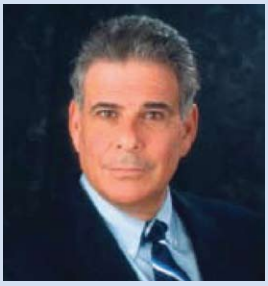
Research Review
SPEAKER SERIES

HOW TO *RAISE THE BAR* ON PATIENT ADHERENCE IN ASTHMA – NEW TOOLS AND STRATEGIES
June 2009

This publication is a summary of a recent presentation by Dr William Berger, a renowned asthma specialist from California USA, who spoke to a panel of general practitioners and health professionals in Auckland, Palmerston North and Dunedin in June 2009, about various tools that enable clinicians to objectively measure asthma control and some new strategies for managing asthmatic patients.



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Dr Berger is a past President of the American College of Allergy, Asthma and Immunology, and as an acknowledgement of his cumulative efforts in the field, has received the title of Distinguished Fellow of the American College of Allergy, Asthma and Immunology.

What is adherence?

The many excellent medications available for treating chronic diseases, including asthma, can only be successful if patients adhere to them, i.e. if they follow a prescribed treatment regimen. It includes how willing they are to start treatment and their ability to take medications exactly as directed.

Probably every clinician who prescribes drugs, no matter where, would agree that one of the main issues they face in their daily practice includes persuading their patients to take the medication. Up to 60% of all medication prescribed is taken incorrectly, or not at all.[1] Poor medicine adherence leads to unnecessary disease progression, disease complications, reduced functional abilities, a lower quality of life, and even death.

Nonadherence can be defined in many different ways:[1,2]

- 6%–44% of all prescriptions that are written are never filled
- forgetting to take medication, overmedication or deliberate underdosing, taking the wrong medication, taking the right medication at the wrong time, taking someone else's medication, and hoarding old medications to take later
- poor clinic attendance
- discontinuing medication prematurely
- difficulty in persuading younger patients to take the medication.

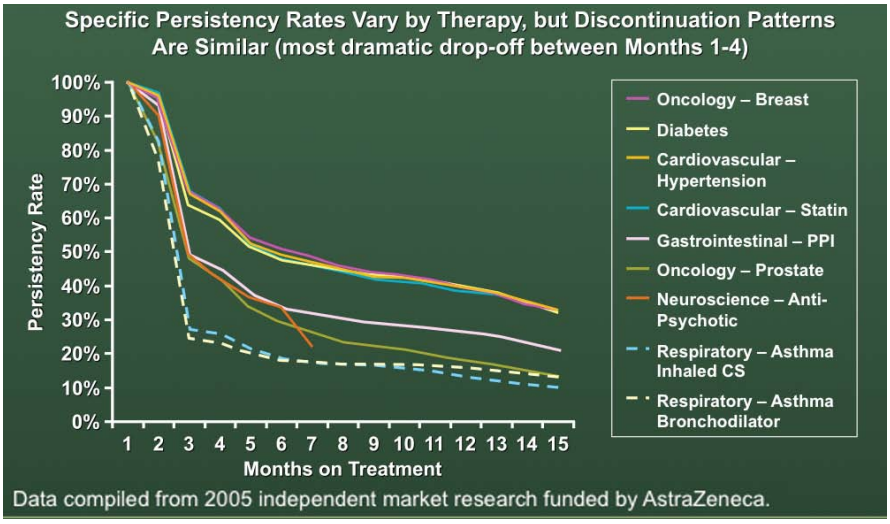
The problem of nonadherence crosses disease states

Data from independent market research based on patient-level data (n=960,797) commissioned by AstraZeneca in 2005 reveals how specific persistence rates vary by therapy but that discontinuation rates generally follow a similar pattern [see slide 1]. Persistency rates were examined for nine market areas, each of which included patients who were new to that market in July 2002 and followed them through July 2004. A patient was considered persistent if the days' supply from a previous month allowed for therapy to continue into the current month.

The analysis shows how the most dramatic drop-off from therapy occurs within the first four months of the prescription being issued, with asthma medications demonstrating a particularly sharp decrease. At the end of 12 months, fewer than 50% of patients are still taking the drug, across disease areas.

Researchers need to determine if there are economic factors (i.e., cannot afford co-pays) or factors related to the patient (patient's acceptance of the disease and treatment).

In asthma, long-term controller-specific adherence rates range from 9%[3] to 34%[4] with inhaled corticosteroid (ICS) therapy, from 18%[3] to 68%[4] with leukotriene receptor antagonist (LTRA) therapy, and 22%[5] with inhaled corticosteroid/long-acting β_2-agonist (ICS/LABA) therapy.



