Research Review Speaker Series™

40 years of asthma care: the good, the bad and the ugly

Making Education Easy March 2013

Professor Matthew Peters

Professor Matthew Peters is head of Respiratory Medicine at Concord Hospital and has academic appointments at Sydney University and the Australian School of Advanced Medicine at Macquarie University. He has also recently been appointed as President of the Thoracic Society of Australia and New Zealand.

During his training, he received the Concord Young Investigator Award and, as the inaugural recipient of the Allen and Hanbury's Travelling Fellowship, he spent three years at the (then) National Heart and Lung Institute in London with Professor Peter Barnes.

Matthew has contributed to the training of more than 30 thoracic physicians. His interests include asthma and lung cancer and improvement in public health; with notable contributions in tobacco control and better care of patients with lung cancer.

This publication summarises a recent presentation by Professor Matthew Peters, head of Respiratory Medicine at Concord Hospital, Sydney, Australia. He addressed general practitioners and other health professionals in Christchurch, Wellington and Auckland from 5–7 March 2013 on the use of Symbicort SMART in the management of moderate-severe asthma.

Asthma

Asthma is an extremely complex disease in humans; an immunologically-driven systemic disease targeting respiratory epithelium and subjacent connective tissue. Its various effects include physiological and symptomatic markers, with important impacts upon psychological, social and economic domains. Not surprisingly, these sorts of impacts will alter the expression of the asthma. Thus, the treatment of asthma has to be within the reality of a broader existence.

This underlines why optimal treatment of asthma must treat the inflammatory process – this is core to achieving good outcomes in asthma.

Overall, although the current treatment of asthma is far from perfect, in reality, we have never had it as good as we do now, said Prof. Peters. Poor lung function used to be common and asthma mortality epidemics have not been seen since the 1980s.[1,2]

One of the reasons for the improved situation in asthma is that good treatments are available and have been available for decades. The single most important treatment is inhaled corticosteroids (ICS). Evidence shows that over a period as short as 12 weeks, budesonide delivered by Turbuhaler (200, 400, 800 or 1600 µg total daily dose) in adults with chronic asthma was significantly more effective than placebo, with all budesonide doses achieving a sharp improvement in lung function.[3] Notably, most of the effect obtained from high doses of Pulmicort® is reflected by the low dose of 100 µg twice daily. Clinicians should therefore have great faith in the efficacy of low-dose ICS and not feel the need to prescribe an extremely high dose, advised Prof. Peters.

Deaths from asthma are much diminished. The evidence demonstrates that it requires only a low dose of ICS to reduce the risk of asthma-related mortality – just two × 50 µg puffs of beclomethasone dipropionate per day reduces the risk of asthma-related death to <10% as compared with an asthmatic patient not using any ICS.[4]

Design of structured & organised care

Co-ordinated care and guidelines have built upon and amplified the benefits of ICS and include:

- Guideline development
- Asthma self-management plans
- Written asthma action plans

Effective management has improved critical outcomes, with subsequent reductions in rates of asthma epidemics and in asthma mortality worldwide[2] with evidence demonstrating that asthma mortality started to decrease with the introduction of beclomethasone and budesonide in the 1980s, even before the introduction of Flixotide®, Serevent®, Seretide® and Symbicort®.

There should be universal agreement with the following statements:

- The critical treatment class in asthma is ICS
- When ICS are used and the therapeutic outcome is not optimal (in terms of lung function and loss of symptoms) attend first to simple explanations (check medication adherence, correct use of the device, or the lack of expected improvement is because the condition was not asthma in the first place) before attributing the therapeutic outcome to ICS failure
- After this, add a long-acting bronchodilator:
  - Improves lung function
  - Reduces symptoms
  - Reduces exacerbations
  - Does not reduce mortality (and in Prof. Peters' opinion does not increase mortality, unlike the short-acting β-agonists [SABA])

- LABA (long-acting β-agonist) therapy should be added in a combo-device with an ICS.
- No particular reason to favour one or other combination inhaler – if patient is not experiencing exacerbations and has satisfactory device technique.

Both Seretide (fluticasone/salmeterol) and Symbicort (budesonide/formoterol) have proven to be very effective drugs in situations where ICS has failed to fully control asthma. Using combination LABA and ICS inhalers in the treatment of asthma is a quality use of pharmaceuticals; most notably, the combination therapies avoid the adverse events associated with LABA monotherapy.

