INTRODUCTION

Asthma is a common medical condition which affects approximately 300 million people worldwide and the number is expected to increase exponentially in the coming years.\(^1\) The rate of severity of the disease is different and vary in different countries depending upon the diagnostic standards (Table 1).\(^2\) According to World Health Organization (WHO) asthma and chronic obstructive pulmonary disease (COPD) will be the third leading cause of death by 2020. The prevalence of asthma rates is severe among children’s in young age.

<table>
<thead>
<tr>
<th>Country</th>
<th>Prevalence/1000</th>
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<tbody>
<tr>
<td>Scotland</td>
<td>184</td>
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<td>U.K.</td>
<td>153</td>
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<td>New Zealand</td>
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<td>Australia</td>
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<td>Canada</td>
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<td>U.S.A.</td>
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<td>Brazil</td>
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<td>Pakistan</td>
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<td>Turkey</td>
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<td>France</td>
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<td>Japan</td>
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<td>Thailand</td>
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<td>China</td>
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<td>Macau</td>
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Asthma is a chronic obstructive pulmonary disease which affects the bronchi airways and results in the inflammation of bronchioles along with the hyper-responsiveness to some direct or indirect stimuli which leads to bronchoconstriction.\(^3\) COPD is a very common chronic and serious allergic disease across the globe. The Global Strategy for Asthma Management and prevention defines asthma as “a
chronic inflammatory disorder of the airways in which many cells and cellular elements play a vital role.” The chronic inflammation causes an associated increase in airway hyper-responsiveness which leads to recurrent episodes of wheezing, breathlessness, chest tightness and coughing, particularly at the night or in the early morning.

These episodes are usually associated with airflow obstruction that is often reversible either spontaneously or with treatment. The airflow limitation from smooth muscle contraction, edema and hyper-secretion is a major cause of airway tissue reactions.4 The various drug management groups such as the National Institutes of Health (USA), the Global Initiative for Asthma (GINA) and the Japanese Society of Allergology (JSA) have published several asthma prevention and management guidelines.5-9

The implementation of the treatment given in these guidelines is found to be effective in both children and adults. But the complete remission of the disease by pharmacotherapy is very difficult as on date.8 Asthma may be triggered by a number of factors such as mold, dust, pets, cockroach, certain chemical odors, smoke, grass, weeds etc.

Depending on the age and number of factors involved, asthma can be classified as:

- Childhood Asthma
- Adult onset Asthma
- Exercise induced Asthma
- Cough induced Asthma
- Occupational Asthma
- Nocturnal Asthma
- Steroid resistant Asthma

In certain cases, the preliminary symptoms of asthma are usually seen during the pre-school years and even those who develop chronic symptoms in young age, episodic wheezing and bronchial hyper-responsiveness are detected in early life.10

Chronic airflow limitation is the strongest predictor of the continued and increasingly severe symptoms of asthma and includes three phases11-17:
The post-natal acquired airflow obstruction is usually seen in patients with recurrent exacerbations. The impairment in lung function is also associated with occupational asthma and exposure to air pollution. Some children show only mild, transient and sporadic episodes of airway obstruction that does not lead to chronic asthma. Depending upon the severity of asthmatic episodes, it can be further classified as in table 2.

Table 2: Classification of Asthma

<table>
<thead>
<tr>
<th>Classification</th>
<th>Description</th>
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<tbody>
<tr>
<td>Mild Intermittent</td>
<td>Attacks not more than twice a week and night time attacks not more than twice a month. Attacks last for few hours and severity of attack varies.</td>
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<tr>
<td>Mild Persistent</td>
<td>Attacks more than twice a week and night time symptoms more than twice a month. Sometimes attacks are severe enough to interrupt regular activities.</td>
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<tr>
<td>Moderate Persistent</td>
<td>Daily attacks, Night time symptoms more than once in a week. Severe attacks at least twice a week lasting for days. Attacks require daily use of rescue medication and changes in daily activities.</td>
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<tr>
<td>Severe Persistent</td>
<td>Frequent severe attacks, continual daytime symptoms and frequent night time symptoms. Symptoms require limits on daily activity.</td>
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The susceptibility to asthma seems to be associated with the microbial colonization of airways. The infants who have been detected with increased amounts of pathogenic bacteria in upper airways found to develop symptoms of asthma in early stages.
The symptoms of asthma may also be triggered by exposure to certain allergens such as weeds, pollen, pets, dust, mites etc. or due to the presence of some irritants in air such as smoke, chemical irritants or certain odors or due to some extreme weather conditions or the presence of sulfites in certain food stuffs. Certain conditions like respiratory illness, emotions, exercise and flu makes a person more susceptible to asthmatic attack.

The various signs and symptoms associated with asthmatic attacks are:

- Coughing, especially at night, during exercise and laughing
- Wheezing
- Shortness of breath
- Tightness in chest
- Pain and pressure in chest

The diagnosis of asthma is done by the medical history of the person, physical examination, lung function test and methacholine challenge test.

