BRONCHIAL ASTHMA: A GLOBAL HEALTH PROBLEM

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ABSTRACT

Among the several diseases, asthma is categorized to be a chronic disorder or inflammatory ailment of the airways across the globe. Almost 18-20 million people in the United States and more than 250 million people worldwide are affected with this syndrome. Numbers of patients are refractory to the available therapies. Newer agents are needed day by day to control symptoms and exacerbations in all patients. Over the years, there have been extensive advances in the understanding of asthma physiology at genetic level, airway biology, and immune cell signaling. Due to progression in the molecular level, diverse research groups have led to the development of number of molecules which may improve asthma care in the future. Several new classes of anti-asthma drugs—including ultra long acting β agonists, modulators of the interleukin pathways, adenosine receptor antagonist are named to be few. Some of the agents are in earlier phases of the development. Even though various groups have some preliminary efficacy data, there is insufficient confirmation to make strong recommendations about the use of these newer drugs. The mainstay of future research is on the clinical efficacy of newer agents, the effect of biological agents on severe asthma patients, and the understanding at cellular level of corticosteroid resistant asthma is needed to reduce the morbidity of asthma worldwide. The present review article is intended to give comprehensive information about the pathophysiology, pathogenesis and the medications for the management of asthma.

KEYWORDS: Asthma, bronchodilators, anti-inflammatory. adenosine receptors, bronchospasm, anticholinergics

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INTRODUCTION

Throughout a life span, consider the new born’s first gasp of air outside the mother’s womb, signifying the wonderful act of entry into this world, the infant’s first vocal sounds and lips that express emotions, enabling communication with the world, and finally, the inevitable act of dying, marked by giving the spirit away with the last breath - all tied to the respiratory tract. The human respiratory tract is universally exposed to air pollution and rapidly changing atmospheric conditions. The care for the respiratory tract should be stressed more often now-a-days, especially in view of a dramatic increase in the incidence of life-threatening diseases like asthma.\(^1\) Alarming fact is the rate of morbidity and mortality associated with the asthma. Approx. 300 million people suffer from asthma with number of annual deaths attributed to the disease worldwide. In the last five years, it has been observed that incidence of asthma are higher among children’s than adults. Chronic inflammation of the airways, airflow obstruction and airway hyper reactivity are caused due to exposure of some allergens, occupational irritants, chemical irritants and drugs. The symptoms includes relentless, exacerbation of disease, airflow obstacles and low quality of life in spite of using various bronchodilators. It is mostly well controlled by low doses of anti-inflammatory agents with or without bronchodilators in addition to high doses of steroids. The clinical features and test results of the airways disease are tabulated in the Table 1. Chronic respiratory diseases are the major causes of morbidity and mortality, which comprises 7% of deaths and 4% of disability adjusted life year (DALY).\(^2\)

<table>
<thead>
<tr>
<th>Airway disease</th>
<th>Component</th>
<th>Clinical features</th>
<th>Test result</th>
</tr>
</thead>
<tbody>
<tr>
<td>A Airways hyper-responsiveness</td>
<td>Short-term uncertain breathlessness and cough</td>
<td>Methacholine challenge optimistic &gt;12% bronchodilator response &gt;20% PEFR variability in 24 hrs</td>
<td></td>
</tr>
<tr>
<td>B Bronchitis</td>
<td>May be none Subacute marked deteriorations Morning productive cough</td>
<td>Raised induced sputum cell count Potentially high FeNO Otherwise unexplained blood eosinophilia</td>
<td></td>
</tr>
<tr>
<td>C Cough reflex hypersensitivity</td>
<td>Dry cough in relation to temperature change, talking, laughing</td>
<td>Excessive response to inhaled tussive stimuli (e.g. capsaicin)</td>
<td></td>
</tr>
<tr>
<td>D Damage</td>
<td>Fixed limitation in exercise due to breathlessness</td>
<td>Fixed airflow obstruction Impaired gas transfer Emphysema or bronchiectasis on CT scan</td>
<td></td>
</tr>
<tr>
<td>E Extrapulmonary co-morbidity Obesity, rhinitis, vocal cord dysfunction</td>
<td>Dependent on nature of co-morbidity</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Asthma and chronic obstructive pulmonary disease (COPD) are categorized as chronic disease all over the globe and its pervasiveness is increasing especially in the pediatric population.\(^3\) Airway hyperactivity, inflammation and bronchospasm are the problem of asthmatic patients which share common functional defect, i.e. airflow limitation as shown in figure 1.\(^4\)

