Drug Class Review

Newer Antihistamines

Final Report
Update 2

May 2010

The purpose of Drug Effectiveness Review Project reports is to make available information regarding the comparative clinical effectiveness and harms of different drugs. 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.

Original Report: November 2004
Update 1: April 2006

The literature on this topic is scanned periodically.

Update 2 prepared by:
Susan Carson, MPH
Nancy Lee, PharmD
Sujata Thakurta, MPA:HA

Drug Effectiveness Review Project
Marian McDonagh, PharmD, Principal Investigator

Oregon Evidence-based Practice Center
Mark Helfand, MD, MPH, Director

Oregon Health & Science University

The medical literature relating to this topic is scanned periodically. (See http://www.ohsu.edu/ohsuedu/research/policycenter/DERP/about/methods.cfm for description of scanning process). Prior versions of this report can be accessed at the DERP website.

TABLE OF CONTENTS

TABLES

FIGURES

APPENDIXES

EVIDENCE TABLES

Published in a separate document.

Acknowledgments
We thank Leah Williams, our publications editor, for putting this report into its present form for you to read. We also thank Patricia Thieda MA, Laurie Huffman, MS, Miranda Walker, MA, for assistance with data abstraction and quality assessment of studies, and Jennifer Nguyen for retrieval of articles and assistance with editing and formatting.

Suggested citation for this report
Carson S, Lee N, Thakurta S. Drug class review: Newer antihistamines. Update 2.

Funding
The Drug Effectiveness Review Project, composed of 12 organizations including 11 state Medicaid agencies and the Canadian Agency for Drugs and Technology in Health commissioned and funded for this report. These organizations selected the topic of the report and had input into its Key Questions. The content and conclusions of the report were entirely determined by the Evidence-based Practice Center researchers. The authors of this report have no financial interest in any company that makes or distributes the products reviewed in this report.

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,[2] brain, adrenal medulla, skin vasculature, and the heart.[3]

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

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 manifest clinically as characteristic allergic signs and symptoms: sneezing, rhinitis, rhinorrhea, erythema, pruritus, and urticaria.[2] 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.[4]

Antihistamines are classified[5] as first generation (sedating, including chlorpheniramine, diphenhydramine, promethazine, and hydroxyzine) and newer. The newer antihistamines are sometimes referred to as second generation (relatively nonsedating, including terfenadine, astemizole, loratadine, cetirizine, and levocetirizine) and third generation (including 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.[6]

Newer antihistamines were developed to decrease the adverse effects of first generation drugs. Second-generation antihistamines emerged in the early 1980's and had 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.[6] Third-generation antihistamines are active metabolites of first-generation drugs, developed with the goal of improving clinical efficacy and minimizing side effects.[5]

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.

The newer oral antihistamines available in the United States and Canada and addressed in this review are cetirizine, desloratadine, fexofenadine, loratadine (which is now available over-the-counter), levocetirizine, and azelastine, and olopatadine nasal sprays. These drugs and their indications are listed below in Table 1.

Table 1. Included drugs and their labeled indications

Drug	Trade name(s)	Labeled indications	Dosage form/Route
Cetirizine hydrochloride	Zyrtec®	SAR; PAR; Chronic Urticaria	Syrup/Oral
	Reactine®[a]	SAR[b]; PAR; Chronic Urticaria[c]	Tablet; Chewable tablet; Syrup/Oral
Loratadine	Claritin®	SAR; PAR[a]; Chronic Urticaria	Tablet; ODT[a]; Syrup; Capsule[d]/Oral
Fexofenadine hydrochloride	Allegra®	SAR; PAR[a]; Chronic Urticaria	Tablet; ODT; Suspension; Capsule[a] /Oral
Desloratadine	Clarinex®[d]	SAR; PAR; Chronic Urticaria	Tablet; ODT; Syrup/ Oral
	Aerius®[a]	Allergic Rhinitis[c]; SAR[b]; Chronic Urticaria	Tablet; Syrup/Oral
Levocetirizine	Xyzal®[d]	SAR; PAR; Chronic Urticaria	Tablet; Solution/Oral
Azelastine	Astelin®[d]	SAR	Spray; Metered/Nasal
	Astepro®[d]	SAR; PAR	Spray; Metered/Nasal
Olopatadine	Patanase®[d]	SAR	Spray; Metered/Nasal

Abbreviations: ODT, orally disintegrating tablet; PAR, perennial allergic rhinitis; SAR, seasonal allergic rhinitis.
[a] Only available in Canada.
[b] For children only.
[c] For adults only.
[d] Not available in Canada.

Rhinitis

Rhinitis refers to disease involving inflammation of the nasal membranes.[7] 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 (allergic rhinitis) may be seasonal (seasonal allergic rhinitis) or perennial (perennial allergic rhinitis), 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 seasonal allergic rhinitis, 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.[7] Persons with perennial allergic rhinitis, on the other hand, have year-round symptoms (although there may be some seasonal variation) related to allergens that are largely indoors (house dust mites [*D. pteronyssinus*], animal dander, and mold spores).[7, 8]

As it is often difficult to differentiate between seasonal allergic rhinitis and perennial allergic rhinitis, and the World Health Organization's Allergic Rhinitis and its Impact on Asthma Group has recommended instead that allergic rhinitis be classified as "intermittent" or "persistent".[9]

Allergic rhinitis is a very common condition worldwide, with estimates of global prevalence ranging between 10% and 25%,[10] and epidemiologic evidence suggests that the prevalence of allergic rhinitis is increasing.[11, 12] Approximately 40 million people in the United States experience significant symptoms of allergic rhinitis for all or part of each year.[13-15] Allergic rhinitis is even more prevalent in younger populations and is thought to affect up to 40% of children and adolescents.[7, 10, 16, 17]

Allergic rhinitis has a number of important sequelae. Health-related quality of life is impacted by allergic rhinitis, including effects on physical function, energy, social function, mental health, bodily pain, mood, learning ability, and workplace productivity.[18, 19] If left untreated, allergic rhinitis can be associated with serious complications, including asthma, sinusitis, respiratory infections, and otitis media.[19, 20] In addition, allergic rhinitis appears to be linked to a number of other conditions. Allergic rhinitis may be considered an independent risk factor for asthma and the 2 diseases often coexist.[6, 9] Atopic dermatitis is also linked to both allergic rhinitis and asthma.

Allergic rhinitis among children is particularly problematic, as the condition is often undiagnosed or misdiagnosed. Allergic rhinitis can have a large impact on the health and quality of life of children, including school absenteeism, diminished school performance, and mental health consequences.[19, 20] In the United States, it is estimated that children with allergic rhinitis miss 2 million days of school per year.[16] Allergic rhinitis and its treatment can affect school performance by causing diminished cognitive function,[20] irritability, disrupted sleep patterns and sleep loss, mood disturbances, and impaired social function.[6] Children with poorly-controlled allergic rhinitis are at an increased risk for developing asthma, chronic sinusitis, and otitis media, as well as other respiratory complications.

The objective of treatment of allergic rhinitis 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 allergic rhinitis include allergen avoidance and environmental control, however the evidence for the effectiveness of these interventions is limited.[3] Pharmacotherapy treatment recommendations depend on symptom severity and may include antihistamines, decongestants, corticosteroids, leukotriene-receptor antagonists, mast cell stabilizers, anticholinergics, and allergen-specific immunotherapy.[21]

Urticaria

Urticaria, or hives, is a condition characterized by transient, pruritic wheals (swellings) that are primarily the result of histamine release from mast cells. It is estimated that at least 50% of the general population have experienced urticaria at one time or another.[2] Chronic urticaria is usually defined as recurring episodes of urticaria lasting 6 weeks or more.[2]

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),[22] 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% to 50% of patients.[23] Chronic idiopathic urticaria is self-limited for most patients; 50% undergo

spontaneous remissions within 1 year. Twenty percent, however, have intermittent symptoms for years.[22]

Acute urticaria is much more common than the chronic form in both adults and children, accounting for 70% of cases.[22] 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 inhibitors, and blood products.[22]

Purpose and Limitations of Systematic Reviews

Systematic reviews, also called evidence reviews, are the foundation of evidence-based practice. They focus on the strength and limits of evidence from studies about the effectiveness of a clinical intervention. Systematic reviews begin with careful formulation of research questions. The goal is to select questions that are important to patients and clinicians then to examine how well the scientific literature answers those questions. Terms commonly used in systematic reviews, such as statistical terms, are provided in Appendix A and are defined as they apply to reports produced by the Drug Effectiveness Review Project.

Systematic reviews emphasize the patient's perspective in the choice of outcome measures used to answer research questions. Studies that measure health outcomes (events or conditions that the patient can feel, such as fractures, functional status, and quality of life) are preferred over studies of intermediate outcomes (such as change in bone density). Reviews also emphasize measures that are easily interpreted in a clinical context. Specifically, measures of *absolute risk* or the probability of disease are preferred to measures such as relative risk. The difference in absolute risk between interventions depends on the number of events in each group, such that the difference (absolute risk reduction) is smaller when there are fewer events. In contrast, the difference in relative risk is fairly constant between groups with different baseline risk for the event, such that the difference (relative risk reduction) is similar across these groups. Relative risk reduction is often more impressive than absolute risk reduction. Another useful measure is the *number needed to treat* (or harm). The number needed to treat is the number of patients who would need be treated with an intervention for 1 additional patient to benefit (experience a positive outcome or avoid a negative outcome). The absolute risk reduction is used to calculate the number needed to treat.

Systematic reviews weigh the quality of the evidence, allowing a greater contribution from studies that meet high methodological standards and, thereby, reducing the likelihood of biased results. In general, for questions about the relative benefit of a drug, the results of well-executed randomized controlled trials are considered better evidence than results of cohort, case-control, and cross-sectional studies. In turn, these studies provide better evidence than uncontrolled trials and case series. For questions about tolerability and harms, observational study designs may provide important information that is not available from controlled trials. Within the hierarchy of observational studies, well-conducted cohort designs are preferred for assessing a common outcome. Case-control studies are preferred only when the outcome measure is rare and the study is well conducted.

Systematic reviews pay particular attention to whether results of *efficacy studies* can be generalized to broader applications. Efficacy studies provide the best information about how a drug performs in a controlled setting. These studies attempt to tightly control potential

confounding factors and bias; however, for this reason the results of efficacy studies may not be applicable to many, and sometimes to most, patients seen in everyday practice. Most efficacy studies use strict eligibility criteria that may exclude patients based on their age, sex, adherence to treatment, or severity of illness. For many drug classes, including the antipsychotics, unstable or severely impaired patients are often excluded from trials. In addition, efficacy studies frequently exclude patients who have comorbid disease, meaning disease other than the one under study. Efficacy studies may also use dosing regimens and follow-up protocols that are impractical in typical practice settings. These studies often restrict options that are of value in actual practice, such as combination therapies and switching to other drugs. Efficacy studies also often examine the short-term effects of drugs that in practice are used for much longer periods. Finally, efficacy studies tend to assess effects by using objective measures that do not capture all of the benefits and harms of a drug or do not reflect the outcomes that are most important to patients and their families.

Systematic reviews highlight studies that reflect actual clinical *effectiveness* in unselected patients and community practice settings. Effectiveness studies conducted in primary care or office-based settings use less stringent eligibility criteria, more often assess health outcomes, and have longer follow-up periods than most efficacy studies. The results of effectiveness studies are more applicable to the "average" patient than results from the highly selected populations in efficacy studies. Examples of effectiveness outcomes include quality of life, frequency or duration of hospitalizations, social function, and the ability to work. These outcomes are more important to patients, family, and care providers than surrogate or intermediate measures, such as scores based on psychometric scales.

Efficacy and effectiveness studies overlap. For example, a study might use very narrow inclusion criteria like an efficacy study, but, like an effectiveness study, might examine flexible dosing regimens, have a long follow-up period, and measure quality of life and functional outcomes. For this report we sought evidence about outcomes that are important to patients and would normally be considered appropriate for an effectiveness study. However, many of the studies that reported these outcomes were short-term and used strict inclusion criteria to select eligible patients. For these reasons, it was neither possible nor desirable to exclude evidence based on these characteristics. Labeling a study as either an efficacy or an effectiveness study, although convenient, is of limited value; it is more useful to consider whether the patient population, interventions, time frame, and outcomes are relevant to one's practice or to a particular patient.

Studies anywhere on the continuum from efficacy to effectiveness can be useful in comparing the clinical value of different drugs. Effectiveness studies are more applicable to practice, but efficacy studies are a useful scientific standard for determining whether characteristics of different drugs are related to their effects on disease. Systematic reviews thoroughly cover the efficacy data in order to ensure that decision makers can assess the scope, quality, and relevance of the available data. This thoroughness is not intended to obscure the fact that efficacy data, no matter how large the quantity, may have limited applicability to practice. Clinicians can judge the relevance of studies' results to their practice and should note where there are gaps in the available scientific information.

Unfortunately, for many drugs there exist few or no effectiveness studies and many efficacy studies. Yet clinicians must decide on treatment for patients who would not have been included in controlled trials and for whom the effectiveness and tolerability of the different drugs are uncertain. Systematic reviews indicate whether or not there exists evidence that drugs differ

in their effects in various subgroups of patients, but they do not attempt to set a standard for how results of controlled trials should be applied to patients who would not have been eligible for them. With or without an evidence report, these decisions must be informed by clinical judgment.

In the context of development of recommendations for clinical practice, systematic reviews are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of an intervention are based on strong evidence from clinical studies. By themselves, they do not say what to do. Judgment, reasoning, and applying one's values under conditions of uncertainty must also play a role in decision making. Users of an evidence report must also keep in mind that *not proven* does not mean *proven not*; that is, if the evidence supporting an assertion is insufficient, it does not mean the assertion is untrue. The quality of the evidence on effectiveness is a key component, but not the only component, in making decisions about clinical policy. Additional criteria include acceptability to physicians and patients, potential for unrecognized harm, applicability of the evidence to practice, and consideration of equity and justice.

Scope and Key Questions

The goal of this report is 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. The participating organizations of the Drug Effectiveness Review Project 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 report:

> 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 harms?
>
> Key Question 3. Are there subgroups of patients based on demographics (age, racial groups, gender), socioeconomic status, other medications (drug-drug interactions), co-morbidities (drug-disease interactions), or pregnancy for which one newer antihistamine is more effective or associated with fewer harms?

METHODS

Study Selection and Inclusion Criteria

Populations

- Adult or pediatric outpatients with the following conditions:
  - Seasonal allergic rhinitis
  - Perennial allergic rhinitis
  - Urticaria (acute and chronic)
- Subgroups of interest included, but were not limited to, different races, ages (older adult compared with 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.

Interventions

Drugs included in this review are listed below. This review is restricted to drugs currently available on the United States and Canadian markets. No black box warnings were found for any of the included drugs.

Active ingredient	Brand name
Cetirizine hydrochloride	Zyrtec®, Reactine®
Loratadine	Claritin®
Fexofenadine hydrochloride	Allegra®
Desloratadine	Clarinex®
Levocetirizine	Xyzal®[a]
Azelastine	Astelin®, Astepro®[a,b]
Olopatadine	Patanase®[a,b]

[a] Not available in Canada.
[b] Nasal spray.

Outcomes

The following were the primary outcomes for this review:

- Efficacy and effectiveness
  - Symptoms (nasal congestion, rhinorrhea, sneezing, itching and pain from skin irritations)
  - Functional capacity (physical, social and occupational functioning, quality of life)
  - Time to relief of symptoms (time to onset, duration of relief)
  - Duration of effectiveness (switch rate)
- Harms
  - Total withdrawals
  - Withdrawals due to adverse events

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

Study Design

1. Efficacy and effectiveness
    a. Randomized controlled trials, controlled clinical trials, and systematic reviews of fair or better quality.
    b. Direct comparisons (head-to-head studies) were preferred over indirect comparisons using active or placebo-controlled trials. Inclusion of indirect evidence will be considered where there is insufficient direct evidence.
    c. Studies ≥1 week in duration were included.
    d. Studies conducted in artificial study settings (for example, antigen exposure chambers) were not be included. Abstracts and conference proceedings are also excluded.

2. Harms
    a. Randomized controlled trials, controlled clinical trials, pre-compared with post-design studies, and observational studies with comparative groups.
    b. To be included, reports about overall harms or adverse events had to report total withdrawals, withdrawals due to specific adverse events (for example, central nervous system effects, sedation, gastrointestinal effects, dry mouth, urinary retention, etc.), or the frequency and severity of these specific adverse events.

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 2 dossiers received from pharmaceutical companies for fexofenadine HCL (Allegra®) and desloratadine (Clarinex®), and reference lists of review articles. For Update 2, we searched Ovid MEDLINE® (1996-November Week 3, 2009), the Cochrane Database of Systematic Reviews® (4th Quarter 2009), the Cochrane Central Register of Controlled Trials® (4th Quarter 2009), and Database of Abstracts of Reviews of Effects (4th Quarter 2009). We attempted to identify additional studies through hand searches of reference lists of included studies and reviews. The complete search strategy for electronic searches for Update 2 is in Appendix B. Finally, we requested dossiers of published and unpublished information from the relevant pharmaceutical companies for this review. All received dossiers were screened for studies or data not found through other searches. All citations were imported into an electronic database (Endnote® XI, Thomson Reuters).

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.

Study Selection

Selection of included studies was based on the inclusion criteria created by the Drug Effectiveness Review Project participants, as described above. Two reviewers independently assessed titles and abstracts of citations identified through literature searches for inclusion using the criteria below. Full-text articles of potentially relevant citations were retrieved and again were assessed for inclusion by both reviewers. Disagreements were resolved by consensus. Results published only in abstract form were not included because inadequate details were available for quality assessment.

Validity Assessment

We assessed the internal validity (quality) of trials based on the predefined criteria listed in Appendix C. These criteria are based on the US Preventive Services Task Force and the National Health Service Centre for Reviews and Dissemination (United Kingdom) criteria.[24, 25] We rated the internal validity of each trial based on the methods used for randomization, allocation concealment, and blinding; the similarity of compared groups at baseline; maintenance of comparable groups; adequate reporting of dropouts, attrition, crossover, adherence, and contamination; loss to follow-up; and the use of intention-to-treat analysis. Trials that had a fatal flaw were rated poor quality; trials that met all criteria were rated good quality; the remainder were rated fair quality. As the fair-quality category is broad, studies with this rating vary in their strengths and weaknesses: The results of some fair-quality studies are likely to be valid, while others are only possibly valid. A poor-quality trial is not valid; the results are at least as likely to reflect flaws in the study design as a true difference between the compared drugs. A fatal flaw is reflected by failure to meet combinations of items of the quality assessment checklist. A particular randomized trial might receive 2 different ratings, one for effectiveness and another for adverse events.

Appendix C also shows the criteria we used to rate observational studies of adverse events. These criteria reflect aspects of the study design that are particularly important for assessing adverse event rates. We rated observational studies as good quality for adverse event assessment if they adequately met 6 or more of the 7 predefined criteria, fair quality if they met 3 to 5 criteria, and poor quality if they met 2 or fewer criteria.

