Research Review Speaker Series™

Hot Topics in Respiratory Medicine – COPD and Asthma

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Professor Chapman is an internationally respected researcher in the field of asthma, COPD and airway diseases. His publications have appeared in the New England Journal of Medicine and the Lancet. With more than 8,000 citations to his work, Professor Chapman is in the top 1% of cited medical researchers.

Professor Chapman is Director of the Asthma and Airway Centre of the University Health Network, President of the Canadian Network for Asthma Care and Director of the Canadian Registry for Alpha-1-Antitrypsin Deficiency. His academic appointments are as Professor of Medicine in the Faculty of Medicine with a cross-appointment to the School of Graduate Studies (Institute of Medical Science, Toronto). He chaired Canada's first Consensus Conference to establish Canadian guidelines for the management of COPD and is the inaugural holder of the CIHR-GSK Research Chair in Respiratory Health Care Delivery at the University Health Network.

This publication summarises two recent presentations by Professor Kenneth Chapman, Director of the Asthma and Airway Centre, University Health Network, Toronto. He addressed general practitioners and other health professionals in Auckland in March 2013 on the changing face of chronic obstructive pulmonary disease (COPD) and spoke at the Goodfellow Symposium on optimal strategies for asthma control.

THE CHANGING FACE OF COPD

Introduction

Highlighting the relative difficulties encountered when diagnosing and managing patients with COPD, Professor Chapman compared the cases of two 58-year-old overweight former smokers, both referred for follow-up management 2-weeks post hospitalisation, one for an uncomplicated acute myocardial infarction (Mr Weir), the other for an uncomplicated exacerbation of COPD (Mr Smith). Professor Chapman pointed out that while the assessment and treatment plan for Mr Weir was relatively clear cut – exercise stress test, echocardiogram, acetylsalicylic acid, beta blockers, statin and an ACE inhibitor, that for Mr Smith is less well understood. Mr Smith would most likely receive a chest x-ray and auscultation. His treatment might include short-acting puffers (ipratropium and/or salbutamol).

The 1-year mortality for patients like Mr Weir is generally considered to be 5-15%, while that for patients like Mr Smith is closer to 22%.[1] For those patients experiencing an exacerbation of COPD requiring Intensive Care Unit admission, the hospital mortality rate is reported to be 20-24%, the relapse rate (within 14 days) for those admitted to the emergency department (ED) 22-32% and the treatment failure rate (within 14 days) in outpatients 13-33%.[2-4]

How big is the COPD problem?

In Canada between 2006 and 2007, COPD was the leading cause of hospitalisation among all ambulatory care sensitive conditions (those that would normally be manageable on an outpatient basis – COPD, angina, asthma, heart failure, diabetes and epilepsy), with a rate of 96 per 100,000 population.[5] Furthermore, during that period COPD accounted for the highest number of repeat hospitalisations; 18% and 14% of the 17,200 patients admitted were readmitted once or two or more times for COPD or another ambulatory care sensitive condition.[5]

Data from the US collected between 1965 and 1998, a time period during which the rates of smoking tobacco significantly declined, show a corresponding decline in the mortality rates associated with diseases such as coronary heart disease (59% decrease), cerebrovascular disease (35% decrease) and stroke (64% decrease), but a surprising 163% increase in age-adjusted death rates from COPD.[6]

The effects of smoking

According to Professor Chapman, the increase in the rate of COPD seen during the era of quit smoking programmes may be explained by the long-term effects of smoking on FEV_1 (forced expiratory volume in 1 second). While FEV_1 declines gradually over a lifetime, most non-smokers and many smokers do not develop clinically relevant symptoms of airflow obstruction.[7] On the other hand, some susceptible smokers (1 in every 6-7) at risk of developing COPD, experience an accelerated decline (3-4 fold) in their FEV_1. If these individuals

quit smoking, their subsequent rate of FEV_1 decline will be similar to that of a non-smoker, but the loss of lung function will not be recovered and, even if they quit early, they are likely to go on to develop clinically significant symptoms of COPD.[7] Therefore, it is quite likely that the increased rates of COPD observed between 1965 and 1998 were a consequence of the high rates of tobacco smoking during the middle of the 20th century.

COPD is underdiagnosed

A recent Canadian study used spirometry to investigate the prevalence and underdiagnosis of COPD among high-risk individuals aged >40 years with a >20 pack-year history of smoking who were seen in primary practice for any reason. Screening spirometry in 1003 patients revealed a COPD prevalence of 20.7%.[8] Of the 208 patients meeting the spirometric criteria for COPD in this study, only 33% had previously been diagnosed.