Inflammation results into a number of structural changes in airways including the thickening of basement membrane, sub-epithelial fibrosis, metaplasia of goblet cells, neo-vascularization and increased smooth muscle mass of airways. All asthmatic patients experience serious effects on the structure and function of airways, regardless of the duration of disease. Airway remodeling is usually associated with an irreversible decrease in forced expiratory volume (FEV1), increase in the hyper-responsiveness of airways, increase in the thickness of basement membrane of airways and loss of bronchodilator reversibility.\(^{21,22}\)

These all structural changes in the airways of asthmatics facilitate in the development and progression of disease. It is unclear whether inflammation precedes or coexists with airway remodeling but remodeling can occur early in the disease even in the absence of inflammation. There is a direct relationship between mechanical stress and airway remodeling in asthma.\(^ {23}\) The mechanical stress itself has the ability to regulate certain structural changes in airways which contribute towards the dissociation between airway remodeling and inflammation.
The various pathophysiological changes which occur during asthma are due to the release of a number of inflammatory mediators, which can be classified on the basis of their chemical nature as:

- **Amine mediators**
  - Histamine, Serotonin (5-Hydroxytryptamine, 5-HT), Adenosine
- **Lipid derived mediators**
  - Leukotrienes, Platelet-activating Factor, Prostanoids
- **Peptide mediators**
  - Bradykinin, Trachykinin, Calcitonin, Endothelin, Gene-related peptide
- **Other mediators**
  - Lipoxins (LXs), Hydroperoxyeicosatetraenoic acid (HPETES), mono-, di-HPETEs.

The inflammation perpetuates itself by cell to cell communication and recruitment of many more inflammatory cells expressed by inflammatory mediators. A number of therapies are available which target inflammatory mediators but none of them always proved beneficial clinically. So the other evidences were studied and reports the role of phosphodiesterase-4 (PDE-4) inhibitors which is involved in the pathogenesis and treatment of asthma.²⁴

PDEs (Phosphodiesterases) belong to a large family of enzymes that catalyze the hydrolysis of secondary messenger’s cAMP (cyclic adenosine monophosphate) or cGMP (cyclic guanosine monophosphate). Secondary messenger’s mediates a number of biological processes such as the release and function of various hormones, neurotransmitters, chemokines and cytokines. The 5’-nucleotide triphosphates, ATP (Adenosine triphosphate) and GTP (Guanosine triphosphate) regulate the cellular levels of cyclic nucleotides, cAMP and cGMP by the activity of adenylyl cyclase and guanylyl cyclase and PDEs hydrolyze them into 5’-nucleotide monophosphates. An increase in the concentration of these secondary messengers (cAMP and cGMP) results in the activation of protein kinase A and G respectively (Fig. 1). These kinases then further phosphorylate various transcription factors and ion channels which are an important factor in the regulation of a number of physiological processes that includes the contraction of cardiac and smooth
muscles, platelet aggregation, visual responses, glycogenolysis, ion channel conductance, growth control and apoptosis.25

![Fig. 1: Mechanism of action of phosphodiesterase](image)

The PDE-4 inhibitors are associated with the activation of β2-adrenoceptor agonist, vasoactive intestinal peptide (VIP) and prostaglandin E2 (PGE2). Their activation increases the concentration of cAMP by a stimulatory G protein (Gs) which activates adenylate cyclase. An increase in the level of cAMP results in the activation of PKA which mediates the phosphorylation of certain targeted proteins, opening Ca2+-activated K+ channel, decreases the hydrolysis of phosphoinositide (PI), increases Na+/K+ ATPase activity and decreases myosin light chain kinase (MLCK) activity, which results in the relaxation of airway smooth muscles (Fig. 2).

![Fig. 2: PKA mediated bronchodilation](image)
The cAMP is broken down into AMP by the enzyme phosphodiesterase (PDE), which reveals that the PDE inhibitors are one of the potential targets in the treatment of asthma.\textsuperscript{26} PDE inhibitors have also considerable therapeutic importance as anti-inflammatory agents, vasodilators, anti-asthmatics, smooth muscle relaxants, anti-depressants, anti-thrombotic, memory and cognition enhancers.\textsuperscript{27-29}

The functional diversity of PDEs is due to their different classes. The human cyclic nucleotide phosphodiesterase are classified into 11 classes among which PDE4 family of enzyme is specific for cAMP while PDE5 is for cGMP.\textsuperscript{30-31} PDE4B is involved in inflammatory responses of lymphocytes. PDE4 inhibitors are usually associated with nausea and vomiting as side effects because they also cause the inhibition of PDE4D in brain.\textsuperscript{32}

**Approaches for the treatment of asthma**

The study about the pathogenesis of asthma gave a view on various available targets whose activation or blockage will be beneficial in the treatment of asthma. The approaches are:

- **Prevention of antigen-antibody reaction**: Antigen avoidance, hyposensitization
- **Neutralization of IgE (reaginic antibody)**: Omalizumab
- **Prevention of the release of mediators**: Mast cell stabilizers
- **Suppression of inflammation and bronchial hyper reactivity**: Corticosteroids
- **Antagonism of released mediators**: Leukotriene antagonist, Antihistamines, PAF antagonists.
- **Blockade of constrictor neurotransmitter**: Anticholinergics
- **Mimicking dilator neurotransmitter**: Sympathomimetics
- **Directly acting bronchodilators**: Methylxanthines

Based on the above approaches, anti-asthmatics can be classified broadly as bronchodilators and corticosteroids. The chemical structure of some approved antiasthmatic drugs are given in Fig. 3 and 4.
Fig. 3: $\beta_2$-sympathomimetics

