Research Review
EDUCATIONAL SERIES

Long Acting Beta-Agonists (LABA) & Asthma

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About the commenter - Dr Shaun Holt

Dr Holt founded medical trials company P3 Research which has its head office in Wellington and a trial centre in Tauranga. Dr Holt has conducted over 50 clinical trials, mostly in respiratory medicine and has over 50 publications in medical literature. He is also an advisor to the Asthma and Respiratory Foundation, an Honorary Fellow of the Medical Research Institute of New Zealand and the principal advisor to Research Review.

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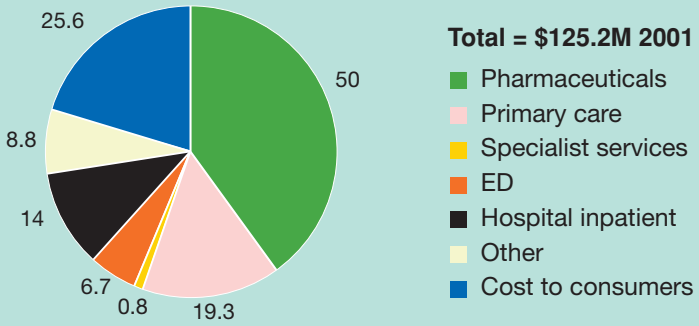
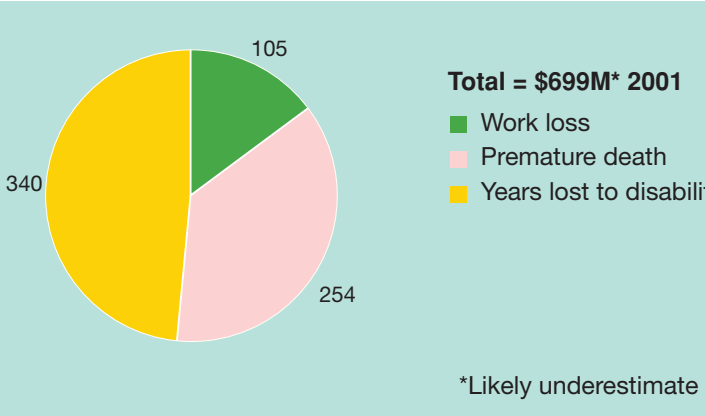
The following publication is intended as an educational resource for health professionals. It presents a short background on asthma in New Zealand together with a summary and review of selected peer reviewed studies featuring long acting beta-agonist (LABA) medicines used to manage asthma. It is intended to help readers stay informed of developments and advancing clinical practice in the areas covered.

The Cost and the Cause

Asthma continues to be a significant problem in New Zealand, affecting around one in six people at a cost of around $825 million each year[1]. Most of this cost is incurred indirectly through poorly controlled asthma resulting in time off work or school or even premature death. It is important for those involved in treatment to know that most of this cost can be attributed to patients whose asthma is poorly controlled: around half of the costs of asthma are incurred by just 10% of patients[2]. Also, it has been estimated the cost of uncontrolled asthma can be as much as 100 times greater than the cost of asthma in patients who are well controlled[3].