Professor Chapman pointed out that there is a tremendous reservoir of patients with COPD who are yet to be diagnosed. He explained that one of the problems is that many health professionals believe that they don't need to use spirometry to diagnose COPD. Instead, they attempt to diagnose this condition with the use of a stethoscope. The widely accepted Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria for the classification of COPD includes the definition that the disease is characterised by airflow limitation due to chronic exposure to a noxious substance (e.g. tobacco smoke, occupational dusts and chemicals or smoke from home heating and cooking fuels).[9] It thus makes sense to measure airflow in order to diagnose this condition.

Previously, diagnosis of COPD has looked at factors such as a history of chronic bronchitis with cough and pathological features. Nowadays, with spirometry, we have a simple clinical diagnosis that can be used in general practice. **Figure 1** shows the differences in forced expiratory flow-volume loops that can be expected in a patient with normal lung function and one with COPD.

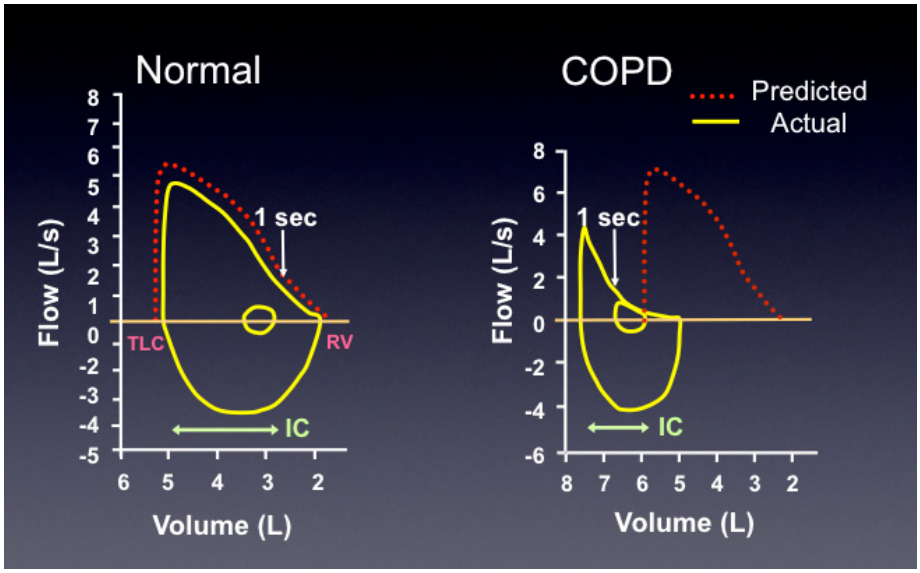

Figure 1: Differences in forced expiratory flow-volume loops in normal lung function vs COPD. The subject with the curve on the left has a normal peak flow and expiratory flow tracing, while the trace on the right exhibits a pattern of flow limitation typical of that of a patient with COPD; a lower peak and slower flow depicted by the concave expiratory limb of the flow volume loop.

IC = inspiratory capacity; RV = residual volume; TLC = total lung capacity

Who are the patients?

Physical appearance may be deceptive with regards to COPD. We need to be mindful that young, fit looking patients may also be susceptible if they have genetic risk factors such as alpha-1-antitrypsin deficiency. Furthermore, the face of COPD is changing with more women being diagnosed with the condition.[10] Professor Chapman pointed out that tobacco companies were targeting women with their marketing as early as the 1920s. By 1965, women were responsible for one-third of the tobacco consumption in the US and this trend has continued to rise.

Hospitalisation and mortality rates for COPD in Canada prior to the 21st century were higher for men than for women, but since the turn of the century rates for women have exceeded those for men.[11] It is projected that in Canada by 2016, 2-fold more women than men will be hospitalised with COPD.[11] Professor Chapman explained that more Canadian women will die this year as the result of COPD than will die as a result of breast cancer. He believes this would most likely also be the case in New Zealand.

Findings from a worldwide COPD true prevalence investigation, the BOLD (Burden of Obstructive Lung Disease) study, published in the Lancet in 2007, revealed prevalence rates in ever-smoking patients ≥40 years of age in Sydney of ≈8% for men and ≈13% for women.[12] Findings from New Zealand show a similar trend, but also show that New Zealand Māori have higher mortality rates from COPD than non-Māori and that COPD mortality rates for Māori women in New Zealand are higher than reported for any other known population of women wordwide.[13] It is projected that in New Zealand by 2025, the prevalence of COPD among never smokers, former smokers and smokers will be 8.9% of women and 8.0% of men over 40 years of age[13] Professor Chapman pointed out that there is an appreciable percentage of patients with COPD who have never smoked.

