



Review article

A review of the burden and management of mild asthma in adults — Implications for clinical practice



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ABSTRACT

Keywords:

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Mild asthma is present in 50–75% of patients with asthma and is defined by the Global Initiative for Asthma as asthma that can be well controlled with low-intensity treatments (Steps 1 and 2). Despite this definition, ‘mild’ asthma is often not well controlled in reality, and can have a significant impact on an individual's symptom burden and quality of life.

We performed a PubMed literature search to investigate the burden of ‘mild’ asthma in the lives of patients, including future risk and asthma control, and the current management strategies. While clinical guidelines recommend long-term, daily, low-dose inhaled corticosteroids (ICS) for ‘mild’ asthma, published data suggest that ICS are often under-prescribed or used intermittently as symptoms arise. Furthermore, patients and physicians tend to overestimate disease control, impacting the accuracy of diagnosing ‘mild asthma’ and subsequent management. This disconnect may be amplified by miscommunication between patients and physicians, limited objective assessment of control, and differences in guidelines.

As with moderate and severe asthma, current evidence supports early initiation of regular ICS in ‘mild’ asthma to address the underlying inflammation, achieve symptom control and reduce risk of exacerbations. Adherence to ICS treatment is key and can be improved by educating both patients and healthcare professionals. The results of this literature search challenge the term ‘mild’ asthma and suggest strategies to improve the proactive management of the disease to enable patients to live symptom-free.

1. Introduction

Asthma is a variable chronic respiratory disease characterised by airway inflammation, airflow obstruction and hyperresponsiveness [1,2]. It presents a substantial global healthcare burden, with an estimated 334 million people affected worldwide [3] and an increasing global incidence [4].

1.1. Disease burden of mild asthma

‘Mild’ asthma accounts for a considerable proportion (50–75%) of patients with asthma [5]. While traditionally presented as benign, ‘mild’ asthma is emerging as a condition that requires proactive management for improving symptom control, preventing future risk of exacerbations and limiting disease progression [6]. The frequency of severe exacerbations (defined by the need for oral or systemic

Abbreviations: ACT, Asthma Control Test; FABA, fast-acting beta₂-agonist; FEV₁, forced expiratory volume in 1 second; GINA, Global Initiative for Asthma; HCP, healthcare provider; ICS, inhaled corticosteroids; IPCRG, International Primary Care Respiratory Group; LABA, long-acting beta₂-agonist; NAEPP, National Asthma Education and Prevention Program; PCP, primary care physician; QoL, quality of life; RCT, randomised controlled trial; SABA, short-acting beta₂-agonist; SIMPLES, Smoking, Inhaler technique, Monitoring, Pharmacotherapy, Lifestyle, Education, Support; START, Inhaled Steroid Treatment as Regular Therapy in Early Asthma; SYGMA, Symbicort Given as Needed in Mild Asthma

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corticosteroids, or hospital admission) in patients with ‘mild’ asthma has been estimated at 0.12–0.77 per patient-year, yet severe exacerbations in ‘mild’ asthma represent 30–40% of all exacerbations requiring emergency care [5]. Furthermore, in a US survey, 3.6% of all patients with ‘mild’ asthma ($n = 1788$) reported they had been hospitalised for exacerbations; and 16.1% and 28.4% of patients with intermittent and mild persistent asthma, respectively, had required emergency care in the previous year [7]. The burden of ‘mild’ asthma has been further highlighted by the National Review of Asthma Deaths in the UK, which found that, of 155 patients for whom severity could be estimated, 14 (9%) were being treated for ‘mild’ asthma [8]. The issues of mortality and exacerbations in ‘mild’ asthma suggest a problem with severity classification in patients with infrequent symptoms or under-reporting of frequent symptoms and highlight the lack of alignment between patient, physician and guideline definitions of ‘mild’ asthma.

1.2. Differences in the guideline definitions of mild asthma

International and national guidelines and reports have been published on the diagnosis and management of asthma, including the Global Initiative for Asthma (GINA), National Asthma Education and Prevention Program (NAEPP), National Institute for Health and Care Excellence and the British Thoracic Society [9–12]. The International Primary Care Respiratory Group (IPCRG) mapped national respiratory guidelines used in primary care, creating a resource to enable sharing of information between members [13]. The aims of asthma management are to achieve and maintain control of symptoms, sustain unrestricted activity levels and reduce the risk of future exacerbations, which can be fatal [9]. Accordingly, most guidelines propose a stepwise approach reflecting an increasing intensity of treatment required to achieve and maintain asthma control. The GINA recommendations for a stepwise approach to control symptoms and minimise future risk are illustrated in Fig. 1 [9].