The Global Initiative for Asthma (GINA) and Global Strategy for Asthma Management and Prevention (updated 2003) defined asthma as a chronic inflammatory disorder of the air route in which many cells and cellular elements play a role. The chronic inflammation causes an accompanying rise in airway hyper responsiveness that leads to repeated episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. These episodes are usually associated with widespread but variable airflow obstruction that is often reversible both spontaneously or with treatment.\(^5\) Hyper secretion, followed by bronchospastic crisis is an important symptom in bronchial asthma.\(^6\) Asthma is associated with an increased expression of components of the inflammatory cascade (figure 2).\(^7\) The inflammatory proteins includes cytokines, chemokines, growth factors, enzymes, receptors and adhesion molecules.\(^8\)
Factors triggering intrinsic asthma

Many inflammatory and structural cells are activated and results in the release of various mediators of inflammation, which causes pathophysiological alterations in asthma. Various inflammatory mediators are categorized as follows:

I. Amines
   a. Histamine
   b. Serotonin (5-hydroxytryptamine)
   c. Adenosine

II. Lipids
   a. Prostanoids
   b. Leukotrienes
   c. Platelet-activating factor

III. Miscellaneous lipids
   a. Hydroperoxyeicosatetraenoic acid (HPETES)
   b. Mono – and di-HETEs and lipoxins (LXs)

IV. Peptides
   a. Bradykinin
   b. Tachykinins
   c. Calcitonin
   d. gene-related peptide
   e. endothelins

Pathophysiology of asthma

In postmortem studies, asthma pathology has been examined which showed remarkable definite structures, containing the bronchial lumina occlusion with a combination of mucus, proteins of serum and cellular debris, epithelial remodeling and sloughing, stiffening of the epithelial basement membrane, oedema and WBC (mainly eosinophil), submucosa infiltration, mucous glands hyperplasia, and bronchial smooth muscle hypertropy. The overall cascade of events are represented in figure 3.

Pathogenesis of asthma

Airway inflammation in asthma is a multicellular method involving mainly eosinophils, neutrophils, CD T-lymphocytes and mast cells, with eosinophilic infiltration being the best striking feature. The inflammatory process is mostly constrained to the conducting airways but as the disease turn out to be more severe and chronic, the inflammatory infiltrate blow outs both proximately and distally to contain the small airways and in some cases adjacent alveoli. The inflammation is mutual to chronic allergic inflammatory responses at numerous tissue sites and indeed is seen at these sites in patients with asthma who recurrently express comorbidities such as chronic rhinitis, sinusitis, atopic dermatitis, and food allergy. Pathogenesis involves (figure 4)

- Differentiation and activation of eosinophils.
- IgE production and release.
• Expression of IgE receptors on mast cells and eosinophils.
• Besides activation of mast cells, macrophages and T lymphocytes in the airway mucosa, eosinophil infiltration into the airways plays a key role in the pathogenesis of asthma.

The mast cells bounded antibodies reaginic (IgE) mediates asthma in the airway mucus. The antigen reexposure, ‘antigen-antibody interaction’ on the surface of the mast cells activates both the discharge and synthesis of mediators stored in the cells granules. The agents liable for the early effects ‘immediate bronchoconstriction’ involves histamine, tryptase and various proteases (neutral), leukotrienes C₄, D₄, and prostaglandins. These agents distribute through the wall of airway and cause contraction of muscle and vascular leakage. An allergic asthma is the most predominant form of the disease, number of in vivo models has been developed to mimic allergen-induced lung inflammation and lung function changes.

Medication for asthma
The drugs mostly useful for management of asthma, bronchitis and emphysema are adreno-receptor agonists (used as relievers or bronchodilators) and inhaled corticosteroids (used as controller and anti-inflammatory agents) are mentioned in table 2. Bronchodilators are used for prevention of bronchospasm whereas anti-inflammatory drugs are used to reduce the inflammation of the airways. Reducing inflammation also reduces bronchospasm by decreasing mucosal edema and mucus secretions.

