

Drug Class Review on Newer Antihistamines

Update #2: Preliminary Scan Report

May 2007

The purpose of this report is to make available information regarding the comparative effectiveness and safety profiles of different drugs within pharmaceutical classes. Reports are not usage guidelines, nor should they be read as an endorsement of, or recommendation for, any particular drug, use or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

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OBJECTIVE

The purpose of this preliminary updated literature scan process is to provide the Participating Organizations with a preview of the volume and nature of new research that has emerged subsequent to the previous full review process. Provision of the new research presented in this report is meant only to assist with Participating Organizations' consideration of allocating resources toward a full update of this topic. Comprehensive review, quality assessment and synthesis of evidence from the full publications of the new research presented in this report would follow only under the condition that the Participating Organizations ruled in favor of a full update. The literature search for this report focuses only on new randomized controlled trials and actions taken by the FDA or Health Canada since the last report. Other important studies could exist.

Date of Last Update

April 2006 (searches through August 2005)

Scope and Key Questions

The Oregon Evidence-based Practice Center wrote preliminary key questions, identifying the populations, interventions, and outcomes of interest, and based on these, the eligibility criteria for studies. These key questions were reviewed and revised by representatives of organizations participating in the Drug Effectiveness Review Project (DERP). The participating organizations of DERP are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to both clinicians and patients.

Key Questions

1. For outpatients with seasonal or perennial allergic rhinitis or urticaria, do newer antihistamines differ in effectiveness?
2. For outpatients with seasonal or perennial allergic rhinitis or urticaria, do newer antihistamines differ in safety or adverse events?
3. Are there subgroups of patients based on demographics (age, racial groups, gender), other medications (drug-drug interactions), comorbidities (drug-disease interactions), or pregnancy for which one newer antihistamine is more effective or associated with fewer adverse events?

Inclusion Criteria

Populations

Adult or pediatric outpatients with the following indications:

- Seasonal allergic rhinitis
- Perennial allergic rhinitis
- Urticaria

Interventions

Cetirizine hydrochloride (Zyrtec, Reactine)

Loratadine (Claritin)

Fexofenadine hydrochloride (Allegra)

Desloratadine (Clarinex)

Effectiveness outcomes

- Symptom alleviation (e.g., nasal congestion, rhinorrhoea, sneezing, itching and pain from skin irritations, etc.)
- Functional capacity (e.g., physical, social and occupational functioning, quality of life, etc.)
- Time to relief of symptoms (e.g., time to onset, duration of relief)
- Duration of effectiveness (e.g., switch rate)

Safety outcomes

- Overall adverse effects reported
- Withdrawals due to adverse effects
- Serious adverse events reported
- Specific adverse events or withdrawals due to specific adverse events (e.g., CNS effects, sedation, GI effects, dry mouth, urinary retention, etc.)

Study designs

1. For effectiveness, controlled clinical trials and systematic reviews
2. For safety, controlled clinical trials and observational studies

METHODS

Literature Search

To identify relevant citations, we searched Ovid MEDLINE, Ovid MEDLINE Daily Update, and Ovid MEDLINE In-Process & Other Non-Indexed Citations from August 2005 through April 2006 using terms for included drugs and indications, and limits for humans, English language, and randomized controlled trials or controlled clinical trials. We also searched FDA (<http://www.fda.gov/medwatch/safety.htm>) and Health Canada (http://www.hc-sc.gc.ca/dhp-mpps/medeff/advisories-avis/prof/2006/index_e.html) websites for identification of new drugs, indications, and safety alerts. All citations were imported into an electronic database (EndNote v 9.0[®]) and duplicate citations were removed.

Study Selection

One reviewer assessed abstracts of citations identified from literature searches for inclusion, using the criteria described above.

RESULTS

Overview

Searches resulted in 255 citations. Of those, there are 13 new, potentially relevant trials, including 2 head-to-head trials, 9 active-controlled trials and 3 placebo-controlled trials. In addition, 4 potentially relevant systematic reviews were identified. Titles and abstracts (where available) appear in Appendix A.

New Drugs/Indications

No new drugs or indications were identified, however a new formulation (oral suspension) of fexofenadine (Allegra[®]) for the treatment of seasonal allergic rhinitis in children 2 to 11 years of age and urticaria in children 6 months to 11 years of age was approved by the FDA in October 2006.

