# Does inhaler adherence really matter in severe asthma?

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Shareable abstract (@ERSpublications)
**Medicines adherence matters in severe asthma, but rather than persist with the one-size-fits-all approach advocated currently, inhaled corticosteroid therapy should be tailored to patient capability and clinical need through biomarker-led management** https://bit.ly/47RdZzD

**Cite this article as:** d'Ancona G, Kent BD. Does inhaler adherence really matter in severe asthma? *Breathe* 2024; 20: 240001 [DOI: 10.1183/20734735.0001-2024].



Received: 9 July 2024
Accepted: 30 Sept 2024

## Abstract

Inhaled therapies, primarily the inhaled corticosteroid (ICS), have been the cornerstone of asthma treatment since the 1960s. They have been shown to reduce symptom burden, morbidity and mortality, and potentially avoid unnecessary and unscheduled healthcare. However, some people have severe asthma, defined by an inability to gain or maintain consistent disease control despite appropriate use of high dose ICS-containing inhalers. In this review, we discuss whether it is appropriate to demand adherence to a treatment this cohort are demonstrably resistant to.

## Introduction

Asthma is one of the most common respiratory diagnoses, affecting ~300 million people around the world [1]. Most patients can successfully achieve disease control with inhaled corticosteroids (ICS), which have been the bedrock of asthma care since their introduction 50 years ago [2]. However, in the region of one in every 20 people with asthma has severe asthma, defined by an inability to gain or maintain consistent disease control despite appropriate use of high dose ICS-containing inhalers, often necessitating a step up to treatment with high-cost biologic agents [1]. One might anticipate that bad asthma would beget good adherence to therapies designed to control it, but this is not always be the case [3]. Non-adherence to maintenance therapy is common in most chronic diseases [4], and asthma proves to be no exception [5, 6]. But does it matter? Does a failure to use an inhaler which – by definition – has not succeeded in controlling someone's asthma actually worsen outcomes? Are there people with severe asthma receiving a biologic agent who could maintain control without daily ICS therapy? In this review, we describe how we can assess adherence to inhaler therapy and how this can influence care decisions, discuss the prevalence of non-adherence in poorly controlled asthma populations, and finally examine the impact of inhaler adherence in people with severe asthma.

## What is medicines adherence?

The terms adherence and compliance are often used interchangeably, but as the latter suggests the patient is a passive subordinate [7] it undermines the concept of healthcare as a partnership where patient perceptions and preferences are central to treatment decisions. The World Health Organization (WHO) defines adherence as: "the extent to which a person's behaviour corresponds with agreed recommendations from a health care provider" and for this reason adherence has largely superseded compliance as the apposite term [4]. The purpose of establishing inhaler adherence in asthma is to understand whether the asthma is uncontrolled due to not taking the inhaler as suggested (regularly at a suitable dose) or despite appropriate inhaler use. Indeed, the classification of asthma severity has medicines adherence at its core. International guidelines suggest that the label of severe asthma should only apply if the asthma remains uncontrolled in spite of adherence to maximal optimised treatment with high-dose ICS and another controller (*e.g.* a long-acting $\beta_2$-agonist (LABA) or maintenance oral corticosteroids (mOCS)) or the asthma worsens when this high-dose treatment is decreased [8]. This terminology emphasises not only the clinician (often physician) control of how medicines should be used but alludes to the consequences to patients for deviations from this advice [9]. The numerical cut-offs that determine non-adherence are

somewhat arbitrary, and not based on prospective data regarding outcomes at demarcated levels of medication usage. That said, use of <50% of prescribed treatment is generally considered to be consistent with poor adherence, and anything above 75–80% to be optimal adherence [10].

## How is adherence in asthma measured?

Adherence to a regular therapy can be measured in many ways, varying significantly in both complexity and accuracy [11, 12]. In asthma, the commonest methods adopted are those which are least expensive or are easiest to complete but are also the least accurate. Aside from simply asking the patient about their inhaler use, the most frequently used method is assessment of the medicines possession ratio (MPR), a measure of how frequently an individual has collected their inhalers in a particular period of time compared to that which would be expected if they were using their medication as prescribed [3]. This, and other currently available methods to quantify adherence are outlined in table 1 [13], but all methods are flawed: some by their utility only to specific medicines (*e.g.* applicable to people taking methylxanthines or mOCS); some by tending to over-estimate adherence (*e.g.* asking the patient about their medicines taking behaviours verbally or *via* a questionnaire [14]); or the combination of both seen when using prescription refill rates to calculate MPR. It is also worth noting that the MPR is not useful in cases of patient-led ICS dosing, *i.e.* maintenance and reliever therapy (MART) or the anti-inflammatory reliever (AIR) regimen where budesonide–formoterol is taken as required instead of a short-acting $\beta_2$-agonist (SABA) [1, 15].

