

Respiratory Research Review™

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Issue 143 - 2017

In this issue:

- *E-cigarette use increases bronchitic symptoms in adolescents*
- *Occupational pesticide exposure increases fixed airflow obstruction*
- *Poverty influences chronic airflow obstruction*
- *Pedometer targets during pulmonary rehabilitation for COPD*
- *Telerehabilitation improves exercise capacity in COPD*
- *Poor preventer inhaler adherence in COPD*
- *Tiotropium improves FEV₁ in early-stage COPD*
- *Doxycycline does not reduce exacerbations in COPD outpatients*
- *Pulmonary complications increased by airflow limitation after extrapulmonary surgery*
- *Immediate-release morphine in advanced COPD*

Abbreviations used in this issue

COPD = chronic obstructive pulmonary disease
FEV = forced expiratory volume
FVC = forced vital capacity

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Welcome to the last issue of *Respiratory Research Review* for 2017, and thank you to those who contacted us via e-mail or in person. Sometimes I feel I only write these reviews so I can read the cool research. I am aware that I am in a privileged position having to only worry about a handful of conditions; others, particularly colleagues in general practice, have an average of 176 conditions to keep in mind. For the time-poor, I hope that these introductory summaries and bottom lines assist in managing and mastering the information tsunami.

Metin Başoğlu from the Istanbul Center for Behavior Research and Therapy has written the most passionate and at times chilling [editorial](#) on the management of breathlessness, which has shifted my view. He reports some rather sobering research of torture survivors. Asphyxiation is the strongest predictor of post-traumatic stress syndrome and is rated the worst torture of a list of 46. This research could not be published out of concerns by the participants that the findings could be used to design more effective torture methods. If breathlessness causes helplessness, post-traumatic stress disorder and depression, how awful it must be for people who know that they have to live with debilitating conditions that cause chronic breathlessness for the rest of their lives. Başoğlu reflects that we may have an empathy gap, as we can imagine pain; however, we find it harder to relate to breathlessness. Furthermore, he elegantly points out that it would clearly be torture to perform an operation without anaesthesia and pain relief, and that it is part of the State's mandate to secure access to pain medications to protect against cruel, inhumane or degrading treatment. Given that we have effective medications available to treat breathlessness, not treating breathlessness appropriately can be seen as a human rights issue.

A group of European physicians offer practical help by clearly defining the clinical syndrome of chronic breathlessness, which is probably experienced by 10% of the population and rivals the prevalence of pain ([Eur Respir J](#)). Breathlessness is a key symptom of cardiorespiratory, neuromuscular and oncological disorders; still, patients tend to under-report it and physicians tend to focus on the underlying disease. Having a framework and definition of chronic breathlessness syndrome will improve clinical focus and research, and ultimately reduce suffering. The second article in the [Lancet](#) series on COPD covers 'Palliative care and management of troublesome symptoms for people with chronic obstructive pulmonary disease'. It is a guide full of practical advice, particularly on the use of morphine, benzodiazepines and antidepressants, and, naturally, is well evidence based. Locally, we have published on how to recognise and transition a patient to palliative care; check it out ([Breathe](#)).

The respiratory community is rather active and this last paragraph just summarises some excellent reads you may wish to click on, as your time permits: a tribute and reflection on Fletcher and Peto, 40 years on ([Am J Respir Crit Care Med](#)), a brief history of time to celebrate 20 years of Global Initiative of Chronic Obstructive Lung Disease (GOLD; [Eur Respir J](#)), and a great review of wearable technology in respiratory health and disease ([Breathe](#)). Also, three important and relevant guidelines have been published that govern our clinical practice: British Thoracic Society oxygen guidelines ([Thorax](#)), the ATS/ERS policy statement on enhancing, implementing, use and delivery of pulmonary rehabilitation ([Eur Respir J](#)) and finally, the office ERS/ATS clinical practice guidelines on noninvasive ventilation for acute respiratory failure ([Eur Respir J](#)).