New Safety Alerts

A labeling revision was issued for desloratidine (Clarinet[®]) on December 14, 2006, reflecting the addition of palpitations, seizures, psychomotor hyperreactivity and “very rarely” hepatitis to the ‘Adverse Reactions - Observed During Clinical Practice’ section of the product label. In addition, the following language was added to the ‘Carcinogenesis, Mutagenesis, and Impairment of Fertility - Precautions’ section: *In a 2-year dietary study in mice, males and females given up to 16 mg/kg/day and 32 mg/kg/day of desloratidine, respectively, did not show significant increases in the incidence of any tumors. The estimated desloratidine and metabolite exposures of mice at these doses were 12 and 27 times, respectively, the AUC in humans at the recommended daily oral dose.*

Appendix A. Abstracts of potentially relevant trials of Newer Antihistamines

Head-to-head RCTs

Berger, W. E., W. R. Lumry, et al. (2006). "Efficacy of desloratadine, 5 mg, compared with fexofenadine, 180 mg, in patients with symptomatic seasonal allergic rhinitis." *Allergy & Asthma Proceedings* 27(3): 214-23.

This is the first U.S.-based study to compare efficacy and safety of desloratadine with fexofenadine in subjects with symptomatic seasonal allergic rhinitis (SAR). In this double-blind study, subjects were randomized to desloratadine, 5 mg (n = 290), fexofenadine, 180 mg (n = 288), or placebo (n = 144) once daily for 15 days. Primary end point was mean change from baseline to study end in morning instantaneous total symptom score (AM NOW TSS) excluding congestion. Secondary measures included change from baseline in the morning/evening reflective TSS (AM/PM PRIOR TSS) excluding congestion, AM NOW individual symptom score (AM NOW ISS) including congestion, and the AM/PM PRIOR ISS including congestion. Subjects self-evaluated their symptoms on a five-point scale. Mean AM NOW TSSs were significantly reduced from baseline at day 15 with desloratadine (p = 0.006) and fexofenadine (p = 0.024) versus placebo. Desloratadine and fexofenadine were not statistically different (p = 0.491); the upper limit of the 95% CI for desloratadine to fexofenadine (0.259) was within the prespecified noninferiority margin of 0.7 U. Decrease in mean AM/PM PRIOR TSS excluding congestion was comparable between desloratadine and fexofenadine (p = 0.405; CI = 0.221) but was significantly greater with both active treatments versus placebo (desloratadine, p < 0.001; fexofenadine, p = 0.003). Desloratadine and fexofenadine provided greater reduction in the AM NOW ISS and AM/PM PRIOR ISS (both including congestion) versus placebo; reductions were comparable between active treatments. All treatments were well tolerated. Desloratadine, 5 mg, and fexofenadine, 180 mg, provide comparable efficacy and tolerability in the treatment of SAR. Both treatments are significantly more effective than placebo.

Chiang, Y.-C., S.-D. Shyur, et al. (2006). "A randomized controlled trial of cetirizine plus pseudoephedrine versus loratadine plus pseudoephedrine for perennial allergic rhinitis." *Asian Pacific Journal of Allergy & Immunology* 24(2-3): 97-103.

The purpose of this study was to compare the safety and efficacy of cetirizine plus pseudoephedrine (C+P) with loratadine plus pseudoephedrine (L+P) in the treatment of perennial allergic rhinitis. This was a double blind, randomized, parallel trial with an active control. Subjects aged 12 to 70 years with perennial allergic rhinitis for at least 2 years were enrolled and randomized to receive either of the active study medications plus a placebo resembling the other, twice daily for 4 weeks. Nasal total symptom scale (NTSS) including sneezing, rhinorrhea, nasal itching and nasal stuffiness is evaluated by subjects daily and at baseline, 2 weeks, and 4 weeks by the investigator as efficacy measurement. A total of 51 eligible patients were enrolled and 45 patients completed the treatment course. Both groups had significant reductions in NTSS after 4 weeks of treatment as assessed by the subjects, but there was no significant difference between the two groups (mean +/- SD) reduction of 4.25 +/- 2.45 with C+P vs. 3.52 +/- 2.41 with L+P, p = 0.215. As assessed by the investigator, sneezing was significantly better at 2 weeks (-1.13 vs. -0.52, p = 0.028) and nasal congestion at 4 weeks (-1.71 vs. -1.19, p = 0.031) in subjects treated with C+P compared to those treated with L+P. There were 37 treatment-related adverse events (5 in 4 subjects in the C+P group and 32 in 16 subjects in the L+P group). It was concluded that both cetirizine plus pseudoephedrine and loratadine plus pseudoephedrine are efficacious for

perennial allergic rhinitis in Taiwanese subjects. Relief of sneezing and nasal congestion may be marginally better with the cetirizine preparation, which also seemed to be slightly better tolerated, although the incidence of side effects did not differ significantly.

