Drug Class Review
on
Newer Antihistamines

Final Report Update 1

April 2006

Original Report Date: November 2004
A literature scan of this topic is done periodically

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

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Note: A scan of the medical literature relating to the topic is done periodically (see http://www.ohsu.edu/ohsuedu/research/policycenter/DERP/about/methods.cfm for scanning process description). Upon review of the last scan, the Drug Effectiveness Review Project governance group elected not to proceed with another full update of this report. Some portions of the report may not be up to date. Prior version of this report can be accessed at the DERP website.

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INTRODUCTION

Antihistamines inhibit the effects of histamine at H1 receptors. Histamine is a physiologically active, endogenous substance that binds to and activates histamine H1 and H2 receptors in the respiratory tract (including the nose), the gastrointestinal tract,[1] the brain, adrenal medulla, skin vasculature, and the heart.[2] H2-receptor antagonists are usually referred to as H2 receptor antagonists (e.g., cimetidine).

In allergic conditions, histamine and other substances are secreted from mast cells, basophils, and other cell types. Histamine then binds to, and activates, specific receptors, causing smooth muscle constriction, vasodilation, endothelial permeability, and sensory nerve stimulation. These actions of histamine are manifest clinically as characteristic allergic signs and symptoms: sneezing, rhinitis, rhinorrhea, erythema, pruritis and urticaria.[1] Oral antihistamines generally provide relief of these symptoms, which are all associated with the early response to histamine. Symptoms of nasal obstruction are characteristic of late allergic reaction and are minimally relieved by antihistamines.[3]

Antihistamines can be classified[4] as first generation (sedating, e.g., chlorpheniramine, diphenhydramine, promethazine, and hydroxyzine), second generation (relatively nonsedating, e.g., terfenadine, astemizole, loratadine, and cetirizine) and third generation (fexofenadine, norastemizole, and descarboethoxyloratadine). First-generation antihistamines are highly lipophilic and therefore readily cross the blood-brain barrier, contributing to adverse central nervous system effects, including sedation, drowsiness, and decreased cognitive processing. First generation drugs also have relatively short half-lives, necessitating multiple daily doses.[5]

Newer antihistamines were developed to decrease the adverse effects of first generation drug. 'Second generation' antihistamines emerged in the early 1980s and have higher specificity for binding to H1 receptors, lower affinity for non-histamine receptors, and are lipo-phobic (thus have poor penetration of the blood brain barrier). These drugs are thereby less likely to be sedating than first generation drugs. They also have longer half-lives, permitting once- or twice-daily dosing.[5] Third generation antihistamines are natural metabolites of second generation drugs, developed with the goal of improving clinical efficacy and minimizing side-effects.[4]

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. Both of these drugs exhibited K+ blocking properties in cardiac conducting tissues, and had Cytochrome P450 (CP450) isoenzyme CYP3A4-dependent metabolism. Case reports of the use of terfenadine with concomitant ketoconazole were the first link between altered drug metabolism and adverse events. While the QT-prolonging properties of astemizole were not as well defined, its long half-life of 48 hours (up to 12 days for its metabolite) and the presence of active metabolites, presented a potential risk for adverse events.

Antihistamines have a number of clinical indications including allergic conditions (e.g., rhinitis, dermatoses, atopic dermatitis, contact dermatitis, allergic conjunctivitis, hypersensitivity reactions to drugs, mild transfusion reactions, and urticaria), chronic idiopathic urticaria (CIU), motion sickness, vertigo, and insomnia.

The second and third 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 over-the-counter{OTC}).

Rhinitis

Rhinitis refers to disease involving inflammation of the nasal membranes.[6] Symptoms include nasal discharge, sneezing, and congestion. Rhinitis is considered pathologic when symptoms are severe enough to require therapy. Rhinitis may be infectious or noninfectious. Noninfectious, or allergic, rhinitis (AR) may be seasonal (SAR) or perennial (PAR), and is characterized by nasal mucous membrane swelling and blockage, reflex sneezing and hypersecretion, and ocular manifestations including itching, tearing, and conjunctival edema and redness. Non-allergic (vasomotor, "irritant") rhinitis is also common, and responds better to topical nasal steroids than oral antihistamines (although moderate response can often be seen with topical nasal antihistamines).

Persons with SAR, otherwise known as hay fever or pollinosis, have symptoms primarily in the spring, summer, or fall, during the pollinating season of the plants to which affected persons are sensitive, including trees, grass, or weeds.[6] Persons with PAR, on the other hand, have year-round symptoms (although there may be some seasonal variation) related to allergens that are largely indoors (e.g., house dust mites {*D. pteronyssinus}*, animal dander, and mold spores).[6; 7]

It is often difficult to differentiate between SAR and PAR, and the World Health Organization's Allergic Rhinitis and its Impact on Asthma Group has recommended instead that AR be classified as 'intermittent' and 'persistent'.[8]

AR is a very common condition worldwide, with estimates of global prevalence ranging between 10 and 25%,[9] and epidemiologic evidence suggests that the prevalence of AR is increasing.[10; 11] Approximately 40 million people in the United States experience significant symptoms of AR for all or part of each year.[12-14] AR is the sixth most common chronic disease in the U.S. affecting as many as 35 million people.[13] AR is even more prevalent in younger populations; AR is thought to affect up to 40% of children and adolescents.[6; 9; 15; 16]

AR has a number of important sequelae. Health-related quality of life is impacted by AR, including effects on physical function, energy, social function, mental health, bodily pain, mood, learning ability, and workplace productivity.[17; 18] If left untreated, AR can be associated with serious complications, including asthma, sinusitis, respiratory infections, and otitis media.[18; 19] In addition, AR appears to be linked to a number of other conditions. AR may be considered an independent risk factor for asthma and the two diseases often coexist.[5; 8] Atopic dermatitis is also linked to both AR and asthma.

AR among children is particularly problematic, as the condition is often undiagnosed or misdiagnosed. AR can have a large impact on the health and quality of life of children, including school absenteeism, diminished school performance, and mental health consequences.[18; 19] In the U.S., it is estimated that children with AR miss 2 million days of school per year.[15] AR and its treatment can affect school performance by causing diminished cognitive function,[19] irritability, disrupted sleep patterns and sleep loss, mood disturbances, and impaired social function.[5] Children with poorly-controlled AR are at an increased risk for developing asthma, chronic sinusitis, and otitis media, as well as other respiratory complications.

The objective of treatment of AR is to diminish symptoms and decrease progression to other sequelae and complications. Since this is a chronic condition, treatments must be safe, well-tolerated, and effective in the long-term. First-line treatments for AR include allergen avoidance and environmental control; however, the evidence for the effectiveness of these interventions is limited.[2] Pharmacotherapy treatment recommendations depend on symptom severity and may

include antihistamines, decongestants, corticosteroids, leukotriene-receptor antagonists, mast cell stabilizers, anticholinergics, and allergen-specific immunotherapy.[20]

Urticaria

Urticaria is a condition characterized by transient, pruritic wheals, which are primarily the result of histamine release from mast cells. It is estimated that at least 50% of general populations have experienced urticaria at one time or another.[1] Chronic urticaria is usually defined as recurring episodes of urticaria lasting 6 weeks or more.[1]

The etiology of chronic urticaria can be physical stimuli or may be idiopathic. Types of chronic urticaria that occur in response to physical stimuli include dermatographism (urticaria in response to stroking, friction, or rubbing), cholinergic urticaria (where stimuli that raise the core temperature of the body elicit urticaria), cold urticaria (where wheals occur after exposure to cold; this condition is rarely associated with underlying diseases),[21] solar urticaria (provoked by ultraviolet light), and aquagenic urticaria (precipitated by contact of the skin with water of any temperature). So-called "idiopathic urticaria", may be due to an autoimmune process in 40-50% of patients.[22]

CIU is self-limited for most patients; 50% undergo spontaneous remissions within 1 year. Twenty percent, however, have intermittent symptoms for years.[21]

Acute urticaria is much more common than the chronic form in both adults and children, accounting for 70% of cases.[21] Acute urticaria is idiopathic in greater than 50% of cases. It can, however, occur as a hypersensitivity reaction to food, wasp or bee stings, as a response to blood products, infection, or febrile illness, or as a response to various drugs. A variety of drugs can cause acute as well as chronic urticaria, most commonly antimicrobial agents, anti-inflammatory drugs, analgesics, angiotensin-converting enzyme (ACE) inhibitors, and blood products.[21]

Scope and Key Questions

The purpose of this review was to compare the efficacy, effectiveness, and adverse effects of newer antihistamines in both adult and pediatric populations. The Oregon Evidence-based Practice Center wrote preliminary key questions and identified the populations, interventions, and outcomes of interest. Based on these key questions, the eligibility criteria were developed for studies included in this review. The key questions were reviewed and revised by representatives of organizations participating in the Drug Effectiveness Review Project (DERP). The participating organizations of DERP are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to clinicians, patients, and policy-makers. The participating organizations approved the following key questions to guide this review:

Key Question 1. For outpatients with seasonal or perennial allergic rhinitis or urticaria, do newer antihistamines differ in effectiveness?

Key Question 2. For outpatients with seasonal or perennial allergic rhinitis or urticaria, do newer antihistamines differ in safety or adverse effects?

Key Question 3.Are there subgroups of patients based on demographics (age, racial groups, gender), other medications (drug-drug interactions), co-morbidities (drug-

disease interactions), or pregnancy for which one newer 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 (3rd Quarter 2005), MEDLINE (1966 to August Week 4 2005), EMBASE (1991 to August Week 4, 2005), the two dossiers we received from pharmaceutical companies for fexofenadine HCL (Allegra ®) and desloratadine (Clarinex ®), and reference lists of review articles. The complete search strategy for electronic searches is in Appendix A. All citations were imported into an electronic database (EndNote 9.0).

Study Selection and Inclusion Criteria

1. Populations

Adult or pediatric outpatients with the following conditions were included in this review:

- Seasonal allergic rhinitis
- Perennial allergic rhinitis
- Urticaria, including both acute and chronic urticaria

Subgroups of interest included, but were not limited to, different races, ages (older adult versus younger adult), concomitant use of other medications (in consideration of drug-drug interactions), persons with various comorbidities (pregnancy and consideration of drug-disease interactions), and sex.

2. Interventions

Drug included in this review are listed below. This review is restricted to drugs currently available on the U.S. and Canadian markets. No new oral antihistamines were identified that have become available in the U.S. or Canada in the last 12 months.

- Cetirizine hydrochloride (Zyrtec®, Reactine®)
- Loratadine (Claritin®)
- Fexofenadine hydrochloride (Allegra®)
- Desloratadine (Clarinex®)

3. Outcomes

The following were the primary outcomes for this review:

Efficacy and effectiveness outcomes

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

Safety outcomes

- Overall adverse effects
- Withdrawals due to adverse effects
- Serious adverse events or withdrawals due to specific adverse events (e.g., central nervous system effects, sedation, gastrointestinal effects, dry mouth, urinary retention)

4. Settings

Studies had to occur in an outpatient setting, including the emergency department. There were no restrictions on the geographic location of studies.

5. Study design

Efficacy and effectiveness

a. For efficacy and effectiveness we included randomized controlled trials (RCTs), controlled clinical trials, and systematic reviews of fair or better quality.

b. Both direct and indirect comparisons were included (head-to-head, placebo-controlled, and active-controlled trials).

c. Studies of any duration of follow-up were included.

d. Studies in artificial environments (e.g., antigen exposure chambers) were included.

e. Studies published only as abstracts were not included as these studies generally have insufficient information describing the intervention and quality of the trial is difficult to assess.

Safety

a. For the review of safety and adverse events, we included studies with any design, including RCTs, controlled clinical trials, pre-versus post-design studies, and observational studies (cohort studies with or without a comparison group, case series, and case reports). 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, have longer follow-up, or examine larger sample sizes.

