

Treatment for Allergic Rhinitis and Chronic Idiopathic Urticaria: Focus on Oral Antihistamines

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OBJECTIVE: To review the efficacy and safety of first- and newer-generation antihistamines for the management of allergic rhinitis and chronic idiopathic urticaria (CIU), with a focus on management in the pharmacy.

DATA SOURCES: A literature review was performed using MEDLINE (1966–October 2005), with no time or language restrictions. Key words or phrases used were histamine, antihistamine(s), first- and second-generation, allergic rhinitis, chronic idiopathic urticaria, quality of life, impairment, sedation, cost-effectiveness, astemizole, cetirizine, desloratadine, diphenhydramine, fexofenadine, loratadine, hydroxyzine, ketotifen, and mizolastine. Additional references were found in the bibliographies of the articles cited.

STUDY SELECTION AND DATA EXTRACTION: Clinical trials and other experimental studies of the use of antihistamines for the management of allergic rhinitis and CIU were selected. Review papers and guidelines were also included.

DATA SYNTHESIS: First-generation antihistamines are effective at ameliorating the symptoms of allergic rhinitis and CIU; however, they are associated with adverse effects due to a lack of selectivity for the histamine H₁-receptor and an ability to bind to cerebral H₁-receptors. Newer-generation agents, in general, possess high H₁-receptor selectivity and a low tendency to cross the blood–brain barrier, while maintaining efficacy. In general, safety at elevated doses has been demonstrated for the newer antihistamines, although higher rates of sedation and impairment have been reported with increasing doses for some agents.

CONCLUSIONS: Pharmacists can play an important role in the management of allergic rhinitis and CIU by considering the relative advantages of newer-generation agents when reviewing treatment options.

KEY WORDS: allergic rhinitis, antihistamine(s), chronic idiopathic urticaria.

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Allergic rhinitis and chronic idiopathic urticaria (CIU) are both common conditions. Allergic rhinitis affects 10–25% of adults and up to 40% of children and repre-

sents the most common chronic condition in outpatient medical practice.¹⁻³ The prevalence of CIU, defined as recurrent urticaria >6 weeks in duration and without identifiable cause, is estimated at 0.1% of the population, and up to 20% of patients still have symptoms 20 years after onset.⁴ In addition, the prevalence of all forms of chronic urticaria, including physical and exogenous urticarias, may be as high as 30%.⁵

While not life-threatening, allergic rhinitis and CIU significantly impact patients' quality of life, overall health, and productivity and lead to increased healthcare costs. For example, untreated allergic rhinitis has been associated with fatigue, irritability, and restlessness.⁶ In children, the consequences of allergic rhinitis can include disturbed sleep patterns, reduced ability to concentrate, reduced learning performance, social handicap, anxiety, and family dysfunction.⁷ The importance of treating allergic rhinitis is magnified by the additional potential benefit of improving other associated comorbidities.⁸ Symptoms of CIU include relentless pruritus, cosmetically disfiguring wheals, sleep

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disturbance, social isolation, altered emotions, and difficulties with daily activities.⁹ Furthermore, quality-of-life studies have indicated a moderate-to-high degree of disability in patients with chronic urticaria.¹⁰

Pathophysiology

The pathophysiologies of allergic rhinitis and CIU involve complex inflammatory processes. However, histamine is recognized as one of the key mediators responsible for the signs and symptoms in both conditions.¹¹

In allergic rhinitis, exposure to allergens leads to the production of immunoglobulin (Ig) E antibodies that bind to mast cells and basophils. Subsequent allergen exposure in a sensitive individual leads to mast cell degranulation and the release of histamine and other inflammatory mediators of the allergic response. Symptoms arise from the interaction between these mediators and neural, vascular, and glandular structures within the nose. Nasal itch, sneezing, and rhinorrhea are predominantly neural in origin,¹² while nasal obstruction is predominantly vascular.¹³

Etiology in CIU is less well understood. Up to 50% of CIU patients have autoimmune urticaria, involving the production of autoantibodies against the high-affinity IgE receptor, IgE, or both, resulting in the release of histamine from mast cells, as well as other processes. In the remaining half of cases, the cause is still unclear.¹⁴

Management

Allergen avoidance, including environmental control, is considered the first step in the management of allergic rhinitis. Similarly, avoidance of precipitating or exacerbating factors is the first consideration in the management of CIU.⁴ However, these measures alone are typically not effective in either condition. Safe and effective pharmacotherapy plays an important role in the management of these global public health burdens.