- **Bronchodilators**
  - $\beta_2$-sympathomimetics (Salbutamol, Terbutaline, Bambuterol, Salmeterol, Formoterol, Ephedrine)
  - Methylxanthines (Theophylline, Aminophylline, Choline theophyllinate, Hydroxyethyl theophylline, Doxophylline)
  - Anticholinergics (Ipratropium bromide, Tiotropium bromide)
- **Leukotriene antagonist** (Montelukast, Zafirlukast)
- **Mast cell stabilizers** (Sodium Cromoglycate, Ketotifen)
- **Corticosteroids**
  - Systemic corticosteroids (Hydrocortisone, Prednisolone)
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- **Inhalational Corticosteroids** (Beclomethasone, Budesonide, Fluticasone propionate, Flunisolide, Ciclesonide)
- **Anti IgE antibody** (Omalizumab)
- **Miscellaneous drugs** (Prostaglandins, Antihistamines, Adrenocorticotropic hormone)

![Diagram of various antiasthmatic drugs]

**Fig. 4:** Various antiasthmatic drugs
There is no strategy to prevent primary asthma and the limitation of airflow in the asthmatics. The avoidance of allergens even during pregnancy and early infancy has no effect on outcomes of asthma. The environmental control and pharmacological therapy are the important aspects to treat asthma.

The main causative agent is environmental exposure but still the treatment in terms of allergen avoidance is controversial. In case of occupational asthma also, only 1/3rd patients showed improvement after cessation to exposure. In adults, the allergen avoidance is not much beneficial but reduction in indoor allergens exposure among asthmatic children, resulted in a reduction in asthma associated morbidity.

The pharmacological therapy includes the use of inhaled corticosteroids with or without long acting beta agonists, leukotriene receptor antagonists, anti IgE antibody, antibodies against chemokines and cytokines, phosphodiesterase inhibitors, antihistamines etc.

SYMPATHOMIMETICS

As the name indicates, they mimic the action of dilator neurotransmitter and are also known as adrenoreceptors. The asthma therapy with the adrenoreceptor stimulants is based on the release of bronchial spasm by stimulation of specific $\beta_2$-adrenoceptors in bronchial muscles (Fig. 5).

![Fig. 5: Mechanism of action of adrenoreceptor stimulants](image)

**α-Adrenoreceptor stimulants**

These receptors stimulate the decongested bronchial mucous membranes. They are associated with bronchoconstriction by inhibiting the enzyme adenyl cyclase thus decreasing the concentration of cAMP and also exacerbate the effect of histamine.
thus explain the reason of increasing infections in case of bronchial spasm. Their stimulation also increases antigen-antibody reaction thus liberates endogenous spasmogens. These receptors, on stimulation, are also associated with exercise-induced asthma.

α-adrenoceptor blockers decreases histamine induced bronchoconstriction but they also have antihistaminic activity or direct smooth muscle relaxing activity so the exact observation is hard to interpret. They also decreases spasmogens liberation and are effective in exercise-induced asthma.37

The stimulation of α-receptors is also associated with greater negative effect in certain cases and thus sometimes worsens mucus decongesting effect. So the treatment with α-blockers needs caution before treatment as they provide a narrow therapeutic window.

β-Adrenoreceptors stimulants

The stimulation of these receptors is of high therapeutic importance in the treatment of asthma. The β-receptor stimulation of bronchial muscles releases bronchial spasm and also inhibits the liberation of inflammatory mediators. They also have a negative effect on mast cells and increases mucociliary clearance by increasing transport of mucus.38-40

Relative effect of adrenoceptors stimulation

Non-selective adrenergic drugs act on both α- and β-receptors in the whole body. The resistance vessels in bronchial muscles and those in systemic circulation posses same type of β-receptors. The treatment with β2-stimulants causes bronchodilation and simultaneously dilates peripheral vessels which decrease the blood pressure. Similarly, long term treatment with α-stimulants causes urinary retention by contracting upper part of urethra. The skeletal muscle tremors are also dose related side effects with the use of selective β2-stimulants.41

Ephedrine is an indirect adrenergic stimulant and releases norepinephrine which acts on receptors but it has poor β2-stimulant affect so ought to be replaced by other drugs such as isoprenaline, salbutamol, terbutaline and feneterol.42 All the adrenergic drugs are available in various forms such as inhalation, parenterally,
perorally or subcutaneous. The inhaled $\beta_2$-stimulants in therapeutic doses are more effective than the parenteral and peroral ones. The selective $\beta_2$-inhaleders are safer when given as metered aerosols. The requirements for increased high selectivity of a drug as inhalation depend on strong local effect and fast metabolism within lung by COMT. All the $\beta$-stimulants have high first-pass metabolism so the inhalation form gives increased selectivity as only 10% of dose taken by metered aerosol is retained in lungs rest in mouth and throat.

**METHYLXANTHINES**

Xanthines act by inhibiting the enzyme phosphodiesterase (PDE) thus prevents the conversion of cAMP to 5'-AMP. The increased concentration of cAMP is responsible for the activation of protein kinase A resulting in bronchodilation by relaxing the smooth muscles and also by inhibiting histamine release from mast cells.\(^{44}\) (Fig. 6)

![Mechanism of action of xanthines](image)

**Fig. 6: Mechanism of action of xanthines**

The combination of xanthines with sympathomimetics gives maximum bronchodilator effect. Theophylline is indicated in case of non-response of $\beta_2$-adrenostimulants in severe asthma, as combination drug with $\beta_2$-stimulants orally in patients who cannot use aerosol.