Active-controlled trials

Chen, S.-T., K.-H. Lu, et al. (2006). "Randomized placebo-controlled trial comparing montelukast and cetirizine for treating perennial allergic rhinitis in children aged 2-6 yr." *Pediatric Allergy & Immunology* 17(1): 49-54.

Leukotriene receptor antagonists (LTRAs) were recently added to the method of treating allergic rhinitis (AR). However, in children under 6 yr old, there has been no study about its efficacy in treating AR. We aim to compare the clinical efficacy of montelukast, cetirizine and placebo in the treatment of children from 2 to 6 yr old with perennial allergic rhinitis (PAR), to see if there are any significant differences. Sixty children were selected and treated with montelukast, or cetirizine, or placebo once daily. The efficacy of the three agents was compared with the Pediatric Rhinoconjunctivitis Quality of Life Questionnaire (PRQLQ) and Total Symptom Score (TSS) by diary. In addition, we also examined serum IgE, serum eosinophil cationic protein (ECP), blood eosinophil counts, nasal airway resistance (NAR) and eosinophil percentage in nasal smears. The results revealed that both montelukast and cetirizine were significantly efficacious compared with placebo in NAR, eosinophil percentage in nasal smears, PRQLQ, TSS and all symptom items except nasal itching, throat itching and tearing. For nasal itching, only cetirizine was significantly efficacious. On the other hand, for night sleep quality, montelukast was significantly superior to cetirizine.

Chervinsky, P., A. Nayak, et al. (2005). "Efficacy and safety of desloratadine/pseudoephedrine tablet, 2.5/120 mg two times a day, versus individual components in the treatment of patients with seasonal allergic rhinitis." *Allergy & Asthma Proceedings* 26(5): 391-6.

Although antihistamines are highly effective in alleviating many symptoms associated with seasonal allergic rhinitis (SAR), relief from nasal congestion is variable. The efficacy of desloratadine, an effective antihistamine, in combination with pseudoephedrine, a potent nasal decongestant, was evaluated to determine whether combination therapy was more effective than individual component therapy in reducing nasal congestion, as well as other SAR symptoms. This multicenter, randomized, double-blind, three-arm study included 650 patients with SAR. For 2 weeks, patients were administered a combination tablet of desloratadine plus pseudoephedrine (desloratadine/pseudoephedrine, 2.5/120 mg) twice per day (b.i.d.), desloratadine (5 mg) once per day, or pseudoephedrine (120 mg) b.i.d. Patients assessed the severity of their SAR symptoms twice daily on symptom diary cards. The primary variable-change from baseline in the reflective A.M./P.M. total symptom score, excluding nasal congestion-was significantly superior (-6.7) compared with desloratadine (-5.4) or pseudoephedrine (-5.3) alone ($p < \text{or} = 0.001$ versus either group). Secondary efficacy variables including total symptom scores (plus congestion), total nasal symptom scores, and total nonnasal symptom scores were significantly reduced after desloratadine/pseudoephedrine therapy compared with the individual components. The most frequently reported adverse events were insomnia, headache, and dry mouth. Desloratadine/pseudoephedrine, 2.5/120 mg b.i.d., therapy was more effective in reducing total symptom scores of SAR, including nasal congestion, than were the individual components. These results support the use of this combination therapy over desloratadine or pseudoephedrine alone.

Ciebiada, M., M. Gorska-Ciebiada, et al. (2006). "Montelukast with desloratadine or levocetirizine for the treatment of persistent allergic rhinitis." *Annals of Allergy, Asthma, & Immunology* 97(5): 664-71.

