The paradoxes of asthma management: time for a new approach?

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ABSTRACT Poor adherence to maintenance pharmacotherapy is a reality in asthma. Studies confirm that when symptoms worsen, most patients increase short-acting β_2-agonist (SABA) use, instead of using controller medication. This behaviour might be attributable to several paradoxes in the current treatment approach. These paradoxes include the recommended use of a SABA bronchodilator alone at Global Initiative for Asthma (GINA) step 1, despite the fact that asthma is a chronic inflammatory disease. At step 1, the patient has autonomy and their perception of need and disease control is accepted, but at higher asthma treatment steps a fixed-dose approach is recommended, irrespective of symptom severity. The unintended consequence is the establishment of a pattern of early over-reliance on SABA. New approaches that avoid these paradoxes are needed, such as patient-adjusted therapy, in which patients adopt a symptom-driven approach using a combination reliever/controller. We propose that SABA reliever monotherapy should be replaced by a combination of inhaled corticosteroid (ICS) and formoterol, or similar rapid-onset bronchodilator, as reliever therapy for patients at GINA steps 1 or 2. This will ensure early and more regular administration of a controller medication. However, a significant body of clinical data will be needed before this approach can be approved by regulatory authorities.

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Introduction

paradox (ˈparədɒks) - a statement or proposition which, despite sound (or apparently sound) reasoning from acceptable premises, leads to a conclusion that seems logically unacceptable or self-contradictory (Oxford Dictionary)

Asthma is one of the most common chronic diseases in the world, with a prevalence that is still growing in some developing countries. In recent decades, asthma mortality rates have fallen dramatically [1]. However, despite this progress, national and international surveys continue to reveal inadequate asthma control in more than 50% of patients [2–4].

As with all chronic diseases, poor adherence to regular maintenance medication is a reality in asthma [5]. The most commonly observed pattern is the use of medication only when symptoms occur, and avoidance of treatment when it is perceived to be unnecessary [6]. Thus, healthcare providers may monitor and advise, but day-to-day management of asthma remains in the hands of the patient (or parent/carer of a child) and outcomes are dependent on the patients' perception of need and self-medication. To address this, management guidelines for asthma stress the importance of providing a written action plan for self-management. However, this alone is insufficient if it does not include a treatment strategy that is in accordance with anticipated patient behaviour and in particular, patient preference for reliever therapies. Several studies confirm that when symptoms worsen, most patients simply increase their use of a short-acting β_2-agonist (SABA) and are less likely to increase use of their controller medication. This symptomatic treatment delays the initiation of effective controller treatment and exacerbations follow [6, 7].

We hypothesise that the roots of this behaviour, and the poor outcomes of asthma treatment in many patients with even mild asthma, are attributable to a number of paradoxes in our treatment approach and advice, which are confusing to patients (table 1). These paradoxes feed the patients' poor understanding of effective treatment and lead to poor adherence to treatment, particularly underuse of controllers and overuse of, and over-reliance on SABA reliever medication [3, 6]. Here, we examine these paradoxes, their potential impact, and consider solutions to overcome these and improve asthma management and control.

The asthma treatment paradoxes

The *first treatment paradox* occurs at treatment step 1 in most asthma treatment strategy documents or guidelines [8–10]. It is well established that asthma is a disease of chronic inflammation, with episodes of worsening inflammation associated with increased symptoms and/or exacerbations; however, current guidelines paradoxically recommend that initial treatment is only symptomatic, rather than directed at the underlying mechanism. A SABA bronchodilator, which has no inherent anti-inflammatory pharmacological properties, is recommended, rather than an anti-inflammatory medication such as an inhaled corticosteroid (ICS) [9, 10]. Hence, from the outset, patients are taught that treating symptoms alone is acceptable. While at future medical visits, other medications might be added or doses adjusted alongside the SABA [8–10], the consistent prescription of as-needed SABA reinforces in the minds of patients, the key and central role of SABA in asthma management. This impression is further supported

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.