Included systematic reviews were also rated for quality (see Appendix C). We rated the internal validity based a clear statement of the questions(s); reporting of inclusion criteria; methods used for identifying literature (the search strategy), validity assessment, and synthesis of evidence; and details provided about included studies. Again, these studies were categorized as good when all criteria were met.

The overall strength of evidence for a body of evidence pertaining to a particular key question or outcome reflects the risk of bias of the studies (based on quality and study designs), consistency of results, directness of evidence, and precision of pooled estimates resulting from

the set of studies relevant to the question. Strength of evidence is graded as insufficient, low, moderate, or high.

Data Synthesis

We constructed evidence tables showing the study characteristics, quality ratings, and results for all included studies. We reviewed studies using a hierarchy of evidence approach, where the best evidence is the focus of our synthesis for each question, population, intervention, and outcome addressed. Studies that evaluated one newer antihistamine against another provided direct evidence of comparative effectiveness and adverse event rates. Where possible, these data are the primary focus. Direct comparisons were preferred over indirect comparisons; similarly, effectiveness and long-term safety outcomes were preferred to efficacy and short-term tolerability outcomes.

In theory, trials that compare newer antihistamines with other drug classes or with placebos can also provide evidence about effectiveness. This is known as an indirect comparison and can be difficult to interpret for a number of reasons, primarily heterogeneity of trial populations, interventions, and outcomes assessment. Data from indirect comparisons are used to support direct comparisons, where they exist, and are used as the primary comparison where no direct comparisons exist. Indirect comparisons should be interpreted with caution.

Public Comment

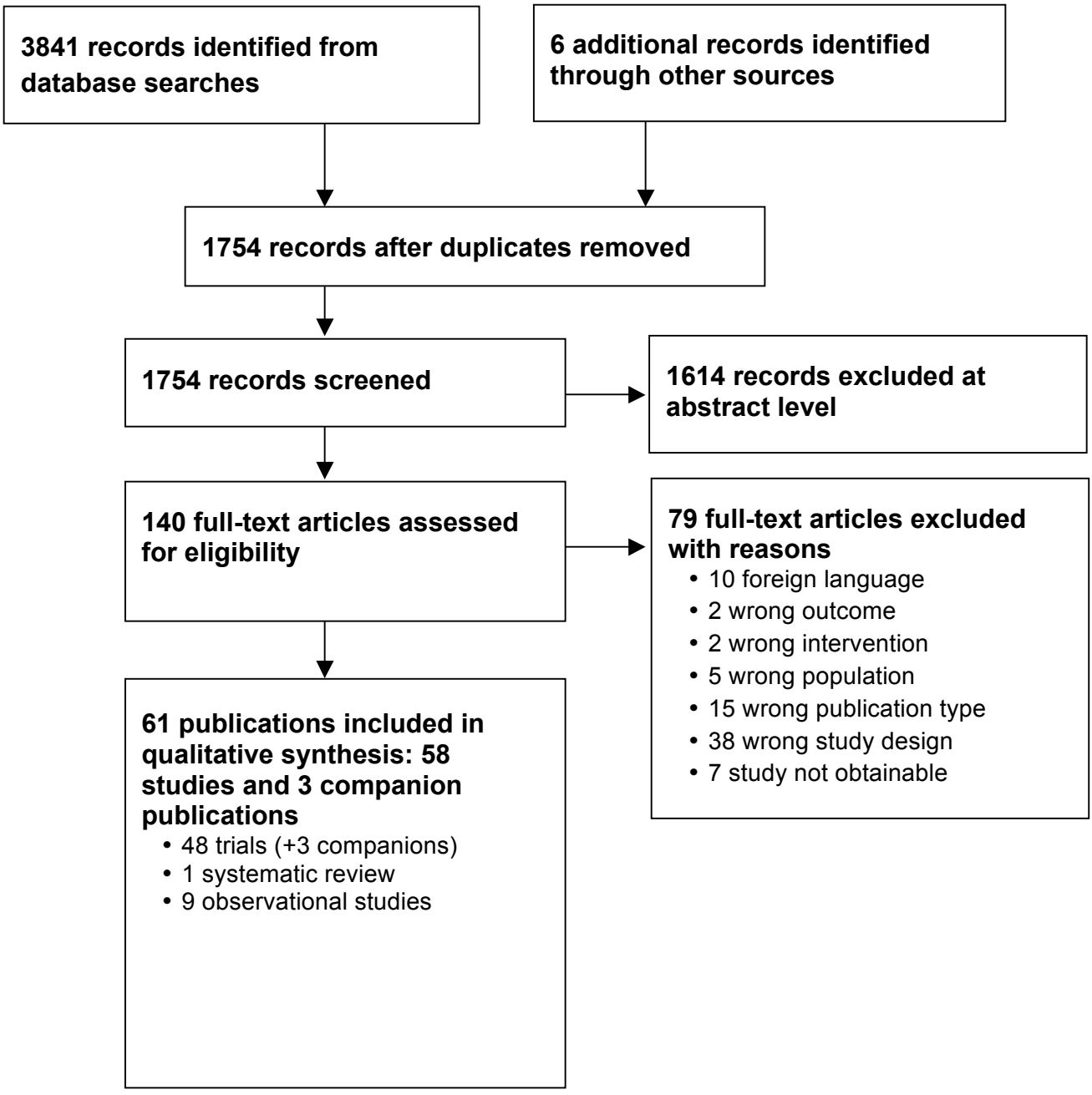
This report was posted to the Drug Effectiveness Review Project website for public comment. For Update 2, we received comments from 1 pharmaceutical manufacturer.

RESULTS

Overview

Literature searches for Update 2 identified 1754 new citations. We received dossiers from the manufacturers of azelastine, desloratadine, and levocetirizine. By applying the eligibility and exclusion criteria to titles and abstracts of all identified citations, we obtained full-text copies of 140 citations. After re-applying the criteria for inclusion, we ultimately included 61 publications, representing 58 unique studies. See Appendix D for a list of excluded studies and reasons for exclusion at this stage. Figure 1 shows the flow of study selection.

Figure 1. Results of literature search for Update 2[a]



[a] A modified PRISMA flow diagram was used.[1]

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

Summary of findings

Adults

Seasonal allergic rhinitis

- Eleven short-term trials (1 good quality, 1 fair) showed no significant difference in comparisons of cetirizine to fexofenadine and loratadine, fexofenadine to loratadine and desloratadine, levocetirizine to loratadine, and azelastine nasal spray to desloratadine and olopatadine nasal spray.
- Two fair-quality trials found azelastine nasal spray superior to oral cetirizine for reduction in symptoms and quality of life.
- Quality of life was better with fexofenadine than loratadine in 1 fair-quality study.

Perennial allergic rhinitis

- Two head-to-head trials (1 poor quality, 1 fair) showed no significant difference in reduction in symptoms with levocetirizine compared with loratadine and desloratadine.
- Two fair-quality 6-month trials of levocetirizine 5 mg showed improved quality of life at 6 months relative to placebo.
- Ten placebo-controlled trials demonstrated efficacy for azelastine nasal spray, cetirizine, desloratadine, levocetirizine, and loratadine, but did not provide information about comparative effectiveness.

Urticaria

- Loratadine was superior to cetirizine for reduction in symptoms in 2 fair-quality trials. Response (defined as asymptomatic) rates were higher with loratadine, but the differences were not statistically significant.
- Levocetirizine was superior to desloratadine for symptom reduction in 1 fair-quality trial, but there was no difference in quality of life.
- Cetirizine was more efficacious than fexofenadine in 1 fair-quality trial limited by a high dropout rate and no intention-to-treat analysis.

Children

Seasonal allergic rhinitis

- No head-to-head studies were identified.
- Placebo-controlled trials showed efficacy for cetirizine and fexofenadine.
- Cetirizine and loratadine were similarly efficacious compared with first-generation antihistamines.

Perennial allergic rhinitis

- One fair-quality study suggested that cetirizine may be more efficacious than loratadine.
- Cetirizine was superior to levocetirizine for symptoms in 1 fair-quality study, but there was no difference in quality of life.
- There was insufficient evidence for other drug comparisons.

Urticaria

- No head-to-head studies were identified.
- Cetirizine was similar to oxatomide for efficacy in children ages 2 to 6 years in 1 fair-quality trial.
- Cetirizine prevented urticaria in atopic children over 18 months in 1 fair-quality trial.

Detailed Assessment

Adults

Seasonal allergic rhinitis

Direct evidence

Eleven head-to-head trials with a duration of 2 weeks or longer assessed efficacy in adults with seasonal allergic rhinitis (Tables 2 and 3; Evidence Tables 1 and 2).[26-36] The trials varied in country, season, number of patients, and baseline Total Symptom Score. One trial was of 4 weeks duration and the rest were of 2 weeks duration. One trial was rated good quality[30] and the rest were fair.

Table 2. Head-to-head trials in adults with seasonal allergic rhinitis

Comparison	Number of trials (references)	Number of patients
Cetirizine vs. fexofenadine	2[31, 32]	1316
Cetirizine vs. loratadine	1[29]	20
Fexofenadine vs. loratadine	2[33, 36]	1347
Fexofenadine vs. desloratadine	1[28]	722
Levocetirizine vs. loratadine	1[35]	67
Azelastine nasal spray vs. cetirizine	2[26, 30]	667
Azelastine nasal spray vs. desloratadine	1[27]	440
Azelastine nasal spray vs. olopatadine nasal spray	1[34]	544

Most studies found no significant difference between newer antihistamines in the change from baseline in Total Symptom Score, with few exceptions (Table 3). A comparison of azelastine nasal spray to oral cetirizine 10 mg found a greater reduction in Total Symptom Score with azelastine (29.3% compared with 23.0%; P=0.015).[30] One other trial compared azelastine nasal spray to cetirizine and also found a greater reduction in Total Symptom Score with azelastine, although the difference was not statistically significant (23.9% compared with 19.6%; P=0.08).[26] A trial of loratadine 10 mg compared to fexofenadine 10 mg found a significantly greater reduction in Total Symptom Score with loratadine as rated by the patient (39% compared with 33%; P=0.019). The difference between treatment groups in investigator-rated change in Total Symptom Score was not statistically significant in this same trial (35% compared with 29%; P=0.063).[33] Six studies also had a placebo arm, and all found the active treatment superior to placebo.

Table 3. Total Symptom Score change from baseline in head-to-head trials in adults with seasonal allergic rhinitis

Author, year	N Duration	Comparisons	Decrease from baseline in Total Symptom Score
Berger 2003[27]	440 2 weeks	A: Azelastine nasal spray, 2 sprays per nostril twice daily B: Azelastine nasal spray twice daily plus loratadine 10 mg C: Desloratadine 5 mg plus placebo nasal spray D: Placebo	A: –21.9% B: 21.5% C: 17.5% D: 11.1% NSD between treatment groups All treatment groups better than placebo
Berger 2006a[28]	722 2 weeks	A: Desloratadine 5 mg B: Fexofenadine 180 mg C: placebo	(Data reported graphically) NSD between treatment groups (*P*=0.405) Both better than placebo
Berger 2006b[26]	360 2 weeks	A: Azelastine nasal spray 2 sprays twice daily B: Cetirizine 10 mg	A: 23.9% B: 19.6% *P*=0.08
Ciprandi 1997[29] Fair	20 2 weeks	A: Cetirizine 10 mg B: Loratadine 10 mg	A: 85.7% B: 84.6% (NS)
Corren 2005[30] Good	307 2 weeks	A: Azelastine nasal spray 2 sprays twice daily B: Cetirizine 10 mg	A: 29.3% B: 23.0% *P*=0.015
Hampel 2003[31] Fair	495 2 weeks	A: Cetirizine 10 mg B: Fexofenadine 180 mg	A: 21.6% B: 19.0% (NS)
Howarth 1999[32] NR Fair	821 2 weeks	A: Cetirizine 10 mg B: Fexofenadine 120 mg C: Fexofenadine 180 mg D: Placebo	A: 45% B: 42% C: 45% (NS) D: 26% (*P*<0.0001 vs. treatment)
Prenner 2000[33] NR Fair	659 2 weeks	A: Loratadine 10 mg B: Fexofenadine 120 mg	Patient assessment: A: 39% B: 33% (*P*=0.019) Investigator assessment: A: 35% B: 29% (*P*=0.063)
Shah 2009[34] Fair	544 2 weeks	A: Azelastine nasal spray 2 sprays twice daily B: Olopatadine nasal spray 2 sprays twice daily C: Placebo nasal spray 2 sprays twice daily	A: 29.9% B: 26.8% C: 18.4% NSD between treatment groups (95% CI, –2.5 to +8.7) Both better than placebo
UCBa[35]	67 2 weeks	A: Levocetirizine 5 mg B: Loratadine 10 mg	Least squares mean change from baseline: A: –5.54 B: –5.99 (*P*=0.4798)
Van Cauwenberge 2000[36] NR Fair	688 2 weeks	A: Loratadine 10 mg B: Fexofenadine 120 mg C: Placebo	Mean change in points (unable to calculate percent change) A: –3.0 (*P*<0.001 vs. C) B: –3.3 (*P*<0.0001 vs. C) C: –2.1 NSD between treatments

Abbreviations: NS, not significant; NSD, no significant difference.

Three head-to-head trials measured quality of life outcomes, all using the Rhinoconjunctivitis Quality of Life Questionnaire.[26, 30, 36] Quality-of-life scores at 2 weeks were better for patients taking azelastine nasal spray compared with cetirizine in 2 studies[26, 30] and better with fexofenadine than loratadine in 1 study.[36]

Indirect evidence

Fifteen placebo-controlled trials demonstrated short-term efficacy of newer antihistamines in adults with seasonal allergic rhinitis, including 4 studies of desloratadine,[37-40] 2 of levocetirizine,[41, 42] 6 of azelastine nasal spray,[43-48] and 3 of olopatadine nasal spray.[49-51] Details of these studies are presented in Evidence Tables 1 and 2.

Comparisons of newer antihistamines to active controls revealed mixed results. Cetirizine was generally comparable to rupatadine (an antihistamine).[52] Loratadine demonstrated few significant differences from ebastine (an antihistamine),[53] mixed results compared to montelukast (a selective leukotriene receptor antagonist),[54] and was generally less efficacious than rupatadine.[55] In 1 trial,[56] loratadine was as effective as clemastine.

Perennial allergic rhinitis

Direct evidence

We identified 2 head-to-head trials in adults with perennial allergic rhinitis (Evidence Tables 3 and 4).[57, 58] One of these was not published,[57] but results are available at ClinicalTrials.gov. In this 2-week trial, there was no significant difference between levocetirizine 5 mg and loratadine 10 mg in the change from baseline in Total Symptom Score.[57] A 4-week placebo-controlled trial compared levocetirizine to desloratadine, both at 5 mg daily.[58] Although both treatments improved total nasal symptom scores more than placebo, there was no significant difference between the treatment groups.

Indirect evidence

Ten placebo-controlled trials demonstrated efficacy in adults with perennial allergic rhinitis. Details of these studies are shown in Evidence Tables 3 and 4. We identified 2 trials of azelastine,[59, 60] 2 of cetirizine,[61-63] 3 of desloratadine,[64-66] 3 of levocetirizine (in 4 publications),[67-71] and 1 of loratadine.[72] Most of the efficacy trials were short term, however 2 trials of levocetirizine 5 mg reported improved quality of life compared with placebo at 6 months.[67, 68]

Urticaria

Direct evidence

Five head-to-head trials in adults with urticaria are shown in Table 4 and in Evidence Tables 5 and 6.[73-77] Two fair-quality, head-to-head trials compared cetirizine to loratadine.[74, 77] In 1 trial, loratadine reduced mean Total Symptom Score more than cetirizine. Response rates were higher with loratadine in both trials, but the difference was not statistically significant in one (63% compared with 45%)[74] and the *P* value was not reported in the other (81% compared with 60%).[77] The latter study reported that the number, size, and duration of lesions was significantly improved in patients taking loratadine ($P<0.05$) and the mean score of pruritus was significantly greater with loratadine ($P<0.05$), but data were not given.

One trial compared cetirizine to fexofenadine. Cetirizine 10 mg daily was more efficacious than fexofenadine 180 mg daily at 28-day follow-up.[75] This study was limited by an attrition rate of 16%, and data were presented only for those completing the study.

Two head-to-head trials compared levocetirizine to another newer antihistamine.[73, 76] A trial of 886 adults with urticaria compared mean pruritus score of levocetirizine 5 mg compared with desloratadine 5 mg after 4 weeks of treatment.[76] Levocetirizine decreased pruritus severity significantly more than desloratadine after 1 week, the primary outcome. Mean symptom scores were improved more with levocetirizine. Levocetirizine was also significantly better than desloratadine on patients' global satisfaction at 1 week and 4 weeks, and on investigators' global satisfaction at 1 week, but not on endpoint. Quality-of-life was assessed, and was improved in both treatment groups, but no analysis was done. In a crossover trial, 45 patients who had achieved complete symptomatic control with cetirizine 10 mg after 6 weeks were then switched to levocetirizine 5 mg for an additional 6 weeks.[73] Wheal and flare response was similar with both drugs, but the itch response was better with cetirizine in 70% of patients. This study was open-label and had a high dropout rate.

Table 4. Head-to-head trials in adults with urticaria

Author Year Condition Quality	Drug, dosage Number of subjects Duration	Results
Cetirizine compared with fexofenadine		
Handa 2004[75] Fair	Cetirizine 10 mg qd Fexofenadine 180 mg qd 116 4 weeks	Cetirizine vs. fexofenadine Symptom-free at endpoint: 51.9% vs. 4.4% Partial improvement at endpoint: 36.5% vs. 42.2% No improvement at endpoint: 11.5% vs. 53.3% *P*=NR
Cetirizine compared with levocetirizine		
Garg 2007[73] Fair	Cetirizine 10 mg Levocetirizine 5 mg 30 6 weeks	Cetirizine vs. levocetirizine (N) Wheal response 30 vs. 28 Flare response 30 vs. 30 Itch response 30 vs. 9
Cetirizine compared with loratadine		
Guerra et al 1994[74] Fair	Cetirizine 10 mg Loratadine 10 mg Placebo 116 4 weeks	Significant (*P*<0.01) loratadine vs. cetirizine on days 3, 14, 28 (NS on day 7) Day 3/7/14/28: Loratadine: -23% / -46% / -65% / -81% Cetirizine: -35% / -50% / -60% / -69% Placebo: -19% / -23% / -34% / -55% Response rate (symptom-free): Loratadine 63% vs. cetirizine 45%; NSD Placebo 13%
Thomas 1998[77] Fair	Cetirizine 10 mg Loratadine 10 mg 202 4 weeks	Data reported in graphs Loratadine vs. cetirizine The number, size, and the duration of lesions (*P*<0.05) Fall in the mean score of pruritus (*P*<0.05)
Levocetirizine compared with desloratadine		
Potter 2009[76] Fair	Levocetirizine 5 mg Desloratadine 5 mg 886 4 weeks	Levocetirizine vs. desloratadine Pruritus severity score First treatment week 1.02 (0.04) vs. 1.18 (0.04); *P*<0.001 Entire treatment period 0.86 (0.04) vs. 0.99 (0.04); *P*=0.004 Chronic idiopathic urticaria composite score First treatment week 1.98 (0.08) vs. 2.23 (0.08); *P*=0.005 Entire treatment period 1.71 (0.07) vs. 1.88 (0.07); *P*=0.041

Abbreviations: NR, not reported; NS, not significant; NSD, no significant difference; qd, once daily.