As patients with allergic rhinitis and, to a lesser extent, CIU self-diagnose and present at the pharmacy, the pharmacist has a major role in ensuring proper management of these conditions by providing information to patients on both prescribed and over-the-counter (OTC) medications. In the case of CIU, pharmacists must be able to appreciate specialized dosages or regimens that may be prescribed by physicians for optimal management.

Evidence-based pharmacotherapy recommendations for the management of allergic rhinitis have been developed by the Allergic Rhinitis and its Impact on Asthma (ARIA) expert panel in collaboration with the World Health Organization.¹⁵ Indeed, these guidelines also include specific recommendations for the management of allergic rhinitis symptoms in the pharmacy.

Treatment Options

Oral, intranasal, and intraocular antihistamines; intranasal corticosteroids; decongestants; leukotriene modifiers; in-

tranasal anticholinergics; chromates; and nasal irrigation are all indicated for the treatment of allergic rhinitis.¹⁵ Antihistamines can also be used in combination with other common allergic rhinitis therapies, especially intranasal corticosteroids and oral decongestants. Combination therapy with agents such as leukotriene modifiers and other intranasal medications is possible but not well established.

Treatment of patients with CIU involves reducing the symptoms of pruritus and the number of wheals with the most appropriate therapy in terms of balancing risk and benefit. Topical agents are not effective and are limited to emollients, such as menthol 1% in aqueous cream.⁴ Treatment options must include systemic drugs such as H₁-receptor antagonists, with or without H₂-receptor antagonists. Alternate therapies include leukotriene modifiers, corticosteroids, and a variety of other antiinflammatory or immunosuppressive agents.

However, as histamine plays a key role in both allergic rhinitis and CIU, antihistamines represent an appropriate first-line therapy for both conditions.^{4,16} The H₁-receptor antagonists can be widely classified as first-generation (eg, diphenhydramine, hydroxyzine, chlorpheniramine) and newer-generation (eg, loratadine, cetirizine, fexofenadine, desloratadine, azelastine) agents. H₂-receptor antagonists include cimetidine, famotidine, ranitidine, and nizatidine. Among the agents prescribed for urticaria, doxepin and cyproheptadine may also be grouped with the first-generation antihistamines.

Most antihistamines available OTC in the US are first-generation agents, with the exception of loratadine, which obtained OTC approval in 2002. The oral antihistamines available in the US are summarized in Table 1. The wide range of available antihistamines varies with respect to efficacy and safety and, therefore, antihistamine dosages must be tailored specifically to the individual. All the aspects of an agent should be assessed to provide the greatest relief with the least potential for adverse effects.¹⁶ Careful selection will improve quality of life and avoid effects that may worsen quality of life.⁷

First-Generation Antihistamines

Although first-generation antihistamines are effective at ameliorating the symptoms associated with allergic rhinitis and CIU, they are also associated with a number of adverse effects due to their lack of selectivity for H₁-receptors and their ability to bind to cerebral receptors.¹⁶ The adverse effects associated with the first-generation antihistamines are summarized in Table 2. First-generation agents are well recognized as causing antimuscarinic or anticholinergic effects, including dry mouth and tachycardia, as well as certain agent-specific effects such as appetite stimulation, weight gain, and gastrointestinal effects.¹⁵ Drugs often classified together with the older antihistamines, such as doxepin and cyproheptadine, have other receptor-blocking properties, including serotonergic and peripheral adrenergic effects. Physicians may prescribe these older antihistamines to help block other non-histamine receptors in some patients with CIU. Severe toxic reactions, including cardiotoxicity, and

deaths have been reported following overdoses of first-generation antihistamines.¹⁶⁻²⁰ It should be noted, however, that although patients taking these antihistamines have an increased risk of these adverse effects, the absolute risk is small.¹⁶