There is a lack of consistency in how asthma severity is classified between different guidelines. The NAEPP guidelines [11] classify severity based on symptom intensity and frequency, airflow limitation and lung function, and impact on activity (Fig. 2). Intermittent asthma is defined as symptoms occurring for ≤ 2 days/week, night-time awakenings ≤ 2 times/month, reliever use ≤ 2 days/week, no interferences with normal activity, and forced expiratory volume in 1 second (FEV_1) $> 80\%$ predicted. Mild persistent asthma is defined as symptoms > 2 days/week (but not daily), night-time awakenings 3–4 times/month, reliever use ≥ 2 days/week (but not daily), minor interference of normal activities and $FEV_1 > 80\%$ predicted.

While useful for initial assessment, the symptom severity-based classification of asthma, such as that used in previous versions of the GINA report and the NAEPP guidelines [11,14], has little value in predicting what treatment may be needed after diagnosis or what a patient's response to that treatment might be [15]. The 2018 GINA

report [9] assesses severity based on the intensity of treatment required to control symptoms and prevent future risks (Fig. 2), which has been deemed more relevant to the patient, with symptom-based severity classification recommended for research purposes only [9,15]. Specifically, the 2018 GINA report classifies mild asthma as asthma that is controlled by Step 1 (occasional as-needed short-acting beta₂-agonists [SABA]) and Step 2 treatments (regular maintenance low-dose inhaled corticosteroids [ICS] and occasional as-needed SABA) (Fig. 1).

1.3. Gaps and needs in the management of patients with mild asthma

The use of ‘mild’ implies a disease of low clinical significance. The high rates of exacerbations of ‘mild’ asthma requiring hospital admission indicate that, contrary to perception, ‘mild’ asthma has significant clinical implications. Exacerbations may also lead to worsening of the disease and thus to a change in severity classification [16]. Indeed, Step 1 and Step 5 patients have been shown to have the highest rates of asthma-related mortality, further highlighting the risk of severe and potentially fatal exacerbations in ‘mild’ asthma and the need to initiate regular maintenance therapy [17].

Similarly, patients with ‘mild’ asthma commonly suffer from impaired quality of life (QoL); in some studies, impaired QoL was seen as frequently as in patients with severe disease [16] and QoL is significantly worse in patients with asthma who are not well controlled [18]. Patients with ‘mild’ asthma use considerable healthcare resources, including emergency department care and hospital admissions [16], with poorly controlled ‘mild’ asthma making up an estimated 11% of the total direct cost of asthma in a Canadian study [19]. ‘Mild’ asthma is also associated with indirect costs, due to loss of productivity, highlighting the significant disease burden from ‘mild’ asthma [16]. However, with proactive management, a patient with ‘mild’ asthma can expect to live symptom-free and experience no limitations to their daily activities – a goal that is achievable, particularly compared with other chronic respiratory diseases where it is not.

To improve control in patients with ‘mild’ asthma, the GINA report was recently updated to recommend long-term, regular, low-dose ICS as an option for treatment in patients with asthma soon after diagnosis. This was supported by START (Inhaled Steroid Treatment as Regular Therapy in Early Asthma), a multicentre, randomised controlled trial (RCT) of 7241 patients with recent-onset, mild persistent asthma, in which long-term, once-daily, low-dose ICS was associated with a reduced risk of severe exacerbations and improved asthma control compared with placebo [20]. Similarly, the OPTIMA trial found that low-dose ICS reduced severe exacerbation rates and poorly controlled asthma days by more than half versus placebo in patients with mild asthma [21]. Furthermore, a severe exacerbation can lead to greater long-term decline in lung function in those not receiving ICS, compared with those taking regular ICS [22].