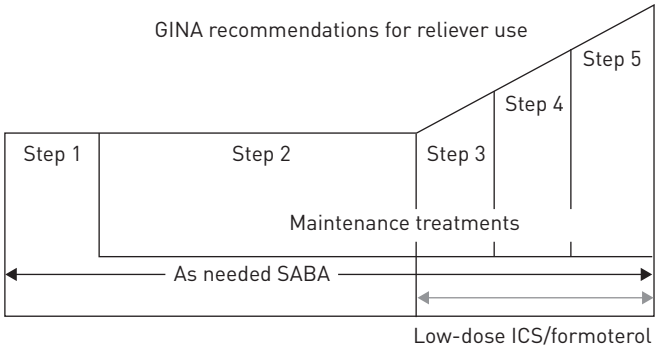

FIGURE 1 Current Global Initiative for Asthma (GINA) recommendations for reliever use. SABA: short-acting β_2-agonist; ICS: inhaled corticosteroid.

by the physician's instructions to carry the SABA around at all times to treat symptoms, in addition to the personal experience of patient in the rapid relief it provides (figure 1). Surveys confirm that the great majority of patients are confident and willing to self-treat, but want immediate relief from symptoms. This was the response of 90% of the subjects in the INSPIRE study [6].

The *second paradox* also occurs at treatment step 1. Patients are asked to recognise when their condition is becoming troublesome and respond appropriately with SABA use. However, these self-management instructions are countermanded at steps 2 and higher, when physicians attempt to emphasise the key role of a controller that needs to be taken regularly, and patients are advised and expected to take fixed doses of their controller treatment regardless of the level of symptoms. Thus, at step 1 the patient has autonomy and their perception of need and disease control is accepted, but at higher asthma treatment steps, a fixed-dose approach is recommended. Indeed, one of the goals of regular maintenance ICS is to eliminate the as-needed use of SABA. This means that the management approach used at step 1 has to be unlearnt. In addition, this switch in approach from as-needed to regular treatment is confusing, as is the need to recall which inhaler to use when symptoms occur. Patients quickly learn that symptom relief is best achieved with the SABA, again reinforcing their view that use of the SABA is the main treatment for asthma. This results in patients frequently taking less than 50%, and usually about 30%, of the prescribed dose of controller medication, with many continuing to rely on as-needed SABA [5, 11].

The *third paradox* is the switch when patients are instructed to reduce the treatment that they perceive is most beneficial, the SABA, and rather take one with no immediate perceived benefit. For many patients, the message that regular use of a SABA might be unsafe and even associated with asthma deaths [12, 13] is hard to grasp. The relevance of this paradox is evident from the continued high ratio of reliever: preventer medication prescriptions in many countries, often well above a ratio of 2:1. As this ratio decreases, asthma morbidity declines, thereby reducing the utilisation of emergency services, hospitalisations and deaths [14]. At the population level, ratios of 1 or 0.5 are associated with greatly reduced emergency use of health facilities and overall cost savings for funders of health facilities.

A *fourth paradox* occurs at treatment step 3, when patients are given what appears to be conflicting advice for the self-administration of SABA and long-acting β_2-agonist (LABA). The LABA, they are advised, should never, under any circumstance, be used as monotherapy in asthma, but only in combination (preferably in a single-inhaler combination) with an ICS [8–10]. However, monotherapy with SABA is standard. Yet, there is evidence indicating that both SABA and LABA have serious risks as monotherapy [13, 15], and no evidence to suggest that there is any difference in the risks associated with regular "maintenance" use of either.

The *fifth paradox* is caused by conflicting perceptions of need between patients and physicians, which might reinforce a patient's false belief that the asthma has been effectively controlled. This results from poor communication and failure of physicians to adequately interrogate their patients at follow-up visits with testing questions about their asthma status, or failure to use asthma control scoring methods like the Asthma Control Test or Global Initiative for Asthma (GINA) assessment of symptom control. This communication gap results in under-recognition of need and poor control. In the REALISE study [3], conducted in patients with asthma in European countries, more than 80% of the respondents considered their asthma to be controlled, and over 70% did not regard their condition as serious. Even among those whose asthma was uncontrolled, more than 80% of respondents who had experienced acute exacerbations requiring oral steroid use, an emergency department visit or hospitalisation in the previous year, also regarded their asthma as "controlled" [3]. One possible explanation for this might be the differences in terminology and understanding of the term "control" between patients and physicians. This explanation is