Table 2
Classification of anti-asthmatic drugs (GINA)

<table>
<thead>
<tr>
<th>RELIEVERS (BRONCHIODILATORS)</th>
<th>CONTROLLERS (ANTI-INFLAMMATORY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selective adrenergic agonists</td>
<td>Inhaled glucocorticoids</td>
</tr>
<tr>
<td>Inhaled β2 agonists (short acting)</td>
<td>Beclomethasone</td>
</tr>
<tr>
<td>Albuterol</td>
<td>Fluticasone</td>
</tr>
<tr>
<td>Terbutaline</td>
<td>Budesonide</td>
</tr>
<tr>
<td>Pirbuterol</td>
<td>Flunisicole</td>
</tr>
<tr>
<td>Levobuterol</td>
<td>Triamcinolone</td>
</tr>
<tr>
<td>Oral short acting β2 agonist</td>
<td>Systemic glucocorticosteroids</td>
</tr>
<tr>
<td>Salbutamol</td>
<td>Prednisone</td>
</tr>
<tr>
<td>Terbutaline</td>
<td>Prednisolone</td>
</tr>
<tr>
<td>Inhaled β2 agonist (long acting)</td>
<td>Methylprednisolone</td>
</tr>
<tr>
<td>Formoterol</td>
<td>Cromoly</td>
</tr>
<tr>
<td>Salmeterol</td>
<td>Nidocromyl</td>
</tr>
<tr>
<td>Non-selective adrenergic agonists</td>
<td>Theophylline</td>
</tr>
<tr>
<td>Isoprotenerol</td>
<td>Long acting oral β2 agonists</td>
</tr>
<tr>
<td>Ephedrine Mist</td>
<td>Leukotriene modifiers</td>
</tr>
<tr>
<td>Anticholinergics</td>
<td>Montelukast</td>
</tr>
<tr>
<td>Ipratropium bromide (short acting)</td>
<td>Zafirlukast</td>
</tr>
<tr>
<td>Thiotropium bromide (long acting)</td>
<td>Theophylline</td>
</tr>
<tr>
<td>Theophylline</td>
<td></td>
</tr>
<tr>
<td>Systemic glucocorticosteroids</td>
<td></td>
</tr>
<tr>
<td>Prednisone</td>
<td></td>
</tr>
<tr>
<td>Prednisolone</td>
<td></td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td></td>
</tr>
</tbody>
</table>

Relievers (Bronchiodilators)
Relievers are the medications which are used on as essential basis for quick relieve. They give immediate action in reversing the bronchoconstriction and get rid of asthma related symptoms. They includes:

a. Rapid acting inhaled β₂ agonists
b. Systemic glucocorticosteroids
c. Anticholinergics
d. Theophylline
e. Short acting oral β₂ agonists

Rapid acting inhaled β₂ agonists
Beta-2-agonists are the most commonly used drugs in the treatment of obstructive airway disease (OAD), which is well-defined as asthma or chronic obstructive...
pulmonary disease (COPD). Even though β₂ agonists are typically inhaled with low systemic absorption, there have been reports of augmented plasma levels. β₂-receptors are present in the myocardium, where they facilitate contraction. Examples are:

- Salbutamol (1)
- Isoproterenol (2)
- Albuterol (3)
- Metaproterenol (4)
- Terbutaline (5)

They are commonly known as “rescue medications” since they halt asthma symptoms very rapidly by opening the bronchial airways. They act within 30 minutes and precede for about 4-6 hours.

**Systemic glucocorticoids**

Example of systemic glucocorticoids includes:

- Prednisone (6)
- Beclomethasone (7)
- Budesonide (8)
- Flunisonide (9)
- Triamcinolone (10)

In acute, severe asthma, a systemic corticosteroid in relatively high doses is indicated in patients whose respiratory distress is not relieved by multiple doses of an inhaled β₂-agonist. Systemic corticosteroids show an essential part in the treatment of many immunologic and inflammatory conditions, then these drugs are similarly related with severe risks. They are used in case of simple uncontrolled asthma. All corticosteroids decrease inflammation in the airways that transport air to the lungs (bronchial tubes). They also reduce the mucus made by the bronchial tubes and make it easier to breathe. Primary effect of gluco-corticoids are

- Anti-inflammatory
- Immunosuppressive
- Anti-proliferating
- Vasoconstructive

'Prednisone' is possibly the utmost extensively used drug of the systemic corticosteroids.