Slide 1: The Problem of Nonadherence Crosses Disease States

Multiple factors affect adherence to asthma controller therapy

According to the World Health Organisation (WHO), patient-related factors are just one determinant of adherence behaviour.[2] The WHO defines adherence as a complex behavioural process strongly influenced by the environments in which people live, health care providers' practice, and health care systems that deliver care.

Studies across a range of chronic diseases have found that low rates of adherence are associated with doubts about the need for medication and concerns about possible side effects. Slide 2 illustrates a need-versus-concern framework that may help clinicians understand why many patients do not use ICS therapy as prescribed, and how the provider can influence that choice.

Medication adherence is related to people's knowledge and beliefs about their illness, motivation to manage it, confidence in their ability to engage in illness-management behaviours, and expectations regarding the outcome of treatment and the consequences of poor adherence. These beliefs and expectations affect how patients weigh factors that directly affect their decisions: namely, the perceived need for the drug and concerns and fears about side effects and negative consequences. Because ICS medications do not provide immediate symptom relief, patients may believe that these agents are ineffective and unnecessary. Concerns about side effects, those that the patient has actually experienced or those that are feared as long-term consequences, also influence a patient's decision.

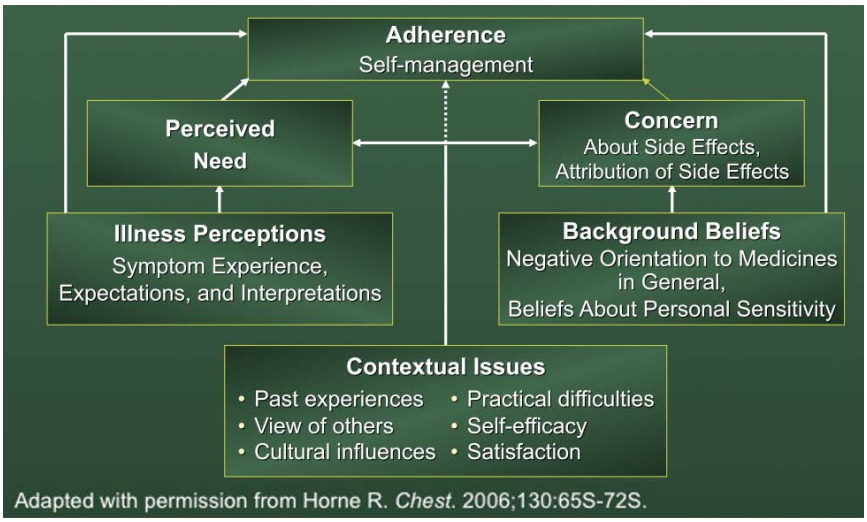
The research determined that additional investigation is necessary to identify those factors that cause this drop-off after the first few months of therapy.

Measuring asthma control

As asthma is a variable disease, its control should be measured through multiple parameters, on an ongoing basis. Subjective measures include patient self-reporting of daytime symptoms and night-time awakenings, use of rescue medication, days of missed school and/or work, and functional status, including limitations on daily activities.[6] Objective, accurate measurements of asthma control are provided by patient-centric questionnaires (e.g., Asthma Control Test™ [ACT], Asthma Control Questionnaire [ACQ], and the Asthma Therapy Assessment Questionnaire [ATAQ]), as well as markers of inflammation, including sputum eosinophils, fraction of exhaled nitric oxide (FE_{NO}), and airway hyperresponsiveness (AHR). Utilisation of healthcare resources can also be used as an indication of asthma control. Lung function tests, including peak expiratory flow (PEF) and FEV_1 provide an objective measurement of asthma control, although lung function can be close to normal even among patients with persistent asthma.[6]

Factors complicating measures of control

The tendency for patients to fluctuate widely between severity categories over time makes the use of a single measure of control as in other disease states difficult.[7] Asthma control should therefore be assessed by several parameters, including FEV_1, PEF, daily symptom scores, β_2-agonist use, nocturnal symptoms, and activity limitations. Exacerbations and unscheduled health visits over time should also be taken into account.



Slide 2: Multiple Factors Affect Adherence to Asthma Controller Therapy

Low perception of dyspnoea (POD), or subjective shortness of breath, may also make it difficult to assess and achieve control. Israeli researchers measured the POD in 113 patients with stable asthma and related it to the incidence of near-fatal and fatal attacks over a two-year period.[8] At baseline, 26% of patients had low POD, 59% had normal POD and 15% had high POD. Compared with those with normal or high POD, patients with low POD, even without a history of near-fatal asthma, were significantly more likely to visit the emergency room, be hospitalised, suffer near-fatal asthma or die. In comparison with the other groups, low POD patients tended to be older, female, be a long-time asthma sufferer, and have more severe asthma.

