analyses have shown that tiotropium (LAMA) could result in lung function improvement in COPD GOLD stage 1 and early stage 2. This Chinese randomised controlled trial involved patients with mild-moderate COPD (GOLD stage 1/2). It showed tiotropium improved lung function (assessed by annual FEV₁ decline) and quality of life and reduced acute COPD exacerbations when compared with placebo. Future studies should examine if early intervention with maintenance therapy could reduce hospitalisation/mortality in COPD.

Abstract
The impact of statin drug use on all-cause mortality in patients with COPD

Authors: Raymakers A et al.

Summary: This population-based Canadian cohort study evaluated the impact of statin drug use on all-cause and lung-related mortality in patients with COPD. 39,678 patients with COPD were included. 7,775 (19.6%) of them had received at least 1 statin in the first year after COPD diagnosis. Multivariate analysis showed that statins decreased the risk of all-cause mortality by 21% (estimated HR, 0.79; p=0.0016), and the risk of lung-related mortality by 45% (HR, 0.55; p=0.0025).

Comment: Statin use in COPD remains controversial due to a lack of therapeutic benefits in prospective clinical trials. This Canadian population study (39,678 patients) found reduced risk of all cause/respiratory-related mortality with statin therapy. However, the criteria of COPD was not well defined, leading to potential inclusion of patients with adult-onset asthma and other non-respiratory conditions which necessitate new prescriptions of a short-acting inhaled bronchodilator in patients older than 50 years. Identification of appropriate COPD phenotype benefiting from statin therapy would be important. A recent meta-analysis suggested statin use in COPD patients with hyperlipidaemia, concomitant cardiovascular disease/systemic inflammation could improve lung function and exercise tolerance.

Reference: Chest 2017;152(3):486-93

Decrease in an anti-ageing factor, growth differentiation factor 11, in chronic obstructive pulmonary disease

Authors: Onodera K et al.

Summary: This Japanese study measured plasma levels of growth differentiation factor 11 (GDF11) in patients with COPD, and elucidated the possible role of GDF11 in cellular senescence. Western blot analysis revealed that plasma levels of GDF11 were lower in patients with COPD than in controls, and were significantly correlated with pulmonary function data. mRNA expression of GDF11 was decreased in mesenchymal cells from COPD patients compared with controls. Chronic exposure to cigarette smoke extract (CSE) decreased the production of GDF11. Treatment with GDF11 significantly inhibited CSE-induced cellular senescence and upregulation of inflammatory mediators in vitro. Daily treatment with GDF11 attenuated cellular senescence and airspace enlargement in a mouse model of emphysema.

Comment: Smoking cessation is the most significant intervention to reduce the risk of developing COPD. However, despite reduction of cigarette consumption in developed countries via public health campaigns, prevalence and mortality of COPD remains high. The role of senescence has been suggested with approximately 10% of lifelong non-smokers developing COPD by the age of 75. Previous studies have shown premature emphysematous changes in animal models suggestive of accelerated ageing process in COPD. GDF11 is a circulating protein with a postulated role in anti-ageing. This Japanese molecular study showed a protective effect of GDF11 in cellular senescence. More importantly, cigarette smoke exposure may lead to reduced GDF11 production. Cigarette smoking may result in cellular senescence which in turn induces dampened cellular protective mechanisms. This process could ultimately lead to development of COPD in susceptible individuals.

Reference: Thorax 2017;72(10):905-11

Cardiovascular and neuropsychiatric risks of varenicline and bupropion in smokers with chronic obstructive pulmonary disease

Authors: Kotz D et al.

Summary: This retrospective cohort study investigated whether varenicline and bupropion have adverse cardiovascular and neuropsychiatric effects in smokers with COPD. 10,426 patients with COPD across England who received a prescription for nicotine replacement therapy (n=10,426), bupropion (n=350) or varenicline (n=3574) in 2007–2012 were followed up for 6 months to compare incident cardiovascular and neuropsychiatric events. Neither bupropion nor varenicline were associated with an increase in adverse events compared with nicotine replacement therapy. In addition, varenicline reduced the risk of heart failure (HR, 0.56) and depression (HR, 0.73) compared with nicotine replacement therapy.

Comment: Pharmacotherapy including varenicline and bupropion is used to assist smokers in achieving abstinence from cigarette smoking. Concerns are raised with regards to the potential cardiovascular and neuropsychiatric adverse events arising from varenicline and bupropion treatment, including ischaemic heart disease, cerebral infarction, heart failure, arrhythmia, depression and self-harm. This retrospective cohort study found no association between varenicline and bupropion use in smoking cessation and the above-mentioned adverse events. Interestingly, it also showed varenicline was associated with a significantly reduced risk of heart failure. Such findings are in keeping with previous studies on safety of varenicline and bupropion, supporting a broader use in patients with cardiovascular and neuropsychiatric diseases.