A 12-week trial involving patients with asthma not fully controlled with inhaled glucocorticosteroids alone assessed the reduction in asthma symptoms using a fixed combination inhaler (Symbicort; budesonide/formoterol 400/12 µg BD) compared with concurrent administration of budesonide and formoterol from separate inhalers (Pulmicort 400 µg + Oxis 12 µg BD), and with budesonide alone (Pulmicort 400 µg BD).[5] Morning peak expiratory flow (PEF) was improved after 12 weeks by statistically significantly greater amounts with single inhaler therapy (35.7 L/min) and separate-inhaler therapy (32 L/min) than with budesonide alone (0.2 L/min; $p<0.001$, both comparisons); the effect was apparent after 1 day ($p<0.001$ versus budesonide, both comparisons). The reduction in asthma symptoms was comparable using either a fixed combination inhaler or separate inhalers.

In another investigation involving patients with persistent asthma despite treatment with inhaled glucocorticoids, patients were randomised to one of four twice-daily treatments: Pulmicort 100 µg, budesonide 100 µg plus formoterol 12 µg (low-dose Symbicort), Pulmicort 400 µg, or budesonide 400 µg plus formoterol 12 µg (Symbicort).[6] After 1 year of treatment, the proportions of patients with severe exacerbations were 38.6% with low-dose Pulmicort alone, 29.7% with low-dose Symbicort, 28.2% with high-dose Pulmicort alone and 19.2% with Symbicort. The evidence clearly shows that combination ICS treatment is associated with effective improvements in lung function, asthma symptoms and exacerbations.

Patients who require additional therapy

A smaller, but nevertheless important, group of patients consists of those who continue to experience persistent symptoms and/or exacerbations despite being prescribed combination therapy.

- Two excellent initial options
  - Higher than entry ICS + continued SABA
  - Use of Symbicort as maintenance and reliever (Symbicort SMART)
- Effects of both in randomised trials
  - Well tolerated treatments
  - Improvement in lung function
  - Improvement in asthma symptom scores
  - Probably fewer exacerbations for higher ICS
  - Definitely fewer exacerbations for Symbicort SMART

Symbicort SMART is a simple concept:

Patients use a maintenance treatment (as has been the case for the last 30 years)

Patients use a reliever treatment (as has been the case for the last 30 years)

The difference is that patients use the same product for both.

Formoterol in Symbicort is a rapid-onset, long-acting bronchodilator – it differs from the long-acting salmeterol, which has a slower onset of action

- Symbicort addresses symptoms
- Treatment tailored to fluctuations in disease
- Earlier intervention for imminent deterioration

Effect of Symbicort SMART on exacerbations

A 12-month study by Rabe and colleagues compared the effects of three reliever strategies in symptomatic patients with asthma receiving maintenance Symbicort: terbutaline (Bricanyl®) 0.4 mg; Oxis 4.5 µg; or Symbicort SMART 160/4.5 µg.[7] The total number of severe exacerbations (defined as an event resulting in oral steroid treatment for ≥3 days or a hospital visit) were 377, 296 and 194 with as-needed terbutaline, Oxis, and Symbicort SMART, respectively ($p<0.001$ for Symbicort SMART vs terbutaline and $p<0.01$ for Symbicort SMART vs Oxis). Notably, as-needed Symbicort SMART was more effective than the other reliever strategies at avoiding the need for oral steroids or hospitalisations/ER treatments (see Fig. 1).

This study demonstrates a proof-of-concept: substituting a SABA with Symbicort reduces severe exacerbations (defined as oral steroid treatment or a hospital visit).