At standard doses, first-generation antihistamines are also associated with the central nervous system (CNS) adverse effects of sedation and cognitive function impairment, including attention, memory, sensori-motor coordination, information processing, and psychomotor performance deficits, due to the blockade of H₁-receptors in the brain.¹⁶⁻²¹

In addition, first-generation antihistamines are commonly administered in 3 or 4 daily doses (Table 1); such regimens can be inconvenient and difficult for the patient, which may lead to underadherence and a subsequent lack of efficacy. Pharmacists should advise patients to adhere to

the prescribed dosing regimen to receive the full benefit of the medication. Adherence can be improved by advising the patient to schedule doses and select an appropriate reminder mechanism, such as at mealtimes or daily rituals.¹⁵ Other useful aids include written instructions or a well-designed reminder chart during times of dosing interval.

NEWER-GENERATION ANTIHISTAMINES

Newer-generation antihistamines were developed to avoid the adverse effects experienced with the first-generation agents while maintaining comparable efficacy. In general, they possess higher H₁-receptor selectivity and have a lower tendency to cross the blood-brain barrier than their earlier counterparts and are, therefore, associated with sig-

Table 1. First- and Newer-Generation Histamine H₁ Antihistamines Available in the US

Antihistamine	Indication	Recommended Dosage ^a
First-generation		
diphenhydramine	AR/CIU ^b	adults: 25–50 mg 3–4 times daily; children >9.1 kg: 12–25 mg 3–4 times daily (maximum 300 mg/day)
hydroxyzine	AR/CIU ^b	adults: 25 mg 3–4 times daily; children >6 y: 50–100 mg/day divided; children <6 y: 50 mg/day divided
chlorpheniramine	AR/CIU ^b	adults and children ≥12 y: 4 mg every 4–6 h (maximum 24 mg/day); 6–12 y: 2 mg every 4–6 h; 2–6 y: 1 mg every 4–6 h
cycloheptadine	AR/CIU ^b	adults: 4–20 mg/day (maximum 0.5 mg/kg/day); 2–6 y: 2 mg 2–3 times daily (maximum 12 mg/day); 7–14 y: 4 mg 2–3 times daily (maximum 16 mg/day)
Newer-generation		
loratadine	SAR/PAR/CIU	adults and children ≥6 y: 10 mg/day; 2–5 y: 5 mg/day
cetirizine	SAR/PAR/CIU	adults and children ≥12 y: 5 or 10 mg/day; 6–11 y: 5 or 10 mg/day; 2–5 y: 2.5 mg syrup/day (maximum 5 mg/day) or one 5-mg chewable tablet per day; 6 mo to <2 y: 2.5 mg/day syrup (for children 12–23 mo, maximum dose 5 mg/day)
fexofenadine	SAR CIU	adults and children ≥12 y: 60 mg twice daily or 180 mg/day; 6–11 y: 30 mg twice daily
desloratadine	SAR (≥2 y)/ PAR (≥6 mo)/ CIU (≥6 mo)	adults and children ≥12 y: 5 mg/day; 6–11 y: 2.5 mg/day (syrup); 6–11 mo: 1.0 mg/day; 12 mo to 5 y: 1.25 mg/day (syrup);
AR = allergic rhinitis; CIU = chronic idiopathic urticaria; PAR = perennial allergic rhinitis; SAR = seasonal allergic rhinitis.		
^a Where agents are over-the-counter and numerous formulations are available, the key tablet dose option is provided.		
^b Recommended dosages provided are for AR.		

Table 2. Adverse Events Associated with First-Generation Antihistamines

Adverse Effects	Agent	Dose	Reference
Antimuscarinic or anticholinergic effects including dry mouth, tachycardia, and urine voiding	general (eg, chlorpheniramine, diphenhydramine, promethazine)	recommended/higher than recommended	15
Sedation and cognitive function impairment including attention, memory, sensory-motor coordination, information processing, and psychomotor performance deficits	general (eg, chlorpheniramine, diphenhydramine, promethazine)	recommended/higher than recommended	15–21
Severe toxic reactions (eg, cardiotoxicity) and deaths	general (eg, diphenhydramine, brompheniramine)	overdose	16–19
Gastrointestinal disturbances including nausea, vomiting, diarrhea, appetite loss, and epigastric distress	ethylenediamine class	recommended/higher than recommended	15
Appetite stimulation and weight gain	cycloheptadine	recommended/higher than recommended	15
α-Adrenergic receptor-blocking properties	promethazine	recommended/higher than recommended	15

nificantly fewer adverse effects than their predecessors. Indeed, the ARIA guidelines suggest that newer-generation antihistamines are preferable over the older drugs due to their favorable efficacy and safety profiles.¹⁵ In addition, newer agents have a once- or twice-daily dosing regimen, which can lead to improved patient adherence.