supported by findings from the Asian REALISE survey, in which two-thirds of the physicians stated that they believed that their patients' definition of "well-controlled asthma" was aligned with their own: the physicians' view was that "well-controlled" asthma meant either "asthma symptoms are non-existent or minimal" (60%) or "asthma having minimal impact on patient's daily life" (47.7%) [16]. In contrast, patients perceived "well-controlled" as being able to manage their exacerbations with medical help or the use of medication, whereas approximately 10% only, agreed with the physicians' view that "asthma symptoms are non-existent or minimal" [16]. Such divergence in communication could be a factor in the over-reliance on SABA and underuse of ICS.

Practical solutions to these paradoxes and the continuum of care approach

The most obvious solution to paradox one is to introduce effective anti-inflammatory treatment earlier in the treatment algorithm. Indeed, the most recent update to the GINA strategy document suggests that low-dose ICS may be introduced at step 1 [8]. The introduction of ICS therapy at the time of diagnosis, or shortly thereafter, is known to lead to improved lung function, reduced risk of severe asthma exacerbations [17], and improved asthma control, and thus, is more effective than waiting until symptoms have been present for several years [18, 19]. At the population level, in the Finnish Asthma Programme for example, the introduction of anti-inflammatory treatment (principally ICS) was associated with improved control and reduction of the burden and cost of asthma [20]. In patients with mild or intermittent asthma, low-dose ICS has been shown to be effective in improving lung function and quality of life and reducing asthma symptoms, risk of exacerbation and asthma-related hospitalisations [17].

The early introduction of ICS at the time of diagnosis is attractive, but there are several factors that could limit the efficacy of this approach. First, it would mean the elimination of treatment step 1, as-needed SABA as monotherapy. In addition, this approach does not overcome paradox two, namely, that patients will always favour the SABA over the ICS or other controller, because of the rapid relief of symptoms. Thus, the temptation to stop the ICS, from which no benefit is perceived, and revert to SABA use alone is overwhelming for most, and there is little hope of re-institution of regular ICS therapy unless there is significant deterioration.

An alternative approach is to combine steps 1 and 2 and replace SABA and ICS with combination treatment comprising SABA or fast-acting LABA and ICS in a single inhaler, for use as-needed in patients with intermittent or infrequent symptoms, and increase this to regular maintenance plus as-needed use in patients whose symptoms are persistent [21]. This would also help to resolve both paradoxes three and four. The use of ICS/SABA or ICS/fast-acting LABA combinations, as an alternative to a SABA as rescue medication, would accommodate typical patient behaviours and would be acceptable with the self-titration strategies of patients [1, 3]. It would also allay safety concerns about the overuse of SABA monotherapy, which also exist for LABA monotherapy.

One of the LABAs currently available, formoterol, has an onset of action that is as fast as that of SABA salbutamol [22]. The benefit of ICS/formoterol combinations for both maintenance and reliever therapy (MART) is now well established in patients with moderate to severe asthma with a history of severe exacerbations. This approach ensures that patients receive a dose of ICS whenever they feel the need for symptomatic relief. This can help to overcome the problems associated with poor adherence to maintenance ICS and overuse of SABA, which in turn, could improve asthma control [21] and reduce the "need" for SABA reliever use. A number of studies have shown that MART reduces severe asthma exacerbation risk by 40–50%, while demonstrating that asthma control is at least as good as conventional regimens, and often with a lower long-term steroid load (figure 2) [23–25]. Hence, if the stepwise approach to asthma management is changed and a SABA at step 1 was replaced with an ICS/fast-acting LABA or ICS/SABA, then the SABA might lose its "key medication" status in the minds of asthma patients. Indeed, completely replacing a SABA with these combinations for asthma patients could prevent this perceived key medication status from developing in the first place.