The use of electronic sensors that clip onto inhalers to objectively record the date and time of dose administration in real-time is increasing, so too is the associated technology that delivers feedback and endorsement of appropriate inhaler technique. The hope is that these will soon be routinely integrated with the inhaler device itself [16]. In the simplest terms, these methods may quantify adherence by indicating whether the patient followed clinician instructions as defined by WHO, but in the era of individualised treatment plans and medicines optimisation, is this sufficient or appropriate?

The presence of elevated levels of nitric oxide in the exhaled breath can indicate Type-2 inflammation in the airways [17]. As fractional expired nitric oxide ($F_{ENO}$) can be measured quickly and easily in practice, this point-of-care surrogate marker can support the confirmation of an asthma diagnoses and may differentiate between symptoms needing oral corticosteroid (OCS) treatment or not. The subsequent development of the $F_{ENO}$ suppression test (FST) [18], where ICS use is assessed in the context of biomarker response, adds a critical dimension. The FST (particularly its amalgamation with inhaler sensors [19]) not only facilitates assessment of ICS adherence in terms of the patient having done what was advised but aligns it with demonstrable clinical benefit (reduced inflammation).

**TABLE 1** Common methods to measure medicines adherence and their applicability to asthma

| | Advantages | Disadvantages |
|---|---|---|
| **Therapeutic effect** | Not considered useful in asthma | |
| **Canister weighing** | Not considered useful in asthma | |
| **Self-report (verbally or by answering a questionnaire)** | Quick and easy to complete | Tends to over-estimate adherence |
| **Examine prescription orders or pharmacy refill records compared to those expected in the timeframe (MPR)** | Relatively easy and quick to complete; if figures are low, adherence is unlikely | Tends to over-estimate adherence; if high, adherence may be mistakenly assumed (that is, all doses issued are taken) |
| **Examine blood for the presence of medicine or metabolite** | Relatively cheap and easy to interpret blood test | Only useful in asthma to detect methylxanthines |
| **Electronic monitors (devices that are integrated with or clip onto inhalers that record dose actuation)** | Potentially very useful (accurate, real-time data that can be interpreted alongside biomarkers) | Currently expensive, so poor access to devices and limited evidence of their utility |
| **Measure a physiological marker (*e.g.* blood cortisol with prednisolone level)** | Relatively cheap and easy to interpret blood test | Only useful for patients reporting maintenance prednisolone of ⩾5 mg daily; test may not be widely available |
| **Directly observed therapy (*e.g.* witnessed administration or FST)** | Robust evidence to support intervention | Inconvenient, not appropriate for some ICS regimens and resource-intensive; FST: inadequate access to $F_{ENO}$ and useful only in those with baseline $F_{ENO}$ ⩾45 ppb |

MPR: medicines possession ratio; $F_{ENO}$: fractional expired nitric oxide; FST: $F_{ENO}$ suppression test; ICS: inhaled corticosteroids. Reproduced and modified from [13] with permission.

## Are people with severe asthma non-adherent to their inhalers?

As mentioned previously, bad asthma does not necessarily translate into good ICS adherence. The incidence of inhaler non-adherence in asthma is consistently reported to be ∼50% [5], a phenomena which is seen in severe as well as mild disease [20]. The level of ICS usage that constitutes adequate adherence is likely to vary significantly from patient to patient [10], but good adherence is often (slightly arbitrarily) considered to be taking at least 70–75% of recommended doses. The concept of a binary cut-off to define satisfactory adherence is being increasingly challenged because it does not consider patient need – based either on coincident airway inflammation using $F_{ENO}$ or symptoms [1, 21, 22] – or reflect the side-effect profile of an ICS particularly when administered at a high dose for prolonged periods of time [23]. Rather, the principles of medicines optimisation would suggest that ICS usage should be an individualised decision that minimises inflammation and ICS dose [24].

Data from prospective trials suggest that it may be feasible to tailor ICS dosage according to biomarkers to optimise the balance between the benefits and harms of steroid therapy, at least in patients who are motivated to cooperate [25]. The UK Refractory Asthma Stratification Programme randomised severe asthma patients to either a Type-2 inflammation biomarker dose adjustment group or to standard care, with the goal of achieving ICS dose reduction. In the overall population, no difference was seen between the two groups, but this turned out to be largely due to participants in the biomarker ICS-dose adjustment group deciding not to follow their clinicians' treatment advice. Amongst those who did follow this advice, Type-2 inflammation biomarkers appeared to be a useful medicines optimisation tool, with a significant reduction in ICS dose in the per protocol group.