Reference: Thorax 2017;72(10):893-904

NEW INDICATION

BIG NEWS IN COPD

ULTIBRO® BREEZHALER®
110/50 is the only LABA/LAMA indicated for the reduction of exacerbations

PBS Information: Authority required (STREAMLINED). Chronic obstructive pulmonary disease (COPD). Refer to PBS Schedule for full authority information.

STREAMLINED AUTHORITY CODE 5763. PLEASE REVIEW PRODUCT INFORMATION BEFORE PRESCRIBING. APPROVED PRODUCT INFORMATION IS AVAILABLE BY CLICKING HERE.


Novartis Pharmaceuticals Pty Limited. 54 Waterloo Road, Macquarie Park NSW 2113. Ph (02) 9805 3555. For medical enquiries please contact 1800 671 203 (phone) or medinfo.phauno@novartis.com (email). ®Registered Trademark. AU-3439. NOV3525a. Prepared September 2017.

www.researchreview.com.au a RESEARCH REVIEW publication
A prospective, observational cohort study of the seasonal dynamics of airway pathogens in the aetiology of exacerbations in COPD

Authors: Wilkinson T et al., on behalf of the AERIS Study Group

Summary: This observational study evaluated the seasonal dynamics of airway pathogens in the aetiology of acute exacerbations of COPD. Over a 1-year period, patients with COPD provided sputum samples for analysis of pathogens at monthly intervals and at the time of exacerbations. The mean exacerbation rate per patient-year was 3.04. The most common bacterial species found at the time of exacerbations were non-typeable Haemophilus influenzae (NTHi) and Moraxella catarrhalis, and the most common virus was rhinovirus. Logistic regression analyses showed increased risk for acute exacerbations when M. catarrhalis was detected regardless of season (odds ratio [OR], 5.09). When NTHi was detected, the increased risk of exacerbation was greater in high season (OR, 3.04) than low season (OR, 1.22). Bacterial and viral co-infection was more common at exacerbation (24.9%) than stable state (8.6%). A significant association was found between NTHi and rhinovirus presence and risk of exacerbation (OR, 5.18; p=0.031).

Comment: Viral and bacterial infections play an important role in triggering and modifying the severity of acute COPD exacerbations. The airway microbiology has been a focus for COPD research with abnormal microbial pattern identified in COPD. Microbial dysbiosis may induce airway inflammation and increase the risk of COPD exacerbations. This prospective, observational cohort study found changes in lung microbiome due to the seasonal effects of viral and bacterial infections may account for the increased incidence of COPD exacerbations during winter. COPD patients are susceptible to the adverse effects of viral and bacterial respiratory tract infections. Microbial dysbiosis and recurrent exacerbations would eventually lead to irreversible loss of lung function and worse clinical outcomes.

Reference: Thorax 2017;72(10):919-27

Treating breathlessness via the brain: changes in brain activity over a course of pulmonary rehabilitation

Authors: Herigstad M et al.

Summary: This study investigated the impact of pulmonary rehabilitation (PR) on neural responses to breathlessness. 31 patients with COPD had brain activity measured by functional magnetic resonance imaging (fMRI) during a breathlessness-related word-cue task before and after PR. Changes in ratings of breathlessness word cues positively correlated with changes in insula and anterior cingulate cortex activity; whereas changes in ratings of breathlessness-anxiety negatively correlated with activations in attention regulation and motor networks. Baseline activity in the insula, anterior cingulate cortex and prefrontal cortex correlated with improvements in breathlessness and breathlessness-anxiety.

Comment: Breathlessness is highly anxiety-provoking amongst COPD patients. Sensory perception of breathlessness could be significantly disproportional to the underlying COPD severity. PR should be offered to COPD patients with exertional dyspnoea. This UK study used functional MRI to analyse neural responses in COPD patients before and after completion of an outpatient PR. It found improved expectations of breathlessness and symptom-related anxiety amongst patients completing PR with parallel changes in the respective brain network responses. Future research should focus on identifying the neural pathway/mechanisms responsible for the linkage between breathlessness and anxious expectations in COPD.

Reference: Eur Respir J 2017, published online Sep 12

Characteristics of newly diagnosed COPD patients treated with triple inhaled therapy by general practitioners

Authors: Di Marco F et al.