Assessing COPD

Therapeutic prescribing for COPD is driven by three factors: lung function, symptoms and exacerbation tendency. The GOLD Guidelines provide a rubic for combining these variables in the assessment of this condition and classify patients into four groups A-D (see **Figure 2**).[14]

Lung function impairment should be assessed using spirometry post-bronchodilator and classified according to the GOLD staging classification of airflow limitation in patients with FEV_1/FVC (forced vital capacity) <0.70.[14,15]

Symptoms should be assessed using a validated questionnaire such as the CAT™ test (COPD Assessment Test: http://www.catestonline.org/) or the modified British Medical Research Council (mMRC) breathlessness scale.[16,17]

Exacerbation history should be determined. Exacerbation of COPD is defined as a significant worsening of respiratory symptoms leading

to a change in medication.[14] Mortality has been shown to increase with the frequency of acute exacerbations and exacerbation history has been identified as the single most powerful predicator of subsequent exacerbations, independent of GOLD stage.[18,19]

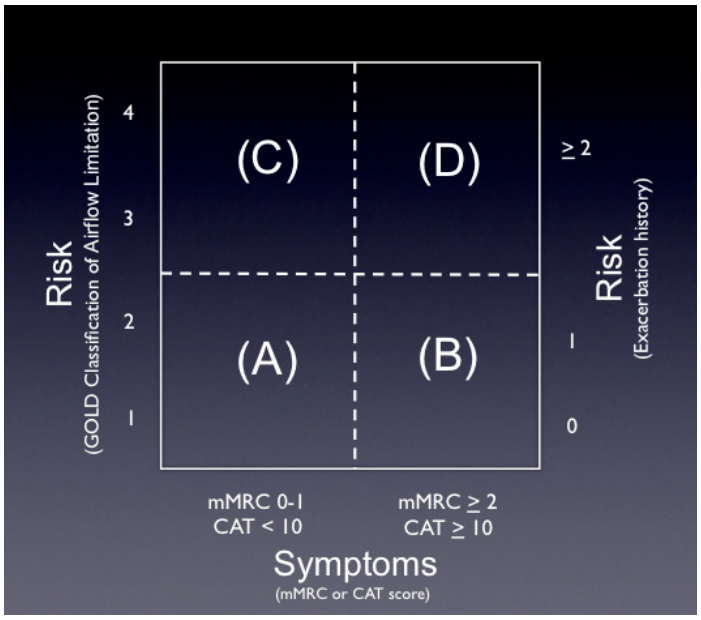

Figure 2: Combined assessment of COPD.[14]

CAT = COPD Assessment Test; mMRC = modified British Medical Research Council breathlessness scale

Treating COPD

Smoking cessation

The Lung Health Study revealed a 15% decrease in all-cause 14.5-year mortality in patients with COPD with mild-to-moderate airway obstruction who had undergone an intensive 10-week smoking cessation programme, when compared to those receiving usual care.[20]

Long- vs short-acting bronchodilators in COPD

Mahler et al 1999 found that inhaled salmeterol 42 µg twice daily over 12 weeks was more effective than inhaled ipratropium or placebo at improving lung function and reducing the probability of exacerbations in patients with COPD.[21] A subsequent study by van Noord and colleagues showed an added benefit with regard to improvement in airway obstruction when inhaled salmeterol was coadministered with ipratropium in patients with severe stable COPD.[22] These researchers also compared tiotropium, a long-acting muscarinic antagonist (LAMA), with ipratropium and found that inhaled tiotropium 18 µg once daily was significantly more effective than 40 µg ipratropium four times daily in improving trough, average and peak lung function over a 13-week period.[23] Once-daily inhaled tiotropium was also found to delay the onset of first hospitalisation due to COPD exacerbation when compared with placebo.[24]

Inhaled steroids for stable COPD

Four large COPD studies investigating the use of inhaled steroids (EUROSCOP [budesonide], Copenhagen [budesonide], ISOLDE [fluticasone] and LHS 2 [triamcinolone]) failed to show an improvement in the loss of long function over a 3-4-year period in patients with mild, moderate or severe COPD.[25-28] However, in the ISOLDE trial, fluticasone was shown to significantly reduce the number of COPD exacerbations; this has become a robust finding in other studies.[27]

