

Selecting the Optimal Oral Antihistamine for Patients with Allergic Rhinitis

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Abstract

Allergic rhinitis (AR) is now recognised as a global health problem that affects 10–30% of adults and up to 40% of children. Each year, millions of patients seek treatment from their healthcare provider. However, the prevalence of AR may be significantly underestimated because of misdiagnosis, under diagnosis and failure of patients to seek medical attention. In addition to the classical symptoms such as sneezing, nasal pruritus, congestion and rhinorrhoea, it is now recognised that AR has a significant impact on quality of life (QOL). This condition can lead to sleep disturbance as a result of nasal congestion, which leads to significant impairment in daily activities such as work and school. Traditionally, AR has been subdivided into seasonal AR (SAR) or perennial AR (PAR). SAR symptoms usually appear during a specific season in which aeroallergens are present in the outdoor air such as tree and grass pollen in the spring and summer and weed pollens in the autumn (fall); and PAR symptoms are present year-round and are triggered by dust mite, animal dander, indoor molds and cockroaches. Oral histamine H₁-receptor antag-

onists (H₁ antihistamines) are one of the most commonly prescribed medications for the treatment of AR. There are several oral H₁ antihistamines available and it is important to know the pharmacology, such as administration interval, onset of action, metabolism and conditions that require administration adjustments. When prescribing oral H₁ antihistamines, the healthcare provider must take into account the clinical efficacy and weigh this against the risk of adverse effects from the agent. In addition to the clinical efficacy, potential for improvement in QOL with a particular treatment should also be considered.

Allergic rhinitis (AR) is now recognised as a global health problem that affects 10–30% of adults and up to 40% of children.^[1] Each year, there are millions of office visits for AR and its complications, such as sinus disease and otitis media with effusion. However, the prevalence of AR may be underestimated because of misdiagnosis, under diagnosis and failure of patients to seek medical attention.^[2-4]

AR is a disorder of the nasal tissue caused by IgE-mediated inflammation and manifests clinically as sneezing, itching, rhinorrhoea and nasal obstruction.^[3,5] Ocular symptoms including pruritus, oedema and lacrimation are also commonly associated with AR. In addition to the classical symptoms, it is now recognised that AR has a significant impact on the quality of life (QOL) of those who experience it. A major condition commonly encountered as a result of AR is sleep disturbance. Failure to get a good night's sleep as a result of symptoms of AR can cause significant impairment in daily activities such as work and school.^[1,6,7] The vast majority of patients with asthma have AR. Several studies have also shown severe rhinitis symptoms in patients with asthma was associated with worse asthma outcomes.^[8-10]

Traditionally, AR has been subdivided into seasonal AR (SAR) or perennial AR (PAR). SAR symptoms usually appear during a specific season in which aeroallergens are present in the outdoor air such as tree and grass pollen in the spring and summer and weed pollens in the autumn (fall); and PAR symptoms are present year-round and are triggered by dust mite, animal dander, indoor molds and cockroaches.^[3] The recent Allergic Rhinitis and its Impact on Asthma (ARIA) recommendations, com-

posed of a panel of experts in conjunction with the WHO, have proposed a new classification for AR.^[5] These guidelines were intended to educate healthcare providers and aid in the diagnosis and treatment of AR on the basis of symptom duration and severity. However, it was shown that the classic types of seasonal and perennial rhinitis cannot be used interchangeably with the new classification of intermittent/persistent, because they do not represent the same stratum of disease.^[4] Furthermore, to date all clinical trials have utilised SAR and PAR.

Treatment of AR includes avoidance of allergic triggers, the use of pharmacological agents and allergen specific immunotherapy. There are numerous pharmacological agents available to help control AR. These include oral first- and second-generation histamine H₁ receptor antagonists (H₁ antihistamines), intranasal antihistamines, intranasal corticosteroids, leukotriene receptor antagonists, mast cell stabilisers, intranasal anticholinergics, and oral and intranasal decongestants. Oral H₁ antihistamines and intranasal corticosteroids are recommended as first-line therapy.^[1,2,5,11] This review focuses on oral H₁ antihistamines and helps to guide the healthcare provider in selecting the most appropriate oral H₁ antihistamine based on favourable effects including rapid onset of action, low potential for drug interaction and improvements in QOL and avoidance of undesired side effects such as sedation and dry mouth.