The as-needed use of an ICS/SABA or ICS/fast-acting LABA combination has been proposed as a potential treatment strategy for intermittent and mild asthma [21]. Using this as-needed asthma treatment approach for symptom relief would also fit the patient-adjusted therapy model, and would titrate both the ICS and β_2-agonist dose according to need. In all probability, this would increase ICS use in patients who are likely to be poorly adherent to ICS and who tend to over-rely on the SABA reliever [21]. In mild asthma, these as-needed strategies, employing co-administered ICS/SABA or ICS/LABA ("partnered ICS approach"), better match treatment to patient behaviour than the current once- or twice-daily maintenance regimens. It will be vital to conduct studies to show this as a superior approach to SABA as needed, and not inferior to regular ICS for mild asthma [26, 27], as well as ensure effective communication, especially to those with mild asthma, regarding the safety of intermittent use of ICS.

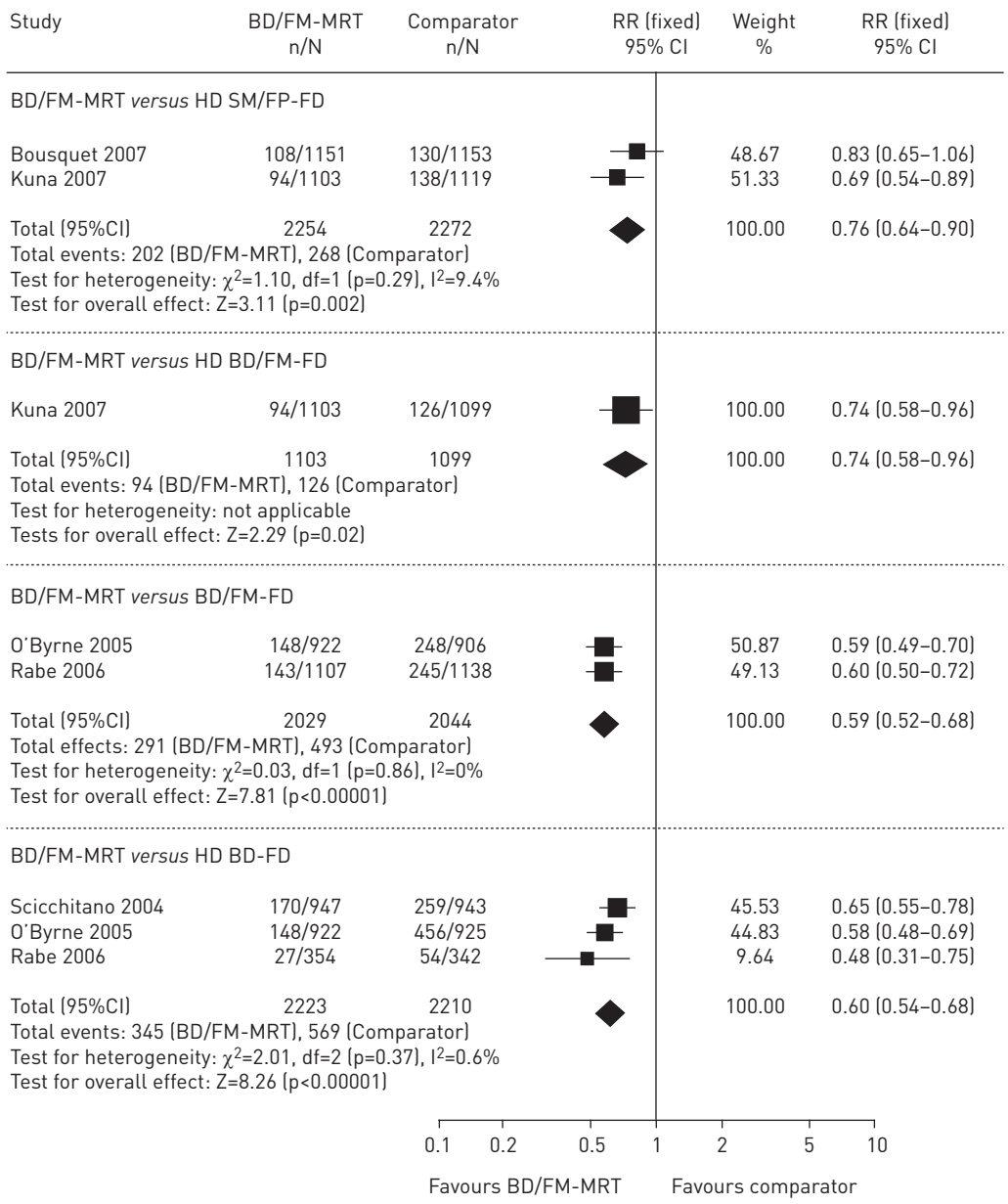

FIGURE 2 Meta-analysis of the primary outcome variable, severe asthma exacerbations, from six randomised controlled trials in the BD/FM MRT development programme. Reproduced with permission from the publisher [25]. BD: budesonide; FD: fixed-dose; FM: formoterol; FP: fluticasone propionate; HD: high dose; MRT: maintenance and reliever therapy; RR: relative risk; SM: salmeterol.

