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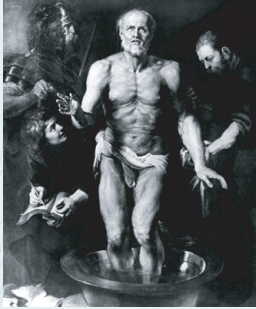
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# Asthma FOCUS



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## FAMOUS ASTHMATICS



Lucius Annaeus Seneca  
(4 B.C.- 79 A.D.)

Roman orator,  
author, and  
statesman

Lucius Annaeus Seneca, son of Marcus (Lucius) Annaeus Seneca (Seneca the Elder), was extensively trained in rhetoric and the philosophy of Stoicism - indeed, Seneca the Younger was one of the principle figures in the development of Roman Stoicism, the only form of that philosophy for which we still have extensive primary material.

Banished to Corsica on a charge of adultery, Seneca had become content to live out his life in study of nature and philosophy when he was recalled to Rome by the emperor's wife, Agrippina, who wanted him to tutor her son, L. Domitius - the future emperor Nero. While under Seneca's guidance Nero's rule was relatively benign, but before long that influence waned and Nero's rule became more and more brutal.

Eventually, Seneca felt it necessary to retire in order to remove himself from Nero's presence. He was accused of participating in a plot to assassinate Nero. Without trial, Seneca was ordered to commit suicide; his wife, Pompeia Paulina, chose to join him in his fate.

Seneca likened his asthma attacks to a "last gasp," and wrote "nothing seems to me more troublesome." Yet he was a powerful Roman leader, a wealthy merchant, and prolific author.

## Combination Therapy: A paradigm shift in asthma management

### Introduction

Although a number of different drugs are available to treat asthma, not all of them will work as well as expected. If one drug isn't keeping asthma in check, options generally are either to increase the dose of that medication or to take an additional medication of a different type. Inhaled corticosteroids (ICS) is a safe, effective and preferred first-line therapy for both children and adults who have persistent asthma. But at the same time, some research indicates that they may carry a small risk of steroid-like side effects - such as cataracts, osteoporosis and, in children, growth suppression.

Experience with long-acting beta agonists (LABAs, or 'symptom controllers') over the last 10 years indicates that these drugs are potent and effective bronchodilators, capable of improving asthma control in those with moderate to severe disease. They are optimally used in combination with ICS, these two classes thereby providing a dual anti-inflammatory and bronchodilator action. Combination therapy with these agents is most appropriate in patients with moderate to severe asthma who remain symptomatic on ICS therapy, requiring frequent symptom relief with short-acting beta agonists.

### The Rationale for Combination Therapy

#### Pathophysiology:

Asthma is a disease of two components: inflammation and bronchoconstriction (Figure). No single drug effectively treats both the underlying inflammation and the bronchoconstriction. Thus, pharmacotherapy for asthma has focused on treating both components of the disease individually. Consequently, the drugs administered most frequently to treat asthma are those that promote bronchodilatation and those that reduce inflammation.

The ICS acts on the cellular mechanisms which causes inflammatory mediator release, airway injury and remodeling, leading to poorer lung function and unstable disease. On the other hand LABAs are potent bronchodilator drugs that are not suitable for use as monotherapy in asthma. Their use in combination with ICS has led to the rethinking of some important issues in asthma management.

#### Is there any evidence of an anti-inflammatory effect of LABAs in addition to ICS?

Some studies have found that although LABAs alone do not act as anti-inflammatory agents, they may enhance the anti-inflammatory effect of ICS. In studies examining airway inflammation in people with asthma who remain symptomatic on ICS, the addition of a LABA resulted in less airway inflammation. Studies on sputum and peripheral blood have indicated that LABAs in combination with ICS may exert an anti-eosinophilic effect.