Indirect evidence

Nine placebo-controlled trials examined efficacy in adults with chronic idiopathic urticaria.[78-86] Two of these were rated poor quality and are listed in Appendix F.[85, 86] Of the 7 fair- or better-quality trials, 4 included desloratadine 5 mg,[78, 81, 83, 84] 2 included levocetirizine 5 mg,[80, 82] and 1 included fexofenadine 180 mg.[79] All found the active treatment group superior to placebo for

reducing symptoms. Indirect comparisons that can be made from these studies were limited due to differences in outcome measures and reporting. Improved quality-of-life was reported with desloratadine and levocetirizine compared with placebo in 2 studies, both using the validated Dermatology Life Quality Index.[78, 80]

In a 4-week trial of 188 patients,[87] cetirizine had a faster onset than the first-generation antihistamine hydroxyzine but was effective in a similar proportion of patients.

A search for literature on the efficacy or effectiveness of newer antihistamines in other types of urticaria in adults identified only poor-quality studies.[88-92]

Children

Seasonal allergic rhinitis

Ten studies examined the efficacy of newer antihistamines among children (Evidence Tables 7 and 8), and 2 of these studies were of poor quality (See Appendix F for poor-quality studies).[93, 94] One head-to head study of azelastine nasal spray compared with olopatadine nasal spray enrolled both adolescents and adults, but the results for children were not reported separately.[34] The results of placebo-controlled trials of cetirizine[95-99] and fexofenadine[100] demonstrated significant improvements in symptoms with the study drug compared with placebo.

Active-control studies compared cetirizine[101] and loratadine[102] to first-generation antihistamines, with no significant differences between groups. Jordana and colleagues[103] found that fluticasone nasal spray was more efficacious than loratadine for nasal symptoms, but there were no significant differences for eye symptoms.

Perennial allergic rhinitis

Eleven studies (see Table 5 and Evidence Tables 9 and 10) were identified which examined the efficacy of newer antihistamines among children with perennial allergic rhinitis,[99-101, 104-111,] 1 of which was of poor quality. [103] Two studies examined children 2 to 6 years old,[110, 112] most examined children 6 to 12 or 14 years old. Two studies primarily focused on adults, but included participants 12 years of age and older.[55, 113] These studies are presented with the adult studies, as data were not stratified by age group to allow for examination of adolescents only.

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 perennial allergic rhinitis. Children with major systemic illnesses were excluded.

Two head-to-head trials were identified. One trial compared cetirizine to loratadine among children 2 to 6 years of age.[110] 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 pruritus. No significant differences were noted between groups in investigator-assessed global evaluation score or in nasal eosinophil count.

The second head-to-head trial compared cetirizine to levocetirizine over 12 weeks in 80 children ages 6 to 12 years with perennial allergic rhinitis.[114] Both drugs improved Total Symptom Score and quality of life as measured by the Pediatric Rhinoconjunctivitis Quality of Life Questionnaire compared with placebo. There was significantly more improvement in Total Symptom Score at 8 and 12 weeks with cetirizine, but no difference between groups in improvement in quality of life.

In 3 studies with active controls, cetirizine improved symptoms compared with placebo arms and compared with ketotifen and oxatomide.[109] Cetirizine was comparable to montelukast in 1 study,[107] but similar in efficacy in another.[112] Three fair-quality, placebo-controlled studies[104, 105, 108] 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.

A single study examining loratadine noted it to be efficacious at a dosage of 5 to 10 mg daily when compared to placebo.[111] One study found azelastine nasal spray efficacious compared to placebo at 6 weeks.[115] There were no data on any of the other newer antihistamines in children.

Table 5. Outcomes from trials in children with perennial allergic rhinitis[a]

Author Year Quality	Drug dosage Number of subjects	Mean age Range (years)	Length of follow-up (weeks)	Total Symptom Score	Other outcomes
Head-to-head trials					
Sienra-Monge 1999[110] 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 pruritus (*P*<0.001)
Lee 2009[114] Fair	C: cetirizine 10 mg L: Levocetirizine 5 mg P: Placebo N=80	8 6-12	12	C: –5.54 (P<0.05 vs. levocetirizine) L: –3.30 P: –0.18 Both treatment groups better than placebo	Both treatment groups improved quality of life vs. placebo, but no difference between treatment groups.
Active-control trials					
Hsieh 2004[107] 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[109] 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)

Author Year Quality	Drug dosage Number of subjects	Mean age Range (years)	Length of follow-up (weeks)	Total Symptom Score	Other outcomes
Placebo-controlled trials					
Baelde 1992[104] 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 pruritus: NSD, data not reported Overall average score for all symptoms: C1 vs. P, *P*=0.01	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
Ciprandi 2001[105] 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[108] 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[111] 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)	

Abbreviations: bid, twice daily; NR, not reported; NSD, no significant difference; NS, not significant; qd, once daily; tid, 3 times daily; TSS, Total Symptom Score; wk, week.

[a] Only fair- and good-quality studies are presented in the table. Poor-quality studies are listed in Appendix F.

Urticaria

Two studies examined the efficacy of newer antihistamines for the treatment of urticaria in children (Evidence Tables 11 and 12). In 1 study examining the efficacy of cetirizine compared with oxatomide in children 2 to 6 years of age with chronic idiopathic urticaria,[116] no significant differences were noted between groups. The other study examined the efficacy of cetirizine in preventing acute urticaria among young children with atopic dermatitis who were at high risk of acute urticaria.[117] 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.

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

Summary of findings

Adults

- Total withdrawals and withdrawals due to adverse events were low with cetirizine, levocetirizine, loratadine, desloratadine, fexofenadine, azelastine, and olopatadine and were comparable to rates observed with placebo.
- Sedation and headaches were commonly reported adverse events.
    - First generation antihistamines (diphenhydramine, chlorpheniramine) were more sedating than newer generation antihistamines.
    - Of the newer agents, cetirizine and levocetirizine were more sedating than loratadine and desloratadine, and possibly more sedating than fexofenadine.
    - Rates of headaches were similar in cetirizine, loratadine, and fexofenadine-treated patients.
- Bitter taste or taste alteration and nasal discomfort were common with both azelastine and olopatadine nasal sprays relative to placebo.
    - Direct evidence found higher rate of bitter taste and nasal discomfort with azelastine while indirect assessment of the evidence suggested minimal difference between the groups.
- One cohort study suggested a greater risk of cardiovascular events with cetirizine when compared to non-users. A nonsignificant increase in risk was observed with loratadine in this study. Eleven short-term trials detected no clinically relevant electrocardiogram changes.

Children

- There was insufficient evidence on comparative harms.
- Overall, newer antihistamines were well-tolerated in this population with low withdrawal rates due to adverse events.
- Minor neurologic and respiratory symptoms were frequently reported in both treatment and placebo groups. These included headaches, insomnia, nervousness, somnolence, and upper respiratory tract infections.

- Based on short-term fair evidence, newer antihistamines including cetirizine did not significantly prolong QTc interval.

Detailed assessment

Adults

In this update we identified 14 trials,[38, 40, 50, 58, 60, 68, 69, 76, 78, 80, 82-84, 118] 2 observational studies,[119, 120] and 1 systematic review[121] of adults only, while 16 trials[26, 28, 34, 43, 45-49, 51, 65, 69, 77, 122-124] included mixed populations of children and adults. Because most patients in the 16 trials were adults, we included results from these trials here.

Total withdrawals and withdrawals due to adverse events

Withdrawal rates due to adverse events were generally low, in the range of 2% to 5% for azelastine, olopatadine, levocetirizine, desloratadine, and fexofenadine. Serious adverse events were rare. One patient taking fexofenadine had an asthma attack requiring hospitalization [79] and 1 patient taking desloratadine and 3 patients using placebo had heart rhythm disorder that did not require study discontinuation.[65]

Commonly reported adverse events

Four observational studies[125-128] and 1 systematic review[121] from this update provided additional data on adverse effects of long-term use of newer antihistamines.[129-132] Three of these studies [121, 127, 128] assessed effects of newer antihistamines in pregnancy and are discussed in Key Question 3. Sedation was the main focus of 6 studies,[125, 126, 129-132] and the overall incidence of sedation was both variable and low. Results from the above studies and 8 new head-to-head trials[26, 28, 34, 57, 76, 77, 133, 134] are discussed below in addition to publications from previous updates.

First-generation antihistamines compared with newer antihistamines

A fair-quality meta-analysis,[135] a 1-week active-control trial,[123] and a 2-week placebo-controlled trial[48] suggested that both first-generation and newer antihistamines resulted in sedation compared to placebo, and that first-generation agents diphenhydramine or chlorpheniramine caused more sedation than cetirizine, fexofenadine, loratadine, desloratadine, and azelastine nasal spray. A fair-quality cohort study resulted in more claims for serious injury with diphenhydramine compared with loratadine.[129]

Cetirizine compared with loratadine

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.[130] Similar results were seen in a fair- to poor-quality trial where cetirizine produced greater sedative effects and adverse effects on motivation than loratadine.[136] Only 1 head-to-head trial did not find significant differences in adverse events in patients using cetirizine, loratadine, and fexofenadine.[137]

No trial evidence was found on tolerance to the sedation with antihistamines. The labeling for cetirizine included a statement of caution when driving a car or operating potentially

dangerous machinery and to avoid concomitant use of alcohol or other central nervous system depressants, as an additional reduction in alertness or performance may occur.

Levocetirizine compared with desloratadine

A fair-quality observational study[125] compared the risk of drowsiness and sedation between levocetirizine and desloratadine using prescription-event monitoring in the UK (N=24 195). The first occurrence of sedation was low for both groups but was significantly lower with desloratadine (0.08%; $P<0.0001$) than levocetirizine (0.37%). Crude odds ratio for levocetirizine and sedation was almost 5 times greater (odds ratio, 4.9; 95% CI, 2.40 to 10.02). Adjusting for gender, indication, and previous antihistamine use, the risk remained similar. Patients with or without asthma were assessed and patients without asthma were 6 times more likely to report sedation than patients with asthma (odds ratio, 6.75; 95% CI, 2.37 to 19.22).

Results from 2 smaller head-to-head studies comparing levocetirizine with desloratadine concurred with the findings above.[76, 133] In these 2 head-to-head trials, common adverse events included headaches, somnolence, and dry mouth. Four additional smaller head-to-head trials comparing cetirizine, levocetirizine, and loratadine also confirmed that levocetirizine and cetirizine were more sedating (or having nervous system disorders) than loratadine.[57, 77, 134, 138]

Cetirizine compared with fexofenadine

One fair- to poor-quality head-to-head trial[75] compared cetirizine and fexofenadine (83% of randomized analyzed). Cetirizine-treated patients noted more drowsiness complaints than fexofenadine but no statistical difference was found (7.7% compared with 4.5%, $P=0.29$). No significant differences were found for constipation, abdominal pain, epigastric pain, or cough.

Desloratadine compared with fexofenadine

Rates for somnolence and upper respiratory tract infection were comparable and low in both groups (≤1%).[28] Compared with desloratadine, a few more fexofenadine-treated patients withdrew from a 2-week study primarily because of headaches (3.8% compared with 1.0%).

Astelin nasal spray compared with olopatadine nasal spray

In a 16-day head-to-head trial, total withdrawal from treatment groups was low (overall 2.5%). This trial reported adverse events for all screened patients which included patients during run-in phase. Of the commonly reported events, azelastine-treated patients reported more frequent bitter taste (19.7% compared with 12.2%; placebo, 1.7%) and nasal discomfort (3.7% compared with 1.7%; placebo, 1.7%) than in olopatadine-treated patients. One case of nasal ulceration with azelastine occurred at day 30; this resolved in 7 days.[34]

We identified 3 placebo-controlled trials of azelastine spray and 3 placebo-controlled trials of olopatadine spray.[43, 46, 49-51, 60] Indirectly, azelastine 0.137 mg and olopatadine 0.4% exhibited similar rates of bitter taste (range: azelastine, 5.8% to 9.5%; olopatadine, 5.8% to 8.7%; placebo, 0% to 2.2%). Patients using higher-strength olopatadine 0.6% reported the highest incidence of bitter taste (range: 9.2% to 16.1%).

One of the azelastine trials also evaluated a newer formulation product, Astepro®.[43] This trial found less bitter taste with the new formulation than with the standard product at both the low and high doses (Astepro® 1 spray twice daily, 5.8% compared with azelastine 1 spray twice daily, 9.5% compared with placebo, 1.5%; Astepro 2 sprays twice daily, 6.8% compared with azelastine 2 sprays twice daily, 8.0% compared with placebo, 2.2%).

Azelastine nasal spray compared with cetirizine

Total withdrawal rate and withdrawals due to adverse events were low for azelastine nasal spray users and for cetirizine-treated patients over a 2-week study period (Evidence Table 1).[26] More reports of bitter taste were however associated with azelastine spray than cetirizine (7.7% compared with 0%). Rates of somnolence, headaches, epistaxis, and sore throat were not significantly different between treatment groups and occurred in <2% of patients.

Electrocardiogram changes

Prolongation of the QT interval is a concern with this class of agents since the withdrawal of terfenadine and astemizole.

A fair-quality nested-case control cohort study[132] using the UK-based General Practice Research Database reported that for 5 newer-generation 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% CI, 1.6 to 39.3) and loratadine 3.2 (95% CI, 0.4 to 26.9). The safety and tolerability of fexofenadine (an active metabolite of terfenadine) was shown in over 16638 patients in a UK Prescription-event monitoring cohort[131] as well as in a placebo-controlled trial where no significant electrocardiogram changes were noted.[79] A total of 11 studies[37, 53, 65, 66, 79, 81-83, 113, 139-141] noted no clinically significant electrocardiogram changes compared with the placebo group. One patient using desloratadine (0.2%) and 3 placebo-treated patients (0.5%) reported heart and rhythm disorders; patients did not require study withdrawal.[65]

Other

A small, poor-quality trial showed an increase in postprandial glucose with cetirizine compared with loratadine and clemastine.[142] Three observational studies that examined adverse events were of poorer quality and are not discussed.[119, 120, 143]

Children

Total withdrawals and withdrawals due to adverse events

Overall, newer antihistamines were well tolerated in children. Across 16 placebo-controlled trials[95, 98, 100, 104, 108, 112, 114-117, 144-149] that reported total withdrawals, up to 18.9% of patients treated with newer antihistamines (cetirizine, levocetirizine, desloratadine, azelastine, and fexofenadine) and up to 23% of children treated with placebo withdrew from the trials. Up to 3.1% of those treated with newer antihistamines withdrew as a result of an adverse event compared with up to 4.7% of placebo-treated patients.

Commonly reported adverse events

In this update, we identified 7 additional trials[76, 112, 114, 115, 145, 150, 151] and 1 observational study.[152] Adverse events in studies of children are summarized Evidence Tables 9,[76, 112, 114, 115]13,[152] 20,[145, 150] and 22.[151] Adverse events reported from the last update are listed in Appendix E. There were no major events reported. In the only head-to-head trial in children,[110] 2 adverse events were reported in the cetirizine group, with none reported in the loratadine group (N=80). One participant developed somnolence and irritability, the other a generalized rash. These 2 adverse

events necessitated participant withdrawal from study. Three observational studies[143, 152, 153] presented data on adverse events but were of poor quality (Appendix F).

Minor neurologic and respiratory symptoms were the most common adverse events, particularly headache, insomnia, nervousness, somnolence, and upper respiratory tract infections with oral antihistamines. Rates varied widely, however, and adverse events were also very common among placebo groups. Three placebo-controlled trials[112, 114, 151] reported somnolence in <2% to 10% of patients treated with cetirizine compared with <2% patients treated with placebo. One trial[150] of desloratadine reported somnolence in 5.3% of patients compared with 7.3% of those receiving placebo.

Upper respiratory tract infections were observed in 3 trials[145, 146, 151] with no significant difference between active treatment and placebo (Evidence Tables 20, 9, and 22 respectively).

One trial evaluating azelastine nasal spray found increased incidence of pharyngitis (7.8% compared with 4.9%) and cough (4.7% compared with 1.6%) relative to placebo.[115]

Electrocardiogram changes

Nine studies examined the effects of newer antihistamines on electrocardiogram changes, particularly on the QT and QTc interval.[99, 136, 145, 147-150, 154, 155] No study demonstrated significant prolongation of the QT interval with cetirizine,[99, 144, 147-149] fexofenadine,[144, 145] or desloratadine.[150, 156] One poor-quality study examined concurrent use of cetirizine or loratadine and erythromycin estolate[154] and noted no abnormality of the QT or QTc interval.

One head-to-head study examined the effects of terfenadine, astemizole, loratadine, and cetirizine on electrocardiogram among children with perennial allergic rhinitis.[154] 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.

Other

The Early Treatment of the Atopic Child (ETAC)[117, 147, 157, 158] 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 (Evidence Tables 22 and 23). 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), it was included in this paper because 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 the study medication occurred in 1 child receiving cetirizine and 5 children receiving placebo. Hospitalization rates did not differ between the treatment groups (P=0.189). There were 10 accidental overdoses of study medications by study participants; 2 of these participants were receiving cetirizine. Symptoms and events (Evidence Table 22) were reported with similar frequency in cetirizine- and placebo-treated groups. Age-appropriate increases in height and weight were observed during the study period. No clinically relevant differences between groups for changes in electrocardiograms were observed, and cetirizine therapy was not associated with prolongation of the QTc interval in any participant.

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 harms?

Summary of findings

- Insufficient evidence was available to determine whether any of the newer antihistamines had an advantage in efficacy or harms based on age, gender, or race/ethnicity.
- Patients with allergic rhinitis with mild intermittent asthma or atopic dermatitis tolerated newer antihistamines similar to patients without these comorbidities.
- There was minimal increased risk of birth defects observed with H-1 receptor antagonists including cetirizine, fexofenadine, and loratadine.

Detailed assessment

Age, gender, race/ethnicity

No direct evidence was available to determine whether any antihistamine has an advantage in efficacy or harms for any gender or racial group.