## Does non-adherence to inhalers in asthma have consequences?

The WHO attributes significant morbidity and mortality to poor medication adherence generally [4], and in asthma there is compelling evidence that inhaler use affects patient outcome in direct and indirect ways. Non-adherence leads to more frequent and more severe exacerbations (necessitating treatment with OCS), unnecessary treatment escalation, absences from work, higher levels of unscheduled healthcare use and even death [10, 26–31]. The sequela of systemic corticosteroids is widely described [32–35] and led Heaney and Horne [5], in 2011, to propose that addressing ICS non-adherence was likely to deliver more benefits to patients and healthcare systems than any novel treatments in the pipeline, a view reinforced in 2017 by clinicians urging non-adherence be considered a higher priority [36] and the call for a consolidated approach to its management [37].

With the arrival of seemingly expensive biologic therapies for use in severe asthma, the impact of poor adherence extends beyond the clinical and financial, it may also prevent initiation of biologic therapy. For example, in the UK National Health Service, demonstrable adherence to "routine therapies" (including an ICS, LABA, leukotriene receptor antagonist, theophylline or OCS) is essential. Hence, rationing biologic use to patients adherent to a high-dose ICS (and meeting the relevant OCS exposure threshold) is perceived to deliver value by not using biologics in patients who could be controlled with appropriate inhaled treatment alone [38]. Moreover, identifying non-adherence to ICS may significantly influence treatment decisions in difficult asthma cohorts. In the INCA-SUN trial, patients with difficult asthma were randomised to usual care or digital monitoring of adherence and peak flow [39]. Having objective evidence of inhaler usage appeared to modify clinician prescribing, with significantly fewer patients in the digital monitoring arm having a net increase in treatment compared to baseline, including a reduced likelihood of receiving biologic therapy. Hence, thoroughly assessing ICS adherence prior to initiation of biologic therapy may help reduce both costs and longer-term burden of care.

## Does non-adherence to an ICS matter when you are receiving a biologic?

The impact of ICS adherence on outcomes while receiving biologic therapy may vary significantly according to the biologic agent used and its mechanism of action. Among patients receiving the interleukin (IL)-5 blocker mepolizumab, optimal ICS adherence by patients receiving mepolizumab was associated with a statistically significantly lower exacerbation frequency and more successful reduction of maintenance OCS (figure 1) [40]. This contrasted with the results from a similar cohort receiving the IL-5 receptor α-targeting monoclonal antibody benralizumab, where the outcomes did not appear to be affected by ICS adherence (figure 2) [41]. These studies were limited both by their retrospective nature and their use of MPR to measure adherence. However, they had biological plausibility: eosinophils remain in the airway at the licensed dose of mepolizumab, and a significant proportion of the exacerbations that occur whilst receiving mepolizumab appear to be eosinophil mediated [42]. This contrasts with benralizumab, which effectively eliminates airway eosinophils, thus potentially reducing the need for concomitant ICS therapy to mitigate their effects [43].

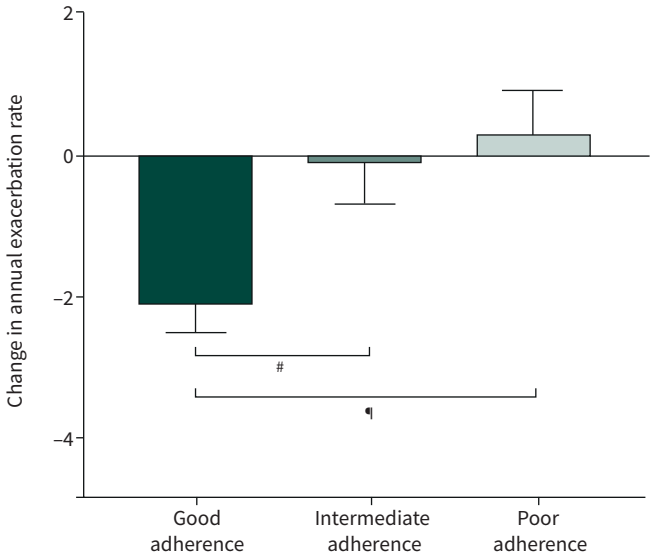


**FIGURE 1** Changes in annual exacerbation rate stratified by inhaled corticosteroid adherence following 12 months of mepolizumab therapy. ANOVA p=0.004; #: p=0.065; ¶: p=0.011. Reproduced from [40] with permission.