Continuous monitoring and re-evaluation to achieve control

Because asthma control can vary widely over a relatively short time frame, the level of control should be assessed on an ongoing basis and therapy modified as needed. Asthma control should be reassessed at every clinical encounter, and the patient should be educated to monitor control of his or her asthma. The NAEPP guidelines recommend that assessments be conducted at 1- to 6-month intervals to determine if the goals of therapy are being met and if adjustments in therapy are needed.

Asthma control is evaluated according to the frequency of asthma symptoms, use of rescue medication, sleep disturbance, limitations of daily activities, patient and physician overall assessment, and lung function. If control worsens, a detailed assessment should be conducted to determine potential causes, such as exposure to triggers, lack of adherence/compliance with therapy for a variety of reasons, and a review of the asthma action plan.

New tools may help physicians assess asthma control and guide therapeutic decisions, including when to increase maintenance doses or use adjunctive agents.

Asthma in New Zealand

Asthma has a significant impact upon New Zealand morbidity and mortality statistics:[9-11]

- 15–20% of New Zealand children and adults have asthma.
- New Zealand has the second highest prevalence of asthma in the world (behind the UK).
- Asthma is the most common cause of admission to hospital for children.[10]
- Severe asthma is common – up to 8% of teenagers report wheeze limiting speech, and 10% of adults report waking with breathlessness occurring within the previous 12 months.
- Hospitalisation rates for asthma have more than doubled in the past 30 years.
- Asthma is the highest-ranking specific disease in terms of Years Lost to Disability in males, and third highest for females.
- The rates of asthma are disproportionately high in Māori and Pacific Island adults.
- Currently 1 in every 200 deaths in New Zealand is due to asthma.

Analyses of data from the New Zealand mini-INSPIRE study regarding outcomes for patients with asthma in New Zealand are of concern; 76% of the patients surveyed were using their reliever inhaler at least daily, and a third were using it three or four times a day.[12] This contrasts with international best practice guidelines, which suggest that using reliever inhalers more than two or three times a week indicates a level of asthma control which could be improved.[13-15]

Poor compliance with asthma treatments is identified as a major contributor to the poor outcomes that are consistently seen in surveys of patients with asthma.[16-20] New Zealand data have revealed that, when compliance is defined as taking ≥90% of prescribed doses of twice-daily ICS, in a motivated group of patients who had volunteered to take part in a clinical study, compliance was less than 20%.[21]

Markers of inflammation and biomarkers

Airway hyperresponsiveness (AHR) is a characteristic feature of asthma and has been linked with both inflammation and repair of the airways.[22] Measurements of airway responsiveness are useful in making a diagnosis of asthma, particularly in patients who have symptoms that are consistent with asthma and who have no evidence of airflow obstruction.[23] These tests can be performed quickly, safely, and reproducibly.

Sputum eosinophils are a helpful marker for asthma control, as they appear to correlate with disease severity, lung function, and bronchial hyperreactivity.[24] A strategy that manages patients according to their induced sputum eosinophil count and specifically aims to reduce eosinophilic inflammation may decrease asthma exacerbations versus standard care (management by a modified version of the British Thoracic Society guidelines).[24]

FE_{NO} (fractional exhaled nitric oxide) correlates with airway inflammation in asthma; increased concentrations are associated with lower levels of asthma control. Results from a New Zealand study that evaluated the diagnostic utility of FE_{NO} for asthma suggest that the measurement of FE_{NO} levels could be used to guide asthma treatment.[25] In that study, ICS doses were adjusted on the basis of either regularly performed NO breath testing or a clinical algorithm based on conventional guidelines (control group) [see Slide 3].

Both FE_{NO} and sputum eosinophils provided higher levels of sensitivity for asthma (88% and 86%, respectively) than did traditional lung function assessments (which ranged in sensitivity from 0% to 47%). Both FE_{NO} and sputum eosinophils provided significantly higher levels of diagnostic accuracy compared with peak flow analysis or FEV_1 corticosteroid responsiveness. In addition, the use of FE_{NO} measurements resulted in 40% lower maintenance ICS doses, compared with the control group, without compromising major clinical outcomes, such as exacerbation rates and the use of prednisone.

