

APSR Respiratory Research Review

Making Education Easy

Issue 23 – 2008

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Welcome to this edition of the APSR Respiratory Research Review and thank you for the feedback.

This edition of the APSR Respiratory Research Review may help you to negotiate the seven sins of COPD care: *Sloth*, as in therapeutic minimalism in the light of airway therapy and smoking cessation therapy; *Gluttony*, in the form of wasteful overprescribing of antibiotics; *Pride*, as expressed by the unmet hope to have found the magic bullet of inhaler therapy; *Lust*, as in the burning desire to focus on physiology and biology and not acknowledging behaviour issues, anxiety and depression; *Wrath*, when seeing the smoking cessation rate; *Greed*, as in wanting to 'cure' all aspects of COPD – both systemically and pulmonary, before clinical data are available and *Envy*, when seeing the 25% reduction in COPD exacerbation rate in China at a cost of \$US90 per year.

Kind regards,

Dr Lutz Beckett

lutzbeckett@researchreview.co.nz

Varenicline versus transdermal nicotine patch for smoking cessation

Authors: Aubin H-J et al

Summary: The efficacy of varenicline for smoking cessation was compared with nicotine replacement therapy (NRT) in this study. Participants were randomised to receive 12 weeks' treatment with varenicline uptitrated to 1mg twice daily (n = 376) or 10 weeks' treatment with transdermal NRT 21 mg/day decreased to 7 mg/day (370), and followed for 52 weeks after treatment. The self-reported continued abstinence rate for the last 4 weeks of treatment (primary outcome measure) was significantly greater for varenicline recipients than it was for NRT recipients (55.9% vs. 43.2%; OR 1.70; 95% CI 1.26, 2.28, p<0.001), although the difference at 52 weeks' follow up was not significant (26.1% vs. 20.3%; 1.40; 0.99, 1.99; p = 0.056). Cravings, withdrawal symptoms and smoking satisfaction were all significantly reduced with varenicline compared with NRT (p<0.001 for all three comparisons)

Comment: This trial was conducted in 24 centres throughout Europe and USA. Participants were offered 10-minute counselling, telephone follow-up and randomised to treatment groups receiving either NRT or varenicline. At three months, 55.6% of the varenicline and 43.2% of the NRT group were smoke free. Even with therapy and in centres of excellence, only 26% of the varenicline and 20% of the NRT group remained smoke-free at 1 year. The accompanying editorial reminds us that around two thirds of patients will resume smoking again within 2 years, as smoking is a behaviour largely explained by addiction. We have a long way to go with smoking cessation therapies, but we can now add varenicline to our pharmacological weaponry of bupropion, nortriptyline and NRT.

Reference: *Thorax* 2008; 63(8): 717-24

<http://thorax.bmj.com/cgi/content/abstract/63/8/717>



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Tiotropium in combination with placebo, salmeterol, or fluticasone-salmeterol for treatment of COPD

Authors: Aaron SD et al

Summary: The addition of salmeterol (SAL) and salmeterol plus fluticasone propionate (SFC) to tiotropium bromide (TIO) to improve outcomes in COPD was explored in this RCT. Participants (n = 449) received 1 year of treatment with TIO + placebo, TIO+SAL or TIO+SFC. There was no significant difference between the proportion of TIO + placebo recipients and TIO+SAL or TIO+SFC recipients who experienced an exacerbation of COPD requiring systemic corticosteroid or antibiotic therapy, although sensitivity analyses revealed a shift in the confidence intervals favouring TIO+SAL and TIO+SFC. However, compared with TIO + placebo, TIO+SFC was associated with significant improvements in lung function (p = 0.049), disease-specific quality of life (p = 0.01) and number of hospitalisations for both COPD exacerbation and all causes (incidence rate ratios 0.53; 95% CI 0.33, 0.86 and 0.67; 0.45, 0.99, respectively); lung function and hospitalisation rates did not differ significantly between the TIO+SAL and TIO + placebo groups.

Comment: This Canadian study investigates the clinical outcomes of triple therapy in COPD. Just like the TORCH study, which did not reach its primary endpoint of mortality reduction, this study also failed to reach its primary endpoint of reducing COPD exacerbation rates. However, the study does find improvements in lung function, quality of life and hospitalisation rates. The accompanying editorial calls it 'the search for the magic combination'. It reminds us of the possibility of increased cardiac morbidity and pneumonias, but hopes that we are at the brink of identifying therapy that decreases morbidity and mortality in COPD. We need cardiology type studies with more patients, international scope and endpoints that reflect disease modification.