Asthma

Three fair-quality placebo-controlled trials were identified in patients with allergic rhinitis and asthma (Evidence table 24).[139, 159, 160] Patient assessment of asthma significantly improved on cetirizine compared with placebo in 2 studies,[159, 160] however no improvement (or worsening) of pulmonary function tests occurred. Berger and colleagues[139] examined desloratadine in patients with seasonal allergic rhinitis and asthma and found a significant decrease in total asthma symptom scores in the treatment group.

There were no significantly different adverse events reported in primarily adult patients with allergic rhinitis and asthma compared with patients without asthma. There were no reports of worsening asthma with active treatment; only 2 placebo-treated patients[146] reported asthma aggravated. Most patients included in these studies had mild intermittent asthma and were likely not using inhaled corticosteroids. Two trials evaluated cetirizine,[159, 160] levocetirizine (Evidence Table 3),[68, 146] and azelastine nasal spray (Evidence Table 1).[45, 48] One trial evaluated desloratadine.[139] Commonly reported adverse events for oral antihistamines were headache, fatigue, nausea, dry mouth, and sedation. Nasal burning, bitter taste or altered taste, and epistaxis were observed more often in azelastine-treated patients than with placebo.

Atopic dermatitis

An 18-month, placebo-controlled trial studied levocetirizine in 510 children 12 to 24 months in age who had atopic dermatitis, allergy to grass pollen or house dust mites, and family history of allergies.[151] The dose of levocetirizine was in the higher range (0.125 mg/kg twice daily; total daily dose ranged from 2.8 mg to 3.8 mg) but the overall withdrawal rates due to adverse events were low between levocetirizine and placebo (2.0% compared with 1.2%) and there were no significant differences in achieving developmental milestones in treatment groups.

About 96% of enrolled children reported at least 1 adverse event during the trial. The most commonly reported event was upper respiratory tract infections (levocetirizine, ~51% compared with placebo, ~50%). Worsening atopic dermatitis was low and occurred similarly between groups (levocetirizine, ~5% compared with placebo, ~6%). Febrile convulsions, however, were reported more often in levocetirizine-treated children than placebo (2.0% compared with 0.4%). Although the investigators suspected the convulsions were not study medication-related, they could not rule out the possibility and recommend that this be explored further. There was one 30-month-old child that developed lymphadenopathy and was diagnosed with acute lymphoblastic leukemia. The investigators judged that a relationship of study drug and this occurrence was unlikely.

Pregnancy

Rhinitis is one of the most common conditions during pregnancy, affecting more than 20% of pregnant women.[161] 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.

We identified 1 additional cohort study (N=1882) that evaluated cetirizine exposure in the first trimester of pregnant women.[128] The findings from this observational study concurred with 5 other observational studies[131, 162-165] and a meta-analysis,[166] which found no significant increase risk in birth defects in women exposed to H-1 receptor blockers, including fexofenadine and loratadine (Evidence Tables 13 and 24).

Results from a systematic review with meta-analysis,[121] a nested case-control study,[127] and data from the National Birth Defects Prevention Study,[167] indicated that loratadine exposure during pregnancy does not significantly increase risk of hypospadias in male infants. Additional analyses of these 2 studies[121, 167] showed that non-sedating and sedating antihistamines did not significantly increase the risk of hypospadias.

SUMMARY OF THE EVIDENCE

Results of this review are summarized in Table 6.

Table 6. Summary of the evidence

	Strength of the evidence	Conclusions
Key Question 1. Comparative efficacy For outpatients with seasonal or perennial allergic rhinitis or urticaria, do newer antihistamines differ in effectiveness?		
Adults		
Seasonal allergic rhinitis (SAR)	Fair for efficacy (symptoms) Fair to poor for quality of life	Eleven short-term trials showed no significant difference in comparisons of cetirizine to fexofenadine and loratadine, fexofenadine to loratadine and desloratadine, levocetirizine to loratadine, and azelastine nasal spray to desloratadine and olopatadine nasal spray. Two fair-quality trials found azelastine nasal spray superior to oral cetirizine for reduction in symptoms and quality of life. Quality of life was better with fexofenadine than loratadine in 1 study.
Perennial allergic rhinitis (PAR)	Fair for comparisons of levocetirizine to loratadine and desloratadine. Insufficient for other comparisons.	Two head-to-head trials showed no significant difference in reduction in symptoms with levocetirizine compared with loratadine and desloratadine. Two 6-month trials of levocetirizine 5 mg showed improved quality of life at 6 months relative to placebo. Ten placebo-controlled trials demonstrated efficacy for azelastine nasal spray, cetirizine, desloratadine, levocetirizine, and loratadine, but did not provide information about comparative effectiveness.
Chronic idiopathic urticaria (CIU)	Fair to poor for comparisons of cetirizine to fexofenadine, levocetirizine, and loratadine. Fair for comparison of levocetirizine to desloratadine. Insufficient for other comparisons.	Loratadine was superior to cetirizine for reduction in symptoms in 2 fair-quality trials. Response (defined as asymptomatic) rates were higher with loratadine, but the differences were not statistically significant. Levocetirizine was superior to desloratadine for symptom reduction in 1 trial, but there was no difference between drugs in quality-of-life scores. Cetirizine was more efficacious than fexofenadine in 1 trial limited by a high dropout rate and no intention-to-treat analysis.
Other urticaria	No fair- or good-quality evidence identified	No available data on comparative effectiveness in other types of urticaria.
Children		

	Strength of the evidence	Conclusions
Seasonal allergic rhinitis (SAR)	Poor for comparative effectiveness	Ten fair-quality placebo-controlled and active-control studies. No head-to-head studies.
Perennial allergic rhinitis (PAR)	Fair for comparison of cetirizine to loratadine in children ages 2 to 6 years. Fair for comparison of cetirizine to levocetirizine in children ages 6 to 12 years.	One fair-quality study suggested cetirizine may be more efficacious than loratadine. Cetirizine was superior to levocetirizine for symptoms in 1 fair-quality study, but there was no difference in quality of life. Insufficient evidence on the comparative effectiveness of other drug combinations.
Urticaria	Poor for comparative effectiveness	No head-to-head studies.
Key Question 2. Harms For outpatients with Seasonal allergic rhinitis, Perennial allergic rhinitis or urticaria, do newer antihistamines differ in safety or adverse effects?		
Overall adverse events	Fair	Rates of discontinuation due to adverse events was low with included newer antihistamines.
Sedation	Fair	First-generation antihistamines (diphenhydramine, chlorpheniramine) more sedating than newer-generation agents. Cetirizine and levocetirizine were more sedating than loratadine and desloratadine. Some evidence suggested that cetirizine may be more sedating than fexofenadine. There was no significant difference in reports of sedation between loratadine and fexofenadine in 1 observational study.
Headache	Fair	Headache was reported with similar rates in cetirizine, loratadine, and fexofenadine.
Cardiac effects	Fair	A large, fair-quality cohort study provided evidence of a significant risk of cardiac arrhythmias with cetirizine compared with non-use. A nonsignificant increase in risk was noted with loratadine. Limited evidence suggested no QTc prolongation with loratadine and fexofenadine.
Bitter taste/nasal discomfort	Fair	Incidence was higher with azelastine than olopatadine in head-to-head trials but indirect assessment suggested minimal difference between groups.
Children	No head-to-head data on adverse events except 2 events in cetirizine group (vs. loratadine)	Insufficient evidence on comparative safety. Newer antihistamines were well-tolerated

	Strength of the evidence	Conclusions
	Overall, Fair	in this population with little withdrawal due to adverse events. 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 did not prolong QTc interval.
Key Question 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?		
Age, gender, race/ethnicity	There was 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.
Asthma or atopic dermatitis	Fair	There were no differences in rate of adverse events in patients with allergic rhinitis and asthma or atopic dermatitis.
Pregnancy	Fair	There was minimal increase risk of birth defects observed with newer antihistamines in pregnant women. Newer antihistamine drug exposure in pregnant women did not significantly increase the risk of hypospadias in male infants.

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

REFERENCES

1. Liberat A, Altman D, Tetzlaff J, Mulrow C, al. e. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Ann Intern Med.* 2009;151(4):W-65 - W-94.
2. Golightly LK, Greos LS. Second-generation antihistamines: actions and efficacy in the management of allergic disorders. *Drugs.* 2005;65(3):341-384.
3. Baena-Cagnani CE. Safety and tolerability of treatments for allergic rhinitis in children. *Drug Safety.* 2004;27(12):883-898.
4. American Society of Health-System Pharmacists. Antihistamine Drugs. *http://online.statref.com/document.aspx?fxid=1&docid=16.* 2005(Accessed Sept. 14, 2005).
5. Handley DA, Magnetti A, Higgins AJ. Therapeutic advantages of third generation antihistamines *Expert Opin Inv Drug.* 1998;7:1045-1054.
6. Blaiss MS. Allergic rhinitis and impairment issues in schoolchildren: A consensus report. *Curr Med Res Opin.* 2004;20(12):1937-1952.
7. Blaiss M. Current concepts and therapeutic strategies for allergic rhinitis in school-age children. *Clin Ther.* 2004;26(11):1876-1889.
8. van Cauwenberge P, Bachert C, Passalacqua G, et al. Consensus statement on the treatment of allergic rhinitis. European Academy of Allergology and Clinical Immunology. *Allergy.* 2000;55(2):116-134.
9. Bousquet J, Van Cauwenberge P, Khaltaev N, ARIA Workshop Group, World Health Organization. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol.* 2001;108(5 Suppl):S147-334.
10. International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. *Lancet.* 1998;351(9111):1225-1232.
11. Schoenwetter WF. Allergic rhinitis: epidemiology and natural history. *Allergy Asthma Proc.* 2000;21(1):1-6.
12. Skoner DP. Allergic rhinitis: definition, epidemiology, pathophysiology, detection, and diagnosis. *J Allergy Clin Immunol.* 2001;108(1 Suppl):S2-8.
13. Malone DC, Lawson KA, Smith DH, Arrighi HM, Battista C. A cost of illness study of allergic rhinitis in the United States. *J Allergy Clin Immunol.* 1997;99(1 Pt 1):22-27.
14. McCrory DC, Williams JW, Dolor RJ, et al. *Management of allergic rhinitis in the working-age population.* Washington, DC: Agency for Healthcare Research and Quality (AHRQ); March 2003. No. 67.
15. Segura T, Casale TB. Allergic rhinitis: basic pathophysiology and therapeutic strategies. *Can J Allergy Clin Immunol.* 1999;4:318-330.
16. Galant SP, Wilkinson R. Clinical prescribing of allergic rhinitis medication in the preschool and young school-age child: what are the options? *Biodrugs.* 2001;15(7):453-463.
17. Wright AL, Holberg CJ, Martinez FD, Halonen M, Morgan W, Taussig LM. Epidemiology of physician-diagnosed allergic rhinitis in childhood. *Pediatrics.* 1994;94(6 Pt 1):895-901.
18. Bousquet J, Duchateau J, Pignat JC, et al. Improvement of quality of life by treatment with cetirizine in patients with perennial allergic rhinitis as determined by a French

version of the SF-36 questionnaire. *Journal of Allergy & Clinical Immunology.* 1996;98(2):309-316.

19. Meltzer EO. Quality of life in adults and children with allergic rhinitis. *J Allergy Clin Immunol.* 2001;108(1 Suppl):S45-53.

20. Settipane RA. Complications of allergic rhinitis. *Allergy Asthma Proc.* 1999;20(4):209-213.

21. American Academy of Allergy A, and Immunology. *Overview of allergic diseases: diagnosis, management, and barriers to care.* 2000.

22. Kozel MMA, Sabroe RA. Chronic urticaria: aetiology, management and current and future treatment options. *Drugs.* 2004;64(22):2515-2536.

23. Kaplan AP. Chronic urticaria: pathogenesis and treatment. *J Allergy Clin Immunol.* 2004;114(3):465-474; quiz 475.

24. Center for Reviews and Dissemination. Undertaking systematic reviews of research on effectiveness: CRD's guidance for those carrying out or commissioning reviews CRD Report Number 4 (2nd edition). 2001.

25. Harris RP, Helfand M, Woolf SH, et al. Current methods of the third U.S. Preventive Services Task Force. *Am J Prev Med.* 2001;20(3Suppl):21-35.

26. Berger W, Hampel F, Jr., Bernstein J, Shah S, Sacks H, Meltzer EO. Impact of azelastine nasal spray on symptoms and quality of life compared with cetirizine oral tablets in patients with seasonal allergic rhinitis. *Ann Allerg Asthma Im.* 2006;97(3):375-381.

27. Berger WE. Efficacy of azelastine nasal spray in patients with an unsatisfactory response to loratadine. *Ann Allerg Asthma Im.* 2003;91(2):205-211.

28. Berger WE, Lumry WR, Meltzer EO, Pearlman DS. Efficacy of desloratadine, 5 mg, compared with fexofenadine, 180 mg, in patients with symptomatic seasonal allergic rhinitis. *Allergy & Asthma Proceedings.* 2006;27(3):214-223.

29. Ciprandi G, Pronzato C, Ricca V, Passalacqua G, Danzig M, Canonica GW. Loratadine treatment of rhinitis due to pollen allergy reduces epithelial ICAM-1 expression. *Clin Exp Allergy.* 1997;27(10):1175-1183.

30. Corren J, Storms W, Bernstein J, Berger W, Nayak A, Sacks H. Effectiveness of azelastine nasal spray compared with oral cetirizine in patients with seasonal allergic rhinitis. *Clin Ther.* 2005;27(5):543-553.

31. Hampel F, Ratner P, Mansfield L, Meeves S, Liao Y, Georges G. Fexofenadine hydrochloride, 180 mg, exhibits equivalent efficacy to cetirizine, 10 mg, with less drowsiness in patients with moderate-to-severe seasonal allergic rhinitis. *Ann Allerg Asthma Im.* 2003;91(4):354-361.

32. Howarth PH, Stern MA, Roi L, Reynolds R, Bousquet J. Double-blind, placebo-controlled study comparing the efficacy and safety of fexofenadine hydrochloride (120 and 180 mg once daily) and cetirizine in seasonal allergic rhinitis. *J Allergy Clin Immunol.* 1999;104(5):927-933.

33. Prenner BM, Capano D, Harris AG. Efficacy and tolerability of loratadine versus fexofenadine in the treatment of seasonal allergic rhinitis: a double-blind comparison with crossover treatment of nonresponders. *Clin Ther.* 2000;22(6):760-769.

34. Shah SR, Nayak A, Ratner P, Roland P, Michael Wall G. Effects of olopatadine hydrochloride nasal spray 0.6% in the treatment of seasonal allergic rhinitis: a phase III, multicenter, randomized, double-blind, active- and placebo-controlled study in adolescents and adults. *Clin Ther.* 2009;31(1):99-107.

35. UCBa. A monocenter, double-blind, randomized trial, with two parallel groups comparing the clinical efficacy of levocetirizine 5 mg capsules and desloratadine 5 mg capsules taken once a day over 3 weeks of treatment in adult subjects suffering from seasonal allergic rhinitis (SAR) due to grass pollen [completed]. *ClinicalTrials.gov.* 2008;31.

36. Van Cauwenberge P, Juniper EF. Comparison of the efficacy, safety and quality of life provided by fexofenadine hydrochloride 120 mg, loratadine 10 mg and placebo administered once daily for the treatment of seasonal allergic rhinitis. *Clin Exp Allergy.* 2000;30(6):891-899.

37. Bachert C, Kuna P, Sanquer F, et al. Comparison of the efficacy and safety of bilastine 20 mg vs desloratadine 5 mg in seasonal allergic rhinitis patients. *Allergy.* 2009;64(1):158-165.

38. Demoly P, Dreyfus I, Dhivert-Donnadieu H, Mesbah K. Desloratadine for the treatment of cypress pollen-induced allergic rhinitis. *Ann Allerg Asthma Im.* 2009;103(3):260-266.

39. Meltzer EO, Jalowayski AA, Vogt K, Iezzoni D, Harris AG. Effect of desloratadine therapy on symptom scores and measures of nasal patency in seasonal allergic rhinitis: results of a single-center, placebo-controlled trial. *Ann Allerg Asthma Im.* 2006;96(2):363-368.

40. Pradalier A, Neukirch C, Dreyfus I, Devillier P. Desloratadine improves quality of life and symptom severity in patients with allergic rhinitis. *Allergy.* 2007;62(11):1331-1334.

41. Mahmoud F, Arifhodzic N, Haines D, Novotney L. Levocetirizine modulates lymphocyte activation in patients with allergic rhinitis. *Journal of Pharmacological Sciences.* 2008;108(2):149-156.

42. Ucb. Evaluation of the efficacy and safety of levocetirizine during 8 weeks preceding and following the anticipated onset of the grass pollen season in subjects suffering from seasonal allergic rhinitis associated with pollen-induced asthma [completed]. *ClinicalTrials.gov.* 2008;31.

43. Bernstein JA, Prenner B, Ferguson BJ, Portnoy J, Wheeler WJ, Sacks HJ. Double-blind, placebo-controlled trial of reformulated azelastine nasal spray in patients with seasonal allergic rhinitis. *American Journal of Rhinology & Allergy.* 2009;23(5):512-517.

44. Dorow P, Aurich R, Petzold U. Efficacy and tolerability of azelastine nasal spray in patients with allergic rhinitis compared to placebo and budesonide. *Arzneimittel-Forsch.* 1993;43(8):909-912.

45. LaForce C, Dockhorn RJ, Prenner BM, et al. Safety and efficacy of azelastine nasal spray (Astelin NS) for seasonal allergic rhinitis: a 4-week comparative multicenter trial.[see comment]. *Ann Allerg Asthma Im.* 1996;76(2):181-188.

46. Lumry W, Prenner B, Corren J, Wheeler W. Efficacy and safety of azelastine nasal spray at a dose of 1 spray per nostril twice daily. *Ann Allerg Asthma Im.* 2007;99(3):267-272.

47. Ratner PH, Findlay SR, Hampel F, Jr., van Bavel J, Widlitz MD, Freitag JJ. A double-blind, controlled trial to assess the safety and efficacy of azelastine nasal spray in seasonal allergic rhinitis. *Journal of Allergy & Clinical Immunology.* 1994;94(5):818-825.

48. Storms WW, Pearlman DS, Chervinsky P, et al. Effectiveness of azelastine nasal solution in seasonal allergic rhinitis. *Ear, Nose, & Throat Journal.* 1994;73(6):382-386.

49. Hampel FC, Jr., Ratner PH, Amar NJ, et al. Improved quality of life among seasonal allergic rhinitis patients treated with olopatadine HCl nasal spray 0.4% and olopatadine

HCl nasal spray 0.6% compared with vehicle placebo. *Allergy & Asthma Proceedings.* 2006;27(3):202-207.

50. Meltzer EO, Hampel FC, Ratner PH, et al. Safety and efficacy of olopatadine hydrochloride nasal spray for the treatment of seasonal allergic rhinitis. *Ann Allerg Asthma Im.* 2005;95(6):600-606.

