# Overview of Allergic Disorders with Focus on Bilastine

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## Allergic Disorders: An Overview

Allergic disorders, such as allergic rhinitis and urticaria, are common worldwide; and the prevalence is constantly increasing. Allergic disorders constitute a significant cause of morbidity, such that presence of one allergic disorder has been found to increase the risk of other allergic disorders affecting different organ systems. Allergies and related diseases including asthma, rhinosinusitis, and atopic dermatitis affect at least 30% of the population and nearly 80% of families. These disorders have a detrimental effect on patients' physical, psychological, social, educational, and work functioning, with huge socioeconomic implications for healthcare systems and also for the society.[1-3]

## Burden of Allergic Disorders

### *Allergic Rhinitis*

Allergic rhinitis (AR) is an allergic disorder that is frequently encountered in primary care. AR, having characteristic symptoms of nasal congestion, clear rhinorrhea, sneezing, postnasal drip, and nasal pruritus, has a marked detrimental effect on the affected individual's sleep, social life, quality of life, and attendance and functioning at school and work. Apart from the nasal symptoms, patients with AR may also present with associated allergic conjunctivitis, non-productive cough, Eustachian tube dysfunction, and chronic sinusitis.[4,5]

AR often has long-term physical consequences on the affected population. The disease *per se* is a well known risk factor for a myriad of disease conditions such as asthma, sinusitis, otitis media, nasal polyposis, respiratory infections, and even orthodontic malocclusions. Among the known comorbidities, asthma appears to have the strongest link with AR.[6-10]

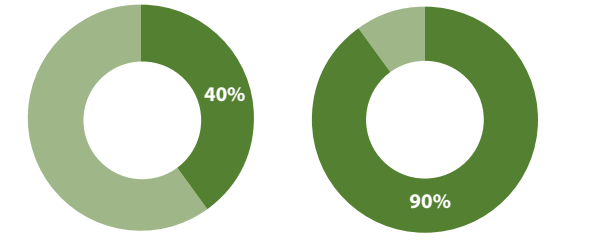
### *Epidemiology of Allergic Rhinitis*

Allergic rhinitis, with a prevalence estimated at 10-30%, affects the lives of more than 500 million people worldwide. The burden is particularly high and increasing in Asia Pacific, where many people now live in overpopulated cities with high levels of environmental pollution.[5] The incidence of AR in the pediatric population is also quite high; epidemiological studies suggest that AR affects up to 40% of children, thus making it one of the most common chronic pediatric disorders. Seasonal allergic rhinitis (SAR) seems to be more common in the pediatric age group, whereas perennial AR is more prevalent in adults.[4,11,12] The prevalence of AR has been gradually increasing in India over the past few decades. It is estimated that AR affects 20–30% of the Indian population with 15-20% of them also developing asthma. AR and asthma coexist in 70–80% of Indian patients. Allergic rhinitis has been reported to have a significant adverse impact on health-related quality of life in Indian patients.[13-15]

## Coexistence of Allergic Rhinitis and Asthma

Previously, AR was considered a disease process of the nasal airway alone. Of late, however, the unified airway theory classifies AR as a component of systemic allergic response,

**Figure 1: Coexistence of allergic rhinitis and asthma**




with other associated conditions, such as asthma, sharing a core systemic pathology.[4] There is ample evidence to suggest a strong relationship between AR and asthma. In fact, AR and asthma appear to be interrelated at the epidemiologic level as well as at the pathophysiologic level.[16-18] It is estimated that up to 40% of patients with AR have asthma while nearly 90% of asthmatic patients exhibit symptoms of AR (Figure 1).[9,10]

### *Allergic Rhinitis and Asthma in Indian Population*

An increasing prevalence of AR and asthma has also been reported in the Indian subcontinent.[19] A recent questionnaire-based survey – Coexistence of Allergic Rhinitis and ASthma (CARAS) survey – highlighted the high prevalence of concomitant AR in Indian patients with asthma and revealed the prevalence of coexisting AR to be 65.24%, with the highest prevalence (80%) in the southern regions of India. Males were found to have a higher prevalence of concomitant AR-asthma as compared to females.[20]