The available evidence suggests some differences in efficacy among the newer-generation antihistamines; however, these findings have been inconsistent. Differences have also been noted in safety and the potential for adverse effects, although these differences are markedly fewer than those between the first- and newer-generation agents.¹⁵ Although 2 antihistamines, astemizole and terfenadine, have been associated with quinidine-like prolongation of the QT interval and ventricular arrhythmias, they are no longer available in the US and are not representative of the newer-generation antihistamine class.^{15,17,22,23}

In terms of CNS safety, meta-analyses of published data about antihistamines have shown that newer-generation agents, such as loratadine and cetirizine, have lower impairment/non-impairment ratios than the older agents, while fexofenadine was non-impairing in all of the studies included in the meta-analyses.^{24,25} The precise clinical relevance of these differences still requires further investigation. As of September 21, 2005, such comparisons are not yet available for the most recently available agent, desloratadine.

Positron emission tomography imaging studies have also provided objective evidence of the differences between first- and newer-generation antihistamines in terms of their ability to bind to cerebral H₁-receptors. One study indicated that the first-generation agent chlorpheniramine occupied approximately 77% of the available H₁-receptors in the frontal cortex after a single oral dose of 2 mg.²⁶ A more recent study showed that cetirizine 20 mg occupied 20–50% of H₁-receptors in the cerebral cortex, depending on brain region, while fexofenadine HCl 120 mg had an H₁-receptor occupancy of 0%.²⁷

In addition, cardiovascular issues have not been observed with the 4 currently available newer-generation agents in the US to date.¹⁵ For example, the safety profile of fexofenadine has been extensively studied in >6000 patients in controlled clinical trials and, even at doses higher than those used in clinical practice, had no effect on QTc.²⁸

Finally, clinicians have long appreciated the phenomenon of individual patients preferring one newer-generation antihistamine over another; in the end, a lack of evidence for predicting differential responsiveness may require a trial-and-error approach to selecting the best agent for individual patients. The tolerability and efficacy of the newer-generation drugs available in the US for allergic rhinitis and CIU are discussed in greater detail below.

EFFICACY AND TOLERABILITY IN ALLERGIC RHINITIS

Clinical Studies in Adults

The newer-generation antihistamines have demonstrated efficacy in reducing the symptoms of allergic rhinitis, in-

cluding sneezing, rhinorrhea, mucosal pruritus, conjunctivitis, and, in some studies, nasal congestion. For example, a number of double-blind, randomized, placebo-controlled clinical studies have demonstrated the efficacy and tolerability of loratadine, cetirizine, desloratadine, and fexofenadine in patients with allergic rhinitis.^{29–36}

Clinical studies investigating the onset of action and efficacy of antihistamines have included 1- to 2-day pollen chamber and outdoor “park” studies, as well as outpatient studies, which are typically performed over 2 weeks. Pollen chamber studies can provide advantages over “park” studies by controlling pollen levels, the exposure of participants to a single allergen, air quality, temperature, and humidity. However, outpatient studies more appropriately assess exposure after chronic use (steady-state), which accounts for daily and diurnal variability in the subject’s environment and biology.