Summary: This real world Italian study determined the predictors of triple therapy use in newly diagnosed COPD patients in primary care. 32,046 patients were included. In the 2 years prior to diagnosis, fewer than 13% of patients were evaluated by a pulmonologist and <5% underwent spirometry; 65.1% were prescribed a respiratory drug (6.6% received an ICS/LABA fixed-dose combination), 2028 patients (6.3%) were treated with triple therapy during the first year of follow-up; 858 (42.3%) started immediately and 762 (37.6%) started after initial treatment with an ICS/LABA fixed-dose combination. Independent predictors of triple therapy use were older age, pulmonologist evaluation or spirometry testing, and being prescribed an ICS/LABA combination at diagnosis.

Comment: The 2017 GOLD guidelines recommend ICS as add-on therapy in COPD patients who continue to suffer from exacerbations despite LAMA/LABA therapy. Triple therapy (ICS/LAMA/LABA) should be used in COPD patients at high risk of exacerbations with at least 2 exacerbations (or 1 hospitalisation) in the preceding 12 months. The COPD-X guidelines also support the use of triple therapy in moderate to severe COPD patients with frequent exacerbations (FEV<50%, predicted and ≥2 exacerbations in 12 months) with ICS as an add-on therapy to LAMA and LABA therapy. This Italian study analysed the characteristics of COPD patients receiving triple therapy in the primary care setting. It found 6% of newly diagnosed COPD patients were receiving triple therapy with 42% of them proceeding to such treatment immediately after the diagnosis was made. Interestingly, initial prescription with ICS/LABA combination treatment was an independent predictor of triple therapy use. Despite the proven benefits of ICS in reducing exacerbations and improving quality of life/lung function, vigilant use of triple therapy should be advocated in view of the potential risks associated with ICS.

Reference: NPJ Prim Care Respir Med 2017; published online Sep 7

Independent commentary by Dr Philip Lee, MBBS (Hons) FRACP.

Dr Philip Lee is a Respiratory and Sleep Physician currently working at the St. George Hospital Centre for Sleep Disorders & Respiratory Failure in Sydney. His research interests include non-invasive ventilation, respiratory failure and sleep disordered breathing.
Impact of overweight and obesity on acute exacerbations of COPD

Authors: Wei Y-F et al., on behalf of the TOLD Study Group

Summary: This subgroup analysis of the Taiwan Obstructive Lung Disease cohort examined whether a high body mass index (BMI) is associated with frequent exacerbations in Taiwanese patients with COPD. Among the whole study cohort (n=1096), 67.1% of patients had no exacerbations and 13.5% were frequent exacerbators in the previous year. BMI values of patients with 0, 1, and ≥2 exacerbations were 23.6, 23.5, and 22.6 kg/m², respectively. 23.4% of patients were overweight (BMI 24–27 kg/m²) and 17.9% were obese (>27 kg/m²). After adjustment for confounding factors, overweight (odds ratio, 0.49) and obesity (odds ratio, 0.49) were both significantly associated with a decreased frequency of exacerbations.

Comment: The “obesity-survival paradox” has been described in COPD. It is postulated that obesity may have a positive impact on COPD survival. It is generally agreed that underweight/cachexia is associated with poor prognosis in COPD with studies identifying better long-term survival in overweight COPD patients. This subgroup analysis of 1096 COPD patients in Taiwan found high BMI (overweight/obese) was associated with a lower risk of COPD exacerbations. However, BMI may not be the most appropriate surrogate marker. Future research should focus on analysis via fat-free mass which could better reflect the underlying nutritional status of COPD patients.


Abstract

Self-management behaviors to reduce exacerbation impact in COPD patients

Authors: Korpershoek Y et al.

Summary: This Delphi study determined which self-management behaviours have the highest potential for influencing exacerbation impact in patients with COPD. An international expert panel was asked to rate the relevance and feasibility of predetermined self-management behaviours. The panel reached consensus on 17 self-management behaviours for reducing exacerbation impact in COPD: 5 during stable phase, 1 during symptom deterioration, 5 during an exacerbation, 4 during recovery, and 2 after recovery.

Comment: Studies have found improved outcomes in COPD patients who took appropriate responsibility for their own management. Self-management interventions are advocated in COPD-X guidelines, and are a structured intervention that aims to improve self-management health behaviours and skills. Systematic reviews showed self-management interventions reduced hospital admissions with improvement in health-related quality of life. Based on consensus within an international expert panel, this study identified 17 self-management behaviours that can be targeted to reduce the impact of COPD exacerbation. They should be performed before, during and after the exacerbation. Self-management interventions should be extended to COPD patients in primary care with appropriate written action plans.


Abstract

ONE LABA/LAMA STANDS ALONE™

† THE ONLY LABA/LAMA INDICATED FOR REDUCTION OF EXACERBATIONS IN COPD™