Combination therapy (ICS + LABA)

The TORCH study investigated 3-year mortality in 6112 patients with COPD receiving either the LABA (Long-Acting β-Agonist) salmeterol 50 µg plus the inhaled corticosteroid (ICS) fluticasone propionate 500 µg twice daily (combination therapy), salmeterol alone, fluticasone alone or placebo and found a 17.5% risk reduction with combination therapy when compared with placebo (this only barely reached significance).[29] A stronger finding from the TORCH study was a 43% reduction in the number of exacerbations per year with combination therapy when compared with placebo ($p < 0.001$). There is also evidence that combination therapy reduces the rate of FEV_1 decline.[30]

LAMAs vs LABAs

A recent Canadian population-based, retrospective cohort study investigating the use of inhaled LAMAs such as tiotropium bromide and LABAs such as salmeterol and formoterol found that older patients (>65 years) with moderate COPD initially prescribed LABAs ($n = 15,532$) had a significantly ($p < 0.001$) lower 5-year mortality rate than those initially prescribed LAMAs ($n = 15,532$).[31]

Pharmacological choices in the management of COPD

Treatment choice in stable COPD is dependent upon which class (A-D) the patient falls within according to the rubic shown in **Figure 2**. The preferred first choices for pharmacological treatment according to the GOLD guidelines are as follows:[14]

Patient group	Treatment choice
A	SABA or SAMA as needed
B	LABA or LAMA
C	ICS + LABA/LAMA
D	ICS + LABA/LAMA

ICS = Inhaled Corticosteroids; LABA = Long-Acting β-agonist; LAMA = Long-Acting muscarinic Antagonist; SABA = Short-Acting Anticholinergic; SAMA = Short-Acting β_2-Antagonist

Professor Chapman pointed out that many patients fail to use their inhalers in an optimal manner and that they need to be properly educated on their use.[32] There is strong evidence regarding the benefit of self-management interventions, including patient education programmes, for patients with COPD.[33] A self-management plan should include antibiotics and prednisone prescribed for early self use.

Professor Chapman's Take-Home Messages:

- The prevalence of COPD is increasing worldwide, but the disease remains underdiagnosed
- Bronchodilators improve lung function, exercise tolerance, quality of life and reduce exacerbation rate
- ICSs reduce exacerbation rate and with LABAs appear to reduce COPD mortality and rate of FEV_1 loss
- Patients with COPD must be educated to become more effective partners in their own care.

ASTHMA MANAGEMENT STRATEGIES

Case examples

Professor Chapman set the scene for his presentation by describing two of his typical asthma patients. The first, Ms Weir, was a 43-year-old woman with a 5-year history of asthma, referred to him by her new family physician who felt that she was using her quick reliever salbutamol inhaler a little too often. She reported the use of salbutamol daily and fluticasone 125 µg twice daily and that she had woken approximately once per week with cough or wheeze. She had no prior history of hospitalisation or emergency department visits for her asthma symptoms. She had previously received prednisone for `bronchitis' and this had settled.

The second case was 23-year-old Ms Khan, referred to his clinic by the emergency department for assessment of new-onset asthma. She had presented with marked wheeziness and breathlessness after spending a weekend at a cottage where she was exposed to wood smoke, mould and cat dander. She had a childhood history or allergies and frequent episodes of bronchitis. In the emergency room she had responded well to salbutamol with her peak flow rising from 150 L/min to 400 L/min after two administrations of six puffs each. At that time she had been discharged home with Ventolin® and prednisone. In retrospect, she had been having symptoms of exercise-induced asthma for two years and her reported `bronchitis' was probably an exacerbation of asthma. She was scheduled for a methacholine challenge and allergy skin tests. Professor Chapman presented the following possible options for treatment for Ms Khan: salbutamol as needed; salbutamol plus fluticasone 100 µg twice daily; salbutamol plus fluticasone/salmeterol 250/50 twice-daily combination; montelukast 10 mg/day (these are looked at in more detail below).

Evaluating asthma control

The process of determining asthma control has been simplified for healthcare providers by a well-validated tool, the 5-question Asthma Control Test™ (ACT), available from: www.asthmacontrol.co.nz. The ACT covers the previous 4 weeks and scores each question from 1–5. A score of 20–25 indicates good control of asthma, whereas a score of 19 or less indicates poor asthma control. The ACT score has been validated in a number of studies, one of which evaluated ACT scores at baseline and risk of subsequent exacerbation over 12 months.[1] In that study, an ACT score of 15 at baseline suggested a much higher risk of asthma exacerbation than a score of 20 (OR 1.60; 95% CI 1.58 -1.62), while an ACT score of 19 was minimally associated with future asthma exacerbations (OR 1.09; 95% CI 1.07-1.11).

