Review Article

Pharmacotherapy of patients with stable bronchial asthma

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ABSTRACT

Several reliever and controller medications are available for managing patients with stable asthma. Inhaled corticosteroids (ICS) are the mainstay of treatment, and can be combined with long-acting beta-agonists (LABA) for patients with moderate or severe disease. An ICS–LABA combination is best administered as a single inhaler used for both maintenance and emergency use. A stepwise approach to therapy has recently been proposed as part of Indian guidelines for management of asthma. Clinicians should advise proper use of inhaled medications, and step up or step down treatment based on adequacy of asthma control.

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INTRODUCTION

Treatment of bronchial asthma is aimed at providing symptomatic relief to patients, and preventing disease progression by limiting airway inflammation. A properly tailored prescription leads to adequate asthma control and enables the patient to continue to carry out all day-to-day, work-related and recreational activities normally. It is equally essential to design a prescription that safeguards patients from any treatment-related adverse events. Although pharmacotherapy is currently the mainstay for achieving these goals, other areas such as patient education and avoidance of environmental triggers are also important.

Several international guidelines have outlined management principles for patients with stable bronchial asthma.[1–5] However, management of asthma continues to be suboptimal in India. This is attributed both to patients' reluctance or inability to adhere to standard therapy, as well as physicians' ignorance about recent evidence-based modifications in principles of treatment. To standardize diagnostic and management protocols for Indian patients, the Indian Chest Society and National College of Chest Physicians (India) supported a workshop of experts in 2014 to frame consensus guidelines. These guidelines were published in 2015, and are based on quality evidence gathered across the world and in India.[6] This review is based on the discussions and recommendations that resulted in the formulation of these management guidelines; it focuses on pharmacotherapeutic options currently available in India.

BASIC DEFINITIONS

Pharmacological agents useful in managing asthma can be categorized as either 'controllers' or 'relievers'. Controller medications are anti-inflammatory drugs (inhaled corticosteroids [ICS], leukotriene antagonists, mast cell stabilizers, etc.) or long-acting bronchodilators, and are responsible for control of airway inflammation. They need to be administered on a regular basis, even if the patient remains asymptomatic. In contrast, reliever medications (also termed rescue medications) relieve acute symptoms but do not control airway inflammation. They should therefore be taken only on an as-needed basis (not regularly) for immediate relief during episodes of symptomatic worsening. Bronchodilators with rapid onset of action are the commonest relievers.

RELIEVER MEDICATIONS

Several inhaled agents can be used as reliever medicines on an as-needed basis, either alone or in combination, for managing patients with asthma. These include (i) short-acting beta-agonists (SABA) such as salbutamol, levosalbutamol and terbutaline; (ii) long-acting beta-agonists (LABA) with quick onset of action such as formoterol; and (iii) short-acting anti-muscarinic agents (SAMA) such as ipratropium. SABA are traditionally the most common agents used for immediate symptomatic relief by patients with asthma. Formoterol is equally effective in this regard.[7] However, its use as a rescue medication is generally discouraged due to concerns related to LABA monotherapy in asthma. SAMA are generally less preferred as their onset of action is delayed as compared to SABA, although direct comparisons between the two agents have not been performed. A Cochrane review also noted that although SAMA was superior to placebo, a combination of SABA plus SAMA was not better than SABA alone.[8]

Oral beta-agonists (salbutamol, terbutaline) are also commonly used as reliever medications in India because these are less expensive. However, they have an unfavourable risk–benefit ratio and cannot be recommended for routine use.

INHALED CORTICOSTEROIDS (ICS)

ICS are the most potent and consistently effective long-term controller medication for asthma. ICS suppress airway inflammation, thereby improving asthma control. Therefore, they are uniformly recommended by all major guidelines as the first-line controller agent for managing stable asthma. Five molecules are currently marketed in India: beclomethasone, budesonide, fluticasone, ciclesonide and mometasone. Although these agents differ slightly in their pharmacokinetic and pharmacodynamic properties, all have largely similar efficacy and safety profile when used in equivalent doses.[9–11]

All ICS are clearly superior to placebo in reducing severity of symptoms, improving pulmonary function, improving asthma

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control and quality of life, and reducing the need for reliever medication, exacerbations, emergency visits and hospitalizations.[12–15] ICS monotherapy has also been shown to be superior to LABA monotherapy in reducing inflammatory markers, treatment failures and asthma exacerbations in the SOCS (Salmeterol Or Cortico-steroids Study) trial.[16] Another Cochrane review showed that ICS monotherapy was better than treatment with anti-leukotriene agents in improving symptoms, pulmonary function and quality of life, and decreasing the use of rescue medication and asthma exacerbations.[17] ICS monotherapy has also been shown to be superior to oral methylxanthine therapy in six randomized controlled trials.[18–23] Thus, current evidence clearly supports the use of ICS as the primary controller agent for managing patients with stable asthma.