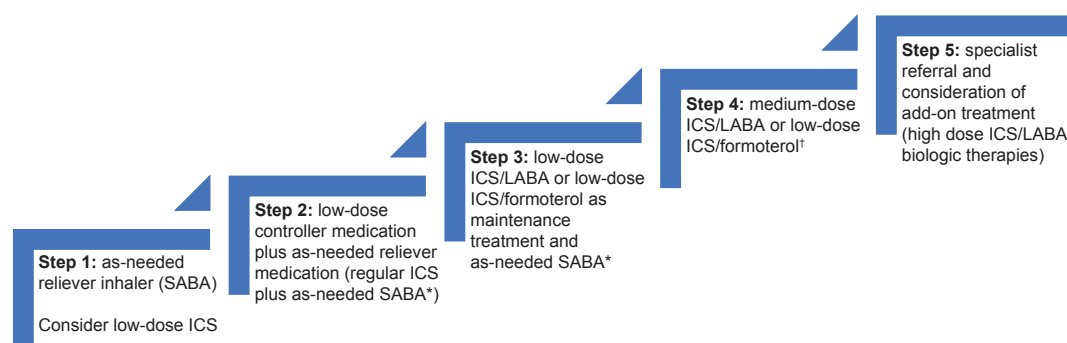


Fig. 1. Stepwise treatment recommendations according to the 2018 GINA report

*For patients not well controlled with ICS alone. †Dependent on the therapy used in Step 3 ICS, inhaled corticosteroid; LABA, long-acting beta₂-agonist; SABA, short-acting beta₂-agonist.

GINA	NAEPP
Mild asthma: well controlled with Step 1 or Step 2 treatment	Intermittent asthma: symptoms ≤ 2 days/week, night waking ≤ 2 times a month, $FEV_1 > 80\%$ predicted, 0–1 exacerbations per year
Moderate asthma: well controlled with Step 3 treatment	Mild persistent asthma: symptoms > 2 days/week, night waking 3–4 times per month, $FEV_1 > 80\%$ predicted, ≥ 2 exacerbations per year
Severe asthma: requires Step 4 or 5 treatment to control symptoms, or remains uncontrolled despite this treatment	Moderate persistent asthma: daily symptoms, weekly night waking, some interference with normal activity, FEV_1 60–80% predicted
	Severe persistent asthma: symptoms throughout the day, nightly awakening, extremely limited normal activity, $FEV_1 < 60\%$ predicted

Fig. 2. Asthma severity classification according to the GINA report and NAEPP guidelines
 FEV_1 , forced expiratory volume in 1 second.

Table 1

Search keywords.

Search terms	Number of items retrieved
Mild asthma AND adherence	145
Mild asthma AND mortality	101
Mild asthma AND short acting beta agonist	45
Mild asthma AND activity limitation	20
Mild asthma AND exacerbations AND inhaled corticosteroid	165
Mild asthma AND inflammation AND inhaled corticosteroids	162
Mild asthma AND inhaled corticosteroids AND quality of life	73
Mild asthma AND daily dose of inhaled corticosteroids	116
Mild asthma AND intermittent inhaled corticosteroids	70
Mild asthma AND controller medication	58
Mild asthma AND reliever therapy	37
Mild asthma AND as-needed medication	22

Note: Initially, a set of ‘scoping’ literature searches were carried out with broad categories to assess the extent of data available and its relevance to the present review. To narrow down the results to a relevant subset, the search strategy was refined using combinations of keywords, particularly with regards to pharmacologic interventions. Introducing more targeted keywords, such as: ‘controller medication’, ‘reliever therapy’, ‘low-dose ICS’, ‘intermittent ICS’ also resulted in a manageable (less than or around 100) number of hits.

1.4. Limitations of current treatment guidelines

There are several uncertainties in the GINA report regarding treatment of ‘mild’ asthma, highlighting gaps within the current algorithms [23]. For example, the GINA report states that low-dose ICS should be considered at Step 1, but is only recommended for patients with more frequent symptoms or at risk of an exacerbation (Step 2). Initial treatment recommendations for patients with asthma experiencing infrequent symptoms is symptomatic treatment with a SABA bronchodilator (GINA Step 1), rather than ICS, which treats the underlying inflammation in asthma. However, it has been established that airway inflammation warranting treatment is present at an early stage of the disease [24].

Furthermore, the report states that patients needing SABA more than two times per week have partially uncontrolled asthma [9]. This guidance may affect patients’ perception of the goal of treatment (i.e. to control symptoms, rather than prevent them) [23]. This highlights the need for partnership between healthcare providers (HCPs) and patients, with physicians helping their patients understand the importance of

regular ICS from the start to control symptoms and reduce the risk of future exacerbations, as well as reassuring patients of the favourable benefit-risk profile of ICS, particularly at low doses.