1. Pathophysiology of Allergic Rhinitis

The tendency to develop a T helper type 2 (Th₂) cell immune response is inherited in atopic patients.^[3] Sensitisation to specific inhalant allergens

occurs when they are presented by antigen presenting cells to CD4+ T cells that belong to the Th₂ subset, leading to the production of interleukin (IL)-3, IL-4, IL-5, IL-13 and other Th₂ cytokines. These cytokines stimulate B cells to become plasma cells, which produce IgE specific for that allergen. The IgE then binds to high affinity IgE receptors on mast cells and basophils. Upon re-exposure to the specific allergen, it binds to the IgE on mast cells and basophils and starts a cascade of events leading to the symptoms of AR. The allergic response in AR can be subdivided into the acute or early phase and the late phase.

1.1 Early Phase

Allergen binds to IgE on mast cells which causes these cells to degranulate and release pre-formed inflammatory mediators such as histamine, tryptase, chymase, heparin and other enzymes.^[3,12] In addition to the preformed mediators, mast cells also synthesise mediators *de novo* such as prostaglandin (PG)D₂, cysteinyl leukotrienes (LTC₄, LTD₄ and LTE₄) and platelet activating factor (PAF).^[2,3,13] Histamine is a prominent mediator of the early phase resulting in vascular leakage via H₁ receptors and stimulation of nerve endings, thus resulting in the symptoms of rhinorrhoea, sneezing and nasal pruritus.^[2,3]

1.2 Late Phase

The late-phase response occurs several hours after the early phase. It involves cellular infiltration of eosinophils, basophils, T cells, neutrophils and macrophages into the nasal tissue.^[14,15] These cells release cytokines and other inflammatory mediators leading to a clinically similar response to the early phase. Eosinophil-derived mediators such as major basic protein, eosinophil cationic protein and leukotrienes have been shown to distort the epithelium ultimately leading to chronic allergic inflammation.^[3]

2. Pharmacology

Histamine is primarily produced by mast cells and basophils, and is released upon antigen binding

to IgE on the cell surface and crosslinking FcεRI (a high-affinity receptor for IgE).^[16] Histamine then acts in the nose to cause vasodilatation and increased vascular permeability, and stimulation of sensory nerves leading to the sensation of itching. This manifests clinically as sneezing, rhinorrhoea and pruritus.^[17] There are at least four types of histamine receptors that have been identified. However, the majority of allergic responses are mediated via the H₁ receptor.^[16] The second-generation H₁ antihistamines have very high avidity and selectivity for H₁ receptors.^[18-21] H₁ antihistamines are inverse agonists that combine with and stabilise the inactive form of the H₁ receptor leading toward a shift in equilibrium to the inactive state.^[22,23] In addition to antagonising histamine at the H₁ receptor, the newer second-generation agents have both antiallergic and anti-inflammatory properties. They have been shown to inhibit the release of mediators from mast cells and basophils through a direct inhibitory effect on calcium-ion channels.^[24] Pretreatment with an H₁ antihistamine has been shown to decrease the early response to an allergen challenge through decreasing the levels of proinflammatory cell adhesion molecules, cytokines, mediators such as histamine, leukotrienes and prostaglandins.^[25-27]

2.1 First-Generation Oral Antihistamines

The older first-generation H₁ antihistamines such as diphenhydramine, chlorphenamine (chlorpheniramine), brompheniramine and hydroxyzine are also referred to as the sedating antihistamines. These agents are effective at controlling the rhinorrhoea, sneezing and pruritus associated with AR. However, because these older agents cross the blood-brain barrier they are associated with significant adverse effects, such as sedation leading to impaired performance at home, work and school.^[1,28] Even when first-generation antihistamines are taken at bedtime, they may still cause significant residual daytime sedation, decreased alertness and performance impairment.^[28] These agents have poor H₁-receptor selectivity and act on muscarinic receptors causing anticholinergic effects such as dry mouth, urinary retention, constipation and tachycardia.^[1,29,30] The

high risk to benefit ratio makes the first-generation H₁ antihistamines a less attractive therapeutic option and they are not recommended as first-line therapy in AR.