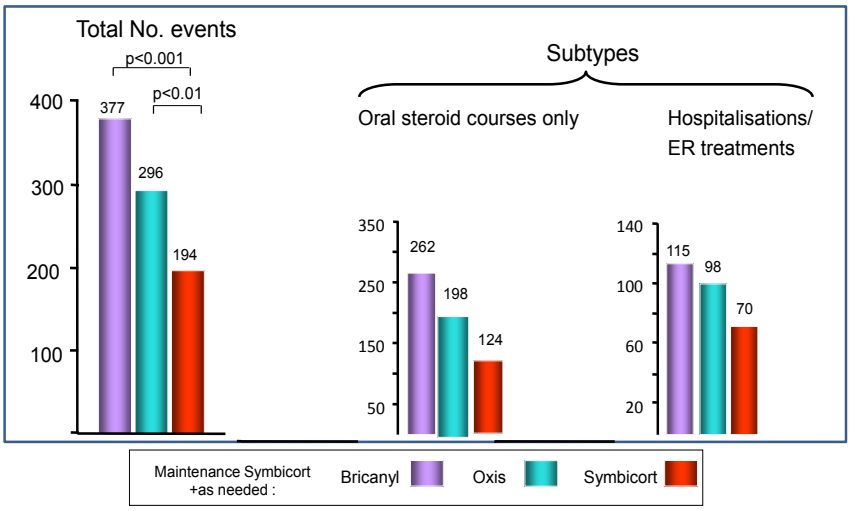

Figure 1. Effect of Symbicort SMART on exacerbations.[7]

Two valid treatment options are available for treating patients with persistent asthma: Symbicort 200/6 µg 2BD as maintenance therapy, or an equally valid alternative of Symbicort 200/6 BD, switching to using Symbicort as a reliever. Thus, when Symbicort SMART patients use a reliever, they obtain extra treatment.

The diagram in Figure 2 uses data from the COMPASS study to illustrate how Symbicort SMART works.[8] COMPASS compared budesonide/formoterol for maintenance and relief (160/4.5 µg BD + additional inhalations as needed; Symbicort SMART) with Symbicort Fixed-Dose (FD) (320/9 µg BD + as-needed terbutaline) or Seretide (50/250 µg BD + as-needed terbutaline). In Figure 2, the black data points represent Symbicort FD; the red represent Symbicort SMART. The shaded area indicates an event leading to an increase in symptoms, a reduction in peak flow and increased reliever use. As depicted in the diagram, simply by following their symptoms and using more reliever as needed, even before a normal action plan would require a treatment change, the Symbicort SMART group is already receiving a higher dose of ICS. Thus, based on short-term symptoms, Symbicort SMART users avoid a severe exacerbation and avoid a course of oral steroids. While the SMART approach does not prevent all exacerbations or oral steroids, it avoids about half.

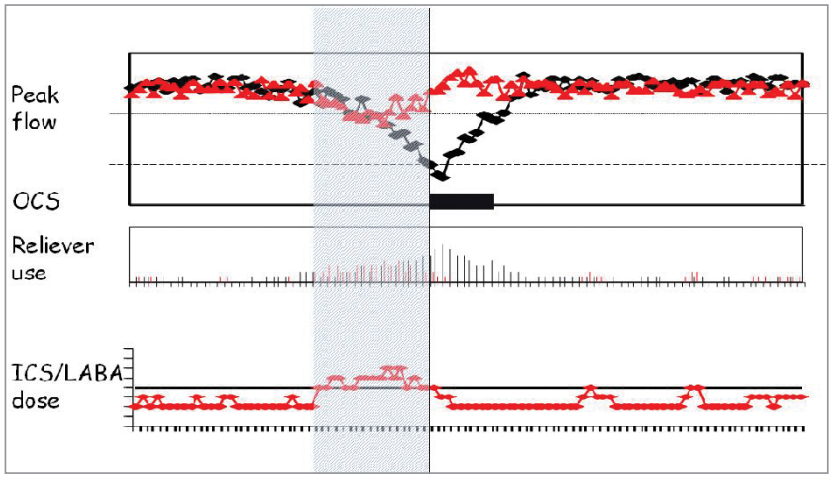

Figure 2. COMPASS study: Symbicort SMART vs Symbicort 2 x Fixed-Dose + SABA.[8]

The principle is that patients use more medication in response to symptoms.

The other key feature is that as soon as patients' symptoms improve, their medication usage returns to baseline levels. Commonly, an Action Plan will advise increasing maintenance treatment in response to a reduction in peak flow by 20% and remain on that higher dose for 2 weeks; if after 2 weeks peak flow is 80–100% of personal best, patients are instructed to return to their usual treatment. One of the virtues of Symbicort SMART is that patients naturally up/down titrate in response to symptoms so as soon as symptoms begin to ease off, patients on the SMART regime can titrate back to maintenance dosing levels. Every patient acts as his/her own control for treatment.