Recent evidence supports this view, showing that ICS have enhanced activity at glucocorticoid receptors after exposure to LABAs. Recent studies have also found a plateau effect with ICS. There is minimal clinical benefit of increasing doses above 250-500mcg/day of

fluticasone propionate (FP). This has been observed with other ICS. This finding is a clear indication for the addition of a LABA to achieve better asthma control in symptomatic patients taking higher doses of ICS.

So evidence indicates that there is likely to be an interaction between the two drugs, manifesting as reduced airway inflammation with prolonged and enhanced bronchodilatation.

It should be noted that, ICS remain the mainstay of asthma treatment. LABAs do not replace them and should never be used as monotherapy. LABAs do not possess clinically important anti-inflammatory activity and therefore cannot control the underlying disease process.

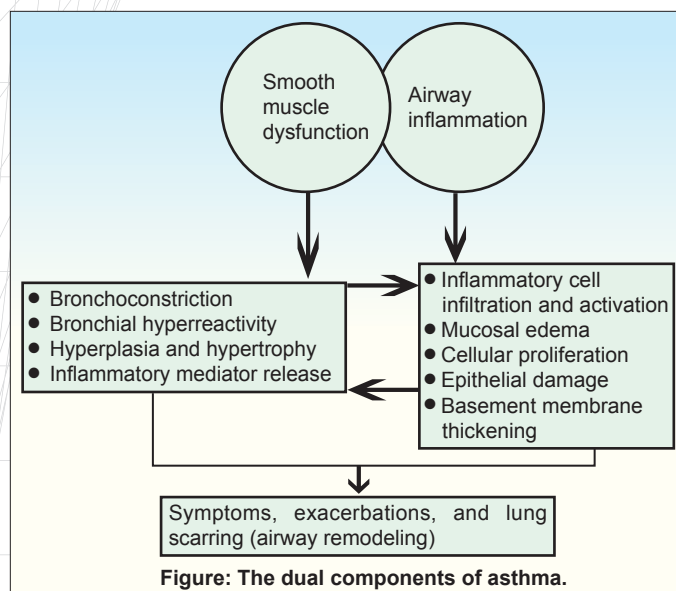


Figure: The dual components of asthma.

In combination with ICS they provide greater symptom control, morning and evening peak flow benefits and reduce mild and severe exacerbation rates, compared to ICS alone.

**Clinical Use of Combination Therapy**

Many carefully conducted studies in symptomatic patients on ICS indicate that the addition of a LABA to ICS results in greater improvement in:

- Symptoms, Lung function, and
- Quality of life, Exacerbation rates

In symptomatic patients, there is clear evidence indicating that adding a LABA is more effective than increasing the dose of ICS. Moreover, LABAs achieve better control of asthma symptoms without the adverse effects that may occur with additional high doses of ICS. As LABAs produce prolonged bronchodilatation (up to 12 hours), they can be combined with ICS and given in a

twice-daily dosing regimen. The combination can achieve improved asthma control in symptomatic patients when the total ICS dose is unchanged, or can maintain stability in well-controlled patients when the total ICS dose is reduced.

Adverse effects are pharmacologically predictable, based on the beta-adrenergic activity of LABAs (tremor, tachycardia, palpitations and headache) and are not different when the drugs are administered separately or together in one preparation. Similarly, there is no evidence that administration of a LABA and ICS in a single device alters the adverse effect profile of ICS.

The combination of a LABA and ICS should be considered when:

1. Symptoms or sub-optimal lung function persist on ICS alone.
2. It is desirable to reduce the current dose of ICS while maintaining optimal asthma control.
3. Initiating asthma treatment in a patient in whom rapid symptom improvement is needed.

**Combination Therapy in Children**

Clinical trials have demonstrated combination therapy to be as effective as component medications taken individually. However, before starting combination therapy, consider the indications for LABAs in children. Most children with persistent asthma should be adequately controlled on a dose of ICS equivalent to 250mcg/day of Fluticasone or less, and should not require LABAs. LABAs should only be prescribed for children with persistent asthma that is not adequately controlled on 200-250mcg/day of Fluticasone. Other issues to consider are adequate adherence with previously prescribed ICS, and that the child has an appropriate delivery device and reasonable technique.

