Drug Class Review
on
Second Generation Antihistamines

Final Report

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INTRODUCTION

The most common form of rhinitis is allergic, occurring in 20 to 40 million patients annually in the United States alone, affecting as many as 40% of children and 10% to 30% of adults. Allergic rhinitis (AR) symptoms range from mild to severe, and patients may present with related conditions such as sinusitis and asthma.[1] Health-related quality of life adds to the overall burden as half of patients are symptomatic for over 4 months per year, with 20% affected for 9 or more months per year.[2] While the majority of patients do not seek medical care,[3] AR results in significant lost productivity of both school and workdays. Direct expenditures for AR were estimated at $3.4 billion in 1996, with 46.6% from prescription medications, half of which were for second generation antihistamines.[4, 5]

AR is characterized by nasal mucous membrane swelling and blockage, reflex sneezing and hypersecretion, and ocular manifestations including itching, tearing, and conjunctival redness. Airborne allergens are known to cause an IgE-mediated response of histamine release by basophils and mast cells on cellular histamine receptors, thereby creating a role for antihistamine therapy. Seasonal allergic rhinitis (SAR), otherwise known as hay fever or pollinosis, occurs with tree pollen in the spring, grass pollen in early summer, and wheat pollen or ragweed in late summer. Perennial allergic rhinitis (PAR) may manifest with daily or periodic symptoms from house dust mites (*D. pteronyssinus*), animal dander, and mold. Allergic symptoms have been historically scored using a scale of 0-3, with 0=no symptoms, however the Joint Task Force on Practice Parameters[6] has recently suggested a 7-point scale for improved accuracy.[7]

Chronic idiopathic urticaria (CIU) manifests as daily transient wheals lasting at least 6 weeks. Urticaria symptoms may be daily or episodic and include pruritis with or without pain and burning, erythema, and circumscribed or coalescent wheals. The trunk and extremities are the most common sites, but lesions may appear anywhere. The etiology is difficult to identify but patients should be asked for a detailed history for avoidance or management of known triggers such as recent medications, including over-the-counter (OTC) supplements and herbals, foods, alcohol, physical triggers, insect bites, viral infections, contactants, occupational and natural allergen exposures, and medical disorders. Punch skin biopsy in difficult cases identifies the perivascular lymphocyte-predominant urticaria that is responsive to antihistamine therapy (as opposed to polymorphonuclear, which may require corticosteroids).[6]

Antihistamines inhibit peripheral histamine receptors, and the second generation agents were introduced 20 years ago to provide selective H_1 inhibition. These agents offer longer dosing intervals, negligible anticholinergic, antiseretoninergic, $alpha_1$ and beta-adrenergic properties, and decreased central nervous system (CNS) effects such as sedation. The second generation oral antihistamines available in the United States and Canada and addressed in this review are cetirizine, desloratadine, fexofenadine, and loratadine (which is now available OTC). (Refer to Table 1.)

Table 1. Agents included in this review

Second generation antihistamine (oral)	Protein binding	Onset T_{max} (hours)	Half-life t ½ (hours)	Elimination t 1/2 (hours)	Usual adult dose and interval	Pregnancy category	Cardiac K+ channel blocking	Metabolism	Renal or hepatic impaired
cetirizine (Zyrtec, Pfizer) *metabolite of hydroxyzine	93%	1	7-10	8.3	5-10 mg qd, geriatrics 5mg dose	B	No	Limited 1st pass, 70%/10% unchanged in urine/feces No active metabolites	Decrease dose by 50%
desloratadine (Clarinex, Schering) *metabolite of loratadine	82-89%	3	17.23-24	27	5 mg qd	C	No	Extensive 87% No active metabolites	No adjustment
fexofenadine (Allegra, Aventis) * metabolite of off-market terfenadine	60-70%	2.6	16-23	14.4	60 mg bid or 180 mg qd	C	Possible	Limited 1st pass, unchanged 80%/11% feces/urine No active metabolites	Decrease dose by 50% and dose qd
loratadine (Claritin OTC, Schering)	97%	1.3 to 2.5 for metabolite	7.8-11	8.4 to 28 for metabolite	10 mg qd	B	No	High CYP 3A4, lower CYP 2D6, 40%/40% urine/feces Active metabolite desloratadine with antihistaminic properties	Decrease interval to every other day

Sources: Drug Facts and Comparisons eFacts accessed 05/24/04, Renwick et al, 1999,[8] Mattila et al, 1999,[9] Horak et al, 1999.[10]

Scope and Key Questions

The purpose of this review is to compare the efficacy and adverse effects of different second generation antihistamines. 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 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 clinicians, patients. The participating organizations approved the following key questions to guide this review:

Key Question 1. For adult patients with seasonal or perennial allergic rhinitis (SAR, PAR) or chronic idiopathic urticaria (CIU), do second generation antihistamines differ in effectiveness?

Key Question 2. For adult patients with SAR, PAR, or CIU do second generation antihistamines differ in safety or adverse effects?

Key Question 3. Are there subgroups of patients based on demographics (age, racial groups, gender), concomitant medications (drug-drug interactions), co-morbidities (drug-disease interactions or pregnancy), for which one second generation antihistamine is more effective or associated with fewer adverse effects?

METHODS

Literature Search

To identify articles relevant to each key question, we searched the Cochrane Library (2003, Issue 4), MEDLINE (1966 to February Week 1 2004), EMBASE (1991 to 1st Quarter 2004), and reference lists of review articles. The complete search strategy for electronic searches is in Appendix A. Pharmaceutical manufacturers were invited to submit dossiers, including citations. All citations were imported into an electronic database (EndNote 6.0).

Study Selection

We applied the following eligibility criteria to identify eligible articles:

Exclusion criteria:

1. No original data: Paper does not contain original data (e.g., non-systematic review, editorial, letter).

2. Studies of multiple drugs (e.g., second generation antihistamine/nasal steroid) where the effect of the second generation antihistamine cannot be delineated.

3. Non-English title and abstract.

4. Article published in abstract form only.

Inclusion criteria: Good-quality and fair-quality studies in which:

1. The patients were adults with SAR, PAR, or CIU. Subgroups of interest included, but were not limited to, different races, ages (older adult versus younger adult), other medications (drug-drug interactions), comorbidities (drug-disease interactions or pregnancy), and gender.

2. Intervention included:
   - cetirizine hydrochloride (Zyrtec)
   - desloratadine (Clarinex)
   - fexofenadine hydrochloride (Allegra)
   - loratadine (Claritin, Alavert)

3. For efficacy, we included fair-or-better-quality systematic reviews and controlled trials (including crossover trials) in an outpatient setting (including emergency department).

Trials for AR were limited to 2 or more weeks because the agents continue to improve response between 1 and 2 weeks and this length was necessary for antihistamine approval. Effectiveness outcomes included symptom alleviation (e.g., nasal congestion, rhinorrhoea, sneezing, 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), and duration of effectiveness (e.g., switch rate).

4. To be included, reports about overall safety or adverse events had to report total withdrawals, withdrawals due to specific adverse events (e.g., CNS effects, sedation, GI effects, dry mouth, urinary retention, etc.); or the frequency and severity of these specific adverse events.

When properly designed, direct comparator ("head-to-head") trials provide the best-quality evidence to compare the efficacy and safety of different drugs. Direct comparator trials were available for some drug-drug comparisons.

Observational studies were eligible for the review of adverse events. Clinical trials are often not designed to assess adverse events, and may select low-risk patients (in order to minimize dropout rates) or utilize inadequately rigorous methodology for assessing adverse events. Observational studies designed to assess adverse event rates may include broader populations, carry out observations over a longer time period, utilize higher quality methodological techniques for assessing adverse events, or examine larger sample sizes.

Data Abstraction

One reviewer abstracted the following data from included trials: study design, setting, population characteristics (including sex, age, ethnicity, diagnosis), eligibility and exclusion criteria, interventions (dose and duration), comparisons, numbers screened, eligible, enrolled, and lost to follow-up, method of outcome ascertainment, and results for each outcome. We recorded intention-to-treat results if available and the trial did not report high overall loss to follow-up.

Validity Assessment

We assessed the internal validity (quality) of trials based on the predefined criteria listed in Appendix B. These criteria are based on those developed by the US Preventive Services Task Force and the National Health Service Centre for Reviews and Dissemination (UK).[11, 12] We rated the internal validity of each trial based on the methods used for randomization, allocation concealment, and blinding; the similarity of compared groups at baseline; maintenance of comparable groups; adequate reporting of dropouts, attrition, crossover, adherence, and contamination; loss to follow-up; and the use of intention-to-treat analysis. Trials that had a fatal flaw in one or more categories were rated poor quality and were excluded from the review; trials that met all criteria were rated good quality; the remainder were rated fair quality. As the "fair quality" category is broad, studies with this rating vary in their strengths and weaknesses: the results of some fair quality studies are *likely* to be valid, while others are only *probably* valid. A "poor quality" trial is not valid—the results are at least as likely to reflect flaws in the study design as the true difference between the compared drugs. External validity of trials was assessed based on whether the publication adequately described the study population, how similar patients were to the target population in whom the intervention will be applied, and

whether the treatment received by the control group was reasonably representative of standard practice. We also recorded the funding source and role of the funder.

Appendix B also shows the criteria we used to rate observational studies of adverse events. These criteria reflect aspects of the study design that are particularly important for assessing adverse event rates. We rated observational studies as good quality for adverse event assessment if they adequately met six or more of the seven predefined criteria, fair if they met three to five criteria, and poor if they met two or fewer criteria.

Overall quality ratings for the individual study were based on ratings of the internal and external validity of the trial. A particular randomized trial might receive two different ratings: one for efficacy and another for adverse events. The overall strength of evidence for a particular key question reflects the quality, consistency, and power of the set of studies relevant to the question.

Data Synthesis

We summarized our results in evidence tables and in a narrative summary and table.

RESULTS

Our computerized search strategies identified 1,014 citations, of which 912 were excluded (Figure 1). Seventy-seven trials were reviewed. Of these, 29 were excluded because they were rated poor quality (Appendix C) and 31 were excluded because they used an off-market comparator (terfenadine or astemizole, see Appendix D).

Ten comparative trials were rated fair quality or better and are included in our efficacy analysis: 6 head-to-head trials and 4 active-control trials. Detailed quality assessment of all included trials is described in Evidence Table 1.

For assessment of adverse effects, we included 2 trials, 4 observational studies, and one meta-analysis. Three placebo-controlled trials provided additional information about adverse events.

To assess efficacy and safety in subgroups, we included 2 trials, 4 observational studies, and one meta-analysis.

We identified no trial that was designed to measure effectiveness. Trials measuring efficacy in selected populations may be limited in their generalizability to clinical practice.

Key Question 1. For adult patients with SAR, PAR or CIU, do second generation antihistamines differ in efficacy?

Seasonal allergic rhinitis

Five fair-quality, 2-week head-to-head trials assessed efficacy in seasonal allergic rhinitis (Table 2 and Evidence Table 2).[13-17] The trials varied in country, season, number of patients, and baseline Total Symptom Score (TSS). There were no significant TSS differences in a small Italian trial of loratadine vs. cetirizine;[13] in two large trials of fexofenadine vs. cetirizine;[14, 15] and in one of the two trials of loratadine vs. fexofenadine.[16] In the other trial of loratadine vs. fexofenadine,[17] the primary outcome measure was the proportion of patients who had a 25% or greater decrease in TSS from baseline. The proportion of responders was not significantly different (61% for loratadine vs. 57% for fexofenadine, p=0.29). We did not identify any fair or better trials comparing desloratadine to other antihistamines.

Two trials[18, 19] compared a second generation antihistamine to a first generation antihistamine in patients with SAR (Table 3, Evidence Table 3). In one,[18] desloratadine was 40% less effective than azelastine nasal spray in previous nonresponders to loratadine, but it was not clear from the report whether or not this difference was statistically significant. In the other,[19] loratadine was as effective as clemastine.

Perennial allergic rhinitis

There were no head-to-head efficacy trials of at least fair quality and 2 weeks duration in patients with perennial allergic rhinitis. In one active-control trial of a first-generation versus a second generation antihistamine,[20] symptom relief at 2 and 3 weeks was higher for loratadine than for clemastine (Table 3 and Evidence Table 3). The differences were not statistically significant, however, except for quicker onset with loratadine at day 1 and week 1.