Interestingly, a subanalysis by Prof. Peters of reliever medication use in the COMPASS study has revealed a patient profile that is very suitable for Symbicort SMART. Dividing the group into above and below average reliever use cohorts demonstrates that approximately 300 used more than 1 reliever dose per day, while about 700 used less than 1 reliever dose per day (see Fig. 3). What happens to the effect of Symbicort SMART in the frequent versus the non-frequent users? For the non-frequent users, exacerbations are about the same. The analysis reveals that most of the protection from exacerbations occurs in the more frequent users. This group is deriving the most benefit from Symbicort SMART and so if they are removed to FD therapy, they are being denied therapeutic benefit. Notably, Symbicort SMART is associated with a very low number-needed-to-treat (NNT): treating only 8 people who are frequent reliever users with Symbicort SMART rather than Symbicort double-strength FD will prevent 1 severe exacerbation per year.

	All subjects	Reliever use <1/day	Reliever use >1/day
Symbicort SMART	1100	714	386
Seretide FD	1090	718	372
Symbicort FD	1115	742	373

Data from COMPASS study

Figure 3. Frequent reliever use of study: above and below average reliever use cohorts.[8]

Symbicort SMART and comparators

Good evidence demonstrates that the SMART approach works well in the real world. A recent analysis of the exacerbation burden in the 3- to 4-week period immediately following a single day with high reliever use (>6 inhalations/day) used data from the COMPASS and SMILE studies, which compared Symbicort SMART 160/4.5 µg twice daily plus as needed with similar or higher maintenance doses of ICS/LABA plus SABA or formoterol (i.e. comparing Symbicort SMART with both conventional Symbicort and Seretide stable dosing regimens).[7,9]

The Symbicort SMART strategy was found to be associated with the least likelihood of requiring oral steroids or hospitalisation/ER treatments in the period after high reliever episodes. Prof. Peters noted that after a bad day (where patients are using a lot of reliever medication in response to symptoms), most people do not have an exacerbation. They might survive one or even two bad days. Notably, an Action Plan will likely state that following a bad day, patients should double or quadruple their steroid dosage, when in fact they never needed it in the first place; 80% of them were going to improve anyway.

Thus, the Symbicort SMART strategy deals effectively with the vast majority of patients who were going to improve anyway and halves the number of patients who progress to an event. However, some patients will still develop a severe exacerbation. Any Action Plan must therefore include provisions for how to cope with a severe event, particularly as Symbicort SMART is targeted for those patients who are intrinsically more likely to have an asthma event.

Concepts of control are changing, creating confusion

Prof. Peters notes that as asthma has improved over time, the resulting changes in concepts of asthma control are causing confusion at the GP level, among nurses, pharmacists and primary care physicians. On the one hand, the Global Initiative for Asthma (GINA) guidelines have endorsed the concept of total control, with the eradication of asthma. The possibility of achieving guideline-defined asthma control was examined in the GOAL (Gaining Optimal Asthma ControL) comparison of fluticasone propionate and salmeterol/fluticasone in patients with uncontrolled asthma.[10] Treatment was stepped-up until total control was achieved (or maximum 500 µg corticosteroid twice daily). The study findings revealed that total control was only possible in around 25% of all patients. In other words, it is not realistic to expect guideline-derived total control very often in the majority of patients in the real world.

The revised, evidence-based 2006 GINA guidelines for asthma management and prevention are also based on control of the disease, yet are more practical for use in the real world, allowing for use of the Symbicort SMART strategy (maintenance AND reliever therapy).[11] A review of a recent American Thoracic Society/European Respiratory Society Task Force emphasises that two broad categories are needed for the assessment of asthma control: assessment of the current level of clinical control (e.g. symptoms, reliever use and lung function) and assessment of future risk to the patient (e.g. exacerbations and lung function decline).[12] This review provides a framework for understanding the relationship between current concepts of asthma phenotype, severity and control.