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

Data Abstraction

Two reviewers abstracted the following data from included trials: study design, setting, population characteristics (including sex, age, race/ethnicity, diagnosis); eligibility and exclusion criteria; interventions (dose and duration); comparison group treatment; numbers screened, eligible, enrolled, and lost to follow-up; methods of outcome ascertainment; and results for each outcome. Any discrepancies in abstraction were resolved through discussion and consensus was achieved. We recorded intention-to-treat results if available and if 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).[23; 24] 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; the use of intention-to-treat analysis, and the funding source and role of the funder. 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.

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. Poor quality studies are listed in Appendix C and are generally excluded from consideration in the results.

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.

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.

Overall quality ratings for each 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 that addressed a specific key question.

Data Synthesis

We summarized our results in evidence tables and in a narrative summary (see Table 18).

RESULTS

Search results are indicated in Figure 1, including studies identified in the original search as well as in the update.

Key Question 1. For outpatients with SAR, PAR, or urticaria, do newer antihistamines differ in effectiveness?

Adults

Seasonal allergic rhinitis

Five fair-quality, head-to-head trials of two weeks' duration assessed efficacy in adults with SAR (Table 1 and Evidence Tables 1 and 2).[25-29] The trials varied in country, season, number of patients, and baseline Total Symptom Score (TSS). At followup there were no significant differences in TSS in a small Italian trial of loratadine vs. cetirizine;[25] in two large trials of fexofenadine vs. cetirizine;[26; 27] and in one of the two trials of loratadine vs. fexofenadine.[28] In the

other trial of loratadine vs. fexofenadine,[29] the primary outcome 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). Dosages of drugs varied for fexofenadine, between 120 and 180 mg daily.

Table 1. Outcomes from head-to-head trials in adults with SAR*

Author Year Season Quality	Drug dosage # of subjects	Duration of trial (weeks)	Total Symptom Score (TSS)	Other Outcomes
Ciprandi 1997[25] Spring Fair	L: loratadine 10 mg qd C: cetirizine 10 mg qd N=20	2	Change in TSS from baseline: L: -84.6% C: -85.7% (NSD for L vs C)	
Hampel 2003[26] Spring Fair	C:cetirizine 10 mg qd F:fexofenadine 180 mg qd N=495	2	Change in TSS from baseline: C: -21.6% vs F: -19.0% NSD	
Howarth 1999[27] NR Fair	C: cetirizine 10 mg qd F1: fexofenadine 120 mg qd F2: fexofenadine 180 mg qd P: Placebo N=821	2	Change in TSS from baseline: C: -45% F1: -42% F2: -45% (NSD between treatments) P: -26% (p<0.0001 vs treatment)	
Prenner 2000[29] NR Fair-Poor	L: loratadine 10 mg qd F: fexofenadine 120 mg qd N=659	2	Patient assessment of TSS change: L: -39% vs F: -33% (p=0.019) Investigator assessment of TSS change: L: -35% vs F: -29% (p=0.063)	
Van Cauwenberge 2000[28] NR Fair	L: loratadine 10 mg qd F: fexofenadine 120 mg qd P: placebo N=688	2	Mean change in points in TSS from baseline: L: –3.0 points (p<0.001 vs P) F: –3.3 points (p<0.0001 vs P) P: –2.1 points NSD between treatments (baseline TSS scores not reported, unable to calculate % change)	Patient assessment of overall effectiveness, L vs F vs P: 42% vs 47% vs 37% (NSD) Physician assessment of overall effectiveness, L vs F vs P: 40% vs 44% vs 36% (NSD)
Guerra 1994[30] NR Fair	C: cetirizine 10mg L: loratadine 10mg P: placebo N=116	4	TSS: L > C days 3, 14, 28 (p<0.01), L> C NSD on day 7 (estimated from figure) day 3/7/14/28: L: -23%/ -46%/ -65% / -81% C: -35%/-50%/ -60%/ -69% P: -19%/ -23%/-34% /-55% Response rate: L 63%, C 45% (NSD for L vs C), P 13%	

Author Year Season Quality	Drug dosage # of subjects	Duration of trial (weeks)	Total Symptom Score (TSS)	Other Outcomes
*Only fair- and good-quality studies are presented in the table. Poor-quality studies are listed in Appendix C. Abbreviations: qd-once a day; bid-twice a day; tid-three times daily; NSD-no significant difference; NR-not reported; mg-milligrams; vs-versus; CI-confidence interval				

Two trials[31; 32] compared a newer antihistamine to a first generation antihistamine in patients with SAR (Table 4, Evidence Table 1). In one study,[31] desloratadine was less effective than azelastine nasal spray in previous nonresponders to loratadine for all nasal symptom outcomes and both treatment groups were more effective than placebo. However, p-values for between-treatment-group comparisons were not provided. In the other trial,[32] loratadine was as effective as clemastine.

In the updated search, 12 additional studies were identified (Tables 2 and 3 and Evidence Tables 1 and 2), three of which were of poor quality,[33-35] including the only head-to-head study.[33] Only one placebo-controlled trial was identified, which examined fexofenadine and found that this drug produced significant improvements in rhinitis-specific quality of life and work productivity, as well as total symptom scores. Loratadine was compared to placebo in three other studies with multiple arms and active controls,[36-38] but little data were provided on the placebo comparisons, and those data presented demonstrated mixed results (in the context of multiple comparisons).

Table 2. Head-to-head and placebo-controlled trials in adults with SAR

	Cetirizine	Desloratadine	Fexofenadine	Loratadine	Placebo
Cetirizine	--	--	--	--	--
Desloratadine	Ciprandi 2004[33] (Poor quality)	--	--	--	--
Fexofenadine			--	--	--
Loratadine				--	--
Placebo	Noonan 2003[39]	Meltzer 2001[40]	Okubo 2004, 2005[41; 42]	Hampel 2004[38] (4 arm) Bernstein 2004[37] (3 arm) van Adelsberg 2003[36] (3 arm)	--

Comparisons of newer antihistamines to active controls (Tables 3 and 4) revealed mixed results. Cetirizine was generally comparable to rupatadine (an antihistamine)[43] and azelastine (an antihistamine).[44] Loratadine demonstrated few significant differences from ebastine (an antihistamine),[38] mixed results compared to montelukast (a selective leukotriene receptor antagonist),[36] and was generally less efficacious than rupatadine.[45]

Table 3. Active-controlled trials in adults with SAR

	Fluticasone	Budesonide	Azelastine	Ebastine	Emadastine	Montelukast	Rupatadine	Other drugs
Cetirizine			Corren 2005[44]		Horak 2004[34] (Poor	Kurowski 2004[35] (4 arm)	Martinez-Cocera 2005[43]	

	Fluticasone	Budesonide	Azelastine	Ebastine	Emadastine	Montelukast	Rupatadine	Other drugs
					quality)	(Poor quality)		
Desloratadine		Bhatia 2005[46]	Berger 2003[31]					Dockhorn 1987[32] (clemastine)
Fexofenadine								
Loratadine	Bernstein 2004[37] (3 arm)			Hampel 2004[38] (4 arm) Ratner 2004[47]		van Adelsberg 2003[36] (3 arm)	Saint-Martin 2004[45] (3 arm)	

Table 4. Outcomes from active-controlled and placebo-controlled trials in adults with SAR*

Author Year Quality	Drug dosage # of subjects	Trial duration (weeks)	Total Symptom Score (TSS)	Other Outcomes
Active–controlled trials				
Berger 2003[31] **Fair**	D: desloratadine 5 mg A: azelastine nasal A+L: azelastine nasal + loratadine P: placebo N=440 (All were previous nonresponders to loratadine)	2	% improvement from baseline in TSS: D: 17.5% (p=0.039 vs P) A: 21.9% (p<0.001 vs P) A+L: 21.5% (p<0.001 vs placebo) P: 11.1% (p-values between active treatments not reported)	
Dockhorn 1987[32] **Fair**	L: loratadine 10 mg C: clemastine 2 mg P: placebo N=330	2	L: -49% C: -46% P: 23% NSD between active treatments	
Bernstein 2004[37] **Fair**	L: loratadine 10 mg + placebo spray F: Fluticasone profonate 0.20 mg spray + placebo tablet P: placebo (spray+ capsule) N=471	4	Mean change from baseline to day 28: TOSS total score: -72.5 vs -88.7 vs -59.5 (p<0.05 for F vs L) Individual scores for itching, tearing, redness showed larger decrease for F vs L (p<0.05)	Pt evaluated response: % reporting improvement: 64% vs 82% vs 65% (p<0.05 for F vs L; NSD L vs P)
Bhatia 2005[46] **Fair**	D: desloratadine 5 mg + placebo spray B: budesonide 64 µgm spray + placebo N=61	2	Individual symptoms: NSD between groups	Average change in total RQoLQ (on scale 0-6, 6=worse): -1.5 vs -2.0, NSD D vs B
Corren 2005[44] **Good**	C: cetirizine 10 mg qam + placebo spray bid A: azelastine nasal spray bid + placebo tablet qam	2	% change in TNSS total between baseline and day 14 (% improvement), C vs A: 23.0% vs 29.3%, p=0.015 for A vs C.	Overall mean change of RQoLQ scores from baseline: 1.11 vs 1.41, p = 0.049 for A vs C Individual QOL domains: improved for C and A, NSD between groups on

Author Year Quality	Drug dosage # of subjects	Trial duration (weeks)	Total Symptom Score (TSS)	Other Outcomes
	N=307			any individual domains
Hampel 2004[38] **Fair**	L: loratadine 10mg E1: ebastine 10mg E2: ebastine 20mg P: placebo (all qam) N=749	4	TSS, L vs E1 vs E2 vs P: 33.3 vs 35.9 vs 39.3 vs 28.2 (NSD for E1 and E2 vs L; p<0.05 for E1 and E2 vs P) TSS w/o congestion: 35.3 vs 37.4 vs 41.7 vs 28.7 (NSD for E1 and E2 vs L; p<0.05 for El, E1, and E2 vs D)	Patient global efficacy: improved, no change, worsened (%): 62.1%, 25.9% 12.0% (pts found E2> L, p=0.0052) Physician global efficacy rating: improved, no change, worsened (%): 60.0%, 29.0%, 11.0% (NSD between groups)
Martinez-Cocera 2005[43] **Fair**	C: cetirizine 10mg R: rupatadine 10mg N=249	2	mean change in TSS, C vs R: -0.65 vs -0.87, NSD	
Ratner 2004[47] **Fair**	L: loratadine 10mg E: ebastine 20mg P: placebo qd N=703	4	TSS: E<L<P; NSD L vs P, E<L (p=0.0018) Mean % change from baseline: L -24.6, E -32.3, P -23.4	
Saint-Martin 2004[45] **Fair**	L: loratadine 10mg R1: rupatadine 10mg R2: rupatadine 20mg N=347	2	NSD in TSS among groups among patients who took 1+ dose of treatment (n=339); CSS for sneezing and nasal itching was improved in L and R1 vs R2 (p=0.01)	
van Adelsberg 2003[36] **Fair**	L: loratadine 10mg M: montelukast 10mg P: placebo qd N=1079	4	L more effective than P for: daytime nasal symptoms score, composite symptoms score daytime eye symptoms score, patient's global evaluation at 2 and 4 weeks; NSD for night-time symptoms M had a lower eosinophil count L had a lower daytime nasal symptoms score at 2w than M (p<0.05, data not shown) NSD other comparisons	
Placebo-controlled trials				
Meltzer 2001[40] **Fair**	D: desloratadine 5 mg qd P: placebo Spring N=150 Fall N=164	2	Average change in TSS days 2 to 15 (% change of score), D vs P: Spring: -4.3 vs -2.5 points (-28% vs 12.5%), p<0.001 Fall: -5.1 vs -3.8 points (-30% vs 22%), p=0.02.	
Noonan 2003[39] **Fair**	C: cetirizine 10 mg qd P: placebo N=403	2	Mean change in TSSC (TSS with nasal congestion): C - 4.4 vs P -2.8 at end of study p<0.001	All outcomes, C vs P: % patients perceived improvement to be major or moderate: 41% vs 20%, p<0.001 % patients satisfied or