Besides their potential in providing a useful alternative for adjusting ICS dose,[25] FE_{NO} falls rapidly during treatment with ICS but rises quickly after stopping ICS, making it potentially useful in assessing patient compliance with controller therapy.[26] In addition, German research has recently suggested that FE_{NO} measurements may be used to effectively rule in and rule out asthma in general practice.[27] That investigation also suggested that FE_{NO} measurement might be a reasonable alternative to bronchial provocation, which is a time consuming procedure and carries a small risk of severe bronchospasm.

FE_{NO} and FEV_1 predict risk of exacerbations

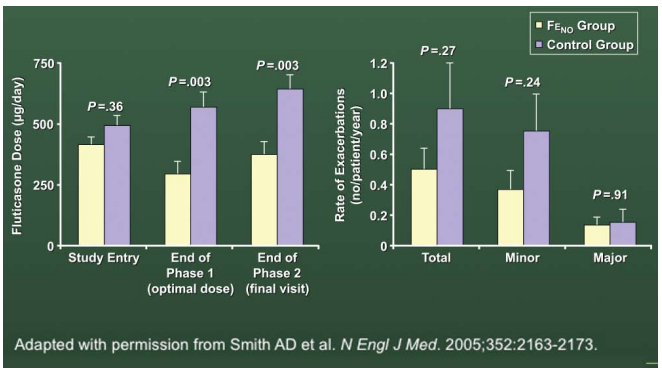
Combined assessment of FE_{NO} with postbronchodilator FEV_1 in clinically stable, treated, nonsmoking patients with asthma may help to stratify the risk of subsequent exacerbations.

A prospective study measured lung function and exhaled NO in 44 nonsmoking patients with asthma who were receiving combination ICS/LABA therapy for three years.[28] Over an 18-month study period, 22 asthmatics had ≥1 exacerbations, 16 had two exacerbations, and 6 were hospitalised, including 1 asthmatic with near-fatal asthma. Of all exacerbations, 91% (20/22) occurred in patients with asthma whose baseline FEV_1 was ≤76% of predicted values; 59% (13/22) of all exacerbations occurred when FE_{NO} was elevated ≥28 ppb. Independent of the baseline FEV_1, FE_{NO} ≥28 ppb increased the relative risk for exacerbation by 3.4. Independent of baseline FE_{NO}, FEV_1 ≤76% of predicted increased the relative risk of an exacerbation by 1.7.

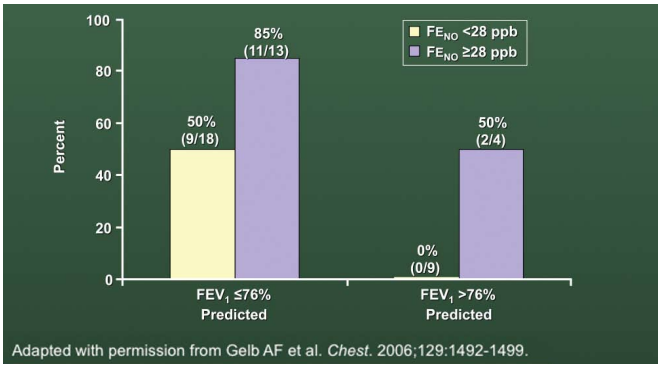
The probability of an asthma exacerbation in 18 months was 85% with a combined baseline FEV_1 ≤76% predicted and FE_{NO} ≥28 ppb, whereas a combined baseline FEV_1 >76% and FE_{NO} <28 ppb had a 0% probability [see Slide 4].

The role of Vannair in asthma adherence and control

The pressurised metered dose inhaler (pMDI) combination inhaler Vannair (budesonide/eformoterol) can potentially play a very important role in asthma adherence and control. Combination inhalers containing an ICS + LABA are likely to improve adherence with long-term asthma treatment, by reducing the physical number of inhalers. In addition, the short-term improvements in symptoms and lung function which the patient attributes directly to these combination inhalers are likely to further enhance adherence. This increased adherence leads to improved asthma outcomes by ensuring that the patient takes regular ICS, thereby reducing the inflammation in the airways that characterises asthma. Coupled with the long-acting bronchodilator effects of the LABA, these combination inhalers lead to improved asthma symptoms, as demonstrated in many clinical studies.