**Dosage & Administration of Combination Therapy**

Combination therapy medications are available in both metered dose inhaler (MDI) and dry powder inhaler (DPI) forms. Comparison of the medication delivery between devices and resulting asthma control has produced similar results. However, individual variation in clinical response between devices may occur. Regardless of which type of device is considered to provide the best results, the choice of inhaler device for an individual should be based upon patient factors, e.g. the cost, age, strength, dexterity, vision, cognition, inspiratory flow rate and personal preference of the person with asthma.

Combination medications are available in a range of strengths. The difference lies in the ICS dose; the LABA dose remains constant. Dosing guidelines matching a combination medication to a person's asthma severity

have been developed for adults.

**Mild persistent asthma** - person on low dose ICS (e.g. 200-250 mcg/day of Fluticasone or 400-500 mcg/day Beclomethasone/Budesonide) & has persistent symptoms, consider combination medication with low dose ICS or increase the dose of ICS.

**Moderate asthma** - try a moderate dose of ICS (e.g. 500mcg/day of Fluticasone or 800-1000 mcg/day of Beclomethasone/Budesonide) in combination medication at first before increasing the ICS dose.

**Severe asthma** - use a higher strength ICS in combination with LABA (e.g. 500-1000 mcg/day of Fluticasone or 1000-2000 mcg/day Beclomethasone/Budesonide) and consider referral for specialist assessment if this does not achieve optimal asthma control.

There is limited evidence supporting an increase in ICS for management of acute exacerbations of asthma, but there is no current evidence regarding increases in medication for those already using combination therapy. The traditional practice of increasing the patient's usual ICS dose would also increase the dose of the LABA. At present there is limited evidence to support this approach. However, it is acknowledged that the most practical and cost-effective option for the patient may be to do this while seeking medical advice. Effective use of combination therapy requires a few steps to ensure the patient is managed on the optimal dose for their age, disease severity and symptoms.

**Gaining control**

- The addition of a LABA leads to significant improvements in control in most patients.
- The initial dose of combination therapy may be higher than the maintenance dose. The aim will be to gradually reduce dose once control is achieved.
- 'Control' will be measured by improvements in lung function (PEF, FEV<sub>1</sub>) and a decrease in the frequency and severity of symptoms. Good control is characterised by reliever use <1 time per day, as indicated in the National Asthma Guidelines published by Asthma Association, Bangladesh.

**Assessing control -**

1- 3 months after adding a LABA to ICS

- If patients are persistently symptomatic or continue to require reliever medication daily, consider other contributing causes/triggers and/or specialist referral. Further increases in doses may be beneficial, but current evidence does not support exceeding recommended maintenance doses (salmeterol 50mcg BD, formoterol 24mcg BD).

- If stability is achieved with optimal lung function for the individual patient, consider a reduction in ICS.

**Stepping down -**

- reducing to a maintenance dose
- Once control is achieved, reduction of the daily dose to the lowest effective dose is the next aim.
- Step down by reducing to the next lowest dose of combination therapy. Some patients may require the addition of a separate ICS inhaler to facilitate gradual reduction of the corticosteroid component.

**Maintenance**

- Maintain at the lowest effective ICS dose and reinforce trigger factor avoidance and management
- Schedule a follow-up appointment to assess the appropriate dose of each component (LABA and ICS).