Reference: *Ann Intern Med* 2007; 146: 545-55

<http://www.annals.org/cgi/content/abstract/146/8/545>

Superiority of salmeterol/fluticasone propionate plus tiotropium bromide versus individual components in moderate to severe COPD

Authors: Singh D et al

Summary: In this randomised cross-over study, the combination of salmeterol and fluticasone propionate (SFC) combined with tiotropium bromide (TIO) was compared with SFC alone and TIO alone in 41 patients with COPD. The postdose specific airways conductance area under the curve on day 14 (primary endpoint) was significantly better with SFC+TIO than with SFC or TIO alone (p<0.001 for both comparisons). SFC+TIO was also associated with significant improvements in trough FEV₁ and inspiration measurements on day 14, compared with SFC and TIO alone. Furthermore, clinically relevant improvements were seen in Transition Dyspnoea Index scores among SFC plus TIO recipients compared with TIO alone (but not SFC alone). Also, SFC plus TIO recipients required rescue medication on 1.0 less occasion than those who received TIO alone (p<0.001) and 0.06 less occasions than those who received SFC alone (p = 0.01). The investigators concluded that triple therapy with SFC plus TIO improves bronchodilation compared with TIO or SFC alone, and that the advantages of such therapy can be seen across a variety of physiologically important parameters.

Comment: Researchers from Britain and Belgium recruited 41 patients with COPD in five centres. In addition to traditional respiratory measurements, the authors measured the area under the curve of airway conductance. Patients receiving 'triple therapy' with tiotropium, salmeterol/fluticasone reported a reduction in their dyspnoea index, less rescue medication use and higher airway conductance when compared with the single components after 2 weeks of therapy. Interestingly, no improvement in the FEV₁ was noted. This short trial in a small number of patients provides a rationale to a widely employed clinical practice and calls for adequately powered long-term studies.

Reference: *Thorax* 2008; 63(7): 592-8

<http://thorax.bmj.com/cgi/content/abstract/63/7/592>

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Comparison of a combination of tiotropium plus formoterol to salmeterol plus fluticasone in moderate COPD

Authors: Rabe KF et al

Summary: The combinations of two bronchodilators (tiotropium bromide 18µg once daily plus formoterol 12µg twice daily; TBF) and a bronchodilator plus inhaled corticosteroid (salmeterol 50µg twice daily plus fluticasone dipropionate 500µg twice daily; SFC) were compared in 592 evaluable participants in this study. After 6 weeks' treatment, TBF recipients had significantly better FEV₁, AUC_{1-12h} and FVC AUC_{1-12h} than SFC recipients (mean differences 78mL; p = 0.0006 and 173mL; p < 0.0001, respectively). Peak FEV₁ and FVC responses at individual time points after each dose were also significantly superior with TBF. Predose FEV₁ and rescue medication use did not differ significantly between the treatment groups, but TBF was associated with a significantly higher predose FVC.

Comment: This Dutch RCT of about 600 COPD patients compared the use of two separate bronchodilators with a combined product of a bronchodilator and inhaled corticosteroid (ICS). The primary outcome of this 6-week study was an improvement in lung function, measured by AUC of FEV₁ and peak FEV₁. This study showed that there was a greater improvement in lung function when using two bronchodilators than an ICS/LABA combination product. Despite some limitations of the study, which the authors acknowledge, there is reason to believe that the improved lung function could translate to reduced exacerbations and better quality of life.

Reference: *Ann Intern Med* 2007; 146: 545-55

<http://www.annals.org/cgi/content/abstract/146/8/545>

Serum magnesium is an independent predictor of frequent readmissions due to acute exacerbation of COPD

Authors: Bhatt SP et al

Summary: Predictors of readmission for acute exacerbations of COPD were investigated in 100 patients (mean age 71.9 years) admitted with this condition over a 2-year period and retrospectively followed until readmission or death. Among the study population, 87 patients were readmitted once or more during the first follow-up year, 23% had frequent readmission (≥3 per year) and 5% died. Low serum magnesium level at the time of admission was a predictor of frequent readmission (adjusted OR 0.003; 95% CI <0.001, 0.55; p = 0.03). Vaccination against influenza or pneumococcal disease, and corticosteroid (inhaled or oral) or diuretic administration at discharge were not predictors of frequent readmission.