2. Review rationale and objectives

Since the first opinion-based asthma guidelines were published in the mid-1980s, a multitude of evidence-based guidelines have been developed, leading to reduced mortality rates. However, the suboptimal management of ‘mild’ asthma still poses a risk of disease mortality and exacerbations.

The disconnect between the guideline definition of ‘mild’ asthma and the current perceptions of disease may affect how physicians formulate their treatment plans. Patients may also underestimate their need for anti-inflammatory therapy if they have insufficient disease information or if they perceive ‘mild’ asthma as a benign condition, combined with variable symptoms. Alternatively, symptoms may not be considered mild from a patient’s perspective, and the description of the disease as ‘mild’ by their primary care physician may under-represent the patient’s experience.

From relevant literature, we outline the current challenges and review the clinical evidence for management strategies in ‘mild’ asthma. We aim to examine best practices for managing mild asthma, focussing on the issues around regular treatment with low-dose ICS, and challenge the use of the term ‘mild’ asthma. By diagnosing asthma as ‘mild’, are we minimising the understanding of it as a chronic inflammatory disease and its associated risks, thus increasing the impact of asthma on the patient?

3. Methodology

A PubMed search was performed using keyword combinations (Table 1), with a publication date defined from 01/01/2006 to 31/12/2018. Our search focussed on assessing appropriate use of current treatment strategies for mild asthma. We assessed the evidence around timely intervention and regular maintenance treatment with ICS to effectively manage patients with ‘mild’ asthma. Results were filtered to those investigating the treatment of adult patients with ‘mild’ asthma, although studies including adolescent patients were also included. More methodological details are included alongside Table 1.

4. Re-examining the classification of ‘mild’ asthma

Despite the reduction in asthma-related mortality and the introduction of treatment guidelines, surveys across Europe indicate that inadequate control is present in approximately half of all patients with

asthma [25,26]. These patients reported a greater impact of their disease on activity and work productivity, as well as lower health-related QoL, compared with patients who were well controlled.

The REALISE survey found that, of patients whose asthma was classed as uncontrolled according to GINA criteria, 83.7% considered their asthma to be controlled; of those, 55.5% of patients had symptoms that interfered with daily activities. Similarly, 69.9% of patients did not regard their condition as serious; among these, 19.5% had an asthma-related emergency department visit in the previous year [25].

The CHOICE survey of 1000 patients from the USA reported that only 14.3% (73/510) of patients on controller medication had well-controlled asthma (based on NAEPP guidelines) [27]. However, most patients on controller medication perceived their asthma as completely (21.8%) or well controlled (45.5%), with only a small minority indicating their disease was somewhat or poorly controlled. Furthermore, 49% (490/1000) of patients were not using maintenance therapy; most (79%) had persistent asthma, including 47% who had mild or moderate persistent asthma, contrary to the current guidelines recommending regular ICS for the treatment of mild persistent asthma [27]. Similarly, a global survey of 10,302 patients with asthma indicated that a median 67% of patients perceived their asthma as completely or well controlled, even though only a median of 9% had well-controlled asthma using guideline-based criteria. Furthermore, most patients felt that SABAs could be used daily as-needed, against current guideline recommendations [28].

In a large, multinational, cross-sectional survey of 520 patients with mild asthma (according to GINA classification), only 2.9% of Step 1 and 2.8% of Step 2 patients self-classified as poorly controlled or uncontrolled. Physicians provided similar ratings of 1027 patients, with 3.5% of Step 1 and 7.1% of Step 2 patients rated as poorly controlled or uncontrolled. However, Asthma Control Test (ACT) scores indicated 25.3% of patients were not well controlled; 19% of patients had experienced one or more exacerbations during the previous 12 months, with an overall mean of 0.4 exacerbations/year [29]. Similar findings were obtained in a study investigating treatment patterns and disease burden of patients with mild asthma residing in urban areas of China [30].

The Living and Breathing Study found that patients with mild-to-moderate asthma had low expectations of treatment and how well their asthma could be controlled. In a sample of 517 patients, 76% felt their asthma would not improve over time; 91% felt their asthma was controlled, despite 66% reporting symptoms at least 2–3 times a week. Before being shown the GINA asthma management goals, 58% of patients said they were satisfied with their care, but this fell to 33% after reading the treatment goals [31].