**Anticholinergics**

There are currently two drugs available under this category i.e. ipratropium bromide (11) and tiotropium bromide (12).

The most commonly used drug is ipratropium bromide however it is less effective than rapid acting inhaled β₂-agonist and, consequently, it is used as second-line treatment for patients who are unable to use short acting β₂-agonists. Ipatropium bromide (11) and oxitropium bromide (12) can also be used to widen the airways in patients having chronic bronchitis and to treat contraction of the airways precipitated by β₂-adrenoceptor antagonists. Theophylline

Xanthine is a purine base found in most human body tissues and fluids and in other organisms. Xanthines have been commonly used as a reasonable oral therapy
for both asthma and COPD. It shows their effectiveness on bronchi dilation, and now a days these drugs also shows its effect on inflammation. Examples of methyl xanthines are:

- Theophylline (13)
- Theobromine (14)
- Caffeine (15)

Xanthines have been reported to be effective in the management of asthma, but their mode of action remains imprecise till date. Prophylactic effects of various xanthines against bronchospasm induced by an aerosol of ovalbumin in normal guinea pigs occurred by an unrelated mechanism of bronchodilation. These results may also not be readily ascribed to phosphodiesterase (PDE) inhibition or adenosine A1/A2 receptor antagonism. This concludes that the bronchodilator, anti-allergic and anti-inflammatory effects of xanthines occurs through multiple mechanisms of action, including at least one of the unknown mechanism. Theophylline and related xanthines has been used for the treatment of asthma which reduces the contractile potential of smooth muscle by inhibiting PDE enzyme and decreases the cytosolic calcium concentration as shown in figure 5.

Theophylline and related xanthines has been used for the treatment of asthma which reduces the contractile potential of smooth muscle by inhibiting PDE enzyme and decreases the cytosolic calcium concentration as shown in figure 5.

**Literature review reveals that a more selective A2B- adenosine receptor antagonist devoid of phosphodiesterase inhibition activity may have an improved therapeutic index.** In recent time’s new pharmacodynamics that may consider for the efficiency of theophylline in intense asthma have been explained. Since side effects causes problem, attempts are made to get better on theophylline and increasing interest has been develop in particular phosphodiesterase (PDE) inhibitors, which results into the probability of fixing the profitable and decreasing the side effects of theophylline.

The expected mechanisms of action of theophylline are:

- Inhibition of phosphodiesterase (non-selective)
- Adenosine receptor antagonism (A1, A2A, A2B receptors)
- Nuclear factor inhibition
- Phosphoinositide 3 kinase inhibition
- Interleukin-10 secretion is increases
- Apoptosis of inflammatory cells increases
- Poly-(ADP-ribose)-polymerase-1 decreases
- Histone deacetylase action

Some of the mechanism of action of theophylline has been described below in detail.

**Inhibition of phosphodiesterase**

Theophylline is a weak nonselective inhibitor of phosphodiesterase (PDE) iso-enzymes induces bronchodilation which interrupt cyclic nucleotides in the cell, leading to augmentation of intracellular concentrations of cAMP and cyclic 3’,5’ guanosine monophosphate to competitively inhibit both high and low affinity cAMP and cGMP phosphodiesterases and to cause muscle relaxation.

**Adenosine receptor antagonism** A countless work had completed in last era to describe adenosine receptors and their physiological role. Certain evidences suggested the well-defined role of adenosine is present in airways and its participation in various ‘allergic inflammation’ along with restoration of airways. Adenosine acts on adenosine receptors present in the airways cells and causes constriction in the bronchi of the person suffering from asthma and COPD.

Adenosine is an intermediate catabolic product of adenosine triphosphate having very short half-life because of its metabolism as depicted in figure 6.
The four receptor subtype of adenosine are present which are marked as: $A_1$, $A_{2A}$, $A_{2B}$ and $A_3$. The comparison of different subtypes of adenosine receptors and their effects and mentioned in table 3 and table 4, respectively.