Barriers to achieving good asthma treatment outcomes

The most likely pitfalls to asthma control are: suboptimal compliance with inhaled therapy; poor inhaler technique; living or working with a potent antigen; fear of corticosteroids; Churg-Strauss vasculitis.

A number of studies have shown poor compliance with respiratory medications in clinical trials and in practice. The Lung Health Study investigated the use of an inhaler containing ipratropium bromide or placebo and found that only 15% of participants actually used the inhaler as prescribed.[2] A rough estimate from the literature would be that only 30-40% of doses prescribed actually get taken. Professor Chapman believes that our choice of prescriptions may be able to influence this low figure.

Among those patients who are compliant, a large proportion fail to be adequately dosed with their medication due to poor inhaler technique. One study suggested that up to 89% of patients when first seen at a specialist centre exhibit a poor inhaler technique.[3] Professor Chapman believes that overall, a rough estimate across studies would be that 30-40% of patients fall into this category.

Furthermore, it is not uncommon for patients to report that they are afraid of corticosteroid side effects. Many patients are prepared to use Ventolin® and to live with occasional wheezing and emergency room visits as part of having asthma. In the case of Ms Khan, she was afraid of facing the same disability as a maternal aunt who had suffered progressive disability from asthma before her death. Ms Khan believed that she would be wise to save her asthma medications for later when she really needed them to work, rather than use them daily now and have them not work in the future. Professor Chapman pointed out this this belief is common among patients who often translate their beliefs about antibiotic over exposure to their asthma medications. They should be informed that their asthma controlling medications are ideally taken as they would take a medication to lower their cholesterol levels for example, and not just for acute attacks.

Asthma treatment guidelines

The Canadian Thoracic Society Asthma Management Guidelines stress the importance of confirming the diagnosis for all patients, addressing the environment, educating patients on the effective management of their condition and providing them with a written action plan.[4] The guidelines state that very mild, intermittent asthma may be treated with a bronchodilator taken as needed. For patients with persistent disease, early use of inhaled ICSs are recommended, even in patients experiencing symptoms less than three times per week. The guidelines recommend that LABAs be added if ICSs alone are ineffective at controlling symptoms.

The benefit of ICS therapy has been demonstrated at a cellular level.[5] The population benefits of such therapy have been demonstrated in a Finnish study.[6] From 1994 to 2004, Finland undertook a national programme to improve asthma care, signed up to by the government and health professionals. The programme has resulted in an 85% reduction in asthma deaths and a 90% fall in asthma admissions, statistics that remain unmatched worldwide. The programme has lessened the burden of asthma to society, with a reduction in costs per patient per year of 36% (from €1611 to €1031), due to less expenditure on hospital admissions and disability pensions. This study highlighted the fact that patients are being treated effectively outside the hospital.

Limits of ICS monotherapy

Toogood and colleagues evaluated different dosages of beclomethasone and the percentages of patients who would achieve certain therapeutic asthma endpoints.[7] Outcomes are apparently improved upon increasing beclomethasone dose. However, most of the benefits from ICS therapy occur at low dosages; as the dosages are increased, the dividends lessen.

Ind and colleagues investigated whether the benefit of adding salmeterol was superior to doubling the dose of fluticasone propionate over 6 months, compared to a control group who remained on a lower dose of fluticasone propionate (250 µg twice daily).[8] At 6 months, mean morning peak expiratory flow rates improved identically with either dose of fluticasone propionate alone; there was no additional benefit from doubling the dose, whereas adding a LABA to the lower dose of fluticasone propionate resulted in more than twice the improvement achieved with either dose of fluticasone propionate alone.

ICS safety concerns

While the therapeutic dose-response to ICSs is clearly not linear, the side-effect dose-response does appear to be linear. An investigation by Hanania and colleagues found dose-related reductions in bone density amongst asthma patients treated with ICS.[9] In another study, Australian researchers reported an association between the use of ICS and the development of cataracts.[10] High doses of beclomethasone (28 puffs/week) were associated with triple the risk of cataract formation when compared with patients using ≤14 puffs/week of beclomethasone.