The naturally occurring xanthines (1) such as caffeine (2), theobromine (3), theophylline (4) and other xanthines derivatives contain purine scaffold and known to exert significant physiological effects at very low doses and used from several years as pharmaceuticals, narcotics and stimulants.\(^{45,46}\)
Theophylline was the first xanthines used for the treatment of asthma followed by enprofylline and other xanthines derivatives. The theophylline was also found to be effective in treating refractory asthma by potentiation of HDAC2 (Histone deacetylase) activity at nuclear level. The increased HDAC2 activity blocks the transcription of pro-inflammatory genes. The various proposed mechanisms through which xanthines act are:

- Non-selective inhibition of phosphodiesterase
- Adenosine receptor antagonism at $A_1$, $A_{2A}$, $A_{2B}$-receptors
- Inhibition of Nuclear factor (NF) and phosphoinositide-3 kinase
- Increased secretion of IL-10
- Increased apoptosis of inflammatory cells
- Increase in histone deacetylase activity (HDAC2)
- Decreased activity of poly(ADP-ribose)polymerase-1

**ANTICHOLINERGICS**

Acetylcholine acts on the cells which release certain mediators for antigen-antibody reactions. Anticholinergics help in revealing reflexogenic bronchoconstriction due to noxious stimuli. Atropine, an effective bronchodilator, inhibits the bronchoconstriction due to dust, histamine and cough reflex.\(^{47,48}\) Atropine also decreases sputum production in asthmatics without decrease in viscosity.\(^{49}\)

An another atropine-like anticholinergic, Ipratropium bromide (SCH 1000) acts selectively on bronchial smooth muscles and is effective in chronic bronchitis.\(^{50}\) Its selectivity is based on its particular type of pharmacokinetics when inhaled.

**GLUCOCORTICOIDS**

They are life saving in the treatment of difficult asthma and act by several different mechanisms at cellular level. They are taken up by cells of target organ and binds to
specific receptor proteins in cytoplasm. The receptor and steroid complex so formed then transports to nucleus resulting in the synthesis of new mRNA molecules which initiates synthesis of a new type of protein, responsible for steroid mediated antiasthmatic effect. Corticosteroids usually act through gene activation and suppression. Glucocorticoid (GC) binds to its receptor (GR) in cytoplasm, resulting in conformational changes which release heat shock protein 90 (HSP-90) and then crosses nuclear membrane. The GC/GR complex binds to GRE (Glucocorticoid response element) on DNA and alters a number of transcription factors and kinases.51 This leads to transcription of two anti-inflammatory proteins such as glucocorticoid induced leucine zipper and mitogen activated protein kinase phosphatase-1 (MKP-1) thus inhibiting pro-inflammatory gene transcription.52,53

![Diagram of Mechanism of Action of Glucocorticoids (GCs)](image)

The pro-inflammatory genes such as nuclear factor-kappa B (NF-κB) and activating protein-1 (AP-1) are also inhibited by GR through histone deacetylase 2 (HDAC2).
HDAC2 causes deacetylation of GR thus forms a complex with NF-κB/AP-1 and inhibits their activity to transcribe pro-inflammatory genes.\textsuperscript{54} (Fig. 7)

The target cells for corticosteroid therapy are bronchial and vessel musculature, blood vessels, mucous glands, mast cells, white blood cells, connective tissues, motor and sensory nerve endings. Steroids stabilize the cell membrane; protect the smooth muscle cells and endothelium from further injury by mediators as high dose of cortisol inhibits the synthesis of prostaglandins.\textsuperscript{55,56} Steroids also inhibit monocytes in the blood which further form macrophages and increases cAMP level.\textsuperscript{57}

The commonly prescribed steroids are beclomethasone dipropionate, fluticasone propionate and budesonide, alone or in combination with long acting $\beta_2$-agonists (LABA). The two fixed combination as convenient controllers in persistent asthma are salmeterol/fluticasone and formoterol/budesonide. The use of oral CSs is limited because of possible side effects after absorption thus inhaled corticosteroids (ICSs) are commonly prescribed to treat bronchial asthma (BA) but they also show potential side effects at higher doses after absorption from lungs into systemic circulation.

Ciclesonide, a soft steroid in the form of inactive prodrug was developed which activates in response to esterases of airways, an approach which makes steroid available for systemic absorption only after it is taken by airway cells.\textsuperscript{58} It also has anti-inflammatory properties and extended lung-retention time.\textsuperscript{59}

Severe/refractory asthma is very difficult to treat and is a poorly controlled disease due to the development of steroid resistance. Steroid-resistance asthma is a subset of severe asthma defined as a failure to increase FEV1 (Forced Expiratory Volume) by 15% following a 7-day course of oral steroid therapy at a dose of 20 mg of prednisolone daily or equivalent.\textsuperscript{60} The development of steroid resistant may be due to defects in the ability of GR to bind drug and translocate into nucleus, increased activation of NF-κB/AP-1, abnormality in histone acetylation, increased production of pro-inflammatory cytokine (IL-17) due to Th17 cells resulting in neutrophil-predominant steroid-resistant asthma.\textsuperscript{61,62}
LEUKOTRIENE ANTAGONISTS

Anti-leukotrienes such as montelukast, pranlukast and zafirlukast and 5-lipoxygenase inhibitor, zileuton found to have clinical success in treating asthma but they are costly and less efficacious than corticosteroids and also cause liver toxicity.  