BACKGROUND: Montelukast sodium is approved as a treatment for intermittent and persistent allergic rhinitis (AR), but it has not been evaluated as combined therapy with antihistamines for persistent AR. **OBJECTIVE:** To investigate the effects of 6 weeks of treatment of persistent AR with desloratadine, levocetirizine, or montelukast alone or in combination. **METHODS:** A randomized, double-blind, placebo-controlled crossover study was performed. Patients were assigned to 2 arms: 20 received montelukast, 10 mg/d, desloratadine, 5 mg/d, or both or placebo and 20 received montelukast, levocetirizine, or both, 5 mg/d, or placebo. The treatment periods were separated by 2-week washout periods. Symptom scoring, skin prick tests, spirometry, rhinometry, and nasal lavage were performed the day before and the last days of the treatment periods. Eosinophil cationic protein levels were evaluated by means of nasal lavage. **RESULTS:** The mean \pm SD total baseline nasal symptom score was 7.7 \pm 0.49 before treatment, 3.74 \pm 0.54 after desloratadine use, 3.6 \pm 0.48 after montelukast use, and 3.04 \pm 0.4 after montelukast-desloratadine use. The mean \pm SD baseline nasal symptom score was 7.95 \pm 0.68 before treatment, 3.02 \pm 0.64 after levocetirizine use, 3.44 \pm 0.55 after montelukast use, and 2.14 \pm 0.39 after montelukast-levocetirizine use. The greatest improvement in nasal symptoms occurred after combination treatment. Decreases in the level of eosinophil cationic protein were greater after the combined use of montelukast and antihistamine than after each agent given alone. **CONCLUSIONS:** For persistent AR, the combination of montelukast and either desloratadine or levocetirizine is more effective than monotherapy with these agents.

Ciprandi, G., I. Cirillo, et al. (2005). "Desloratadine and levocetirizine improve nasal symptoms, airflow, and allergic inflammation in patients with perennial allergic rhinitis: a pilot study." *International Immunopharmacology* 5(13-14): 1800-8.

BACKGROUND: Nasal obstruction is the main symptom in patients with perennial allergic rhinitis. Some new antihistamines have been demonstrated to be capable of improving this symptom. **OBJECTIVE:** The aim of this pilot study was to evaluate nasal symptoms, nasal airflow, eosinophils, and IL-4 in patients with perennial allergic rhinitis, before and after treatment with two new antihistamines: desloratadine and levocetirizine. **METHODS:** Thirty patients with perennial allergic rhinitis were evaluated, 26 males and 4 females (mean age 26 \pm 7.1 years). All of them received either desloratadine (5 mg/daily) or levocetirizine (5 mg/daily) or placebo for 4 weeks. The study was double-blind, parallel-group, placebo-controlled, and randomized. Total symptom score (including: rhinorrhea, nasal itching, sneezing, and nasal obstruction) was assessed before and after treatment. Rhinomanometry and decongestion test, nasal lavage, and nasal scraping were performed in all subjects before and after treatment. Eosinophils were counted by conventional staining; IL-4 was measured by immunoassay of fluids recovered from nasal lavage. **RESULTS:** Desloratadine and levocetirizine treatment induced significant symptom relief and significant reduction of IL-4. Both antihistamines significantly affected all parameters in comparison with placebo. **CONCLUSIONS:** This pilot study demonstrates the effectiveness of antihistaminic treatment in: i) relieving nasal symptoms, including obstruction, ii) improving nasal airflow, iii) exerting decongestant activity, iv) reducing eosinophil infiltration, and v) diminishing IL-4 levels.

Godse, K. V. (2006). "Oral montelukast monotherapy is ineffective in chronic idiopathic urticaria: a comparison with oral cetirizine." *Indian Journal of Dermatology, Venereology & Leprology* 72(4): 312-4.

Jiang, R.-S. (2006). "Efficacy of a leukotriene receptor antagonist in the treatment of perennial allergic rhinitis." *Journal of Otolaryngology* 35(2): 117-21.

The objectives of this study were to investigate the efficacy of leukotriene receptor antagonists in the treatment of perennial allergic rhinitis. The study was designed as a randomized, 14-day treatment to compare the efficacy of zafirlukast, loratadine, and the combination of loratadine and pseudoephedrine in the treatment of perennial allergic rhinitis. Rhinitis symptom scores, acoustic rhinometry, and rhinomanometry were used to evaluate the efficacy. The results showed that after a 14-day treatment period, patients in all treatment groups had a lower mean score for the symptoms of rhinorrhea, nasal itching, and nasal obstruction ($p < .05$). Patients who took zafirlukast did not report a significant decrease in sneezing score ($p = .1456$), but the decrease in nasal obstruction score was more pronounced than in those who took loratadine or loratadine- pseudoephedrine ($p = .014$). However, the results of acoustic rhinometry and rhinomanometry did not have a significant difference among the three groups ($p > .05$). The study concluded that zafirlukast seemed to have a better effect on relieving the symptom of nasal obstruction in patients with perennial allergic rhinitis, but the actual mechanism needs further investigation.