Author Year Quality	Drug dosage # of subjects	Trial duration (weeks)	Total Symptom Score (TSS)	Other Outcomes
				very satisfied with treatment: 65% vs 44%, p-value NR
Okubo 2004[41] Okubo 2005[42] **Fair**	F: fexofenadine 60 mg bid P: placebo N=210	2	Change in TSS from baseline to day 14, F vs P: -0.5 vs +0.8 points, p<0.0001	Change RQLQ overall score: F -0.45 vs P -0.12, p=0.0052 WPAI-AS improvement: overall work impairment decreased 5.5% vs 3.4%, p=0.016

*Only fair- and good-quality studies are presented in the table. Poor-quality studies are listed in Appendix C.
Abbreviations: TNSS-total nasal symptom score; TOSS-time oriented score system; QOL-quality of life; RQLQ-Rhinoconjunctivitis Quality of Life Questionnaire; WPAI-AS-Work Productivity and Activity Impairment-Allergy Specific Questionnaire; qam-once in the morning; qd-once a day; bid-twice a day; tid-three times daily; NSD-no significant difference; NS-not significant; NR-not reported; mg-milligrams; vs-versus

Perennial allergic rhinitis

There were no head-to-head efficacy trials of at least fair quality and 2 weeks duration in adults with PAR. We identified one active-controlled[48] and one placebo-controlled trial[49] in this population (Table 5 and Evidence Tables 3 and 4). One trial found that symptom relief at 2 and 3 weeks was higher for loratadine than for clemastine. The differences were not statistically significant, however, except for quicker onset with loratadine at day 1 and week 1. A placebo-controlled trial found desloratadine 5 mg more effective than placebo in reducing instantaneous and 12-hour reflective TSS over 4 weeks of treatment.[49] Results were similar for both nasal and non-nasal symptoms.

A systematic review[50] examined oral antihistamines for the treatment of nasal obstruction in PAR. Hore and colleagues included RCTs of both first-generation and newer antihistamines compared to placebo; they did not examine head-to-head trials. These authors concluded that oral antihistamines produce statistically significant improvement in both patient- and healthcare worker-assessed symptoms of nasal obstruction.

Table 5. Outcomes from trials in adults with PAR*

Author Year Quality	Drug dosage # of subjects	Duration of trial (weeks)	Total Symptom Score (TSS)	Other Outcomes
Head –to-head trials				
No studies identified				
Active-controlled trials				
Frolund et al. 1990[48] **Fair**	L: loratadine 10 mg qd C: clemastine 1 mg bid P: placebo N=155	3	Change in TSS from baseline, L vs C vs P: Week 2: −61% vs −40% vs −8% Week 3: −53% vs −44% vs −10% NSD, L vs C (estimated from figure)	Onset, L vs C: Day 1 p<0.05 Week. 1 p<0.05 NSD for L vs C for rhinoscopy
Placebo-controlled trials				
Simons et al. 2003[49] **Fair**	D: desloratadine 5 mg qd P: placebo N=676	4	Change in instantaneous TSS from baseline (mean, days 1 through 29), D vs P: −35.0% vs −27.4% (p=0.005)	

Author Year Quality	Drug dosage # of subjects	Duration of trial (weeks)	Total Symptom Score (TSS)	Other Outcomes
			Change in reflective TSS from baseline (mean, days 1 through 29), D vs P: D: −37.9% vs −32.3% (p=0.007)	

*Only fair- and good-quality studies are presented in the table. Poor-quality studies are listed in Appendix C.
Abbreviations: qd-once a day; bid-twice a day; NS-not significant; mg-milligrams; vs-versus

Allergic rhinitis studies with less than 14 days' follow-up

Eleven trials (in 12 publications) had follow-up periods less than 14 days (Evidence Tables 5 and 6).[51-62] One trial in patients with PAR was rated poor quality.[57] Two fair quality, crossover trials did not specify the type of allergic rhinitis.[59; 61] The remaining eight trials included patients with SAR.[51-56; 58; 60; 62] One of these was rated poor quality;[56] the rest were fair. (Poor quality studies are included in evidence tables but are not discussed further.)

These studies assessed outcomes after a single dose,[53; 55; 59; 61; 62] two days,[51; 52; 54; 58] or three doses.[60] Two studies used simulated performance measures;[60; 62] the others assessed symptoms. Four studies that assessed symptoms were conducted in environmental exposure units[51-54] and two were conducted in outdoor park settings during pollen season.[55; 58]

Seasonal allergic rhinitis. Three studies conducted by the same research group measured the efficacy of symptom relief with cetirizine in an environmental exposure unit. The comparators were loratadine in two studies and fexofenadine in one. All also included a placebo arm (one trial also included comparisons to astemizole and terfenadine, but these comparisons are not addressed here). Cetirizine reduced TSS more than loratadine in one 2-day study,[52] and more than fexofenadine in another.[63] Time to onset was similar for the two treatments. In a single-dose study,[53] cetirizine and loratadine had similar efficacy for relief of symptoms; time to onset was faster with cetirizine.

In fair-quality studies conducted in outdoor parks during spring allergy season, fexofenadine was more effective in relieving symptoms after a single dose than placebo,[55] and cetirizine was more effective than loratadine over 2 days.[58]

As a group, these studies provide evidence that cetirizine, loratadine, and fexofenadine can reduce seasonal allergic rhinitis symptoms after one or two doses. Although cetirizine had advantages in some studies, the evidence is conflicting. The generalizability of studies conducted in environmental exposure units is limited.

Allergic rhinitis, not specified. A fair quality, single-dose crossover study[59] compared desloratadine to levocetirizine. Symptoms were significantly reduced from baseline to 24 hours with both drugs, but there was no difference between the active treatments. A second study in patients with allergic rhinitis measured suppression of wheals; cetirizine was more effective in suppressing wheals than loratadine, although both were more effective than placebo.[61]

Simulated performance measures. A fair quality study measured the effect of fexofenadine, diphenhydramine, or placebo, all with or without alcohol, on simulated driving performance.[62] On various measures, patients who took fexofenadine performed better than those who took diphenhydramine or alcohol. Steering instability was worse with fexofenadine than placebo. On subjective measures of drowsiness before and after drives, participants were most drowsy after taking diphenhydramine and least drowsy after taking placebo or fexofenadine.

Urticaria

Trials in adults with urticaria are shown in Table 7 and Evidence Tables 7 and 8. One fair-quality, head-to-head trial compared loratadine to cetirizine in adults with CIU.[30] In this trial, loratadine reduced mean TSS more than cetirizine but did not result in a higher response rate. There was no fair or better evidence comparing fexofenadine to loratadine or cetirizine; or desloratadine with other antihistamines.

In a four-week trial in 188 patients,[64] cetirizine had a faster onset than the first generation antihistamine hydroxyzine but was effective in a similar proportion of patients.

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

Four additional studies that examined the efficacy of newer antihistamines among adults with CIU were identified in the updated search.[65-68] Two of these studies, however, were of poor quality.[65; 67] In a head-to-head trial, Handa and colleagues[66] concluded that cetirizine 10 mg daily was more efficacious than fexofenadine 180 mg daily at 28-day follow-up. This study was limited by an attrition rate of 16%, and data were presented only for those completing the study. Kaplan and colleagues[68] found fexofenadine superior to placebo for decreasing urticaria symptoms at 28 days.

A search for literature on the efficacy or effectiveness of newer antihistamines in other types of urticaria in adults identified only poor quality studies.[69-73]

Table 6. Head-to-head and placebo-controlled trials in adults with urticaria

	Cetirizine	Desloratadine	Fexofenadine	Loratadine	Placebo
Cetirizine	xxxxxx	xxxxxx	xxxxxx	xxxxxx	xxxxxx
Desloratadine		xxxxxx	xxxxxx	xxxxxx	xxxxxx
Fexofenadine	Handa 2004[66]		xxxxxx	xxxxxx	xxxxxx
Loratadine	Guerra 1994[30]			xxxxxx	xxxxxx
Placebo	Juhlin 1988[67] (poor quality)	Di Lorenzo 2004[65] (4 arm) (poor quality) Ring 2001[74]	Kaplan 2005[68]		xxxxxx

Table 7. Outcomes from trials in adults with urticaria

Author Year Condition Quality	Drug dosage # of subjects	Duration of trial (weeks)	Total Symptom Score (TSS) or symptom change	Other Outcomes
Head-to-head trials				
Guerra et al 1994[30]	L: loratadine 10 mg C: cetirizine 10 mg P: placebo N=116	4 weeks	Significant ($p<0.01$) L vs C on days 3, 14, 28 (NSD on day 7) day 3/7/14/28: L: -23%/ -46%/ -65% / -81% C: -35%/-50%/ -60%/ -69%	

Author Year Condition Quality	Drug dosage # of subjects	Duration of trial (weeks)	Total Symptom Score (TSS) or symptom change	Other Outcomes
			P: -19%/ -23%/-34% /-55% Response rate: L 63% vs C 45%, NSD for L vs C placebo 13%	
Handa 2004[66] **CIU** **Fair**	C: cetirizine 10 mg qd F: fexofenadine 180 mg qd N= 116	4	Symptom-free at endpoint: C 51.9% vs F 4.4% Partial improvement at endpoint: C 36.5% vs F 42.2% No improvement at endpoint: C: 11.5% vs F 53.3% p: NR for all comparisons	
Active-controlled trials				
Breneman 1996[64] **CIU** **Fair**	C: cetirizine 10mg qd H: hydroxyzine 25 mg tid P: placebo N=188	4	Change in TSS (estimated from figure): C: -64% H: -68% P: -42% NSD between C vs H	NSD between C and H for definite/complete response Onset: day 1: C > H p<0.002
Placebo-controlled trials				
Ring 2001[74] **CIU** **Fair**	D: desloratadine 5 mg qd P: placebo N=190	6	Change in TSS scores (baseline to week 6): D had a greater % reduction than P, p<0.001 Change in pruritus score (baseline to week 6): D: -74.0% vs P: 48.7% P<0.001	
Kaplan 2005[68] **CIU** **Fair**	F: fexofenadine 180 mg qd P: placebo N=259	4	Mean reductions in TSS daily scores: F >P p<.001 Change in mean pruritis score (0-4) from baseline: F: -1.04, P: -0.57, p<0.001	Mean change in daily number of wheals: F -0.78, P -0.4, p<.001 Global evaluations of efficacy by both patient and investigator: F more efficacious than P, p<0.001

*Only fair- and good-quality studies are presented in the table. Poor-quality studies are listed in Appendix C.
Abbreviations: qd-once a day; tid-three times daily; NSD-no significant difference; NS-not significant; NR-not reported; mg-milligrams; vs-versus; CIU-chronic idiopathic urticaria

Children

Seasonal allergic rhinitis

Ten studies examined the efficacy of newer antihistamines among children (see Tables 8, 9, and 10 and Evidence Tables 9 and 10); two of these studies were of poor quality.[75; 76] (See Appendix C for poor-quality studies.) No head-to-head studies were identified. The results of placebo-controlled trials of cetirizine[77-81] and fexofenadine,[82] all demonstrated significant improvements in symptoms with the study drug compared to placebo.