MAST CELL STABILIZER

_Disodium cromoglycate (DSCG)_

Experimentally induced asthma can be treated by inhalation of disodium Cromoglycate. DSCG is a bisacromon derivative, derived from a natural substance Khellin and has general pharmacological effects.

It acts by temporary stabilization of the membrane of the mast cells, prevents degranulation of mast cells and inhibits liberation of histamine by non-antigen stimuli. The membrane stabilization by DSCG inhibits calcium ion transport thus decreasing intracellular calcium ion concentration. This decrease in turn increases the level of cAMP causing relaxation of muscles.

DSCG also inhibits PDE more than twice as strongly as xanthines. It is believed to act by inhibiting calcium penetration in mast cells by increasing intracellular cAMP but it must have specific action on PDE of small fraction of lung i.e. mast cells.

DSCG shows best effect in case of type I allergy in children and is also highly effective in case of exercise induced asthma (EIA) and has moderate steroid-decreasing effect. The young patients with strong allergy and a variable pattern of post exercise bronchoconstriction shows best results on treatment with DSCG.

MISCELLANEOUS DRUGS

_PROSTAGLANDINS_

Prostaglandins are pro-inflammatory mediators and acts at various receptors as PGD₂, PGE₁, PGE₂, PGE₃, PGF₂ and PGI₂. Prostaglandin E₁ and E₂ relaxes human bronchial muscles and also reduces the contraction due to PGF₂α. PG’s act directly via cAMP not through blockade of β-receptors. PGD₂, a major product of cyclooxygenase pathway in mast cells, activates chemo-attractant receptors of Th2
cells and its antagonist, anti-DP agent, (\((Z)-7-[(1R,2R,3R,5S)-2-(5-hydroxybenzo-[b]-thiophen-3-ylcarbonylamino)-10-norpinan-3-yl]-hept-5-enoic acid\)), showed clear inhibition of allergic airway hyper responsiveness. Other PGs also play protective role such as EP3 agonist (PGE \(_2\) receptor 3), ONO-AE-248, (\(Z\)-7-[(1R, 2R, 3R)-3-methoxy-2-[(E, 3S)-3-1-enyl]-5-oxocyclopentyl]-hept-5-enoic acid and IP agonist (PGI \(_2\) receptor), beraprost.\(^70\) PG’s sometimes either cause bronchodilation or bronchoconstriction depending on the individual so they do not find much importance as therapeutic drugs in asthmatics.

**ANTIHISTAMINES**

They act as antagonists of the bronchoconstriction effect of histamine (H \(_1\) receptor) but they have restricted value even in extrinsic type of asthma.\(^71,72\) Recent discovery about expression of H \(_4\) receptors on mast cells, T cells and eosinophils raised possibility to the development of selective H \(_4\) receptor antagonists (JNJ7777120) but their therapeutic results are limited as they are unable to block other inflammatory mediators.\(^73\)

**ADRENOCORTICOTROPIC HORMONE (ACTH)**

ACTH in some cases has a better effect on asthma than oral steroids. It increases the amount of cAMP in bronchial muscles thus has direct relaxing effect on bronchial muscles. It is effective in the treatment of small children who are unable to use glucocorticoid aerosols.\(^74\)

**OTHER TARGETS FOR ASTHMA**

The treatment of asthma in acute stages should be aggressive and requires treatment with optimal doses of drugs which are directed against all factors. As a number of factors are involved in the pathogenesis of asthma, anti-asthmatic therapy can be targeted against any of the factors thus providing a large range of targets to treat asthma. The use of immunosuppressant like methotrexate, gold, cyclosporine, also had not achieved much benefit.\(^75\) Thus there is considerable scope to refine traditional guidelines on the use of inhaled therapies in asthma and there is a need for the development of novel therapeutic agents and newer strategies for the
betterment of existing therapies. The existing therapies for most forms of asthma includes the use of inhaled corticosteroids and LABAs but unfortunately it failed to give good control on the symptoms of asthma in a significant portion of asthmatics. There are a number of reasons why this traditional therapy failed in terms of efficacy and includes:

- Inappropriate timing of introduction of treatment
- Inadequate use of doses
- Poor understanding of different subgroups of asthmatics
- Patient incompliance to adhere to prescribed regimens
- Development of resistance

There is need for the introduction of novel therapies which are targeted specifically against components of inflammatory pathway. The three major approaches for the development of newer anti-asthmatic drugs are: improvement of existing class of effective drugs (ICs and LABAs but have systemic side effects), development of novel compounds and serendipity development. The first approach was applied by improving pharmacokinetics and increasing duration of action of existing drugs. The last approach needs lots of research while the second approach needs newer targets which includes anticytokines and chemokines therapy, monoclonal antibodies against IgE, TNF-α, thermal bronchoplasty and antifungal agents.

The inhibition of Th-2 associated cytokines, such as IL-4, IL-5, IL-9 and IL-13, are potential targets for the treatment of asthma. IL-4 monoclonal antibody blocks allergic response of airways improves FEV1 and decreases asthma exacerbations. The recombinant human IL-4, pitrakinra and monoclonal IL-4Rα antibody, dupilumab were shown to reduce the complications of asthma in patients on high dose of ICS/LABA. Another anti IL-5 human antibody, mepolizumab, found to decrease the recruitment of eosinophils in airways after allergen exposure. The humanized anti-IL-9 monoclonal antibody MEDI-528 and anti IL-13 antibody, lebrikizumab, were able to reduce the Th2 associated cytokine production but this treatment has very short duration of action.