Best wishes for the season, and we are grateful for the comments and feedback.

Kind regards

Professor Lutz Beckert

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Electronic cigarette use and respiratory symptoms in adolescents

Authors: McConnell R et al.

Summary: Questionnaires were used to gather data on chronic bronchitis symptoms, wheeze and use of e-cigarettes for 2086 US adolescents. Ever-use of e-cigarettes was reported by 24.0% of the respondents, with 9.6% reporting current use (within the prior 30 days). Compared with never users of e-cigarettes, past users and current users were more likely to report bronchitic symptoms (respective odds ratios 1.85 [95% CI 1.37, 2.49] and 2.02 [1.42, 2.88]), with increasing odds as frequency of current use increased (1.66 [1.02, 2.68] and 2.52 [1.56, 4.08] for 1–2 and ≥3 days use within the prior 30 days, respectively). Although adjustments for lifetime cigarette use and second-hand smoke exposure attenuated the associations, the risk of bronchitic symptoms remained elevated after adjustments for relevant potential confounders among past e-cigarette users, including those who reported never-use of cigarettes (1.70 [1.11, 2.59]). E-cigarette use was not significantly associated with wheeze after adjustment for cigarette use.

Comment: The e-cigarette market is growing rapidly; it has an estimated value of US\$2 billion, 466 distinct brands and more than 7000 unique flavours as of 2014. Some of these flavours may be toxic to the lung itself – the vapour is certainly toxic to mouse lungs and cell cultures. Long-term data on vaping are naturally not available. These researchers used participants from their cohort study and identified more than 2000 with an average age of 17 years. Even after adjusting for the possible concurrent use of tobacco, the results remained significant. **Bottom line: e-cigarette use was associated with bronchitic symptoms in adolescents.**

Reference: *Am J Respir Crit Care Med* 2017;195(8):1043–9

[Abstract](#)



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Occupational exposure to pesticides are associated with fixed airflow obstruction in middle-age

Authors: Alif SM et al.

Summary: This study investigated associations between occupational exposure to pesticides and herbicides and fixed airflow obstruction in middle-age. The research included 1335 individuals who were assessed by spirometry, and their occupational history was determined using lifetime work history calendars. Occupational exposure was defined as ever-exposure and cumulative exposure unit-years. Fixed airflow obstruction was defined as a postbronchodilator FEV₁/FVC ratio of <0.7 and the lower limit of normal. A logistic regression analysis showed that ever-exposure to biological dust, pesticides or herbicides was associated with fixed airflow obstruction (respective relative risks 1.58 [95% CI 1.01, 2.48], 1.74 [1.00, 3.07] and 2.09 [1.18, 3.70]). Cumulative exposure to pesticides and herbicides was also associated with fixed airflow obstruction, and exposure to pesticides was consistently associated with chronic bronchitis.

Comment: Tobacco smoking remains the predominant risk factor for COPD; however, people who have never smoked also develop airways disease. In the past we have commented on five disadvantages in childhood: mother with asthma, father with asthma, rhinovirus infection, passive smoking and asthma in childhood (Respiratory Research Review [issue 139](#)). These Australian-based researchers used data from the Tasmanian Longitudinal Health Study to explore the relationships between occupational exposure and ever-exposure to pesticides and fixed airways obstruction. Pesticides included insecticides (organophosphates and others), herbicides (like phenoxyated agents [Roundup®]) and fungicides like dithiocarbamates. **Bottom line: the longer the occupational exposure to pesticides, the more airway obstruction.**

Reference: *Thorax* 2017;72(11):990–7

[Abstract](#)

The association between chronic airflow obstruction and poverty in 12 sites of the multinational BOLD study

Authors: Townend J et al.