Chronic Urticaria

One large, fair-quality head-to-head trial compared loratadine to cetirizine for patients with chronic idiopathic Urticaria (Table 2 and Evidence Table 2, final row).[21] In this trial, loratadine* reduced mean TSS more than cetirizine but did not result in a higher response rate. There is no fair or better evidence comparing fexofenadine to loratadine or cetirizine; or desloratadine with other antihistamines.

In a four-week trial in 188 patients,[22] cetirizine had a faster onset than the first generation antihistamine hydroxyzine but was effective in a similar proportion of patients (Table 3 and Evidence Table 3).

No evidence is available to determine duration of effectiveness or switch-rates.[23] No fair or better comparative trial assessed quality of life measures, however patient's response and satisfaction with treatment was reported when available and did not differ significantly.

* Over-the-counter loratidine was approved for the treatment of urticaria in 2003.

Table 2. Fair- or better quality head-to-head trials

SAR (Author, Year, Drugs and Dosages)	Country, Season, # of Subjects	Length	Reduction in Total Symptom Score	Other Outcomes	Rating
Ciprandi et al 1997[13] loratadine 10 mg qd vs. cetirizine 10 mg qd	Italy Spring N=20.	2 weeks	loratadine 10 mg -84.6% cetirizine 10 mg -85.7% (not significant between treatments)		Fair
Hampel et al 2003[14] fexofenadine 180 mg qd vs. cetirizine 10 mg qd	US Spring, N=495	2 weeks	Equivalent preset margin 0.7 (between treatment 0.22, 95% CI -0.59 to 0.15) fexofenadine 180 mg -19.0% cetirizine 10 mg-21.6%		Fair
Howarth et al 1999[15] fexofenadine 120 mg qd vs. fexofenadine 180 mg qd vs. cetirizine 10 mg qd vs. placebo	UK, US, France, Peak grass pollen season for the region (season not specified) N=821	2 weeks	fexofenadine 120 mg: -42% fexofenadine 180 mg: -45% cetirizine 10 mg: -45% (not significant between treatments) placebo: -26% (p<0.0001 vs treatment)		Fair
Prenner et al, 2000[17] loratadine 10 mg qd vs. fexofenadine 120 mg qd	US, Season not specified N=659	2 weeks	Patient assessment: loratadine 10 mg -39% fexofenadine 120 mg -33% (p=0.019) Investigator assessment: Loratadine 10 mg –35% fexofenadine 120 mg –29% (p=0.063)		Fair-Poor
Van Cauwenberge et al 2000[16] loratadine 10 mg qd vs. fexofenadine 120 mg qd vs. placebo	Europe (9 countries) and South Africa Season not specified N=688	2 weeks	Not significant between treatments loratadine 10 mg –3.0 (p<0.001 vs placebo) fexofenadine 120 mg –3.3 (p<0.0001 vs placebo) placebo –2.1 (estimated from Fig 2; baseline TSS scores not reported, unable to calculate % change)	Physician assessment of overall effectiveness: loratadine 10 mg 40% fexofenadine 120 mg 44% placebo 36% (NS) Patient assessment of overall effectiveness: loratadine 10 mg 42% fexofenadine 120 mg 47% placebo 37% (NS)	Fair

Table 2. Fair- or better quality head-to-head trials - Continued

CIU (Author, Year, Drugs and Dosages)	Country, # of Subjects	Length	Difference in Total Symptom Score	Other	Rating
Guerra et al 1994[21] loratadine 10mg vs. cetirizine 10mg vs. placebo	Italy, N=116	4 weeks	Significant loratadine 10 mg vs. cetirizine 10 mg day 3, 14, 28 (p<0.01, NS day 7) (*estimated from figure) day 3/7/14/28: loratadine 10 mg -23%/ -46%/ -65% / -81% cetirizine 10 mg -35%/-50%/ -60%/ -69% placebo -19%/ -23%/-34% /-55% Response rate: loratadine 63%, cetirizine 45% (not significant between treatments) placebo 13%		Fair

Table 3. Fair- or better quality active control trials

SAR	Country, Season, # of Subjects	Length	Difference in Total Symptom Score	Other Outcomes	Rating
Berger et al. 2003[18] desloratadine 5 mg vs azelastine nasal vs azelastine nasal + loratadine vs placebo	US Autumn N=440 All were previous nonresponders to loratadine	2 weeks	% improvement from baseline in Total Nasal Symptom Score: (p-values between active treatments not reported) desloratadine 17.5% (p=0.039 vs placebo) azelastine nasal 21.9% (p<0.001 vs placebo) azelastine nasal + loratadine 21.5% (p<0.001 vs placebo) placebo 11.1%		Fair
Dockhorn et al. 1987[19] loratadine 10 mg vs clemastine 2 mg vs placebo	US Spring N=330	2 weeks	NS between active treatments loratadine -49% clemastine -46% placebo 23%		Fair
PAR	**Country, # of Subjects**				
Frolund et al. 1990[20] loratadine 10 mg qd vs. clemastine 1 mg bid vs. placebo	Norway N=155	3 weeks	NS between. active treatment, (*estimated from figure): Week 2: loratadine -61% clemastine -40% placebo -8% Week 3: loratadine -53% clemastine -44% placebo -10%	NS between active treatment for rhinoscopy Onset loratadine vs. clemastine: day 1 p<0.05 week. 1 p<0.05	Fair
CIU					
Breneman et al. 1996[22] cetirizine 10mg qd vs. hydroxyzine25 mg tid vs. placebo	US N=188	4 weeks	NS between. active treatments (*est. from figure): cetirizine -64% hydroxyzine -68% placebo -42%	NS between active treatment for definite/complete response Onset: Sig. cetirizine day 1 vs. hydroxyzine p<0.002	Fair

Key Question 2. For adult patients with SAR, PAR or CIU do second generation antihistamines differ in safety or adverse effects?

Adverse Events

The second generation antihistamines were developed to improve H_1 receptor selectivity and lessen sedation and other side effects associated with first generation agents. The original second generation agents were terfenadine and astemizole; both were removed from the market after case reports of prolonged QT interval resulting in torsade de pointes. Astemizole and terfenadine both exhibited K+ blocking properties in cardiac conducting tissues, and had Cytochrome P450 (CP450) isoenzyme CYP3A4 dependent metabolism. Terfenadine's case reports with concomitant ketoconazole were the first link between altered drug metabolism and adverse events. While astemizole's QT prolonging properties were not as well defined, its long half-life of 48 hours (up to 12 days for its metabolite) and presence of active metabolites presented a potential risk for adverse events. Terfenadine's active metabolite fexofenadine has been introduced to the market, and while a CYP3A4 substrate it has not shown similar cardiac effects.

While loratadine undergoes CYP3A4 metabolism, neither it nor its metabolites affect cardiac K+ channels at usual plasma concentrations and therefore have not been shown to prolong repolarization. Desloratadine (loratadine's active metabolite) and cetirizine have also not shown QT interval effects.

Studies of adverse events are shown in Evidence Table 4. Observational studies[24-27] provide the best available data on adverse effects of long-term use of second generation antihistamines. Sedation was the main focus of these studies, and the overall incidence of sedation was both variable and low. A fair quality meta-analysis[28] suggested both the first and second generation antihistamines result in sedation versus placebo, and the first generation agent diphenhydramine causes more sedation than the second generation agent's cetirizine, fexofenadine, and loratadine. Likewise, a fair quality cohort study comparing loratadine with other second generation antihistamines showed that cetirizine had significantly higher odds of sedation, and no significant difference with fexofenadine.[25] Similar results were seen with a fair- to poor-quality trial of loratadine and cetirizine on sedation and motivation.[29] A second fair-quality cohort study resulted in more claims for serious injury with diphenhydramine versus loratadine.[24] No trial evidence was found on tolerance to the sedation with antihistamines. Cetirizine's labeling includes a statement for using precaution when driving a car or operating potentially dangerous machinery, as well as avoiding concomitant use with alcohol or other CNS depressants as an additional reduction in alertness or performance may occur.

As stated above, prolongation of the QT interval is a concern with this class of agents. A fair quality cohort study[27] reported for all antihistamines combined there was a 4.2 times higher risk of ventricular arrhythmias, with first generation agents posing the highest risk; cetirizine was the highest risk second generation antihistamines at 7.9 times higher risk. The safety and tolerability of fexofenadine was shown in over 16,638 patients in a UK PEM cohort.[26]

Lastly a small, poor-quality trial observed an increase in post-prandial glucose with cetirizine over loratadine or clemastine.[30]

The head-to-head trials reported high (15-25%) incidences of adverse events, but rates of discontinuation due to adverse events were low (Evidence Table 5 and Table 4). This suggests

that, for most patients, the side effects are tolerable. Of 22 placebo-controlled trials in SAR, PAR, and CIU patients, we identified 3 of fair-or-better quality (Appendix E).[31-33] The incidence of adverse events in these trials ranged from 21-51% but caused discontinuation of treatment in less than 3% of patients.

Table 4. Adverse events in head-to-head and active control trials

Head-to-Head Trials	Adverse Events (AEs)	Total withdrawals	Withdrawals from AEs
Ciprandi et al 1997[13] loratadine 10 mg qd vs. cetirizine 10 mg qd	NS AEs reported	0	0
Hampel et al 2003[14] fexofenadine 180mg qd vs. cetirizine 10mg qd	fexofenadine less overall drowsiness p=0.0110, NS effect on motivation 83/495 (16.7%) Total 42/248 (16.9%) fexofenadine 41/247 (16.6%) cetirizine	16 (3.2%) 7 (2.8%) fexofenadine 9 (3.6%) cetirizine	6 (1.2%) AEs 3 efficacy Safety evaluated in AE pop.
Howarth et al 1999[15] fexofenadine 120 mg qd vs. fexofenadine 180 mg qd vs. cetirizine 10 mg qd vs. placebo	Treatment-related AEs: fexofenadine 120 mg: 50/213 (23%) fexofenadine 180 mg: 47/208 (23%) cetirizine 10 mg: 52/209 (25%) placebo: 53/209 (25%)	117 (14% of total) Similar among groups (numbers per group not reported)	fexofenadine: 8/421 (2%) cetirizine: 1/209 (<1%) placebo: 4/209 (2%)
Prenner et al., 2000[17] loratadine 10 mg qd vs. fexofenadine 120 mg qd	22.1% of fexofenadine, 18.2% loratadine had 1 or more adverse event. Considered treatment related in 8.3% fexofenadine, 5.3% loratadine	NR	NR
Van Cauwenberge et al 2000[16] loratadine 10 mg qd vs. fexofenadine 120 mg qd vs. placebo	112/685 (16.4% of total) 39/232 (16.8%) fexofenadine 40/228 (17.5%) loratadine 33/225 (14.7%) placebo	71/685 (10% of total) 22/232 (9%) fexofenadine 27/228 (12%) loratadine 25/225 (11%) placebo	3/232 (1%) fexofenadine 5/228 (2%) loratadine 7/225 (3%) placebo
Guerra et al 1994[21] loratadine 10mg vs. cetirizine 10mg vs. placebo	24 (20.7%) Total NS diff. 6 (15.8%) loratadine 11 (27.5%.) cetirizine 6 (15.8%) placebo	1 cetirizine	1 (2.5%) cetirizine stomach pain

Table 4. Adverse events in head-to-head and active control trials - Continued

Active with Placebo Control Trials	Adverse Events	Total withdrawals	Withdrawals from Adverse Events
Frolund et al. 1990[20] loratadine 10 mg qd vs. clemastine 1 mg bid vs. placebo	51/155 (32.9%) Total 8/53 (15%) loratadine ($p<0.05$) vs. clemastine & placebo 30/51 (58.8%) clemastine, sedation significant 25/51 (49%) placebo	21 (13.5%) 5 (9.4%)loratadine 3 (5.8%)clemastine 13 (25.4%) placebo	0 loratadine 3 (1.9%) clemastine: 1ADE/ 2 efficacy 0 placebo
Breneman et al. 1996[22] cetirizine 10mg qd vs. hydroxyzine25 mg tid vs. placebo	Sedation hydroxyzine vs. placebo p=0.001 18% cetirizine 30% hydroxyzine 6% placebo	5 (4.8%) 1 (1.7%) cetirizine 4 (6.3%) hydroxyzine 4 (6.1%) placebo	1 (1.7%) cetirizine somnolence 4 (6.3%) hydroxyzine somnolence 4 (6.1%) placebo 1 somnolence
Berger et al. 2003[18] desloratadine 5 mg vs azelastine nasal vs azelastine nasal + loratadine vs placebo	Most common per treatment: Bitter taste azelastine nasal (11%), azelastine nasal + loratadine (4%) Headache (3%) and pharyngitis (4%) DES Somnolence: 2% azelastine nasal, 1% azelastine nasal + loratadine, 1% DES, 1% placebo	2 (2%) azelastine nasal 1 (1%) DES 1 (1%) placebo	2/106 (2%) azelastine nasal (moderate chest pain, lightheadedness) 1/111 (1%) DES (headache and nausea) 1/110 (1%) placebo (rash)
Dockhorn et al. 1987[19] loratadine 10 mg vs clemastine 2 mg vs placebo	More AEs (considered probably or possibly treatment-related) in clemastine group: clemastine 37%, loratadine 21%, placebo 20% ($p\leq0.01$) More sedation in clemastine group: clemastine 22%, loratadine 6% ($p\leq0.01$)	NR	NR

Key Question 3. Are there subgroups of patients based on demographics (age, racial groups, gender), concomitant medications (drug-drug interactions), co-morbidities (drug-disease interactions or pregnancy), for which one second generation antihistamine is more effective or associated with fewer adverse effects?

