

Respiratory Research Review™

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Issue 149 – 2018

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Abbreviations used in this issue

COPD = chronic obstructive pulmonary disease
FEV₁ = forced expiratory volume in 1 sec
FVC = forced vital capacity
GOLD = Global Initiative for Chronic Obstructive Lung Disease
ICS = inhaled corticosteroid
LABA = long-acting β -agonist
LAMA = long-acting muscarinic antagonist

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Welcome to this Respiratory Research Review mid-winter selection on the topic of COPD.

The number of articles relevant to this review is huge. The quality and breadth of research is refreshing and it is good to see that NZ colleagues are among the esteemed authors.

The Global Initiative for Chronic Obstructive Lung Disease, GOLD COPD, (<http://goldcopd.org/>) has established itself as a strategic document since 2001. It has been updated in 2018 to account for new emerging evidence; however, the last major update was in 2017. Prior to 2017, the severity of airflow obstruction was taken into account when assessing the severity of COPD. Since 2017, spirometry remains a crucial diagnostic step in the management of COPD; however, the severity is assessed in two ways: a) symptoms of breathlessness assessed via the modified MRC score or the CAT (COPD Assessment Tool); and b) the exacerbation history assessed by number of hospital admissions. Biologically this is sensible, as shortness of breath and exacerbation rates are two biological biomarkers that respond to treatment with either bronchodilators or ICSs. Carlos López and colleagues review the impact of the classification change in their [paper](#) using two well-described cohorts from Spain and the US. According to the 2017 symptom-based GOLD classification, almost 80% of patients are in COPD GOLD groups A and B and should be offered bronchodilators only. Less than 20% are in groups C and D, where ICSs could be considered. We are reviewing a [paper](#) from Dunedin that suggests that this doesn't reflect our current prescribing reality; the most commonly prescribed therapy for COPD appears to be ICSs and LABAs.

'Should an attempt be made to withdraw inhaled corticosteroids in all patients with stable GOLD 3 (30% \leq FEV₁ < 50% predicted) COPD?' is the title of a [debate](#) between James Chambers and Ian Pavord in Chest. This is my pick of reading for a journal club or in-service – the language is beautiful, the manners impeccable and the information density brilliant – and at the end a consensus appears to be emerging between the two specialists that ICSs may have a role in COPD patients with frequent exacerbations, particularly if the blood eosinophil count were to be raised. Some 'minor' quibbles need addressing, like the optimal cutoff for the eosinophil count; however, both are optimistic that one can move away from a 'one size fits all' to a more biomarker-directed approach, in which some patients (perhaps 20%) may benefit from ICSs.

Hopefully, you enjoy the selection of articles in this review. Of the many articles that we couldn't include, I'd like to draw your attention to two: one is a [research letter](#) from France expressing concern about the level of training in respiratory physiology and interpretation of pulmonary lung function tests; the other [article](#) is on the physiological effects of high-flow nasal cannula in acute hypoxaemic respiratory failure, with the outstanding [editorial](#) by Ewan Goligher and Arthur Slutsky, with the best graphic summary of possible mechanism of high-flow humidified nasal cannula treatment I have seen.

We are looking forward to your comments and feedback.

Kind regards

Professor Lutz Beckert

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Independent commentary by Professor Lutz Beckert.

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Smoking duration alone provides stronger risk estimates of chronic obstructive pulmonary disease than pack-years

Authors: Bhatt SP et al., on behalf of the COPDGene Investigators

Summary: This analysis of cross-sectional data from the COPDGene cohort of 10,187 current and former smokers sought to establish the contribution of cigarettes smoked per day versus duration on the development of structural lung disease. The authors analyses of adjusted means of outcomes by categories of pack-years and combined groups of categorised smoking duration and cigarettes per day, and their estimates of linear trends of adjusted means for each outcome by categorised cigarettes per day, smoking duration and pack-years, suggested that smoking duration alone was better for estimating COPD risk than the composite index of pack-years.

Comment: All of us may have had problems calculating a pack-year history, and once we have managed it, we have problems explaining it to our patients. Findings from this study based on more than 10,000 participants suggest that the associations between smoking duration and clinical outcomes, like FEV₁, 6-minute walk distance, diagnosis of emphysema and quality of life, are just as strong as the associations with pack-year history of smoking. Smoking duration was the strongest predictor of the reduction of the FEV₁/FVC ratio. **Bottom line: smoking duration, rather than the pack-year history, may be an equally strong or stronger predictor of smoking-related illnesses.**

Reference: *Thorax* 2018;73:414–21

[Abstract](#)

Smoking prevalence among doctors and nurses – 2013 New Zealand census data

Authors: Edwards R et al.