51. Ratner PH, Hampel FC, Amar NJ, et al. Safety and efficacy of olopatadine hydrochloride nasal spray for the treatment of seasonal allergic rhinitis to mountain cedar. *Ann Allerg Asthma Im.* 2005;95(5):474-479.

52. Martinez-Cocera C, De Molina M, Marti-Guadano E, et al. Rupatadine 10 mg and cetirizine 10 mg seasonal allergic rhinitis: A randomised, double-blind parallel study. *Journal of Investigational Allergology and Clinical Immunology.* 2005;15(1):22-29.

53. Hampel F, Howland W, Van Bavel J, Ratner P. A randomized, double-blind, placebo-controlled study comparing the efficacy and safety of ebastine (20 mg and 10 mg) to loratadine 10 mg once daily in the treatment of seasonal allergic rhinitis. *Journal of Investigational Allergology and Clinical Immunology.* 2004;14(1):56-63.

54. van Adelsberg J, Philip G, Pedinoff AJ, et al. Montelukast improves symptoms of seasonal allergic rhinitis over a 4-week treatment period. *Allergy.* 2003;58(12):1268-1276.

55. Saint-Martin F, Dumur JP, Perez I, Izquierdo I, French Rupatadine-Rhinitis Study Group. A randomized, double-blind, parallel-group study, comparing the efficacy and safety of rupatadine (20 and 10 mg), a new PAF and H1 receptor-specific histamine antagonist, to loratadine 10 mg in the treatment of seasonal allergic rhinitis. *Journal of Investigational Allergology and Clinical Immunology.* 2004;14(1):34-40.

56. Dockhorn RJ, Bergner A, Connell JT, et al. Safety and efficacy of loratadine (Sch-29851): a new non-sedating antihistamine in seasonal allergic rhinitis. *Ann Allergy.* 1987;58(6):407-411.

57. Ucb. A study evaluating the efficacy and safety of 5 mg levocetirizine oral tablets, once daily versus 10 mg loratadine oral tablets, once daily for the treatment of perennial allergic rhinitis [completed]. *ClinicalTrials.gov.* 2008;31.

58. Ciprandi G, Cirillo I, Vizzaccaro A, et al. Desloratadine and levocetirizine improve nasal symptoms, airflow, and allergic inflammation in patients with perennial allergic rhinitis: a pilot study. *International Immunopharmacology.* 2005;5(13-14):1800-1808.

59. Berlin JM, Golden SJ, Teets S, Lehman EB, Lucas T, Craig TJ. Efficacy of a steroid nasal spray compared with an antihistamine nasal spray in the treatment of perennial allergic rhinitis. *Journal of the American Osteopathic Association.* 2000;100(7 Suppl):S8-13.

60. Golden S, Teets SJ, Lehman EB, et al. Effect of topical nasal azelastine on the symptoms of rhinitis, sleep, and daytime somnolence in perennial allergic rhinitis. *Ann Allerg Asthma Im.* 2000;85(1):53-57.

61. Bruttmann G, Charpin D, Germouty J, Horak F, Kunkel G, Wittmann G. Evaluation of the efficacy and safety of loratadine in perennial allergic rhinitis. *Journal of Allergy & Clinical Immunology.* 1989;83(2 Pt 1):411-416.

62. Ho C-Y, Tan C-T. Comparison of antileukotrienes and antihistamines in the treatment of allergic rhinitis. *Am J Rhinol.* 2007;21(4):439-443.

63. Amat P, Novella A, Roma J, Valero A, Lluch M, Malet A. Treatment of perennial allergic rhinitis with cetirizine. *Allergol Immunopathol.* 1992;20(4):139-143.

64. Holmberg K, Tonnel AB, Dreyfus I, et al. Desloratadine relieves nasal congestion and improves quality-of-life in persistent allergic rhinitis. *Allergy.* 2009;64(11):1663-1670.
65. Kim K, Sussman G, Hebert J, Lumry W, Lutsky B, Gates D. Desloratadine therapy for symptoms associated with perennial allergic rhinitis. *Ann Allerg Asthma Im.* 2006;96(3):460-465.
66. Simons FE, Prenner BM, Finn A, Jr. , Desloratadine Study Group. Efficacy and safety of desloratadine in the treatment of perennial allergic rhinitis. *J Allergy Clin Immunol.* 2003;111(3):617-622.
67. Canonica GW, Tarantini F, Compalati E, Penagos M. Efficacy of desloratadine in the treatment of allergic rhinitis: a meta-analysis of randomized, double-blind, controlled trials. *Allergy.* 2007;62(4):359-366.
68. Pasquali M, Baiardini I, Rogkakou A, et al. Levocetirizine in persistent allergic rhinitis and asthma: effects on symptoms, quality of life and inflammatory parameters. *Clin Exp Allergy.* 2006;36(9):1161-1167.
69. Bachert C, Bousquet J, Canonica GW, et al. Levocetirizine improves quality of life and reduces costs in long-term management of persistent allergic rhinitis. *The Journal of Allergy and Clinical Immunology.* 2004;114(4):838-844.
70. Canonica WG, Bousquet J, Van Hammee G, et al. Levocetirizine improves health-related quality of life and health status in persistent allergic rhinitis. *Respiratory Medicine.* 2006;100(10):1706-1715.
71. Klimek L, Bachert C, Canonica GW, et al. Long-term treatment of persistent allergic rhinitis with levocetirizine - Improvements in activity and sleep items of the Rhinoconjunctivitis quality of life questionnaire (RQLQ). *Allergy and Clinical Immunology International.* 2007;19(1):4.
72. Frolund L, Etholm B, Irander K, et al. A multicentre study of loratadine, clemastine and placebo in patients with perennial allergic rhinitis. *Allergy.* 1990;45(4):254-261.
73. Garg G, Thami GP. Comparative efficacy of cetirizine and levocetirizine in chronic idiopathic urticaria. *Journal of Dermatological Treatment.* 2007;18(1):23-24.
74. Guerra L, Vincenzi C, Marchesi E, et al. Loratadine and cetirizine in the treatment of chronic urticaria. *Journal of the European Academy of Dermatology & Venereology.* 1994;3(2):148-152.
75. Handa S, Dogra S, Kumar B. Comparative efficacy of cetirizine and fexofenadine in the treatment of chronic idiopathic urticaria. *Journal of Dermatological Treatment.* 2004;15(1):55-57.
76. Potter PC, Kapp A, Maurer M, et al. Comparison of the efficacy of levocetirizine 5 mg and desloratadine 5 mg in chronic idiopathic urticaria patients. *Allergy.* 2009;64(4):596-604.
77. Thomas J, Pandhi RK, Oberoi C, et al. A multicentric trial of loratadine and cetrizine in urticaria. *Indian Journal of Dermatology, Venerology and Leprology.* 1998;64:12-15.
78. Grob JJ, Auquier P, Dreyfus I, Ortonne JP. Quality of life in adults with chronic idiopathic urticaria receiving desloratadine: a randomized, double-blind, multicentre, placebo-controlled study. *Journal of the European Academy of Dermatology & Venereology.* 2008;22(1):87-93.
79. Kaplan AP, Spector SL, Meeves S, Liao Y, Varghese ST, Georges G. Once-daily fexofenadine treatment for chronic idiopathic urticaria: A multicenter, randomized, double-blind, placebo-controlled study. *Ann Allerg Asthma Im.* 2005;94(6):662-669.

80. Kapp A, Pichler WJ. Levocetirizine is an effective treatment in patients suffering from chronic idiopathic urticaria: a randomized, double-blind, placebo-controlled, parallel, multicenter study. *Int J Dermatol.* 2006;45(4):469-474.
81. Monroe E, Finn A, Patel P, et al. Efficacy and safety of desloratadine 5 mg once daily in the treatment of chronic idiopathic urticaria: a double-blind, randomized, placebo-controlled trial. *Journal of the American Academy of Dermatology.* 2003;48(4):535-541.
82. Nettis E, Colanardi MC, Barra L, Ferrannini A, Vacca A, Tursi A. Levocetirizine in the treatment of chronic idiopathic urticaria: a randomized, double-blind, placebo-controlled study. *Br J Dermatol.* 2006;154(3):533-538.
83. Nettis E, Colanardi MC, Soccio AL, Ferrannini A, Vacca A. Desloratadine in combination with montelukast suppresses the dermographometer challenge test papule, and is effective in the treatment of delayed pressure urticaria: a randomized, double-blind, placebo-controlled study. *Br J Dermatol.* 2006;155(6):1279-1282.
84. Ortonne J-P, Grob J-J, Auquier P, Dreyfus I. Efficacy and safety of desloratadine in adults with chronic idiopathic urticaria: a randomized, double-blind, placebo-controlled, multicenter trial. *American Journal of Clinical Dermatology.* 2007;8(1):37-42.
85. Di Lorenzo G, Pacor ML, Mansueto P, et al. Randomized placebo-controlled trial comparing desloratadine and montelukast in monotherapy and desloratadine plus montelukast in combined therapy for chronic idiopathic urticaria. *J Allergy Clin Immunol.* 2004;114(3):619-625.
86. Juhlin L, Arendt C. Treatment of chronic urticaria with cetirizine dihydrochloride a non-sedating antihistamine. *Br J Dermatol.* 1988;119(1):67-71.
87. Breneman DL. Cetirizine versus hydroxyzine and placebo in chronic idiopathic urticaria. *Ann Pharmacother.* 1996;30(10):1075-1079.
88. Kontou-Fili K, Maniatakou G, Demaka P, Gonianakis M, Paleologos G. Therapeutic effects of cetirizine in delayed pressure urticaria. Part 1. *Ann Allergy.* 1990;65(6):517-519.
89. Kontou-Fili K, Maniatakou G, Demaka P, Gonianakis M, Palaiologos G, Aroni K. Therapeutic effects of cetirizine in delayed pressure urticaria: clinicopathologic findings. *Journal of the American Academy of Dermatology.* 1991;24(6 Pt 2):1090-1093.
90. Sharpe GR, Shuster S. The effect of cetirizine on symptoms and wealing in dermographic urticaria. *Br J Dermatol.* 1993;129(5):580-583.
91. Zuberbier T, Aberer W, Burtin B, Rihoux JP, Czarnetzki BM. Efficacy of cetirizine in cholinergic urticaria. *Acta Derm-Vernereol.* 1995;75(2):147-149.
92. Zuberbier T, Munzberger C, Haustein U, et al. Double-blind crossover study of high-dose cetirizine in cholinergic urticaria. *Dermatology.* 1996;193(4):324-327.
93. Bender BG, Milgrom H. Comparison of the effects of fluticasone propionate aqueous nasal spray and loratadine on daytime alertness and performance in children with seasonal allergic rhinitis. *Ann Allerg Asthma Im.* 2004;92(3):344-349.
94. Segal AT, Meltzer EO, Lockey RF, et al. Once-Daily Cetirizine Is Safe and Effective for Children with Allergic Rhinitis with and without Intermittent Asthma. *Pediatric Asthma, Allergy and Immunology.* 2003;16(4):265-274.
95. Allegra L, Paupe J, Wieseman HG, Baelde Y. Cetirizine for seasonal allergic rhinitis in children aged 2-6 years. *Pediatric Allergy & Immunology.* 1993;4(3):157-161.
96. Ciprandi G, Tosca M, Ricca V, et al. Cetirizine treatment of allergic cough in children with pollen allergy. *Allergy.* 1997;52(7):752-754.

97. Ciprandi G, Tosca M, Ricca V, et al. Cetirizine treatment of rhinitis in children with pollen allergy: evidence of its antiallergic activity. *Clin Exp Allergy.* 1997;27(10):1160-1166.
98. Masi M, Candiani R, van de Venne H. A placebo-controlled trial of cetirizine in seasonal allergic rhino-conjunctivitis in children aged 6 to 12 years. *Pediatric Allergy & Immunology.* 1993;4(4 Suppl):47-52.
99. Pearlman DS, Lumry WR, Winder JA, Noonan MJ. Once-daily cetirizine effective in the treatment of seasonal allergic rhinitis in children aged 6 to 11 years: a randomized, double-blind, placebo-controlled study. *Clin Pediatr.* 1997;36(4):209-215.
100. Wahn U, Meltzer E, Finn AJ, Kowalski M, Decosta P, et al. Fexofenadine is efficacious and safe in children (aged 6-11 years) with seasonal allergic rhinitis. *J Allergy Clin Immunol.* 2003;111(4):763-769.
101. Tinkelman DG, Kemp J, Mitchell DQ, Galant SP. Treatment of seasonal allergic rhinitis in children with cetirizine or chlorpheniramine: A multicenter study. *Pediatric Asthma, Allergy and Immunology.* 1996;10(1):9-17.
102. Boner AL, Miglioranzi P, Richelli C, Marchesi E, Andreoli A. Efficacy and safety of loratadine suspension in the treatment of children with allergic rhinitis. *Allergy.* 1989;44(6):437-441.
103. Jordana G, Dolovich J, Briscoe MP, et al. Intranasal fluticasone propionate versus loratadine in the treatment of adolescent patients with seasonal allergic rhinitis. *J Allergy Clin Immunol.* 1996;97(2):588-595.
104. Baelde Y, Dupont P. Cetirizine in children with chronic allergic rhinitis. *Drug Investigation.* 1992;4(6):466-472.
105. Ciprandi G, Tosca M, Passalacqua G, Canonica GW. Long-term cetirizine treatment reduces allergic symptoms and drug prescriptions in children with mite allergy. *Ann Allerg Asthma Im.* 2001;87(3):222-226.
106. Ciprandi G, Tosca MA, Milanese M, Ricca V. Cetirizine reduces cytokines and inflammatory cells in children with perennial allergic rhinitis. *Allerg Immunol.* 2004;36(6):237-240.
107. Hsieh JC, Lue KH, Lai DS, Sun HL, Lin YH. A comparison of cetirizine and montelukast for treating childhood perennial allergic rhinitis. *Pediatric Asthma, Allergy and Immunology.* 2004;17(1):59-69.
108. Jobst S, van den Wijngaart W, Schubert A, van de Venne H. Assessment of the efficacy and safety of three dose levels of cetirizine given once daily in children with perennial allergic rhinitis. *Allergy.* 1994;49(8):598-604.
109. Lai DS, Lue KH, Hsieh JC, Lin KL, Lee HS. The comparison of the efficacy and safety of cetirizine, oxatomide, ketotifen, and a placebo for the treatment of childhood perennial allergic rhinitis. *Ann Allerg Asthma Im.* 2002;89(6):589-598.
110. Sienra-Monge JJ, Gazca-Aguilar A, Del Rio-Navarro B. Double-blind comparison of cetirizine and loratadine in children ages 2 to 6 years with perennial allergic rhinitis. *American Journal of Therapeutics.* 1999;6(3):149-155.
111. Yang YH, Lin YT, Lu MY, Tsai MJ, Chiang BL. A double-blind, placebo-controlled, and randomized study of loratadine (Clarityne) syrup for the treatment of allergic rhinitis in children aged 3 to 12 years. *Asian Pac J Allergy Immunol.* 2001;19(3):171-175.

112. Chen S-T, Lu K-H, Sun H-L, Chang W-T, Lue K-H, Chou M-C. Randomized placebo-controlled trial comparing montelukast and cetirizine for treating perennial allergic rhinitis in children aged 2-6 yr. *Pediatric Allergy & Immunology.* 2006;17(1):49-54.
113. Ratner P, Hampel F, Van Bavel J, Howland W. Efficacy and safety of ebastine 20 mg compared to loratadine 10 mg once daily in the treatment of seasonal allergic rhinitis: a randomized, double-blind, placebo-controlled study. *Int Arch Allergy Immunol.* 2004;133(4):371-379.
114. Lee C-F, Sun H-L, Lu K-H, Ku M-S, Lue K-H. The comparison of cetirizine, levocetirizine and placebo for the treatment of childhood perennial allergic rhinitis. *Pediatric Allergy & Immunology.* 2009;20(5):493-499.
115. Herman D, Garay R, Le Gal M. A randomized double-blind placebo controlled study of azelastine nasal spray in children with perennial rhinitis. *International Journal of Pediatric Otorhinolaryngology.* 1997;39(1):1-8.
116. La Rosa M, Leonardi S, Marchese G, et al. Double-blind multicenter study on the efficacy and tolerability of cetirizine compared with oxatomide in chronic idiopathic urticaria in preschool children. *Ann Allerg Asthma Im.* 2001;87(1):48-53.
117. Simons FE. Prevention of acute urticaria in young children with atopic dermatitis. *J Allergy Clin Immunol.* 2001;107(4):703-706.
118. Meltzer EO, Garadi R, Laforce C, et al. Comparative study of sensory attributes of two antihistamine nasal sprays: olopatadine 0.6% and azelastine 0.1%. *Allergy & Asthma Proceedings.* 2008;29(6):659-668.
119. Gastpar H, Dorow P, Aurich R, Petzold U. Investigation of long-term efficacy and tolerability of azelastine nasal spray in the treatment of perennial allergic rhinitis. *Arzneimittel-Forsch.* 1993;43(7):771-776.
120. Wober W, Diez Crespo C, Bahre M. Efficacy and tolerability of azelastine nasal spray in the treatment of allergic rhinitis: large scale experience in community practice. *Curr Med Res Opin.* 1997;13(10):617-626.
121. Schwarz EB, Moretti ME, Nayak S, Koren G. Risk of hypospadias in offspring of women using loratadine during pregnancy: a systematic review and meta-analysis. *Drug Safety.* 2008;31(9):775-788.
122. Bruttmann G, Arendt C, Bernheim J. Double-blind, placebo controlled comparison of cetirizine 2HC1 and terfenadine in atopic perennial rhinitis. *Acta Therapeutica.* 1989;15(1):99-109.
123. Raphael GD, Angello JT, Wu M-M, Druce HM. Efficacy of diphenhydramine vs desloratadine and placebo in patients with moderate-to-severe seasonal allergic rhinitis.[see comment]. *Ann Allerg Asthma Im.* 2006;96(4):606-614.
124. Spector SL, Shikiar R, Harding G, Meeves S, Leahy MJ. The effect of fexofenadine hydrochloride on productivity and quality of life in patients with chronic idiopathic urticaria. *Cutis.* 2007;79(2):157-162.
125. Layton D, Wilton L, Boshier A, Cornelius V, Harris S, Shakir SAW. Comparison of the risk of drowsiness and sedation between levocetirizine and desloratadine: a prescription-event monitoring study in England. *Drug Safety.* 2006;29(10):897-909.
126. Layton D, Wilton L, Shakir SAW. Examining the tolerability of the non-sedating antihistamine desloratadine: a prescription-event monitoring study in England. *Drug Safety.* 2009;32(2):169-179.