Summary: This analysis of the BOLD (Burden of Obstructive Lung Disease) study evaluated the association between chronic airflow obstruction and poverty in 9255 adults aged ≥40 years from 12 study sites. Poverty was evaluated using a wealth score (0–10) based on household assets, and obstruction was measured as FEV₁/FVC ratio after administration of salbutamol 200µg and prevalence of FEV₁/FVC below the lower limit of normal. Mean wealth scores ranged from 4 in Blantyre (Malawi) and Kashmir (India) to 10 in Riyadh (Saudi Arabia). The prevalence of obstruction ranged from 16% in Kashmir to 3% in Riyadh and Penang (Malaysia). After adjustment for age and sex, FEV₁/FVC ratio increased by 0.36% per unit increase in wealth score. Adjustments for other confounders reduced the effect to 0.23%. Mean wealth scores explained 38% of the variation in mean FEV₁/FVC ratio among sites.

Comment: Poverty is strongly associated with COPD, although 'it can't be inhaled and it is not a genetic condition' as Carlos A Torres-Duque points out in his [editorial](#). These international researchers used data from the BOLD study to confirm that the risk of airflow obstruction is related to decreased wealth both within a country and across eleven countries. The article and the editorial speculate about possible causes, and while many explanations are plausible, this study design can't identify a cause and points towards childhood influences. **Bottom line: poverty is a strong predictor of chronic airflow obstruction independent of age, sex, smoking and tuberculosis.**

Reference: *Eur Respir J* 2017;49(6):1601880

[Abstract](#)



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Pedometer step count targets during pulmonary rehabilitation in chronic obstructive pulmonary disease

Authors: Nolan CM et al.

Summary: Patients with COPD were randomised to an intervention of pulmonary rehabilitation plus pedometer-directed step targets with weekly review for 8 weeks (n=76) or a control intervention of pulmonary rehabilitation for 8 weeks with two supervised sessions per week (n=76). There was no significant difference between the intervention and control groups for the primary outcome of median change in accelerometer-measured daily time expending ≥ 3 metabolic equivalents between baseline and 8 weeks or 6 months (respective differences 0.5 [p=0.87] and 7.0 [p=0.16]).

Comment: Researchers from the Brompton explore the role of wearable technology on the activity levels of patients with COPD. Our knowledge of the impact of wearable technology is still limited and some authors have reported amazing impacts of a pedometer alone (Respiratory Research Review [issue 113](#)). In this study participants were randomised to a pedometer in addition to pulmonary rehabilitation. The study results were negative, and as Carlos Martinez points out in his accompanying [editorial](#), that may be an effect of the success of pulmonary rehabilitation itself. **Bottom line: a pedometer does not enhance the activity level of COPD patients participating in a rehabilitation programme.**

Reference: *Am J Respir Crit Care Med* 2017;195(10):1344–52

[Abstract](#)

Home-based telerehabilitation via real-time videoconferencing improves endurance exercise capacity in patients with COPD

Authors: Tsai LLY et al.

Summary: The TeleR trial randomised 37 patients with COPD to a supervised home-based telerehabilitation group with exercise training 3 times per week for 8 weeks or usual care without exercise training. Compared with the usual care group, participants assigned to telerehabilitation exhibited significant increases in mean endurance shuttle walk test time (difference 340 sec [p<0.001]) and mean self-efficacy score (p<0.007), and a trend for an increase in mean Chronic Respiratory Disease Questionnaire total score (8 points [p=0.07]), with no significant difference in mean physical activity (475 steps per day [p=0.16]).

Comment: Pulmonary rehabilitation is the first-line management to improve breathlessness, increase exercise capacity and improve quality of life; however, lack of transport, poor mobility or the cost of travel may at times be a barrier to participation. In this Sydney study, a physiotherapist set up a laptop with an inbuilt camera, a cycle ergometer and an oximeter in the participants' homes. During the scheduled training sessions 3 times per week, the participant could see and talk to both the physiotherapist and other participants. **Bottom line: telerehabilitation improves exercise capacity and self-efficacy in patients with COPD.**

Reference: *Respirology* 2017;22(4):699–707

[Abstract](#)

Objective assessment of adherence to inhalers by patients with chronic obstructive pulmonary disease

Authors: Sulaiman I et al.