**Conclusion**

Combination therapy is an appropriate intervention in symptomatic patients with persistent asthma previously treated with short-acting β<sub>2</sub>-agonists alone, a leukotriene modifier alone, or an inhaled corticosteroid. Combination therapy with a long-acting β<sub>2</sub>-agonist and an inhaled corticosteroid offers distinct clinical and economic advantages compared with other multiple drug regimens for the long-term control of persistent asthma. Complementary mechanisms of action of these two classes of drugs achieve a superior level of asthma control and increasing quality of life, compared with increasing the dosage of the inhaled corticosteroid. The safety profile similar to that of the individual agents used alone at the same dosages and may permit asthma control to be achieved at a lower dosage for the corticosteroid, thereby reducing the likelihood of systemic adverse effects. Airway inflammation effectively is controlled by the addition of a long-acting β<sub>2</sub>-agonist to an inhaled corticosteroid, and exacerbations are greatly reduced with combination treatment. This also likely simplify and increase patient adherence to an asthma treatment plan.

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**Umbilical cord blood may hold clue to childhood allergy and asthma**

High levels of antibodies to allergens in a baby's umbilical cord blood might be more important in the development of childhood allergies and asthma than exposure to allergens, or lack of them, after birth, suggests a latest research.

The authors base their findings on more than 1300 children born between 1989 and 1990, from whom a sample of cord blood serum was taken at birth to measure levels of IgE, an immune system response indicating sensitization to allergens, such as pet dander, house dust mite, and grass pollens.

The children were also assessed at the ages of 1, 2, 4 and 10 years of age to find out if they had developed allergies and/or asthma. By the age of 4, one in five children had become sensitized to allergens, and by the age of 10 more than one in four (27%) had done so.

Children who had high umbilical cord blood levels of IgE at birth were around twice as likely to have become sensitized. One in 10 of the children had been diagnosed with asthma by the time they were 1 to 2 years old; by the age of 4, one in seven (15.2%) of the children had asthma. Almost 13% of the children had asthma by the time they were 10.

High IgE cord blood levels were not associated with the development of asthma up to the age of 4, but children with high IgE levels in their umbilical cord blood were around 66% more likely to have a diagnosis of asthma by the age of 10.

Such a finding suggests a late onset type of asthma, say the authors, pointing out that this is backed up by the percentage of asthmatic children with high IgE rising by age, from just under 9% at 12 to 24 months to 18.5% by the age of 10.

Children who were not sensitized to allergens at any age were more than three times as likely to be diagnosed with asthma by the age of 10 if they had high IgE levels in their umbilical cord blood.

Exposure to pets at birth was not associated with cord blood IgE, nor did it explain the patterns of allergic sensitization and asthma. Dramatic changes in the immune system occur during pregnancy, and the immune response of the fetus can start as early as 10 weeks, say the authors. They suggest their findings indicate that fetal immune system programming could be more important than what happens after birth in influencing the development of childhood allergies.

Source: Sadeghnejad A, Karmaus W, Davis S, Kurukulaaratchy RJ, Matthews S, Arshad SH. *Thorax* 2004 Nov; 59(11): 936-42

**Exclusive breastfeeding protects against asthma**

Infants who are fed on a combination of breast and formula milk have higher rates of asthma and atopy than those who are exclusively breastfed for the first six months of life, according to a new study.

A recent research examined the association between breastfeeding, asthma and atopy, and body mass index (BMI) in 2,195 children prospectively followed from birth to 6 years.

The study group defined asthma as doctor-diagnosed asthma and wheeze in the last year and skin prick tests were used to determine atopy for 1,596 children.

There was a significant association between a shorter duration of any breastfeeding and increased BMI at 6 years. The effect of longer breastfeeding did not significantly decrease a child's risk of being overweight after adjustment for gender, birth weight and maternal smoking during pregnancy.

There was also a link between less exclusive breastfeeding and increased asthma and atopy after adjustment for BMI. With each additional month of breastfeeding, there was a 4% reduction in the risk of asthma. No significant effects of breastfeeding on atopy were observed.

'Public health interventions to promote exclusive breastfeeding for at least 6 months may reduce the prevalence and subsequent morbidity of asthma and atopy in early childhood,' conclude the authors.

Source: Oddy WH, Sherriff JL, de Klerk NH, Kendall GE, Sly PD, Beilin LJ, Blake KB, Landau LI, Stanley FJ. *Am J Public Health*. 2004 Sep; 94(9): 1531-7.