127. Pedersen L, Norgaard M, Skriver MV, Olsen J, Sorensen HT. Prenatal exposure to loratadine in children with hypospadias: a nested case-control study within the Danish National Birth Cohort. *American Journal of Therapeutics.* 2006;13(4):320-324.
128. Weber-Schoendorfer C, Schaefer C. The safety of cetirizine during pregnancy. A prospective observational cohort study. *Reproductive Toxicology.* 2008;26(1):19-23.
129. Finkle WD, Adams JL, Greenland S, Melmon KL. Increased risk of serious injury following an initial prescription for diphenhydramine. *Ann Allerg Asthma Im.* 2002;89(3):244-250.
130. Mann RD, Pearce GL, Dunn N, Shakir S. Sedation with 'non-sedating' antihistamines: Four prescription-event monitoring studies in general practice. *BMJ.* 2000;320(7243):1184-1187.
131. Craig-McFeely PM, Acharya NV, Shakir SAW. Evaluation of the safety of fexofenadine from experience gained in general practice use in England in 1997. *Eur J Clin Pharmacol.* 2001;57(4):313-320.
132. De Abajo FJ, Rodriguez LAG. Risk of ventricular arrhythmias associated with nonsedating antihistamine drugs. *Br J Clin Pharmacol.* 1999;47(3):307-313.
133. Ucb. A multicentre, double-blind, parallel, randomized, placebo-controlled study : evaluation of the efficacy and safety of levocetirizine 5 mg and desloratadine 5 mg administered orally as capsules once daily, in the morning, over 2 weeks in patients suffering from allergic rhinitis (AR) [completed]. *ClinicalTrials.gov.* 2008;31.
134. UCBb. Study evaluating the efficacy and safety of 5 mg levocetirizine oral tablets, once daily versus 10 mg loratadine oral tablets, once daily for the treatment of seasonal allergic rhinitis (SAR) [completed]. *ClinicalTrials.gov.* 2008;31.
135. Bender BG, Berning S, Dudden R, Milgrom H, Tran ZV. Sedation and performance impairment of diphenhydramine and second-generation antihistamines: a meta-analysis. *J Allergy Clin Immunol.* 2003;111(4):770-776.
136. Salmun LM, Gates D, Scharf M, Greiding L, Ramon F, Heithoff K. Loratadine versus cetirizine: assessment of somnolence and motivation during the workday. *Clin Ther.* 2000;22(5):573-582.
137. Satish U, Streufert S, Dewan M, Voort SV. Improvements in simulated real-world relevant performance for patients with seasonal allergic rhinitis: impact of desloratadine. *Allergy.* 2004;59(4):415-420.
138. Meltzer EO, Weiler JM, Widlitz MD. Comparative outdoor study of the efficacy, onset and duration of action, and safety of cetirizine, loratadine, and placebo for seasonal allergic rhinitis. *J Allergy Clin Immunol.* 1996;97(2):617-626.
139. Berger WE, Schenkel EJ, Mansfield LE, Desloratadine Study Group. Safety and efficacy of desloratadine 5 mg in asthma patients with seasonal allergic rhinitis and nasal congestion. *Ann Allerg Asthma Im.* 2002;89(5):485-491.
140. Meltzer E. Efficacy and tolerability of once-daily 5mg desloratadine, an H1-receptor antagonist, in patients with seasonal allergic rhinitis: Assessment during the spring and fall allergy seasons. *Clin Drug Invest.* 2001;21(1):25-32.
141. Ring J, Hein R, Gauger A, Bronsky E, Miller B. Once-daily desloratadine improves the signs and symptoms of chronic idiopathic urticaria: a randomized, double-blind, placebo-controlled study. *Int J Dermatol.* 2001;40(1):72-76.
142. Lal A. Effect of a few histamine1-antagonists on blood glucose in patients of allergic rhinitis. *Indian J Otolaryngol.* 2000;52(2):193-195.

143. Zuberbier T, Ifflander J, Semmler C, Henz BM. Acute urticaria: clinical aspects and therapeutic responsiveness. *Acta Derm-Vernereol.* 1996;76(4):295-297.
144. Graft DF, Bernstein DI, Goldsobe A, Meltzer EO, Portnoy J, Long J. Safety of fexofenadine in children treated for seasonal allergic rhinitis. *Ann Allerg Asthma Im.* 2001;87(1):22-26.
145. Milgrom H, Kittner B, Lanier R, Hampel FC. Safety and tolerability of fexofenadine for the treatment of allergic rhinitis in children 2 to 5 years old. *Ann Allerg Asthma Im.* 2007;99(4):358-363.
146. Potter PC, Paediatric Levocetirizine Study G. Efficacy and safety of levocetirizine on symptoms and health-related quality of life of children with perennial allergic rhinitis: a double-blind, placebo-controlled randomized clinical trial. *Ann Allerg Asthma Im.* 2005;95(2):175-180.
147. Simons FE. Prospective, long-term safety evaluation of the H1-receptor antagonist cetirizine in very young children with atopic dermatitis. ETAC Study Group. *J Allergy Clin Immunol.* 1999;104(2 Pt 1):433-440.
148. Simons FE, Silas P, Portnoy JM, et al. Safety of cetirizine in infants 6 to 11 months of age: a randomized, double-blind, placebo-controlled study. *J Allergy Clin Immunol.* 2003;111(6):1244-1248.
149. Winder JA, Noonan MJ, Lumry WR, Pearlman DS. Absence of QT(c) prolongation with cetirizine in children aged 6 to 11 years. *Pediatric Asthma, Allergy and Immunology* 1996;10(4):181-190.
150. Prenner B, Ballona R, Bueso A, et al. Safety of desloratadine syrup in children 6 months to younger than 2 years of age: A randomized, double-blinded, placebo-controlled study. *Pediatric Asthma, Allergy and Immunology.* 2006;19(2):91-99.
151. Simons FER, Early Prevention of Asthma in Atopic Children Study G. Safety of levocetirizine treatment in young atopic children: An 18-month study. *Pediatric Allergy & Immunology.* 2007;18(6):535-542.
152. Wober W, Diez Crespo CD, Bahre M. Evaluation of the drug monitoring programme of azelastine hydrochloride nasal spray in the treatment of allergic rhinitis in children under 13 years of age. *Arzneimittel-Forsch.* 1997;47(7):841-844.
153. Rossi GA, Tosca MA, Passalacqua G, Bianchi B, Le Grazie C, Canonica GW. Evidence of desloratadine syrup efficacy and tolerability in children with pollen-induced allergic rhinitis. *Allergy.* 2005;60(3):416-417.
154. Delgado LF, Pferferman A, Sole D, Naspitz CK. Evaluation of the potential cardiotoxicity of the antihistamines terfenadine, astemizole, loratadine, and cetirizine in atopic children. *Ann Allerg Asthma Im.* 1998;80(4):333-337.
155. Grimfeld A, Holgate ST, Canonica GW, et al. Prophylactic management of children at risk for recurrent upper respiratory infections: the Preventia I Study. *Clin Exp Allergy.* 2004;34(11):1665-1672.
156. Bloom M, Staudinger H, Herron J. Safety of desloratadine syrup in children. *Curr Med Res Opin.* 2004;20(12):1959-1965.
157. Diepgen TL. Long-term treatment with cetirizine of infants with atopic dermatitis: A multi-country, double-blind, randomized, placebo-controlled trial (the ETAC trial) over 18 months. *Pediatric Allergy & Immunology.* 2002;13(4):278-286.

158. Stevenson J, Cornah D, Evrard P, et al. Long-term evaluation of the impact of the H1-receptor antagonist cetirizine on the behavioral, cognitive, and psychomotor development of very young children with atopic dermatitis. *Pediatric Research.* 2002;52(2):251-257.
159. Grant JA, Nicodemus CF, Findlay SR, et al. Cetirizine in patients with seasonal rhinitis and concomitant asthma: prospective, randomized, placebo-controlled trial. *J Allergy Clin Immunol.* 1995;95(5 Pt 1):923-932.
160. Aaronson DW, Mitchell J, Hinton S, Evans C. Evaluation of cetirizine in patients with allergic rhinitis and perennial asthma. *Ann Allerg Asthma Im.* 1996;76(5):440-446.
161. Blaiss MS, Food Drug Administration, Acaai A. Management of rhinitis and asthma in pregnancy. *Ann Allerg Asthma Im.* 2003;90(6 Suppl 3):16-22.
162. Diav-Citrin O, Shechtman S, Aharonovich A, et al. Pregnancy outcome after gestational exposure to loratadine or antihistamines: a prospective controlled cohort study. *J Allergy Clin Immunol.* 2003;111(6):1239-1243.
163. Einarson A, Bailey B, Jung G, Spizzirri D, Baillie M, Koren G. Prospective controlled study of hydroxyzine and cetirizine in pregnancy. *Ann Allerg Asthma Im.* 1997;78(2):183-186.
164. Moretti ME, Caprara D, Coutinho CJ, et al. Fetal safety of loratadine use in the first trimester of pregnancy: a multicenter study. *J Allergy Clin Immunol.* 2003;111(3):479-483.
165. Wilton LV, Pearce GL, Martin RM, Mackay FJ, Mann RD. The outcomes of pregnancy in women exposed to newly marketed drugs in general practice in England. *Br J Obstet Gynaecol.* 1998;105(8):882-889.
166. Seto A, Einarson T, Koren G. Pregnancy outcome following first trimester exposure to antihistamines: Meta-analysis. *Am J Perinatol.* 1997;14(3):119-124.
167. Centers for Disease Control and Prevention. Evaluation of an association between loratadine and hypospadias--United States, 1997-2001. *MMWR Morbidity & Mortality Weekly Report.* 2004;53(10):219-221.
168. Bernstein DI, Levy AL, Hampel FC, et al. Treatment with intranasal fluticasone propionate significantly improves ocular symptoms in patients with seasonal allergic rhinitis. *Clin Exp Allergy.* 2004;34(6):952-957.
169. Salmun LM, Herron JM, Banfield C, Padhi D, Lorber R, Affrime MB. The pharmacokinetics, electrocardiographic effects, and tolerability of loratadine syrup in children aged 2 to 5 years. *Clin Ther.* 2000;22(5):613-621.

Appendix A. Glossary

This glossary defines terms as they are used in reports produced by the Drug Effectiveness Review Project. Some definitions may vary slightly from other published definitions.

Absolute risk: The probability or chance that a person will have a medical event. Absolute risk is expressed as a percentage. It is the ratio of the number of people who have a medical event divided by all of the people who could have the event because of their medical condition.

Add-on therapy: An additional treatment used in conjunction with the primary or initial treatment.

Adherence: Following the course of treatment proscribed by a study protocol.

Adverse drug reaction: An adverse effect specifically associated with a drug.

Adverse event: A harmful or undesirable outcome that occurs during or after the use of a drug or intervention but is not necessarily caused by it.

Adverse effect: An adverse event for which the causal relation between the intervention and the event is at least a reasonable possibility.

Active-control trial: A trial comparing a drug in a particular class or group with a drug outside of that class or group.

Allocation concealment: The process by which the person determining randomization is blinded to a study participant's group allocation.

Applicability: see *External Validity*

Before-after study: A type nonrandomized study where data are collected before and after patients receive an intervention. Before-after studies can have a single arm or can include a control group.

Bias: A systematic error or deviation in results or inferences from the truth. Several types of bias can appear in published trials, including selection bias, performance bias, detection bias, and reporting bias.

Bioequivalence: Drug products that contain the same compound in the same amount that meet current official standards, that, when administered to the same person in the same dosage regimen result in equivalent concentrations of drug in blood and tissue.

Black box warning: A type of warning that appears on the package insert for prescription drugs that may cause serious adverse effects. It is so named for the black border that usually surrounds the text of the warning. A black box warning means that medical studies indicate that the drug carries a significant risk of serious or even life-threatening adverse effects. The US Food and Drug Administration (FDA) can require a pharmaceutical company to place a black box warning on the labeling of a prescription drug, or in literature describing it. It is the strongest warning that the FDA requires.

Blinding: A way of making sure that the people involved in a research study — participants, clinicians, or researchers —do not know which participants are assigned to each study group. Blinding usually is used in research studies that compare two or more types of treatment for an illness. Blinding is used to make sure that knowing the type of treatment does not affect a participant's response to the treatment, a health care provider's behavior, or assessment of the treatment effects.

Case series: A study reporting observations on a series of patients receiving the same intervention with no control group.

Case study: A study reporting observations on a single patient.

Case-control study: A study that compares people with a specific disease or outcome of interest (cases) to people from the same population without that disease or outcome (controls).

Clinical diversity: Differences between studies in key characteristics of the participants, interventions or outcome measures.

Clinically significant: A result that is large enough to affect a patient's disease state in a manner that is noticeable to the patient and/or a caregiver.

Cohort study: An observational study in which a defined group of people (the cohort) is followed over time and compared with a group of people who were exposed or not exposed to a particular intervention or other factor of interest. A prospective cohort study assembles participants and follows them into the future. A retrospective cohort study identifies subjects from past records and follows them from the time of those records to the present.

Combination Therapy: The use of two or more therapies and especially drugs to treat a disease or condition.

Confidence interval: The range of values calculated from the data such that there is a level of confidence, or certainty, that it contains the true value. The 95% confidence interval is generally used in Drug Effectiveness Review Project reports. If the report were hypothetically repeated on a collection of 100 random samples of studies, the resulting 95% confidence intervals would include the true population value 95% of the time.

Confounder: A factor that is associated with both an intervention and an outcome of interest.

Controlled clinical trial: A clinical trial that includes a control group but no or inadequate methods of randomization.

Control group: In a research study, the group of people who do not receive the treatment being tested. The control group might receive a placebo, a different treatment for the disease, or no treatment at all.

Convenience sample: A group of individuals being studied because they are conveniently accessible in some way. Convenience samples may or may not be representative of a population that would normally be receiving an intervention.

Crossover trial: A type of clinical trial comparing two or more interventions in which the participants, upon completion of the course of one treatment, are switched to another.

Direct analysis: The practice of using data from head-to-head trials to draw conclusions about the comparative effectiveness of drugs within a class or group. Results of direct analysis are the preferred source of data in Drug Effectiveness Review Project reports.

Dosage form: The physical form of a dose of medication, such as a capsule, injection, or liquid. The route of administration is dependent on the dosage form of a given drug. Various dosage forms may exist for the same compound, since different medical conditions may warrant different routes of administration.

Dose-response relationship: The relationship between the quantity of treatment given and its effect on outcome. In meta-analysis, dose-response relationships can be investigated using meta-regression.

Double-blind: The process of preventing those involved in a trial from knowing to which comparison group a particular participant belongs. While double-blind is a frequently used term

in trials, its meaning can vary to include blinding of patients, caregivers, investigators, or other study staff.

Double-dummy: The use of two placebos in a trial that match the active interventions when they vary in appearance or method of administrations (for example, when an oral agent is compared with an injectable agent).

Effectiveness: The extent to which a specific intervention *used under ordinary circumstances* does what it is intended to do.

Effectiveness outcomes: Outcomes that are generally important to patients and caregivers, such as quality of life, responder rates, number and length of hospitalizations, and ability to work. Data on effectiveness outcomes usually comes from longer-term studies of a "real-world" population.

Effect size/estimate of effect: The amount of change in a condition or symptom because of a treatment (compared to not receiving the treatment). It is commonly expressed as a risk ratio (relative risk), odds ratio, or difference in risk.

Efficacy: The extent to which an intervention produces a beneficial result *under ideal conditions* in a selected and controlled population.

Equivalence level: The amount which an outcome from two treatments can differ but still be considered equivalent, as in an equivalence trial, or the amount which an outcome from treatment A can be worse than that of treatment B but still be considered noninferior, as in a noninferiority trial.

Equivalence trial: A trial designed to determine whether the response to two or more treatments differs by an amount that is clinically unimportant. This lack of clinical importance is usually demonstrated by showing that the true treatment difference is likely to lie between a lower and an upper equivalence level of clinically acceptable differences.

Exclusion criteria: The criteria, or standards, set out before a study or review. Exclusion criteria are used to determine whether a person should participate in a research study or whether an individual study should be excluded in a systematic review. Exclusion criteria may include age, previous treatments, and other medical conditions. Criteria help identify suitable participants.

External validity: The extent to which results provide a correct basis for generalizations to other circumstances. For instance, a meta-analysis of trials of elderly patients may not be generalizable to children. (Also called generalizability or applicability.)

Fixed-effect model: A model that calculates a pooled estimate using the assumption that all observed variation between studies is due to by chance. Studies are assumed to be measuring the same overall effect. An alternative model is the random-effects model.

Fixed-dose combination product: A formulation of two or more active ingredients combined in a single dosage form available in certain fixed doses.

Forest plot: A graphical representation of the individual results of each study included in a meta-analysis and the combined result of the meta-analysis. The plot allows viewers to see the heterogeneity among the results of the studies. The results of individual studies are shown as squares centered on each study's point estimate. A horizontal line runs through each square to show each study's confidence interval—usually, but not always, a 95% confidence interval. The overall estimate from the meta-analysis and its confidence interval are represented as a diamond. The center of the diamond is at the pooled point estimate, and its horizontal tips show the confidence interval.

Funnel plot: A graphical display of some measure of study precision plotted against effect size that can be used to investigate whether there is a link between study size and treatment effect.

Generalizability: See *External Validity.*

Half- life: The time it takes for the plasma concentration or the amount of drug in the body to be reduced by 50%.

Harms: See *Adverse Event*

Hazard ratio: The increased risk with which one group is likely to experience an outcome of interest. It is similar to a risk ratio. For example, if the hazard ratio for death for a treatment is 0.5, then treated patients are likely to die at half the rate of untreated patients.

Head-to-head trial: A trial that directly compares one drug in a particular class or group with another in the same class or group.

Health outcome: The result of a particular health care practice or intervention, including the ability to function and feelings of well-being. For individuals with chronic conditions – where cure is not always possible – results include health-related quality of life as well as mortality.

Heterogeneity: The variation in, or diversity of, participants, interventions, and measurement of outcomes across a set of studies.

I^2: A measure of statistical heterogeneity of the estimates of effect from studies. Values range from 0% to 100%. Large values of I^2 suggest heterogeneity. I^2 is the proportion of total variability across studies that is due to heterogeneity and not chance. It is calculated as (Q-(n-1))/Q, where n is the number of studies.

Incidence: The number of new occurrences of something in a population over a particular period of time, e.g. the number of cases of a disease in a country over one year.

Indication: A term describing a valid reason to use a certain test, medication, procedure, or surgery. In the United States, indications for medications are strictly regulated by the Food and Drug Administration, which includes them in the package insert under the phrase "Indications and Usage".

Indirect analysis: The practice of using data from trials comparing one drug in a particular class or group with another drug outside of that class or group or with placebo and attempting to draw conclusions about the comparative effectiveness of drugs within a class or group based on that data. For example, direct comparisons between drugs A and B and between drugs B and C can be used to make an indirect comparison between drugs A and C.

Intention to treat: The use of data from a randomized controlled trial in which data from all randomized patients are accounted for in the final results. Trials often incorrectly report results as being based on intention to treat despite the fact that some patients are excluded from the analysis.

Internal validity: The extent to which the design and conduct of a study are likely to have prevented bias. Generally, the higher the interval validity, the better the quality of the study publication.