The chemokine receptors also acts as potential targets for asthma therapy especially CCR3, against which antibody was developed but failed in phase II
clinical trials. Others are p38MAPK inhibitors which interfere the phosphorylation of
GR and decreases release of inflammatory mediators.\textsuperscript{78} Jun-N-terminal kinase
(JNK) inhibitors are also useful in asthma as they decrease steroid resistance.\textsuperscript{79}

An immunomodulator drug to treat imbalance between Th1/Th2 immune
response was methylmethionine sulfonium chloride (vitamin U) and its derivative
Suplatast (IPD) showed potent immunomodulating and anti-inflammatory activity in
the Th2-polarised immune response. It suppresses IgE antibody production, inhibits
eosinophilic inflammation and chloride ion channel activation on eosinophils. It is first
successful Th2 immunomodulator for allergic diseases.\textsuperscript{80,81} CpG-oligonucleotides
(ODNs) are another category of immunomodulators effective in preventing antigen-
induced asthma. They inhibit alteration of histological changes in airways.\textsuperscript{82}

Allergens are the main triggers in asthma which results in the production of
IgE leading to inflammation of airways due to the release of pro-inflammatory
cytokines by mast cells. A recombinant humanized monoclonal anti-IgE antibody,
Omalizumab was found to significantly reduce the level of free IgE by binding to Fc
region of its receptor. Omalizumab was found to be better tolerated with very few
side effects but the high cost associated limits its use. If more funding will be
available then this may become a promising therapy for severe asthma patients.\textsuperscript{83}

In response to allergy, mast cells also release TNF-\(\alpha\) either through IgE-
dependent mechanism or by autocrine mechanism. TNF-\(\alpha\) is responsible for the
activation of NF-\(\kappa\)B and activator protein-1. The most widely studied humanized
monoclonal antibody against TNF-\(\alpha\) is infliximab and anti-TNF receptor agent till
date is, Etanercept, but they are associated with higher risk of serious infections on
prolonged use.\textsuperscript{84}

Another target is airways itself and to reduce bronchoconstriction, bronchial
thermoplasty is used. It is an outpatient procedure in which controlled thermal
energy (65°C) is applied in consecutive sessions through a bronchoscope to reduce
smooth muscle mass of airways.\textsuperscript{85} It uses radiofrequency ablation by delivering
thermal energy through a bronchoscope containing a catheter with expandable
basket. On extension, it contacts the walls of targeted airways and depletes the
smooth muscle mass.
The exposure to allergenic fungi marks its presence in the sputum of airways of asthmatic patients thus establishing a link between sensitization by fungi and bronchial asthma.\textsuperscript{86} In a FAST (Fungal Asthma Sensitization Trial) study, sensitization of patients with fungal allergens followed by treatment with oral antifungal drug, itraconazole, improved the quality of life in asthmatics.\textsuperscript{87} But itraconazole is active against only few species of \emph{Aspergillus}, has variable absorption pattern and requires careful monitoring of treatment. It can be replaced with newer triazole antifungals with better oral bioavailability.\textsuperscript{88}

Atrial natriuretic peptide (ANP) on intravenous infusion gives bronchodilator response but is susceptible to enzymatic breakdown so the development of non-peptide agonists of ANP can be developed. Ularitide, a related peptide, developed successfully with longer duration of action, less susceptible to degradation and more potent than $\beta_2$-agonists.\textsuperscript{89}

Levcromakalim, a potassium channel opener, is an effective bronchodilator as it inhibits activation of sensory nerves thus inhibiting cough reflex but is associated with dose-limiting side effects such as postural hypotension and headache.\textsuperscript{90}

In asthmatics, there is an increased expression of inducible nitric oxide synthase (iNOS) thus increased concentration of nitric oxide in exhaled air of asthma patients.\textsuperscript{91} The development of the inhibitors of iNOS reduces levels of exhaled NO and is potent with long-lasting effect. The iNOS inhibitor SC-51 (L-$N^\beta$-1-iminoethyl lysine-5-tetrazole amide) is a produg which converts to its active metabolite, L-$N^\beta$-1-iminoethyl) lysine (L-NIL), \textit{in vivo} which reduces NO levels.\textsuperscript{92}

Mast cell tryptase is also responsible for the recruitment of eosinophils, stimulation of fibroblasts and also increases the response of airway smooth muscles to constrictors. Its inhibitor, APC366 and BMS-363131 are under development and are effective in nanomolar doses.\textsuperscript{93}

The pro-inflammatory signalling molecule NF-$\kappa$B, is responsible for the transcription of inflammatory genes. This transcription factor can be inhibited by $I\kappa$B (inhibitor of $\kappa$B), which in turn gets degraded by the activation of specific $I\kappa$B kinase (IKKs). The selective inhibitors of IKK and NF-$\kappa$B are currently under development but long term suppression of NF-$\kappa$B results in immune suppression of host.\textsuperscript{94}
Theohylline is the oldest treatment used for asthma but it acts by non-selective inhibition of phosphodiesterase (PDEs). Till date eleven families of PDE enzymes have been discovered. The main member of PDEs which is involved is inflammation is PDE4 so selective PDE4 inhibitors also make a new target for asthma therapy (Fig. 8). Roflumilast and cilomilast have been tested in asthmatics with better tolerance but are associated with unwanted side effects of nausea and vomiting. So the selective subtype PDE4 inhibitors should be developed as PDE4D is involved in vomiting while PDE4B is involved in inflammation.