There is no direct evidence that any antihistamine has an advantage in efficacy for any gender or racial group. Pharmacokinetic data in the cetirizine and desloratadine labeling reports no differences were found necessitating dosage adjustment in African Americans and Caucasians. Old age is a risk factor for falls and therefore sedation or impairment is of concern. Cetirizine labeling suggests starting at a lower dosage in the elderly. For patients with renal or hepatic impairment, dosage reduction may be needed (refer to Table 1).

We did not identify head-to-head comparative studies of drug interactions. Information about known drug interactions is shown in Table 5, below. The source of this information is Micromedex, which uses an evidence rating system of *excellent*, *good*, *fair*, *poor*, or *unlikely* to describe the documentation of the interaction. Interactions with *good* or *fair* ratings are included in Table 5. None were rated *excellent* (Controlled studies have clearly established the existence of the interaction) or *unlikely* (Documentation is poor and lacks a sound pharmacologic basis). Interactions rated *poor* (Documentation is poor, such as limited case reports; but the clinical conflict is theoretically possible) are not presented.

Table 5. Potentially significant drug interactions

Drug	Good Documentation: Strongly suggests the interaction exists, but well-controlled studies are lacking.
desloratadine	KETOCONAZOLE Plasma levels of desloratadine are increased in the presence of ketoconazole, although there appears to be no increased risk of electrocardiographic abnormalities in patients without evidence of cardiovascular disease (Affrime, 2000).
fexofenadine	GRAPEFRUIT JUICE Grapefruit juice reduced fexofenadine bioavailability by 60% to 70% in 10 healthy subjects in a single-dose, randomized, crossover study (Dresser et al, 2002). The mechanism was proposed to be due to inhibition of organic anion transporting polypeptide (OATP) by grapefruit juice rather than alteration of P-glycoprotein, resulting in reduced absorption of fexofenadine. Similar results were reported in a subsequent study by Banfield et al (2002). APPLE JUICE Apple juice reduced fexofenadine bioavailability by 80% in 10 healthy subjects in a single-dose, randomized, crossover study (Dresser et al, 2002). The mechanism was proposed to be due to inhibition of organic anion transporting polypeptide (OATP) by apple juice rather than alteration of P-glycoprotein, resulting in reduced absorption of fexofenadine.
Drug	**Fair Documentation: Available documentation is poor, but pharmacologic considerations lead clinicians to suspect the interaction exists; or, documentation is good for a pharmacologically similar drug.**
cetirizine	THETHEOPHYLLINE Coadministration of theophylline and cetirizine may cause decreased cetirizine clearance resulting in elevated cetirizine serum concentrations and possibly cetirizine toxicity (Prod Info Zyrtec(TM), 1995). Until further studies of clinical impact are available, caution is warranted if cetirizine and theophylline are to be used concurrently. Results in elevated cetirizine concentrations, somnolence, fatigue, and dry mouth.
fexofenadine	DROPERIDOL Any drug known to have the potential to prolong the QT interval should not be used together with droperidol. Possible pharmacodynamic interactions can occur between droperidol and potentially arrhythmogenic agents such as antihistamines that prolong the QT interval (Prod Info Inapsine(R), 2001). An increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest) is possible. ERYTHROMYCIN Coadministered erythromycin significantly increased fexofenadine area under the concentration-time curve, maximal concentration at steady state, and time to maximal concentration at steady state. However, changes in fexofenadine plasma concentrations were within the range observed during controlled clinical trials with the drug. Erythromycin pharmacokinetic parameters were unaffected. No significant increases in mean and maximum QT interval, QTc interval, PR interval, or QST complex were seen (Prod Info Allegra(R), 2000; Tech Info Allegra(R), 1997). ORANGE JUICE Orange juice reduced fexofenadine bioavailability by 60% to 70% in 10 healthy subjects in a single-dose, randomized, crossover study (Dresser et al, 2002). The mechanism was proposed to be due to inhibition of organic anion transporting polypeptide (OATP) by orange juice rather than alteration of P-glycoprotein, resulting in reduced absorption of fexofenadine.
loratadine	CIMETIDINE Coadministered oral doses of loratadine and cimetidine produce an increase in loratadine serum concentrations. No significant adverse effects, however, were reported as a result of this comedication, although the studies were done in healthy volunteers receiving a 10-day course of loratadine (Prod Info Claritin(R), 2000). ERYTHROMYCIN Coadministered oral doses of loratadine and erythromycin produce an increase in loratadine serum concentrations (Brannan et al, 1995). However, no adverse effects have been reported as a result of this comedication (Affrime et al, 1993; Brannan et al, 1995). KETOCONAZOLE Coadministered oral doses of loratadine and ketoconazole result in significantly elevated loratadine serum concentrations. However, in a study involving healthy volunteers, no significant adverse effects resulted from concomitant use of these agents (Prod Info Claritin(R), 2000; Kosoglou et al, 2000; Prod Info Nizoral(R), 1998). NEFAZODONE Concomitant administration of nefazodone and terfenadine or loratadine may predispose individuals to torsades de pointes, the arrythmia associated with QTc prolongation (Abernethy et al, 2001).

Source: Micromedex, accessed 10/12/04

Two fair quality placebo-controlled trials were identified in patients with AR and asthma.[34, 35] Patients' assessment of asthma scores significantly improved on cetirizine versus placebo, however no improvement (or worsening) of pulmonary function tests occurred.

The second generation antihistamines are not recommended for use in pregnancy or in lactating women as they pass easily into breast milk (refer to Table 1). Second generation antihistamines cetirizine and loratadine are Federal Drug Administration (FDA) Category B (animal studies have not shown fetal danger however no evidence in humans OR adverse effects in animal studies however no risk in human studies). Fexofenadine and desloratadine are Category C (no or adverse fetal effects seen in animals or however no evidence in humans).[36] First generation antihistamines are all Category B except hydroxyzine, which is Category C. The treatment of choice in pregnant women is cromolyn sodium nasal spray, an anti-inflammatory agent without systemic absorption now available OTC. Additionally, women who were pregnant, lactating, or not using adequate birth control were excluded from clinical trials. That being said, rhinitis is one of the most common conditions during pregnancy, affecting more than 20% of pregnant women.[36] The UK PEM cohort[26] reviewed 16,638 patients finding 30 exposures of first trimester pregnant women; 10 adverse outcomes were all determined not related to antihistamines. Fair evidence from 4 observational studies[37-40] and a meta-analysis[37-41] concurs with the findings of no significant difference in antihistamine use during the first trimester of pregnancy (Evidence Table 6).

SUMMARY

Table 6. Summary of the Evidence

Key Question	Evidence*	Overall Quality of the Evidence
1. Comparative Efficacy For adult patients with SAR, PAR, or CIU, do second generation antihistamines differ in effectiveness?	**SAR** fexofenadine vs. cetirizine: equivalent loratadine vs. cetirizine: NS difference between groups loratadine vs fexofenadine: equivalent **PAR** loratadine vs. clemastine: NS difference. **CIU** loratadine vs. cetirizine: significant difference with loratadine in TSS cetirizine vs. hydroxyzine (first generation): NS diff.	Fair evidence for SAR trials suggests no significant difference between fexofenadine and cetirizine, loratadine and cetirizine, or loratadine and fexofenadine. No fair or better evidence comparing fexofenadine to desloratadine; cetirizine to desloratadine; loratadine to desloratadine. No fair or better head-to-head trials. Fair evidence for PAR suggests no significant difference between loratadine and clemastine, except onset at one week. Fair evidence for CIU suggests a significant difference between loratadine and cetirizine for TSS; and no significant difference in cetirizine vs. first generation hydroxyzine except onset at 1 day. No fair or better evidence comparing desloratadine to cetirizine, fexofenadine, or loratadine; cetirizine to fexofenadine; or fexofenadine to loratadine.

Table 6. Summary of the Evidence

Key Question	Evidence*	Overall Quality of the Evidence
2.Safety/Adverse Effects For adult patients with SAR, PAR or CIU, do second generation antihistamines differ in safety or adverse effects?	**First and second generation antihistamines** more sedation vs. placebo **first vs second generation cetirizine, fexofenadine, or loratadine**. diphenhydramine more sedation Cetirizine significantly higher sedation of second generation antihistamines, NS difference with fexofenadine diphenhydramine more claims for serious injury vs. loratadine **All antihistamines:** 4.2 x risk of arrythmias **Second generation antihistamine arrythmias** Cetirizine highest at 7.9x risk	Fair meta-analysis of first and second generation antihistamines resulted in sedation versus placebo; and diphenhydramine causes more sedation than cetirizine, fexofenadine, or loratadine. Fair cohort comparing loratadine with 2nd generation antihistamines showed cetirizine had significantly higher odds of sedation, NS difference with fexofenadine; similar fair-poor trial of loratadine and cetirizine on sedation and motivation. Fair cohort study with more claims for serious injury with diphenhydramine vs. loratadine. Fair quality cohort study for all antihistamines, a 4 .2 x risk of arrythmias, with cetirizine as the highest risk second generation antihistamine at 7.9. Fair quality safety and tolerability study of fexofenadine in 16, 638 patients in a UK PEM cohort. Poor -quality small trial with an increase in ppg with cetirizine vs. loratadine or clemastine. Fair head-to-head trials low rates of d/c from AEs; 3 fair placebo-controlled trials 21-51% incidence of AEs, NS between groups; caused d/c <3% pts.

Table 6. Summary of the Evidence

Key Question	Evidence*	Overall Quality of the Evidence
3. Subgroups Are there subgroups of patients based on demographics (age, racial groups, gender), concomitant medications (drug-drug interactions), co-morbidities (drug-disease interactions or pregnancy), for which one second generation antihistamine is more effective or associated with fewer adverse effects?	There is no direct evidence that any antihistamine has an advantage in efficacy for any gender, racial group or age. We did not identify head-to-head comparative studies of drug interactions. Two fair-quality placebo-controlled trials were identified in patients with AR and asthma. Patients' assessment of asthma scores significantly improved on cetirizine versus placebo, but no improvement (or worsening) of pulmonary function tests occurred. Fair evidence from 4 cohort studies and a meta-analysis including antihistamine exposures in pregnant women found no significant difference in antihistamine use during the first trimester of pregnancy.	