Table 8. Head-to-head and placebo-controlled trials in children with SAR

	Cetirizine	Desloratadine	Fexofenadine	Loratadine	Placebo
Cetirizine	--	--	--	--	--
Desloratadine		--	--	--	--
Fexofenadine			--	--	--
Loratadine				--	--
Placebo	Allegra 1993[77] Ciprandi 1997[79] Ciprandi 2001[83] Masi 1993[80] Pearlman 1997[81] (3 arm) Segal 2003[76] (poor quality)		Wahn 2003[82]	Bender 2004[75] (3 arm) (poor quality)	--

Active-controlled studies compared cetirizine[84] and loratadine[85] to first-generation antihistamines (see Tables 9 and 10), with no significant differences between groups. Jordana and colleagues[86] demonstrated that fluticasone nasal spray was more efficacious than loratadine for nasal symptoms, but there were no significant differences for eye symptoms.

Table 9.Active-controlled trials in children with SAR

	Fluticasone	Dexchlorpheniramine	Chlorpheniramine
Cetirizine	Bender 2004[75] (3 arm) (poor quality)		Tinkleman 1996[84]
Desloratadine			
Fexofenadine			
Loratadine	Jordana 1996[86]	Boner 1989[85]	

Table 10. Outcomes from trials in children with SAR

Author Year Quality	Drug dosage # of subjects	Mean age Range (years)	Length of follow-up (weeks)	Total Symptom Score (TSS) or Disease Severity Score (DSS)	Other Outcomes
Head-to-head trials					
No studies identified					
Active-controlled trials					
Boner 1989[85] **Fair**	L: loratadine 5 mg qam (range: 2.5-5 mg/d) D: dexchlorpheniramine 1mg q8h (range: 1.5-3 mg/d) Patients <6y or weighing <20 kg received half dose of drug N=40	7.7 4-12	2	Change in mean TSS from day 0 to 14, L vs D: -6.9 points vs -8.2 points, NSD	TSS, as assessed by both investigator and patient/parent, decreased for L and D, NSD for L vs D

Author Year Quality	Drug dosage # of subjects	Mean age Range (years)	Length of follow-up (weeks)	Total Symptom Score (TSS) or Disease Severity Score (DSS)	Other Outcomes
Jordana 1996[86] **Fair**	L: loratadine 10 mg qam + placebo spray F: fluticasone propionate 200 µgm aqueous spray qam + placebo tablet N=242	NR 12-17	4	Symptom-free days (%): F> L for all nasal symptoms; NSD for eye-watering or eye-irritation SS F<L for all nasal symptoms; NSD for eye symptoms. Rescue-free days, L vs F: 96 vs 93 days, NSD	% of patients receiving rescue antihistamines, L vs F: 39% vs 21%, p<0.0025
Tinkelman 1996[84] **Fair**	CE1: cetirizine 5mg for pts <25kg ; 10mg for pts ≥ 25kg qd CE2: cetirizine 2.25mg for pts <25kg; 5mg for pts ≥ 25kg bid CH: chlorpheniramine 2 mg tid N=188	8.8 6-11	2	Mean change in patient-reported TSS (excluding nasal congestion): CE1: -2.6 CE2: -2.6 CH: -2.6 NSD among groups	Mean change in investigators' TSS: CE1:-3.5 CE2: -3.6 CH: -3.8 NSD for all comparisons
Placebo-controlled trials					
Ciprandi, 1997a, 1997b[78; 79] **Fair**	C: cetirizine 0.15 mg/kg qam P: placebo qam N=20	8.5 6-15	4	Clinical signs and symptoms score improved in C vs P at: W 1 (p=0.03) W 2 (p=0.01) W 3 (p=0.01) W 4 (p=0.01)	Cough intensity: C < P at wk 2 (p<0.02), 3 (p=0.01), and 4 (p=0.02) Cough frequency: C < P at wk 1 (p=0.03), 2 (p=0.006), 3 (p=0.01) and 4 (p=0.02)
Masi 1993[80] **Fair**	C: cetirizine 5 mg bid P: placebo N=124	10.15 6-12	2	Change in investigator-assessed DSS between baseline and week 2, C vs P: -1.75 vs -1.22, p<0.001	% investigator rated as "excellent" or "good" for global evaluation of rhinoconjunctivitis at end of 2 wks, C vs P: 79% vs 50%, p<0.001
Allegra 1993[77] **Fair**	C: cetirizine 5 mg qd P: placebo qd N=107	4.45 2-6	2	Change in investigator-assessed mean DSS between baseline and last visit: C -1.4 vs P -1.1, p = 0.040	Global evaluation of rhinitis by investigators as excellent or good, C vs P: 63% vs 45.3%, p = 0.039
Pearlman 1997[81]	C1: cetirizine 5 mg qd C2: cetirizine 10 mg qd P: placebo qd	NR 6-11	4	Change in patient-assessed TSS: C1 vs P: NSD C2 vs P: decrease in C2; p<0.05 Investigator-assessed TSS: NSD among groups	
Wahn 2003[82] **Fair**	F: fexofenadine 30 mg bid P: placebo bid N=935	9.0 5-12	2	Mean change from baseline, F vs P: pm-reflective TSS: -1.94 vs -1.21 points (p<0.0001) TSS in am: -1.67 vs -0.93 points (p<0.0001)	Individual symptom scores in pm all decreased : F> P (p<0.05)

*Only fair- and good-quality studies are presented in the table. Poor-quality studies are listed in Appendix C.
Abbreviations: q8h-every eight hours; qam-every morning; qd-once a day; bid-twice a day; tid-three times daily; NSD-no significant difference; NR-not reported; kg-kilograms; mg-milligrams; vs-versus; d-day; y-year; w-week; SS-symptom score

Perennial allergic rhinitis

Eight studies (see Tables 11,12, and 13 and Evidence Tables 11 and 12) were identified which examined the efficacy of newer antihistamines among children with PAR,[83; 87-93] one of which was of poor quality.[88] All but one study examined cetirizine (loratadine was examined by Yang and colleagues[93]). One study examined younger children (2-6 years);[92] most examined 6 to 12 or 14 year-old children. Two studies primarily focused on adults, but included participants 12 years of age and older.[45; 47] These studies are presented with the adult studies, as data were not stratified by age group to allow for examination of adolescents only.

Table 11. Head-to-head and placebo-controlled trials in children with PAR

	Cetirizine	Desloratadine	Fexofenadine	Loratadine	Placebo
Cetirizine	xxxxxx	xxxxxx	xxxxxx	xxxxxx	xxxxxx
Desloratadine		xxxxxx	xxxxxx	xxxxxx	xxxxxx
Fexofenadine			xxxxxx	xxxxxx	xxxxxx
Loratadine	Sienra-Monge 1999[92]			xxxxxx	xxxxxx
Placebo	Baelde 1992[87] (3 arm, 2 doses of drug) Ciprandi 2001[83] Ciprandi 2004[88] (poor quality) Hsieh 2004[89] (3 arm) Jobst 1994[90] (4 arm, 3 doses of drug) Lai 2002[91] (4 arm)			Yang 2001[93]	xxxxxx

Inclusion criteria generally required a positive response to a skin test for house-dust mite allergy or other non-seasonal respiratory allergens, along with a clinical history consistent with PAR. Children with major systemic illnesses were excluded.

One head-to-head trial was identified, which compared cetirizine to loratadine among children 2 to 6 years of age.[92] The primary outcome was the histamine skin prick test and cetirizine produced greater inhibition of the wheal response than loratadine ($p<0.001$). Both drugs produced improvements in parent- and investigator-assessed symptoms, with loratadine significantly more efficacious than cetirizine ($p<0.001$) for parent assessment of rhinorrhea, sneezing, nasal obstruction, and nasal pruritis. No significant differences were noted between groups in investigator-assessed global evaluation score or in nasal eosinophil count.

Two studies with active controls (see Tables 12 and 13) were identified and cetirizine improved symptoms compared to placebo arms, as well as in comparison to ketotifen and oxatomide[91] and cetirizine was comparable to montelukast.[89] Three fair-quality, placebo-controlled studies[83; 87; 90] found cetirizine efficacious for nasal symptoms, particularly at a dosage of 10 mg daily (either at bed time or divided doses twice daily) for children 6 to 12 years.

Table 12. Active-controlled trials in children with PAR

	Ketotifen	Oxatomide	Montelukast
Cetirizine	Lai 2002[91] (4 arm)	Lai 2002[91] (4 arm)	Hsieh 2004[89] (3 arm)

	Ketotifen	Oxatomide	Montelukast
Desloratadine			
Fexofenadine			
Loratadine			

A single study examining loratadine noted it to be efficacious at a dosage of 5 to 10 mg daily when compared to placebo.[93] There were no data on any of the other newer antihistamines in children.

Table 13. Outcomes from trials in children with PAR*

Author Year Quality	Drug dosage # of subjects	Mean age Range (years)	Length of follow-up (weeks)	Total Symptom Score (TSS)	Other Outcomes
Head-to-head trials					
Sienra-Monge 1999[92] **Fair**	C: cetirizine 0.2 mg/kg qd L: loratadine 0.2 mg/kg qd N=80	4.4 2-6	4	NR	Global Evaluation Score assessed by investigator: (C vs L): -62.8% vs -64.6% (NSD) Parent assessment of patient symptoms: C more effective in relieving rhinorrhea, sneezing, nasal obstruction, and nasal pruritis (p<0.001)
Active-controlled trials					
Hsieh 2004[89] **Fair**	C: cetirizine 20 mg qd M: montelukast 5 mg qd P: placebo qd N=65	8.1 6-12	12	TSS: C<M<P weeks 4,8,12 (p<0.05) Mean rhinorrhea score C and M<P weeks 4,8,12 (p<0.01), C<M weeks 8 and 12 (p<0.01) Nasal itching and sneezing C<P weeks 4,8,12, (p<0.05)	Quality of life: Improved in C and M more than in P at 12 weeks (p<0.01)
Lai 2002[91] **Fair**	C: cetirizine 10mg qd K: ketotifen 1 mg bid O: oxatomide 1 mg/kg bid P: placebo N=80	8.07 6-12	12	C, K, and O improved mean TSS from baseline compared to P at 12 wk (p<0.01) Lower TSS for C than K and O for week 12 (p<0.05) C, K and O all demonstrated improved individual symptom scores compared to P, and results were generally significant (p<0.05)	Quality of life: higher for C and K at 12 weeks (p<0.05 vs P)
Placebo-controlled trials					
Baelde 1992[87] **Fair**	C1: cetirizine 5.0 mg bid C2: cetirizine 2.5 mg bid P: placebo bid N=138	8.6 2-14	2	Mean % change from baseline, assessed by investigator (C1 vs C2 vs P) Nasal obstruction: -47.9% vs -33.2% vs -28.7% (C1 vs P, p=0.03) Rhinorrhea: 59.4% vs 47.3% vs 37.9% (C1 vs P, p=0.03) Sneezy: 68.2% vs 47.3% vs 37.9% (C2 vs P, p=0.04) Pharyngeal drip: 77.2% vs 53.2% vs 54.9% (C1 vs C2, p=0.03) Nasal pruritis: NSD, data not reported Overall average score for all	Global evaluation by investigators: C1 > C2 (p=0.04) C1 > P (p=0.006) Evaluation by parents: C1 vs P and C2 vs P, both NSD