2.2 Second-Generation Oral Antihistamines

The newer second-generation H₁ oral antihistamines were first developed in the early 1980s to improve on the sedative and anticholinergic adverse effects in the first-generation agents. The second-generation antihistamines have improved H₁-receptor selectivity, absence or decreased sedation, faster onset and longer duration of action and fewer adverse effects.^[13,31] The currently available second-generation H₁ antihistamines are shown in table I. Most second-generation H₁ antihistamines have been shown to have antiallergic and anti-inflammatory properties *in vivo* or *in vitro*.

In general, second-generation antihistamines exhibit favourable pharmacokinetics.^[32] They have a relatively quick onset of action, near complete absorption, widespread tissue distribution with minimal CNS penetration, unlike first-generation antihistamines, and relatively long half-life allowing for once-daily administration.^[33] The pharmacodynamics and pharmacokinetics of second-generation antihistamines are summarised in table II.^[34-40] The second-generation H₁ antihistamines have a similar core moiety, but it is the radicals or side chains adjoining the core which determine the absorption, distribution and elimination of each agent.^[41]

It is rather difficult to study the clinical effectiveness of AR treatment because of the variability that is associated with the disorder. Therefore, several standardised methods have been developed to objectively assess the clinical efficacy of AR treatment

such as exposure unit and pollen chamber studies and unique outcome measures such as measuring nasal airflow obstruction or patient symptom recording.^[42] One method that has become increasingly important in efficacy trials is assessment of QOL.^[43] Several controlled trials of second-generation H₁ antihistamines have been published and have shown overall relief of symptoms reported by patients.^[42,44-75] Notably, all clinical trials that have been published to date assessing second-generation H₁ antihistamines in the treatment of AR have been on patients with SAR and PAR and not intermittent AR or persistent AR.^[5] Examination of these trials has lead to several conclusions: (i) the overall effectiveness of second-generation antihistamines for symptomatic treatment of AR was quite good; (ii) patient acceptance and overall satisfaction was good; and (iii) adverse effects were mild.^[62] Several clinical trials assessing QOL in patients with AR have also been reported. Overall, treatment with second-generation antihistamines consistently improves QOL.

2.2.1 Cetirizine

Cetirizine, a metabolite of hydroxyzine, exists mainly as a zwitterion allowing for low volume of distribution, low serum concentration and a decreased affinity for myocardium with decreased risk for cardiotoxicity.^[76] Cetirizine is rapidly absorbed and achieves peak plasma concentration in ≈1 hour. In addition to H₁ receptor antagonism, cetirizine was found to inhibit eosinophil chemotaxis during the allergic response and, therefore, blunted the late-phase reaction.^[77]

Cetirizine is the only second-generation H₁ antihistamine to cause an increased incidence of sedation at its recommended dose in patients ≥12 years of age.^[78] Therefore, cetirizine is classified as mildly sedating and should not be prescribed to patients whose jobs require high psychomotor skills such as pilots.^[79] Cetirizine has been shown in numerous clinical trials to be more efficacious compared with placebo in the treatment of both SAR and PAR.^[46-50,80] Cetirizine significantly improved QOL measures of general health, physical functioning, vitality, social functioning, and emotional and

Table I. Available second-generation oral H₁ antihistamines

Antihistamine	Usual daily adult dose
Cetirizine	5–10mg
Desloratadine	5mg
Fexofenadine	60mg bid or 120–180mg
Loratadine	5–10mg
Levocetirizine ^a	5mg

a Not available in the US at the time of publication.

bid = twice daily.