Inter-rater reliability: The degree of stability exhibited when a measurement is repeated under identical conditions by different raters.

Intermediate outcome: An outcome not of direct practical importance but believed to reflect outcomes that are important. For example, blood pressure is not directly important to patients but it is often used as an outcome in clinical trials because it is a risk factor for stroke and myocardial infarction (hear attack).

Logistic regression: A form of regression analysis that models an individual's odds of disease or some other outcome as a function of a risk factor or intervention.

Masking: See *Blinding*

Mean difference: A method used to combine measures on continuous scales (such as weight) where the mean, standard deviation, and sample size are known for each group.

Meta-analysis: The use of statistical techniques in a systematic review to integrate the results of included studies. Although the terms are sometimes used interchangeably, meta-analysis is not synonymous with systematic review. However, systematic reviews often include meta-analyses.

Meta-regression: A technique used to explore the relationship between study characteristics (for example, baseline risk, concealment of allocation, timing of the intervention) and study results (the magnitude of effect observed in each study) in a systematic review.

Mixed treatment comparison meta analysis: A meta-analytic technique that simultaneously compares multiple treatments (typical 3 or more) using both direct and indirect evidence. The multiple treatments form a network of treatment comparisons. Also called multiple treatment comparisons, network analysis, or umbrella reviews.

Monotherapy: the use of a single drug to treat a particular disorder or disease.

Multivariate analysis: Measuring the impact of more than one variable at a time while analyzing a set of data.

N-of-1 trial: A randomized trial in an individual to determine the optimum treatment for that individual.

Noninferiority trial: A trial designed to determine whether the effect of a new treatment is not worse than a standard treatment by more than a prespecified amount. A one-sided version of an equivalence trial.

Nonrandomized study: Any study estimating the effectiveness (harm or benefit) of an intervention that does not use randomization to allocate patients to comparison groups. There are many types of nonrandomized studies, including cohort studies, case-control studies, and before-after studies.

Null hypothesis: The statistical hypothesis that one variable (for example, treatment to which a participant was allocated) has no association with another variable or set of variables.

Number needed to harm: The number of people who would need to be treated over a specific period of time before one bad outcome of the treatment will occur. The number needed to harm (NNH) for a treatment can be known only if clinical trials of the treatment have been performed.

Number needed to treat: An estimate of how many persons need to receive a treatment before one person would experience a beneficial outcome.

Observational study: A type of nonrandomized study in which the investigators do not seek to intervene, instead simply observing the course of events.

Odds ratio: The ratio of the odds of an event in one group to the odds of an event in another group. An odds ratio of 1.0 indicates no difference between comparison groups. For undesirable outcomes an odds ratio that is <1.0 indicates that the intervention was effective in reducing the risk of that outcome.

Off-label use: When a drug or device is prescribed outside its specific FDA-approved indication, to treat a condition or disease for which it is not specifically licensed.

Outcome: The result of care and treatment and/ or rehabilitation. In other words, the change in health, functional ability, symptoms or situation of a person, which can be used to measure the

effectiveness of care/treatment/rehabilitation. Researchers should decide what outcomes to measure before a study begins; outcomes are then assessed at the end of the study.

Outcome measure: Is the way in which an outcome is evaluated---the device (scale) used for measuring. With this definition YMRS is an outcome measure, and a patient's outcome after treatment might be a 12-point improvement on that scale.

One-tailed test (one-sided test): A hypothesis test in which the values that reject the null hypothesis are located entirely in one tail of the probability distribution. For example, testing whether one treatment is better than another (rather than testing whether one treatment is either better or worse than another).

Open-label trial: A clinical trial in which the investigator and participant are aware which intervention is being used for which participant (that is, not blinded). Random allocation may or may not be used in open-label trials.

Per protocol: The subset of participants from a randomized controlled trial who complied with the protocol sufficiently to ensure that their data would be likely to exhibit the effect of treatment. Per protocol analyses are sometimes misidentified in published trials as intention-to-treat analyses.

Pharmacokinetics: the characteristic interactions of a drug and the body in terms of its absorption, distribution, metabolism, and excretion.

Placebo: An inactive substance commonly called a "sugar pill." In a clinical trial, a placebo is designed to look like the drug being tested and is used as a control. It does not contain anything that could harm a person. It is not necessarily true that a placebo has no effect on the person taking it.

Placebo-controlled trial: A study in which the effect of a drug is compared with the effect of a placebo (an inactive substance designed to resemble the drug). In placebo-controlled clinical trials, participants receive either the drug being studied or a placebo. The results of the drug and placebo groups are then compared to see if the drug is more effective in treating the condition than the placebo is.

Point estimate: The results (e.g. mean, weighted difference, odds ratio, relative risk or risk difference) obtained in a sample (a study or a meta-analysis) which are used as the best estimate of what is true for the relevant population from which the sample is taken. A confidence interval is a measure of the uncertainty (due to the play of chance) associated with that estimate.

Pooling: The practice of combing data from several studies to draw conclusions about treatment effects.

Power: The probability that a trial will detect statistically significant differences among intervention effects. Studies with small sample sizes can frequently be underpowered to detect difference.

Precision: The likelihood of random errors in the results of a study, meta-analysis, or measurement. The greater the precision, the less the random error. Confidence intervals around the estimate of effect are one way of expressing precision, with a narrower confidence interval meaning more precision.

Prospective study: A study in which participants are identified according to current risk status or exposure and followed forward through time to observe outcome.

Prevalence: How often or how frequently a disease or condition occurs in a group of people. Prevalence is calculated by dividing the number of people who have the disease or condition by the total number of people in the group.

Probability: The likelihood (or chance) that an event will occur. In a clinical research study, it is the number of times a condition or event occurs in a study group divided by the number of people being studied.

Publication bias: A bias caused by only a subset of the relevant data being available. The publication of research can depend on the nature and direction of the study results. Studies in which an intervention is not found to be effective are sometimes not published. Because of this, systematic reviews that fail to include unpublished studies may overestimate the true effect of an intervention. In addition, a published report might present a biased set of results (for example, only outcomes or subgroups for which a statistically significant difference was found).

P value: The probability (ranging from zero to one) that the results observed in a study could have occurred by chance if the null hypothesis was true. A *P* value of ≤0.05 is often used as a threshold to indicate statistical significance.

Q-statistic: A measure of statistical heterogeneity of the estimates of effect from studies. Large values of Q suggest heterogeneity. It is calculated as the weighted sum of the squared difference of each estimate from the mean estimate.

Random-effects model: A statistical model in which both within-study sampling error (variance) and between-studies variation are included in the assessment of the uncertainty (confidence interval) of the results of a meta-analysis. When there is heterogeneity among the results of the included studies beyond chance, random-effects models will give wider confidence intervals than fixed-effect models.

Randomization: The process by which study participants are allocated to treatment groups in a trial. Adequate (that is, unbiased) methods of randomization include computer generated schedules and random-numbers tables.

Randomized controlled trial: A trial in which two or more interventions are compared through random allocation of participants.

Regression analysis: A statistical modeling technique used to estimate or predict the influence of one or more independent variables on a dependent variable, for example, the effect of age, sex, or confounding disease on the effectiveness of an intervention.

Relative risk: The ratio of risks in two groups; same as a risk ratio.

Retrospective study: A study in which the outcomes have occurred prior to study entry.

Risk: A way of expressing the chance that something will happen. It is a measure of the association between exposure to something and what happens (the outcome). Risk is the same as probability, but it usually is used to describe the probability of an adverse event. It is the rate of events (such as breast cancer) in the total population of people who could have the event (such as women of a certain age).

Risk difference: The difference in size of risk between two groups.

Risk Factor: A characteristic of a person that affects that person's chance of having a disease. A risk factor may be an inherent trait, such as gender or genetic make-up, or a factor under the person's control, such as using tobacco. A risk factor does not usually cause the disease. It changes a person's chance (or risk) of getting the disease.

Risk ratio: The ratio of risks in two groups. In intervention studies, it is the ratio of the risk in the intervention group to the risk in the control group. A risk ratio of 1 indicates no difference between comparison groups. For undesirable outcomes, a risk ratio that is <1 indicates that the intervention was effective in reducing the risk of that outcome.

Run-in period: Run in period: A period before randomization when participants are monitored but receive no treatment (or they sometimes all receive one of the study treatments, possibly in a blind fashion). The data from this stage of a trial are only occasionally of value but can serve a valuable role in screening out ineligible or non-compliant participants, in ensuring that participants are in a stable condition, and in providing baseline observations. A run-in period is sometimes called a washout period if treatments that participants were using before entering the trial are discontinued.

Safety: Substantive evidence of an absence of harm. This term (or the term ‘‘safe’’) should not be used when evidence on harms is simply absent or is insufficient.

Sample size: The number of people included in a study. In research reports, sample size is usually expressed as "n." In general, studies with larger sample sizes have a broader range of participants. This increases the chance that the study's findings apply to the general population. Larger sample sizes also increase the chance that rare events (such as adverse effects of drugs) will be detected.

Sensitivity analysis: An analysis used to determine how sensitive the results of a study or systematic review are to changes in how it was done. Sensitivity analyses are used to assess how robust the results are to uncertain decisions or assumptions about the data and the methods that were used.

Side effect: Any unintended effect of an intervention. Side effects are most commonly associated with pharmaceutical products, in which case they are related to the pharmacological properties of the drug at doses normally used for therapeutic purposes in humans.

Standard deviation (SD): A measure of the spread or dispersion of a set of observations, calculated as the average difference from the mean value in the sample.

Standard error (SE): A measure of the variation in the sample statistic over all possible samples of the same size. The standard error decreases as the sample size increases.

Standard treatment: The treatment or procedure that is most commonly used to treat a disease or condition. In clinical trials, new or experimental treatments sometimes are compared to standard treatments to measure whether the new treatment is better.

Statistically significant: A result that is unlikely to have happened by chance.

Study: A research process in which information is recorded for a group of people. The information is known as data. The data are used to answer questions about a health care problem.

Study population: The group of people participating in a clinical research study. The study population often includes people with a particular problem or disease. It may also include people who have no known diseases.

Subgroup analysis: An analysis in which an intervention is evaluated in a defined subset of the participants in a trial, such as all females or adults older than 65 years.

Superiority trial: A trial designed to test whether one intervention is superior to another.

Surrogate outcome: Outcome measures that are not of direct practical importance but are believed to reflect outcomes that are important; for example, blood pressure is not directly important to patients but it is often used as an outcome in clinical trials because it is a risk factor for stroke and heart attacks. Surrogate endpoints are often physiological or biochemical markers that can be relatively quickly and easily measured, and that are taken as being predictive of important clinical outcomes. They are often used when observation of clinical outcomes requires long follow-up.

Survival analysis: Analysis of data that correspond to the time from a well-defined time origin until the occurrence of some particular event or end-point; same as time-to-event analysis.

Systematic review: A review of a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant research and to collect and analyze data from the studies that are included in the review.

Tolerability: For therapeutic drugs, it refers a drug's lack of "nuisance side effects," side effects that are thought to have no long-term effect but that are unpleasant enough to the patient that adherence to the medication regimen is affected.

The extent to which a drug's adverse effects impact the patient's ability or willingness to continue taking the drug as prescribed. These adverse effects are often referred to as nuisance side effects, because they are generally considered to not have long-term effects but can seriously impact compliance and adherence to a medication regimen.

Treatment regimen: The magnitude of effect of a treatment versus no treatment or placebo; similar to "effect size". Can be calculated in terms of relative risk (or risk ratio), odds ratio, or risk difference.

Two-tailed test (two-sided test): A hypothesis test in which the values that reject the null hypothesis are located in both tails of the probability distribution. For example, testing whether one treatment is different than another (rather than testing whether one treatment is either better than another).

Type I error: A conclusion that there is evidence that a treatment works, when it actually does not work (false-positive).

Type II error: A conclusion that there is no evidence that a treatment works, when it actually does work (false-negative).

Validity: The degree to which a result (of a measurement or study) is likely to be true and free of bias (systematic errors).

Variable: A measurable attribute that varies over time or between individuals. Variables can be

- *Discrete*: taking values from a finite set of possible values (e.g. race or ethnicity)
- *Ordinal*: taking values from a finite set of possible values where the values indicate rank (e.g. 5-point Likert scale)
- *Continuous:* taking values on a continuum (e.g. hemoglobin A1c values).

Washout period: [In a cross-over trial] The stage after the first treatment is withdrawn, but before the second treatment is started. The washout period aims to allow time for any active effects of the first treatment to wear off before the new one gets started.

Appendix B. Search strategy for Update 2

Medline, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and Database of Abstracts of Reviews of Effects were searched again in December 2009 using the following search strategies to identify additional citations.

Database: Ovid MEDLINE(R) <1950 to September Week 2 2009>
Search Strategy:
---
1 (Cetirizine or zyrtec).mp. (1173)
2 (Loratadine or Claritin).mp. (1048)
3 (Fexofenadine or Allegra).mp. (514)
4 (Desloratadine or Clarinex).mp. (307)
5 (Levocetirizine or Xyzal).mp. (166)
6 (Azelastine or Astelin or Astepro).mp. (524)
7 (Olopatadine or Patanase).mp. (196)
8 1 or 2 or 3 or 4 or 5 or 6 or 7 (2950)
9 limit 8 to (english language and humans) (2136)
10 from 9 keep 1-2136 (2136)

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <3rd Quarter 2009>
Search Strategy:
---
1 (Cetirizine or zyrtec).mp. (609)
2 (Loratadine or Claritin).mp. (541)
3 (Fexofenadine or Allegra).mp. (234)
4 (Desloratadine or Clarinex).mp. (200)
5 (Levocetirizine or Xyzal).mp. (115)
6 (Azelastine or Astelin or Astepro).mp. (204)
7 (Olopatadine or Patanase).mp. (94)
8 1 or 2 or 3 or 4 or 5 or 6 or 7 (1598)
9 from 8 keep 1-1598 (1598)

Database: EBM Reviews - Cochrane Database of Systematic Reviews <3rd Quarter 2009>
Search Strategy:
---
1 (Cetirizine or zyrtec).mp. (11)
2 (Loratadine or Claritin).mp. (10)
3 (Fexofenadine or Allegra).mp. (7)
4 (Desloratadine or Clarinex).mp. (2)
5 (Levocetirizine or Xyzal).mp. (4)
6 (Azelastine or Astelin or Astepro).mp. (4)
7 (Olopatadine or Patanase).mp. (0)

8 1 or 2 or 3 or 4 or 5 or 6 or 7 (14)
9 from 8 keep 1-14 (14)

Database: EBM Reviews - Database of Abstracts of Reviews of Effects <3rd Quarter 2009>
Search Strategy:
---
1 (Cetirizine or zyrtec).mp. (7)
2 (Loratadine or Claritin).mp. (10)
3 (Fexofenadine or Allegra).mp. (5)
4 (Desloratadine or Clarinex).mp. (1)
5 (Levocetirizine or Xyzal).mp. (1)
6 (Azelastine or Astelin or Astepro).mp. (6)
7 (Olopatadine or Patanase).mp. (0)
8 1 or 2 or 3 or 4 or 5 or 6 or 7 (14)
9 from 8 keep 1-14 (14)
10 from 9 keep 1-14 (14)

Appendix C. Methods used to assess quality of studies

Study quality was objectively assessed using predetermined criteria for internal validity, which were based on a combination of the US Preventive Services Task Force and the National Health Service Centre for Reviews and Dissemination[24, 25] criteria.

All included studies, regardless of design, were assessed for quality and assigned a rating of "good," "fair," or "poor". Studies that have a fatal flaw were rated poor quality. A fatal flaw was the failure to meet combinations of criteria that may be related to indicate the presence of bias. An example would be inadequate procedures for allocation concealment combined with important differences between groups in prognostic factors at baseline and following randomization. Studies that meet all criteria were rated good quality; the remainders were rated fair quality. As the fair-quality category was broad, studies with this rating varied in their strengths and weaknesses: The results of some fair-quality studies were *likely* to be valid, while others were only *possibly* valid. A poor-quality trial was not valid; the results were at least as likely to reflect flaws in the study design as a true difference between the compared drugs.

Criteria for assessing applicability (external validity) are also listed, although they were not used to determine study quality.

Systematic Reviews

1. Does the systematic review report a clear review question and clearly state inclusion and exclusion criteria for primary studies?

A good-quality review focuses on a well-defined question or set of questions, which ideally refer to the inclusion/exclusion criteria by which decisions are made about whether to include or exclude primary studies. These criteria would relate to the four components of study design, indications (patient populations), interventions (drugs), and outcomes of interest. A good-quality review also includes details about the process of decision-making, that is, 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 find all relevant research?

If details of electronic database searches and other identification strategies are given, the answer to this question usually is yes. Ideally, search terms, date restrictions, and language restrictions are presented. In addition, descriptions of hand-searches, attempts to identify unpublished material, and any contact with authors, industry, or research institutes should be provided. The appropriateness of the database(s) searched by the authors should also be considered. For example, if only MEDLINE is searched for a systematic review about health education, then it is unlikely that all relevant studies will be located.

3. Is the validity of included studies adequately assessed?

If the review systematically assesses the quality of primary studies, it should include an explanation of the basis for determining quality (for example, method of randomization, whether outcome assessment was blinded, whether analysis was on an intention-to-treat basis) and the process by which assessment is carried out (that is, how many reviewers are involved, whether the assessment is independent, and how discrepancies between reviewers are resolved). Authors

may have used either a published checklist or scale or one that they designed specifically for their review.

4. Is sufficient detail of the individual studies presented?

The review should show that the included studies are suitable to answer the question posed and that a judgment on the appropriateness of the authors' conclusions can be made. It is usually considered sufficient if a paper includes a table giving information on the design and results of individual studies or includes a narrative description of the studies. If relevant, the tables or text should include information on study design, sample size for each study group, patient characteristics, 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 (for example, according to sample size or according to inverse of the variance) so that studies that are thought to provide the most reliable data have greater impact on the summary statistic.

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 number, birth date, or day of week

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

Inferior approaches to concealment of randomization:

Use of alternation, case record number, birth date, or day of week

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 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 (that is, 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 follow-up or overall high loss to follow-up? (Study should give number for each group.)

Nonrandomized studies

Assessment of Internal Validity

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

2. Was there important differential loss to follow-up or overall high loss to follow-up? (Numbers should be given for 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 unbiased and accurate ascertainment of events (that is, by independent ascertainers using a validated ascertainment technique)?

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

7. Was the duration of follow-up reasonable for investigated events?

References

1. Center for Reviews and Dissemination, University of York, 2001. Undertaking systematic reviews of research on effectiveness: CRD's guidance for those carrying out or commissioning reviews. *CRD Report Number 4(2nd edition).*

2. Harris RP, Helfand M, Woolf SH. Current methods of the US Preventive Services Task Force: a review of the process. *American Journal of Preventive Medicine.* 2001;20(3 Suppl):21-35.