### Table 3

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Gene</th>
<th>Mechanism</th>
<th>Agonists</th>
<th>Antagonists</th>
</tr>
</thead>
<tbody>
<tr>
<td>$A_1$</td>
<td>ADORA1</td>
<td>$G_{10}$cAMP decreases</td>
<td>N$_7$-cyclopentyladenosine, CCPA, 2’-MeCCPA, GR79236, SDZ WAG994</td>
<td>Caffeine, Theophylline, CPX, DPCPX, PSB 36</td>
</tr>
<tr>
<td>$A_{2A}$</td>
<td>ADORA2A</td>
<td>$G_3$ cAMP increases</td>
<td>ATL-146e, CGL21680, Regadenoson</td>
<td>Caffeine, Theophylline, SCH-58261, SCH-442,416</td>
</tr>
<tr>
<td>$A_{2B}$</td>
<td>ADORA2B</td>
<td>$G_0$ cAMP decreases</td>
<td>5’-N ethylcarboxamidoadenosine, BAY 60-6583, LUF-5835</td>
<td>Theophylline, CVT-6883, MRS-1705, MRS-1754, PSB-603, PSB-0786, PSB-1115</td>
</tr>
<tr>
<td>$A_3$</td>
<td>ADORA3</td>
<td>$G_{10}$ cAMP decreases</td>
<td>2-[(1-hexynyl)N-methyl adenosine, CF-101(IB-MECA), 2-CL-IB-MECA, CP-532</td>
<td>Theophylline, MRS-1191, MRS-1220, MRS-1334, MRS-1523</td>
</tr>
</tbody>
</table>

### Table 4

**Adenosine receptor effect on different organ system**

<table>
<thead>
<tr>
<th>Receptor subtypes</th>
<th>Effects on stimulating the receptors</th>
</tr>
</thead>
<tbody>
<tr>
<td>$A_1$</td>
<td>Cardiovascular</td>
</tr>
<tr>
<td></td>
<td>• Slow AV nodal conduction</td>
</tr>
<tr>
<td></td>
<td>• Decrease heart rate</td>
</tr>
<tr>
<td></td>
<td>• Decrease atrial contractility</td>
</tr>
<tr>
<td></td>
<td>• Decrease β-adrenergic tone</td>
</tr>
<tr>
<td></td>
<td>• Inhibit pacemaker and L-type calcium currents</td>
</tr>
<tr>
<td></td>
<td>Renal</td>
</tr>
<tr>
<td></td>
<td>• Inhibit release of renin</td>
</tr>
<tr>
<td></td>
<td>• Increase reabsorption of Na in proximal convoluted tubules</td>
</tr>
<tr>
<td></td>
<td>• Vasocostriction of afferent arteriole</td>
</tr>
<tr>
<td></td>
<td>CNS</td>
</tr>
<tr>
<td></td>
<td>• Decrease neurotransmitter release</td>
</tr>
<tr>
<td></td>
<td>• Sedation</td>
</tr>
<tr>
<td></td>
<td>• Anticonvulsant effect</td>
</tr>
<tr>
<td></td>
<td>Metabolic</td>
</tr>
<tr>
<td></td>
<td>• Inhibit lipolysis</td>
</tr>
<tr>
<td></td>
<td>• Increase insulin sensitivity</td>
</tr>
<tr>
<td>$A_{2A}$</td>
<td>Cardiovascular</td>
</tr>
<tr>
<td></td>
<td>• Coronary and peripheral vasodilation</td>
</tr>
<tr>
<td></td>
<td>• Inhibit platelet aggregation</td>
</tr>
<tr>
<td>$A_{2B}$</td>
<td>Pulmonary</td>
</tr>
<tr>
<td></td>
<td>• Vasodilation</td>
</tr>
<tr>
<td></td>
<td>• Mast cell release of IL-8</td>
</tr>
<tr>
<td>$A_3$</td>
<td>Pulmonary</td>
</tr>
<tr>
<td></td>
<td>• Mast cell release of allergic mediators</td>
</tr>
</tbody>
</table>

The various targets for the dissimilar drugs for the treatment of asthma are adenosine ($A_1$, $A_{2A}$ and $A_{2B}$) receptors. Various literatures support the explanation that numbers of antagonist are used for $A_1$ and $A_{2B}$ adenosine receptor whereas agonists are used for $A_{2A}$ adenosine receptor. The biological role of $A_3$ adenosine receptor in the area of asthma is still uncovered. Theophylline is an effective restrainer of adenosine receptors at curative aggregations. The $A_1$ and $A_2$ receptors both are restrained signifying the role of bronchodilator activity. Interleukin-10 (IL-10) secretion Interleukin 10 has a wide range of anti-inflammatory activity and which has is indication as its release is increase in asthma and COPD. IL 10 discharge is
enhanced through theophylline and its activity might be arbitrated over PDE inhibition, but when low dose is given it shows effectiveness in asthma.  