![Fig. 8: Selective PDE4 inhibitors in asthma](image)

The anti-allergy drugs acts as another approach to inhibit allergen induced diseases. These include cromones and furosemide, both acts by inhibiting chloride channels that are expressed in mast cells and sensory nerves. Various approaches are possible for asthma but still there are only few drugs in past 30 years that have reached clinic. There is a need to understand completely about the accurate phenotype of asthmatic patients so that each patient will receive the appropriate therapy and also maximize the pathway for the development of newer drugs.

**Xanthine and its derivatives**

The antiasthmatic drug development is mostly based on three main classes of drugs: sympathomimetics, corticosteroids and xanthines. The various new sympathomimetics and corticosteroids with increased specificity have been introduced till date. The last class, xanthines still represents as a prototype for new
drug development. Xanthines usually act by inhibiting the enzyme phosphodiesterase and also by antagonism at adenosine receptors. The research on xanthines had brought into focus the various other sites of action like inhibition of histone deacetylase activity, inhibition of nuclear factor which focused the attention of researchers on this moiety again.

The basis for the popularity of xanthine and methylxanthine containing beverages has been the ancient belief that these beverages possess stimulant action which results in elevated mood, decreased fatigue, increased work capacity and awakensness. Naturally occurring xanthines belongs to the group of purine alkaloids. Among them, caffeine was isolated from fruits of *Coffea arabica*, seeds of *Theobroma cacao* which also contain theobromine and other volatile components responsible for aroma. *Thea sinensis* belonging to the family *Ternstroemiaceae*, cultivated in India, Sri Lanka, Japan and other countries, contains caffeine and named as “thein” which was further renamed as theophylline, a dimethylxanthine. Theophylline is chemically related to natural metabolite, xanthine. H.H. Salter made an important contribution in reporting the value of xanthines in asthma.

![Structure of Theophylline](image)

Earlier research was based on synthesizing the theophylline derivatives by retaining methyl groups at 1st- and 3rd-positions. To increase the water solubility, polar substituents were introduced at 7th-position but results in reduced potency than theophylline. Further substitutions and their pharmacological profile led to a structure-activity relationship studies which indicates the development of more potent xanthine derivatives by increasing the carbon chain at 3rd-position upto three carbons (Enprofylline, 5) while keeping the methyl group at 1st-position (Fig. 9).
Fig. 9: Structure activity relationship of xanthines

The SAR studies represented in Fig. 9 clearly indicates that the substitutions at 7th- and 9th- position results in loss of potency and activity whereas substitutions at 1-, 3- and 8- position showed development of more potent compounds.\textsuperscript{102} The metabolism of xanthines usually takes place at 8th-position by oxidation to uric acids. The introduction of certain groups at 8th-position will increase the stability of xanthines.

The increased alkyl chain length at 3rd-position resulted in enhanced bronchorelaxing potency (enprofylline) and is associated with the inhibition of cyclic AMP phosphodiesterase.\textsuperscript{103} They produces a great variety of extra-pulmonary effects, to minimize these, there is a great need of significant drug development within xanthines.

Xanthines are considered as “side door bronchodilators” because their actual mechanism of action is not known.\textsuperscript{104} Xanthines usually contain attachments of methyl group thus also known as methyl-xanthine. Xanthines possess a number of physiological effects such as CNS stimulation, cardiac muscle stimulation, diuresis, bronchial, uterine and vascular smooth muscle relaxation, peripheral and coronary
vasodilation and cerebral vasoconstriction. Caffeine also causes tachycardia and cerebral vasoconstriction which is associated with the treatment of headache in migraine. The methyl xanthines are also considered as the first line drugs to stimulate breathing for the treatment of apnea of prematurity specially citrate salt of caffeine as it can penetrates cerebrospinal fluid easily and has higher therapeutic index with minimum number of side effects. The main action of theophylline is not due to bronchodilator effect but due to stimulation of contraction in respiratory muscles which results in the prevention of fatigue on muscles with increased resistance. It also inhibits PDE3 and PDE4 in pro-inflammatory cells and tissues to give anti-inflammatory and bronchoprotective effect.

Xanthines perform a number of pharmacological actions which are of therapeutic importance. The methylated xanthines are usually associated with smooth muscle bronchodilation in bronchi.\textsuperscript{105} Theophylline is a CNS stimulant, decreases peripheral resistance and stimulates heart to increase the perfusion of most organs. It also causes diuresis due to renal vasodilation and its direct effect on tubules. Thus can be used in the treatment of CHF, angina and also as a diuretic. Theophylline is associated with a number of side effects and drug interactions thus limiting its use. It is rapidly absorbed but food usually affects its rate of absorption whereas extent of absorption is not affected. Theophylline is not only a bronchodilator but also possess anti-inflammatory properties. Its use is limited due to toxicity profile but today it is a topic of research due to its anti-inflammatory properties. Theophylline and preparations containing them are indicated to produce bronchodilation, relaxes bronchial muscles, and improves pulmonary functions.

The precise mechanism of anti-asthmatic effect of xanthines and its derivatives is not clearly understood but the proposed mechanisms are inhibition of enzyme phosphodiesterase (PDE) and antagonism at adenosine receptors.