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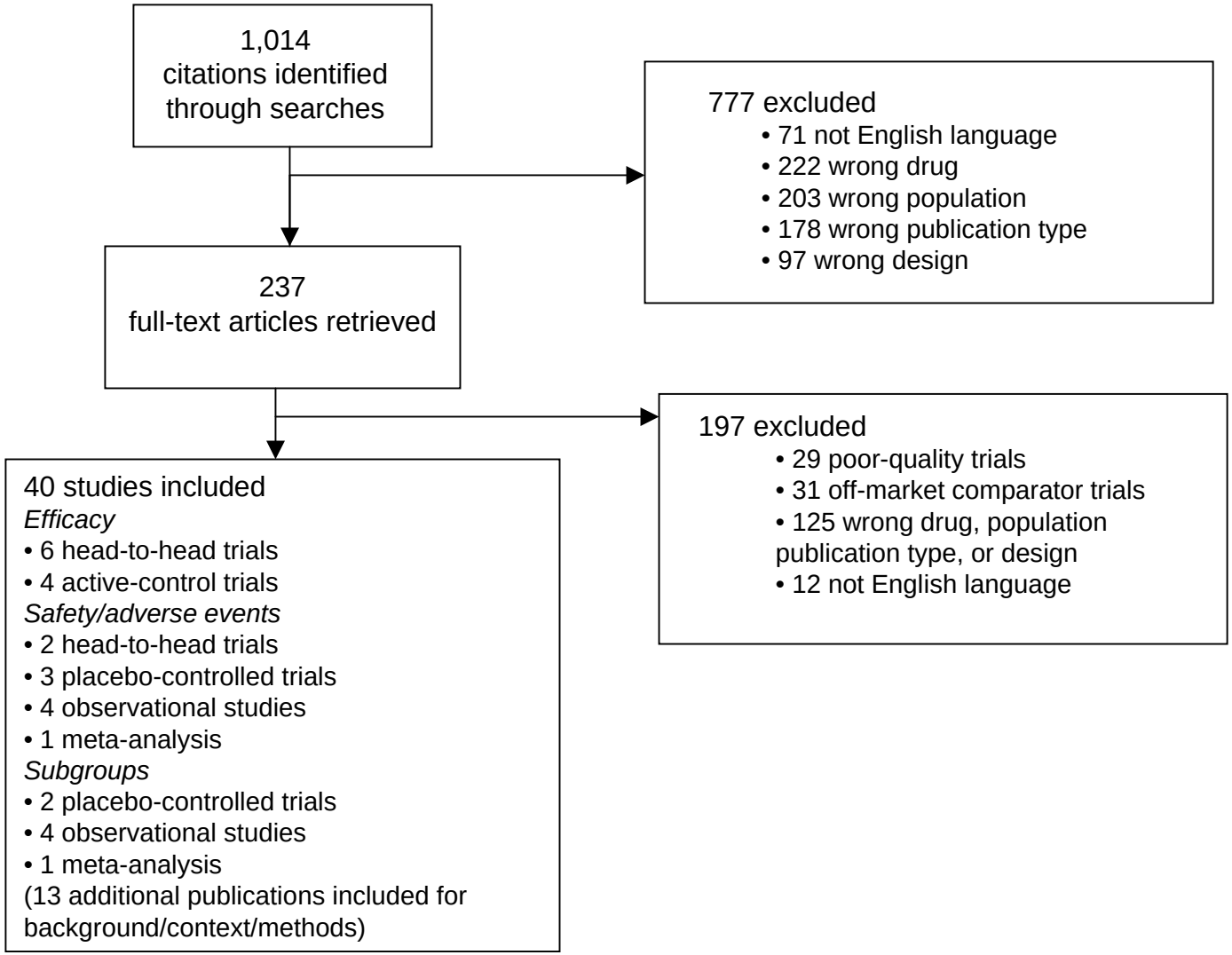
Figure 1. Results of literature search



Evidence Table 1. Quality assessment of included trials

Author, Year Country	Internal Validity: Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?
Head-to-Head Trials						
Ciprandi et al, 1997	Yes, method NR	NR	Yes	Q4. Y	Q5. NR	NR
Hampel et al, 2003	NR	No	Yes	Yes	Safety Yes	NR

Evidence Table 1. Quality assessment of included trials

Author, Year Country	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Quality Rating
Ciprandi et al, 1997	NR	NR	No	Yes	NR	FAIR
Hampel et al, 2003	Yes	NR	No, none	Yes	NR	FAIR

Evidence Table 1. Quality assessment of included trials

	External Validity					
Author, Year Country	**Number screened/eligible/enrolled**	**Run-in/Washout**	**Class naïve patients only**	**Control group standard of care**	**Funding**	**Exclusions**
Ciprandi et al, 1997	NR	NR	No	Yes	Manufacturer funded	Asthma, pregnant/lactating, no method of contraception, upper respiratory infection, anatomic nasal problems or other significant diagnosis, immune therapy, any treatments affecting allergy in 1 month or during study.
Hampel et al, 2003	Yes	5-7 day run-in	No	Yes	Manufacturer funded	Previous lack of response to antihistamines, previous 1 month history of upper respiratory infection, otitis media or sinusitis or investigational drug; pregnant or lactating; immunotherapy not stable for 6 months; serious disease affecting interpretation of results.

Evidence Table 1. Quality assessment of included trials

	Internal Validity					
Author, Year Country	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**
Howarth et al 1999	NR	NR	Yes	Yes	Yes	NR
Prenner et al, 2000	NR	NR	Yes	Yes	Yes	NR

Evidence Table 1. Quality assessment of included trials

Author, Year Country	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Quality Rating
Howarth et al 1999	Yes	NR	No	No	Yes	FAIR
Prenner et al, 2000	Yes	NR	No	Yes	No	FAIR

Evidence Table 1. Quality assessment of included trials

	External Validity					
Author, Year Country	**Number screened/eligible/enrolled**	**Run-in/Washout**	**Class naïve patients only**	**Control group standard of care**	**Funding**	**Exclusions**
Howarth et al 1999	1094/NR/842	3-5 day placebo run-in	No	Yes	Manufacturer funded	Received intranasal or oral prophylactic therapy that season; had received immunotherapy (unless stable for at least 6 months), upper respiratory infection within 30 days, serious renal, cardiac, or hepatic disease, pregnant or lactating, received oral or topical H1 receptor antagonists within last 48 hours
Prenner et al, 2000	810/NR/659	Washout before randomization	No	Yes	Manufacturer funded	Clinically significant diseases, respiratory tract infection within 14 days, known nonresponders to antihistamines, pregnant or lactating.

Evidence Table 1. Quality assessment of included trials

	Internal Validity					
Author, Year Country	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**
Van Cauwenberge et al, 2000	NR	NR	Yes	Yes	Yes	NR
Guerra et al, 1994	Yes, method NR	NR	Yes	Yes	NR	NR

Evidence Table 1. Quality assessment of included trials

Author, Year Country	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Quality Rating
Van Cauwenberge et al, 2000	Yes	Yes/No/No/Yes	No	Yes	Yes	FAIR
Guerra et al, 1994	Yes	NR	Yes	Yes	NR	FAIR

Evidence Table 1. Quality assessment of included trials

External Validity

Author, Year Country	Number screened/eligible/enrolled	Run-in/Washout	Class naïve patients only	Control group standard of care	Funding	Exclusions
Van Cauwenberge et al, 2000	NR/NR/688	3-7 day placebo run-in	No	Yes	Manufacturer funded	Upper respiratory infection or sinusitis in previous 30 days, or any clinically significant medical or mental disorder, recent history of drug abuse, pregnant or lactating, history of hypersensitivity to any study drugs.
Guerra et al, 1994	Yes	Yes	No	Yes	NR	Pregnant/lactating, chronic steroids, physical urticaria, angioneurotic edema, adverse effects due to antihistamines or multiple adverse effects.

Evidence Table 1. Quality assessment of included trials

Author, Year Country	Internal Validity: Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?
	Active-Control Trials					
Frolund et al, 1990	Yes, computer generated code	NR	Yes	Yes	NR	NR, same assessor each time
Breneman et al, 1996	Yes, method NR	NR	Yes	Yes	NR	NR

Evidence Table 1. Quality assessment of included trials

Author, Year Country	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Quality Rating
Frolund et al, 1990	Yes, identical capsules all twice daily	NR	Yes (16%)	Appears yes for AEs	NR	FAIR* Patient diary responses reported in figures without individual values
Breneman et al, 1996	Yes, double dummy	NR	No (5%)	Yes	NR, NR	FAIR

Evidence Table 1. Quality assessment of included trials

	External Validity					
Author, Year Country	**Number screened/eligible/enrolled**	**Run-in/Washout**	**Class naïve patients only**	**Control group standard of care**	**Funding**	**Exclusions**
Frolund et al, 1990	NR	No	No	Yes	Manufacturer funded	History of adverse effects, diagnosis i/a with treatment, pregnant/lactating, nasal polyps, deviated septum or structural defect, active SAR, abnormal labs, immunotherapy in 12 months, loratadine in past 3 months, astemizole in past 1 month, other antihistamines in past 3 days, systemic or topical steroids, cromolyn in past 2 weeks, decongestants in past 24 hours.
Breneman et al, 1996		NR	No	Yes	NR	Antihistamines within 36 hours, central acting agents within 1 week, astemizole within 6 weeks, asthma except bronchodilator only

Evidence Table 1. Quality assessment of included trials

	Internal Validity					
Author, Year Country	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**
Berger et al., 2003	NR	NR	Yes	Yes	Yes	NR

Evidence Table 1. Quality assessment of included trials

Author, Year Country	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Quality Rating
Berger et al., 2003	Yes	NR	No	Yes	Yes	FAIR

Evidence Table 1. Quality assessment of included trials

External Validity

Author, Year Country	Number screened/eligible/enrolled	Run-in/Washout	Class naïve patients only	Control group standard of care	Funding	Exclusions
Berger et al., 2003	596/NR/440	7 day active run-in with loratadine	No	Yes	Manufacturer funded	Limited to patients with poor response to loratadine. Exclusions: Use of concomitant medications that could affect evaluation of efficacy; any medical or surgical condition that could affect metabolism of study medications; clinically significant nasal disease other than SAR or significant nasal structural abnormalities; respiratory or other infection requiring antibiotics with 2 weeks, significant pulmonary disease and/or active asthma requiring daily medication, history or current drug or alcohol abuse.

Evidence Table 1. Quality assessment of included trials

	Internal Validity					
Author, Year Country	**Randomization adequate?**	**Allocation concealment adequate?**	**Groups similar at baseline?**	**Eligibility criteria specified?**	**Outcome assessors masked?**	**Care provider masked?**
Dockhorn et al., 1987	NR	NR	Yes	Yes	Yes	NR

Evidence Table 1. Quality assessment of included trials

Author, Year Country	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Quality Rating
Dockhorn et al., 1987	Yes	NR	No	Yes	Yes	FAIR

Evidence Table 1. Quality assessment of included trials

External Validity

Author, Year Country	Number screened/eligible/enrolled	Run-in/Washout	Class naïve patients only	Control group standard of care	Funding	Exclusions
Dockhorn et al., 1987	NR/NR/330	No	No	Yes	NR	Women of childbearing potential, history of asthma in past 2 years, immunotherapy with pollen extracts started in past 12 months, any significant current disease or abnormal lab test result, multiple drug allergies or history of idiosyncratic reactions to antihistamines, use of any investigational drug in previous month.

Evidence Table 2. Included Head-to-head Efficacy Trials

Author, Year, Country	Indication, trial characteristics	Interventions (dose, duration)	Population Characteristics
Ciprandi et al., 1997 Italy	SAR, randomized, double-blind, parallel, 1994 May pollen season	loratadine 10 mg qd vs cetirizine 10 mg qd for 2 weeks	29 patients, history of SAR, ≥2 years treatment, skin test positive. Baseline: 38% female, mean age 31 years, range 18-44 years. TSS median 13-14 (scale 0-3), pollen counts range 0-200. All baselines similar except eosinophil cationic protein nasal lavage levels.

Evidence Table 2. Included Head-to-head Efficacy Trials

Author, Year, Country	Outcome Measures	Results
Ciprandi et al., 1997 Italy	TSS	TSS: loratadine: -11 (-84.6%) vs cetirizine: -12 (-85.7%); p<0.002. Significant vs baseline NS between groups. Nasal lavage also for inflammatory markers, NS between agents.