Asthma - direct medical costs

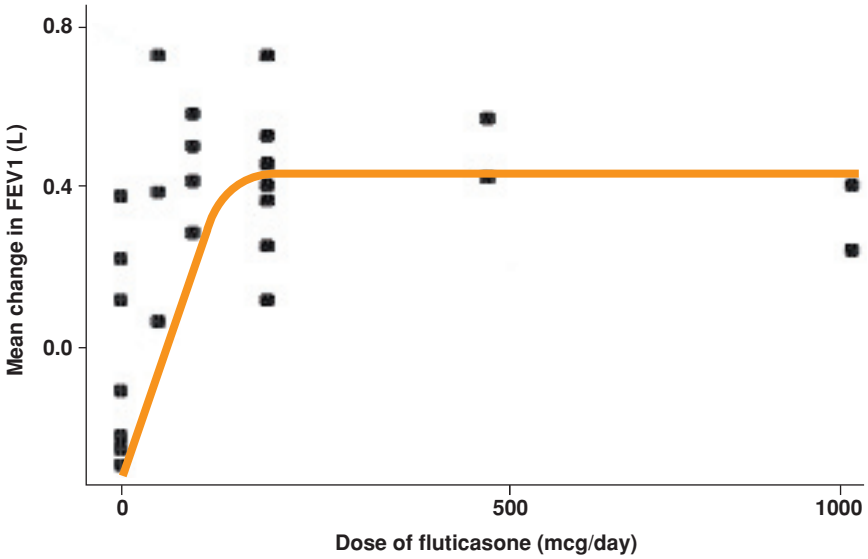


Asthma - indirect costs

LABAs Place in Asthma Therapy - Guidelines

Major international guidelines for the treatment of asthma, including those produced by the Global Initiative for Asthma (GINA) and the British Thoracic Society (BTS) state that asthma should be managed in a step-wise manner[4,5].

- **Step 1:** Patients with mild disease who only experience occasional symptoms, for example with exercise, can be managed using short-acting beta agonist (SABA) drugs like salbutamol or terbutaline on an "as required" basis.
- **Step 2:** If this is not sufficient, or if patients are using a SABA more than three times a week, then prescribe a low dose of inhaled corticosteroid (ICS) eg. beclomethasone or budesonide 100-400 mcg twice a day or fluticasone propionate 50-250 mcg twice a day.
- **Step 3:** If the patient is still not well controlled (we will discuss later in detail how to decide if a patient is well controlled), then various guidelines have traditionally given clinicians a choice:
  - Either increase the dose of ICS
  - Or co-prescribe a long-acting beta agonist (LABA) medicine



Change in FEV_1 vs dose FP

This choice has been at the forefront of a great deal of asthma research over the last 10 years or so. To make this decision, the clinician needs to consider:

1. The dose-response relationship of ICS
2. The safety of LABA
3. Evidence from studies on the efficacy and safety of both approaches

With respect to the dose-response relationship of ICS, many clinical trials and meta-analyses of existing data have shown that, for all important outcome measures including prevention of exacerbations, the majority of the benefit can be achieved with doses of around 400-800 mcg a day of beclomethasone or budesonide or 250 mcg a day of fluticasone propionate[6,7]. In other words, for a patient being treated at Step 2 of the guidelines with a low dose of ICS, little if any further clinical improvements will be achieved by increasing the dose further.

Many studies have looked at the efficacy and safety of either increasing the dose of ICS or adding a LABA. The meta-analysis by Shrewsbury et al showed clearly the addition of LABA was far superior[8] (see later). The consensus of almost all researchers and leading respiratory physicians, based on all available evidence, is that patients who are not well controlled on a low dose of ICS would benefit most from the addition of a LABA.

Guidelines and Funding

Uptake of LABA drugs in New Zealand has been slower than in other countries with similarly high incidence rates. This is due to a lack of budget availability for public subsidy of LABAs as opposed to concerns over safety or efficacy. Recent changes to the funding criteria for LABAs have significantly improved the availability of these medications.

There are currently two separate LABA medicines marketed in New Zealand as single inhalers, and two combination inhalers with both ICS and LABA components. In November 2005, access to single inhaler LABA improved significantly. Those who had been on ICS for three months or more (200mcg FP or equivalent in adults or 100mcg FP for children 12 or under) but were still uncontrolled could now be prescribed a LABA without the previous special authority approvals.

The latest change in August 2006* allowed doctors to apply for special authority approval to prescribe a combination ICS/LABA inhaler to a patient if:

- The patient has been treated for 3 months or more with a LABA
- And the patient has been treated for 3 months or more an ICS at a dose of at least 800 mcg/day of beclomethasone or budesonide or 500 mcg/day of fluticasone propionate (400 mcg/day of beclomethasone or budesonide or 200 mcg/day of fluticasone propionate for children 12 and under)
- And the prescriber believes that the patient would receive additional clinical benefit from switching to a combination product

It is worth noting at this point, these are funding eligibility criteria as opposed to independent guidelines.

***Note: for full details see the current pharmaceutical schedule at www.pharmac.govt.nz**

Why Use Combination?

Combination inhalers have a number of advantages over the same medications given in two separate inhalers. First, an important advantage is that this is the safest way to prescribe LABA (discussed in more detail later).

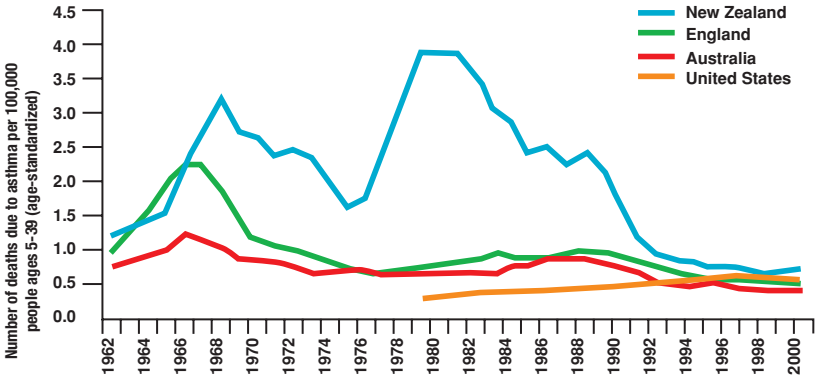
Another advantage of combination inhalers is of course simplicity: it is easier and more convenient to take one inhaler than two inhalers. This is likely to lead to increased compliance with treatment, although this has not yet been demonstrated in a clinical study.

Third, several studies have shown a 10-15% additional benefit when both medications are taken from a single inhaler. (One such study which demonstrates this synergistic effect is described in detail later[10])

Safety of LABAs and ICS

LABAs

The safety of beta agonist medications is of particular relevance in New Zealand, given the epidemic of related asthma deaths the country has experienced[11]. Most researchers and clinicians accept the cause of this epidemic of deaths was a particular preparation of the beta agonist medication fenoterol, marketed until the mid-80's. The rate of asthma deaths in New Zealand reduced back to that of other similar Westernised countries when the medication was withdrawn.



Asthma mortality in NZ, Commonwealth Fund Report 2004

It has been shown that LABA are safe when the patient also takes regular ICS. When given in separate inhalers the major safety concern is that patients may decide to take their LABA and not their ICS. This is usually because they perceive the LABA is more effective than the ICS due to bronchodilation that occurs soon after taking a dose. In this situation, the patient may feel their asthma is well controlled, but without regular ICS, the underlying inflammation of the airways may well be increasing. It is critically important patients are made aware of this risk.

Recent studies of LABA have generated considerable controversy about the safety/risks of long-acting beta agonist therapy[12]. It has not been widely recognised in these studies LABA use was essentially "off label" and involved many patients not using additional ICS. The findings are not applicable to the recommended use in New Zealand of LABAs in combination with inhaled corticosteroids. Reassuringly, a case-control study from the United Kingdom has provided contrasting findings, with no increased risk of mortality associated with LABA use[13].

The safest way to prescribe LABA is as a one inhaler combination. In New Zealand, to access subsidised combination products we must first prescribe individual components and then graduate to the combination product. This is not an entirely evidence based approach but must be undertaken to allow access to public funding.

ICS

Low to moderate doses of ICS in adults (up to 1000 mcg/day of beclomethasone or budesonide or up to 500 mcg/day of fluticasone propionate) are very unlikely to cause serious side effects. In children, the lowest dose of ICS possible should be used, and again, low doses (up to 400 mcg/day of beclomethasone or budesonide or up to 200 mcg/day of fluticasone propionate) are very unlikely to cause serious side effects.

Isolated international incidents of adrenal suppression and growth retardation have been reported from ICS use and have understandably hit the headlines. These are extremely unusual and in almost every case the result of high dose off-label use. In fact, in terms of reduced growth, a child is more likely to have reduced growth from frequent attacks of severe uncontrolled asthma than from a low dose of ICS.

Ways to Spot Uncontrolled Asthma – Who Can Benefit From LABA?

How are busy health practitioners, having to manage dozens of conditions, able to identify patients who should be taking a LABA? And how many of their patients are likely to benefit from treatment with a LABA?

The landmark POMS (Patients Outcomes Management Survey) study published in 2001 revealed a huge health burden and morbidity due to asthma in New Zealand[14]. The study showed 93% of adults and 90% of children in New Zealand had asthma that was sub-optimally-controlled. Very few of these patients were taking a LABA so it is likely most GPs will have many patients who will benefit from the addition of a LABA to their ICS medication.

Most patients, when asked by their GP how their asthma is, will say that "it is fine". The POMS study also showed most patients thought their asthma was fine, despite most experiencing potentially controllable and often debilitating symptoms. The reasons for this paradox are complex and not fully understood, but are mostly a result of patients being stoic with respect to their symptoms; patients not recognising their symptoms are due to asthma and, in particular, patients not knowing that with modern medications it is possible to dramatically reduce or even eliminate symptoms of asthma.

Finally, there are two specific types of asthma that are particularly sensitive to treatment with LABAs. Studies have shown LABAs are very effective at reducing nocturnal asthma symptoms. Also, they are of particular benefit to patients who frequently have asthma which is induced by exercise.

The following questions may be useful when identifying patients who may benefit from the addition of a LABA:

1. How many doses of your reliever inhaler are you taking every day / week?
2. Do you ever wake from sleep coughing or wheezing, and if so how often?
3. Are there any activities, such as singing, football or gardening, that your asthma stops you from doing or makes harder for you?
4. Do you smoke?
5. Have you been to hospital or been prescribed a course of oral steroid tablets in the last year?
6. Do you ever have time off work / school due to asthma? How often?
7. Would it be easier if you were able to reduce the number of inhalers you take?
8. Do you often forget to take your inhalers?

Effect of inhaled formoterol and budesonide on exacerbations of asthma. Formoterol and Corticosteroids Establishing Therapy (FACET) International Study Group.

Authors: Pauwels RA et al

Summary: The addition of the LABA formoterol to the inhaled corticosteroid budesonide improved lung function and asthma symptoms without a deterioration in asthma control in patients with persistent asthma.

Method: In this double-blind, placebo-controlled study, 852 patients were randomised to receive budesonide 100µg or 400µg twice daily with or without formoterol 12µg twice daily for one year. Terbutaline rescue medication was permitted in all four treatment groups. All patients received budesonide 800 µg twice daily during a 4-week run-in period prior to starting treatment. A severe exacerbation of asthma was defined by a requirement for oral corticosteroids or a >30% decrease from baseline in peak expiratory flow on two consecutive days.

Results: The addition of formoterol to inhaled budesonide decreased the incidence of both severe and mild asthma exacerbations. Reductions were greatest when formoterol was added to the higher dose of budesonide, with a decrease of more than 60% in the rate of severe and mild exacerbations. When added to the lower dose of budesonide, formoterol decreased the rate of severe exacerbations by 26% and mild exacerbations by 40%. The higher dose of budesonide given alone without formoterol decreased the rate of severe exacerbations by 49% and mild exacerbations by 37%. Improvements in asthma symptoms and lung function were also observed with the addition of formoterol and with the higher dose of budesonide. The improvements with the addition of formoterol were more marked than those observed with the higher dose of budesonide alone. There was no evidence of deterioration in asthma control when formoterol was added to budesonide therapy.

Patients with persistent asthma despite treatment with inhaled corticosteroids may benefit from the addition of formoterol or an increase in corticosteroid dose.

Comment: This was a true "landmark" study in which the benefits of LABA treatment were demonstrated to such a degree that these treatments have since become gold standard. The beneficial effects in terms of lung function were well known, but this study showed that LABA also significantly reduce mild and severe exacerbations. Patients receiving 800 mcg/day of budesonide did better than those receiving 200 mcg/day of budesonide, and this is consistent with our knowledge of the dose-response relationship of budesonide. Other studies have shown that doubling the dose to 1600 mcg/day of budesonide does not lead of further benefits. The take home message from the FACET study was that addition of LABA to low or moderate dose of ICS leads to significant improvements.

Reference: N Engl J Med. 1997 Nov 13;337(20):1405-11.

Meta-analysis of increased dose of inhaled steroid or addition of salmeterol in symptomatic asthma (MIASMA)

Authors: Shrewsbury, S et al

Summary: MIASMA showed the addition of salmeterol to inhaled corticosteroids to be more effective than increasing the dose of inhaled corticosteroids in patients with symptomatic asthma.

	Mean difference between treatment groups (95% CI)		
	3 months	6 months	P value
Morning PEF (L/min)	22.4 (15.0-30.0)	27.7 (19.0-36.4)	<0.001
FEV1 (L)	0.10 (0.04-0.16)	0.08 (0.02-0.14)	<0.001
Symptom-free days (%)	-12 (9-15)	-15 (12-18)	<0.001
Symptom-free nights (%)	-5 (3-7)	-5 (3-7)	<0.001
Days without rescue treatment (%)	-17 (14-20)	-20 (17-23)	<0.001
Nights without rescue treatment (%)	-9 (7-11)	-8 (6-11)	<0.001

Method: This meta-analysis reviewed the results of randomised, double-blind clinical trials that compared the clinical efficacy of adding salmeterol or increasing the dose of inhaled corticosteroids. Nine studies including a total of 3685 patients aged ≥12 years were included in the analysis. All patients had symptomatic asthma despite current use of inhaled corticosteroids and were studied for a minimum of 12 weeks.

Results: Lung function was significantly better with the addition of salmeterol than with an increased inhaled corticosteroid dose. Patients who received salmeterol also experienced significantly more symptom-free days and nights and required less rescue medication than those whose inhaled corticosteroid dose was increased. Salmeterol recipients experienced fewer asthma exacerbations with a significant reduction in moderate or severe exacerbations compared with recipients of an increased inhaled corticosteroid dose (-2.42%; 95% CI 0.24-4.6; p=0.03).

The addition of salmeterol in patients with symptomatic asthma on low to moderate doses of inhaled corticosteroids improved lung function, increased symptom-free days and nights and reduced need for rescue medication. The effects of salmeterol were significantly greater than those achieved with an increased dose of inhaled corticosteroids and occurred with no increase in asthma exacerbations.

Comment: This study built on the results of FACET. By undertaking a meta-analysis of all the relevant studies, the authors demonstrated with enormous power that adding salmeterol to patients who had asthma symptoms despite being on low or moderate doses of ICS led to important improvements in lung function and asthma symptoms, with no increase in exacerbations. Studies such as this have led to changes in international asthma management guidelines, with the result that it is strongly recommended that LABA should be prescribed rather than to keep increasing the dose of ICS

Reference: BMJ. 2000; 320: 368–73.

Enhanced synergy between fluticasone propionate and salmeterol inhaled from a single inhaler versus separate inhalers.

Authors: Nelson, H et al

Summary: Combination therapy with the inhaled corticosteroid fluticasone propionate and the LABA salmeterol in a single inhaler was more effective than concurrent use of these medications from separate inhalers in a meta-analysis of four studies in patients with persistent asthma.

Method: Individual patient data were combined from four similarly designed double-blind studies that demonstrated equivalence between combination and concurrent therapy with fluticasone propionate and salmeterol. All four studies reported a consistent trend in favour of combination therapy.

Results: The trend favouring combination therapy became significant in the meta-analysis. Improvements from baseline in morning peak expiratory flow (PEF) over 12 weeks were significantly greater for combination therapy than concurrent therapy. The mean difference between treatment groups was 5.4 L/min (95% CI 1.5-9.2; p=0.006). Patients who received combination therapy were 40% more likely to have improvements in PEF of more than 15 L/min or more than 30 L/min than those who received concurrent therapy (95% CI 1.1-1.8; both p<0.01). This translated to 5-14% additional patients responding to treatment when fluticasone propionate and salmeterol were administered in combination rather than concurrently.

The authors suggested that the increased clinical efficacy of combination therapy over concurrent therapy is the result of an increased opportunity for a synergistic interaction to occur due to fluticasone propionate and salmeterol being co-deposited in the airways.

Comment: Several papers, looking at different ICS/LABA combinations, have found similar results. This meta-analysis from Harold Nelson and colleagues showed a clear advantage from having a single inhaler in terms of lung function. The mechanism is not known but the authors of this study suggest that it may be because the two medications are deposited in the same position in the airways. Other researchers have suggested that the reason may be better compliance in patients using one inhaler rather than two. Whatever the mechanism, this synergistic effect is worth knowing about and is worth considering when deciding how best to prescribe both ICS and LABA.

Reference: J Allergy Clin Immunol 2003;112:29-36.

Can guideline-defined asthma control be achieved? The Gaining Optimal Asthma controL study

Authors: Bateman E, et al

Summary: Guideline-defined asthma control was shown to be achievable with combination salmeterol/fluticasone propionate treatment in the majority of patients with uncontrolled asthma.

Method: In this double-blind study, 3421 patients with uncontrolled asthma were randomised to receive fluticasone propionate alone or in combination with salmeterol for one year. Treatment was stepped up until totally controlled asthma was achieved or until a maximum fluticasone dose of 500µg twice daily. Patients were stratified prior to randomisation according to their pre-study use of corticosteroids.

Results: Salmeterol/fluticasone achieved asthma control in significantly more patients, irrespective of previous inhaled corticosteroid use, than fluticasone alone. Total control was achieved after dose-escalation in significantly more patients with salmeterol/fluticasone than with fluticasone alone (31% vs 19%, p<0.001). Total control was maintained at one year in 41% of patients who received the combination versus 28% of patients who received fluticasone alone. A similar trend favouring the combination was observed for well-controlled asthma. Significantly more patients who received salmeterol/fluticasone than fluticasone alone had well-controlled asthma after dose-escalation (63% vs 50%; p<0.001) with more patients maintaining this level of control at one year (71% vs 59%). Control was achieved at a lower fluticasone dose and within a shorter time period with salmeterol/fluticasone compared with fluticasone alone. Asthma exacerbation rates were low in both treatment groups, but still significantly in favour of the combination. Improvement in health status was also significantly better with salmeterol/fluticasone.

Salmeterol/fluticasone achieved sustained control of asthma in more patients, more rapidly and at a lower dose of inhaled corticosteroids than fluticasone alone. Guideline-defined asthma control can be achieved and maintained in a majority of patients.

Comment: The Goal study was a huge study conducted in 44 countries and 326 centres including 7 in New Zealand (one of which was myself, Dr Shaun Holt). It was the first real test of guideline defined control to see whether the high targets of achieving total asthma control were realistic and whether medications could really do it. To those treating asthma, the target of total control (no reliever use, no exacerbations, no symptoms, no night-time waking) seems unachievable not least because of the limitations of home-medicating patients and corresponding compliance issues. The Goal study showed clearly the improved outcomes achievable through the use of combination products instead of ICS alone and that the stepwise approach to asthma management could effectively control the majority of patients' symptoms. Most importantly it provides a stark reminder of what is achievable and why we should continue aiming high rather than accepting some degree of failure which we have come to expect with asthma symptoms.

Reference: Am J Respir Crit Care Med 2004:169(7):A318. 23

Efficacy and Safety of Salmeterol/Fluticasone Propionate Combination Delivered by the Diskus™ or Pressurised Metered-Dose Inhaler in Children with Asthma

Authors: Bracamonte T et al

Summary: This study showed salmeterol/fluticasone propionate can be administered to children between 4 and 11 years old with persistent asthma safely and effectively. It produces clinically similar results from the variety of delivery devices available including the Diskus™ and the metered dose inhaler (MDI).

Method: This randomised, double-blind, double-dummy, parallel-group study involved children with asthma aged between 4–11 who used beclomethasone dipropionate 500 g/day (or equivalent). Following a 2-week run-in using their current inhaled corticosteroid, they were randomised to receive salmeterol/fluticasone propionate via Diskus™ (n = 213) or MDI (n = 215, 82% used a spacer) for 12 weeks. Salbutamol was used for symptomatic relief. Mean morning peak expiratory flow rate was recorded for the duration. Also recorded were lung function, daily symptoms, rescue medication use and symptom/salbutamol-free days.

Results: Both devices proved highly effective at improving morning PEF and other symptoms. Increases in PEF were 37.7 ± 3.1 L/min for the Diskus™ group and 38.6 ± 3.0 L/min in the MDI group. The small difference was within the pre-set equivalence measure. Symptom free and salbutamol free days increased considerably for both groups and improvements for all ages began as quickly as 1-4 weeks from initial treatment. Improvements continued for the duration of the 12 week study and both delivery devices were well tolerated and produced similar safety profiles.

The authors concluded children as young as four could use either device effectively and the choice of device made little difference to the improvements in outcome.

Comment: The main focus of this study was to identify if different devices produced different results for children and clearly the results were comparable. Treating children with persistent asthma symptoms despite regular ICS use is always a concern, particularly young children. The results of this study show we can be confident prescribing combination therapy for children and the improvements are clinically significant. In New Zealand there are a variety of devices available when prescribing combination therapy. The choice of which to use may be based on variety of parameters eg patient choice, existing device use, requirement for education, or patient outcomes from using different medicines. This study proves children can gain significant clinical benefits from combination treatment and also that the results are not dependent on the device chosen.

Reference: Clinical Drug Investigation, Volume 25, Number 1, 2005, pp. 1-11(11)

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