Author Year Quality	Drug dosage # of subjects	Mean age Range (years)	Length of follow-up (weeks)	Total Symptom Score (TSS)	Other Outcomes
				symptoms: C1 vs P, p=0.01	
Ciprandi 2001[83] **Fair**	C: cetirizine 5 mg qd P: placebo qd N=20	6.5 3-10	24	Weekly mean rhinitis scores: C< P for 24/24 weeks; between-group difference significant for 11/ 24 weeks (p<0.05) Weekly mean asthma symptom scores: C <P for 6/24 weeks (p<0.05); for 10/24 weeks P<C (NSD); for 8/24 weeks C=P	
Jobst 1994[90] **Fair**	C1: cetirizine 2.5 mg qd C2: cetirizine 5 mg qd C3 cetirizine 10 mg qd P: placebo qd N=330	NR 6-12	2	Investigator-assigned severest symptom scores: between-group differences, week 2 (p=0.052), P had highest score; NSD among C1, C2, and C3 at end week 2 Over time patient's severest symptom score decreased in all groups, most marked for C3, least marked for P	Considering patient's severest symptom (% days asymptomatic): C3>P (p=0.008), NSD C1 vs P and C2 vs P % days when symptoms were absent or mild: C3>P (p=0.016), NSD C1 vs P and C2 vs P % days when no severe symptoms: C1>P (p=0.012), C2>P (p=0.006), C3>P (p=0.002)
Yang 2001[93] **Fair**	L: loratadine syrup 5 mg if < 30 kg, 10 mg if >30 kg P: placebo N=46	6.3 3-12		Mean % change in investigator-assessed TSS from baseline, L vs P Day 21: -42.2% vs -22.7% (p=0.063) % decrease in patient-evaluated TSS from baseline Week 3: -13.2% vs -5.6% (p=0.014)	

*Only fair- and good-quality studies are presented in the table. Poor-quality studies are listed in Appendix C.
Abbreviations: qd-once a day; bid-twice a day; tid-three times daily; NSD-no significant difference; NS-not significant; NR-not reported; mg-milligrams; kg-kilograms; vs-versus; wk-week

Urticaria

Two studies examined the efficacy of newer antihistamines for the treatment of urticaria in children (Table 14 and Evidence Tables 13 and 14). One study examined the efficacy of cetirizine compared to oxatomide in children 2 to 6 years of age with CIU;[94] no significant differences were noted between groups. The second study examined the efficacy of cetirizine in preventing acute urticaria among young children with atopic dermatitis (who are at high risk of acute urticaria).[95] Efficacy was demonstrated during the 18-month treatment period in this placebo-controlled, randomized study, but positive effects did not persist after treatment was stopped.

Table 14. Outcomes from trials in children with urticaria*

Author Year Condition Quality	Drug dosage # of subjects	Mean age Range (years)	Length of follow-up (weeks)	Total Symptom Score (TSS)	Other outcomes
Head-to-head trials					
No studies identified					
Active-controlled trials					
La Rosa 2001[94] **CIU** **Fair**	C: cetirizine 5 mg qd O: oxatomide 25 mg qd N=62	3.85 2-6	4	Investigators' mean symptom score (sum of individual symptom scores): progressive reduction in scores in both C and O; NSD between groups Change in score from baseline at day 28: - 58 vs -58 points, NSD	Change in VAS parents' score from days 0 to 28, C vs O: +62mm vs +57mm, (NSD between groups) Clinical evaluation by investigators at end of study, C vs. O: Excellent: 33.3 vs 20.7%, NSD Good: 53.3% vs 69.0%, NSD Moderate: 13.4 % vs 6.9%, NSD Bad: 0% vs 3.4%, NSD
Placebo-controlled trials					
Simons 2001[95] **Simons 1999[96]** **Prevention of acute urticaria in children with atopic dermatitis** **Fair**	C: cetirizine 0.25 mg/kg bid (range: 5-11 mg /d) P: placebo N=817	16.8 mos during treatment; 17.2 mos during no treatment 1-2	Treatment for 18 mos, followed by 6 mos of no treatment	% with urticaria episodes during 18-month treatment, A vs B: 5.8% vs 16.2%, p<0.001 % with urticaria episodes during 6-month follow-up (after treatment stopped), A vs B: 3.4% vs 5.2% , NSD	

*Only fair- and good-quality studies are presented in the table. Poor-quality studies are listed in Appendix C
Abbreviations: qd-once a day; bid-twice a day; NSD-no significant difference; mg-milligrams; kg-kilograms; vs-versus; d-day; CIU-chronic idiopathic urticaria; VAS-visual analog score; mm-millimeters; mos-months

Key Question 2. For outpatients with SAR, PAR or CIU do newer antihistamines differ in safety or adverse effects?

Adverse Events

Adults

Adverse events in studies in adults are shown in Evidence Tables 15-19 and Tables 15-16. Observational studies[97-100] provide the best available data on adverse effects of long-term use of newer antihistamines (Evidence Table 15). Sedation was the main focus of these studies, and the overall incidence of sedation was both variable and low. A fair quality meta-analysis[101] suggested both the first generation and newer antihistamines resulted in sedation compared to placebo, and the first generation agent diphenhydramine caused more sedation than cetirizine, fexofenadine, and loratadine. Likewise, a fair quality cohort study showed that cetirizine had significantly higher odds of sedation than loratadine and fexofenadine; loratadine was not significantly different from fexofenadine.[98] Similar results were seen with a fair- to poor-quality trial where cetirizine produced greater sedative effects and adverse effects on motivation than loratadine.[102] A fair-quality cohort study resulted in more claims for serious injury with diphenhydramine versus loratadine.[97] No trial evidence was found on tolerance to the sedation with antihistamines. The labeling for cetirizine includes a statement for using caution when driving a car or operating potentially dangerous machinery, as well as avoiding concomitant use with alcohol or other central nervous system depressants as an additional reduction in alertness or performance may occur.

Prolongation of the QT interval is a concern with this class of agents. A fair quality cohort study[100] reported, for five newer antihistamines combined, a 4.2 times higher risk of ventricular arrhythmias compared to non use. Astemizole posed the highest risk (relative risk 19.0); the relative risk for cetirizine was 7.9 (95% confidence interval, 1.6-39.3) and loratadine 3.2 (0.4-26.9). The safety and tolerability of fexofenadine was shown in over 16,638 patients in a UK PEM cohort[99] as well as in a placebo-controlled trial where no significant ECG changes were noted.[68] A number of studies of desloratadine noted no significant ECG changes compared to the placebo group.[40; 49; 74; 103; 104]

A small, poor-quality trial demonstrated an increase in postprandial glucose with cetirizine compared to loratadine and clemastine.[105]

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 16 and Table 14). This suggests that, for most patients, the side effects are tolerable. Of 22 placebo-controlled trials in SAR, PAR, and CIU patients, we identified three trials of fair-or-better quality (Evidence Tables 2 and 4 and 6).[39; 40; 74] The incidence of adverse events in these trials ranged from 21-51% but discontinuation of treatment occurred in less than 3% of patients.

Table 15. Adverse events from head-to-head and active-controlled trials in adults from the original report*

Author, year	Adverse events (AEs)	Total withdrawals	Withdrawals from AEs
Head-to-head trials			
Ciprandi 1997[25] L: loratadine 10 mg qd C: cetirizine 10 mg qd	No significant AEs reported	Total: 0	0
Hampel 2003[26] F: fexofenadine 180mg qd C: cetirizine 10mg qd	Total AEs: 16.7% AEs per group: F: 16.9% C: 16.6% F: less overall drowsiness p=0.0110, NS effect on motivation	Total: 3.2% F: 2.8% C: 3.6%	1.2% AEs 3 efficacy Safety evaluated in AE population
Howarth 1999[27] F1: fexofenadine 120 mg qd F2: fexofenadine 180 mg qd C: cetirizine 10 mg qd P: placebo	Treatment-related AEs: F1: 23% F2: 23% C: 25% P: 25 %	Total: 14% Similar among groups (numbers per group NR)	F: 2% C: <1% P: 2%
Prenner 2000[29] L: loratadine 10 mg qd F: fexofenadine 120 mg qd	F 22.1% vs L 18.2% had ≥1 AE. Considered treatment related in F 8.3% L 5.3%	NR	NR
Van Cauwenberge 2000[28] L: loratadine 10 mg qd F: fexofenadine 120 mg qd P: placebo	16.4% of total F: 16.8% L: 17.5% P: 14.7%	Total: 10% F: 9% L: 12% P: 11%	F: 1% L: 2% P: 3%
Guerra 1994[30] L: loratadine 10mg C: cetirizine 10mg P: placebo	20.7% Total NSD. L: 15.8% C: 27.5% P: 15.8%	C: 1	C: 2.5% stomach pain
Active-controlled trials			
Frolund 1990[48] L: loratadine 10 mg qd C: clemastine 1 mg bid P: placebo	32.9% Total L: 15% (p<0.05) C: 58.8%, sedation significant P: 49% placebo	Total: 13.5% L: 9.4% C: 5.8% P: 25.4%	L: 0% C: 1.9%: 1 AE/ 2 efficacy P: 0%
Breneman 1996[64] C: cetirizine 10mg qd H: hydroxyzine 25 mg tid P: placebo	C: 18% H: 30% P: 6% H vs P. p=0.001	Total: 4.8% C: 1.7% H: 6.3% P: 6.1%	Somnolence: C: 1.7% H: 6.3% P: 6.1%
Berger 2003[31] D: desloratadine 5 mg A1: azelastine nasal A2: azelastine nasal + loratadine P: placebo	Most common per treatment: Bitter taste A1: 11% vs A2: 4% D: Headache 3%, pharyngitis 4% P: headache 7% Somnolence: A1: 2%; A2: 1%; D: 1%; P: 1%	A1: 2% D: 1% P: 1%	A1: 2% (moderate chest pain, lightheadedness) D: 1% (headache and nausea) P: 1% (rash)

Author, year	Adverse events (AEs)	Total withdrawals	Withdrawals from AEs
Dockhorn 1987[32] L: loratadine 10 mg C: clemastine 2 mg P: placebo	More AEs (considered probably or possibly treatment-related) in C C: 37% L: 21% P: 20% ($p \leq 0.01$) More sedation in C: C: 22% L: 6% ($p \leq 0.01$)	NR	NR

*Only fair- and good-quality studies are presented in the table. Poor-quality studies are listed in Appendix C.
Abbreviations: qd-once a day; bid-twice a day; tid-three times daily; NSD-no significant difference; NR-not reported; mg-milligrams; vs-versus

The adverse events noted in the 11 fair or good quality trials identified in the updated review are presented in Table 16 and in Evidence Table 16. The most frequent adverse event was headache which was reported for cetirizine in 7.7%[66] and 19.7%[43] of patients. Lower frequencies of headache were noted with fexofenadine (2.2%[66] and 5%[68]) and loratadine (5.8%[38]). Somnolence was also reported with cetirizine (2.6%[36] and 8.5%[43]) and loratadine (7.8%[45] and 0%[26]).

Handa and colleagues[66] presented the only head-to-head data, with a comparison of cetirizine and fexofenadine. They noted no significant differences between groups for drowsiness, constipation, abdominal pain, epigastric pain, or cough.

Prolonged QTc interval was examined in three studies.[38; 47; 68] Ratner and colleagues[47] reported similar rates among the treatment groups: 3.6% in the loratadine 10 mg group, 3.9% in the ebastine 20mg group, and 5.6% in the placebo group. All cases of prolonged QTc were mild and none resulted in discontinuation of treatment. Hampel and colleagues[38] noted similar findings in their randomized controlled trial: 1.6% in the loratadine 10 mg group, 3.2% in the ebastine 10 mg group, 2.2% in the ebastine 20 mg group, and 0.5% in the placebo group. Kaplan et al.[68] reported no clinically-relevant ECG changes with fexofenadine.