Evidence Table 2. Included Head-to-head Efficacy Trials

Author, Year, Country	Indication, trial characteristics	Interventions (dose, duration)	Population Characteristics
Hampel et al., 2003 US	SAR, multicenter, randomized, double-blind, double-dummy, parallel-group, autumn & winter/spring pollen season	fexofenadine 180 mg qd vs cetirizine 10 mg qd for 2 weeks	784 screened, 495 randomized, age >12 years, history of SAR, positive skin test to grass, TSS ≥6 with ≥2 symptoms. Moderate or severe. Baseline similar: 12-70 years, mean 34.8 years, 66% female, 67% Caucasian, 17 years. average allergic rhinitis history.
Howarth et al., 1999 UK, US, France	SAR, multicenter, randomized, double-blind, peak grass pollen season	fexofenadine 120 mg qd vs fexofenadine 180 mg qd vs cetirizine 10 mg qd vs placebo for 2 weeks	1094 screened, 842 randomized, 821 analyzed, history of SAR at least 2 years, positive skin test to mixed grass pollens, age 12 to 65. Baseline similar: mean 33 years, 51% male, mean TSS 7.3.

Evidence Table 2. Included Head-to-head Efficacy Trials

Author, Year, Country	Outcome Measures	Results
Hampel et al., 2003 US	TSS=sneezing, rhinorrhea, itchy nose or palate or throat, itchy or watery or red eyes, each on scale 0-4.	TSS 24 hr overall (95% CI): fexofenadine -19.0 % vs cetirizine -21.6% between treatment -0.22 (-0.59 to 0.15) Within preset 0.7 margin for 2-sided 95% CI, therefore equivalent. A.M. instantaneous: fexofenadine -1.27(-1.64 to -0.90) vs cetirizine -1.44 (-1.83 to -1.06); between treatment –0.18 (-0.55 to 0.20) = equivalent 24 hr reflective, at week 1: fexofenadine -1.34 (-1.70 to -0.99) vs cetirizine -1.56 (-1.93 to -1.19). at week 2: fexofenadine: -1.84 (CI -2.25 to -1.43) vs cetirizine -2.09 (-2.52 to -1.66) overall: fexofenadine - 19.0% -1.56 (-1.92 to 1.20) vs cetirizine -21.6% -1.78 (-2.15 to -1.40) between treatment -0.22 (-0.59 to 0.15)=equiv. A priori equivalence based on published pediatric results (Pearlman et al 1997) where active agent improved TSS by –1.4, therefore 50% or 0.7 margin was used for total 2-sided 95% CI.
Howarth et al., 1999 UK, US, France	TSS=Sum of sneezing; rhinorrhea; itchy nose, palate, or throat; itchy, watery, or red eyes each on scale 0-5.	NS between active treatments (mean reduction in 24-hour reflective TSS): fexofenadine 120 mg: -3.0 fexofenadine 180 mg: -3.3 cetirizine 10 mg: -3.3 placebo: -1.9 ($p<0.0001$ vs tx)

Evidence Table 2. Included Head-to-head Efficacy Trials

Author, Year, Country	Indication, trial characteristics	Interventions (dose, duration)	Population Characteristics
Prenner et al., 2000 US	SAR, randomized, double-blind, multicenter, season not specified	loratadine 10 mg qd vs fexofenadine 120 mg qd for 2 weeks	659 patients ages 12 to 60, seasonal allergens prevalent during the study period (not specified), confirmed by skin test TSS of 7 or more. 810 screened, 659 r, mean age 35.3 fexofenadine, 32.3 loratadine, otherwise similar at baseline. 60% female, mean TSS 10.6 (investigator assessment), 32.6 (patient assessment)
Van Cauwenberge et al., 2000 Europe and South Africa	SAR, multicenter, double-blind, randomized, placebo-controlled, season not specified	loratadine 10 mg qd vs fexofenadine 120 mg qd vs placebo for 2 weeks	688 randomized, 639 analyzed. Similar at baseline: 55.3% female, 90.2% white, mean age 31.2 (sd 11.95).age 12 to 75, positive skin test for grass and/or tree pollen, history of response to antihistamines to relieve allergic symptoms.

Evidence Table 2. Included Head-to-head Efficacy Trials

Author, Year, Country	Outcome Measures	Results
Prenner et al., 2000 US	TSS	TSS, Patient assessment: loratadine 10 mg -39% fexofenadine 120 mg -33% (p=0.019) TSS, Investigator assessment: loratadine 10 mg –35% fexofenadine 120 mg –29% (p=0.063)
Van Cauwenberge et al., 2000 Europe and South Africa	TSS (patient assessment)=sum of individual symptom scores assessed by the patient for sneezing; rhinorrhea; itchy nose, palate, and/or throat; and itchy, watery and/or red eyes, each on a scale from 0-4.	NS between active treatments: loratadine –3.0 (p<0.001 vs placebo) lexofenadine –3.3 (p<0.0001 vs placebo) placebo –2.1(estimated from Fig 2) Assessment of overall effectiveness, physician assessment: loratadine 40%; fexofenadine 44% placebo 36% Patient assessment: loratadine 42% fexofenadine 47% placebo 37%

Evidence Table 2. Included Head-to-head Efficacy Trials

Author, Year, Country	Indication, trial characteristics	Interventions (dose, duration)	Population Characteristics
Guerra et al., 1994 Italy	CIU, double-blind, randomized, parallel group	loratadine 10 mg vs cetirizine 10 mg and placebo for 4 weeks	116 patients ≥ 12 years old. Baseline similar: 38.8 years old, 61% female, symptoms 1.8-2.4 years.

Evidence Table 2. Included Head-to-head Efficacy Trials

Author, Year, Country	Outcome Measures	Results
Guerra et al., 1994 Italy	4-point scale TSS	TSS: loratadine significant vs.cetirizine p<0.01 days 3,14,28 Day 3/7/14/28 (*estimated from figure): loratadine -23%/ -46%/ -65% / -81% cetirizine -35%/ -50%/ -60% / -69% placebo -19%/ -23%/ -34% / -55% Active treatment significant vs. placebo p<0.05 Responders: loratadine 63% asymptomatic vs. 45% cetirizine (NS difference); placebo was significantly worse at 13% (p< 0.05)

Evidence Table 3. Included active control trials

Author, Year, Country	Indication, trial characteristics	Interventions (dose, duration)	Population Characteristics
Frolund et al, 1990 Norway	PAR, multicenter, randomized double-blind, placebo-controlled, parallel-group.	loratadine 10 mg qd vs. clemastine 1 mg bid vs. placebo for 3 weeks	155 patients ages 18-65. 130 completed 127 patient forms. Loratadine 52 patients, clemastine 31 patients, placebo 51 patients. PAR symptoms for ≥1 year. TSS ≥4 (scale 0-3), skin test wheal 50% of positive control and larger than negative. Baseline: values similar (*estimated from figure TSS 6-6.5, total nasal scores 6, total eye score 1.5-2.5, nasal itching and stuffiness 1-1.5).

Evidence Table 3. Included active control trials

Author, Year, Country	Outcome Measures	Results
Frolund et al, 1990 Norway	TSS	TSS 1 weeks: loratadine significantly better than clemastine (p<0.05, *estimated from figure) loratadine -49% clemastine -31% placebo -10% 2, 3 weeks: NS difference between active treatments, significant vs. placebo (p<0.05 *estimated from figure at 2/3 weeks) loratadine - 61% / 53% clemastine -40% / 44% placebo -8% / 10% Nasal symptom scores: loratadine significantly better than clemastine at 1 week for nasal itching, stuffiness, p <0.05 (concurred w/ patient diaries); NS difference at 2 or 3 weeks. Active treatment significant vs placebo, p<0.01. Eye symptoms scores: NS difference between active treatments. Active treatments significantly better than placebo for itching/redness p<0.05, NS for tearing. Rhinoscopy: Active treatments significantly better vs. placebo, p<0.05 Onset: Loratadine significant vs. clemastine at day , p<0.05. * Diary responses not individually reported

Evidence Table 3. Included active control trials

Author, Year, Country	Indication, trial characteristics	Interventions (dose, duration)	Population Characteristics
Breneman et al., 1996 US	CIU, multicenter, randomized, double-blind, double-dummy, placebo-controlled, parallel-group	cetirizine 10 mg qd vs. hydroxyzine 25 mg tid vs. placebo for 4 weeks	188 patients, CIU 6-week history, unknown etiology, ≥ age 12, similar baseline: 69% female, ages 34.5-38.8.
Berger et al. 2003 US	SAR, multicenter, double-blind, randomized, placebo-controlled	desloratadine 5 mg vs azelastine nasal vs azelastine nasal + loratadine vs placebo for 2 wks	596 screened, 440 randomized, age 12 or older, 2-year history of SAR, positive skin test, unsatisfactory response to loratadine. Similar at baseline: 66% female, 80% white, 11% black, 9% Asian or other, mean age 35 (range 12-79).

Evidence Table 3. Included active control trials

Author, Year, Country	Outcome Measures	Results
Breneman et al., 1996 US	Assessor scale 0-3 (3=≥20 lesions); response efficacy/ sedation pt. scale 0-4, 0=no improvement or worse, sedation 0-3, 0=none.	TSS: cetirizine and hydroxyzine significant vs. placebo, p<0.006. *estimated from figure cetirizine-8.5 (-64%) hydroxyzine -8.7 (-68%) placebo -5.3 (-42%) All other significant weeks 1-4 active treatment vs. placebo for lesion episodes (p=0.001), number/size/ itching (p<0.05), or duration (p=0.001). Onset: cetirizine significantly better at day 1 than hydroxyzine in mean number of episodes greater than 1 hour apart (p<0.002). Responders: Definite or complete improvement significant active treatment vs. placebo (p<0.001).
Berger et al. 2003 US	Total Nasal Symptom Score=combined score of runny nose, sneezing, itchy nose, nasal congestion, each on scale of 0-3	% improvement from baseline in Total Nasal Symptom Score: (p-values between active treatments not reported) desloratadine 17.5% (p=0.039 vs placebo) azelastine nasal 21.9% (p<0.001 vs placebo) azelastine nasal + loratadine 21.5% (p<0.001 vs placebo) placebo 11.1%

Evidence Table 3. Included active control trials

Author, Year, Country	Indication, trial characteristics	Interventions (dose, duration)	Population Characteristics
Dockhorn et al. 1987 US	SAR, multicenter, double-blind, randomized, placebo-controlled.	loratadine 10 mg vs clemastine 2 mg vs placebo for 2 weeks.	330 randomized, 321 analyzed; similar at baseline: 79% male, 93% white, mean age 32 (range 12-65); symptoms of SAR plus positive skin test for spring pollens.