There has been much debate on the optimum ICS dosing. While low doses may fail to achieve adequate disease control, higher doses may be associated with adverse effects. At high doses, ICS use can manifest with systemic side-effects, the most important of which is suppression of the hypothalamo–pituitary–adrenal axis at higher doses. Other complications include eye problems such as cataract and glaucoma, skin bruising, reduction in bone mineral density, growth retardation in children, and most importantly an increased risk of infections. In addition, local oropharyngeal deposition can lead to throat irritation, cough, and sometimes even dysphonia or oral candidiasis. However, evidence suggests that bulk of the clinical improvement observed with ICS occurs at low-to-moderate doses (Table I), beyond which further dose increments provide negligible additional benefit.[24–28] Also, initiating ICS therapy at low-dose may be as effective as using an initial higher dose and later stepping down.[29] This is particularly important in minimizing local and systemic side-effects of ICS therapy. Another recently proposed shift in dosing strategy is relevant for patients with mild persistent asthma. These patients may receive intermittent ICS therapy on an as-needed basis rather than as regular daily therapy, because studies have shown that the former is not inferior to the latter.[30–33] Such an approach may not work for patients with moderate disease.[34]

INHALED LONG-ACTING BETA-AGONISTS (LABA)

Three potent selective LABA are currently marketed in India: salmeterol, formoterol and indacaterol. The last one is an ultra-long-acting agent suitable for once daily dosing. Both formoterol and salmeterol need to be given twice daily. However, formoterol has a more rapid onset of action, and can also be used as a rescue medication. As compared to placebo, salmeterol and formoterol significantly improve pulmonary function, symptoms and quality of life, and decrease the use of rescue medications and exacerbation of asthma.[35] Not much data are available on the use of indacaterol in managing asthma.

Since LABA have no effect on modulating airway inflammation, their use as monotherapy is discouraged in asthma. LABA are excellent bronchodilators and lead to substantial symptomatic improvement. However, they allow airway inflammation to progress unchecked subclinically, and this may lead to poorer long-term outcomes. The Serevent National Surveillance study reported that salmeterol monotherapy was associated with more life-threatening experiences and asthma-related deaths.[36] Other studies have also shown that switching patients from ICS monotherapy to LABA monotherapy results in a loss of disease control. A recent meta-analysis also concluded that monotherapy with salmeterol increased the risk of asthma-related mortality, which was reduced with concurrent ICS use.[37]

Table I. Equipotent doses of inhaled corticosteroids taken through a metered dose inhaler

Corticosteroid	High-dose range (μg)	Medium-dose range (μg)	Low-dose range (μg)
Beclomethasone	>500–1000	>250–500	100–250
Budesonide	>800–1600	>400–800	200–400
Fluticasone	>500–1000	>250–500	100–250
Ciclesonide	>320–1280	>160–320	80–160
Mometasone	>800–1600	>400–800	200–400

COMBINED ICS AND LABA

Since LABA monotherapy is considered improper, LABA are now predominantly used as add-on agents to ICS. Several large trials such as OPTIMA (Oxis and Pulmicort Turbuhaler in Management of Asthma), FACET (Formoterol and Corticosteroid Establishing Trial) and GOAL (Gaining Optimal Asthma controL) have confirmed that this combination further improves asthma control and reduces the risk of exacerbations.[38–40] The SLIC (SaLmeterol with or without Inhaled Corticosteroids) study also showed that in patients poorly controlled on ICS monotherapy, addition of LABA allowed reduction of ICS dose by half.[41] A Cochrane review of 71 studies concluded that the risk of exacerbations requiring oral corticosteroids could be reduced by 28% by adding LABA to ICS, without any increase in side-effects.[42] Further, among patients with asthma uncontrolled on low ICS doses, adding LABA is better than increasing ICS dose in improving asthma symptoms and pulmonary function, and decreasing exacerbations and steroid-related adverse effects.[43] The ICS–LABA combination works best in reducing exacerbations among all long-term treatment strategies for asthma.[44]