Table II. Pharmacodynamics and pharmacokinetics of second-generation H₁ antihistamines^a

Antihistamine	Usual adult dosage	t _{max} (h)	Onset of action (h)	t _{1/2} (h)	Duration of action (h)	Elimination renal/faecal (%)	Conditions that require dose adjustment	References
Cetirizine	5–10 mg/day	0.8	1–1.5	7	24	70/10	Renal and hepatic impairment	35-37
Desloratadine	5 mg/day	4	0.5–3	13–30	24	44/44	Renal and hepatic impairment	35,38
Fexofenadine	60mg bid; 120 mg/day; or 80 mg/day	1.2	1–2	12–15	24	12/80	Renal impairment	34,35,37,39
Loratadine	5–10 mg/day	1.5	1.5–2	11–14	24	20/40	Hepatic impairment	35-37
Levocetirizine ^b	5 mg/day	0.8	1	7	24	86/13	Renal and hepatic impairment	35,36,40

a Results are expressed as mean.

b Not available in the US at the time of publication.

bid = twice daily; **t_{1/2}** = elimination half-life; **t_{max}** = time after dose to reach maximum plasma concentration.

mental health within 1 week of treatment and continued up to 6 weeks.^[81] In a small but similar study, cetirizine improved QOL measures compared with placebo.^[80]

2.2.2 Loratadine

Loratadine has been found to exert protective effects on the early and late phase of conjunctival allergic reactions.^[26,82] Loratadine is a nonsedating antihistamine, and psychomotor tests confirm its safety at the recommended dosage (10 mg/day).^[83] However, performance studies with higher, off-label loratadine doses of 20 and 40mg showed significant impairment and sedation in some objective performance tests compared with placebo.^[84]

Although the placebo-controlled studies with loratadine are limited, two studies^[74,75] have shown that loratadine was superior to placebo in the treatment of AR.

2.2.3 Fexofenadine

Fexofenadine, the active metabolite of terfenadine, is a potent H₁ receptor antagonist that does not display cardiotoxicity like its predecessor.^[85] In addition to blocking H₁ receptors, *in vitro* and *in vivo* studies have shown that fexofenadine reduces allergic inflammatory responses mediated by mast cells, basophils, epithelial cells, eosinophils and lymphocytes.^[71,86] Fexofenadine has proven anti-inflammatory activity and has been shown to in-

hibit intercellular adhesion molecule 1 expression on nasal epithelium *in vitro*.^[82]

Numerous clinical trials have shown fexofenadine to be more efficacious than placebo for the symptoms of SAR.^[64-70] Fexofenadine is approved for use in the US for SAR but not PAR.^[87] Van Cauwenberge et al.^[71] conducted a large, multinational, double-blind, placebo-controlled, 2-week trial of fexofenadine (120mg once daily) versus loratadine (10mg once daily) in patients with SAR. Individual symptoms were self-assessed and no difference in overall symptom scores was observed between fexofenadine and loratadine. However, fexofenadine significantly improved the individual symptoms of nasal congestion and itchy, watery, red eyes compared with loratadine. Fexofenadine was found to decrease work impairment and benefit emotions, sleep and practical problems.^[69]

2.2.4 Desloratadine

Desloratadine is the active metabolite of loratadine and is approved for use in children ≥12 years of age for both SAR and PAR.^[88] Desloratadine has the greatest avidity for the H₁ receptor, although poor selectivity.^[18] Desloratadine has been shown to inhibit IgE mediated and non-IgE mediated release of IL-4 and IL-13 from human basophils *in vitro*.^[27] Like loratadine, desloratadine significantly reduces the symptoms of SAR. However, as in the case of loratadine (see section 2.2.2),

somnolence has been noted at higher, off-label doses.^[35,84,89,90]

Desloratadine has been shown in several randomised, clinical trials to significantly improve patients symptoms.^[60,61] Two, randomised, double-blind, multicentre studies comparing the efficacy of desloratadine with placebo showed a statistically significant reduction in symptoms in patients with SAR over a 2-week study period.^[60] Desloratadine treatment of SAR resulted in improvement of social functioning and symptoms.^[59] Desloratadine rapidly and safely reduced the symptoms of PAR, and its efficacy did not diminish during 4 weeks of treatment.^[91] However, no large clinical trials studying the effect of desloratadine on QOL have been reported.^[40]

2.2.5 Levocetirizine

Levocetirizine is the enantiomer of cetirizine. Levocetirizine, like cetirizine, exists as a zwitterion and, thus, has a lower volume of distribution and also has been shown to inhibit eotaxin-induced transendothelial migration of eosinophils *in vitro*.^[77,90]