Withdrawal rates due to adverse events were generally low, in the range of 2 to 3%. Serious adverse events were rare; one patient taking fexofenadine had an asthma attack requiring hospitalization.[68]

In the review update we identified only two additional observational studies that examined adverse events in adults using newer antihistamines (Evidence Tables 17 and 18). A case-control study[106] examined the effect of loratadine exposure during pregnancy on hypospadias rates among newborns and is discussed further under Key Question #3. The second study was of poor quality and is not discussed further.[107]

Studies with less than 14 days' followup. No serious adverse events were reported in studies with less than 14 days' followup(Evidence Table 19). In head-to-head trials, most adverse events occurred with similar frequency in patients taking cetirizine, loratadine, and fexofenadine (adverse events were not reported in one study of desloratadine).[60] In one study,[58] headache was more common with cetirizine than loratadine (10.8% vs 22.6%; p=0.03) and somnolence was significantly more common with cetirizine compared with placebo (12.9% vs 2.2%, p=0.05), but not with loratadine (5.4%).

Table 16. Adverse events from studies in adults (includes only studies from update 2003-2005)*

Type of AE	Adverse Event	Cetirizine	Fexofenadine	Loratadine
NEUROLOGICAL				
MAJOR				
MINOR	Fatigue/ Asthenia	6.8% vs rupatadine 10.5%, NSD[43]		6.0%; vs rupatadine 10mg 10.7%; vs rupatadine 20mg 11.7%: NSD[45]
	Headache	19.7% vs 15.3% rupatadine, NSD[43]	2.2% vs cetirizine 0%, NSD[66] 5% vs placebo 3%[68]	18%; vs fluticasone 17%[37] 12.1%; vs rupatadine 10mg 23.4%; vs rupatadine 20mg 14.3%, NSD[45] 5.8%; vs ebastine 10mg 4.3%; vs ebastine 20mg 3.2%; vs placebo 4.3%[38]
	Somnolence	2.6% vs azelastine 1.3%[44] 8.5% vs rupatadine 9.6%, NSD[43] Drowsiness: 7.7% vs fexofenadine 4.5%, NSD[66]	Drowsiness: 4.5% vs cetirizine 7.7%, NSD[66]	7.8%; vs rupatadine 10mg 12.5%; vs rupatadine 20mg 25%, significant but p-value not given[45] 0%; vs ebastine 10mg 1.6%; vs ebastine 20mg 2.7%; vs NR placebo[38]
	Unspecified			0% vs ebastine 4.6% vs placebo 0%[47]
GASTROINTESTINAL				
MAJOR				
MINOR	Abdominal pain	0% vs fexofenadine 2.2%, NSD[66]	2.2% vs cetirizine 0%, NSD[66]	
	Constipation	5.8% vs fexofenadine 0 %, NSD[66]	0% vs 5.8% cetirizine, NSD[66]	
	Dry mouth			1.7% vs rupatadine 10mg 1.8% vs rupatadine 20mg 3.6%, NSD[45]
	Epigastric pain	3.8% vs fexofenadine 0%, NSD[66]	0% vs 3.8% cetirizine, NSD[66]	
	Unspecified			0% vs ebastine 3.2% vs placebo 3.5%[47]
HEMATOLOGICAL				
MAJOR				
MINOR	Abnormalities in complete blood count			
RESPIRATORY				
MAJOR			1 patient had asthma requiring	

Type of AE	Adverse Event	Cetirizine	Fexofenadine	Loratadine
			hospitalization[68]	
MINOR	Cough	3.8% vs fexofenadine 0%, NSD[66]	0% vs 3.8% fexofenadine, NSD[66]	4.3% vs rupatadine 10mg 8.0% vs rupatadine 20mg 5.4%[45]
	Epistaxis	<1% vs azelastine 2.0%[44]		
	Nasal discomfort	<1% vs azelastine 1.3%[44]		
	Pharyngitis			1.7% vs rupatadine 10mg 7.1% vs rupatadine 20mg 4.5%, NSD[45]
	Unspecified			12.2% vs ebastine10mg 8.5% vs ebastine 20mg 7.5% vs placebo 10.2%[38]
CARDIAC				
MAJOR	QT interval		No clinically relevant ECG changes vs placebo[68]	Prolonged QTc: 1.6%; vs ebastine 10mg 3.2%; vs ebastine 20mg 2.2%; vs placebo 0.5%[38] Prolonged QTc: 3.6%; vs ebastine 20mg 3.9%; vs placebo 5.6%[47]
MINOR	Unspecified			2.5%; vs ebastine 2.8%; vs placebo 4.2%[47]
OTHER				
MAJOR	Back pain			4.3%; vs rupatadine 10mg 3.6%; vs rupatadine 20mg 4.5%, NSD[45]
MINOR	Bitter taste	<1% vs azelastine 3.3%[44]		
	Feet swelling	0% vs 2.2% fexofenadine, NSD[66]	2.2% vs cetirizine 0%, NSD[66]	
	Hypospadias			OR of hypospadias with loratadine exposure: 1.29 (0.62-2.68)[106] Use of nonsedating antihistamines, including loratadine, OR: 1.33 (0.73-2.40)[106]

*Only fair- and good-quality studies are presented in the table. Poor-quality studies are listed in Appendix C.
Abbreviations: NSD-no significant difference; NR-not reported; mg-milligrams; vs-versus; QT-cardiac output; QTc-corrected QT interval for heart rate; OR-odds ratio
There were no data on desloratadine identified in the update.

Children

Major and minor adverse events in studies in children are summarized in Table 17 (also see Evidence Tables 20-22). In the only head-to-head trial in children,[92] two adverse events were reported in the cetirizine group, with none reported in the loratadine group (total number of participants was 80). One participant developed somnolence and irritability, the other a generalized rash. These two adverse events necessitated participant withdrawal from study.

Adverse event data are presented from the 17 randomized and controlled clinical trials discussed above (Evidence Table 20), and from four trials that presented adverse event data only (Table 17 and Evidence Tables 21 and 22). Two observational studies[107; 108] presented data on adverse events but were of poor quality (Appendix C).

There were no major adverse event data reported, apart from the event noted by Sienra-Monge and colleagues above.[92] Minor neurologic symptoms were the most common adverse event, particularly headache, insomnia, nervousness and somnolence. Rates varied widely, however, and adverse events were also very common among placebo groups.

A number of studies examined the effects of newer antihistamines on ECG changes, particularly on the QT and QTc interval.[81; 96; 109-113] No study demonstrated significant prolongation of the QT interval with cetirizine[81; 96; 112-114] fexofenadine,[114] or desloratadine[115] One poor-quality study examined concurrent use of cetirizine or loratadine and erythromycin estolate[109] and noted no abnormality of the QT or QTc interval.

The Early Treatment of the Atopic Child (ETAC)[95; 96; 116; 117] was a prospective, double-blind, parallel-group study examining the efficacy of cetirizine in preventing onset of asthma among children 12 to 24 months old with atopic dermatitis (Tables 20 and 21, Evidence Tables 23 and 24). Study participants were treated for 18 months and adverse events were assessed at the end of treatment. Although this study did not meet inclusion criteria for this report with respect to population characteristics (the study did not involve allergic rhinitis or urticaria), we included this paper as it provided long-term data on the safety of cetirizine in a large population of young children.

In the ETAC study, serious adverse events were less common with cetirizine (9.3%) than placebo (13.6%) (p=0.053). Serious adverse events attributed to study to the study medication occurred in one child receiving cetirizine and five children receiving placebo. Hospitalization rates did not differ between the treatment groups (p=0.189). There were ten accidental overdoses of study medications by study participants; two of these participants were receiving cetirizine. Symptoms and events (Evidence Table 23) were reported with similar frequency in cetirizine- and placebo-treated groups. There were age-appropriate increases in height and weight during the study period. There were no clinically relevant differences between groups for changes in electrocardiograms, and cetirizine therapy was not associated with prolongation of the QTc interval in any participant.

Table 17. Adverse events from studies in children

Type of AE	Adverse Event	Cetirizine	Desloratadine	Fexofenadine	Loratadine
NEUROLOGICAL					
MAJOR		Somnolence and irritability (1 patient, led to withdrawal)[92]			
MINOR	Behavioral screening	NSD vs placebo[95; 96]			
	Fatigue	4.0% vs chlorpheniramine 6.3% [84] 5.3% vs placebo 0%, NSD[91] 5.9% vs placebo 7.5%[87]			
	Headache	6.3% vs chlorpheniramine 0%[84] 0% vs placebo 6.3%, NSD[91] 15.1% vs placebo 19.7%[81] 3.2% vs placebo 1.6%[80] 15% vs placebo 18.8%[113]	1.8 vs placebo 5.4% (2-5 years)[115] 1.7 vs placebo 6.7% (6-11 years)[115]	1-2% in treatment and placebo groups[114]	25% vs fluticasone 42%[86]
	Somnolence	5.5% vs placebo 0%[77] NSD vs placebo[95; 96] 21.4% vs placebo 30.2%[112] 1/38 patients withdrew due to somnolence vs 0 in loratadine group[92]			0% vs dexchlorpheniramine 4.3%[85] 3% vs placebo 5%, NSD[111] 0.5 vs placebo 1.0%, NSD[110]
	Insomnia	23.8% vs placebo 44.2%[112]			0 vs placebo 1.0%, NSD[110]
	Irritability				0 vs placebo 0.5% , NSD[110]
	Nervousness	28.6% vs placebo 44.2%[112]			
	Vertigo	1.6% vs placebo 0%[80]			
GASTROINTESTINAL					
MAJOR					
MINOR	Abdominal pain	9.6% vs chlorpheniramine 4.8%[84] 9.4% vs placebo 4.5%[81] 9.3% vs placebo 4.3%[113]			

Type of AE	Adverse Event	Cetirizine	Desloratadine	Fexofenadine	Loratadine
	Abnormal liver function	9.4% vs placebo 0%[87] NSD vs placebo in blood chemistry[95; 96]			
	Dry mouth	1.6% vs placebo 0%[80]			
	Increased appetite	1.6% vs placebo 0%[80]			
	Nausea	1.6% vs chlorpheniramine 0%[84]			
HEMATOLOGICAL					
MAJOR				Neutropenia (asymptomatic) in 1 child[82]	
MINOR	Abnormalities in complete blood count	NSD vs placebo[89] Leucocytosis: 5% vs placebo 7%[87] NSD vs placebo[95; 96]			
CARDIAC					
MAJOR	QT interval	NSD vs placebo (2 week follow-up)[81] NSD vs placebo[95; 96] NSD QT cetirizine vs placebo[112] NSD QTc vs placebo[113]	NSD rate, PR, QRS or QT vs placebo[115]	NSD QTc vs placebo[92]	
MINOR					
RESPIRATORY					
MAJOR					
MINOR	Coughing				3% vs placebo 5%, NSD[111]
	Epistaxis	7.1% vs placebo 4.3%[81] 7.1% vs placebo 4.3%[113]			4.8% (moderate) vs dexchlorpheniramine 0%[85] 4% vs fluticasone 7%[86]
	Pharyngitis	10.1% vs placebo 13.6%[81] 1.6% vs placebo 4.9%[80] 10.0% vs placebo 13.0%[113]			10% vs fluticasone 16%[86] 18.8% vs 18.1%, NSD[110]
OTHER					
MAJOR	Accidental overdose	2 children vs 8 placebo[95; 96]			

Type of AE	Adverse Event	Cetirizine	Desloratadine	Fexofenadine	Loratadine
MINOR	Rash	3.2% vs placebo 0%[80] 1/40 patients withdrew due to rash[92]			
	Mean increase height and weight	NSD vs placebo[95; 96]			
	Fever		5.5 vs placebo 5.4% (2-5 years)[115] 5.5 vs placebo 5.4% (6-11 years)[115]		3% vs placebo 5%, NSD[111]

*Only fair- and good-quality studies are presented in the table. Poor-quality studies are listed in Appendix C.
Abbreviations: NSD-no significant difference; vs-versus; QT-cardiac output; QTc-corrected QT interval for heart rate

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 newer antihistamine is more effective or associated with fewer adverse effects?