Fixed-dose ICS–LABA combinations are now commonly available for use as maintenance therapy in asthma. For several years, additional reliever medications were suggested as supplements on an as-needed basis during periods of worsening asthma control immediately before an asthma exacerbation. It has, however, recently been proposed that an additional dose of ICS in this phase augments the anti-inflammatory action, and may help in aborting an impending exacerbation of asthma. This has evolved into the single inhaler therapy (or SiT) approach, using a combination of fast-acting LABA (formoterol) with ICS that can be successfully used as both maintenance and reliever medication in routine clinical practice.[45] Most studies comparing SiT with conventional therapy have used formoterol–budesonide turbuhaler, and have proposed SMART (single agent for maintenance and reliever therapy) as an alternative approach. However, any ICS and any 'good' inhalation device can be used in the SiT approach. Studies comparing SiT with ICS monotherapy have reported better asthma symptoms, disease control and pulmonary function, with longer time to first exacerbation.[46–49] Most studies comparing SiT with fixed-dose ICS–LABA combinations have also shown similar results.[49–58] Other studies comparing the SiT approach with conventional guideline-based best practice have shown better asthma control, but similar lung function and exacerbations of asthma.[59–63] An open-labelled observational study that also recruited Indian patients showed better asthma control with SiT.[64] Notably, the total cumulative dose of ICS in most of these studies was lesser with the SiT approach, probably because equivalent asthma control could be achieved at an overall lower daily ICS maintenance dose. Few meta-analyses have concluded that the

SiT strategy statistically significantly reduces exacerbations of asthma requiring oral corticosteroids.[65–67]

ANTI-LEUKOTRIENE AGENTS

Cysteinyl leukotrienes, generated through the 5-lipoxygenase pathway of arachidonic acid metabolism, are potent inflammatory mediators in asthma. However, their effects cannot be blocked by corticosteroids, and hence anti-leukotriene agents with complementary anti-inflammatory modes of action have been developed.[68] Oral montelukast, a cysteinyl leukotriene-1 receptor antagonist (LTRA), is the most commonly used antileukotriene agent in asthma. A major advantage of montelukast is that it can be administered orally and is well tolerated.

LTRAs can be used alone in patients with mild asthma, or as add-on to ICS or ICS–LABA therapy.[69] When used as a single agent in patients with mild-to-moderate asthma, LTRAs are inferior to ICS in providing symptomatic relief or preventing acute exacerbations.[17,70] However, in a real-world scenario, montelukast and ICS monotherapy appear equivalent for with mild asthma.[71] Large observational studies have shown that addition of LTRA improves asthma control and quality of life in poorly controlled patients while receiving ICS alone or an ICS–LABA combination.[72–75] A recent Cochrane review concluded that addition of LTRAs to ICS therapy leads to a non-significant risk reduction for exacerbations of asthma requiring oral corticosteroids.[76] Another Cochrane review has shown that an ICS–LTRA combination was inferior to an ICS–LABA combination in improving lung function or preventing exacerbations of asthma.[77]

LONG-ACTING ANTI-MUSCARINIC AGENTS

Tiotropium, a long-acting anti-muscarinic agent (LAMA), is widely used as first-line therapy in managing patients with chronic obstructive pulmonary disease. There is now increasing interest in the use of tiotropium as an additional agent for managing patients inadequately controlled with ICS or ICS–LABA therapy.[78] The clinical benefit from addition of tiotropium to ICS therapy in poorly controlled patients has been shown to be similar to that of addition of LABA.[79–81] However, when added to an ongoing treatment with an ICS–LABA combination, tiotropium leads to better pulmonary function and fewer exacerbations.[82–84] Hence, tiotropium can be used as an additional drug for poorly controlled patients despite moderate-to-high dose ICS–LABA combination therapy, or in those having remodelled phenotype of asthma.

METHYLXANTHINES

Theophylline (dimethylxanthine) continues to be commonly prescribed to patients with asthma in India as it is cheap and easily available. The weak bronchodilator action of theophylline, observed at blood levels of 10–20 mg/L after a standard dose, is linked to adenosine receptor antagonism and non-specific phosphodiesterase inhibition. On the other hand, at lower doses, resulting in blood levels of only 5–10 mg/L, theophylline manifests anti-inflammatory action resulting from histone deacetylase activation.[85] At these low doses, the safety profile of theophylline is also much better, and hence this appears to be the current preferred dose.