Evidence Table 3. Included active control trials

Author, Year, Country	Outcome Measures	Results
Dockhorn et al. 1987 US	TSS	NS between active treatments loratadine (-49%) clemastine (-46%) placebo (23%)

Evidence Table 4. Studies of adverse events

Internal Validity

Author, Year	Study Outcomes, Characteristics	Results	Non-biased selection?
Bender et al., 2003	Sedation, performance impairment First and second generation antihistamines, meta-analysis of trials of diphenhydramine vs. astemizole, ACR, cetirizine, fexofenadine, loratadine, terfenadine. Inclusion: 18 trials of allergy, randomized, double-blind, placebo controlled, sedation scores, English, with means and variances, vs. diphenhydramine (mostly healthy patients. or < 2 wks). Exclusion: Non-allergic, no sedation measures, no measure of variance.	Sedation effect size small and variable among trials, however diphenhydramine significantly worse vs. placebo: 0.36 (95% CI 0.20-0.51, p=0.0001; diphenhydramine significantly worse vs. second generation antihistamines: 0.31 (95% CI 0.17-0.45, p=0.0001) Second generation antihistamines significantly worse vs.placebo: 0.14 (95% CI 0.01-0.26, p=0.030)	Yes

Evidence Table 4. Studies of adverse events

Author, Year	Low overall loss to follow-up?	Adverse events pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?
Bender et al., 2003	N/A	Yes	Yes	Yes

Evidence Table 4. Studies of adverse events

External Validity

Author, Year	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Adequate description of population?	Groups similar at baseline?	# screened / eligible / enrolled?
Bender et al., 2003	Yes	Yes	Yes	Yes	Yes, # studies

Evidence Table 4. Studies of adverse events

Author, Year	Exclusion criteria specified?	Funding	Overall Quality
Bender et al., 2003	Yes	NR	Fair

Evidence Table 4. Studies of adverse events

Internal Validity

Author, Year	Study Outcomes, Characteristics	Results	Non-biased selection?
Finkle et al., 2002	Serious injury Diphenhydramine or loratadine at 1 month; cohort. Inclusion: Health care claims database Jan '91-Dec. '98. Baseline: diphenhydramine 12,106 patients; loratadine 24, 968 patients; ages 49-55, 53.1%-55.9% female. NS injury rates same time previous year	Diphenhydramine 308 injuries per 1000 patient years vs.137 in loratadine, age and gender adjusted RR 2.27 (95% CI 1.93, 2.66).	N/A

Evidence Table 4. Studies of adverse events

Author, Year	Low overall loss to follow-up?	Adverse events pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?
Finkle et al., 2002	N/A	Yes	Yes	Yes

Evidence Table 4. Studies of adverse events

External Validity

Author, Year	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Adequate description of population?	Groups similar at baseline?	# screened / eligible / enrolled?
Finkle et al., 2002	NR	Yes	Yes	Yes	NR

Evidence Table 4. Studies of adverse events

Author, Year	Exclusion criteria specified?	Funding	Overall Quality
Finkle et al., 2002	N/A	manufacturer funded	Fair

Evidence Table 4. Studies of adverse events

Internal Validity

Author, Year	Study Outcomes, Characteristics	Results	Non-biased selection?
Mann et al., 2000	Sedation Loratadine vs cetirizine, fexofenadine, acrivastinein, PEM UK cohort. Inclusion: May-Aug '89 cetirizine and loratadine, Mar-Aug '97 fexofenadine Baseline: 43,363 patients, 56%-62% female, 36%-49% < age 30 , 7-14% > age 60..	Sedation vs. loratadine: significantly higher for cetirizine (odds ratio 3.52, 95% CI 2.17 to 5.71, p<0.0001), NS difference for fexofenadine (odds ratio 0.63 (95% CI 0.36-1.11, p=0.1); overall sedation was low with no correlation with accident or injury.	N/A
Salmun et al., 2000	Somnolence and motivation Randomized, double-blind trial assessing VAS scale 1-10 in workday with loratadine 10 mg qd, cetirizine 10 mg qd for 1 week. Inclusion: AR symptoms 2-3 on 0-3 scale, positive skin test wheal 3mm > control or intradermal administration wheal 7mm > control in past year, age ≥12. Exclusion: Interfering disease, asthma requiring steroids, sinusitis or URI, rebound rhinitis, past >2 ADEs or AE to antihistamines, pregnant/lactating. Baseline: 60 patients, ages 31.2 -32.6 years, 52% men, similar scores except cetirizine patients. Baseline 20% difference in somnolence.	Significantly more somnolence and less motivation with cetirizine vs. loratadine at 10 am, noon, and 3 pm. Other AEs NS difference	Yes

Evidence Table 4. Studies of adverse events

Author, Year	Low overall loss to follow-up?	Adverse events pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?
Mann et al., 2000	NR	Yes	Yes	Yes
Salmun et al., 2000	Yes	Yes	Yes	Yes

Evidence Table 4. Studies of adverse events

External Validity

Author, Year	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Adequate description of population?	Groups similar at baseline?	# screened / eligible / enrolled?
Mann et al., 2000	Yes	Yes	Yes	Yes	51%-57% response rate
Salmun et al., 2000	NR	Short f/u 1 week	Yes	Yes	NR, 60 patients enrolled

Evidence Table 4. Studies of adverse events

Author, Year	Exclusion criteria specified?	Funding	Overall Quality
Mann et al., 2000	N/A	Public funding	Fair
Salmun et al., 2000	Yes	manufacturer funded	Fair-poor

Evidence Table 4. Studies of adverse events

Internal Validity

Author, Year	Study Outcomes, Characteristics	Results	Non-biased selection?
Craig-McFeely et al., 2001	Fexofenadine in UK prescription event monitoring cohort. Inclusion: Survey GPs with rxs Mar -Aug '97. Baseline 59% female, ages 36-39, AR 55%, CIU 4.3% (28.4% NR). Cohort 16,638 patients.	AE total: 40 (0.2%) in 27 patients, d/c <2%, 30 unrelated deaths. Cardiac: 8 non-serious, 1 irregular pulse w/ possible grapefruit drug/food interaction. Other possible: 1 aggression, 1 neutropenia, resolved with d/c. Pregnancy-related: 47 total, of 30 exposed 1st trimester, 4 miscarriages, 1 therapeutic termination, 1 PE death, 1 unknown, 23 live births with 3 unrelated AE: premature/incompetent cervix, positional foot deformity and fetal distress	N/A
de Abajo et al., 1999	Cardiac Ventricular arrythmia and AH ACR, astemizole, cetirizine, loratadine, terfenadine, UK cohort. Inclusion: Patients < age 80, rx Jan '92-Sept.'96, 5 years. Exclusion: cancer, arrythmias Baseline: Cohort 197,425 with 2.6 rx/patient, 151events identified, 86 reviewed.	Arrythmia results: Total idiopathic (none fatal) 18 cases Any antihistamine: 9 cases (7 in 1st month); 1.9 per 10,000 person-years (95% CI 1.0-3.6), 4.2 times higher than non-use (95% CI 1.5-11.8). Second generation antihistamines- 1 case in 57,000 rxs, astemizole highest RR 19 (95% CI 4.8-76) cetirizine RR 7.9, (95% CI 1.6-39.3), loratadine RR 3.2 (CI NS) terfenadine RR 2.1 .(CI NS) No interactions with P450Is (low ketoconazole use).	Yes

Evidence Table 4. Studies of adverse events

Author, Year	Low overall loss to follow-up?	Adverse events pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?
Craig-McFeely et al., 2001	8.7% non-evaluble forms	Yes	Yes	Yes
de Abajo et al., 1999	Yes low loss to f/u 5% missing	Yes	Yes	Yes

Evidence Table 4. Studies of adverse events

External Validity

Author, Year	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Adequate description of population?	Groups similar at baseline?	# screened / eligible / enrolled?
Craig-McFeely et al., 2001	Yes	Yes	Yes	Yes	Identified 35,817 rxs from 8057 GPs, 18,238 (50.9%) returned.
de Abajo et al., 1999	Yes	Yes f/u 5 years	Yes	Yes	Yes, screened 3 million

Evidence Table 4. Studies of adverse events

Author, Year	Exclusion criteria specified?	Funding	Overall Quality
Craig-McFeely et al., 2001	N/A	Public funding	Fair
de Abajo et al., 1999	Yes: 60 excluded for non-confirmed diagnosis	Public funding	Fair

Evidence Table 4. Studies of adverse events

Internal Validity

Author, Year	Study Outcomes, Characteristics	Results	Non-biased selection?
Lal et al., 2000	Blood glucose. Randomized, double-blind, placebo-controlled. Cetirizine 10 mg qd, loratadine 10 mg qd, clemastine mg bid. Inclusion: AR, Jan-Nov '97. Exclusion: Diabetes mellitus, cardiac, liver, renal, respiratory disease. Baseline: Similar; ages 31-33 years (age? 10-year-old in clemastine), 58.3% male (usually more females), fasting blood glucose 78.2-81.33 g%, ppg 97.11- 101.50 g%. G	Glucose: cetirizine >ppg p=0.02, loratadine NS difference clemastine NS difference	Yes

Evidence Table 4. Studies of adverse events

Author, Year	Low overall loss to follow-up?	Adverse events pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?
Lal et al., 2000	10% d/c, 1 cetirizine 3 loratadine	No events	Yes	Yes

Evidence Table 4. Studies of adverse events

External Validity

Author, Year	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Adequate description of population?	Groups similar at baseline?	# screened / eligible / enrolled?
Lal et al., 2000	NR	No, f/u only 1 week	Yes	No	NR

Evidence Table 4. Studies of adverse events

Author, Year	Exclusion criteria specified?	Funding	Overall Quality
Lal et al., 2000	Yes	NR	Poor

Evidence Table 5. Adverse events reported in efficacy trials

Author, year	Adverse events (results)	Internal Validity: Non-biased selection?	Internal Validity: Low overall loss to follow-up?
Head-to-head trials			
Ciprandi et al., 1997 Italy	No significant AE reported.	Yes	Yes
Hampel et al., 2003 US	Fexofenadine significantly less overall drowsiness (p=0.0110), no significant effect on motivation; D/C treatment: 16 (7 fexofenadine, 9 cetirizine); AEs: 6 of 16, efficacy 3 of 16. Safety evaluated in the patients with AEs.	Yes	Yes
Howarth et al., 1999 UK, US, France	Treatment-related AEs: fexofenadine 120 mg: 50/213 (23%); fexofenadine 180 mg: 47/208 (23%); cetirizine 10 mg: 52/209 (25%); placebo: 53/209 (25%); D/C treatment: 117 (14% of total), similar among groups (numbers per group not reported)	Yes	Yes
Prenner et al, 2000 US	Adverse events: 22.1% of fexofenadine, 18.2% loratadine group had 1 or more adverse events. Considered treatment related in 8.3% of fexofenadine, 5.3% loratadine Discontinued treatment: NR Discontinued due to AEs: NR	Yes	Yes

Evidence Table 5. Adverse events reported in efficacy trials

Author, year	Adverse events pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?	Statistical analysis of potential confounders?
Head-to-head trials				
Ciprandi et al., 1997 Italy	Yes	Diary	Yes	NR
Hampel et al., 2003 US	Yes	Diary	Yes	NR
Howarth et al., 1999 UK, US, France	Yes	Yes	Yes	No
Prenner et al, 2000 US	No	No	Yes	No

Evidence Table 5. Adverse events reported in efficacy trials

Author, year	Adequate duration of follow-up?
Head-to-head trials	
Ciprandi et al., 1997 Italy	Yes, all patients completed
Hampel et al., 2003 US	Yes
Howarth et al., 1999 UK, US, France	
Prenner et al, 2000 US	Yes

Evidence Table 5. Adverse events reported in efficacy trials

Author, year	Adverse events (results)	Internal Validity: Non-biased selection?	Internal Validity: Low overall loss to follow-up?
Van Cauwenberge et al., 2000 Europe and South Africa	AEs: 112/685 (16.4% of total); 39/232 (16.8%) fexofenadine 40/228 (17.5%) loratadine 33/225 (14.7%) placebo; D/C treatment: 71/685 (10% of total); 22/232 (9%) fexofenadine; 27/228 (12%) loratadine; 25/225 (11%) placebo	Yes	Yes
Guerra et al., 1994 Italy	NS difference in AEs. (loratadine and placebo 15.8%; cetirizine 27.5%.). One cetirizine patient d/c due to stomach pain.	Yes	No
Active-control Trials			
Frolund et al., 1990	AEs significantly less with loratadine than clemastine or placebo ($p<0.05$). AE of sedation significant with clemastine. loratadine: 8/53 AEs. 5 d/c not from AE clemastine: 30/51 AEs, d/c, 1 AE and 2 failures. placebo: 13 d/c, 9 due to failures	Yes	Yes
Breneman et al., 1996	Sedation significantly different hydroxyzine vs placebo $p=0.001$ D/C for somnolence: cetirizine 1 patient, hydroxyzine 4 patients, placebo 1 patient. 3 more placebo patients discontinued.	Yes	Yes

Evidence Table 5. Adverse events reported in efficacy trials

Author, year	Adverse events pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?	Statistical analysis of potential confounders?
Van Cauwenberge et al., 2000 Europe and South Africa	No	Yes	No	No
Guerra et al., 1994 Italy	Yes	NR	Yes	NR
Active-control Trials				
Frolund et al., 1990	Yes	Yes, diary	Yes	NR
Breneman et al., 1996	Yes	Diary	Yes	NR