There was 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. Advanced 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.

Three fair quality placebo-controlled trials were identified in patients with AR and asthma.[104; 118; 119] Patients' assessment of asthma significantly improved on cetirizine versus placebo in two studies,[118; 119] however no improvement (or worsening) of pulmonary function tests occurred. Berger and colleagues[104] examined desloratadine in patients with SAR and asthma and found a significant decrease in total asthma symptom scores in the treatment group.

Rhinitis is one of the most common conditions during pregnancy, affecting more than 20% of pregnant women.[120] However, women who are pregnant, lactating, or not using adequate birth control are excluded from clinical trials. Thus safety data must come solely from observational studies.

The UK PEM cohort[99] reviewed 16,638 patients and identified 30 exposures in first trimester pregnant women; 10 adverse outcomes were all determined not related to antihistamines. Fair evidence from four observational studies[121-124] and a meta-analysis[125] concurred with the findings of no significant difference in antihistamine use during the first trimester of pregnancy (Evidence Table 25).

Data from the National Birth Defects Prevention Study,[106] a multi-state study of environmental and genetic risk factors for major birth defects, were used to examine the relationship between loratadine intake in pregnant women and hypospadias among offspring. No significant relationship was found.

No other studies were identified which examined subgroups based on demographic or co-morbid conditions in the updated search.

One head-to-head study examined the effects of terfenadine, astemizole, loratadine, and cetirizine on the ECG, among children with PAR.[109] Erythromycin estolate was administered to all study participants, and a significant increase in QT interval was noted in the terfenadine group, but not in the other groups. The QTc interval, however, was not prolonged or different in any group.

SUMMARY

Table 18. Summary of the Evidence

Key Question	Evidence	Conclusions
1. Comparative Efficacy For outpatients with seasonal or perennial allergic rhinitis or urticaria, do newer antihistamines differ in effectiveness?	**Adults** **SAR** - Fair evidence suggests NSD between fexofenadine and cetirizine, loratadine and cetirizine, or loratadine and fexofenadine. - No fair or better evidence comparing fexofenadine to desloratadine, cetirizine to desloratadine, or loratadine to desloratadine. - No new fair- or good-quality head-to-head studies identified in the updated review **PAR** - Fair evidence suggests NSD between loratadine and clemastine, except onset quicker for loratadine - Desloratadine superior to placebo in TSS - No new fair or good quality head-to-head studies identified in the updated review **CIU** - Fair evidence for CIU suggests loratadine superior to cetirizine for TSS, but response rate was not higher - Cetirizine vs fexofenadine: one fair-quality study found cetirizine to be more efficacious at 28-day follow-up - No fair or better evidence comparing desloratadine to cetirizine, fexofenadine, or loratadine; or fexofenadine to	**Adults** **SAR** - Fexofenadine vs. cetirizine: NSD - Loratadine vs. cetirizine: NSD - Loratadine vs fexofenadine: NSD - Insufficient evidence on the comparative effectiveness of other drug combinations **PAR** - Insufficient evidence on comparative effectiveness **CIU** - Loratadine may be superior to cetirizine for TSS - Limited evidence cetirizine may be more efficacious than fexofenadine - Insufficient evidence on the comparative effectiveness of other drug combinations **Other urticaria** No available data on comparative

Table 18. Summary of the Evidence

Key Question	Evidence	Conclusions
	loratadine **Other urticaria** - no fair- or good-quality evidence identified **Short-term studies** - follow-up <14 days - SAR in environmental exposure unit: cetirizine reduced TSS more than loratadine in 1 study, equal in another study; cetirizine reduced TSS more than fexofenadine - SAR in park: cetirizine reduced TSS more than loratadine **Children** **SAR** - 8 fair-quality placebo- and active-controlled studies - no head-to-head studies **PAR** - 7 fair-quality placebo- and active--controlled studies - 1 head-to-head trial: cetirizine and loratadine similar efficacy, cetirizine improved parent-assessed outcomes **Urticaria** - 2 fair-quality studies - No head-to-head studies	effectiveness in other types of urticaria **Short-term studies** - Comparative evidence limited - Evidence mixed for cetirizine vs loratadine for TSS - Cetirizine may be more effective than fexofenadine **Children** **SAR** - No data based on direct comparisons for comparative efficacy **PAR** - 1 small, fair-quality study suggests cetirizine may be more efficacious than loratadine. - Data are insufficient to draw definitive conclusions. - Insufficient evidence on the comparative effectiveness of other drug combinations **Urticaria** - No data on comparative efficacy

Table 18. Summary of the Evidence

Key Question	Evidence	Conclusions
2.Safety/Adverse Effects For outpatients with SAR, PAR or urticaria, do newer antihistamines differ in safety or adverse effects?	**Overall adverse events** - Fair evidence in head-to-head trials of low rates of discontinuation due to AEs; 3 placebo-controlled trials: 21-51% incidence of AEs with NSD between groups; caused discontinuation <3% patients. **Sedation** - Loratidine vs cetirizine Cohort study (n=43,000) and 2 small RCTs: loratidine less sedating - Loratidine vs fexofenadine: cohort study (n=43,000), NSD - Cetirizine vs fexofenadine: 3 RCTs, two of which showed more sedation with cetirizine **Headache** - Commonly reported with cetirizine, loratadine, and fexofenadine with similar rates. **Cardiac effects** - In a cohort study of 5 non-sedating antihistamines, a relative risk of 4.2 was noted for arrhythmias for all drugs combined compared to non used. The relative risk with cetirizine was 7.9 ($p<0.05$), loratadine 3.2 ($p>0.05$). - No increase in QTc interval with loratadine (2 studies) and fexofenadine (1 study) compared to placebo - One fair-quality head-to-head study found no significant adverse	**Overall adverse events** Rates of discontinuation due to AEs was low with all 4 drugs and comparable to rates in placebo groups. **Sedation** - Cetirizine is more sedating than cetirizine - Some evidence that cetirizine may be more sedating than fexofenadine. - NSD between loratadine and fexofenadine in one observational study **Headache** Headache was reported with similar rates in cetirizine, loratadine, and fexofenadine in the updated review **Cardiac effects** A large, fair-quality cohort study provides evidence of a significant risk of cardiac arrhythmias with cetirizine compared to non-use. A nonsignificant increase in risk compared was noted with loratadine. - Limited evidence suggests no QTc prolongation with loratadine and fexofenadine

Table 18. Summary of the Evidence

Key Question	Evidence	Conclusions
	effects on the QTc interval with cetirizine or fexofenadine **Other:** - Poor-quality, small trial noted an increase in post-prandial glucose with cetirizine compared to loratadine and clemastine - Fair quality safety and tolerability study of fexofenadine in 16,638 patients in a UK PEM cohort. **Children** - No head-to-head data on adverse events except 2 events in cetirizine group (vs loratadine) - Headache, fatigue, somnolence, pharyngitis were reported at rates >5% in a number of studies, but there was NSD from rates in placebo group - NS ECG abnormalities reported compared to placebo groups	**Children** - Insufficient evidence on comparative safety - Two adverse events led to withdrawal of (cetirizine) - Fair-quality evidence on the safety of cetirizine and loratadine - Limited evidence on the safety of desloratadine and fexofenadine - Fair evidence that cetirizine does not significantly prolong QTc interval - Limited evidence (1 study each) that desloratadine and fexofenadine do not prolong QTc interval

Table 18. Summary of the Evidence

Key Question	Evidence	Conclusions
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 newer antihistamine is more effective or associated with fewer adverse effects?	There is insufficient evidence to determine whether any of the antihistamines examined in this report has an advantage in efficacy or safety for any group based on sex, race/ethnicity, or age. We did not identify head-to-head comparative studies of drug interactions. Three fair-quality placebo-controlled trials were identified in patients with AR and asthma. Patients' assessment of asthma severity significantly improved on cetirizine versus placebo, but no improvement (or worsening) of pulmonary function tests occurred. Desloratadine in patients with SAR and asthma decreased total asthma symptom scores in one study. 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. One case-controlled study examined the relationship between loratadine exposure in pregnancy and found no association with hypospadius. No additional fair or good quality data on subgroups or head-to-head studies of drug-interactions were identified in the updated search of adults, or in the search for data on children.	

Abbreviations: SAR-seasonal allergic rhinitis; PAR-perennial allergic rhinitis; AR-allergic rhinitis; CIU-chronic idiopathic urticaria; SD-significant difference; NSD-no significant difference; NS-not significant; vs-versus; TSS-total symptom score; RCT-randomized control trial; ECG-electrocardiogram; QT-cardiac output; QTc- corrected QT interval for heart rate.

DISCUSSION

There is a paucity of data available on the comparative efficacy of newer antihistamines available in the US and Canada. These drugs appear to be safe and relatively well-tolerated in both adult and pediatric populations. The original report identified some data on the comparative efficacy of several of these drugs in adult populations; the updated search provided little new data. There are thus few available studies upon which to determine comparative efficacy, effectiveness, tolerability, or safety. A systematic review of the literature in pediatric populations also identified few studies upon which to make comparisons of effect. Rates of drug discontinuation due to adverse events were low in both adults and children, and few serious events were noted. One observational study noted an increased relative risk for cardiac arrhythmias with cetirizine (7.9, $p<0.05$) and loratadine (3.2, $p>0.05$) compared to non use. No significant ECG abnormalities were noted in children when compared to placebo. Data were generally insufficient to make comparisons for somnolence among drugs.

This review and update have a number of strengths. The search strategies were broad, public solicitation was made for comments on the key questions and draft report, and unpublished data were sought. Quality assessment was done by two reviewers and consensus was achieved. Other key decisions were also made by at least two experienced systematic reviewers.

This review has several limitations. The search was confined to English-language literature, which may introduce bias,[126] although the contribution of non-English literature to the results of a systematic review may not be large.[127] Although unpublished data were sought, no such additional studies were identified for the update. It is likely that publication bias affects the body of literature reviewed herein, with negative studies less likely to be published and therefore less likely to be included in our review.[128]

We did not summarize the data in this review in a quantitative fashion (i.e., perform a meta-analysis) because outcomes were very heterogeneous among studies. Although most studies presented individual and total symptom scores, many different symptoms and scoring methods were used. In addition, we did not feel that calculating a standardized mean difference for each study would allow meaningful comparison among studies.

There were a number of other characteristics of the body of literature reviewed, in addition to the heterogeneity of outcome measures, which made it difficult to synthesize this literature and evaluate the key questions. All studies measured multiple outcomes and often the primary outcome was not indicated. Adjustment for multiple comparisons was rarely presented in studies. Outcome measures of symptoms were often composite measures (e.g., total symptom score, mean daily symptom score), and there was no consistency in the use of these composite measures among studies. Authors rarely indicated why they chose the measures they used, and it was not clear that authors had chosen their composite measures *a priori.* It is thus unclear whether selective reporting of outcomes may have occurred.

The ideal study design upon which to determine comparative effectiveness is head-to-head, randomized, controlled trials examining the drugs and populations of interest. As few head-to-head studies were identified in this review for adults and only one was located for children, we explored data from active- and placebo-controlled trials. The comparisons from these latter types of studies are termed indirect comparisons, with respect to the drugs of interest, in contrast to the data obtained from head-to-head studies (direct comparisons). Indirect comparisons are subject to greater potential for bias, as the benefit of randomization does not

occur across studies.[129] There are statistical methods available for comparing multiple treatments when both direct and indirect evidence is available,[130] that may be useful in healthcare decision-making (although the potential for bias must be acknowledged). The data in our review were not, however, conducive to such an analysis, as we did not have sufficient studies examining each drug compared to placebo or similar active controls.