Head-to-head studies have also been performed among the newer-generation antihistamines to compare their relative efficacies, although only a few of these have been outpatient studies. A number of pollen chamber studies, as well as an outdoor park study,⁴⁰ have indicated the superior efficacy of cetirizine over loratadine.^{37–40} For example, one study showed that cetirizine produced a significantly greater reduction in overall total symptom complex score (the combination of runny nose, sniffles, itchy nose, nose blows, sneezes, watery eyes, itchy eyes and ears, itchy throat, cough, and postnasal drip) compared with loratadine ($p \leq 0.01$) and placebo ($p \leq 0.01$).³⁸ In addition, 2 outpatient studies have demonstrated equal efficacy between these 2 antihistamines compared with placebo.^{41,42} Although a numerically greater improvement was reported with cetirizine, this difference did not reach statistical significance.⁴²

In a multicenter, randomized, double-blind, placebo-controlled study comparing the clinical effects of fexofenadine HCl 120 mg and loratadine 10 mg, both antihistamines were significantly superior to placebo ($p \leq 0.0001$ and $p \leq 0.005$, respectively) at reducing symptom scores for the previous 24 hours.⁴³ Fexofenadine, however, was significantly superior to loratadine at improving the individual symptoms of itchy, watery, red eyes ($p \leq 0.05$) and nasal congestion ($p \leq 0.05$), as well as quality of life ($p \leq 0.03$).

Another multicenter, randomized, double-blind study, with a similar number of patients, comparing fexofenadine HCl 60 mg twice daily with loratadine 10 mg once daily had disparate results.⁴⁴ Patient-reported symptoms for the previous 24 hours were significantly less in the loratadine group compared with the fexofenadine group ($p = 0.019$). In addition, the comparison of fexofenadine HCl 180 mg and desloratadine 5 mg in a double-blind, placebo-controlled, 2-week, crossover study involving 49 patients with seasonal allergic rhinitis (SAR) indicated equal efficacy between the 2 antihistamines in reducing nasal symptoms and improving peak nasal inspiratory flow.⁴⁵

Similarly, a 2-week, randomized, double-blind, parallel-group study indicated the equivalent efficacy of fexofena-

dine HCl 120 and 180 mg once daily and cetirizine 10 mg once daily at reducing the symptoms associated with SAR versus placebo.⁴⁶ Both antihistamines significantly reduced 24-hour reflective total symptom scores (TSS) compared with placebo ($p \leq 0.0001$). In an additional 2-week study of approximately 500 patients with moderate-to-severe SAR, cetirizine 10 mg and fexofenadine HCl 180 mg once daily again showed equivalent efficacy at improving the symptoms of SAR, while patients receiving fexofenadine experienced significantly less drowsiness versus baseline than those receiving cetirizine ($p = 0.0110$).⁴⁷ Pollen chamber studies have also indicated the equivalent efficacy and comparable onset of action of fexofenadine and cetirizine at reducing SAR symptoms versus placebo, with a longer duration of effect for cetirizine.^{48,49}

All studies have shown that the newer-generation antihistamines have good safety and tolerability profiles, with few serious or unexpected adverse events reported.

Clinical Studies in Children

Fexofenadine, loratadine, cetirizine, and desloratadine also have indications for use in children, and several studies have shown the good efficacy and safety profiles of these antihistamines in pediatric patients.⁵⁰⁻⁵⁷

The efficacy and safety of fexofenadine HCl 30 mg twice daily were studied in a large, placebo-controlled, double-blind trial of 935 children (aged 6–11 y) with SAR.⁵¹ There was a significant improvement ($p \leq 0.0001$) throughout the treatment period in the primary efficacy outcome, the change from baseline in the average 12-hour reflective TSS (sum of sneezing; rhinorrhea; itchy nose, palate, throat, and/or ears; itchy, watery, and/or red eyes), when patients were treated with fexofenadine compared with placebo.

Once-daily treatment with loratadine 5 or 10 mg was effective at improving the symptoms of SAR in children aged 3–6 years in a third-party blind, randomized, parallel-group study.⁵² Loratadine significantly ($p \leq 0.05$) decreased the mean total score for nasal and non-nasal symptoms from baseline at days 3, 7, and 14. Therapeutic response to treatment was good or excellent in 82% of loratadine-treated patients.