Theophylline monotherapy has been shown to be inferior to ICS monotherapy in improving clinical outcomes in asthma.[18–23] Two meta-analyses have also shown LABA monotherapy to be superior to theophylline monotherapy in improving symptoms and pulmonary function.[86,87] Hence, theophylline appears inferior to both ICS and LABA in managing asthma. However, addition of theophylline to low-dose ICS may be as good as doubling the ICS dose.[88–91] Among patients with asthma who are poorly controlled with ICS–LABA therapy, adding theophylline can further improve pulmonary function and reduce exacerbations.[92,93]

Doxofylline is a newer alternative to theophylline which is postulated to have fewer side-effects due to lack of adenosine receptor antagonism and calcium channel receptor blocking ability.[94] Studies comparing standard dose theophylline and doxofylline have shown the drugs to be equally effective, with doxofylline associated with fewer adverse events.[95,96] There are no data comparing low-dose theophylline with doxofylline in asthma.

MONOCLONAL ANTIBODY AGAINST IMMUNOGLOBULIN E

Omalizumab is a recombinant humanized immunoglobulin G1 monoclonal antibody that binds immunoglobulin E (IgE) with high affinity. Meta-analyses have shown that it reduced ICS dose requirement and frequency of asthma exacerbations when used as an adjunct to ICS in patients with moderate-to-severe asthma.[97,98] Similar benefits were not observed among patients receiving oral steroids. Most of these trials evaluated omalizumab in patients with elevated serum IgE levels and a positive skin test to aero-allergens, and the drug is currently reserved for this subset of patients if they respond inadequately to conventional treatment. These studies in general showed that a favourable response to omalizumab therapy occurred within 12 weeks.[99] Hence, omalizumab should be administered for at least 12–16 weeks before evaluating clinical response. The dose of omalizumab is determined by body weight and serum IgE levels (0.016 mg/kg per IU/mL of IgE per month), and is administered subcutaneously every 2 to 4 weeks. Only 30%–50% of patients show some response, and the total duration of treatment is not known.[100] Few experts believe that it may be given lifelong, as discontinuing therapy can lead to severe rebound exacerbations.[101] There is a theoretical risk of parasitic infections or malignancy with long-term use of omalizumab, and more safety data are needed before its routine use can be recommended.

ROUTE OF ADMINISTRATION AND DEVICES

The major classes of drugs useful in managing a patient with stable asthma (corticosteroids and beta-agonists) are available both in oral and inhalational formulations. Wherever possible, the inhaled route is clearly superior to the oral route. Ingested drugs must get absorbed into the systemic circulation first, and only a small fraction finally reaches the lungs. Inhaled drugs, on the other hand, are directly delivered to their site of intended action, and therefore need only a small fraction of the oral dose for equivalent effect. For this reason, inhalational agents are associated with fewer systemic adverse effects. Except for special situations such as severe financial constraints, non-availability of inhaled drugs, etc., there is currently no indication to prescribe oral medications.

The inhaled drugs can be administered through pressurized metered dose inhalers (pMDI), dry powder inhalers (DPI) or nebulizers. In general, pMDIs are the best standardized devices with fractional drug delivery to the lungs in a well-defined range. However, a major issue with pMDI use is the hand–mouth coordination. Studies have shown that a substantial proportion of patients using pMDIs do so incorrectly.[102,103] Therefore, it is important to teach patients how to correctly use their pMDI, and verify their technique at each visit. For patients who cannot coordinate their inhaler well, one can suggest using a valved spacer chamber in conjunction with the pMDI. This not only

removes the problems of coordination, but also reduces oral drug deposition and improves drug delivery to lungs. Alternatively, patients can use a nebulizer for routine use. Contrary to popular belief, drug delivery to lungs through a nebulizer is similar to that achieved when using pMDI with a spacer device.[104] DPIs are a heterogeneous collection of breath-actuated devices with highly variable inspiratory airflow requirements and drug delivery to lungs. Most DPIs are inferior to pMDIs as they generate larger particle size for inhalation, and hence cause more oropharyngeal drug deposition and lesser drug delivery to the lungs. On a long-term basis, they are also costlier than pMDIs. However, several patients find DPIs easier to use. Ultimately, one must strike a balance between efficacy (in terms of drug delivery to lungs at a particular unit dose) and patient preference while selecting the device for inhaled drugs. Whatever be the device, patients must be adequately educated about the proper technique of usage and maintenance of the device, and the technique must be checked at each follow-up visit.

GENERAL APPROACH TO MANAGEMENT

A stepwise approach is considered practical for managing patients with stable asthma (Table II). The decision to treat in any step is based on severity of symptoms as well as response to already prescribed drugs (Fig. 1).