**Asthmatics 12 times more likely to develop chronic lung disease**

A study has revealed that asthmatics are 12 times more likely to develop chronic lung disease than non-asthmatics. The study, carried out at the University of Arizona, took over 20 years to complete and found that the risk of developing COPD (Chronic Obstructive Pulmonary Disease) for an asthmatic is twelve times higher than someone who does not suffer from asthma.

The researchers said that it is crucial to understand the link between COPD and asthma. This could eventually help us detect the condition earlier and offer better treatment. Such conditions as chronic bronchitis and emphysema come under the term COPD. Experts say that asthma does not cause permanent lung damage.

Study leader was Dr. Graciela Silva, Arizona University, USA. Dr. Silva said 'For many years, asthma and COPD have been regarded as distinct conditions, with separate clinical courses. However, over time, the two diseases may develop features that are quite similar. Our study shows a strong link between asthma diagnosis and the development of COPD, which suggest they may share a common background.'

Source: Silva GE, Sherrill DL, Guerra S, Barbee RA. *Chest* 2004 Jul; 126(1): 59-65

**Early allergen contact low asthma risk**

Exposing young children to allergens such as cat fur and house dust mite does not increase the risk of them developing asthma, suggests a new study.

For many years scientists have thought that the likelihood of developing allergic conditions such as asthma is related to the level of contact with allergens early in life. However, a recently published research report casts doubt on this theory, and suggests that genetics and birth order may play more significant roles in the development of asthma.

Scientists monitored 625 children from Ashford, Kent from birth until 5 and half years of age. They measured levels of allergens in cat fur and dust in their homes at the beginning of the study, and each year interviewed mothers about whether their child had experienced wheezing.

At the end of the research period the children were also skin-prick tested to see if they had become sensitized to house dust mite or cat fur allergens. Only one in ten of the children had become sensitized to either allergen by the age of 5 and a half. Both sensitization to allergens and wheezing were significantly more likely if the child's father had a genetic susceptibility to allergy or the child was a firstborn.

The researchers found no clear relationship between levels of allergen measured early in life and sensitisation to those allergens or frequency of wheezing over the next five years. In fact, even when very low allergen levels were measured sensitisation and wheezing were observed.

'The findings from this study, and other recent trials, demonstrate that there is no simple relationship between allergen exposure in early life, sensitisation to allergens and the subsequent risk of developing asthma,' said Dr Matthew Hallsworth, Asthma UK's Research Manager.

'It has become clear that the development of asthma depends on a complex interaction of genetics and environmental exposures, and until we understand more about these processes it is very difficult to give clear advice to concerned parents.'

The study's authors, at the National Heart and Lung Institute in London, concluded that reductions in domestic allergen exposures alone are unlikely to have a major impact in reducing the incidence of allergic sensitization or wheezing in childhood.

Source: Cullinan P, MacNeill SJ, Harris JM, Moffat S, White C, Mills P, Newman Taylor AJ. *Thorax*. 2004 Oct; 59(10): 855-61

**Asthma does not remit at adolescence**

Contrary to the commonly held belief that asthma in children frequently disappears during adolescence, researchers have found in a study that almost 60 percent of the children with asthma during the pre-pubertal period keep experiencing wheezing episodes during the first four years

after the onset of puberty.

Also, from their study results, the investigators revealed that being either overweight or obese at age 11 was associated with a threefold increased risk for the persistence of asthma. The study authors analyzed data on 781 children from a longitudinal birth cohort called the Tucson Children's Respiratory Study.

The investigators examined the youngsters at ages 6,8,11,13 and 16 years to determine factors influencing the persistence or the remission of childhood asthma after the onset of puberty, which was considered to be 12.2 years.

A major finding of the study was the strong, independent effect of elevated body mass index and the early onset of puberty on the persistence of wheezing in adolescence. Of the 781 children in the study, 166 were considered asthmatics either as a result of frequent wheezing or a physician-confirmed diagnosis, plus wheezing.