The continuum of care approach

For all patients with asthma, patient-adjusted therapy would comprise both a controller and reliever (usually ICS/fast-acting LABA) in a single inhaler; this would form part of a continuum of care approach in partnership with doctors who provide periodic and predictive monitoring of the disease, which will help to resolve paradox five (figure 3). At the more severe end of the asthma spectrum, patient-adjusted therapy is supplemented by increased involvement of healthcare providers in monitoring and guiding adjustments to therapy with the help of phenotyping, while the approach of the patient-adjusted therapy remains the same. Assessing blood eosinophilia [28] or other biomarkers may be added as part of the step-up approach at the severe end of the asthma spectrum, as information about endotypes becomes available. It would now be possible to also include electronic inhaler monitoring as a potential "biomarker of behaviour" at the severe end of the spectrum.

Theoretical application of the continuum of care approach

When considering any new treatment approach, it is important to ensure that it is applicable across the full disease severity range and all patient types. While the application of the continuum of care approach is

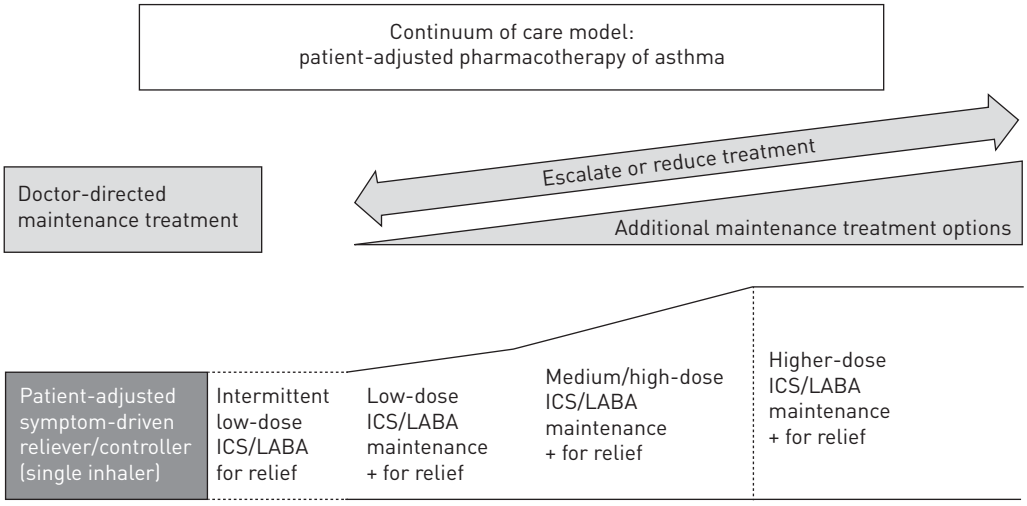

FIGURE 3 Continuum of care: patient-adjusted plus physician-directed step-wedge approach to pharmacotherapy in asthma. LABA: long-acting β_2-agonist; ICS: inhaled corticosteroid.

relatively straightforward across the different disease severities, evaluation of this approach in specific patient populations is worthy of consideration. For example, persons who under-perceive the severity of their asthma will not be at any greater risk than with the current guidelines. The earlier suggestion of patient-adjusted therapy with an ICS/SABA or ICS/LABA for symptom-driven reliever/controller use is likely to increase the amount of ICS delivered, and thus, improve asthma control. At the other end of the spectrum, possible concerns regarding the overuse of an ICS/SABA or ICS/LABA appear to be ill-founded, as recent observations with an ICS/fast-acting β-agonist MART regimen suggest that this is not the case, and "overuse of reliever days" are in fact reduced, rather than increased, with the MART approach [29, 30]. Ongoing trials with electronic monitoring of inhaler use will provide definitive answers in the not-too-distant future.