Together, these studies highlight the discrepancy between the patient and physician assessment of symptom control, and guideline-based severity classifications. Both patients and physicians tend to overestimate the level of disease control, while, according to the guideline definitions, a large proportion of patients with ‘mild’ asthma remain uncontrolled despite using maintenance medication. Objective assessment of asthma control, e.g. with the ACT, the Asthma Control Questionnaire and the consensus-based GINA symptom control tool, can assist in improving awareness of symptoms and the need to review management. Patients may underestimate their symptoms and use different language from the physician to describe their symptoms; therefore, the use of structured questionnaires is recommended [32,33]. Furthermore, patients have low expectations of asthma management and many are not aware that they can be symptom-free with appropriate treatment. These findings suggest that current asthma management is falling short of guideline recommendations and highlight the ongoing need for effective treatment plans and improved education for patients and HCPs [29,30,34].

We speculate that the classification of ‘mild’ asthma is a possible reason for this disconnect. The label ‘mild’ may lead to an underestimation of the importance of treating both the symptoms and the

underlying inflammation. From a wider disease perspective, this disconnect has brought about a shift in the understanding and management of complex, heterogeneous conditions whose symptoms fall on a spectrum of severity. For example, mild hypertension was previously a classification of high blood pressure, but studies revealed that it is important to treat as it can still increase the risk of stroke and cardiovascular events [35]; thus, ‘mild’ is no longer used in favour of the terms ‘grade/stage 1’. Similarly, ‘mild’ diabetes was previously used to indicate blood sugar levels near to normal levels; but as the disease may progress if left untreated, the term ‘mild’ is now frowned upon [36].

5. Management of mild asthma

5.1. Adherence to ICS therapy

The long-term goals of asthma management outlined in the 2018 GINA report are to achieve good control of symptoms and maintain normal activity levels, and to minimise future risk of exacerbations, fixed airflow limitation and side-effects of treatment [9]. Asthma guidelines recommend that low-dose ICS therapy be initiated early after diagnosis, whilst patients' symptoms are mild, to prevent deterioration of their condition [9]. However, our literature search revealed generally low rates of adherence to ICS in adults with ‘mild’ asthma. A multinational survey found that treatment adherence (assessed with the Morisky Medication Adherence scale) [37] at GINA Step 2 was low for 35.6% of patients, medium for 38.1% and high for 26.3% [29]. Similarly, in a series of telephone interviews with 756 adolescents/young adults with mild-to-moderate asthma, 238 patients had a prescription for ICS, but 38% of these patients reported low/medium (< 75% of prescribed medication taken) adherence. These patients experienced less symptom control, more missed activities and had greater use of rescue medication versus patients with high ($\geq 75\%$) adherence [38]. A secondary analysis of the Trial of Asthma Patient Education found that 27% (114/416) of patients with mild persistent asthma overused SABAs; these patients experienced poor asthma control. Most overuse was on symptom-free days, suggesting patients use SABA as maintenance therapy to prevent symptoms [39].

Overall, these findings show that adherence to regular ICS is low in patients with ‘mild’ asthma, which results in reduced asthma control and higher healthcare costs. Instead, patients use symptom-driven therapy, showing a preference for SABA [23,28], suggesting a lack of understanding of both the underlying inflammation and the importance of preventing future risk of exacerbations.

5.2. Addressing compliance and adherence: the role of education

How can we improve adherence to treatment regimens in patients with ‘mild’ asthma? Studies of insurance claims databases have found higher rates of adherence in patients with mild asthma using once-daily versus twice-daily treatment regimens. Improved adherence was associated with fewer exacerbations, decreased SABA use and lower overall asthma-related resource utilisation and costs [40,41]. These results suggest that a simpler dosing regimen could be introduced to improve adherence to treatment which, in turn, is beneficial to patients [40–42].

In addition, a survey of Turkish physicians indicated that low-dose ICS was the preferred first choice for the treatment of mild persistent asthma by 84.5% of physicians. Their choice of treatment was predominantly influenced by guidelines, training background and perceived efficacy. However, they did not often consider patient preference, as recommended by the GINA report, potentially impacting adherence to treatment [43].