In a large, randomized, double-blind, placebo-controlled trial undertaken to assess the efficacy and safety of cetirizine 5 or 10 mg once daily in the treatment of SAR in children aged 6–11 years, cetirizine 10 mg significantly improved the adjusted mean 24-hour reflective TSS versus placebo ($p < 0.05$) at 4 weeks.⁵⁴ Reductions were also achieved with cetirizine in individual symptom scores; some of these were significant at various time points ($p \leq 0.05$). Cetirizine has also been shown to be effective at reducing allergic rhinitis symptoms in double-blind studies in children aged ≥ 2 years.⁵³

The efficacy and safety of desloratadine syrup have been recently assessed in an open trial in children aged 6–12 years. Subjects with SAR for at least 2 years, either with or without concomitant intermittent asthma, were en-

rolled ($N = 54$) and treated with desloratadine syrup 2.5 mg daily for 4 weeks. Rhinorrhea, sneezing, congestion, and itching symptoms were improved in a considerable proportion of children. Eye symptoms improved in almost all children receiving desloratadine. Lower airway symptoms were also reduced and desloratadine syrup had an excellent safety profile; most of the adverse events were mild in intensity.⁵⁶

The only comparative study of the newer-generation antihistamines in pediatrics was a double-blind, randomized, parallel-group comparison of cetirizine and loratadine in perennial allergic rhinitis.⁵⁸ In this study of 80 children, both antihistamines improved symptoms; however, cetirizine was significantly more effective than loratadine ($p < 0.0001$) at relieving symptoms of rhinorrhea, sneezing, nasal obstruction, and nasal pruritus.

EFFICACY AND TOLERABILITY IN CHRONIC IDIOPATHIC URTICARIA

H₁-receptor antagonists have demonstrated efficacy in reducing pruritus and the number, size, and duration of urticarial lesions, but less so in reducing the vascular effects of flare and erythema.⁵⁹ A number of double-blind, randomized clinical studies have demonstrated the efficacy of loratadine, cetirizine, desloratadine, and fexofenadine for global status and specific symptoms in patients with CIU, as well as the safety and tolerability of these compounds.⁶⁰⁻⁶⁷

In a multicenter, double-blind, parallel-group, placebo-controlled study, fexofenadine HCl 180 mg once daily significantly improved mean TSS consistently over the 6-week study period ($p < 0.05$) and significantly reduced pruritus compared with placebo ($p < 0.05$).⁶⁶ Loratadine has been shown to have efficacy in CIU equivalent with that of the first-generation compound hydroxyzine in terms of reducing daily symptom scores.⁶⁰ Furthermore, in a large, double-blind, randomized, placebo-controlled trial in CIU, desloratadine 5 mg once daily significantly reduced pruritus (mean 12-h reflective score; $p < 0.001$) and total symptoms (12-h reflective TSS; $p < 0.001$) over the 6-week study period.⁶⁴

In contrast to allergic rhinitis, there is a paucity of direct comparative trials of newer-generation antihistamines in CIU. A study comparing cetirizine and astemizole demonstrated the efficacy of both agents versus placebo in the treatment of CIU, with cetirizine having a more rapid onset of action.⁶² Another comparative study of newer-generation antihistamines in CIU compared fexofenadine with cetirizine in 116 patients from India.⁶⁸ A higher percentage of patients were symptom free at the end of the 28-day study after receiving cetirizine compared with those receiving fexofenadine (52% vs 4.4%, respectively), while 36.5% and 42.2% of patients, respectively, experienced partial improvement. More comparative studies in CIU are required to make definitive conclusions.

Currently, while newer-generation H₁-receptor-antagonists are the clear choice for first-line therapy, first-generation agents may still have a place as add-on therapy, espe-

cially when administered prior to sleep.⁴ While controlled trials confirming the efficacy of using higher-than-recommended doses of newer-generation antihistamines in CIU are not available, it is our experience, as well as that of many experts in urticaria, that this approach may be very efficacious in CIU patients. Therefore, in patients with CIU, special consideration of safety is required in cases in which higher doses are needed and also because patients have been reported to self-dose and use more than the prescribed dose of their medication.⁶⁹ In addition, in children <12 years old, frequent off-label use of drugs has been reported.¹⁵ As already noted, improved safety has been demonstrated for the newer-generation agents compared with the first-generation antihistamines at recommended doses. In addition, at elevated doses, loratadine, cetirizine, and fexofenadine have shown a lack of cardiovascular effects.⁷⁰ However, the prescribing information for desloratadine suggests that very high single doses (45 mg) can cause an increase in heart rate relative to placebo.⁷¹