Asthma is a heterogeneous disease, so this approach may be considered an oversimplification. For example, how are non-eosinophilic asthma and other phenotypes and endotypes treated in this continuum of care? This approach, like current treatment approaches, acknowledges that recognition of clinical phenotypes and identification of issues that may influence the response to therapy (*e.g.* adolescence, old age, obesity and comorbidity), along with insights gained from the inclusion of more biomarkers at appropriate points (as part of the physician monitoring component), will prompt changes in therapy. The approach is deliberately simple, providing the minimum that is required by the vast majority of patients with asthma; *i.e.* relief and control of symptoms, patient involvement and self-management based on an understanding of their role in controlling the disease, and increasing physician oversight at the more severe end of the spectrum. This simple continuum of care approach also ensures that it can be applied universally, even in the poorest countries. Doctors without access to the tools to phenotype/endotype asthma can provide adequate and acceptable treatment for patients using this approach.

From a cost perspective, it is possible that the use of an ICS/SABA or ICS/LABA rather than SABA monotherapy will result in an increase in purchase cost to patients and payers, but this is likely to be significantly offset by exacerbation reduction in all but the very mildest end of the severity spectrum.

Other commentators have suggested the extension of the use of biologics, currently reserved for patients with severe refractory eosinophilic asthma, to include much milder patients [31]. The advantages associated with this suggestion might include improved adherence to treatment, as the biologics are administered in an observed setting. However, the cost implications of this approach make it currently impractical.

Conclusions

Despite many advances in medication, new treatment guidelines and greater knowledge about the disease, there has been a plateau in improvements to asthma control, which points towards the need for new approaches to asthma management. We describe here five paradoxes in asthma management that are counterproductive to achieving optimal asthma control, but for which there are readily implementable solutions. Patient-adjusted therapy, in which patients adjust their symptom-driven reliever/controller use, would form part of a continuum of care approach in partnership with physician monitoring of symptoms

and exacerbations and periodic monitoring of lung function. Reduced reliance on SABA reliever monotherapy could be achieved by use of ICS/formoterol or ICS/SABA combination products as reliever therapy instead of SABA monotherapy for patients at GINA steps 1 or 2. This would require a significant body of data to justify the necessary regulatory changes and changes in prescriber behaviour. Replacement of as-needed SABA by ICS/fast-acting LABA or SABA from the start of treatment would eliminate the problem of learned reliance and over-reliance on SABA. If clinical studies support this as an effective and safe strategy, it could ultimately eliminate the use of SABA-only products in asthma.