Summary: The 2013 New Zealand census included 7065 male and 5619 female doctors, and 2988 male and 36,138 female nurses; 2% of male and female doctors and 9% of male and 8% of female nurses were regular cigarette smokers. Corresponding rates in the 2006 census were all higher: 4% of male and 3% of female doctors were regular cigarette smokers, as were 20% of male and 13% of female nurses. In the 2013 census, psychiatric nurses had the highest smoking prevalence (15% male, 18% female). Smoking was more common among Māori doctors (6.8%) and nurses (19.3%). Around 96% of young (age <25 years) doctors and 87% of young nurses had never been regular smokers.


Comment: Finally, some good news about smoking. Richard Edwards and colleagues report in *N Z Med J* the results of the recent census data on health professionals and smoking. Smoking prevalence amongst 13,000 doctors was extremely low, with only 2% of doctors smoking – 3.4% of physicians and 6.7% of obstetricians and gynaecologists currently smoke; however, 90% of doctors aged less than 45 years have never smoked. The smoking rate of almost 40,000 nurses is about 8% and the highest smoking rate is amongst psychiatric nurses.

Bottom line: doctors are now a virtually smoke-free professional group and nurses are likely to reach this target by 2025.

Reference: *N Z Med J* 2018;131(1471):48–57

[Abstract](#)

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 Time spent reading this publication has been approved for CNE by The College of Nurses Aotearoa (NZ) for RNs and NPs. For more information on how to claim CNE hours please [CLICK HERE](#).

The health, poverty, and financial consequences of a cigarette price increase among 500 million male smokers in 13 middle income countries

Authors: Global Tobacco Economics Consortium

Summary: The impact of a 50% increase in the market price of cigarettes on health, poverty and financial protection was explored in this compartmental model study with a setting of 2 billion men from 13 middle-income countries, of whom 500 million were smokers. The modelling found that smoking cessation resulting from the 50% increase in cigarette prices would see around 450 million years of life gained across the 13 countries, with half of these in China. Compared with the richest 20% of the population, the poorest 20% had the most to gain from the increased price of cigarettes in terms of both health and finances.

Comment: The clarity of thinking in this article and the accompanying [editorial](#) is refreshing. Would you like to save 450 million life-years? Increase tobacco taxes by 50%, which is an average increase of US\$1.70 in middle-income countries. Using mathematical modelling, the Global Tobacco Economics Consortium argues that men in middle-income countries have the most to gain. High cigarette price is a powerful behaviour modifier to reduce nicotine addiction; less smoking reduced the risk of second-hand smoke exposure and it saves governments from sky-rocking future health costs. **Bottom line: people on low incomes have the most to gain from increased tobacco taxes.**

Reference: *BMJ* 2018;361:k1162

[Abstract](#)

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References: 1. Feldman G.J et al. *Adv Ther* 2017; 34:doi 10.1007/s12325-017-0626-4. Anoro® Ellipta® (umeclidinium bromide/vilanterol trifenatate inhaler 62.5/25mcg per inhalation) is a fully funded Prescription Medicine for the regular treatment of COPD - Special Authority Criteria apply. Anoro® has risks and benefits. GlaxoSmithKline NZ Ltd Auckland. Spiolto® is a registered trademark of Boehringer Ingelheim TAPS DA1852JS/18JU/UCV/0009/18

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Patterns of use of long-acting bronchodilators in patients with COPD

Authors: Parkin L et al.

Summary: Treatment patterns in new long-acting bronchodilator users were explored in this NZ research, which involved the analysis of national health and pharmaceutical dispensing data to identify 83,435 patients aged ≥ 45 years who started LABA and/or LAMA therapy for COPD between February 2006 and December 2013. Over 290,400 person-years of follow-up, a LABA with an ICS was the regimen that was most often initiated. The median first-regimen duration was 46 days, in many instances patients used multiple regimens over time, and periods of nonuse were common. Moreover, it was noted that ICS use was inconsistent with international guidelines, with over-treatment of patients with infrequent exacerbations and under-treatment in those with frequent exacerbations noted, as well as common use of ICS monotherapy.

Comment: This study has been performed by our colleagues in Dunedin. As outlined in the introduction, they also start with the 2017 GOLD COPD guidelines, which suggest that ICSs are only indicated for a small number of patients with COPD with a history of frequent exacerbations. They identified more than 80,000 patients who have been prescribed medications for COPD. In contrary to what is expected from the guidelines, the authors identified the most commonly prescribed regimen was a combination of an ICS and a LABA. **Bottom line: prescribing of ICSs/LABAs does not align with the GOLD COPD guidelines.**

Reference: *Respirology* 2018;23:583–92

[Abstract](#)

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Predictors of exacerbation risk and response to budesonide in patients with chronic obstructive pulmonary disease

Authors: Bafadhel M et al.