In addition, higher rates of sedation and impairment may be seen with increasing doses of cetirizine and loratadine²⁵; however, these effects, while causing more performance and cognition impairment than other newer-generation H₁-receptor antagonists, are considerably lower in magnitude and percentage of patients affected than those seen with first-generation agents.⁷² As of September 21, 2005, the clinical relevance of such small differences among newer-generation antihistamines has not been studied.⁷³

Add-on H₂-receptor antagonists may enhance the control of the vascular effects in urticarial lesions and have been demonstrated to be efficacious in some, but not all, trials.^{74,75} Unlike the previously discussed H₁-receptor antagonists, H₂-receptor antagonists would not be expected to be given at higher-than-normal doses in the setting of CIU.⁴

COST-EFFECTIVENESS

Both allergic rhinitis and CIU are associated with significant healthcare utilization and costs. In 1994, approximately 39 million allergic rhinitis patients in the US accounted for an estimated \$1.2 billion in total costs.⁷⁶ Of those, only 5 million sought medical treatment, and direct medical expenditures were estimated to account for 93% of their total costs. A simulation-model study performed in the US investigated the transitioning of newer-generation agents OTC compared with retaining prescription-only status and demonstrated the cost-effectiveness of the newer-generation antihistamines compared with first-generation agents in allergic rhinitis.⁷⁷ The availability of second-generation antihistamines OTC was associated with annual savings of \$4 billion, or \$100 per patient with allergic rhinitis. The cost-savings were largely due to reduced adverse outcomes as a result of sedation caused by first-generation antihistamines. A further study demonstrated that first-generation antihistamines are associated with increases in work-related injuries; the cost of lost productivity due to allergic rhinitis and the use of sedating OTC antihistamines was estimated to be greater than \$4 billion per year.⁷⁸

As of September 21, 2005, cost-effective analyses for urticaria are currently lacking.⁷⁹ However, since the cost-savings in the aforementioned studies of rhinitis were primarily due to work-related sedation effects of first-generation agents, a similar effect would be expected in urticaria patients. Nevertheless, further studies are needed to determine the economic impact of the different treatment options for CIU, as well as the differential impact of treatment on specific vulnerable populations with allergic rhinitis and CIU.

Summary

Antihistamines represent a primary approach for the treatment of allergic rhinitis and CIU. Safety and efficacy differences require a comprehensive understanding of the various antihistamine classes available. Although the first-generation antihistamines have proven efficacy, they are also associated with a number of unwanted adverse effects. In contrast, the newer-generation antihistamines have improved the management of allergic rhinitis and CIU by reducing adverse effects while retaining the efficacy of the first-generation compounds. While comparative studies have suggested some differences in efficacy as well as potential differences in safety, any of the currently available newer-generation H₁-receptor antagonists would serve as excellent first-line choices in the therapy of allergic rhinitis and CIU and would appear to be cost-effective compared with first-generation agents.

Patients presenting directly to a pharmacist may be tempted to use a first-generation antihistamine or OTC newer-generation agent due to the higher costs and access barriers associated with prescription medications. Pharmacists can play an important role in the management of allergic rhinitis and CIU by considering a newer-generation agent when reviewing the most appropriate treatment with individual patients in terms of efficacy, relevant comorbidities, adverse-effect profile, and cost-effectiveness.

Current indications for first-generation antihistamines remain, but have become more specialized, such as to aid sleep in the case of severe CIU or when an individual prefers a particular agent based on prior use history. Frequently, referral to a physician should be considered, especially for patients with persistent or moderate-to-severe symptoms or children <12 years old, because of difficulties in establishing the diagnosis and selecting the proper medications to avoid adverse effects. For recalcitrant CIU, physicians may also prescribe more sophisticated regimens, notably, higher-than-normal doses or frequencies and multiple simultaneous antihistamines, including add-on H₂-receptor antagonists or agents such as doxepin. The summation of experience to date in allergic rhinitis and CIU indicates that the newer-generation antihistamines have become the treatment of choice in the majority of patients for whom an H₁-receptor antagonist is indicated.