Comment: This group of American researchers used markers such as age, FEV₁, disease duration, performance status or hypercapnia at discharge to predict readmissions for COPD exacerbations. They performed a detailed retrospective multivariate analysis of 20 characteristics of 100 COPD patients. They found that none of these markers, nor corticosteroid use, or pneumococcal or influenza vaccination predicted readmission. However, the authors did discover that a low magnesium level on admission was an independent predictor of frequent admissions. The authors are aware of the limitations of their study, but given a similar observation in asthma exacerbations, find their results plausible and worthy of further investigation.

Reference: *Respir Med* 2008; 102: 999-1003

<http://dx.doi.org/10.1016/j.rmed.2008.02.010>

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APSR Respiratory Research Review is an initiative of the APSR education committee

Short-course antibiotic treatment in acute exacerbations of chronic bronchitis and COPD

Authors: El Moussaoui R et al

Summary: This meta-analysis compared the efficacy of a short antibiotic course (≤5 days) with conventional longer courses in acute exacerbations of COPD and chronic bronchitis. The analysis included 21 eligible studies (mean Jadad score 3.9) involving 10,698 patients. The summary ORs for clinical cure with short courses at early (<25 days) and late follow-up were 0.99 (95% CI 0.90, 1.08) and 1.0 (0.91, 1.10), respectively, while the summary OR for bacteriological cure at late follow-up was 1.05 (95% CI 0.87, 1.26). The summary ORs observed for early cure were similar in subanalyses of trials with the same antibiotic agent in short- and long-course arms, and of trials grouped by antibiotic class used in the short-course arm.

Comment: In light of the recent publicity of adverse effects from antibiotic treatment this meta-analysis has clinical relevance. The authors reviewed 21 studies, enrolling more than 10,000 patients with an acute exacerbation of COPD. In patients with mild-to-moderately severe COPD, a short course of treatment, usually five days, is equally effective as longer courses (7-10 days). As the accompanying editorial points out, advantages include better compliance, fewer adverse effects and perhaps a reduced risk of antibiotic resistance.

Reference: *Thorax* 2008; 63(5): 415-22

<http://thorax.bmj.com/cgi/content/abstract/63/5/415>

Dyspnea on exertion in obese women: association with an increased oxygen cost of breathing

Authors: Babb TG et al

Summary: Whether dyspnoea on exertion in otherwise healthy obese females is due to an increase in the oxygen cost of breathing or cardiovascular deconditioning was explored in this study, which included two independent experiments (n = 16 and 14 for experiments 1 and 2, respectively). The oxygen cost of breathing in obese women who exhibited dyspnoea on exertion was 38-70% greater than in women who did not (p<0.01), and there was a significant correlation between the oxygen cost of breathing and perceived breathlessness during exercise tests (r² = 0.57 and 0.72, for experiments 1 and 2, respectively; p<0.001). There were no between-group differences in fat distribution, cardiovascular exercise capacity and respiratory mechanics.

Comment: This is a further study investigating the relationship between obesity and shortness of breath. This well-conducted American study asked the question whether obese woman who report shortness of breath on exertion have a reduced exercise capacity (deconditioning) or an increased oxygen cost of breathing. Through a number of elegantly conducted experiments, they concluded that: 1) 37% of obese woman report shortness of breath on exercise, 2) obesity-related changes in pulmonary function or fat distribution did not seem to cause breathlessness, 3) peak cardiovascular capacity was not decreased and 4) shortness of breath during exertion is related to the oxygen cost of breathing.

Reference: *Am J Respir Crit Care Med* 2008; 178(2): 116-23

<http://ajrccm.atsjournals.org/cgi/content/abstract/178/2/116>



Independent commentary
by Dr Lutz Beckert,
Respiratory Physician at
Christchurch Hospital,
New Zealand.

Effect of carbocisteine on acute exacerbation of chronic obstructive pulmonary disease (PEACE Study)

Authors: Zheng J-P et al

Summary: The effect of mucolytic treatment on the yearly exacerbation rate in patients with COPD was investigated in this RCT. Patients with COPD stable for 4 weeks and ≥ 2 exacerbations within the previous 2 years were randomised to receive carbocisteine 1500 mg/day (n = 354) or placebo (355) for 1 year. Carbocisteine recipients experienced 1.01 exacerbations per year, compared with 1.35 in the placebo group (risk ratio 0.75; 95% CI 0.62, 0.92; p = 0.004). There were nonsignificant interactions between the preventive effects and smoking, COPD severity and inhaled corticosteroid (ICS) use.