Of this group, 58 percent of the children, or 97 kids, reported the presence of wheezing after the onset of puberty. In contrast, only 30 percent of the children with infrequent wheezing before puberty experienced wheezing after the onset of puberty.

Source: Guerra S, Wright A L, Morgan W J, Sherrill D L, Holberg C J, Martinez F D. *Am. J. Respir. Crit. Care Med*. 2004 Apr; 170: 78-85

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## Drug Delivery Devices for Asthma treatment

When selecting an inhaled corticosteroid for a patient, physicians must consider both the drug molecule & the inhaler device. Although there may be some differences between drugs related to topical potency and perhaps safety, these differences can be magnified or minimized based on the delivery device. One should always take into account the efficacy and safety of the preparation and the ease of use of the delivery system, as well as the frequency of dosing. Clearly, less frequent dosing and more convenient devices lead to better compliance.

Inhaled corticosteroid delivery systems include

- Nebulizer,
- Pressurized metered-dose inhalers (PMDIs),
- Breath-actuated metered-dose inhalers, and
- Dry powder inhalers (DPIs).

### Pressurized, Metered-Dose Inhalers

The successful use of PMDIs depends on several factors, including

- Proper technique,
- Use of a spacer,
- Propellant

Proper technique involves appropriate inspiratory flow at actuation, which requires

- Approximately 25-90 liters per minute
- Actuation during early inspiration
- Adequate breath holding of 4-10 seconds
- Deventilation.

In a study published in the American Journal of Respiratory and Critical Care Medicine in 1994, only 25% of patients achieved all four criteria.[1]

Because oropharyngeal deposition with most-pressurized metered-dose inhalers is over 65%, a spacer may be used to reduce this deposition. But unless the spacer is used properly, it may not improve lung delivery. The proper spacer should be used with the appropriate PMDI. Furthermore, it should be kept in mind that spacers, especially the large-volume plastic ones, have electrostatic charges that cause the drug to stick to the wall. This would decrease the delivery of medication. To circumvent this problem, one can wash the spacer with soap and warm water and let it air dry.

### Why MDI is Better than Tablets ?

MDI should be used as a first line therapy, before tablet or liquid. It is because the inhalers start working within five minutes where as tablets or the liquids take thirty minutes to start. Also the medication in case of MDI deposited directly on to the lung surface and so systemic absorption is minimum and side effect is less. On the other hand in case of tablet or liquid it absorbed in the systemic circulation then goes to the lung. So the side effect is alarmingly high. For example Sulbutamol Tablet preparation contain 2 mg of the drug of which only 200 micrograms needed for the lung, rest of this are going for systemic side effects.

But in MDI preparation the 200 micrograms directly deposited on the lung. The common side effect is the fungal infection on the mouth and throat after the use of inhaled corticosteroids. The risk can be minimized easily by rinsing the mouth with water after the inhaler use.

### Dry Powder Inhalers

Perhaps one of the most exciting innovations in inhaler technology has been the development of Dry Powder Inhalers (DPIs). In comparison to PMDIs, aerosol generation does not require propellants and thus are environmentally safer. These devices are breath-actuated, so less coordination is required, and lung deposition is often greater. Thus, DPIs have many advantages over PMDIs.

In one study, lung deposition was demonstrated to be approximately 32% versus 15% with the DPI and PMDI, respectively.[3] This increased delivery has been translated into greater efficacy with this inhaled corticosteroid as well.

Use of the DPI has been shown to be fairly easy for patients. In a study published in the Journal of Allergy and Immunology,[4] approximately 96% of children 8 and older were able to use this device correctly. 55% of children aged 5-8 were able to use it correctly as well, a significant advance over the previous technology. However, there are some issues with using the DPI. The device may be susceptible to humidity and should not be stored in the bathroom. Furthermore, delivery depends on inspiratory flow rate. Thus, younger children and patients experiencing asthma exacerbations may receive reduced amounts of drug.