Patient education and support can play an important role in improving disease knowledge and treatment adherence. For example, there was an improvement in asthma knowledge and adherence, a decrease in unscheduled doctor visits, an improvement in inhaler technique and an increase in the proportion of patients with controlled

asthma (according to the 30 Second Asthma Test) in a study investigating the benefits of an educational programme offered to adults with mild-to-moderate asthma and delivered by a trained asthma educator at the site of primary care [44]. There is also evidence to suggest that practical strategies can support patient adherence. For example, there was a high observed rate of adherence with twice-daily reminders, approaching 80%, in the Symbicort Given as Needed in Mild Asthma (SYGMA) 1 trial, which assessed the efficacy and safety of regular ICS maintenance treatment versus reliever therapies [45].

Studies have also investigated the compliance of HCPs to asthma guidelines. A survey of 105 asthma nurses in the UK found considerable inconsistency in nurses' compliance to treatment guidelines, with 97% sometimes advising patients to decrease their ICS use, 85% sometimes advising to stop ICS treatment when their asthma is well controlled, and 70% sometimes advising intermittent ICS [46]. In a survey of 756 patients with mild-to-moderate asthma, 420 patients reported that their physician had not prescribed a maintenance medication during the 6-month study period [38].

Educating HCPs can improve compliance to guideline recommendations. Introduction of an evidence-based implementation strategy at rural district hospitals in Australia led to a significant increase in compliance with guidelines, including improvements in the documentation of severity, use of spirometry and written asthma action plans [47]. Similarly, the National Asthma Programme was implemented in Finland from 1994 to 2004, aiming to lessen the burden of asthma on patients and society by improving factors including early diagnosis, proactive treatment, self-management and education. The programme led to increased use of regular ICS (from 33% of patients using ICS in 1987 to over 85% in 2004), decreased hospitalisations and reduced mortality in patients with asthma. Asthma-related costs also decreased, despite the substantial increase in the number of patients with asthma over the course of the study [48]. At the start of the Finnish asthma programme in 1994, an estimated 20% of patients with asthma were uncontrolled; this figure decreased to 10% in 2001 and to 4% in 2010 [49], further evidence to support the use of continuous and widespread patient education to increase adherence.

Furthermore, compliance and patient care may be improved with practical support and tools for daily clinical practice. For example, IPCRG has published guidance as a desktop helper to facilitate detection and management of difficult-to-treat patients with asthma in the primary care setting [50]. They have proposed an acronym – SIMPLES – covering the main factors to be checked in these patients to identify reasons for poor disease control and methods to improve control. The key areas are: Smoking (establish current habits and encourage patients to quit), Inhaler technique (observe the patient using their inhaler), Monitoring (assess asthma control using a validated technique, such as Royal College of Physicians 3 questions), Pharmacotherapy (check the patient is being treated at the appropriate step), Lifestyle (determine exposure to risk factors, such as air pollution), Education (assess patient's understanding of their asthma), and Support (assess the level of family support) [50]. In addition, the use of structured questionnaires to measure patient-reported outcomes, such as the ACT, is recommended in daily clinical practice to assist physicians in assessing level of control and selecting appropriate treatment [32,33].

Our literature search has highlighted a need for open discussion between physician and patient around the risks/benefits of low-dose ICS for mild asthma, the potential impact of not taking ICS regularly or over-relying on SABA, as well as raising expectations to living a symptom-free, unrestricted lifestyle. Patients should be informed of the chronic inflammatory nature of asthma and the need for regular anti-inflammatory treatment. The risks associated with poor adherence are often not communicated to patients and are not included in the asthma guidelines or the curriculum of training for primary care physicians. Likewise, self-monitoring is recommended by both NAEPP guidelines and GINA report, either by monitoring symptoms or peak flow; patients should be taught to recognise symptom patterns that indicate

inadequate asthma control and how to respond to worsening asthma [9,11]. Together, these steps should enable patients to gain the knowledge and skills to assume a major role in their asthma management [9]. To this end, physicians may benefit from health coach training to develop more effective communication skills, improve the patient-physician partnership and motivate patients to be active participants in their own care. Physicians should also consider the patient's health literacy when communicating and designing action plans, as higher health literacy scores are associated with better adherence, QoL and disease control in patients with asthma [51,52].

5.3. Evidence to support early, regular ICS use in 'mild' asthma

Asthma guidelines recommend the early initiation of daily, low-dose ICS; but what evidence is there to support this recommendation?

The timing of treatment initiation and its impact on patient outcomes was examined in several early studies. A 5-year follow-up of the START trial found that early initiation of regular ICS was associated with improved asthma control and less use of additional asthma medication versus delayed ICS therapy [53]. In another study, the regular use of ICS was associated with a reduction in the rate of hospital admissions for long-term regular ICS users versus irregular or non-users [54].