Comment: Mucolytic medications such as carbocisteine, bromhexine or N-acetylcysteine are used to aid sputum elimination. This Chinese study included 709 patients with COPD who were randomised to either a carbocisteine or placebo group. There was a 24.5% reduction in exacerbations in the carbocisteine group (439 in the placebo, 325 in the treatment group). This effect was noted after only 3 months of treatment, with only very few adverse events observed. An improvement in the quality of life with St George's Respiratory Questionnaire was also noted. Only 16.7% of the participants were using ICSs, which may be partially due to the cost of treatment. The cost of ICSs and LABAs is six times greater than the cost of mucolytic medication.

Reference: *Lancet* 2008; 371(9629): 2013-8
<http://ajrccm.atsjournals.org/cgi/content/abstract/178/1/7>

Disclaimer: This publication is not intended as a replacement for regular medical education but to assist in the process. The reviews are a summarised interpretation of the published study and reflect the opinion of the writer rather than those of the research group or scientific journal. It is suggested readers review the full trial data before forming a final conclusion on its merits.

Azithromycin improves macrophage phagocytic function and expression of mannose receptor in COPD

Authors: Hodge S et al

Summary: The effect of azithromycin on alveolar macrophage expression of mannose receptors was investigated in this study. Azithromycin 500 ng/mL increased mannose receptor expression by 50% *in vitro*. In addition, 11 patients received oral azithromycin 250mg for 5 days then twice weekly for 12 weeks. Compared with control subjects, alveolar macrophage expression of mannose receptors and mannose-binding lectin and surfactant protein levels were significantly reduced in participants who received azithromycin. Baseline phagocytic ability also improved from 9.9% to 15.1% after azithromycin treatment, while bronchial epithelial cell apoptosis decreased from 30.0% to 19.7%, peripheral blood mannose receptors increased and peripheral blood inflammatory markers decreased. The investigators commented that these findings show that mannose receptors are: a) implicated in defective alveolar macrophage phagocytic function in patients with COPD; and b) a target for improved phagocytic ability with azithromycin.

Comment: This study from Adelaide reports on azithromycin use in COPD. Based on their *in vitro* data, the research group performed a clinical trial with 11 COPD patients. The patients were treated with azithromycin, and then markers of macrophagic function and inflammation were compared with baseline three months later. The data suggest improved efferocytosis and reduced systemic inflammation, without significant adverse effects or colonisation with resistant bacteria. This study provides new insight into the role of macrolides in COPD. A larger, blinded placebo-controlled study is warranted to see if the improvement of biological parameters matches clinical outcomes, including quality of life.

Reference: *Respir Med* 2008; 102: 999-1003

<http://dx.doi.org/10.1016/j.rmed.2008.02.010>

Panic attacks and perception of inspiratory resistive loads in COPD

Authors: Livermore N et al

Summary: Perceptions of resistive load were explored in 20 COPD patients with panic attacks/disorders, 20 COPD patients without panic and 20 healthy age-matched controls in this study. Using a diagnostic interview for panic attacks/disorders, perceived dyspnoea increased in a linear manner with increased resistive load for all groups. Although there were no between-group differences in respiratory variables, COPD patients with panic attacks/disorders gave a significantly higher perceived dyspnoea rating than the other subjects.

Comment: This excellent, clinically relevant Australian study aids our management of the psychological needs of COPD patients. The authors investigated the role of panic attacks on the perception of respiratory load. Does chronic anxiety and depression blunt the perception of dyspnoea in response to restrictive loads, or does the presence of panic disorders heighten the perception of dyspnoea? The authors designed a clinical model by applying increased respiratory loads using altered mouthpieces. The results suggest that COPD patients with a history of depression and anxiety have a heightened sensitivity to inspiration load, which is at times out of proportion to the stimulus applied. This confirms that managing patients with COPD is more than just managing airway biology.

Reference: *Am J Respir Crit Care Med* 2008; 178(1): 7-12

<http://ajrccm.atsjournals.org/cgi/content/abstract/178/1/7>

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