### *Allergic Rhinitis as a Risk Factor for Asthma*

Epidemiological evidence suggests that patients with AR have a three-fold increased risk of developing asthma than healthy people. Interestingly, the relief of rhinitis symptoms over time correlates with the improvement of asthma symptoms. Patients with more severe and persistent AR are at a higher risk of developing asthma. According to the Allergic Rhinitis and its Impact on Asthma (ARIA) study, allergic and non-allergic rhinitis should be considered risk factors for asthma, along with other known risk factors.[18,21]

## Role of Histamine and the H1 Receptor Subtype in Allergic Disorders

Histamine plays a key role in the pathophysiology of allergic inflammation. After exposure to an allergen, specific antibodies of the immunoglobulin E (IgE) type are produced in genetically predisposed individuals. These interact with receptors on the surface of basophils and mast cells, ultimately leading to the release of histamine and other inflammatory mediators. The consequences of histamine release lead to, among other things, erythema, flushing, nasal congestion, and pruritus. These allergic responses are primarily mediated by the histamine receptor subtype H1.[5]

Antihistamines are not competitive antagonists of histamine binding to H1 receptors; rather, antihistamines bind to different sites from histamine on H1 receptors. Therefore, these antihistamines are inverse agonists rather than receptor antagonists. They are referred to as 'H1 antihistamines' rather than 'histamine antagonists' H1 antihistamines, after binding to H1 receptors, interfere with histamine action on sensory neurons and small blood vessels, directly downregulating allergic inflammation. This downregulation also takes place indirectly through transcription factor nuclear factor-κB and through calcium ion channels.[5]

## Management Considerations for Allergic Rhinitis

Considering the central role of histamines in eliciting the allergic symptoms through H1-receptor, H1-antihistamines have been the most utilized class of medications for the treatment of allergic diseases including AR.[22,23]

### *Properties of the Ideal Antihistamine*

The ARIA guidelines provide a detailed list of 'properties that should be met by oral H1-antihistamines', as described in Table 1. In this context, bilastine – a novel, second-generation H1 antihistamine – has the highest number of desired features for a modern antihistamine according to international ARIA guidelines.[5]

## Bilastine: A potent Antihistamine

Bilastine is a novel, second-generation H1 antihistamine chemically belonging to the piperidine-benzimidazole

| Table 1: Properties of an ideal oral H1 antihistamine | | |
|---|---|---|
| **Pharmacological properties** | **Efficacy** | **Side effects** |
| Potent and selective activity at H1 receptors<br>Other anti-allergic activity | Effective in both intermittent and persistent allergic rhinitis | Devoid of sedation or cognitive or psychomotor impairment |
| No clinically relevant pharmacokinetic interactions with food, medication, or intestinal proteins | Effective against all nasal symptoms, including obstruction | No anticholinergic activity<br>No weight gain |
| No interaction with cytochrome P450 | Improves ocular symptoms | No cardiac safety concerns |
| No interaction with other diseases (thus avoiding toxic reactions) | Studies warranted in young children and elderly patients to assess efficacy | Potential use in pregnancy and breastfeeding |

subgroup. It is highly selective for H1-receptor and its affinity to other receptors such as cholinergic, adrenergic, or serotoninergic receptors is much lower than that to H1-receptor. Bilastine is approved for the symptomatic treatment of AR and rhino-conjunctivitis (seasonal and perennial) and urticaria in adults. Bilastine not only possesses H1-antihistamine activity but also exerts some antiallergic activities.[5,15,23-25]