ICS monotherapy vs ICS/LABA therapy

The 1-year landmark GOAL (Gaining Optimal Asthma ControL) study by Bateman and colleagues demonstrated that in patients with uncontrolled asthma, combination therapy with fluticasone propionate and salmeterol resulted in 80% being well-controlled; fewer achieved control with fluticasone alone.[11] Rates of exacerbations requiring oral corticosteroids and/or hospitalisation or emergency visits were low in both treatment groups, but significantly lower in the combination treatment group, and substantially lower than the participants had suffered during the year prior to study involvement.

A study by Johansson and colleagues revealed significantly greater improvements from baseline in mean morning and evening peak flows in patients receiving ICS/LABA (salmeterol 100 µg/fluticasone propionate 50 µg) than those receiving budesonide 400 µg (see **Figure 3**).[12]

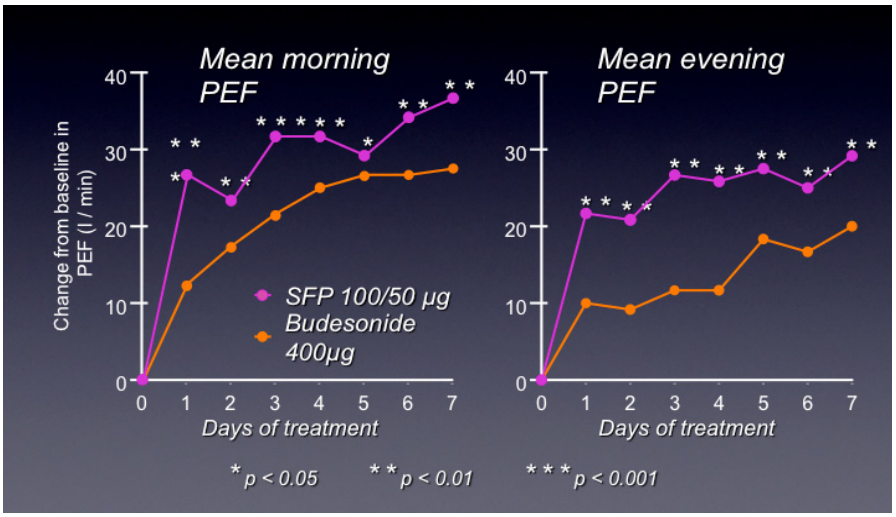

Figure 3: Changes from baseline in mean morning and evening peak flow during the first 7 days of study treatment.[11]

PEF = peak expiratory flow; SFP = salmeterol/fluticasone propionate

A 24-month retrospective observational study by Stempel and colleagues investigated adherence to asthma controller medication regimens and found adherence to be significantly higher for fluticasone and salmeterol in a single inhaler than for fluticasone and salmeterol in separate inhalers, fluticasone and montelukast, or fluticasone alone.[13]

ICS/LABA appears to be a safe combination therapy, and asthma-associated death rates in the US have dramatically declined since the introduction of this combination strategy.[14,15]

Can we achieve good control with a symptom-reactive strategy?

SMART (Single Maintenance And Reliever Therapy) using a combination inhaler containing budesonide and formoterol as both maintenance and quick relief therapy has been recommended as an improved method of using ICS/LABA therapy. Professor Chapman and colleagues reviewed the findings of seven trials of 6-12 months duration in patients using the SMART strategy and found that patients using SMART have used their quick reliever daily (weighted average 0.92 inhalations/day), have suffered asthma symptoms more than half of days (weighted average 54.0% of days), have awakened with asthma symptoms once every 7-10 days (weighted average 11.5% of nights), and have had a severe exacerbation rate of one in five patients per year (weighted average 0.22 severe exacerbations/patient/year).[16]

In a detailed analysis of asthma control involving five studies including a total of over 5000 patients on SMART therapy, only 17% of SMART-treated patients achieved GINA (Global Initiative for Asthma)-defined clinical asthma control (44% were categorised as uncontrolled and 38% were partly-controlled).[17]

The effect of SMART dosing on airway inflammation was investigated by Pavord and colleagues who found worse inflammation with the SMART approach; biopsy specimen subepithelial eosinophils doubled (from 6.2 to 12.3 cells/mm^2) in the SMART cohort whereas sputum and biopsy eosinophil counts decreased with high fixed-dose treatment.[18]

Professor Chapman's Take-Home Messages:

- Achieving control rapidly and completely can encourage patient compliance and establish the long-term treatment targets for both patients and physicians
- ICS/LABA combinations tend to achieve the same or better efficacy as ICS monotherapy earlier and at lower ICS doses
- Variable, symptom-driven dosing (SMART) is associated with poor control and increasing airways inflammation
- The best long-term outcomes have been demonstrated with symptom-preventive rather than symptom-reactive dosing.