Controller medications are taken day-to-day on a long-term basis that achieves control primarily through anti-inflammatory effects to keep the asthma under control. They include:

- a) Corticosteroids (inhaled or systemic)
- b) Long acting β₂ agonists
- c) Leukotriene antagonist
- d) Anti-IgE
- e) Mast cell stabilizer

Corticosteroids (inhaled or systemic)
Corticosteroids are the backbone and the best anti-inflammatory treatment available for the cure of asthma for most patients with asthma. Maximum cases will require long-term inhaled corticosteroids (ICS’s) treatment. ICS is the almost real anti-inflammatory drugs to the management of tenacious asthma.

Longer acting β₂ agonists (LABA)
Example of long acting agents is:
- Salmeterol (18)
- Formoterol (19)

The LABA are the favored and most active bronchodilators for the cure of bronchial spasm, whose onset of action is rapid. It unswervingly acts on airway smooth muscle by exciting β₂ receptor which consecutively raises cyclic AMP level and produces antagonism to broncho-constriction.

Toxicities
- Cardiac arrhythmias
- Hypoxemia
- Tachyphylaxis
- Tolerance
- Decrease arterial oxygen tension

Leukotriene receptor antagonists (LTRAs)
Montelukast (20) and Zafirlukast (21) are the most useful drugs for the management of asthma which are normally measured to be harmless and accepted. However, when these agents are used as monotherapy they are least efficient when compare with ICS therapy, they are generally kept for patients who are disinclined or incapable to use ICS’s. LTRA’s may also be taken as supplementary treatment, if asthma is unrestrained regardless of the usage of less-to-mild dose ICS’s treatment.

Anti-IgE
The IgE plays a vigorous role in the induction and propagation of the inflammatory cascade. The anti-IgE monoclonal antibody ‘omalizumab’ has been used to decrease the level of spasm by approx. 50 percent. It can reduce free IgE levels by up to 98%, when given in sufficient doses. The subcutaneous direction of drug is done for every 2-4 weeks and recognized in Canada for the therapy of mild to severe, constant allergic asthma in patients with 12 years age or older. At present, omalizumab is taken by the patients who found it difficult to control asthma, documented allergies with symptoms remain uncontrollable despite ICS treatment.

Mast cell stabilizer
Mast cell plays an important role in the pathophysiology of immediate hypersensitivity reaction. Mast cell stabilizers avoid the allergic reaction by the release of allergic mediators from the mast cells. In this respect, recent developments of the discovery of mast cell stabilizers (next generation) includes the substances isolated from natural sources, biological, newly synthesized compounds and drugs licensed for other manifestation.