Evidence Table 5. Adverse events reported in efficacy trials

Author, year	Adequate duration of follow-up?
Van Cauwenberge et al., 2000 Europe and South Africa	Yes
Guerra et al., 1994 Italy	Yes
Active-control Trials	
Frolund et al., 1990	Yes
Breneman et al., 1996	Yes

Evidence Table 5. Adverse events reported in efficacy trials

Author, year	Adverse events (results)	Internal Validity: Non-biased selection?	Internal Validity: Low overall loss to follow-up?
Berger et al., 2003	Most common AEs per treatment: Bitter taste: 11% azelastine nasal, 4% azelastine nasal + Loratadine, 3% headache and 4% pharyngitis Somnolence: desloratidine 2%, azelastine nasal 1%, azelastine nasal + Loratadine 1%, desloratidine 1%, placebo. D/C treatment: 2 (2%) azelastine	No	Yes
Dockhorn et al., 1987	More AEs (considered probably or possibly treatment-related) in clemastine group: clemastine 37%, loratadine 21%, placebo 20% ($p<0.01$) More sedation in clemastine group: clemastine 22%, loratadine 6% ($p<0.01$) D/C treatment: NR	Yes	Yes

Evidence Table 5. Adverse events reported in efficacy trials

Author, year	Adverse events pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?	Statistical analysis of potential confounders?
Berger et al., 2003	No	No	NR	No
Dockhorn et al., 1987	No	Yes	Yes	No

Evidence Table 5. Adverse events reported in efficacy trials

Author, year	Adequate duration of follow-up?
Berger et al., 2003	Yes
Dockhorn et al., 1987	Yes

Evidence Table 6. Trials in subgroups

Author, Year, Subgroup	Agents	Trial Characteristics
Aaronson et al., 1996 PAR and Asthma	Cetirizine 20 mg qd; albuterol prn; pseudoephedrine rescue.	PAR and asthma, 28 patients, 26 weeks. ITT efficacy. Inclusion: ages 12-65 + skin test; FEV1 ≥ 50%, prednisone, improved 15% by albuterol w/o seasonal exacerbations. Exclusions: pregnant/lactating/no contraception, i/a diagnosis or meds, ADEs AH. Baseline similar: All caucasian, 54% male, 29.7 years
Grant et al., 1995 SAR and Asthma	Cetirizine 10 mg qd; albuterol prn, pseudoephedrine rescue, theophylline if stable	SAR and asthma, US, Fall, multicenter, randomized, double-blind, placebo-controlled, 6 weeks. Inclusion/exclusion: ages 12-70, SAR, FEV1 50-80%, prednisone and 15% + with bronchodilator, + skin test within 2 years. No severe AR or asthma, i/a dx, ADEs, previous cetirizine investigation or investigational drug in past 1 month. Baseline similar: age 28, 56% female, 82% caucasian, diagnosis 18 years, 23-30% on theophylline, 57-65% FEV1 50-84%, ITT safety ? efficacy
Diav-Citrin et al., 2003 Pregnancy	Prospective controlled cohort on exposure of pregnant women to antihistamines	Israeli teratogen counseling service followed 210 pregnancies exposed to loratadine (77.9% in 1st trimester) and 267 to other antihistamines (64.6% in the first trimester) to 929 controls.
Einarson et al., 1997 Pregnancy	Prospective controlled cohort on exposure of pregnant women to hydroxyzine or cetirizine	Canadian counseling service for safe exposure to drugs followed all patients requesting information on HTD or cetirizine use during pregnancy 1989-1994 for major malformation and pregnancy outcomes.

Evidence Table 6. Trials in subgroups

Author, Year, Subgroup	Results	Quality
Aaronson et al., 1996 PAR and Asthma	Efficacy: Significantly improved asthma score, not albuterol use or PFTs Total AE d/c: 10.28 (35.7%) cetirizine 4 (28.5%) placebo 6 (42.8%) d/c from AE: 0	Fair
Grant et al., 1995 SAR and Asthma	Efficacy: Cetirizine significant vs. placebo SAR, asthma no worse in season, better asthma score, NS PFTs. Total AE over 4% patients: Cetirizine 43 pts (46%) placebo 45 pts (48%) d/c: cetirizine 9/93 (9.6%), placebo 24/93 (25.8%) d/c from AE: cetirizine 0, placebo 1 joint stiffness, nervousness	Fair
Diav-Citrin et al., 2003 Pregnancy	NS difference between groups major anomalies loratadine vs.control RR 0.77 (95% CI 0.27 to 2.19) and loratadine vs. other antihistamines RR 0.56 (95% CI 0.18 to 1.77)	Fair
Einarson et al., 1997 Pregnancy	Of 120 pregnancies, 81 hydroxyzine, 39 cetirizine, 75% in first trimester (hydroxyzine 65%, cetirizine 95%). NS difference between exposed groups or control.	Fair

Evidence Table 6. Trials in subgroups

Author, Year, Subgroup	Agents	Trial Characteristics
Moretti et al., 2003 Pregnancy	Prospective controlled cohort on exposure of pregnant women to loratadine	Teratology information service (Canada, Isreal, Italy and Brazil) followed up on contacts for loratadine exposure in 161 patients during first trimester,
Seto et al., 1997 Pregnancy	Meta-analysis of 1st trimester pregnancy antihistamine exposure 1960-1991.	24 studies met criteria (85 rejected for animal studies, case reports, reviews, duplicates or irrevelant) with over 200,000 women.
Wilton et al., 1998 Pregnancy	Observational cohort on exposure of pregnant womenin 1st trimester to newly marketed agents.	UK prescription event monitoring reported 831 of 2511 pregnancies in 2467 women exposed to newly marketed drug (included 20 cetirizine pregnancies and 18 loratadine) in 1st trimester, 74 in 2nd and 3rd trimesters.

Evidence Table 6. Trials in subgroups

Author, Year, Subgroup	Results	Quality
Moretti et al., 2003 Pregnancy	NS difference RR 0.88 (95% CI 0.27 to 2.82).	Fair
Seto et al., 1997 Pregnancy	Found NS difference in trials of women using antihistamines for nausea and vomiting. OR 0.76 (95% CI:0.60-0.94).	Fair
Wilton et al., 1998 Pregnancy	Follow-up of 780 (94%) of pregnancies showed NS difference with controls.	Fair

Appendix A. Search Strategies for Second Generation Antihistamines

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <4th Quarter 2003>
Search Strategy:
---
1 (Cetirizine or zyrtec).mp. (405)
2 (Loratadine or Claritin).mp. (350)
3 (Fexofenadine or Allegra).mp. (88)
4 (Desloratadine or Clarinex).mp. (48)
5 1 or 2 or 3 or 4 (769)
6 from 5 keep 1-769 (769)

Database: Ovid MEDLINE(R) <1966 to February Week 1 2004>
Search Strategy:
---
1 (Cetirizine or zyrtec).mp. (780)
2 (Loratadine or Claritin).mp. (648)
3 (Fexofenadine or Allegra).mp. (237)
4 (Desloratadine or Clarinex).mp. (89)
5 1 or 2 or 3 or 4 (1394)
6 (adverse effect$ or poison$ or toxic$).mp. (281734)
7 limit 5 to (yr=1980-2004 and (controlled clinical trial or guideline or meta analysis or randomized controlled trial)) (550)
8 5 and 6 (97)
9 limit 8 to yr=1980-2004 (97)
10 7 or 9 (617)
11 limit 10 to human (610)
12 limit 11 to english language (571)
13 limit 11 to abstracts (583)
14 12 or 13 (607)
15 from 14 keep 1-607 (607)

Database: EMBASE Drugs & Pharmacology <1991 to 1st Quarter 2004>
Search Strategy:
---
1 (Cetirizine or zyrtec).mp. (1922)
2 (Loratadine or Claritin).mp. (1771)
3 (Fexofenadine or Allegra).mp. (709)
4 (Desloratadine or Clarinex).mp. (182)
5 1 or 2 or 3 or 4 (3110)
6 Clinical Trial/ (198754)
7 random$.mp. (123352)
8 controlled study/ (931676)

9 6 and (7 or 8) (118454)
10 Meta Analysis/ (11472)
11 (systemat$ adj5 review$).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name] (1862)
12 cohort$.mp. (19413)
13 9 or 10 or 11 or 12 (143294)
14 5 and 13 (522)
15 (adverse effect$ or poison$ or toxic$).mp. (117517)
16 5 and 15 (189)
17 16 and 13 (26)
18 14 or 17 (522)
19 limit 18 to human (522)
20 limit 19 to english language (472)
21 limit 19 to abstracts (464)
22 20 or 21 (514)
23 from 22 keep 1-514 (514)

Appendix B. Quality assessment methods for drug class reviews for the Drug Effectiveness Review Project

The purpose of this document is to outline the methods used by the Oregon Evidence-based Practice Center (EPC), based at Oregon Health & Science University, and any subcontracting EPCs, in producing drug class reviews for the Drug Effectiveness Review Project.

The methods outlined in this document ensure that the products created in this process are methodologically sound, scientifically defensible, reproducible, and well-documented. This document has been adapted from the Procedure Manual developed by the Methods Work Group of the United States Preventive Services Task Force (version 1.9, September 2001), with additional material from the NHS Centre for Reviews and Dissemination (CRD) report on *Undertaking Systematic Reviews of Research on Effectiveness: CRD's Guidance for Carrying Out or Commissioning Reviews* (2nd edition, 2001) and "The Database of Abstracts of Reviews of Effects (DARE)" in *Effectiveness Matters*, vol. 6, issue 2, December 2002, published by the CRD.

All studies or systematic reviews that are included are assessed for quality, and assigned a rating of "good", "fair" or "poor". Studies that have a fatal flaw in one or more criteria are rated poor quality; studies which meet all criteria, are rated good quality; the remainder are rated fair quality. As the "fair quality" category is broad, studies with this rating vary in their strengths and weaknesses: the results of some fair quality studies are *likely* to be valid, while others are only *probably* valid. A "poor quality" trial is not valid—the results are at least as likely to reflect flaws in the study design as the true difference between the compared drugs.

For Controlled Trials:

Assessment of Internal Validity

1. Was the assignment to the treatment groups really random?
    - Adequate approaches to sequence generation:
        - Computer-generated random numbers
        - Random numbers tables
    - Inferior approaches to sequence generation:
        - Use of alternation, case record numbers, birth dates or week days
    - Not reported

2. Was the treatment allocation concealed?
    - Adequate approaches to concealment of randomization:
        - Centralized or pharmacy-controlled randomization
        - Serially-numbered identical containers
        - On-site computer based system with a randomization sequence that is not readable until allocation
        - Other approaches sequence to clinicians and patients
    - Inferior approaches to concealment of randomization:

Use of alternation, case record numbers, birth dates or week days
Open random numbers lists
Serially numbered envelopes (even sealed opaque envelopes can be subject to manipulation)
Not reported

3. Were the groups similar at baseline in terms of prognostic factors?

4. Were the eligibility criteria specified?

5. Were outcome assessors blinded to the treatment allocation?

6. Was the care provider blinded?

7. Was the patient kept unaware of the treatment received?

8. Did the article include an intention-to-treat analysis, or provide the data needed to calculate it (i.e., number assigned to each group, number of subjects who finished in each group, and their results)?

9. Did the study maintain comparable groups?

10. Did the article report attrition, crossovers, adherence, and contamination?

11. Is there important differential loss to followup or overall high loss to followup? (give numbers in each group)

Assessment of External Validity (Generalizability)

1. How similar is the population to the population to whom the intervention would be applied?

2. How many patients were recruited?

3. What were the exclusion criteria for recruitment? (Give numbers excluded at each step)

4. What was the funding source and role of funder in the study?

5. Did the control group receive the standard of care?

6. What was the length of followup? (Give numbers at each stage of attrition.)

For Studies Reporting Complications/Adverse Effects

Assessment of Internal Validity

1. Was the selection of patients for inclusion non-biased (Was any group of patients systematically excluded)?

2. Is there important differential loss to followup or overall high loss to followup? (Give numbers in each group.)

3. Were the events investigated specified and defined?

4. Was there a clear description of the techniques used to identify the events?

5. Was there non-biased and accurate ascertainment of events (independent ascertainer; validation of ascertainment technique)?