Summary: An electronic audio recording device was used to prospectively assess adherence to preventative salmeterol/fluticasone inhaler therapy in 244 patients discharged after hospitalisation for COPD. The mean age of the participants was 71 years, and 59% showed evidence of mild or moderate cognitive impairment. Mean actual adherence to preventer therapy, calculated by combining time of use, interval between doses and critical technique errors, was 22.6%, with only 6% of participants having actual adherence of >80%. Hierarchical clustering revealed the following three clusters corresponding to distinct patterns: i) low inhaler use and high error rates (34%); ii) high inhaler use and high error rates (25%); and iii) overall good adherence (36%). Predictors of poor technique were poor lung function and comorbidities, whereas patients with poor adherence and frequent technique errors differed by age and cognition with poor lung function.

Comment: This is a beautifully conducted study from colleagues in Ireland who used an electronic audio recording device to assess inhaler time of use and technique of use. The adherence was even worse than expected, with only 6% of patients using the inhaler more than 80% of the time. David Au and Laura Feemster summarised these findings in their [editorial](#), 'It's bad – really bad – but does it matter'. They point out that COPD patients live complex lives with dyspnoea, cough, comorbidities and often obesity. **Bottom line: there has never been a randomised trial to assess if improving adherence improves outcomes.**

Reference: *Am J Respir Crit Care Med* 2017;195(10):1333–43

[Abstract](#)

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Tiotropium in early-stage chronic obstructive pulmonary disease

Authors: Zhou Y et al.

Summary: This study from China randomised 841 patients with GOLD stage 1 (mild) or 2 (moderate) COPD to receive inhaled tiotropium 18µg or placebo once daily for 2 years. Mean change in baseline FEV₁ before bronchodilator use was significantly higher among tiotropium recipients than placebo recipients throughout the trial (differences, 127–169mL [$p<0.001$]) as were postbronchodilator differences (71–133mL [$p<0.001$]). No significant amelioration was seen between the tiotropium and placebo groups for mean annual decline in prebronchodilator FEV₁ (difference, 15mL per year [$p=0.06$]), but the annual decline in postbronchodilator FEV₁ was reduced (22mL per year [$p=0.006$]).

Comment: COPD is the third leading cause of death worldwide, affects about 10% of the world's population and is essentially preventable by smoking cessation. This Chinese trial explored the role of tiotropium in patients with early stage 1–2 COPD identified by community screening. Tiotropium reduced the number of exacerbations and loss in FEV₁, which was about 39mL in the tiotropium treated and 54mL in the placebo group. In both groups more than 40% of participants smoked. **The bottom line here is: tiotropium appeared to slow lung function loss; however, smoking cessation may have achieved an even better outcome.**

Reference: *N Engl J Med* 2017;377(10):923–35
[Abstract](#)



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Doxycycline for outpatient-treated acute exacerbations of COPD

Authors: van Velzen P et al.

Summary: Outpatients aged ≥ 45 years with GOLD stage 1–3 COPD, ≥ 1 exacerbation during the prior 3 years and a smoking history of ≥ 10 pack-years were stratified by GOLD stage and randomised to receive oral doxycycline 200mg on day 1 followed by 100 mg/day ($n=152$) or placebo ($n=153$) for 7 days. Next exacerbation rates for the doxycycline and placebo groups were 87% and 83%, respectively, with no significant difference in median time until they occurred (148 vs. 161 days [$p=0.91$]). There was also no significant between-group difference for the frequency of adverse events within 2 weeks of randomisation ($p=0.54$) or for serious adverse events over 2 years of follow-up ($p=1$).