### *Pharmacokinetic Properties of Bilastine*

Bilastine, following oral administration, is rapidly absorbed with a bioavailability of around 60%. Onset of antihistaminic action starts within 30 minutes with the maximum clinical effect persisting from 30 minutes to 8 hours. Bilastine does not interact significantly, either as an inhibitor or as an inducer, with the cytochrome P450 system and consequently is unlikely to be involved in drug-drug interactions. It does not undergo presystemic hepatic metabolism and has no active metabolites. Bilastine has shown a high affinity for the P-gP efflux pump which restricts transit across the blood brain barrier. At therapeutic doses bilastine lacks sedative effects; it does not affect psychomotor performance or driving performance, and it does not interact with alcohol or lorazepam. Bilastine exerts anti-inflammatory actions beyond its antihistaminic effects. Oral bilastine can be administered to patients independently of glomerular filtration rate. No dosage adjustments are needed in patients with mild, moderate, or severe renal impairment (Box 1).[5,15,24-26]

**Box 1: Properties of bilastine**

- Potent and selective activity at H1 receptors
- Rapid onset and long duration of action
- Lack of sedation and cognitive impairment
- Does not affect psychomotor performance or driving performance
- Does not interact with alcohol or lorazepam
- No cardiac safety concerns, and no potential for tachyphylaxis
- Does not undergo presystemic hepatic metabolism
- Does not interact with the cytochrome P450 system
- Unlikely to be involved in drug-drug interactions
- Exerts anti-inflammatory actions beyond its antihistaminic effects

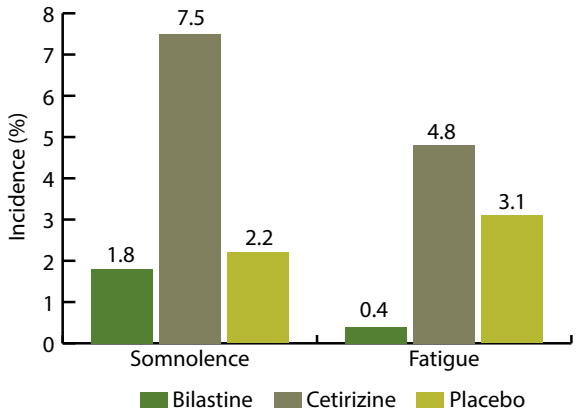
## Evidence-Based Efficacy in Allergic Rhinitis

### *Comparative Analysis of Bilastine Versus Cetirizine in Treatment of Seasonal Allergic Rhinitis*

Kuna *et al*[27] conducted a study to compare the efficacy and safety of bilastine versus cetirizine and placebo in relieving the symptoms of seasonal AR. A total of 683 patients with SAR were randomized to a double-blind treatment with bilastine 20 mg, cetirizine 10 mg, or placebo, once daily for 14 days. Patients were asked to record reflective (over the past 12 h) and instantaneous nasal (obstruction, rhinorrhea, itching and sneezing) and non-nasal (ocular tearing, redness and itching) symptom scores (NSS and NNSS, respectively) in the morning and in the evening, to provide reflective and instantaneous total symptom scores (TSS). The primary efficacy measure was the area under curve (AUC) of reflective TSS over 14 days of treatment (TSS-$AUC_{0\text{-}14\ days}$). The results revealed the following:

- Both bilastine 20 mg and cetirizine 10 mg significantly reduced the TSS-$AUC_{0\text{-}14\ days}$, compared with placebo (76.5, 72.3 and 100.6, respectively; $P<0.001$)

**Figure 2: Incidence of treatment-emergent adverse events with bilastine versus cetirizine and placebo**




- Likewise, bilastine and cetirizine were significantly superior to placebo for all secondary outcomes
- Importantly, although all treatments were well tolerated, the incidence of adverse events was significantly lower in the bilastine 20 mg-treated group than in the cetirizine 10 mg-treated group (Figure 2).