Summary: These researchers conducted a *post hoc* analysis, of data from three randomised controlled trials of budesonide-formoterol, in which eosinophil count was modelled as a continuous variable to identify characteristics that determine both exacerbation risk and clinical response to ICSs in 1528 patients with COPD. The increase in exacerbations with increasing eosinophil count was nonlinear for participants who received formoterol alone. At eosinophil counts of $\geq 0.10 \times 10^9$ cells/L, a significant treatment effect was seen for fewer exacerbations with budesonide-formoterol versus formoterol alone (rate ratio 0.75 [95% CI 0.57, 0.99]; $p=0.015$ for interaction). There were also significant interactions seen between eosinophil count and the treatment effects of budesonide-formoterol versus formoterol on St George's Respiratory Questionnaire score and prebronchodilator FEV₁. The only independent predictors of response to budesonide-formoterol for reducing exacerbations were eosinophil count ($p=0.013$ for interaction) and smoking history ($p=0.015$ for interaction).

Comment: ICSs appear to be overprescribed in COPD. ICSs may have a role in preventing exacerbations, and it is crucial to identify the correct target group for treatment. The authors used data from three randomised controlled trials of steroids in COPD to show that current smoking status in combination with an increased eosinophil count predicts exacerbations of COPD. The insightful accompanying [editorial](#) highlights that the correlation is weak, and that the hypothesis that ICSs may reduce the exacerbation rate in COPD needs to be tested prospectively. **Bottom line: a raised blood eosinophil count predicts exacerbations in COPD, which may respond to ICSs.**

Reference: *Lancet Respir Med* 2018;6:117–26

[Abstract](#)

Once-daily single-inhaler triple versus dual therapy in patients with COPD

Authors: Lipson DA et al., for the IMPACT Investigators

Summary: Patients with COPD were randomised to 52 weeks of a once-daily combination of fluticasone furoate 100 μ g, umeclidinium 62.5 μ g plus vilanterol 25 μ g (triple therapy), fluticasone furoate 100 μ g plus vilanterol 25 μ g or umeclidinium 62.5 μ g plus vilanterol 25 μ g, with each combination administered via a single inhaler. Compared with the respective fluticasone furoate-vilanterol and umeclidinium-vilanterol combinations, triple therapy was associated with a lower rate of moderate or severe exacerbations (primary outcome; 0.91 vs. 1.07 and 1.21 per year; rate ratios 0.85 [95% CI 0.80, 0.90] and 0.75 [0.70, 0.81]); triple therapy was also associated with a lower annual rate of severe exacerbations resulting in hospitalisation compared with umeclidinium-vilanterol (0.13 vs. 0.19; 0.66 [0.56, 0.78]). The ICS-containing regimens were associated with a higher incidence of pneumonia compared with umeclidinium-vilanterol, and the clinician-diagnosed pneumonia rate was significantly higher with triple therapy than with umeclidinium-vilanterol (hazard ratio 1.53 [95% CI 1.22, 1.92]).

Comment: It is almost surprising that it has taken 20 years before somebody combined all three medication classes known to treat airways disease in one inhaler: LABAs, LAMAs and ICSs. This international team of the IMPACT study managed to randomise more than 10,000 patients into three arms. The trial has a few weaknesses highlighted by Samy Suissa and Jeffrey Drazen in the accompanying [editorial](#). ICSs work best in patients with some eosinophilia, but ICSs increase the risk of pneumonia by 50%; however, **bottom line: triple therapy for COPD works.**

Reference: *N Engl J Med* 2018;378:1671–80

[Abstract](#)

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Long-term use of inhaled corticosteroids in COPD and the risk of fracture

Authors: Gonzalez AV et al.

Summary: This Canadian study examined fracture risk associated with long-term ICS use in patients with COPD. In a cohort of 240,110 patients with COPD, 19,396 sustained a fracture during a mean 5.3 years of follow-up (15.2 per 1000 per year). A nested case-control analysis showed that any ICS use was not associated with an increased rate of fracture. However, the fracture rate increased with longer (>4 years) ICS use at higher daily doses ($\geq 1000\mu\text{g}$ fluticasone equivalents). The increase in risk did not differ between men and women.

Comment: Our colleagues from Dunedin suggested that ICSs may be overused in COPD. These Canadian researchers used the Quebec database to identify participants above the age of 55 years who had been prescribed an ICS. They identified about 20,000 patients with major, nonvertebral fractures and matched each case with 20 controls of similar age, similar health and similar COPD diagnosis. High-dose (>1000 μg beclomethasone equivalent) and long-term (>4 years) treatment was associated with an increased risk of fractures. **Bottom line: long-term ICS use increased the risk of nonvertebral fractures in patients with COPD.**

Reference: *Chest* 2018;153:321–8

[Abstract](#)

RV568, a narrow-spectrum kinase inhibitor with p38 MAPK- α and - γ selectivity, suppresses COPD inflammation

Authors: Charron CE et al.