A recognition of the need for prospective, controlled data led to the development of SHAMAL, a randomised controlled trial using electronic inhaler monitoring and the principles of medicines optimisation that when disease control is achieved, therapy should be reviewed, and doses reduced or treatment stopped where appropriate [44]. In SHAMAL, severe eosinophilic asthma patients whose disease had become controlled with benralizumab and high-dose regular ICS–formoterol were randomised to either continue on high-dose ICS or to wean towards a low-dose ICS–formoterol as-required AIR regimen. While arguably not a cohort of patients representative of all people with severe eosinophilic asthma, a remarkable 92% of patients were able to maintain control with a lower ICS–formoterol dose, and 61% were able to have benralizumab and AIR without impact on symptoms or exacerbation frequency (figure 3). Importantly however, as the ICS dose was weaned down to AIR, $F_{ENO}$ levels increased and lung function declined, suggesting that patients with controlled severe eosinophilic asthma on benralizumab should continue on at least regular low-dose ICS therapy alongside their biologic. Within this study there appeared

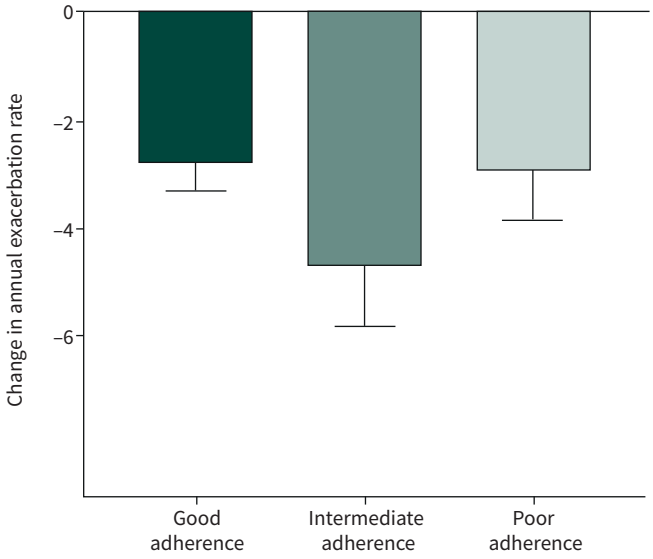


**FIGURE 2** Changes in annual exacerbation rate stratified by inhaled corticosteroid adherence following 12 months of benralizumab therapy. ANOVA p=0.223. Reproduced from [41] with permission.

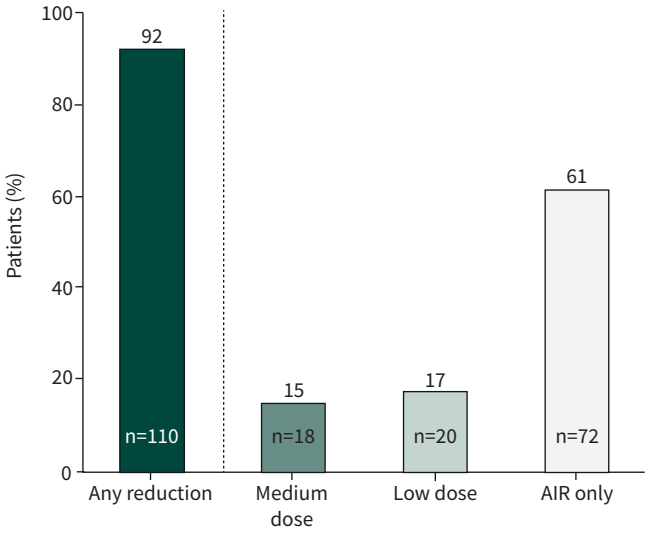


**FIGURE 3** Proportion of patients able to reduce their inhaled corticosteroid dose without leading to an increase in symptoms or exacerbation frequency. Reducing the dose of budesonide–formoterol from high (800/24 µg twice daily) to medium (400/12 µg twice daily) to low dose (200/6 µg twice daily) or anti-inflammatory reliever (AIR) (200/6 µg as required) did not cause an increase in annual exacerbation rate on benralizumab therapy. Reproduced from [44] with permission.

to be little benefit from remaining on higher doses of ICS, a finding that challenges not only the role of a high-dose ICS therapy in severe asthma but the definition of "severe asthma" itself.