Pleskow, W., R. Grubbe, et al. (2005). "Efficacy and safety of an extended-release formulation of desloratadine and pseudoephedrine vs the individual components in the treatment of seasonal allergic rhinitis." *Annals of Allergy, Asthma, & Immunology* 94(3): 348-54.

BACKGROUND: Antihistamine-decongestant combination products generally provide more benefit than individual components for adequately treating patients who have seasonal allergic rhinitis (SAR) with moderate-to-severe nasal congestion. **OBJECTIVE:** To compare the effectiveness and safety of a 24-hour, extended-release formulation of desloratadine and pseudoephedrine with the individual components in patients who have SAR with moderate-to-severe nasal congestion. **METHODS:** Patients with SAR and significant nasal congestion were enrolled in a multicenter, randomized, double-blind, double-dummy study. Patients were randomly assigned for 2 weeks to once-daily treatment with desloratadine-pseudoephedrine, 5/240-mg tablets; desloratadine, 5 mg; or pseudoephedrine, 240 mg. Primary efficacy variables for the antihistamine and decongestant components of desloratadine-pseudoephedrine were morning and evening reflective total symptom score (TSS), excluding nasal congestion, and morning and evening reflective nasal congestion score during the 2-week treatment period, respectively. Secondary variables included morning instantaneous (end-of-interval) TSS (excluding congestion), nasal congestion score, reflective morning and evening individual symptom scores, overall condition of SAR, and therapeutic response. **RESULTS:** A total of 1121 patients were enrolled in the study, and 1047 patients completed the 2-week study. Desloratadine-pseudoephedrine was significantly more effective than desloratadine or pseudoephedrine monotherapy in reducing morning and evening reflective TSS (excluding nasal congestion) during the entire treatment period. Desloratadine-pseudoephedrine also was significantly more effective in reducing the morning and evening reflective nasal congestion score compared with desloratadine or pseudoephedrine monotherapy. Significant differences were seen between the desloratadine-pseudoephedrine and monotherapy groups for changes in morning instantaneous TSS (excluding nasal congestion) and nasal congestion scores. No

unusual or unexpected adverse events were reported. **CONCLUSION:** Desloratadine-pseudoephedrine, 5/240-mg once-daily tablets, provided additional benefit over desloratadine, 5 mg, or sustained-release pseudoephedrine, 240 mg, monotherapy in the treatment of patients with SAR and moderate-to-severe nasal congestion.

Pons-Guiraud, A., K. Nekam, et al. (2006). "Emedastine difumarate versus loratadine in chronic idiopathic urticaria: a randomized, double-blind, controlled European multicentre clinical trial." *European Journal of Dermatology* 16(6): 649-54.

Emedastine difumarate (2 mg b.i.d.) was compared to loratadine (10 mg o.d.) in a randomized, double-blind, multicentre trial for 4 weeks in 192 patients with idiopathic chronic urticaria. After one week of treatment significant differences were recorded: body skin involvement diminished to 0-10% in 57.1% of emedastine patients vs. 38.2% of loratadine patients ($p = 0.0019$) and 83.3% had a total urticaria symptom score of 0-1 vs. 64.5% with loratadine ($p = 0.0134$). After 4 weeks of treatment the efficacy of the two drugs was similar in terms of mean change in total urticaria symptom score (- 5.57 +/- 3.15 with emedastine - 5.67 +/- 3.26 with loratadine), proportion of symptom-free patients (52.4% vs. 54.5%), intensity of erythema, number of hives, size of the largest hive, extent of skin area involved and overall assessment of urticaria symptoms. Twenty-three emedastine patients (23.9%) and 17 loratadine patients (17.7%) experienced an adverse event. Nineteen events in 15 emedastine patients and 9 in 9 loratadine patients were related to treatment ($p = 0.0294$). Only one event caused discontinuation in both treatment groups. The most common adverse event was sleepiness (7 patients with emedastine and 2 with loratadine). Emedastine is well tolerated, and as effective as loratadine in the short-term treatment of chronic idiopathic urticaria

Raphael, G. D., J. T. Angello, et al. (2006). "Efficacy of diphenhydramine vs desloratadine and placebo in patients with moderate-to-severe seasonal allergic rhinitis.[see comment]." *Annals of Allergy, Asthma, & Immunology* 96(4): 606-14.