Slide 3: FE_{NO}: Concentrations Used to Guide Therapy



Slide 4: FE_{NO} and FEV_1 Predict Risk of Exacerbations

Another important facet of adherence with asthma treatment, often overlooked by clinicians, is the type of device delivering the medication. While some patients prefer a dry powder device, which can be easier to use as inhalation does not need to be co-ordinated with actuation of the device, the traditional pMDI is favoured by many patients, perhaps because they are more familiar with these devices (in August 2008, MDIs accounted for 80% of inhalers used in New Zealand).[29]

Vannair dosage and administration

Vannair pMDI is available in New Zealand in two budesonide/eformoterol combination delivery options; Vannair 100/6 or 200/6 (budesonide 100 µg or 200 µg and eformoterol 6 µg per inhalation). Vannair has been granted full funding with Special Authority by New Zealand's Pharmaceutical Management Agency (Pharmac) for asthma (see the pharmaceutical schedule for full details; www.pharmac.govt.nz) and is registered for use as a fixed-dose therapy only, not as maintenance/reliever therapy.[30] Vannair pMDI is indicated in the regular treatment of asthma in adults and children aged ≥6 years where use of a combination (ICS and LABA) is appropriate. It is not indicated for patients successfully managed by ICS and occasional use of a short-acting β_2-agonist (SABA). Vannair pMDI is not indicated for relief of acute bronchospasm. Dosage should be individualised according to disease severity. When control has been achieved, the dose should be titrated to the lowest dose at which effective control of symptoms is maintained.

Adults and adolescents (≥12 years)

- Vannair 100/6: 2 inhalations once or twice daily
  Maximum daily maintenance dose: 4 inhalations
- Vannair 200/6: 2 inhalations once or twice daily
  Maximum daily maintenance dose: 4 inhalations

In some cases, up to a maximum of 4 inhalations twice daily may be required as maintenance dose or temporarily during worsening of asthma.

Children (6–11 years)

- Vannair 100/6: 2 inhalations twice daily
  Maximum daily dose: 4 inhalations

Patients should be instructed to use Vannair pMDI even when asymptomatic for optimal benefit. There are no special dosing requirements for elderly patients.
No data are available for use of Vannair in patients with hepatic or renal impairment. As budesonide and eformoterol are primarily eliminated via hepatic metabolism, an increased exposure can be expected in patients with severe liver diseases.
For full prescribing details regarding Vannair, consult the New Zealand Medsafe data sheet (http://www.medsafe.govt.nz).

Advantages of combination inhalers

Combination ICS + LABA inhalers are more convenient to use than separate inhalers and ensure that the corticosteroid is not discontinued when the LABA is added.

Clinical data have shown that the addition of a LABA is likely to be much more beneficial than increasing the dose of ICS because of the limited ICS dose response.[31]

The concurrent administration of budesonide and eformoterol is not associated with any increased incidence of adverse reactions over those reported for these substances when administered singly.[32]

Evidence suggests that ICS + LABA treatment results in a small but definite improvement in asthma when taken in a single inhaler instead of separately.[33]

Combination therapy inhalers may also improve adherence to long-term treatment, which is notoriously poor in patients with ICS used alone, accounting at least in part for the high proportion of patients with asthma who remain symptomatic despite the availability of effective therapies.

Clinical efficacy and safety

Long-term safety data have established that the safety profile and tolerability of Vannair pMDI is similar to that of Symbicort Turbuhaler.[32] There is no evidence of desensitisation or tachyphylaxis associated with the long-term use of LABAs. Vannair does not result in substantial differences in the rates of adverse events over the rates observed with the individual components of Vannair.

The safety profile of Vannair is commensurate with that seen for this class of medications.

Clinical studies have shown that the addition of eformoterol to budesonide improves asthma symptoms and lung function, and reduces exacerbations.

Notably, Vannair offers a rapid bronchodilatory effect; in a 12-week clinical study, Vannair improved FEV_1 within 15 minutes of the first dose on the day of treatment randomisation.[34] In that same study, the improved asthma control seen with Vannair as early as Day 1 was sustained over the 12 weeks. Predose FEV_1 improved substantially with Vannair within the first 2 weeks of treatment, and remained improved throughout treatment; values were significantly improved compared with budesonide, eformoterol, and placebo at the end of treatment, using the last observation carried forward methodology.

Clinical trials have also shown that Vannair reduces daily rescue medication and increases asthma control, compared to budesonide or eformoterol alone.

Take home messages

- Biomarker use is promising in the effort to achieve and maintain control for asthma patients.
- With ongoing assessment and a focus on metrics of control, asthma control is a realistic and achievable goal.
- The combination pMDI Vannair delivers budesonide and eformoterol as ICS + LABA therapy in a single inhaler with a rapid onset of action and long-lasting effects that reduce the risk of exacerbations. These properties may help adherence as patients only have to use one inhaler for maintenance treatment and they notice an improvement in symptoms soon after taking a dose.

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