Findings of this study demonstrate that bilastine 20 mg once daily was significantly superior to placebo and comparable to cetirizine 10 mg in relieving symptoms of SAR. Since it demonstrated a significantly better adverse event profile than cetirizine, it could be suggested that bilastine may have a more favorable safety profile, and therefore possibly a better therapeutic index, compared with cetirizine.[27]

### *Comparative Efficacy of Bilastine Versus Cetirizine and Fexofenadine in Relieving the Symptoms of Allergic Rhinitis*

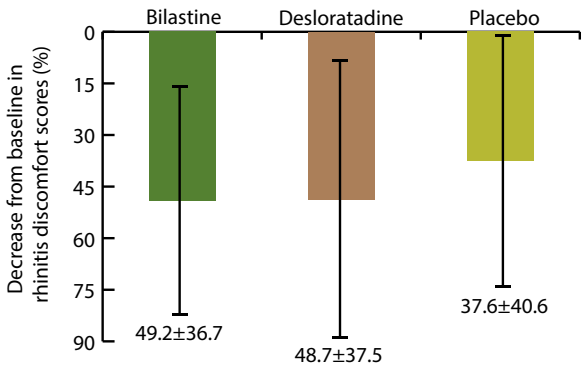
Horak *et al*[28] conducted a double-blind cross-over study to compare the efficacy of bilastine, cetirizine, and fexofenadine on allergen-induced nasal and ocular symptoms in patients exposed to aeroallergen in the Vienna Challenge Chamber (VCC). A total of 75 allergic volunteers were challenged with grass pollen in the VCC on two consecutive days of allergen provocation; 6 h on day 1 and 4 h on day 2. Bilastine 20 mg, cetirizine 10 mg, fexofenadine 120 mg, or placebo was administered orally 2 h after the start of provocation on day 1 only. The results revealed a rapid onset of action with bilastine, within 1 h, and a long duration of action; greater than 26 h. Outcomes with cetirizine were similar. Efficacy of fexofenadine, although similar on day 1, was reduced on day 2, suggesting a shorter duration of action. Bilastine was found to be safe and well tolerated.

### *Comparative Analysis of Bilastine Versus Desloratadine in Treatment of Seasonal Allergic Rhinitis*

A study[31] was conducted to compare the efficacy and safety of a single daily dose of 20 mg bilastine vs placebo and desloratadine 5 mg in patients with SAR. The results revealed the following:

- Bilastine 20 mg progressively improved the symptoms of allergic rhinitis from baseline levels over a period of 2 weeks
- The AUC of total symptom score [TSS; composed of nasal and nonnasal symptom scores (NSS and NNSS, respectively)] was decreased to a greater extent from baseline in the bilastine 20 mg-treated group versus the placebo-treated and the desloratadine-treated group (98.4 versus 118.4 versus 100.5, respectively)
- At day 14, bilastine 20 mg led to markedly greater decreases from baseline in mean rhinitis discomfort scores (-49.2% ± 36.7%), compared with placebo (-37.6% ± 40.6%) and desloratadine 5 mg (-48.7% ± 37.5%); Figure 3

**Figure 3: Decreases from baseline in rhinitis discomfort scores with bilastine versus desloratadine versus placebo in patients with seasonal allergic rhinitis**



- Bilastine 20 mg improved the QOL of patients, as measured by the rhinoconjunctivitis quality of life questionnaire (RQLQ). The total RQLQ score was significantly reduced from baseline by a value of 1.6 in the bilastine 20 mg-treated group as well as desloratadine 5 mg-treated group compared with a value of 1.3 in the placebo-treated group
- Bilastine 20 mg was not different from desloratadine 5 mg but significantly more effective than placebo in improving the NSS, NNSS, and rhinitis-associated discomfort scores and four out of seven individual domain scores.

Thus, it could be concluded that although bilastine and desloratadine were equally efficacious in the treatment of SAR, bilastine may have a slightly more favorable safety profile.