Step 1: As-needed reliever

The lowest step in asthma management is useful only for those patients who experience intermittent symptoms (typically less than twice a month), and are symptom-free between these episodes. These patients can be managed with a reliever medication alone, taken whenever required. A SABA is the preferred agent for these patients.

Step 2: Single controller

Patients having more frequent or regular symptoms (typically between twice a month and twice a week) should not be managed with reliever drugs alone. They should take a controller medication in addition to the reliever medication on an as-needed basis. Low dose ICS is preferred as the controller drug, although LTRA

TABLE II. Stepwise pharmacotherapy for patients with bronchial asthma

Step	Reliever	Preferred choice for controller	Alternative choices for controller
1	SABA	–	–
2	SABA	Low dose ICS	Leukotriene receptor antagonist
3	ICS–LABA (SiT) or SABA	Low dose ICS and LABA	– Medium dose ICS – Low dose ICS plus leukotriene receptor antagonist – Low dose ICS plus methylxanthine
4	ICS–LABA (SiT) or SABA	Increase dose of ICS to medium/high dose Continue LABA If symptoms persist despite above, add one or more of: – Tiotropium – Leukotriene receptor antagonist – Methylxanthine	For patients not using LABA as yet, add LABA to the earlier therapy, and then increase ICS dose if symptoms persist
5	ICS–LABA (SiT) or SABA	Continue as in step 4 and add either of the following: – Low dose oral corticosteroid – Omalizumab	

General measures such as patient education, avoidance of asthma triggers, environmental control and treatment of comorbid conditions should be offered to all patients at each step (see reference 6 for details). ICS inhaled corticosteroid LABA long-acting beta-agonist SABA short-acting beta-agonist SiT single inhaler therapy

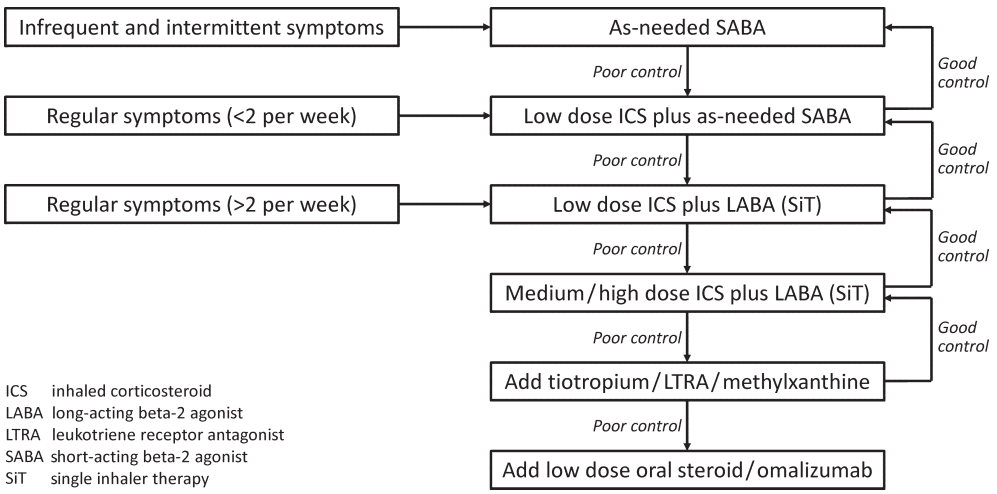

FIG 1. A suggested algorithm to initiate and modulate asthma pharmacotherapy

monotherapy can be prescribed as an alternative to those who cannot take ICS. Monotherapy with either methylxanthine or LABA is discouraged.

Step 3: Dual controllers

If asthma remains poorly controlled despite low dose ICS (step 2), or if symptoms occur more than twice a week or during night in treatment-naïve patients, therapy needs to be augmented. The preferred approach is addition of a LABA to the low-dose ICS which the patient is already taking. Other potential alternatives include doubling the ICS dose or combining a LTRA or theophylline with ICS. However, the options are not as efficacious as adding LABA to ICS. The SiT approach, using a formoterol-based combination, should always be preferred in such (and subsequent) settings.

Step 4: Two or more controllers

This is a complex treatment step for patients uncontrolled despite step 3 therapy, and represents all the sequential increases in medication before a patient is considered a candidate for oral corticosteroid or other therapy.

The preferred therapeutic option for these patients is continuing with an ICS–LABA combination and hiking up the dose of ICS to medium and high doses sequentially. Most patients will not derive additional benefit from increments in ICS dosing beyond the medium dose range. High-dose ICS may be tried for 3 months, and de-escalated if there is no clinical improvement. If a patient was not taking a LABA at step 3, it must be added before any further change in therapy.

