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 FEV1 (forced expiratory volume in 1 second). While FEV1 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 FEV1. If these individuals...
quit smoking, their subsequent rate of FEV1 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. 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%. 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). 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](image)

**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. 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. It is projected that in Canada by 2016, 2-fold more women than men will be hospitalised with COPD. 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 GOLD (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. 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 worldwide. 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. 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 rubric for combining these variables in the assessment of this condition and classify patients into four groups A-D (see Figure 2).

**Lung function** impairment should be assessed using spirometry post-bronchodilator and classified according to the GOLD staging classification of airflow limitation in patients with FEV1/FVC (forced vital capacity) <0.70.

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

**Exacerbation** history should be determined. Exacerbation of COPD is defined as a significant worsening of respiratory symptoms leading...
to a change in medication. Mortality has been shown to increase with the frequency of acute exacerbations and exacerbation history has been identified as the single most powerful predictor of subsequent exacerbations, independent of GOLD stage. 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 lung function over a 3-4-year period in patients with mild, moderate or severe COPD. 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.

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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). 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 FEV₁ decline.

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).

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 rubric shown in Figure 2. The preferred first choices for pharmacological treatment according to the GOLD guidelines are as follows:

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Treatment choice</th>
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<tbody>
<tr>
<td>A</td>
<td>SABA or SAMA as needed</td>
</tr>
<tr>
<td>B</td>
<td>LABA or LAMA</td>
</tr>
<tr>
<td>C</td>
<td>ICS + LABA/LAMA</td>
</tr>
<tr>
<td>D</td>
<td>ICS + LABA/LAMA</td>
</tr>
</tbody>
</table>

ICS = Inhaled Corticosteroids; LABA = Long-Acting β-agonist; LAMA = Long-Acting muscarinic Antagonist; SABA = Short-Acting Anticholinergic; SAMA = Short-Acting β₂-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. There is strong evidence regarding the benefit of self-management interventions, including patient education programmes, for patients with COPD. 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 FEV₁ loss
- Patients with COPD must be educated to become more effective partners in their own care.

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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. 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. 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.

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. 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. The population benefits of such therapy have been demonstrated in a Finnish study. 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. 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). 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 ICSs. In another study, Australian researchers reported an association between the use of ICS and the development of cataracts. 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. 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).

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

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. 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.

**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).

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). 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/mm²) in the SMART cohort whereas sputum and biopsy eosinophil counts decreased with high fixed-dose treatment.

**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: