The further paradoxes of asthma management: time for a new approach across the spectrum of asthma severity

Richard Beasley [1,2,3], Grace Bird [1], James Harper [1] and Mark Weatherall [3,4]

Affiliations: [1]Medical Research Institute of New Zealand, Wellington, New Zealand. [2]Victoria University of Wellington, Wellington, New Zealand. [3]Capital and Coast District Health Board, Wellington, New Zealand. [4]University of Otago, Wellington, New Zealand.

Correspondence: Richard Beasley, Medical Research Institute of New Zealand, Private Bag 7902, Wellington 6242, New Zealand. E-mail: Richard.Beasley@mrinz.ac.nz

@ERSpublications
A paradigm shift in asthma management that addresses the paradoxes of SABA reliever therapy is required; consideration needs to be given to replacement of SABA reliever with ICS/fast-onset β-agonist reliever therapy across the range of asthma severity http://ow.ly/ccff30lNLPv

Cite this article as: Beasley R, Bird G, Harper J, *et al*. The further paradoxes of asthma management: time for a new approach across the spectrum of asthma severity. *Eur Respir J* 2018; 52: 1800694 [https://doi.org/10.1183/13993003.00694-2018].

Should short-acting β-agonist (SABA) reliever monotherapy be replaced by combination inhaled corticosteroid (ICS)/fast-onset β-agonist as reliever therapy in asthma patients at Global Initiative for Asthma step 1 [1]? This uncertainty is the latest chapter in the controversy relating to the risks and benefits of β-agonist therapy in asthma management [2]. This 70-year controversy began with the introduction of isoprenaline and the concerns that it caused severe refractory asthma and an increased risk of death [3–5].

The dilemma of evaluating the relative efficacy and risk of β-agonists has persisted since then. Two asthma mortality epidemics in the 1960s and 1970s/1980s were primarily caused by use of high-dose preparations of the potent, yet poorly β_2-selective agonists, isoprenaline [6] and fenoterol [7], respectively. The epidemics ended abruptly with regulatory restriction and withdrawal of these agents [2, 8]. In response to evidence that regular scheduled use of SABAs could increase asthma severity and the risk of exacerbations, the recommendation for their use was changed to "as required for relief of symptoms". This therapeutic approach, together with the increasing use of ICSs, both as separate inhalers and combination ICS/long-acting β-agonist (LABA) inhalers, has been associated with a marked reduction in asthma mortality since the 1990s, although the global rates of asthma mortality have now plateaued [9]. There is clearly a need for alternative treatment strategies to achieve further reductions in global asthma mortality.

One strategy is to reduce the potential risks associated with starting SABA reliever monotherapy in intermittent and mild persistent asthma. This strategy was the focus of a recent review in the *European Respiratory Journal* [1], which identified five paradoxes of this therapeutic approach. The review summarised evidence that SABA reliever monotherapy exposes patients to significant avoidable risk and leads to learned behaviours, which result in difficulties for both patients and doctors (table 1). SABA reliever therapy not only reduces the potential to achieve optimal control at step 1, but also when patients progress to higher treatment steps in the stepwise approach to pharmacological therapy. In this editorial,

Received: Feb 02 2018 | Accepted after revision: Sept 05 2018

TABLE 1 Paradoxes in current asthma management

Paradox	Description
1	In step 1 treatment, a SABA bronchodilator alone is recommended despite the fact that asthma is a disease of chronic airway inflammation with increased inflammation at the times of exacerbations.
2	In step 1 treatment, the patient has autonomy and their perception of treatment as needed to control symptoms is accepted, whereas at higher asthma treatment steps it is assumed that patients will adopt a fixed-dose approach.
3	There is a switch in recommendation from using a SABA alone as-needed at step 1 to advising an ICS fixed-dose regimen at step 2 and minimising SABA use. The medication that treats the underlying disease, which patients are encouraged to take (the ICS) is not the one that the patient perceives is benefitting them (the SABA), which they are now discouraged from taking.
4	There is a different safety message in the advice given for the use of SABA and LABA within the guidelines; SABA alone being safe and LABA alone being unsafe.
5	There is a dislocation between patients' understanding of "asthma control" and the frequency, impact and severity of their symptoms.

SABA: short-acting β_2-agonist; ICS: inhaled corticosteroid; LABA: long-acting β_2-agonist. Reproduced from [1] with permission.

we propose five related paradoxes that further develop the concepts introduced in this recent review [1] (table 2).

First paradox

The first paradox is that, although the recommendation is that all patients with asthma should be prescribed a SABA, regular use of this medication increases bronchial hyperresponsiveness (BHR). The magnitude of this effect is substantial, with a decreased doubling dose of −0.47 (95% CI −0.7 to −0.2, p<0.001) pooled across all three stimulant classes for BHR, derived from a systematic review and meta-analysis [10]. BHR is a physiological marker of asthma severity, and increasingly severe BHR will result in asthma patients becoming more sensitive to provoking stimuli, as well as increased treatment requirements, symptom burden and diurnal variation in lung function [11]. Although increased BHR has only been reported with regular SABA use, the effect of "as needed" SABA use on BHR may also be important, although this has not been studied [10]. With SABA reliever therapy, worsening asthma control results in an increased frequency of SABA use, which may be equivalent to regular prolonged use [12]. The effect of increased BHR occurs within 1–2 weeks of regular SABA treatment [13, 14], which is similar to the time course of an exacerbation associated with increased SABA reliever use [15].

ICSs improve BHR and the therapeutic approach of concomitant prescription of a maintenance ICS with SABA reliever therapy can arguably counteract the deleterious effects of frequent SABA use [16]. However, in clinical practice, this scenario does not apply to patients prescribed SABA as monotherapy, or to those who have prolonged nonadherence to maintenance ICS-based therapies.

The effects of SABA on BHR also have a major public health significance considered at a population level [17]. Modelling the effect of at least a half doubling dose worsening in BHR across a population, similar to the magnitude of the effect of SABA therapy [10], demonstrates that it will increase the prevalence of moderate and severe asthma (defined by the degree of BHR) from 48% to 63% [18].

TABLE 2 Further paradoxes in asthma management

Paradox	Description
1	It is recommended that all patients with asthma are prescribed a SABA, yet regular SABA use increases BHR. The counterbalancing effect of ICS reducing BHR does not apply to patients on SABA monotherapy or those nonadherent to ICS or ICS/LABA therapy.
2	SABA monotherapy is prescribed when it is known that maintenance ICS and concomitant SABA reliever therapy results in better efficacy.
3	SABA monotherapy is prescribed as initial therapy, which delays the prescribing of ICS therapy, reducing its potential efficacy.
4	ICS/SABA reliever monotherapy and ICS/fast-onset LABA reliever monotherapy have greater efficacy than SABA reliever monotherapy at step 1 and similar efficacy to ICS maintenance and SABA reliever therapy at step 2 in reducing severe exacerbation risk.
5	ICS/fast-onset LABA as reliever therapy has greater efficacy and a better safety profile than SABA reliever therapy, across steps 3 and 4, yet most patients receive SABA reliever therapy.

SABA: short-acting β_2-agonist; BHR: bronchial hyperresponsiveness; ICS: inhaled corticosteroid; LABA: long-acting β_2-agonist.

Second paradox

The second paradox is that SABA monotherapy is prescribed when there is strong evidence that maintenance ICS with concomitant SABA reliever therapy results in superior efficacy [19]. The argument in defence of SABA monotherapy is that, although the efficacy of ICS is evident even in patients with only occasional symptoms and SABA use [20], patients are unlikely to take prescribed ICS daily when experiencing infrequent symptoms. This argument stands only if there is no alternative therapeutic approach to overcome low rates of ICS adherence. However, the alternative approach of using an ICS/fast-onset β-agonist as reliever monotherapy automatically ensures that ICS is titrated in response to symptom frequency and severity, through the vehicle of fast-onset β-agonist reliever use [21].

Third paradox

The third paradox is that prescribing SABA monotherapy as initial therapy may delay prescribing ICS, thereby reducing the potential efficacy of ICS therapy. It could be argued that patients initially prescribed SABA monotherapy should, if guidelines are followed, ultimately be prescribed an ICS if or when their asthma worsens. Unfortunately, patients with poorly controlled asthma that warrants ICS therapy often remain on SABA monotherapy [22]. There is evidence that such a delay in prescribing ICS reduces their potential efficacy [23, 24].

Fourth paradox

The fourth paradox is that ICS/SABA reliever monotherapy is more efficacious than SABA reliever monotherapy at step 1 and has similar efficacy to ICS maintenance and SABA reliever therapy at step 2 [25], and yet is not recommended in international guidelines at either step. More recently, ICS/fast-onset LABA reliever monotherapy has also been shown to be more efficacious than SABA reliever monotherapy at step 1 and has similar efficacy to ICS maintenance and SABA reliever therapy at step 2, in terms of severe exacerbation risk [26, 27]. Those patients who are over-reliant on SABA and nonadherent with ICS may gain particular benefit from combination ICS/fast-onset β-agonist reliever monotherapy, as ICS use will be driven by the use of such combination medications as reliever therapy. Furthermore, ICS/fast-onset LABA reliever monotherapy has similar efficacy in reducing severe exacerbation risk to maintenance ICS/fast-onset LABA with SABA reliever therapy at step 3 [28].

Fifth paradox

The fifth paradox is that, although ICS/fast-onset LABA as reliever therapy has greater efficacy than SABA reliever therapy across steps 3 and 4 [29], in clinical practice most patients receive SABA reliever therapy at these steps. Furthermore, even those prescribed ICS/fast-onset LABA maintenance and reliever therapy are commonly co-prescribed a SABA [30]. This entrenched practice persists, not only despite the greater efficacy of ICS/fast-onset LABA reliever therapy compared with SABA reliever therapy at steps 3 and 4, but also despite the evidence that ICS/fast-onset LABA reliever therapy reduces the excessive use of β-agonist therapy, the number of days of β-agonist overuse associated with delay in obtaining medical help and the number of days without self-administration of ICS [31]. These are all common and important factors associated with increased risk of asthma mortality [32].

Potential limitations of the proposed treatment approaches

The potential limitations of the proposed treatment approaches that arise from the consideration of these paradoxes also need consideration. These include, but are not restricted to, the possibility of overtreatment with both the ICS and LABA components of ICS/fast-onset LABA reliever therapy and the requirement for a stronger evidence base for ICS/SABA reliever therapy. However, such ICS "overtreatment" does not lead to an increased corticosteroid burden. In a randomised controlled trial, although ICS/fast-onset LABA reliever therapy resulted in greater ICS exposure than SABA reliever therapy, the subsequent reduction in severe exacerbations resulted in reduced oral corticosteroid exposure, leading to a similar overall systemic corticosteroid exposure [31]. In the same randomised controlled trial, the potential concern of LABA overuse with ICS/fast-onset LABA reliever therapy was addressed, as ICS/fast-onset LABA reliever therapy resulted in fewer β-agonist overuse episodes compared to SABA reliever therapy [31]. Additionally, there were fewer β-agonist overuse episodes that led to delays in seeking medical review, in high-risk patients receiving maintenance ICS/fast-onset LABA [31].

Prescription of ICS/fast-onset LABA reliever therapy with a different ICS/LABA or ICS/ultra-LABA for regular maintenance use is problematic, as the safety of concurrent use of two different LABAs has not been assessed. In these cases, ICS/SABA reliever therapy is likely to be the preferred approach, as there is an evidence base for the safety of concomitant use of SABA reliever and maintenance ICS/LABA therapy [33]. An alternative would be a change to ICS/fast-onset LABA as both maintenance and reliever therapy [29].

Clearly, further clinical research investigating the efficacy and safety of both ICS/SABA and ICS/fast-onset LABA reliever therapy regimens is required across the spectrum of asthma severity and its treatment. Comparisons between ICS/SABA and ICS/fast-onset LABA reliever therapy at the different steps will also be necessary to determine which patients may preferentially benefit from each regimen, to allow a personalised approach to asthma management.

The long-standing mantra of mandatory self-administration of SABAs for the acute relief of bronchoconstriction for all patients with asthma, and the tacit acceptance of the potential long-term adverse effects of this therapy, should be challenged. There are alternative options with superior efficacy and safety. These options include combination ICS/fast-onset β-agonist reliever therapy, based on supportive trial evidence for ICS/SABA reliever monotherapy at steps 1 and 2, ICS/fast-onset LABA reliever monotherapy at steps 1–3, and ICS/fast-onset LABA as part of the maintenance and reliever therapy regimen at steps 3 and 4. It is clearly time for a paradigm shift in the treatment of asthma that addresses the paradoxes of asthma management with respect to SABA reliever therapy. Strong consideration should be given to ICS/fast-onset β-agonist reliever therapy replacing the current advice for SABA reliever therapy across the range of asthma severity.

Conflict of interest: R. Beasley reports grants and personal fees from Health Research Council of New Zealand, AstraZeneca and GlaxoSmithKline, and grants from Genentech, all outside the submitted work. G. Bird has nothing to disclose. J. Harper has nothing to disclose. M. Weatherall has nothing to disclose.

Support statement: The Medical Research Institute of New Zealand is supported by Health Research Council of New Zealand Independent Research Organisation funding.

References

1 O'Byrne PM, Jenkins C, Bateman ED. The paradoxes of asthma management: time for a new approach? *Eur Respir J* 2017; 50: 1701103.
2 Beasley R, Pearce N, Crane J, *et al.* Asthma mortality and inhaled beta agonist therapy. *Aust N Z J Med* 1991; 21: 753–763.
3 Gay LN, Long JW. Clinical evaluation of isopropyl-epinephrine in management of bronchial asthma. *J Am Med Assoc* 1949; 139: 452–457.
4 Lowell FC, Curry JJ, Schiller IW. A clinical and experimental study of isuprel in spontaneous and induced asthma. *N Engl J Med* 1948; 239: 45–51.
5 Van Metre TE Jr. Adverse effects of inhalation of excessive amounts of nebulized isoproterenol in status asthmaticus. *J Allergy* 1969; 43: 101–113.
6 Stolley PD. Asthma mortality. Why the United States was spared an epidemic of deaths due to asthma. *Am Rev Respir Dis* 1972; 105: 883–890.
7 Crane J, Pearce N, Flatt A, *et al.* Prescribed fenoterol and death from asthma in New Zealand, 1981–83: case–control study. *Lancet* 1989; 1: 917–922.
8 Pearce N, Beasley R, Crane J, *et al.* End of the New Zealand asthma mortality epidemic. *Lancet* 1995; 345: 41–44.
9 Ebmeier S, Thayabaran D, Braithwaite I, *et al.* Trends in international asthma mortality: analysis of data from the WHO Mortality Database from 46 countries (1993–2012). *Lancet* 2017; 390: 935–945.
10 Salpeter SR, Ormiston TM, Salpeter EE. Meta-analysis: respiratory tolerance to regular β_2-agonist use in patients with asthma. *Ann Intern Med* 2004; 140: 802–813.
11 Holgate ST, Beasley R, Twentyman OP. The pathogenesis and significance of bronchial hyper-responsiveness in airways disease. *Clin Sci* 1987; 73: 561–572.
12 Fletcher M, Hiles D. Continuing discrepancy between patient perception of asthma control and real-world symptoms: a quantitative online survey of 1,083 adults with asthma from the UK. *Prim Care Respir J* 2013; 22: 431–438.
13 O'Connor BJ, Aikman SL, Barnes PJ. Tolerance to the nonbronchodilator effects of inhaled β_2-agonists in asthma. *N Engl J Med* 1992; 327: 1204–1208.
14 Kraan J, Koëter GH, vd Mark TW, *et al.* Changes in bronchial hyperreactivity induced by 4 weeks of treatment with antiasthmatic drugs in patients with allergic asthma: a comparison between budesonide and terbutaline. *J Allergy Clin Immunol* 1985; 76: 628–636.
15 Tattersfield AE, Postma DS, Barnes PJ, *et al.* Exacerbations of asthma: a descriptive study of 425 severe exacerbations. The FACET International Study Group. *Am J Respir Crit Care Med* 1999; 160: 594–599.
16 van Grunsven PM, van Schayck CP, Molema J, *et al.* Effect of inhaled corticosteroids on bronchial responsiveness in patients with "corticosteroid naive" mild asthma: a meta-analysis. *Thorax* 1999; 54: 316–322.
17 Mitchell EA. Is current treatment increasing asthma mortality and morbidity? *Thorax* 1989; 44: 81–84.
18 Weatherall M, Fingleton J, Eyers S, *et al.* A half doubling dose change in bronchial hyperresponsiveness in a population represents an important difference. *Transl Respir Med* 2013; 1: 4.
19 Pauwels RA, Pedersen S, Busse WW, *et al.* Early intervention with budesonide in mild persistent asthma: a randomised, double-blind trial. *Lancet* 2003; 361: 1071–1076.
20 Reddel HK, Busse WW, Pedersen S, *et al.* Should recommendations about starting inhaled corticosteroid treatment for mild asthma be based on symptom frequency: a post-hoc efficacy analysis of the START study. *Lancet* 2017; 389: 157–166.
21 Beasley R, Weatherall M, Shirtcliffe P, *et al.* Combination corticosteroid/β-agonist inhaler as reliever therapy: a solution for intermittent and mild asthma? *J Allergy Clin Immunol* 2014; 133: 39–41.

22 Price D, Fletcher M, van der Molen T. Asthma control and management in 8,000 European patients: the REcognise Asthma and LInk to Symptoms and Experience (REALISE) survey. *NPJ Prim Care Respir Med* 2014; 24: 14009.
23 Haahtela T, Järvinen M, Kava T, *et al.* Effects of reducing or discontinuing inhaled budesonide in patients with mild asthma. *N Engl J Med* 1994; 331: 700–705.
24 Selroos O, Pietinalho A, Löfroos AB, *et al.* Effect of early *vs* late intervention with inhaled corticosteroids in asthma. *Chest* 1995; 108: 1228–1234.
25 Papi A, Canonica GW, Maestrelli P, *et al.* Rescue use of beclomethasone and albuterol in a single inhaler for mild asthma. *N Engl J Med* 2007; 356: 2040–2052.
26 O'Byrne PM, FitzGerald JM, Bateman ED, *et al.* Inhaled combined budesonide-formoterol as needed in mild asthma. *N Engl J Med* 2018; 378: 1865–1876.
27 Bateman ED, Reddel HK, O'Byrne PM, *et al.* As-needed budesonide-formoterol *versus* maintenance budesonide in mild asthma. *N Engl J Med* 2018; 378: 1877–1887.
28 Papi A, Marku B, Scichilone N, *et al.* Regular *versus* as-needed budesonide and formoterol combination treatment for moderate asthma: a non-inferiority, randomised, double-blind clinical trial. *Lancet Respir Med* 2015; 3: 109–119.
29 Sobieraj DM, Weeda ER, Nguyen E, *et al.* Association of inhaled corticosteroids and long-acting β-agonists as controller and quick relief therapy with exacerbations and symptom control in persistent asthma: a systematic review and meta-analysis. *JAMA* 2018; 319: 1485–1496.
30 Chapman KR, Hinds D, Piazza P, *et al.* Physician perspectives on the burden and management of asthma in six countries: the Global Asthma Physician Survey (GAPS). *BMC Pulm Med* 2017; 17: 153.
31 Patel M, Pilcher J, Pritchard A, *et al.* Efficacy and safety of maintenance and reliever combination budesonide-formoterol inhaler in patients with asthma at risk of severe exacerbations: a randomised controlled trial. *Lancet Respir Med* 2013; 1: 32–42.
32 Royal College of Physicians. Why asthma still kills: the National Review of Asthma Deaths (NRAD). Confidential Enquiry report. London, Royal College of Physicians, 2014. Available from: www.asthma.org.uk/get-involved/campaigns/publications/national-review-of-asthma-deaths/
33 Busse WW, Bateman ED, Caplan AL, *et al.* Combined analysis of asthma safety trials of long-acting β_2-agonists. *N Engl J Med* 2018; 378: 2497–2505.