Xanthines usually act by inhibiting the enzyme phosphodiesterases (PDE) which in turn increases intracellular cyclic AMP (cAMP) resulting in the relaxation of bronchial smooth muscles. PDE is a generic term used for 11 distinct families all of which differ in substrate specificity, inhibitor sensitivity and cofactor requirements. Among these all PDE4 inhibitors are thought to contribute towards anti-asthmatic
effect by blocking the degradation of cAMP. The elevated cAMP levels led to bronchodilation along with inhibition of mast cell mediator release, inhibition of basophil and neutrophil degranulation and inhibition of macrophage activation. In humans, PDEs are encoded by 21 genes over 60 isoforms with several residues of amino acids. The variations in the amino acid sequence are responsible for substrate specificity, pharmacology and catalytic efficacy giving rise to different isoenzyme from PDE1 to PDE11. They are classified based on their specificity to cAMP, cGMP and towards both. The PDE4 isoenzyme specific to cAMP have four isoforms from PDE4A to PDE4D. The PDE4A, B and D are found in inflammatory cells while PDE4C is expressed in CNS, testis and skeletal muscles. Theophylline is a weak and nonselective inhibitor of PDE4 which explain its side effects due to its association with other PDE enzymes. In recent years, other xanthines derivatives were identified with improved selectivity and acceptable PDE4 activity.

Adenosine, a purine nucleoside, acts by stimulating A\textsubscript{1} (high affinity) and A\textsubscript{2} (low affinity) receptors where A\textsubscript{1} stimulation inhibits cAMP and A\textsubscript{2} stimulation increases cAMP. Theophylline is a potent inhibitor of both A\textsubscript{1} and A\textsubscript{2} receptors. The ability of theophylline and its derivatives to block adenosine receptors had attracted great attention these days. Today, 8-substituted xanthines are in studies for their inhibitory effect on physiological and pharmacological actions of adenosine. Thus representing xanthines as a new structurally rigid scaffold for combinatorial chemistry.

Xanthines act by the inhibition of enzyme PDE but the correlation between PDE inhibition and the relaxation of bronchial smooth muscles is weak in vitro. So an additional pharmacological effect of substituted xanthines that has aroused interest of researchers is the antagonism of the receptor mediated effects of purine nucleoside, adenosine.

Adenosine is a naturally occurring purine nucleoside formed from the cleavage of AMP by the enzyme 5'-nucleotidase. AMP in turn mainly derives from ATP and also by cleavage of cAMP. Adenosine acts as a pharmacological mediator between concentrations from 0.01\textmu m to 10 \textmu m. It affects physiological process
through interaction with specific extracellular cell surface receptors namely $A_1$ and $A_2$ where $A_1$ receptors has high affinity for adenosine, usually stimulated by $N^6$-substituted adenosine analogues and are found in fat cells, brain cells and heart while $A_2$ receptors has low affinity for adenosine, usually stimulated by 5'-substituted adenosine analogues and are found in brain, cardiac muscle, airways smooth muscle, gastrointestinal smooth muscle and presynaptic nerve terminals. $A_1$ is inhibitory while $A_2$ is stimulatory to adenylate cyclase. Adenosine has a very short half life (1.5 s) as it metabolizes easily to inosine (Fig. 10). Except $A_1$ and $A_2$, it also interacts with $A_3$ receptors whereas $A_2$ receptors have two subtypes namely $A_{2a}$ and $A_{2b}$. The $A_{2a}$ receptors are involved mainly in mediating various inflammatory and immunological responses while $A_{2b}$ receptors are mainly implicated in mast cell activation, asthma, vasodilation, regulation of cell growth, intestinal functional and modulation of neurosecretion.

![Fig. 10: Metabolism of adenosine](image)

Adenosine in its stable form as AMP produces bronchoconstriction in asthmatics but not in normal individuals. Adenosine elicits hyperactive airways response in allergic asthmatics by interaction with adenosine receptors. All the adenosine receptors acts as important targets for drug development in asthmatic patients.

Theophylline and other substituted xanthines are competitive inhibitors at $A_1$ and $A_2$ receptors. Enprofylline, 3-propylxanthine was found to posses potent PDE inhibitory activity but without any effect on adenosine receptors. Further studies were conducted to elucidate the effect of enprofylline on adenosine-induced contraction of airways. Enprofylline has been demonstrated to be more potent
than theophylline as $A_2$ adenosine antagonist. Certain evidences also suggest that CNS, CVS and renal effects (diuretic) of methyl xanthines are through the adenosine antagonism not through PDE inhibition.$^{120-121}$

Adenosine induces the release of certain IgE-dependent mediators from human mast cells and basophil thus resulting in bronchoconstriction.$^{122}$ Bronchoconstriction by adenosine in asthma is a result of direct effect of this nucleoside on airways of asthmatics. The methyl xanthines are found to posses pharmacological actions in asthmatics but the action produced by antagonism of adenosine is worth to study.$^{123}$

Adenosine receptors thus act as a very important target for the management of certain conditions such as asthma, refractory primary pulmonary hypertension, ischemia, reperfusion injury, sepsis, epilepsy and inflammatory bowel diseases. All these conditions can be controlled by specific agonists/antagonists of adenosine, few of which are already under clinical trials as in table 3.

**Table 3: Adenosine agonist/antagonist under clinical trials**

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<tr>
<td>5</td>
<td><img src="" alt="Istradefylline (KW6002)" /></td>
<td>Ongoing</td>
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</tr>
</tbody>
</table>

**A3 receptor agonist**

**A1 receptor antagonist**

**A2A receptor antagonist**