The early use of ICS is supported by the results of our literature search. Reddel et al. performed a post hoc analysis of the START study, in which patients (aged 4–66 years) with mild asthma received once-daily, low-dose ICS ($n = 3577$) or placebo ($n = 3561$) for 2 years after diagnosis, after which all patients were prescribed ICS, with a total study period of 5 years. Regular ICS halved the long-term risk of serious asthma-related events, reduced lung function decline and improved symptom control versus placebo [55]. In another study of adults with recent-onset asthma, patients who received ICS within 1 year of first symptoms and those who received ICS after a 2-year delay had similar levels of lung function after 13 years; however, the delayed group exhibited more signs of airway inflammation than the early group [56].

Two early studies compared intermittent versus daily ICS in mild persistent asthma: the double-blind IMPACT trial ($N = 225$) and the double-blind, randomised BEST study ($N = 337$). While the IMPACT study showed that daily ICS significantly improved asthma control scores, increased symptom-free days and reduced inflammatory markers compared with intermittent ICS, there was no significant difference between intermittent and daily ICS groups in exacerbation rates, rate of loss of pulmonary function and QoL scores [57]. The BEST study found comparable lung function and rate of exacerbations over a 6-month period with both as-needed ICS and regular ICS [58]. However, the IMPACT and BEST studies both had study limitations, were not powered to detect differences in exacerbation rates, enrolled only small numbers of patients to each group and were relatively short-term. In contrast, the START ($n = 7241$) and OPTIMA ($n = 1970$) studies monitored large numbers of patients over a longer period and reinforced the benefits of regular ICS in mild asthma [20,21].

Shimoda et al. examined the longitudinal impact of ICS on lung function in adult patients over 15 years, and their findings suggest that regular ICS, introduced early when symptoms are mild, could prevent lung function from worsening significantly [59]. However, the study was small and the number of participants in each group was unbalanced.

The SYGMA trials assessed the efficacy and safety of regular ICS maintenance treatment versus reliever therapies [45,60]. In SYGMA-1, 3836 patients with mild asthma (GINA Step 2) were randomised to twice-daily placebo plus as-needed SABA (terbutaline), twice-daily placebo plus as-needed ICS in combination with a fast-acting beta₂-agonist (FABA; budesonide-formoterol), or twice-daily ICS (budesonide) plus as-needed SABA. The mean percentage of weeks with well-controlled asthma per patient was lower with as-needed ICS/FABA versus regular ICS (34.4% vs 44.4%), although the rates of severe

exacerbations were similar in these groups. The SYGMA-2 trial followed a similar study design, but patients ($n = 4176$) received no daily reminders to use maintenance medication. Again in SYGMA-2, there was no difference in severe exacerbations rate between treatments; but there were small improvements in symptom control, QoL and FEV₁ before bronchodilator use with regular ICS maintenance therapy versus irregular as-needed ICS/FABA [60]. Thus, these studies indicate that regular ICS is more effective in proactively achieving daily asthma control compared with reactive intermittent ICS regimens. It should be noted, however, that the overall rate of adherence to maintenance therapy was much higher in this trial than would be expected in real-world clinical practice.

A systematic review and meta-analysis (which included the IMPACT [57] and BEST [58] studies) found no change in the rate of exacerbations with daily versus intermittent ICS, but there was an increase in the number of symptom-free days and non-significant decrease in use of rescue SABA and fractional exhaled nitric oxide, suggesting greater control with regular ICS [61]. Regular ICS was also shown to significantly reduce the healthcare and asthma-specific costs for patients with mild persistent asthma compared with infrequent ICS, due to fewer hospitalisations and emergency visits [62].

Overall, these findings support the early, regular use of ICS in patients with 'mild' asthma. As with all medicines, the benefit-risk of low-dose ICS should be assessed, and treatment individualised on this basis. The risk of side effects, in terms of bone mineral density, adrenal function and ocular effects, with low doses of ICS is small and can be minimised by using the lowest effective dose of ICS [63,64].