Summary: The p38 mitogen-activated protein kinase- α and - γ and SRC family kinase inhibitor RV568 was studied in primary cultured monocytes, macrophages and bronchial epithelial cells and *in vivo* in lipopolysaccharide and cigarette smoke-exposed murine models. The monocyte and macrophage experiments showed that RV568 had potent anti-inflammatory effects that were often greater than those seen with corticosteroids or Birb796 (a p38 inhibitor). When combined with corticosteroids, RV568 had anti-inflammatory effects suggestive of a synergistic interaction in poly I:C-stimulated BEAS-2B cells and in the cigarette smoke-exposed murine model. The efficacy and safety of 14 days of inhaled RV568 50 μg or 100 μg was evaluated in patients with COPD. Compared with placebo, RV568 was associated with improvements in prebronchodilator FEV₁ of 69mL and 48mL for the 50 μg and 100 μg doses, respectively, and significant reductions in sputum malondialdehyde levels ($p < 0.05$), but no change in sputum cell counts. Adverse events were similar between RV568 and placebo treatment.

Comment: Airway inflammation is one of the processes of COPD; however, the efficacy of ICSs is limited and they can cause side effects. An exciting new area of research is small-molecule agents that inhibit intracellular kinases, which regulate the inflammatory response in COPD. The authors present rather encouraging bench-to-bedside data on a less liver toxic, narrow-spectrum kinase inhibitor. Henrik Watz, who wrote the accompanying [editorial](#), provides excellent background information and alludes to the results of a 200-patient trial. He gives us the **bottom lines: while the data are encouraging, we are eagerly awaiting further clinical trials on these next-generation anti-inflammatory therapies.**

Reference: *Eur Respir J* 2017;50:1700188

[Abstract](#)

Low uptake of palliative care for COPD patients within primary care in the UK

Authors: Bloom CI et al.

Summary: This population-based study assessed the provision of palliative care support for COPD patients in primary care in the UK. Electronic healthcare records were reviewed for 92,365 patients with COPD for the period 2004–2015. Only 7.8% of the whole cohort and 21.4% of those who died received palliative care support. Lung cancer had a strong association with palliative care support compared with other patient characteristics. Only 16.7% of deceased COPD patients without lung cancer received palliative care support, compared with 56.5% of deceased patients with lung cancer. In patients who received palliative care support, a lung cancer codiagnosis significantly increased their chances of receiving palliative care support before the last month of life.

Comment: This is a sobering account of the lack of provision of palliative care for patients with COPD; anecdotally the situation is probably similar in NZ. Identifying patients with COPD who might benefit from palliative care is not always easy, and the [landmark paper](#) that changed my thinking about this is from Hilary Pinnock. The gap in care needs is a challenge for us healthcare professionals; in Europe more than 160,000 patients die of COPD per year. Bearing this in mind makes the authors' **bottom line frightful: co-existing lung cancer, not COPD itself, was the dominant driver for COPD patients receiving any palliative care.**

Reference: *Eur Respir J* 2018;51:1701879

[Abstract](#)

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Contributions of a hand-held fan to self-management of chronic breathlessness

Authors: Lockett T et al.

Summary: The perceived benefits of hand-held fan use by patients with chronic breathlessness, due to nonmalignant ($n=91$) and malignant ($n=21$) causes, and their carers ($n=72$) were evaluated in this secondary multimethod analysis of interview data collected during three clinical trials. Of 111 patients with evaluable data, 3.6% reported no perceived benefit of hand-held fan use, 14.4% reported uncertain benefit, 72.0% reported some benefit and 10.0% reported very substantial benefit; 'benefit' was described in terms of shorter recovery time, particularly following activity. A multivariate analysis was inconclusive. Reductions in home oxygen or inhaled β -agonist medication use were reported by 7.5% of the patients. A few patients reported dislike of the cooling sensation or embarrassment regarding hand-held fan use in public.

Comment: It is good to end this review on a somewhat positive note with this mixed-method, freely available article on the benefits of a simple hand-held fan to relieve breathlessness. The qualitative part of this study is particularly rich when patients share their stories, their strategies and their bewilderment why they had not been offered it earlier. Capucine Morélot-Panzini wrote the comprehensive [editorial](#), concluding that failure to take this concept into account would mean failing to comply with the principle of evidence-based medicine. **Bottom line: overall a fan was considered to be beneficial by more than 80% of patients.**

Reference: *Eur Respir J* 2017;50:1700262

[Abstract](#)

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