## Can we change medicines taking behaviours?

Patients may not follow the instructions they have been given on how to use their inhalers for several and often complex reasons. These will differ between people, in the same individual over time and the person may be adherent to a selection of medicines, but not others [45]. Non-adherence can be described as unintentional or intentional, where unintentional non-adherence is a passive process where medicines are not taken as suggested for reasons outside the control of the individual (*e.g.* they do not understand the instructions, are unable to pay for treatments or they forget to take them), whereas intentional non-adherence is an active decision driven primarily by beliefs about the treatment, disease and previous experiences with medicines. This dichotomy helps us to understand choices, but is an oversimplification as there is overlap; for example, a person is unlikely to forget a medicine they perceive to be essential compared to those they consider inconsequential [45, 46].

A 2017 Cochrane review concluded that a variety of interventions would improve adherence but interestingly, the clinical relevance of this improvement was uncertain [47]. The evidence to support adherence interventions and application of the psychology frameworks COM-B and PAPA in asthma have been explored by D'Ancona and Weinman [45]. They describe common themes in the quest for better adherence: that the extent of non-adherence is often under-estimated, that the influence of the intervention is usually brief, and importantly, reiterate that increasing numerical adherence (against clinician instructions) does not always lead to an improvement in patient outcome. This review article and a similar review [48] clarifies why medicines non-adherence should not be considered an act of akrasia (that is, a lack of self-control or acting against one's better judgement), rather that the patient reasons that translate into medicines non-adherence should be explored and managed. Several interventions have been reported to deliver improved medicines adherence in asthma. They are often multifactorial and need to be repeated to maintain effect. These are outlined in table 2 [13].

## So, does inhaler adherence really matter in severe asthma?

In conclusion, the role of inhaled therapy in asthma is to minimise airway inflammation, reduce exacerbation frequency and severity, preserve lung function, and minimise the risk of death. This translates into fewer day-to-day symptoms experienced by patients and a resultant improvement in quality of life or "asthma remission" [49]. Asthma is a chronic condition characterised by intermittent symptoms, but

**TABLE 2** Evidence-based interventions to improve adherence in asthma

| Intervention | Example |
|---|---|
| **Motivational strategies and shared decision making** | Assess and overcome ambivalence to change; support patients to make their own, informed decisions |
| **Education and inhaler technique optimisation** | Education can be about the disease, or medicines, but must address patient concerns (*e.g.* the side-effects of medicines) |
| **Simplifying the regime** | Using "maintenance and reliever therapy" or once daily preparations may better suit the patient's daily routine |
| **Digital tools, electronic monitoring and reminders** | Electronic sensors recognise when a dose is late and can alert the patient to remind them to take it |
| **Facilitating access to medicines** | Making inhalers affordable through free prescriptions or co-funded items |

Reproduced from [13] with permission.

long-term consequences occur if it is persistently undertreated. ICS, although associated with significantly fewer side-effects than OCS, are not without problems [23]. This all suggests that inhaler use should be less about numerical compliance with clinician instructions for lengthy periods between assessment in consultations, and more about the balance of medicines need using evidence-based biomarkers (*e.g.* $F_{ENO}$) to guide care. Similarly, access to advanced medicines (*e.g.* biologics) should not be dependent on dogged high-dose ICS use, and rather reflect a more pragmatic assessment of the impact of titrating ICS dose and use on clinical outcome.

Within this paradigm, rather than focussing on the number of exacerbations experienced (or more specifically, exposure to OCS) and retrofitting MPR as a potential cause, a prospective evaluation could be more appropriate. In this, patients who experience an inflammatory exacerbation despite optimal ICS adherence (*e.g.* demonstrated by electronic monitoring) would be immediately eligible for a biologic agent. This would better reflect demonstrable need for biologic treatment and minimise unnecessary repeated systemic corticosteroids and their consequences. For this reason, the authors believe that adherence does matter in severe asthma, but that in this era of precision medicine where therapy can be tailored to individual patient need, the therapy regimen to which the patient is asked to subscribe should better use and reflect biomarkers and our evolving understanding of the disease and its measurement, rather than persist with the one-size-fits-all approach advocated currently.

Conflict of interest: G. d'Ancona reports grants from AstraZeneca and Chiesi; consultancy fees from AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, Napp, Novartis, Orien, Pfizer, Sanofi and Teva; payment or honoraria for lectures, presentations, manuscript writing or educational events from AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, Napp, Sanofi, Teva and UCB; support for attending meetings from AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, Napp, Sanofi and Teva; and receipt of equipment, materials, drugs, medical writing, gifts or other services from GSK. B.D. Kent reports consultancy fees from AstraZeneca and Chiesi; payment or honoraria for lectures, presentations, manuscript writing or educational events from AstraZeneca and GSK; support for attending meetings from AstraZeneca and A Menarini; and leadership roles with the European Respiratory Society (*Breathe* Chief editor) and the Irish Sleep Society (President).

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