COPD references:

1. Almagro P et al. Mortality after hospitalization for COPD. Chest 2002;121(5):1441-8
2. Seneff MG et al. Hospital and 1-year survival of patients admitted to intensive care units with acute exacerbation of chronic obstructive pulmonary disease. JAMA. 1995;274(23):1852-7
3. Murata GH et a. Treatment of decompensated chronic obstructive pulmonary disease in the emergency department--correlation between clinical features and prognosis. Ann Emerg Med. 1991;20(2):125-9
4. Adams SG et al. Antibiotics are associated with lower relapse rates in outpatients with acute exacerbations of COPD. Chest 2000;117(5):1345-52
5. Canadian Institute for Health Information, Health Indicators 2008 (Ottawa: CIHI, 2008). Available from: https://secure.cihi.ca/free_products/HealthIndicators2008_ENGweb.pdf (Accessed April 2013)
6. http://www.goldcopd.org/ (Accessed April 2013)
7. Fletcher C and Peto R. The natural history of chronic airflow obstruction. Br Med J. 1977;1(6077):1645-8
8. Hill K et al. Prevalence and underdiagnosis of chronic obstructive pulmonary disease among patients at risk in primary care. CMAJ. 2010;182(7):673-8
9. Pauwels RA et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop summary. AM J Respir Crit Care Med. 2001;163(5):1256-76
10. Health Canada. Respiratory Disease in Canada. Available from: http://www.phac-aspc.gc.ca/publicat/rdc-mrc01/pdf/rdc0901e.pdf (Accessed April 2013)
11. Eds, V. Bryanton, Y. Chen, H. Johanson et al. Ottawa, Health Canada. Canadian Institute for Health Information, Canadian Lung Association, Health Canada, Statistics Canada(2001). Respiratory Disease in Canada. H39-593/2001E
12. Buist AS et al. International variation in the prevalence of COPD (the BOLD Study): a population-based prevalence study. Lancet 2007;370(9589):741-50
13. Broad J and Jackson R for the Thoracic Society of New Zealand. Chronic Obstructive Pulmonary Disease and Lung Cancer in New Zealand. 2003. Available from: http://asthmafoundation.org.nz/wp-content/uploads/2012/03/thoracic_rpt_nov2003.pdf (Accessed April 2013)
14. GOLD: Global Initiative for Chornic Lung Disease: Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease – upsdated 2013. Available from: http://www.goldcopd.org/uploads/users/files/GOLD_Report_2013_Feb20.pdf (Accessed April 2013)
15. O'Donnell DE et al. Canadian Thoracic Society recommendations for management of chronic obstructive pulmonary disease – 2008 update – highlights for primary care. Can Respir J. 2008;15 Suppl A:1A-8A
16. Fletcher CM et al. The significance of respiratory symptoms and the diagnosis of chronic bronchitis in a working population. Br Med J. 1959; 2(5147):257-66
17. O'Donnell DE et al. Canadian Thoracic Society recommendations for management of chronic obstructive pulmonary disease—2003. Can Respir J. 2003; 10(Suppl A):11A-33A
18. Soler-Cataluña JJ et al. Severe acute exacerbations and mortality in patients with chronic obstructive pulmonary disease. Thorax 2005;60:925-31
19. Hurst JR et al. Susceptibility to exacerbation in chronic obstructive pulmonary disease. N Engl J Med. 2010;363(12):1128-38
20. Anthonisen NR et al. The effects of a smoking cessation intervention on 14.5-year mortality: a randomized clinical trial. Ann Intern Med. 2005;142(4):233-9
21. Mahler DA et al. Efficacy of salmeterol xinafoate in the treatment of COPD. Chest 1999;115(4):957-65
22. van Noord JA et al. Long-term treatment of chronic obstructive pulmonary disease with salmeterol and the additive effect of ipratropium. Eur Respir J. 2000;15(5):878-85
23. van Noord JA et al. A randomised controlled comparison of tiotropium and ipratropium in the treatment of chronic obstructive pulmonary disease. Thorax 2000;55(4):289-94
24. Casaburi R et al. A long-term evaluation of once-daily inhaled tiotropium in chronic obstructive pulmonary disease. Eur Respir J. 2002;19(2):217-24
25. Pauwels RA et al. Long-term treatment with inhaled budesonide in persons with mild chronic obstructive pulmonary disease who continue smoking. European Respiratory Society Study on Chronic Obstructive Pulmonary Disease. N Engl J Med. 1999;340(25):1948-53
26. Vestbo J et al. Long-term effect of inhaled budesonide in mild and moderate chronic obstructive pulmonary disease: a randomised controlled trial. Lancet 1999;353(9167): 1819-23
27. Burge PS et al. Randomised, double blind, placebo controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary disease: the ISOLDE trial. BMJ. 2000;320(7245):1297-303
28. Lung Health Study Research Group. Effect of inhaled triamcinolone on the decline in pulmonary function in chronic obstructive pulmonary disease. N Engl J Med. 343(26):1902-9
29. Calverley PM et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. N Engl J Med. 2007;356(8):775-89
30. Celli B et al. Effect of pharmacotherapy on rate of decline of lung function in chronic obstructive pulmonary disease: results from the TORCH study. Am J Respir Crit Care Med. 2008;178(4):332-8
31. Gershon A et al. Comparison of inhaled long-acting β-agonist and anticholinergic effectiveness in older patients with chronic obstructive pulmonary disease: a cohort study. Ann Intern Med. 2011;154(9):583-92
32. Coady TJ et al. Synchronization of bronchodilator release. Practitioner 1976;217(1298): 273-5
33. Bourbeau J et al. Reduction of hospital utilization in patients with chronic obstructive pulmonary disease: a disease-specific self-management intervention. Arch Intern Med. 2003;163(5):585-91