In case patients remain uncontrolled despite a moderate-to-high dose ICS–LABA combination, tiotropium, LTRA, and/or methylxanthine can be added. This treatment is highly individualized, based on preferences of patients and physicians, and availability, tolerability and cost of drugs.

Step 5: Other add-on drugs

For patients who fail to respond to all the treatment approaches mentioned above (sometimes referred to as difficult-to-treat asthma), a trial of oral corticosteroids, or other targeted therapies such as omalizumab, may be considered. Although no clinical trial has specifically studied the role of oral corticosteroids among patients with difficult-to-control asthma, they can be considered in such a scenario at the lowest possible dose and for the shortest possible duration required to achieve asthma control in view of their many adverse effects.

MONITORING AND MODULATION OF THERAPY

The optimal frequency of follow-up visit of patients with asthma is between 1 and 3 months, although it may be more or less depending on an individual clinical scenario. Patients should be assessed for asthma control at each visit, and categorized as having either adequate or poor control of asthma. A patient is considered uncontrolled if she/he has either (i) daytime symptoms or rescue medication use more than twice per week; (ii) nocturnal symptoms or awakening; (iii) limitation of daily activities; or (iv) diminished peak expiratory flow (<80% of predicted best). Patients not having any of these features may be considered well controlled. At each visit, it is also important to enquire about compliance to therapy and any treatment-related adverse effects. An effort should be made at each visit to verify that the patient is indeed taking the inhaled medications using appropriate technique and device.

Therapy needs to be stepped up for patients with poorly controlled asthma on their ongoing treatment (Fig. 1). The best time to make such a decision is not clearly defined. A subgroup analysis of data from the GOAL study showed that each individual item used to assess asthma control took a different time to exhibit control. Improvement in peak expiratory flow or nocturnal symptoms happened much more quickly than other symptoms. In general, daytime symptoms took the longest to improve.[105] Overall, stepping up therapy may be considered at intervals of 1–3 months if a patient remains uncontrolled despite using prescribed medications correctly, although such titration of therapy needs to be individualized. For patients using an ICS–LABA combination (in particular those using SiT), dosage increments should be done after ensuring that the LABA dose stays within the safe therapeutic range.

For those who are adequately controlled on treatment, one can attempt stepping down treatment with an aim to maintain control at lowest possible drug doses (Fig. 1). The optimal timing and sequence of stepping down however remains controversial.[106,107] In general, stepping down treatment should be considered only after 2–3 months of good asthma control. For patients with asthma known to have seasonal exacerbations, such modifications should not be attempted during the time disease control is likely to be poor. All patients whose drugs are reduced should be closely monitored to detect subsequent worsening of disease control. For patients taking more than two controller drugs, the non-ICS, non-LABA controller drugs should be initially reduced/discontinued. Patients well controlled on medium or high-dose ICS, with or without LABA, can decrease/halve their ICS dose every three months till they attain a low ICS dose. Data suggest that patients controlled on high-dose ICS can be switched to a lower dose without losing disease control.[108–110] When stepping down from ICS–LABA combination therapy, it has also been shown that decreasing ICS dose is better than discontinuing LABA in maintaining asthma control.[111–113] Discontinuing LABA might be associated with higher likelihood of exacerbations requiring definitive treatment. Once a patient is well controlled on a low-dose ICS and LABA combination, one can attempt discontinuing LABA altogether. However, there is a possibility of losing asthma control and patients should be carefully monitored for the same.[114–117] When low-dose ICS monotherapy is sufficient to maintain good control, patients can try reducing the frequency of daily dosing. A meta-analysis of nine studies has reported that budesonide given once or twice daily is equally effective.[118] Finally, if a patient remains controlled even on such low ICS doses, one can try stopping regular ICS (step 1). This may, however, increase the risk of exacerbations.[119] Alternatively, one can switch to as-needed ICS, although there is insufficient evidence regarding such a choice.[120]

CONCLUSION

Several classes of inhaled and systemic drugs are available for long-term medical management of patients with asthma. A typical asthma prescription should be tailored to the patient's needs and preferences. Inhaled drugs are preferred to oral agents wherever feasible. ICS are the mainstay of therapy for controlling airway inflammation, and LABA are useful for patients not adequately controlled with ICS alone. Clinicians should build prescriptions based on treatment recommendations from evidence-based guidelines available for Indian patients.

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