Following the promulgation of asthma control, a series of articles that examined the patients' perception of their own control versus GPs' scoring of that control concluded that patients are very bad at assessing their own control and need the health professionals to undertake the scoring. What sort of resonance does the concept of total control have in the real world, where some of our real challenges exist in people with markers of poverty and psychological illness?

Prof. Peters believes it is unhelpful to have the ongoing marketing battle between GlaxoSmithKline (advocating total control in alignment with Seretide) and AstraZeneca (maintenance and reliever strategy with Symbicort SMART) as they attempt to prove the superiority of their respective products. In reality, both provide very effective means for treating asthma. The marketing battle obscures the fact that these products are both excellent as fixed-dose maintenance therapy and Symbicort additionally as maintenace and reliever treatment in suitable patients.

There is no crisis. The reality of most poor control is explained not by the treatment but by:

- Simple human errors by doctors
  - Wrong diagnosis
  - Wrong treatment choice
  - Inadequate education
  - No (or ineffective) asthma action plan
- Simple human errors by patients
  - Poor adherence to treatment
  - Failure to attend for clinical review
  - Not following action plan

Proof is provided by the AHEAD study, in which, unlike other asthma studies, no change was made to the maintenance treatment.[13] Patients entered the run-in/observation phase on exactly the treatment they were using at the time of signing up to the study. Within 2 weeks of entering the study with no treatment change, FEV_1 values increased from an average of 2.1 to 2.3 (i.e. from approximately 70–85% of predicted). This highlights the fact that basic attention to detail (device technique and regular medication usage) was responsible for much of the improvement seen after two weeks of run-in. After 6 months of randomisation to SMART or Seretide at the highest marketed dose, patients gained approximately another 200 mL of FEV_1.

In Conclusion (Professor Peters):

- Both fixed-dose combination and Symbicort SMART are superb ways to manage moderate-severe asthma
- Symbicort SMART has neither advantage nor disadvantage for inflammation
- Symbicort SMART has neither advantage nor disadvantage for current symptom control
- Symbicort SMART has consistent advantage for exacerbation reduction
- Symbicort SMART achieves similar or better outcomes at lower treatment doses and costs
- The relative benefit versus fixed-dosing may be higher in higher PRN users – needs further analysis
- In patients with higher risk of exacerbations, there should be a good reason not to use Symbicort SMART

Commentary from Professor Richard Beasley

Professor Peters provided a timely update of the management of adult asthma during his recent lecture tour of New Zealand. The key clinical messages from his presentation included:

1. ICS remain the most important long-term treatment in asthma and most of their efficacy can be achieved with what is traditionally considered low doses, i.e. beclomethasone dipropionate or budesonide 200 to 400µg per day and fluticasone 100 to 250µg per day.
2. Long-acting beta-agonists must always be prescribed with an inhaled steroid in the form of a combination ICS/LABA inhaler, rather than in separate inhalers, which run the risk of LABA monotherapy in patients poorly compliant with their ICS treatment.
3. The optimal regime by which combination ICS/LABA inhalers can be prescribed is by the SMART regime, in which patients use their budesonide/formoterol inhaler both as regular maintenance and reliever therapy. The SMART regime results in a reduction in severe exacerbations compared with fixed twice-daily ICS/LABA therapy with a short-acting beta-agonist as reliever.
4. Asthma self-management plans remain a core component of asthma management, guiding patients in both their long-term management and also the treatment of severe attacks.

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AstraZeneca

Conflict of Interest: Professor Peters has previously served on Advisory Boards for AstraZeneca (he has no such current involvement) and has received honoraria over a period for lectures and chairing meetings on behalf of AstraZeneca. Amongst many Clinical Investigators, Prof. Peters was an author on several of the Symbicort SMART papers. AstraZeneca Limited paid Prof. Peters an honorarium for this series of lectures that was modestly but still significantly greater than salary foregone for the week. Currently (although unpaid), Prof. Peters is part of a group overseeing a fascinating survey of patients with asthma in Australia and New Zealand. Prof. Peters recently participated in an Advisory Board for GlaxoSmithKline. The publication of this article was supported by an educational grant from AstraZeneca, which has no control over editorial content. The views expressed by Prof. Peters are his clinical opinions and not necessarily those of AstraZeneca. Products mentioned in this presentation are prescription medicines and detailed prescribing information is available at www.medsafe.govt.nz.