Asthma references:

1. Schatz M, et al. The minimally important difference of the Asthma Control Test. J Allergy Clin Immunol. 2009;124(4):719-23.e1
2. Rand CS et al. Metered-dose inhaler adherence in a clinical trial. Am Rev Respir Dis. 146(6):1559-64
3. Epstein SW et al. Survey of the clinical use of pressurized aerosol inhalers. Can Med Assoc J. 1979;120(7):813-6
4. Lougheed MD et al. Canadian Thoracic Society Asthma Management Continuum--2010 Consensus Summary for children six years of age and over, and adults. Can Respir J. 2010;17(1):15-24
5. Laitinen LA et al. A comparative study of the effects of an inhaled corticosteroid, budesonide, and a beta 2-agonist, terbutaline, on airway inflammation in newly diagnosed asthma: a randomized, double-blind, parallel-group controlled trial. J Allergy Clin Immunol. 1992;90(1):32-42
6. Haahtela T, et al. A 10 year asthma programme in Finland: major change for the better. Thorax 2006;61(8):663-70
7. Toogood JH et al. A graded dose assessment of the efficacy of beclomethasone dipropionate aerosol for severe chronic asthma. J Allergy Clin Immunol. 1977;59(4):298-308
8. Ind PW et al. Addition of salmeterol to fluticasone propionate treatment in moderate-to-severe asthma. Respir Med. 2003;97(5):555-62
9. Hanania NA et al. Dose-related decrease in bone density among asthmatic patients treated with inhaled corticosteroids. J Allergy Clin Immunol. 1995;96(5 Pt 1):571-9
10. Cumming RG et al. Use of inhaled corticosteroids and the risk of cataracts. N Engl J Med. 1997;337:8-14
11. Bateman ED et al. Can guideline-defined asthma control be achieved? The Gaining Optimal Asthma ControL study. Am J Respir Crit Care Med. 2004;170(8):836-44
12. Johansson G et al. Salmeterol/fluticasone propionate combination dry powder inhaler (50/100 mcg bid) is more effective than budesonide (400 mcg bid) in mild to moderate asthma. Eur Respir J. 1998;12(Suppl 29): 20S,P162
13. Stempel DA et al. Adherence to asthma controller medication regimens. Respir Med. 2005;99(10):1263-7
14. American Lung Association Epidemiology & Statistics Unit Research And Scientific Affairs. Trends in Asthma Morbidity and Mortality. May 2005. Available from: www.lungusa.org (Accessed April 2013)
15. National Vital Statistics Report. Deaths: Final Data for 2003. April 2006. Available from: www.cdc.gov (Accessed April 2013)
16. Chapman KR et al. Single maintenance and reliever therapy (SMART) of asthma: a critical appraisal. Thorax 2010;65(8):747-52
17. Bateman ED et al. Overall asthma control: the relationship between current control and future risk. J Allergy Clin Immunol. 2010;125(3):600-8
18. Pavord ID et al. Airway inflammation in patients with asthma with high-fixed or low-fixed plus as-needed budesonide/formoterol. J Allergy Clin Immunol. 2009;123(5):1083-9

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