### Safety

One must consider not only the amount of drug delivered to the lungs and their effectiveness but also safety. Each device exhibits relatively equal local side effects. Systemic side effects can vary, depending on total systemic exposure, which is determined by the actual respired dose and amount of drug swallowed. For instance, up to 90% of PMDI beclomethasone may be swallowed. Unless this drug is broken down very rapidly in the liver, the oral bioavailability might contribute to total systemic exposure.

### Summary: Molecules Plus Devices Equals Better Compliance

The inhaler device clearly has an impact on efficacy, safety, and compliance. Dry powder inhalers are generally easier to use but differ considerably in the amount of drug delivered to the lungs. Since there is a reasonable association between pulmonary deposition and pulmonary effects, one must consider the device as well as the molecule. Delivery device technology has allowed better use of older and newer inhaled corticosteroids and will likely provide a mechanism for the treatment of nonrespiratory diseases as well.

References: 1. Goodman DE, Israel E, Rosenberg M, Johnston R, Weiss ST, Drazen JM. The influence of age, diagnosis, and gender on proper use of metered-dose inhalers. *Am J Respir Crit Care Med.* 1994 Nov;150(5 Pt 1):1256-1261. 2. Tashkin DP. Impact of emergency therapies on small airway inflammation in asthma. Program and abstracts of the 1999 Annual Meeting of the American College of Allergy, Asthma, and Immunology; November 12-17, 1999; Chicago, Ill. Symposium: The use of inhaled corticosteroids in asthma: improving treatment goals for the millennium. 3. Thorsson L, Edsbacker S, Conradson TB. Lung deposition of budesonide from Turbuhaler is twice that from a pressurized metered-dose inhaler P-MDI. *Eur Respir J.* 1994 Oct;7(10):1839-1844. 4. De Boeck K, Alifrier M, Warnier G. Is the correct use of a dry powder inhaler (Turbobhaler) age dependent? *J Allergy Clin Immunol.* 1999 May;103(5 Pt 1):763-767.



## The New Asthma Drugs

In recent years, better understanding of the pathogenesis of asthma has opened new avenues of drug development. No cures are yet available, and significant gaps remain in the approach to drug development. Nevertheless, steady progress has been made, and new drugs have been introduced. In particular, three advances have entered clinical practice.

The first of the new advances has been the introduction of cysteinyl leukotriene antagonists (e.g., montelukast, zafirlukast, and pranlukast) and the 5-lipoxygenase inhibitor zileuton. When these drugs are used as add-on therapy with inhaled corticosteroids, they produce a modest improvement in the control of asthma manifestations but do not necessarily permit the glucocorticoid dosage to be decreased. Antileukotriene drugs may also have anti-inflammatory effects in asthma, but the effectiveness of these agents is less than that of the glucocorticoids. Their effectiveness varies significantly among patients, and they may have little effect in patients older than 50 years.

In addition to their well-described effects on bronchoconstriction, it appears that leukotriene antagonists also inhibit the airway remodeling process, at least in experimental models of asthma. Limited data on symptom scores suggest that 4 weeks of treatment with antileukotriene drugs may also be beneficial in children with viral bronchiolitis.

The second new asthma treatment is a recombinant humanized anti-IgE antibody, omalizumab. This approach is based on the likelihood that the generation of IgE and the binding of IgE to its high-affinity receptor (FcεRI) is critical for the development of the allergic response. Phase III studies indicated that treatment with omalizumab decreases early- and late-phase allergic responses and decreases eosinophil levels in sputum. The agent has been shown to be safe and well tolerated. In asthmatic patients, treatment with omalizumab also lowers requirements for inhaled glucocorticoids.