BACKGROUND: Previous studies have shown that diphenhydramine and desloratadine effectively relieve symptoms of seasonal allergic rhinitis (SAR). **OBJECTIVE:** To compare the relative efficacy of 50 mg of diphenhydramine hydrochloride, 5 mg of desloratadine, and placebo in relieving symptoms in patients with moderate-to-severe SAR. **METHODS:** In this 1-week, multicenter, parallel-group, randomized, double-blind, double-dummy, placebo-controlled study, 610 patients with moderate-to-severe SAR received 50 mg of diphenhydramine hydrochloride 3 times daily, 5 mg of desloratadine once daily, or placebo. Daily 24-hour reflective total nasal symptom scores (TNSSs) (primary end point), total symptom scores, and individual symptom scores were evaluated. A global evaluation of response to treatment was conducted at 2 posttreatment visits. **RESULTS:** The mean reduction from baseline in 24-hour reflective TNSSs relative to the placebo response was 77.6% for the diphenhydramine group ($P < .001$) and 21.0% for the desloratadine group ($P = .12$). A TNSS between-treatment difference of -1.81 (46.7%; $P < .001$) was observed when comparing diphenhydramine with desloratadine. A similar between-treatment difference was observed for the 24-hour reflective total symptom score comparing diphenhydramine to desloratadine (-3.35; 45.5%; $P < .001$). Diphenhydramine provided clinically and statistically significant reductions vs placebo and desloratadine in all individual symptoms, including nasal congestion. Desloratadine had a tendency toward improvement compared with placebo for most individual symptom scores. However, a statistically significant result was reached only for sneezing (-0.27; 33.9%; $P = .04$). **CONCLUSIONS:** Diphenhydramine, 50 mg, given for 1 week provided statistically significant

and clinically superior improvements in symptoms compared with 5 mg of desloratadine in patients with moderate-to-severe SAR. Somnolence occurred more frequently with diphenhydramine (22.1%) compared with desloratadine (4.5%) and placebo (3.4%).

Placebo-controlled trials

Kim, K., G. Sussman, et al. (2006). "Desloratadine therapy for symptoms associated with perennial allergic rhinitis." *Annals of Allergy, Asthma, & Immunology* 96(3): 460-5.

BACKGROUND: Perennial allergic rhinitis (PAR) has a substantial negative social and economic impact. Recent studies emphasize the potential seriousness of PAR and the need for improved treatment of this condition. **OBJECTIVE:** To confirm the efficacy and safety of the H1-antihistamine desloratadine in reducing the symptoms of PAR in a randomized, double-blind, placebo-controlled trial. **METHODS:** Patients with PAR (N = 1,179) from 67 US/international centers received desloratadine, 5 mg once daily, or identical placebo tablets. The primary efficacy measure was the change from baseline to week 4 in average morning and evening reflective total symptom scores (TSSs). Secondary end points included changes from baseline in total nasal and nonnasal symptom scores and peak nasal inspiratory flow (PNIF) rates. **RESULTS:** Desloratadine was significantly more effective than placebo in reducing morning and evening reflective TSSs for each week and during weeks 1 through 4 (P = .001). Mean changes in TSSs during the 4-week study were -3.9 (26.6% reduction) and -3.2 (22.3% reduction) for the desloratadine and placebo groups, respectively (P = .001, desloratadine vs placebo). With desloratadine therapy, significant improvements were also seen in secondary efficacy end points compared with placebo use (total nasal and nonnasal symptom scores: P < or = .04). Improvements in mean morning PNIF were significantly greater in the desloratadine-treated group than in the placebo group (P = .03). **CONCLUSIONS:** These results confirm and extend previous findings that desloratadine is safe and is associated with a statistically significant reduction in nasal and nonnasal symptoms in patients with PAR. Objective nasal airflow, evaluated by PNIF, was statistically significantly improved after desloratadine treatment.

Meltzer, E. O., A. A. Jalowayski, et al. (2006). "Effect of desloratadine therapy on symptom scores and measures of nasal patency in seasonal allergic rhinitis: results of a single-center, placebo-controlled trial." *Annals of Allergy, Asthma, & Immunology* 96(2): 363-8.