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References

1 Hancox RJ, Le Souef PN, Anderson GP, *et al.* Asthma: time to confront some inconvenient truths. *Respirology* 2010; 15: 194–201.
2 Nathan RA, Thompson PJ, Price D, *et al.* Taking aim at asthma around the world: global results of the Asthma Insight and Management Survey in the Asia-Pacific Region, Latin America, Europe, Canada, and the United States. *J Allergy Clin Immunol Pract* 2015; 3: 734–742 e735.
3 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.
4 Demoly P, Annunziata K, Gubba E, *et al.* Repeated cross-sectional survey of patient-reported asthma control in Europe in the past 5 years. *Eur Respir Rev* 2012; 21: 66–74.
5 World Health Organization. Adherence to long-term therapies: Evidence for action. Geneva, WHO, 2003.
6 Partridge MR, van der Molen T, Myrseth SE, *et al.* Attitudes and actions of asthma patients on regular maintenance therapy: the INSPIRE study. *BMC Pulm Med* 2006; 6: 13.
7 Patel M, Pilcher J, Hancox RJ, *et al.* The use of beta2-agonist therapy before hospital attendance for severe asthma exacerbations: a post-hoc analysis. *NPJ Prim Care Respir Med* 2015; 25: 14099.
8 Reddel HK, Bateman ED, Becker A, *et al.* A summary of the new GINA strategy: a roadmap to asthma control. *Eur Respir J* 2015; 46: 622–639.
9 National Asthma Council Australia. Australian Asthma Handbook. Melbourne, National Asthma Council Australia, 2016.
10 BTS SIGN. British guideline on the management of asthma. British Thoracic Society, Scottish Intercollegiate Guidelines Network, 2014.
11 Williams LK, Pladevall M, Xi H, *et al.* Relationship between adherence to inhaled corticosteroids and poor outcomes among adults with asthma. *J Allergy Clin Immunol* 2004; 114: 1288–1293.
12 Dissanayake SB. Safety of beta2-agonists in asthma: linking mechanisms, meta-analyses and regulatory practice. *AAPS J* 2015; 17: 754–757.
13 Spitzer WO, Suissa S, Ernst P, *et al.* The use of beta-agonists and the risk of death and near death from asthma. *N Engl J Med* 1992; 326: 501–506.
14 Laforest L, Licaj I, Devouassoux G, *et al.* Prescribed therapy for asthma: therapeutic ratios and outcomes. *BMC Fam Pract* 2015; 16: 49.
15 Nelson HS, Weiss ST, Bleecker ER, *et al.* The Salmeterol Multicenter Asthma Research Trial: a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. *Chest* 2006; 129: 15–26.
16 Price D, David-Wang A, Cho SH, *et al.* Asthma in Asia: Physician perspectives on control, inhaler use and patient communications. *J Asthma* 2016; 53: 761–769.
17 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.
18 Selroos O, Pietinalho A, Lofroos AB, *et al.* Effect of early vs late intervention with inhaled corticosteroids in asthma. *Chest* 1995; 108: 1228–1234.
19 Agertoft L, Pedersen S. Effects of long-term treatment with an inhaled corticosteroid on growth and pulmonary function in asthmatic children. *Respir Med* 1994; 88: 373–381.
20 Haahtela T, Herse F, Karjalainen J, *et al.* The Finnish experience to save asthma costs by improving care in 1987-2013. *J Allergy Clin Immunol* 2017; 139: 408–414 e402.
21 Beasley R, Weatherall M, Shirtcliffe P, *et al.* Combination corticosteroid/beta-agonist inhaler as reliever therapy: a solution for intermittent and mild asthma? *J Allergy Clin Immunol* 2014; 133: 39–41.
22 Cheung D, van Klink HC, Aalbers R, *et al.* Improved lung function and symptom control with formoterol on demand in asthma. *Eur Respir J* 2006; 27: 504–510.
23 O'Byrne PM, Bisgaard H, Godard PP, *et al.* Budesonide/formoterol combination therapy as both maintenance and reliever medication in asthma. *Am J Respir Crit Care Med* 2005; 171: 129–136.
24 Bousquet J, Boulet LP, Peters MJ, *et al.* Budesonide/formoterol for maintenance and relief in uncontrolled asthma vs. high-dose salmeterol/fluticasone. *Respir Med* 2007; 101: 2437–2446.
25 Edwards SJ, von Maltzahn R, Naya IP, *et al.* Budesonide/formoterol for maintenance and reliever therapy of asthma: a meta analysis of randomised controlled trials. *Int J Clin Pract* 2010; 64: 619–627.
26 O'Byrne PM, FitzGerald JM, Zhong N, *et al.* The SYGMA programme of phase 3 trials to evaluate the efficacy and safety of budesonide/formoterol given 'as needed' in mild asthma: study protocols for two randomised controlled trials. *Trials* 2017; 18: 12.
27 Beasley R, Pavord I, Papi A, *et al.* Description of a randomised controlled trial of inhaled corticosteroid/fast-onset LABA reliever therapy in mild asthma. *Eur Respir J* 2016; 47: 981–984.
28 Price DB, Rigazio A, Campbell JD, *et al.* Blood eosinophil count and prospective annual asthma disease burden: a UK cohort study. *Lancet Respir Med* 2015; 3: 849–858.

29 Demoly P, Louis R, Soes-Petersen U, *et al.* Budesonide/formoterol maintenance and reliever therapy versus conventional best practice. *Respir Med* 2009; 103: 1623–1632.
30 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.
31 Bardin PG, Price D, Chanez P, *et al.* Managing asthma in the era of biological therapies. *Lancet Respir Med* 2017; 5: 376–378.