Levocetirizine, like cetirizine, is also considered mildly sedating in placebo-controlled trials.^[92] A randomised trial involving >400 patients with SAR found that levocetirizine significantly reduced symptom scores over an 8-week period. A large, multicentre study in children with SAR and PAR found that 4–6 weeks of treatment with levocetirizine significantly improved symptoms and QOL.^[93] A multinational, placebo-controlled study recently found that levocetirizine significantly improved QOL over 6 months of treatment.^[5]

2.2.6 Comparative Studies

A double-blinded, placebo-controlled, parallel group study comparing fexofenadine, loratadine or placebo in the treatment of SAR showed that both fexofenadine and loratadine were superior to placebo in patient symptom scores; however, fexofenadine decreased the scores for itchy, watery, red eyes and nasal congestion more than loratadine.^[71] Lee et al.^[94] conducted a crossover study comparing the protective effect of single doses of levocetirizine, desloratadine and fexofenadine against adenosine monophosphate in 16 patients with PAR.

All three drugs provided significant improvement in nasal peak inspiratory flow compared with placebo with no differences between them. Several clinical studies have shown that cetirizine and fexofenadine were significantly more efficacious than placebo in the treatment of SAR with no difference between them;^[52-54] however, fexofenadine produced less drowsiness.^[54] It should be noted that both SAR and PAR often coexist in study participants thus making it difficult to interpret the results of these clinical trials.

3. Adverse Effects

First-generation antihistamines have the greatest potential for serious adverse effects. There are no long-term safety studies on the first-generation antihistamines. These older antihistamines have potential for serious adverse effects such as CNS, depression and cardiotoxicity, and have also been associated with fatalities in accidental and intentional paediatric overdose.^[95-97] In contrast, second-generation antihistamines are relatively free of adverse effects and are generally well tolerated. The most prevalent adverse effects associated with second-generation antihistamines reported by the manufacturers from large-scale clinical trials are shown in table III.^[78,87,88,92,98]

3.1 CNS Effects

Undesirable effects of antihistamines include sedation and impairment, and depend on the ability of the drug to cross the blood-brain barrier and bind to central H₁ receptors. The second-generation antihistamines, also referred to as nonsedating, have a decreased tendency to cross the blood-brain barrier.^[99] Consequently, second-generation antihistamines are respected for their low potential to cause CNS effects.

Several studies have been conducted to assess the severity and magnitude of CNS depression that these drugs can cause. The majority of these studies focused on subjective and objective measures of sedation such as: sleepiness/wakefulness scores, sleep latency, EEG changes, driving ability, learning/school performance and memory. Studies in-

Table III. Adverse effects with second-generation H₁ antihistamines (% patients/placebo)

Antihistamine (dosage)	Drowsiness	Fatigue	Headache	Dry mouth	Dizziness	GI distress	Dysmenorrhoea	Reference
Cetirizine 10 mg/day	13.7/6.3	5.9/2.6		5/2.3	2/1.2			78
Desloratadine 5 mg/day	2.1/1.8	2.1/1.2		3/1.9			2.1/1.6	88
Fexofenadine 180 mg/day	1.3/0.9	1.3/0.9	10.6/7.5 ^a			1.3/0.6	1.5/0.3	87
Loratadine 10 mg/day	8/6	4/3	12/11	3/2				98
Levocetirizine 5 mg/day ^b	5.2/1.4	2.5/1.2	2.6/3.2	2.6/1.6				92

a 60mg twice daily.

b Not available in the US at the time of publication.

GI = gastrointestinal.

volving first-generation antihistamines have consistently shown significantly greater effects on sedation scores, psychomotor test performance and cognitive function compared with second-generation H₁ antihistamines.^[89,100-109] Therefore, second-generation antihistamines are generally preferred over first-generation antihistamines especially for people whose jobs require a high level of psychomotor skills.