6. Were potential confounding variables and risk factors identified and examined using acceptable statistical techniques?

7. Did the duration of followup correlate to reasonable timing for investigated events? (Does it meet the stated threshold?)

Assessment of External Validity

1. Was the description of the population adequate?

2. How similar is the population to the population to whom the intervention would be applied?

3. How many patients were recruited?

4. What were the exclusion criteria for recruitment? (Give numbers excluded at each step)

5. What was the funding source and role of funder in the study?

Systematic Reviews:

1. Is there a clear review question and inclusion/exclusion criteria reported relating to the primary studies?

A good quality review should focus on a well-defined question or set of questions, which ideally will refer to the inclusion/exclusion criteria by which decisions are made on whether to include or exclude primary studies. The criteria should relate to the four components of

study design, indications (patient populations), interventions (drugs), and outcomes of interest. In addition, details should be reported relating to the process of decision-making, i.e., how many reviewers were involved, whether the studies were examined independently, and how disagreements between reviewers were resolved.

2. Is there evidence of a substantial effort to search for all relevant research?

This is usually the case if details of electronic database searches and other identification strategies are given. Ideally, details of the search terms used, date and language restrictions should be presented. In addition, descriptions of hand-searching, attempts to identify unpublished material, and any contact with authors, industry, and research institutes should be provided. The appropriateness of the database(s) searched by the authors should also be considered, e.g. if MEDLINE is searched for a review looking at health education, then it is unlikely that all relevant studies will have been located.

3. Is the validity of included studies adequately assessed?

A systematic assessment of the quality of primary studies should include an explanation of the criteria used (e.g., method of randomization, whether outcome assessment was blinded, whether analysis was on an intention-to-treat basis). Authors may use either a published checklist or scale, or one that they have designed specifically for their review. Again, the process relating to the assessment should be explained (i.e. how many reviewers involved, whether the assessment was independent, and how discrepancies between reviewers were resolved).

4. Is sufficient detail of the individual studies presented?

The review should demonstrate that the studies included are suitable to answer the question posed and that a judgement on the appropriateness of the authors' conclusions can be made. If a paper includes a table giving information on the design and results of the individual studies, or includes a narrative description of the studies within the text, this criterion is usually fulfilled. If relevant, the tables or text should include information on study design, sample size in each study group, patient characteristics, description of interventions, settings, outcome measures, follow-up, drop-out rate (withdrawals), effectiveness results and adverse events.

5. Are the primary studies summarized appropriately?

   The authors should attempt to synthesize the results from individual studies. In all cases, there should be a narrative summary of results, which may or may not be accompanied by a quantitative summary (meta-analysis).

   For reviews that use a meta-analysis, heterogeneity between studies should be assessed using statistical techniques. If heterogeneity is present, the possible reasons (including chance) should be investigated. In addition, the individual evaluations should be weighted in some way (e.g., according to sample size, or inverse of the variance) so that studies that are considered to provide the most reliable data have greater impact on the summary statistic.

Appendix C. Poor Quality Comparative Trials

Head-to-Head and Active-Control Trials

	Author	Agents	Design	Fatal Flaw
1.	Campbell A 1997	Cetirizine vs. Loratadine vs. PLA	SAR	No ITT, small sample size (16 tx, 7 control)
2.	Gambardella 1993	Azelastine nasal vs. Loratadine	SAP	No ITT, no info on baseline characteristics
3.	Harvey 1996	Cetirizine vs. Chlorpheniramine vs. Terfenidine	SAR	No ITT, outcome assessment not blinded, randomization inadequate
4.	Irander 1990	Loratadine 40 vs. 1st GEN Clemastine 1 mg bid vs PLA	SAR	No ITT, excluded scores on days requiring additional medication.
5.	Kalivas 1990	Cetirizine vs. 1st GEN Hydroxyzine vs. PLA	CIU	No ITT, no info on baseline characteristics
6.	Nunes C 2000	Cetirizine vs. Loratadine	CIU	No ITT, no info on baseline characteristics
7.	Passali 1994	Azelastine nasal vs. Cetirizine	PAR	No ITT, no info on baseline characteristics
8.	Patel P 1997	Cetirizine vs. Loratadine	CIU	No ITT, withdrawals per group not reported.
9.	Ricard 1999	Loratadine vs. Fexofenadine	SAR	No ITT, # randomized not reported, no info on baseline characteristics
10.	Wilson 2002	Fexofenadine vs. Desloratadine	SAR	No ITT, no info on baseline characteristics.

Placebo Controlled Trials (No ITT analysis)

Author		Characteristics
1. Bernstein 1997	Fexofenadine 60, 120, 240 mg bid	SAR, mc, r db, pc, 57 pts late summer 2 wks
2. Casale 1999	Fexofenadine 120 or 180 mg qd	SAR mc, r, pc, 861 pts. 2 wks
3. Ciprandi 2001	Fexofenadine 120 180mg	PAR, db, pc, 31 pts 4 wks
4. Dolovich 1994	Loratadine 10 mg qd	SAR, db, pc, 180 pts 6 weeks
5. Juhlin 1991	Cetirizine 10 or 20 mg qd	CIU, db, pc, 30 pts 2 wks
6. Juhlin 1988	Cetirizine 10 mg qd	CIU, r, db, pc, 30 pts 2 wks
7. Mansmann 1991	Cetirizine 10, 20 mg qd	PAR, db, pc, 215 pts 4 wk
8. Meltzer 1999	Fexofenadine 120 or 180 mg qd	SAR, r, db, pc, QOL
9. Monroe 2003	Desloratadine 5mg qd	CIU, r, db, pc, 6 wk
10. Monroe 1998	Loratadine 10 mg qd	CIU, mc, db, pc, 169 pts. 4 wks
11. Murray 2002	Cetirizine	SAR mc, r , db, pc, , 865 pts. 2 wks
12. Nelson 2000	Fexofenadine 20, 60, 120, or 240mg	CIU, r, db, pc, 4 wks
13. Raptopoulou 1993	Loratadine 10 mg	SAR, db, pc, 48 pts. 4 wks
14. Salmun 2002	Desloratadine 2.5, 5, 7.5, 10, or 20 mg qd	SAR, r, db, pc, 1026 pts 2 wks
15. Thompson 2000	Fexofenadine 60 mg twice daily	CUI mc, r db, pc 160 & 165 pt trials 4 wks
16. Vena 2002	Fexofenadine 180 mg qd	CIU, open, 20 pts. 4 wks.
17. Wasserman 1991	Cetirizine 10 mg and 5mg qd	SAR, db, pc, 88 pts spring 2 wks
18. Zuberbier 1995	Cetirizine 10 or 20 mg qd	CIU, r, db, 24 pts 3wks
19. Zuberbier 1996	Cetirizine 20 mg qd	CIU, db, pc, 11 pts. 3 wks

Appendix D. Trials with off-market comparators

Author	Agents	Indication
1. Abu S. 1992	Loratadine vs. Terfenidine	CIU
2. Alomar A. 1990	Cetirizine vs. Astemizole	CIU
3. Andri 1993	Cetirizine vs Terfenidine	CIU
4. Arendt 1989	Cetirizine vs. Terfenidine	CIU
5. Berkowitz 1996	Astemizole vs Cetirizine	SAR
6. Bruttman 1987	Loratadine vs Terfenidine	SAR
7. Bruttman 1989	Loratadine vs. Terfenidine	PAR
8. Belaich 1990	Loratadine vs. Terfenidine	CIU
9. Breneman 1995	Cetirizine vs. Astemizole	CIU
10.Bonifazi 1995	Terfenidine vs Cetirizine	SAR
11.Carlsen 1993	Loratadine vs Terfenidine	PAR
12.Chervinsky 1994	Loratadine vs. Astemizole	SAR
13.Crawford 1998	Terfenidine vs. Astemizole	PAR
14.Davies B 1991	Cetirizine vs. Terfenidine	SAR
15.Del Carpio J. 1989	Loratadine vs. Terfenidine	SAR
16.Gutkoski 1984	Loratadine vs. Terfenidine vs. PLA	SAR
17.Harcup J 1993	Astemizole vs. Cetirizine	SAR
18.Horak 1988	Loratadine vs. Terfenidine vs. PLA	SAR
19.Kietzmann 1990	Cetirizine vs. Terfenidine	CIU
20.Klementsson 1990	Cetirizine vs. Terfenidine vs. PLA	SAR
21.Lasar 1992	Loratadine vs. Astemizole	SAR
22.Lee 1994	Loratadine vs. Astemizole	AR
23.Lobaton 1990	Cetirizine vs. Astemizole	PAR
24.Lockey 1995	Cetirizine vs. Terfenidine vs. PLA	SAR
25.Oei 1988	Loratadine vs Astemizole	SAR
26.Olsen 1992	Loratadine vs. Terfenidine	SAR
27.Rajaram 1994	Cetirizine vs. Astemizole	PAR
28.Rihoux 1992	Cetirizine vs. Terfenidine	CIU
29.Renton 1991	Cetirizine vs. Terfenidine	PAR
30.Vijay 1994	Cetirizine vs. Astemizole	CIU
31.Wessel 1997	Loratadine vs. Terfenidine	SAR

Appendix E. Included Placebo-Controlled Trials

Author Year	Agents	Placebo-Controlled Trial Characteristics	Quality
Meltzer et al, 2001	Desloratadine 5 mg qd	SAR, r, db, pc, 2 trials each 2 wks. Inclusion: ≥12 yo, 2 yr hx, positive skin test w/i 1 yr. rhinitis score ≥2, TNS ≥6, non-nasal ≥5. Exclusion: i/a dx. rebound rhinitis, sinusitis, invest. drug w/i 1 mo, preg/lact/URI w/i 1 wk, abx. w.i 2 wks, structural nasal dx, immune therapy non-maintenance, i/a meds. Baseline similar: Spring 18-65 yo, 60% female, 75% caucasian, dx. 17yrs, TSS 14.2-13.7, Fall dx. 20 yrs TSS 17-17.1. computer gen r, ITT. Spring 346 pts:Total AEs 133 (38%) NS dif. btw: 69 Desloratadine 40% 64 PLA 37%d/c from AE's: Desloratadine 2.9%, placebo 5.7%AEs > 10%: headache Desloratadine 16% PLA 14%Fall 328pts:Total AEs: 166pts. (50.6%) NS dif. btw. pts. Desloratadine 81 (49%), PLA 85 (52%) d/c: 5 pts. (3%) d/c from AE's: 1 pt. (0.6%)AEs > 10%: headache Desloratadine 24%, PLA 27%	Fair
Noonan et al., 2003	Cetirizine 10 mg qd	SAR, r, db, pc, 403 pts, 2 wks.Inclusion/Exclusion: 18-65 yo SAR needing rx for 2 yr, + skin test 1 yr, healthy, no i/a meds.Baseline similar: 35.8 yo, 88% caucasian 67% female, 20 yr dx, ITTTotal AEs: 104 in 83 pts (21%). NS diff. btw. Cetirizine 19% PLA 23%d/c: 24 pts (6%). d/c from AEs: Cetirizine 1 pt (0.5%) PLA 6pts. (3%); 5/7 were respiratory sx. AE's most frequent somnolence, 13% treatment related (Cetirizine 6 in 5 pts, PLA 7 in 6 pts).	Fair
Ring et al., 2001	Desloratadine 5mg qd	CIU, r, db, pc, 190 pts, 6 wksInclusion/Exclusion: ≥12 yo, ≥6 wk, hx, active 3 wks 3x/wk, TSS ≥14, healthy, no i/a meds.Baseline similar: 40 yo, 63% female, 83% caucasian, 5 yr dx, comp. gen r, ITTTotal AEs 94 pts (49.4%) NS dif. btw: 53 Desloratadine 55.8%, 41 4 PLA 43.2%d/c: 51 pts (26.8%) d/c from AE's: Desloratadine 3 (3.2%), PLA 2 (2.1%) all unrelated to tx.AEs > 10%: headache Desloratadine 12.6% PLA 16.8%	Fair