Three large placebo-controlled trials demonstrated the utility of omalizumab as add-on therapy in

moderate to severe asthma. In these trials, omalizumab treatment decreased the rate of significant asthma exacerbations and the number of rehospitalizations and improved quality of life, asthma symptom scores, and peak expiratory flow rates. The greatest benefit of omalizumab was found in patients with the most severe asthma. Although omalizumab was approved by the FDA in 2003, clinical use has been limited, likely because of cost, the need for injection, and the uncertainty of its benefits as compared with allergen desensitization regimens.

The third and most popular new asthma treatment has been the packaging of inhaled high-potency glucocorticoids together with long-acting, selective beta2-adrenergic bronchodilators. Clinical studies suggest that this combination (typified by fluticasone-salmeterol and budesonide-formoterol) may provide synergistic effects that are greater than would be expected from the additive actions of the two drugs. Additional research is needed to fully define whether this synergy actually occurs and, if so, by what mechanism. The effect on airway remodeling should also be studied further, because these combinations have been reported to promote airway fibrosis in experimental models of allergic asthma. Long-term use of beta2-adrenergic agonists may also worsen underlying abnormalities in airway behavior; this issue is also under study. Special concerns include the effects of beta2-adrenergic signals on levels of airway inflammation and hyperreactivity. It is noteworthy that the concept of a fixed combination of drugs was previously dismissed as irrational, yet such combinations are now the top-selling agents for asthma treatment.

The higher efficacy of prepackaged combinations may derive at least in part from improved patient acceptance and compliance. Indeed, compliance is a general problem that should be better monitored for both single and combination agents. In that regard, delivery systems that permit better monitoring and dosing are under development. For example, a "smart" system that senses an increased need for bronchodilation may automatically trigger additional delivery of a bronchodilator.

## Asthma Focus

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## Citrus Oils May Hold Key to Asthma Prevention Management

A key to preventing asthma might be found in a lemon, a rose or a pine tree. According to a current study, inhalation of limonene, the main component found in the essential oil of citrus, prevented asthma symptoms in animals.

Inspired by previous findings that show the incidence of asthma to be five times higher in urban areas than in rural and agricultural ones, lead researcher Professor Ehud Keinan studied the connection between ozone and asthma and other lung disorders. He believes this higher incidence of asthma is due in large part to the absence of natural "ozone scavengers" produced by plants.

"Ozone in the outer atmosphere is essential for life on earth because it absorbs the destructive ultraviolet radiation emitted by the sun," he explained. "But on earth, it is a dangerous component of air pollution. Numerous studies have shown exposure to ozone, even at low levels, induces airway inflammation and lung injury in humans and animals."

Keinan's team also found that ozone is produced in inflammatory tissues by antibodies as a defense against asthma. The presence of this ozone activates more antibodies, perpetuating a vicious cycle.

The research team says that "ozone-scavengers" - substances that devour ozone - could be used for preventing asthma. The inhalation of water-repellent ozone scavengers that accumulate in lung membranes could break the cycle of inflammation. Organic compounds called monoterpenes -- produced by all plants -- are ideal sources of such substances.

Limonene, an unsaturated monoterpene and the main component in the essential oil of citrus, functions extremely well as an ozone scavenger. Other ozone scavenging monoterpenes studied by the team came from roses, pine trees and citronella, but limonene was the most effective. Saturated monoterpenes, however -- such as those found in eucalyptol -- were found to have no ozone scavenging properties.

The experiments involved exposing rats with induced asthma-like symptoms to either limonene or eucalyptol for a couple of days. The lung function of the rats showed that limonene inhalation prevented the asthmatic symptoms.

Source: [www.newswise.com](http://www.newswise.com) Bioorganic and Medicinal Chemistry, 10-Dec-2004

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### Editorial Note:

Dear Doctor :

We are happy to present you the inaugural issue of 'Asthma Focus' newsletter. The aim of this newsletter is to help Medical professional in touch with the update information on asthma. This issue is focused on the combination therapy in asthma. We always appreciate your valuable comments to make the newsletter more exclusive.