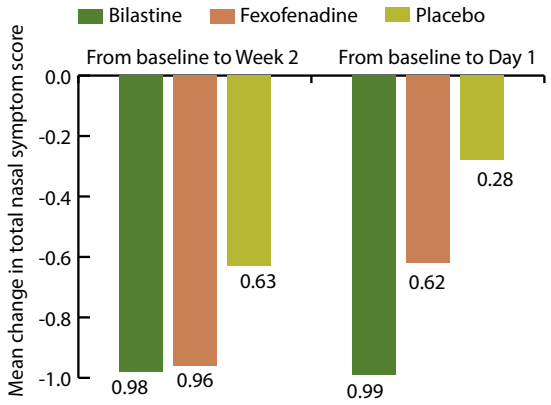
### *Comparative Efficacy and Safety of Bilastine 20 Mg Versus Cetirizine 10 Mg in the Treatment of Perennial Allergic Rhinitis*

- Sastre *et al*[30] conducted a multicenter, randomized, placebo-controlled, double-blind, parallel-group study, that aimed to demonstrate the efficacy and safety of bilastine in patients with perennial AR. Patients with symptomatic PAR (n = 650) were prescribed bilastine 20 mg, cetirizine 10 mg, or placebo once daily for 4 weeks. The primary efficacy outcome was the mean AUC of reflective total 6-symptom scores (rT6SS) from baseline visit to day 28 (D28).
- Considerable differences were observed between active treatments and placebo in the mean AUC of rT6SS and instantaneous total 4-nasal symptom scores (T4NSS), from baseline to day 28 visit for the intent-to-treat population. Findings of this study helped conclude that bilastine and cetirizine were similarly effective; and more effective than placebo, during a 4-week treatment period in patients with PAR. Moreover, bilastine was found to be safe and well-tolerated over a 1-year treatment period.

### *Efficacy and Safety of Bilastine in Patients with Perennial Allergic Rhinitis*

Okubo and colleagues[31] conducted a randomized, double-blind, placebo-controlled, parallel-group, phase III study

**Figure 4: Mean change in total nasal symptom score with bilastine, fexofenadine, and placebo in patients with perennial allergic rhinitis**




to evaluate the effect of a 2-week treatment period with bilastine, fexofenadine, or a matched placebo in patients with PAR. Primary endpoint was the mean change in total NSS (TNSS) from baseline to Week 2. A total of 765 patients were randomly prescribed bilastine (20 mg once daily; n=254), fexofenadine (60 mg twice daily; n=254), or a matched placebo (n=255).

- The result of the primary endpoint analysis revealed a significant decrease in the mean change in TNSS from baseline at Week 2 in bilastine (−0.98) versus the placebo group (−0.63).
- The estimated mean change in the TNSS was −0.96 in fexofenadine group. Importantly, the mean change in TNSS from baseline on Day 1 was more significantly decreased by bilastine (-0.99) than by placebo (-0.28) or fexofenadine (-0.62) (Figure 4).
- Also, there was improvement in instantaneous TNSS 1 h after the first and before the second drug administration on Day 1.

Findings of this study suggest that bilastine 20 mg administered once daily for 2 weeks exhibits a rapid onset of action and may offer an effective and well tolerated therapeutic option for patients with PAR.

### *Comparative Efficacy and Safety of Bilastine Versus Levocetirizine in the Treatment of Allergic Rhinoconjunctivitis*

Sharma *et al*[32] conducted a prospective study to evaluate the efficacy and safety of bilastine 20 mg

**Figure 5: Effect of bilastine versus levocetirizine on total symptom score in patients with allergic rhinoconjunctivitis**

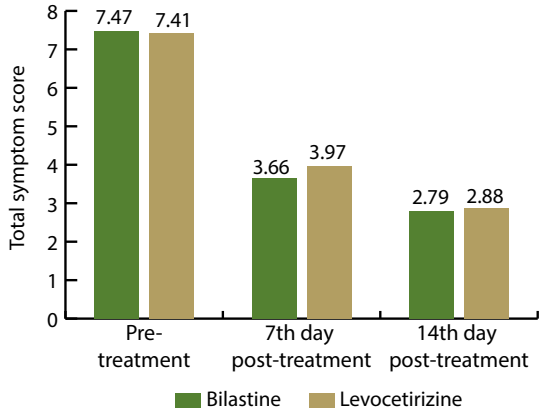
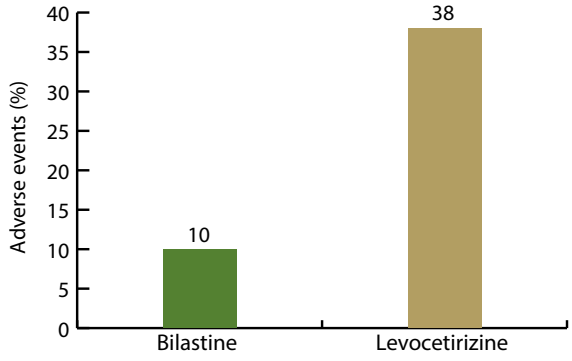