The applicability of the studies identified in this review to general populations is limited. Although we sought evidence on both the efficacy and effectiveness of this drug class, we found that studies primarily examined efficacy. Inclusion criteria were narrowly defined and participants were highly selected. Persons with comorbid conditions were generally excluded, the study settings were most often academic referral centers, and medication adherence was infrequently reported and rates (when reported) were high.

This review suggests several areas where future research should be directed. Additional research is needed to provide direct comparisons of newer antihistamines, particularly comparisons where no data currently exist (e.g., in pediatric populations; studies involving desloratadine in adults).

Additional studies are needed to address the use of newer antihistamines among population subgroups defined by demographic characteristics, comorbid conditions, or concurrent medication use. Examination of the current literature provided no guidance on the efficacy and safety of newer antihistamines in subpopulations where polypharmacy, cognitive impairment, and comorbid conditions are common, most notably older adults. Allergic rhinitis is a significant and increasing problem among the elderly, and data specific to this population are important.[131]

The quality of future comparative effectiveness studies might be improved in a number of areas, based on our findings. Valid methods of generating randomization sequences and concealment of participant allocation in RCTs need to be used and described. Descriptions of methods for study participant recruitment, and information on the representativeness of participants to target and accessible populations would aid the user of the literature in determining applicability of the study to their population of interest.

Outcomes, including adverse events, should be determined *a priori*. More standardized reporting of symptoms and symptoms scores is needed. Outcome measures should be reliable and valid. The primary outcomes should be explicitly stated, and should be limited in number. Statistical adjustments for multiple comparisons of outcomes should be made as needed.

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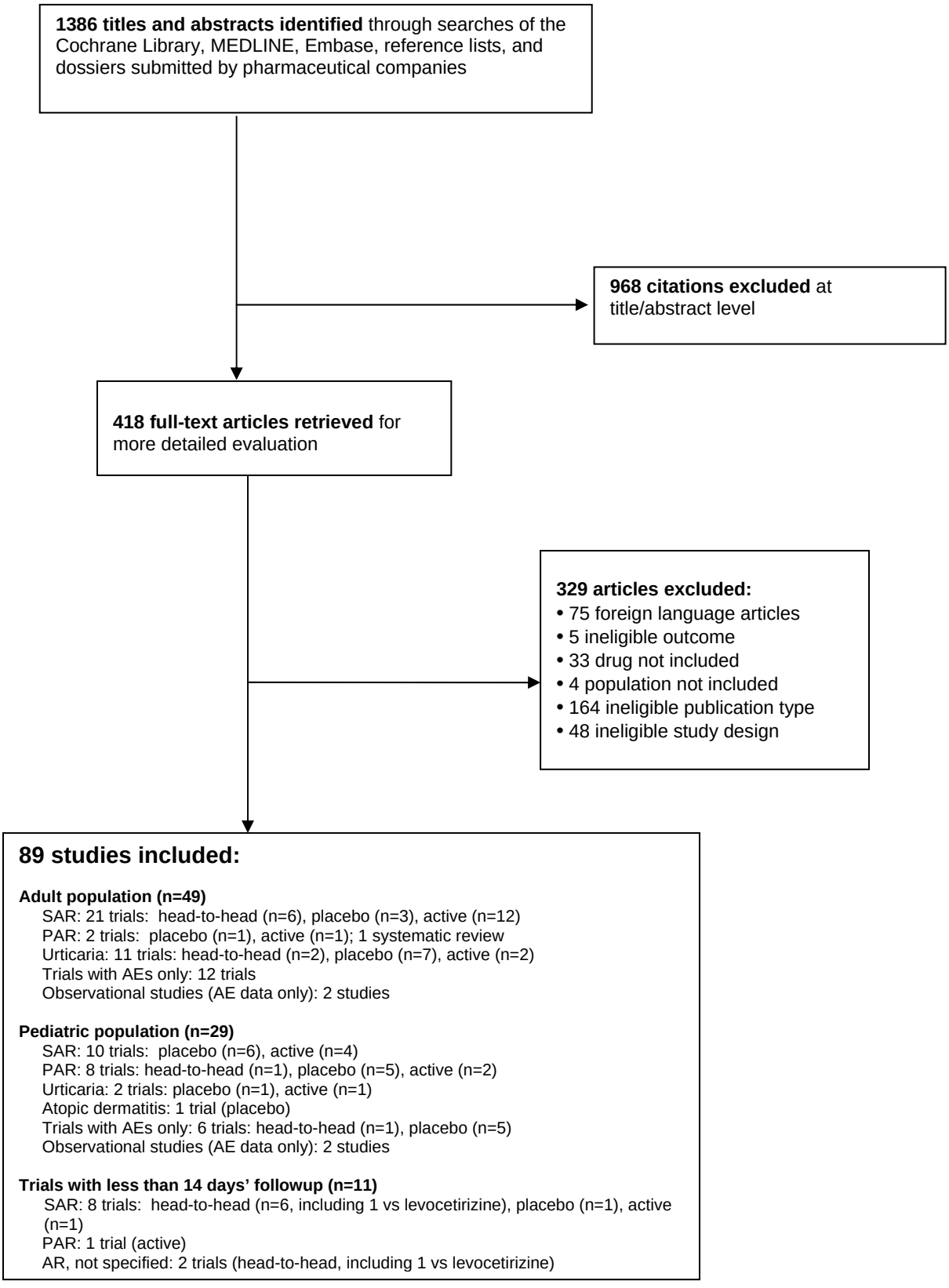
Figure 1. Literature Search Results



Appendix A. Search Strategies for Newer Antihistamines

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <3rd Quarter 2005>
Search Strategy:

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1 (Cetirizine or zyrtec).mp.
2 (Loratadine or Claritin).mp.
3 (Fexofenadine or Allegra).mp.
4 (Desloratadine or Clarinex).mp.
5 1 or 2 or 3 or 4
6 from 5 keep all

Database: Ovid MEDLINE(R) <1996 to August Week 4 2005>
Search Strategy:

---

1 (Cetirizine or zyrtec).mp.
2 (Loratadine or Claritin).mp.
3 (Fexofenadine or Allegra).mp.
4 (Desloratadine or Clarinex).mp.
5 1 or 2 or 3 or 4
6 limit 5 to (controlled clinical trial or guideline or meta analysis or randomized controlled trial)
7 (adverse effect$ or poison$ or toxic$).mp.
8 (ae or po or to).fs.
9 7 or 8
10 5 and 9
11 6 or 10
12 limit 10 to humans
13 limit 12 to english language
14 limit 12 to abstracts
15 13 or 14
16 (2004$ or 2005$).ed.
17 15 and 16
18 from 17 keep all

Database: EMBASE Drugs & Pharmacology <1991 to August Week 4 2005>
Search Strategy:

---

1 (Cetirizine or zyrtec).mp.
2 (Loratadine or Claritin).mp.
3 (Fexofenadine or Allegra).mp.
4 (Desloratadine or Clarinex).mp.
5 1 or 2 or 3 or 4)

6 Clinical Trial/
7 random$.mp.)
8 controlled study/
9 6 and (7 or 8)
10 Meta Analysis/
11 (systemat$ adj5 review$).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
12 cohort$.mp.
13 9 or 10 or 11 or 12
14 5 and 13
15 (adverse effect$ or poison$ or toxic$).mp.
16 5 and 15
17 16 and 13
18 14 or 17
19 limit 18 to human
20 limit 19 to english language
21 limit 19 to abstracts
22 20 or 21
23 from 22 keep all

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 Studies

Author	Agents	Condition, Design	Fatal Flaw
Head-to-head and active-control trials (from original report)			
Campbell A 1997	Cetirizine vs. Loratadine vs. PLA	SAR	No ITT, small sample size (16 tx, 7 control)
Gambardella 1993	Azelastine nasal vs. Loratadine	SAP	No ITT, no info on baseline characteristics
Harvey 1996	Cetirizine vs. Chlorpheniramine vs. Terfenidine	SAR	No No ITT, outcome assessment not blinded, randomization inadequate
Irander 1990	Loratadine 40 vs. 1st GEN Clemastine 1 mg bid vs PLA	SAR	No ITT, excluded scores on days requiring additional medication.
Kalivas 1990	Cetirizine vs. 1st GEN Hydroxyzine vs. PLA	CIU	No ITT, no info on baseline characteristics
Nunes C 2000	Cetirizine vs. Loratadine	CIU	No ITT, no info on baseline characteristics
Passali 1994	Azelastine nasal vs. Cetirizine	PAR	No ITT, no info on baseline characteristics
Patel P 1997	Cetirizine vs. Loratadine	CIU	No ITT, withdrawals per group not reported.
Ricard 1999	Loratadine vs. Fexofenadine	SAR	No ITT, # randomized not reported, no info on baseline characteristics
Wilson 2002	Fexofenadine vs. Desloratadine	SAR	No ITT, no info on baseline characteristics.
Studies from Update 1			
Adults			
Ciprandi 2004	Cetirizine vs Desloratadine	SAR, H2H	Baseline demographic characteristics NR, and randomization and allocation concealment methods NR- may be differences between groups at baseline, also unable to determine number analyzed.
Horak 2004	Cetirizine	SAR, ACT	No ITT; post-randomization exclusions, plus not reported if groups similar at baseline
Kurowski 2004	Cetirizine	SAR, ACT	High loss to f/u, not ITT, also limited baseline characteristics reported.
DiLorenzo	Desloratadine	CIU, ACT	Very high attrition for unclear reasons; patients 'selected' into study
Juhlin 1988	Cetirizine	CIU, PCT	Unclear if randomized, no information on how groups assigned; no wash-out between cross-over; attrition 19/30
Kontou-Fili 1990	Cetirizine	Urticaria, PCT	Bbaseline comparability NR; attrition 1/11
Sharpe 1993	Cetirizine	Urticaria, PCT	Baseline comparability NR; attrition 2/21
Zurberbier 1995	Cetirizine	Urticaria, PCT	Treatment with placebo was single-blind, no baseline characteristics reported, randomization and allocation concealment methods NR
Zurberbier 1996	Cetirizine	Urticaria, PCT	High attrition (15%), no ITT, baseline characteristics not reported by group (unable to determine if groups by order of administration were similar);

Author	Agents	Condition, Design	Fatal Flaw
Zurberbier 1996		Urticaria, Safety	
Children			
Ciprandi 2004	Cetirizine	PAR, PCT	
Bender 2004	Loratadine	SAR, ACT	
Segal 2003	Cetirizine	SAR, PCT	
Delgado 1998		Safety. H2H	
Salmun 2000		Safety PCT	
Rossi 2005		Safety, Obs. Study	

Placebo Controlled Trials

Author	Agents	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. Abbreviations used in this report

AR	allergic rhinitis
bid	twice a day
CDC	Centers for Disease Control
CI	confidence interval
CIU	chronic idiopathic urticaria
CNS	central nervous system
d	day
DERP	Drug Effectiveness Review Project
e.g.	example
ECG	electrocardiogram
FDA	Food and Drug Administration
GI	gastrointestinal
h	hour(s)
kg	kilograms
mg	milligrams
mm	millimeters
NR	not reported
NS	not significant
NSD	no significant difference
OTC	over the counter
PAR	perennial allergic rhinitis
Pt(s)	patient(s)
q8h	every eight hours
qam	every morning
qd	once a day
QOL	quality of life
QTc	corrected QT interval for heart rate
RCT	randomized controlled trials
SAR	seasonal allergic rhinitis
SD	standard deviation
tid	three times daily
TNSS	total nasal symptom score
TOSS	time oriented score system
TSS	total symptom score
TSSC	total symptom score with nasal congestion
VAS	visual analog score
vs	versus
w(k)	week
y	year