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EXTRACTO

OBJETIVO: Revisar la eficacia y seguridad de los antihistamínicos de primera y segunda generación para el tratamiento de la rinitis alérgica (RA) y la urticaria idiopática crónica (UIC), enfocando el manejo de estos fármacos en la farmacia.

FUENTES DE INFORMACIÓN: Se realizó una revisión de la literatura médica sin restricciones de tiempo o idioma. Se usaron las siguientes palabras clave o frases: antihistamínicos, primera y segunda generación, rinitis alérgica, urticaria idiopática crónica, calidad de vida, deterioro, sedación, costo-efectividad, astemizol, cetirizina, desloratadina, difenhidramina, fexofenadina, loratadina, hidroxizina, ketotifeno, y mizolastina. Se encontraron referencias adicionales en la bibliografía de los artículos citados.

SELECCIÓN DE FUENTES DE INFORMACIÓN Y MÉTODO DE OBTENCIÓN DE INFORMACIÓN: Se seleccionaron estudios clínicos y otros estudios experimentales sobre el uso de antihistamínicos para el manejo de la RA y la UIC. También se incluyeron artículos de revisión y guías.

SÍNTESIS: Los antihistamínicos de primera generación son eficaces para aliviar los síntomas de RA y UIC. Sin embargo, éstos se asocian a efectos secundarios no deseados debido a una falta de selectividad para el receptor H₁ y su habilidad para fijarse a receptores H₁ cerebrales. Los agentes de segunda generación poseen una selectividad alta por el receptor H₁ y una tendencia baja a cruzar la barrera hematoencefálica, mientras mantienen su eficacia. En general, se ha demostrado la seguridad a dosis altas de los nuevos antihistamínicos, aunque se han notificado tasas elevadas de sedación y deterioro cuando se aumentan las dosis de algunos de estos fármacos.

CONCLUSIONES: Los autores concluyen que los farmacéuticos pueden jugar un papel importante en el manejo de la RA y la UIC; se aprecian las ventajas relativas de los nuevos fármacos antihistamínicos cuando se revisan opciones de tratamiento.

Juan F Feliú

RÉSUMÉ

OBJECTIF: Réviser l'efficacité et la sécurité des antihistaminiques de première génération et de génération plus récente dans le traitement de la rhinite allergique (RA) et de l'urticaire chronique idiopathique (UCI) en mettant l'accent sur la gestion en pharmacie.

REVUE DE LITTÉRATURE: Une revue de la littérature a été réalisée à l'aide de MEDLINE en indiquant aucune restriction dans le temps ou la langue. Les mots-clé et les phrases qui suivent ont été utilisés: histamine, antihistamine(s), first-and-second-generation, allergic rhinitis, chronic idiopathic urticaria, quality of life, impairment, sedation, cost-effectiveness, astemizole, cetirizine, desloratadine, diphenhydramine, fexofenadine, loratadine, hydroxyzine, ketotifen, et mizolastine. Des références additionnelles ont été trouvées dans les bibliographies des articles cités.

SÉLECTION DES ÉTUDES ET SÉLECTION DE L'INFORMATION: Des essais cliniques et d'autres études expérimentales portant sur l'utilisation des antihistaminiques dans le traitement de la RA et de l'UCI ont été sélectionnées. Les articles de révision et les lignes de conduite ont aussi été considérés.

RÉSUMÉ: Les antihistaminiques de première génération sont efficaces pour améliorer les symptômes de la RA et de l'UCI; cependant, ils sont

associés à des effets secondaires non désirés dû à leur manque de sélectivité pour le récepteur H₁ et leur habilité à se lier aux récepteurs H₁ cérébraux. Les antihistaminiques de nouvelle génération, en général, démontrent une sélectivité élevée pour le récepteur H₁ et une faible tendance à traverser la barrière hémato-encéphalique, tout en maintenant leur efficacité. En général, la sécurité à doses élevées des antihistaminiques de nouvelle génération a été démontrée, bien que des taux élevés de sédation aient été signalés pour certains agents lors de l'utilisation de doses plus élevées.

CONCLUSIONS: Les pharmaciens peuvent jouer un rôle important dans le traitement de la RA et de l'UCI en évaluant les avantages relatifs des agents de nouvelle génération quand ils passent en revue les options thérapeutiques.

Marie Larouche