Some newer anti-inflammatory drugs
Phosphodiesterase inhibitors (PDE): They blocks one or more of the five sub-types of the enzyme PDE, hereby prevent the inactivation of cAMP in inflammatory cells and decreases cell activation and release of inflammatory mediators. The PDE4 is the main enzyme present in inflammatory and immune cells. The PDE4 inhibitors like roflumilast have confirmed its potential as anti-inflammatory drugs, particularly in asthma, COPD and rhinitis. Mitogen activated protein kinase inhibitors: There are three major mitogen activated protein kinase (MAPK) pathways which are present in chronic
inflammation. The p38 MAP kinase inhibitors such as SB203580 and RWJ67657 inhibit the synthesis of various inflammatory cytokines and chemokines which are in the process of development for the medication of asthma and COPD.\textsuperscript{56} \textit{Novel classes of bronchodilators:} Ultra LABAs (once daily \(\beta_2\)-agonists) are in clinical trials that include indacaterol, olodaterol, carmoterol and vilanterol etc. These ultra LABAs must be in a fixed dose combination with corticosteroids. Indacaterol plus mometasone and fluticasone furoate plus vilanterol are at present in the clinical trial phase for the management of asthma.\textsuperscript{57} \textit{Mast cell inhibitors:} Mast cells are the main root in the progression of asthma. The survival of mast cells in the airways relies on the stem cell factor. A persistent rise of stem cell factor in plasma concentration is observed in asthmatics. Restriction of stem cell factor is an useful treatment mode in controlling asthma, which is proved in animal models.\textsuperscript{58} Masitinib is a potent blocker of c-Kit and delivers some symptomatic benefit in patients with severe asthma. Further selective c-Kit inhibitors are in development.\textsuperscript{59} \textit{Non-pharmacological management:} Non-pharmacological methods are not the alternate for recommended pharmacological therapy. The effect of non-pharmacological management of asthma is not well set and it requires more amount of evidence based well controlled intervention studies.\textsuperscript{60} \textit{Allergen avoidance:} Avoidance of recognized allergic triggers can improve symptoms, reduce medication use and diminish bronchial hyper responsiveness).\textsuperscript{61, 62} Though, studies pertaining to allergen avoidance have failed to show beneficial effects. \textit{Dietary manipulation:} Low levels of magnesium intake supplement of diet rich in omega 3 fatty acids might decrease the inflammation associated with asthma.\textsuperscript{63} \textit{Environmental factors:} Series of the study express that, air pollution and tobacco smoke can provoke acute asthma attacks or provoke existing condition. Patients with acute severe asthma are cautioned to receive supplementary oxygen therapy by mask or nasal cannulae titrated to maintain the usual level of \(\text{SaO}_2\). \textit{Immunotherapy in asthma:} Use of specific immunotherapy in the medication of asthma is still controversial. Immunotherapy should not be observed as an alternative to established forms of protective therapy. Numerous studies have been managed to explore the role of immunotherapy in asthma.\textsuperscript{64} The comparison was tough because of the inherent problems of trials comprising asthma, different allergen extract and dosage regimens. Still, meta-analysis concluded that immunotherapy is a treatment of choice in highly selected patients with allergic asthma.\textsuperscript{65} \textit{Alternative and complementary therapies:} It is common to discover patients with asthma, seeking medications from different systems of medicine. Studies have displayed that patients use either complementary or alternative medicine only if they are not pleased with conventional medicine. Adverse effects of conventional medicines, entire approach in the disease management are also the reason for selecting complementary and alternative medicine. A wide range of 6-70% frequency of use of complementary therapy for asthma is reported.\textsuperscript{66} Such treatments contains acupuncture, homeopathy, fish therapy, other herbal therapy, comprising ayurvedic drugs, ionizers and spiritual healing which are tried by many but have not stood the test of controlled clinical trials.

**CONCLUSION**

Asthma remains as an ailment with unmet therapeutic requirements. Though the existing therapies for asthma are useful and well accepted in majority of the patients but the challenge quiet exists in the pharmaceutical industry to design safer, operative and orally active bronchodilatory and anti-inflammatory drugs with improved therapeutic index. The major challenge for a medical chemist is to design a compound that should be effective as well as free from undesirable effects. To combine numerous desirable properties into a single compound is a difficult job. There have not been some substantially new pharmaceutical developments in the past era or two with respect to cure strategies for asthma. There have been different \(\beta\)-agonists or PDE inhibitors, but these signify only amendments of decades-old strategies. New advances have been expected at controlling inflammation, which is also vital but should not conceal any efforts designed at controlling bronchoconstriction openly. With the improved perception of asthma pathophysiology, drugs now are being developed to act in contradiction of different steps in the inflammatory process. In spite of the availability of a wide range of anti-asthmatic drugs, the aid offered by them is largely symptomatic and short survived. Besides their side effects are also quite troubling, hence an uninterrupted search is desirable to identify real and safe medicines to treat bronchial asthma.\textsuperscript{65} Array of new agents are in progress for the treatment of asthma as of an enhanced perception of the pathophysiology of this disorder, mainly the inflammatory processes. This precludes a balanced approach for the design of new and more effective therapeutic agents for the controlling of asthma.

**ACKNOWLEDGEMENTS**

Authors are also thankful to UGC, New Delhi for providing the financial assistance through major research project {F.No. 42-698/2013(SR)}. The authors are thankful to DST, New Delhi for providing financial assistance under DST-CURIE programme to Banasthali University, Banasthali, Rajasthan. Authors are also thankful to Prof. Aditya Shastri, Vice-chancellor, Banasthali University for providing necessary research facilities.

**CONFLICT OF INTEREST**

The authors declare no conflict of interest.
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