BACKGROUND: Desloratadine reduces symptoms and maintains nasal airflow in patients with seasonal allergic rhinitis (SAR) during experimental allergen exposure. **OBJECTIVE:** To compare the effects of desloratadine and placebo on symptom scores, quality of life (QOL), and nasal airway patency in patients with SAR during the allergy season. **METHODS:** Adults with symptomatic SAR were randomized in a double-blind manner to receive desloratadine, 5 mg, or placebo for 14 days. Patient-rated SAR symptoms were recorded twice daily (morning and evening). On days 1 and 15, SAR symptoms were scored jointly (investigator and patient), nasal airflow was measured using 4-phase rhinomanometry, and QOL and the overall condition of SAR were rated. Overall treatment response was scored on day 15. Adverse events were recorded. **RESULTS:** At day 15, total symptom (P = .03) and total nasal symptom (P = .02) scores and patient morning-rated individual nasal symptom scores (except nasal stuffiness) (P < or = .04) decreased significantly from baseline with desloratadine vs placebo. Flow in the descending expiratory nasal airflow phase was significantly greater (P = .046) and the percentage increase in total inspiratory nasal airway resistance was less (P = .03) in the desloratadine group vs the placebo group. The overall condition of SAR was less severe (P = .045), the therapeutic response was greater (P = .004), and the nasal symptom domain of the

QOL score was significantly better ($P = .03$) in the desloratadine group. Adverse event rates were similar in both groups. **CONCLUSION:** Desloratadine treatment for 14 days improved nasal airflow and resistance as well as symptom and QOL scores in patients with symptomatic SAR during the allergy season.

Reinartz, S. M., S. E. Overbeek, et al. (2005). "Desloratadine reduces systemic allergic inflammation following nasal provocation in allergic rhinitis and asthma patients." *Allergy* 60(10): 1301-7.

BACKGROUND: Preclinical studies have demonstrated that some second-generation antihistamines have anti-inflammatory effects. It is not known whether these effects are also demonstrable in vivo. In this study we investigated the effect of treatment with desloratadine (DL) on systemic inflammation and on nasal and bronchial mucosal inflammation after nasal allergen provocation (NP) in subjects with grass-pollen-allergic rhinitis and asthma. **METHODS:** Twenty-six subjects with grass-pollen-allergic rhinitis and asthma were randomly allocated to 8 days of treatment with DL ($n = 13$) or placebo ($n = 13$) outside the grass pollen season. On day 7 they underwent nasal provocation with grass pollen allergen. Nasal and bronchial biopsies were taken for immunohistochemical evaluation, and blood samples were analysed. Rhinitis and asthma symptoms, peak nasal inspiratory flow and peak expiratory flow, were also measured at specified times. **RESULTS:** The number of circulating eosinophils decreased during DL treatment, and there was a reduced increase in circulating eosinophils after NP in these subjects. There was also a significant reduction in early bronchial clinical response. There was no significant lessening in the severity of the nasal symptoms. Nasal and bronchial mucosal inflammation parameters did not alter under DL treatment. **CONCLUSION:** These data suggest that treatment with DL reduces systemic eosinophilia and prevents the increase in circulating eosinophils after NP. DL also significantly reduces the early bronchial clinical response to NP. However, airway mucosal inflammation is not altered by 1 week of treatment.

Systematic reviews

Berger, W. E. (2005). "The safety and efficacy of desloratadine for the management of allergic disease." *Drug Safety* 28(12): 1101-18.

Allergic disease is an increasing problem worldwide. Allergic rhinitis, an inflammatory response to an allergen, affects an estimated 20-40 million people in the US, while chronic idiopathic urticaria is a dermatological condition that affects 0.1-3% of people in the US and Europe. The primary goals of treatment for allergic rhinitis are to reduce symptoms, which include sneezing, rhinorrhoea and nasal congestion, improve quality of life and prevent the sequelae associated with this disease, while the goal for chronic idiopathic urticaria is the rapid and prolonged control of symptoms. Quantitatively, histamine is the most abundant mediator present during an allergic episode - thus, antihistamines (historically called histamine H(1) receptor antagonists, now called H(1) receptor inverse agonists) are a first-line defense against allergic rhinitis and chronic idiopathic urticaria. Although first-generation antihistamines can cause sedation and cognitive impairment, second-generation antihistamines are relatively non-sedating and free of such adverse events owing to their comparative inability to penetrate the blood-brain barrier. Desloratadine is one such second-generation antihistamine and is indicated for the treatment of allergic diseases, including allergic rhinitis and chronic idiopathic urticaria. It has proven efficacy against the symptoms associated with seasonal and perennial allergic rhinitis, including nasal congestion, and chronic idiopathic urticaria. As a result, it has been shown to improve patients' quality of life. The safety and efficacy profiles of desloratadine are