5.4. Alternative treatment strategies for mild asthma

While guidelines recommend low-dose regular ICS with as-needed SABA for 'mild' asthma, other treatment strategies are being investigated. A Cochrane literature review of RCTs examined the efficacy of increasing dose of ICS during an exacerbation as part of a patient-initiated action plan for home management, but they found no difference in patient outcomes compared with a stable ICS dose [65]. Similarly, initiating ICS treatment with a high dose (400 µg budesonide bid) in newly diagnosed patients was not superior to low dose (100 µg budesonide bid) in terms of asthma control [66]. In a study of patients with mild-to-moderate asthma, maintenance treatment with ICS and long-acting beta₂-agonist (LABA) was found to provide greater improvements in lung function versus ICS alone, although there was no difference in inflammatory markers [67]. However, another study found no difference in the risk of exacerbations with ICS/LABA compared with a similar dose of ICS [68]. A meta-analysis of RCTs found no significant difference in the risk of exacerbations with as-needed ICS/FABA compared with regular ICS in patients with intermittent and mild asthma [69].

Similarly, the SYGMA trials found no difference in rate of severe exacerbations with as-needed ICS/LABA or twice-daily ICS, and as-needed ICS/FABA resulted in substantially lower glucocorticosteroid exposure than regular ICS. As-needed ICS/LABA was superior to as-needed SABA in terms of rate of severe exacerbations, asthma symptom control and number of adverse events, highlighting the degree of underlying inflammation in the mild asthma population, which requires proactive management. This is further supported as these studies showed a benefit of regular ICS for asthma-symptom control and QoL, important aspects of holistic asthma management, compared with both as-needed SABA and as-needed ICS/FABA [45,60]. Studies have also indicated an improvement in asthma control when ICS/SABA is used as a reliever therapy versus SABA alone [58,70]. These studies suggest ICS combination reliever therapies may be a useful treatment strategy to reduce risk of exacerbations in patients who struggle with regular maintenance therapy and take medication only when symptoms arise. However, the extent of inflammation control achieved and long-term consequences of treatment with irregular ICS in mild asthma remains

unknown. These treatments are still being investigated and are not currently licensed for treatment of mild asthma.

6. Conclusions and future perspectives

'Mild' asthma imposes a substantial burden on patients and, if treated suboptimally, can increase the risk for disease progression, exacerbations, morbidity and mortality, as well as reduce QoL and performance of daily activities.

This review has revealed a disconnect between the patient and HCP perception of disease severity, and current guideline classifications. Similarly, there seems to be poor compliance to guideline-recommended management. Increasing understanding of the true nature of the disease and awareness of clinical guidelines is particularly important for HCPs, who are in the unique position of seeing many patients with mild asthma several times a year, and being able to positively impact outcomes. The use of standardised questionnaires and simple guides in clinical practice may facilitate the consultation process and guide treatment.

The evidence to date on drug interventions in 'mild' asthma underscores the importance of timely initiation and daily use of low-dose ICS as part of a proactive approach to patient management. Our review has shown the benefits of regular ICS use to gain control of symptoms, improve QoL and reduce risk of exacerbations in patients with mild asthma. However, there is a need for both RCTs and real-world studies to confirm the long-term effects of regular ICS treatment, as well as investigate other potential therapies. Patient education is also critical to improve adherence to maintenance treatment, particularly as there is still a stigma surrounding the use of ICS and potential side effects. Effective asthma management also requires the development of a partnership between patients and HCPs. A precision medicine approach, which focuses on identifying effective individual treatment regimens based on genetic, environmental and lifestyle factors, may improve management of patients with asthma; a personalised approach has been shown to be useful in patients with severe asthma, but not to date in mild asthma.

To conclude, 'mild' asthma poses a considerable disease burden and impacts patients' daily lives. It is time to reconsider the use of the term 'mild' and instead raise awareness of the disease pathophysiology, its chronic inflammatory and progressive nature, and the need for regular anti-inflammatory treatment. With the current classifications, asthma in up to three-quarters of patients may be considered 'mild' — and if 'mild' asthma is the norm, should it simply be described as 'asthma' and managed accordingly?

Contributions

All authors contributed to the concept of the article and design of the literature search, preparation/writing and review of the manuscript, and approved the final version to be submitted.

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Conflicts of interest

Emilio Pizzichini, Aruni Mulgirigama, Monica Fletcher and Neil Barnes are employees and stockholders of GSK. Ioanna Tsiligianni has given presentations at symposia and/or served on scientific advisory boards sponsored by Boehringer Ingelheim, GSK and Novartis. Søren Pedersen has no conflicts of interest to declare.

Declaration of interests

The authors declare that they have no known competing financial

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