Comment: Systematic reviews suggest that antibiotic treatment is beneficial for patients with severe COPD, admitted to hospital. The role of antibiotics in an outpatient setting is less certain. Our Dutch colleagues randomised more than 300 patients with COPD to receive prednisone 30mg daily for 10 days and either placebo or doxycycline 100mg once daily. While the doxycycline was well tolerated, it did not reduce the number of, or the time until, the next exacerbation. The accompanying [editorial](#) points out that the study may have been underpowered, still our **bottom line is: doxycycline, in addition to steroids, may not add value in an outpatient setting.**

Reference: *Lancet Respir Med* 2017;5(6):492–9
[Abstract](#)

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Independent commentary by Professor Lutz Beckert.

Professor Lutz Beckert is the Head of Department of Medicine of the University of Otago, Christchurch. He is also a Respiratory Physician at Canterbury District Health Board with particular clinical interests in interstitial lung disease, pulmonary vascular disease, respiratory physiology and COPD (chronic obstructive pulmonary disease). Lutz is happy to be contacted to discuss research ideas either as a sounding board or considering future collaborations.



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Airflow limitation severity and post-operative pulmonary complications following extra-pulmonary surgery in COPD patients

Authors: Shin B et al.

Summary: The association between FEV₁ and postoperative pulmonary complications with extrapulmonary surgery was explored in a prospective cohort of 694 patients with COPD. Postoperative pulmonary complications occurred in 24.4% of the participants, with rates of 31.4%, 25.8%, 23.7%, 21.6% and 19.7% for the respective ascending percent predicted FEV₁ quintiles. Fully adjusted multivariable models revealed that compared with participants in the fifth percent predicted FEV₁ quintile, those in quintiles 1–4 were at increased risk of postoperative pulmonary complications (respective relative risks 1.69 [95% CI 1.03, 2.79], 1.41 [0.83, 2.37], 1.26 [0.75, 2.11] and 1.30 [0.76, 2.22]; $p=0.046$ for trend); the risk was lower for bronchodilator users versus nonusers.

Comment: This is a practical clinical audit of almost 700 patients with airways disease, who underwent surgery at Samsung Medical Center in Korea. About a quarter of all patients had postoperative pulmonary complications – in particular, a pleural effusion, atelectasis or respiratory failure – and exacerbations occurred in about 1% of the patients. The exacerbation risk was increased in patients who were older, those who had a lower body mass index, current smokers and those with a low albumin level. The perioperative use of bronchodilators may reduce the incidence of complications. **Bottom line: the more severe the airflow limitation, the higher the incidence of postoperative complications in COPD patients undergoing extrapulmonary surgery.**

Reference: *Respirology* 2017;22(5):935–41

[Abstract](#)

Effect of morphine on breathlessness and exercise endurance in advanced COPD

Authors: Abdallah SR et al.

Summary: This Canadian study evaluated the effect of morphine on exertional breathlessness and exercise endurance in advanced COPD. Twenty adults with advanced COPD and chronic breathlessness syndrome were randomised to receive immediate-release oral morphine or placebo in a crossover design. Physiological and perceptual responses of patients were assessed during constant-load cardiopulmonary cycle exercise testing. Compared with placebo, morphine significantly reduced exertional breathlessness, increased exercise endurance time and decreased breathing frequency. Morphine decreased exertional breathlessness by ≥ 1 Borg unit in 11 participants (responders) and by < 1 Borg unit in nine participants (nonresponders). Baseline participant characteristics, including pulmonary function and cardiorespiratory fitness, did not differ between responders and nonresponders.

Comment: It was in 2003 when our colleagues from Australia published their [randomised controlled trial](#) on the role of morphine in the management of refractory dyspnoea and the use of low-dose opioids for the management of breathlessness in advanced COPD, which is now supported by the Canadian, American, European and international guidelines. This study explored the mechanism a little further by assessment of breathlessness during steady exercise. Improved breathlessness was best explained by a reduction in the ventilator rate. **Bottom line: low-dose morphine was associated with meaningful improvements in breathlessness and exercise endurance in COPD patients with chronic breathlessness syndrome.**

Reference: *Eur Respir J* 2017;50(4):1701235

[Abstract](#)



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