well established, and published postmarketing analyses have assessed >54 000 patients. Although earlier second-generation antihistamines have been associated with cardiovascular adverse effects, desloratadine has been shown to be safe and well tolerated at nine times the recommended dose. In addition, it has been shown to not interact with concomitantly administered drugs and food. Overall, current data indicate that desloratadine is a safe and effective treatment for allergic diseases. [References: 149]

Gilbert, C., P. Mazzotta, et al. (2005). "Fetal safety of drugs used in the treatment of allergic rhinitis: a critical review." *Drug Safety* 28(8): 707-19.

Allergic rhinitis is the most common allergic disease. Pharmacological interventions are often not used in pregnancy because of alarming information in drug labels and patient information, even when evidence for safety exists. Low-risk therapies could include immunotherapy, intranasal sodium cromoglycate (cromolyn sodium), beclometasone, budesonide and first-generation antihistamines. In a meta-analysis examining the safety of first-generation antihistamines in pregnancy, 200 000 first trimester exposures failed to show increased teratogenic risk. Loratadine is the most studied second-generation antihistamine (with a total patient cohort of 2147 women who were exposed) and does not appear to increase the risk of major congenital malformations; however, it has not been as well studied as the earlier antihistamines. Since desloratadine is the principal metabolite of loratadine, it can be assumed that a similar safety profile would fit for desloratadine as was described for loratadine although no direct human studies have been done. Decongestants have not been conclusively proven to affect the fetal outcome and may be used for short-term relief when no other safer alternatives are available. Intranasal corticosteroids have not been associated with an increase in congenital malformations in humans. Based on efficacy and the fact that there would be little systemic absorption, they can be considered a first-line treatment over oral antihistamines, decongestants and mast cell stabilisers; however, the number of controlled trials in pregnancy is limited. Intranasal corticosteroids are associated with minimal systemic effects in adults and are the most effective therapy for allergic rhinitis. Benefit-risk considerations must, therefore, be done but favour their first-line use during pregnancy. Because fetal safety is paramount, recommendations should be based both on the safety of the drugs during pregnancy and the comparative efficacy of the agent in the treatment of the underlying condition. This review exemplifies the fact that there are many safe treatment options for the clinician when dealing with allergic rhinitis during pregnancy. [References: 67]

Monroe, E. (2005). "Review of H1 antihistamines in the treatment of chronic idiopathic urticaria." *Cutis* 76(2): 118-26.

Chronic idiopathic urticaria (CIU) can have a profound effect on patient quality of life (QOL). Ideally, any therapy used to treat CIU should be effective across a wide range of doses without causing unwanted side effects; a wide therapeutic window allows the physician to tailor treatment to the individual. Oral H1 antihistamines are the mainstay of therapy for CIU, but agents within this class diverge in their individual therapeutic indices. The literature was reviewed to compare the currently available oral H1 antihistamines regarding their efficacy and safety at a wide range of doses. If sedation and cognitive impairment are considered relevant to treatment selection due to their effect on QOL and safety, then newer-generation agents should be selected over older-generation antihistamines. There are few well-controlled clinical studies in which newer-generation agents have been directly compared. Moreover, there are no evidence-based data demonstrating statistical superiority of one newer-generation agent over another in the

treatment of CIU. However, of the newer agents, those that are labelled non-sedating at recommended doses (fexofenadine, loratadine, and desloratadine) should be selected over cetirizine. In cases where the physician judges that a higher-than-recommended dose should be prescribed, or when the patient is likely to take a higher dose, the relative safety profile of these agents demands detailed consideration. [References: 54]

Morgan, M. M., D. A. Khan, et al. (2005). "Treatment for allergic rhinitis and chronic idiopathic urticaria: focus on oral antihistamines." *Annals of Pharmacotherapy* 39(12): 2056-64.

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 H(1)-receptor and an ability to bind to cerebral H(1)-receptors. Newer-generation agents, in general, possess high H(1)-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. [References: 79]