**Figure 6: Adverse events reported with bilastine versus levocetirizine in patients with allergic rhinoconjunctivitis**




versus levocetirizine 5 mg in the treatment of allergic rhinoconjunctivitis. A total of 100 patients with chronic allergic rhinoconjunctivitis were prescribed either bilastine 20 mg (n=50) or levocetirizine 5 mg (n=50) once daily for 2 weeks. The primary efficacy parameter for assessment was a reduction in TSS after 7th and 14th day of treatment.

- Both bilastine 20 mg and levocetirizine 5 mg markedly reduced the TSS on the 7th and 14th post-treatment days (Figure 5).
- Importantly, a total of 38% patients in the levocetirizine group reported adverse events as compared to 10% patients in the bilastine group (Figure 6).

Findings of this study suggest that bilastine has good efficacy and a more favorable safety profile than another second-generation H1 antihistamine, thus it may be used as a first-line treatment for allergic rhinoconjunctivitis.

### *Long-term Safety and Efficacy of Bilastine in Patients with SAR or PAR*

An open-label, single-arm, phase III study[33] was conducted to evaluate the safety and efficacy of long-term treatment with bilastine in patients with SAR or PAR. A total of 58 patients with SAR and 64 patients with PAR were administered bilastine (20 mg/day) for 12 weeks (treatment period). A total of 55 patients with PAR who met the transition criteria continued the bilastine treatment for an additional 40 weeks.

- In patients with SAR, bilastine markedly decreased the TNSS, total ocular symptom score (TOSS), and total symptom score (TSS) relative to baseline.
- Importantly, in patients with PAR, prolonged treatment with bilastine resulted in the maintenance of a significant reduction in TNSS, TOSS, and TSS from baseline.
- Quality of life was also improved in patients with SAR and PAR.
- During the 12-week treatment period, adverse events (AEs) were reported by 17.2% of patients with SAR and by 31.3% of patients with PAR; and adverse drug reactions (ADRs) were reported by 6.3% of patients with PAR but by no patients with SAR.
- All of the ADRs were mild in severity.
- No deaths were reported and no patient withdrew from the study because of AEs.

Findings of this study helped conclude that bilastine is a safe, well tolerated, and effective treatment option for patients with SAR and PAR.

## Conclusion

Allergic disorders constitute a significant cause of morbidity worldwide, such that presence of one allergic disorder has been found to increase the risk of other allergic disorders affecting different organ systems.

Allergic rhinitis is a frequently-encountered allergic disorder that is often undiagnosed or inadequately treated. Untreated and inadequately treated allergic rhinitis can substantially impair quality of life. Histamine plays a key role in the pathophysiology of allergic inflammation. Considering the central role of histamines in eliciting the allergic symptoms through H1-receptor, H1-antihistamines have been the most utilized class of medications for the treatment of allergic diseases including AR. Bilastine is a potent and specific H1-antihistamine that is approved for the symptomatic treatment of AR and rhino-conjunctivitis (seasonal and perennial) and urticaria in adults. Bilastine not only possesses H1-antihistamine activity but also exerts some antiallergic activities. Bilastine has a rapid onset and longer duration of action than other antihistamines. Unlike other antihistamines, bilastine does not have sedative side effects. A growing pool of evidence has suggested the efficacy of bilastine in treatment of allergic rhinitis with no significant suppressive effect on central nervous system.

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