Multiple studies have evaluated the effects that second-generation antihistamines have on the CNS. Loratadine and desloratadine were found to be comparable with placebo at therapeutic doses, but caused sedation when used off label at higher than recommended doses.^[35,42,84,89] Several studies have shown that cetirizine, given at therapeutic doses, causes a slight to moderate increase in sedation, decreased psychomotor function and worsening cognitive function.^[102-108] In contrast, fexofenadine has been found to be free of sedative effects even at higher than therapeutic doses.^[84,89,110] Memory, attention and tracking performance were unaffected after administration of levocetirizine compared with diphenhydramine and placebo.^[111]

3.2 Cardiotoxicity

The potential for H₁ antihistamines to produce cardiotoxicity is directly related to their plasma concentration and, therefore, appropriate administration and drug-drug interactions are important. The first-generation antihistamines have been found to prolong the QT interval at higher than recommended doses.^[112] Terfenadine and astemizole, both second-generation antihistamines, were withdrawn from the

US market because of their cardiotoxic effects at increased plasma concentrations caused by drug-drug interactions.^[35] Currently, no clinically significant cardiotoxic effects have been reported for loratadine, desloratadine, fexofenadine, cetirizine and levocetirizine.^[40,81,113]

4. Drug Interactions

Drug-drug interactions usually occur as a result of altered metabolism in the hepatic cytochrome P450 (CYP) system or through interference with absorption via active transport mechanisms such as P-glycoprotein and organic-anion transporters.^[13,35] Loratadine and desloratadine undergo CYP metabolism like terfenadine and astemizole, which are no longer on the market.^[35,40,42] Therefore, loratadine and desloratadine are more susceptible to altered plasma concentrations when taken in conjunction with other medications that are metabolised via the CYP system. Conversely, fexofenadine, cetirizine and levocetirizine are not metabolised by the CYP450 system, which makes them less susceptible to interactions involving this mechanism.^[35,40,42] However, they still remain susceptible to interactions involving P-glycoprotein and organic-anion active transport mechanisms.

Fexofenadine is a substrate for P-glycoprotein, which is a membrane-bound transporter that inhibits absorption and promotes excretion.^[114] Grapefruit juice has been found *in vitro* to inhibit P-glycoprotein activity.^[115] Therefore, when consumed with grapefruit juice, the plasma concentration of fexofenadine can be decreased by up to 40%.^[116] This is thought to be caused by inhibition of the organic

Table IV. Guidelines for the treatment of allergic rhinitis

1. Allergen avoidance if allergen identified via history and/or tests
2. For mild symptoms, start with an oral second-generation H₁ antihistamine; for moderate to severe symptoms or the primary treatment of nasal congestion, use an intranasal corticosteroid
3. For persistent nasal symptoms, a combination of intranasal corticosteroids and a combination oral second-generation H₁ antihistamine/decongestant may be tried
4. Consider an intranasal antihistamine and/or leukotriene-receptor antagonist if symptoms continue
5. For ocular symptoms, add a topical mast cell stabiliser/antihistamine (multi-action) agent, e.g. olopatadine, epinastine, azelastine
6. Consider immunotherapy if relief with medication is inadequate or to prevent further progression of allergic disease

anion transporting polypeptide mediated drug uptake.^[116] Rifampin can upregulate P-glycoprotein activity and, thus, when taken in conjunction with fexofenadine, peak plasma concentrations of fexofenadine are decreased.^[117] Conversely, when fexofenadine is taken in conjunction with ketoconazole and erythromycin, plasma concentrations of fexofenadine may be increased thus increasing the potential for adverse effects.^[87,113] It is important to note that these effects have not been found to be clinically significant and that no serious adverse effects attributable to drug interactions with second-generation H₁ antihistamines have been reported.

5. Conclusions

AR is a common chronic disorder that can significantly interfere with a patient's QOL. The goals of treatment are to provide the patient with symptom relief and improvement in QOL with minimal adverse effects. Oral second-generation antihistamines are considered first-line or second-line therapy (table IV)^[5] for the treatment of AR and their use has been supported in numerous clinical trials. Although they are not completely free from adverse effects such as drowsiness or altered cognition, all the second-generation H₁ antihistamines have good benefit with minimal risk compared with oral first-generation antihistamines. These agents can be an important part of the regimen to control the patient's allergy condition.

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