Appendix D. Excluded studies in Update 2

The following full-text publications were considered for inclusion but failed to meet the criteria for this report. See previous versions of the report on the DERP website for studies excluded previously.

2=outcome not included, 3=intervention not included, 4=population not included, 5=publication type not included, 6=study design not included, 7=study not obtainable.

Excluded studies	Exclusion code #
Head-to-head trials	
Day J, Briscoe M, Rafeiro E, et al. Comparative efficacy of cetirizine and fexofenadine for seasonal allergic rhinitis, 5-12 hours postdose, in the environmental exposure unit. Allergy Asthma Proc. 2005;26(4):275-282.	6
Day JH, Briscoe MP, Rafeiro E, Hewlett D, Chapman D, Kramer B. Randomized double-blind comparison of cetirizine and fexofenadine after pollen challenge in the Environmental Exposure Unit: duration of effect in subjects with seasonal allergic rhinitis. Allergy Asthma Proc. 2004;25(1):59-68.	6
Kaiser HB, Gopalan G, Chung W. Loratadine provides early symptom control in seasonal allergic rhinitis. Allergy & Asthma Proceedings. 2008;29(6):654-658.	6
Meltzer EO, Garadi R, Laforce C, et al. Comparative study of sensory attributes of two antihistamine nasal sprays: olopatadine 0.6% and azelastine 0.1%. Allergy & Asthma Proceedings. 2008;29(6):659-668.	2
Pipkorn P, Costantini C, Reynolds C, et al. The effects of the nasal antihistamines olopatadine and azelastine in nasal allergen provocation. Ann Allerg Asthma Im. 2008;101(1):82-89.	6
Sanofi A. Single center, randomized, double-blind, crossover study comparing the effects of single-dose fexofenadine HCl 180 mg, cetirizine 10 mg, and placebo on cognitive performance in naval flight personnel [completed]. ClinicalTrials.gov [accessed. 2008;31.	4
Ucb. Five parallel groups, exploratory clinical trial to compare the efficacy of single dose levocetirizine 2.5 and 5 mg, cetirizine 5 mg and 10 mg to placebo in reducing symptoms of SAR in sensitive subjects exposed to ragweed pollen in a EEU [completed]. ClinicalTrials.gov.	7
Active- control trials	
Day JH, Briscoe M, Widlitz MD. Cetirizine, loratadine, or placebo in subjects with seasonal allergic rhinitis: effects after controlled ragweed pollen challenge in an environmental exposure unit. J Allergy Clin Immunol. 1998;101(5):638-645.	6
Day JH, Briscoe MP, Clark RH, Ellis AK, Gervais P. Onset of action and efficacy of terfenadine, astemizole, cetirizine, and loratadine for the relief of symptoms of allergic rhinitis. Ann Allerg Asthma Im. 1997;79(2):163-172.	6
Horak F, Zieglmayer PU, Zieglmayer R, Kavina A, Lemell P. Levocetirizine has a longer duration of action on improving total nasal symptoms score than fexofenadine after single administration. Br J Clin Pharmacol. 2005;60(1):24-31.	6
Meltzer EO, Weiler JM, Widlitz MD. Comparative outdoor study of the efficacy, onset and duration of action, and safety of cetirizine, loratadine, and placebo for seasonal allergic rhinitis. J Allergy Clin Immunol. 1996;97(2):617-626.	6
Passalacqua G, Guerra L, Compalati E, et al. Comparison of the effects in the nose and skin of a single dose of desloratadine and levocetirizine over 24 hours. Int Arch Allergy Immunol. 2004;135(2):143-147.	6

Excluded studies	Exclusion code #
Weiler JM, Bloomfield JR, Woodworth GG, et al. Effects of fexofenadine, diphenhydramine, and alcohol on driving performance. A randomized, placebo-controlled trial in the Iowa driving simulator. Ann Intern Med. 2000;132(5):354-363.	6
Active and placebo controlled trial	
Sanofi A. Single-center, double-blind, randomized , parallel study comparing onset of action, efficacy & safety of a single-dose of fexofenadine HCl 180 mg vs montelukast Na 10 mg & placebo in treating seasonal allergic rhinitis subjects in an allergen exposure unit (study I) [completed]. ClinicalTrials.gov	6
Placebo controlled trials	
Banov CH, Lieberman P, Vasomotor Rhinitis Study G. Efficacy of azelastine nasal spray in the treatment of vasomotor (perennial nonallergic) rhinitis. Ann Allerg Asthma Im. 2001;86(1):28-35.	4
Chervinsky P, Philip G, Malice MP, et al. Montelukast for treating fall allergic rhinitis: effect of pollen exposure in 3 studies. Ann Allerg Asthma Im. 2004;92(3):367-373.	3
Gehanno P, Deschamps E, Garay E, Baehre M, Garay RP. Vasomotor rhinitis: clinical efficacy of azelastine nasal spray in comparison with placebo. Orl; Journal of Oto-Rhino-Laryngology & its Related Specialties. 2001;63(2):76-81.	5
GlaxoSmithKline. A randomized, double blind, placebo controlled study for evaluation of the efficacy and safety of cetirizine dry syrup (CTZ DS) (2.5 mg or 5 mg twice a day) in children (2 years of age or older but under 15 years old) suffering from perennial allergic rhinitis. [completed]. ClinicalTrials.gov	7
Hyo S, Fujieda S, Kawada R, Kitazawa S, Takenaka H. The efficacy of short-term administration of 3 antihistamines vs placebo under natural exposure to Japanese cedar pollen. Ann Allerg Asthma Im. 2005;94(4):457-464.	6
Institut fur Atemwegsforschung Gmb H. Placebo controlled pilot study on the efficacy of levocetirizine 5 mg in reducing symptoms, airway resistance, and sleep impairment in patients with persistent allergic rhinitis [completed]. ClinicalTrials.gov.	7
Klimek L. Cintinuous intake of levocetirizine for 6 months has no relevant effect on laboratory values: the XPERT trial. 15th Annual Congress of the European Respiratory Society (ERS). 2005;17-21 September,. 2005. Copenhagen, Denmark. European Respiratory Journal 26(49 (Suppl)):370s.	5
Lee DK, Gray RD, Robb FM, Fujihara S, Lipworth BJ. A placebo-controlled evaluation of butterbur and fexofenadine on objective and subjective outcomes in perennial allergic rhinitis. Clin Exp Allergy. 2004;34(4):646-649.	6
Meltzer E, Banov C, Halverson P, Weiler J, Woehler T, Hemsworth G. Comparison of azelastine, clemastine fumarate and placebo for treatment of perennial allergic rhinitis. Ann Allergy. 1990;64(78).	4
Patel P, Philip G, Yang W, et al. Randomized, double-blind, placebo-controlled study of montelukast for treating perennial allergic rhinitis. Ann Allerg Asthma Im. 2005;95(6):551-557.	3
Pearlman DS, Grossman J, Meltzer EO. Histamine skin test reactivity following single and multiple doses of azelastine nasal spray in patients with seasonal allergic rhinitis. Ann Allerg Asthma Im. 2003;91(3):258-262.	2
Sanofi A. A single-center, randomized, double-blind, placebo-controlled, two-way crossover study designed to evaluate the efficacy of fexofenadine HCl 180 mg for preventing and controlling cat allergy symptoms [completed]. ClinicalTrials.gov	7

Excluded studies	Exclusion code #
Satish U, Streufert S, Dewan M, Voort SV. Improvements in simulated real-world relevant performance for patients with seasonal allergic rhinitis: impact of desloratadine. Allergy. 2004;59(4):415-420.	6
Schering Plough, Double-blind, randomized, placebo-controlled, parallel-group, multicenter/multinational, efficacy and safety study of desloratadine 5 mg in the treatment of subjects with allergic rhinitis who meet the criteria for intermittent allergic rhinitis (IAR) [completed]. ClinicalTrials.gov	6
Schering Plough, Double-blind, randomized, placebo-controlled, parallel-group, multicenter/multinational, efficacy and safety study of desloratadine 5 mg in the treatment of subjects with allergic rhinitis who meet the criteria for persistent allergic rhinitis (PER) [completed]. ClinicalTrials.gov	6
Siebenhaar F, Degener F, Zuberbier T, Martus P, Maurer M. High-dose desloratadine decreases wheal volume and improves cold provocation thresholds compared with standard-dose treatment in patients with acquired cold urticaria: a randomized, placebo-controlled, crossover study. Journal of Allergy & Clinical Immunology. 2009;123(3):672-679.	6
Simons FE, Johnston L, Simons KJ. Clinical pharmacology of the H1-receptor antagonists cetirizine and loratadine in children. Pediatric Allergy & Immunology. 2000;11(2):116-119.	6
Torkildsen GL, Gomes P, Welch D, Gopalan G, Srinivasan S. Evaluation of desloratadine on conjunctival allergen challenge-induced ocular symptoms. Clin Exp Allergy. 2009;39(7):1052-1059.	4
Ucb. A multi-center, randomized, double-blind, placebo-controlled, parallel-A multi-center, randomized, double-blind, placebo-controlled, parallel-group study evaluating the efficacy and impact on health-related quality of life of levocetirizine 5 mg once daily given for 2 weeks in subjects 18 yr of age and older with seasonal allergic rhinitis [completed]. ClinicalTrials.gov.	5
Ucb. A multi-center, randomized, double-blind, placebo-controlled, parallel-group study evaluating the efficacy and impact on health-related quality of life of levocetirizine 5 mg once daily given for 2 weeks in subjects 18 yr of age and older with seasonal allergic rhinitis [completed]. ClinicalTrials.gov.	5
Ucb. A multi-center, randomized, double blind, placebo controlled parallel group study of the safety of levocetirizine dihydrochloride oral liquid formulation b.i.d dosing in children aged 1 to < 6 years suffering from allergic rhinitis or chronic urticaria of unknown origin [completed]. ClinicalTrials.gov.	5

Appendix E. Reporting of adverse events

Adverse events from head-to-head and active control trials in adults (Original Report)[a]

Author Year	Adverse events	Total withdrawals	Withdrawals from AEs
Head-to-head trials			
Ciprandi 1997[29] L: loratadine 10 mg qd C: cetirizine 10 mg qd	No significant AEs reported	Total: 0	0
Hampel 2003[31] 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[32] 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[33] 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[36] 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[74] 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 control trials			
Frolund 1990[72] 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[87] C: cetirizine 10mg qd H: hydroxyzine 25 mg tid	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%

Author Year	Adverse events	Total withdrawals	Withdrawals from AEs
P: placebo			
Berger 2003[27] 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)
Dockhorn 1987[56] 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≤0.01) More sedation in C: C: 22% L: 6% (p≤0.01)	NR	NR

[a]Only fair- and good-quality studies are presented in the table. Poor-quality studies are listed in Appendix F.
Abbreviations: bid, twice daily; mg, milligrams; NSD, no significant difference; NR, not reported; qd, once daily; tid, 3 times daily.

Adverse events from studies in adults (includes only studies from update 2003-2005)[a]

Type of AE	Adverse event	Cetirizine	Fexofenadine	Loratadine
NEUROLOGICAL				
MAJOR				
MINOR	Fatigue/ Asthenia	6.8% vs. rupatadine 10.5%, NSD[52]		6.0%; vs. rupatadine 10 mg 10.7%; vs. rupatadine 20 mg 11.7%: NSD[55]
	Headache	19.7% vs. 15.3% rupatadine, NSD[52]	2.2% vs. cetirizine 0%, NSD[75] 5% vs. placebo 3%[79]	18%; vs. fluticasone 17%[168] 12.1%; vs. rupatadine 10 mg 23.4%; vs. rupatadine 20 mg 14.3%, NSD[55] 5.8%; vs. ebastine 10 mg 4.3%; vs. ebastine 20 mg 3.2%; vs. placebo 4.3%[53]
	Somnolence	2.6% vs. azelastine 1.3%[30] 8.5% vs. rupatadine 9.6%, NSD[52] Drowsiness: 7.7% vs. fexofenadine 4.5%, NSD[75]	Drowsiness: 4.5% vs. cetirizine 7.7%, NSD[75]	7.8%; vs. rupatadine 10 mg 12.5%; vs. rupatadine 20 mg 25%, significant but *P* value not given[55] 0%; vs. ebastine 10 mg 1.6%; vs. ebastine 20mg 2.7%; vs. NR placebo[53]

Type of AE	Adverse event	Cetirizine	Fexofenadine	Loratadine
	Unspecified			0% vs. ebastine 4.6% vs. placebo 0%[113]
GASTROINTESTINAL				
MAJOR				
MINOR	Abdominal pain	0% vs. fexofenadine 2.2%, NSD[75]	2.2% vs. cetirizine 0%, NSD[75]	
	Constipation	5.8% vs. fexofenadine 0 %, NSD[75]	0% vs. 5.8% cetirizine, NSD[75]	
	Dry mouth			1.7% vs. rupatadine 10 mg 1.8% vs. rupatadine 20 mg 3.6%, NSD[55]
	Epigastric pain	3.8% vs. fexofenadine 0%, NSD[75]	0% vs. 3.8% cetirizine, NSD[75]	
	Unspecified			0% vs. ebastine 3.2% vs. placebo 3.5%[113]
HEMATOLOGICAL				
MAJOR				
MINOR	Abnormalities in complete blood count			
RESPIRATORY				
MAJOR			1 patient had asthma requiring hospitalization[79]	
MINOR	Cough	3.8% vs. fexofenadine 0%, NSD[75]	0% vs. 3.8% fexofenadine, NSD[75]	4.3% vs. rupatadine 10 mg 8.0% vs. rupatadine 20 mg 5.4%[55]
	Epistaxis	<1% vs. azelastine 2.0%[30]		
	Nasal discomfort	<1% vs. azelastine 1.3%[30]		
	Pharyngitis			1.7% vs. rupatadine 10 mg 7.1% vs. rupatadine 20 mg 4.5%, NSD[55]
	Unspecified			12.2% vs. ebastine 10 mg 8.5% vs. ebastine 20 mg 7.5% vs. placebo 10.2%[53]
CARDIAC				
MAJOR	QT interval		No clinically relevant ECG changes vs. placebo[79]	Prolonged QTc: 1.6%; vs. ebastine 10 mg 3.2%; vs. ebastine 20 mg 2.2%; vs. placebo 0.5%[53] Prolonged QTc: 3.6%; vs. ebastine 20 mg 3.9%; vs. placebo 5.6%[113]
MINOR	Unspecified			2.5%; vs. ebastine 2.8%; vs. placebo

Type of AE	Adverse event	Cetirizine	Fexofenadine	Loratadine
				4.2%[113]
OTHER				
MAJOR	Back pain			4.3%; vs. rupatadine 10 mg 3.6%; vs. rupatadine 20 mg 4.5%, NSD[55]
MINOR	Bitter taste	<1% vs. azelastine 3.3%[30]		
	Feet swelling	0% vs. 2.2% fexofenadine, NSD[75]	2.2% vs. cetirizine 0%, NSD[75]	
	Hypospadias			OR of hypospadias with loratadine exposure: 1.29 (0.62-2.68)[167] Use of nonsedating antihistamines, including loratadine, OR: 1.33 (0.73-2.40)[167]

[a] Only fair- and good-quality studies are presented in the table. Poor-quality studies are listed in Appendix F.
Abbreviations: mg, milligrams; NR, not reported; NSD, no significant difference; OR, odds ratio
QT, cardiac output; QTc, corrected QT interval for heart rate.
There were no data on desloratadine identified in update 1.

Adverse events from studies in children (Original Report and Update 1)[a]

Type of AE	Adverse event	Cetirizine	Desloratadine	Fexofenadine	Loratadine
NEUROLOGICAL					
MAJOR		Somnolence and irritability (1 patient, led to withdrawal)[110]			
MINOR	Behavioral screening	NSD vs. placebo[117, 147]			
	Fatigue	4.0% vs. chlorpheniramine 6.3% [101] 5.3% vs. placebo 0%, NSD[109] 5.9% vs. placebo 7.5%[104]			
	Headache	6.3% vs. chlorpheniramine 0%[101] 0% vs. placebo 6.3%, NSD[109] 15.1% vs. placebo 19.7%[99] 3.2% vs. placebo 1.6%[98] 15% vs. placebo 18.8%[149]	1.8 vs. placebo 5.4% (2-5 years)[156] 1.7 vs. placebo 6.7% (6-11 years)[156]	1-2% in treatment and placebo groups[144]	25% vs. fluticasone 42%[103]
	Somnolence	5.5% vs. placebo 0%[95] NSD vs.			0% vs. dexchlorpheniramine 4.3%[102]

Type of AE	Adverse event	Cetirizine	Desloratadine	Fexofenadine	Loratadine
		placebo[117, 147] 21.4% vs. placebo 30.2%[148] 1/38 patients withdrew due to somnolence vs. 0 in loratadine group[110]			3% vs. placebo 5%, NSD[169] 0.5 vs. placebo 1.0%, NSD[155]
	Insomnia	23.8% vs. placebo 44.2%[148]			0 vs. placebo 1.0%, NSD[155]
	Irritability				0 vs. placebo 0.5% , NSD[155]
	Nervousness	28.6% vs. placebo 44.2%[148]			
	Vertigo	1.6% vs. placebo 0%[98]			
GASTROINTESTINAL					
MAJOR					
MINOR	Abdominal pain	9.6% vs. chlorpheniramine 4.8%[101] 9.4% vs. placebo 4.5%[99] 9.3% vs. placebo 4.3%[149]			
	Abnormal liver function	9.4% vs. placebo 0%[104] NSD vs. placebo in blood chemistry[117, 147]			
	Dry mouth	1.6% vs. placebo 0%[98]			
	Increased appetite	1.6% vs. placebo 0%[98]			
	Nausea	1.6% vs. chlorpheniramine 0%[101]			
HEMATOLOGICAL					
MAJOR				Neutropenia (asymptomatic) in 1 child[100]	
MINOR	Abnormalities in complete blood count	NSD vs. placebo[107] Leucocytosis: 5% vs. placebo 7%[104] NSD vs. placebo[117, 147]			

Type of AE	Adverse event	Cetirizine	Desloratadine	Fexofenadine	Loratadine
CARDIAC					
MAJOR	QT interval	NSD vs. placebo (2 week follow-up)[99] NSD vs. placebo[117, 147] NSD QT cetirizine vs. placebo[148] NSD QTc vs. placebo[149]	NSD rate, PR, QRS or QT vs. placebo[156]	NSD QTc vs. placebo[92]	
RESPIRATORY					
MAJOR					
MINOR	Coughing				3% vs. placebo 5%, NSD[169]
	Epistaxis	7.1% vs. placebo 4.3%[99] 7.1% vs. placebo 4.3%[149]			4.8% (moderate) vs. dexchlorpheniramine 0%[102] 4% vs. fluticasone 7%[103]
	Pharyngitis	10.1% vs. placebo 13.6%[99] 1.6% vs. placebo 4.9%[98] 10.0% vs. placebo 13.0%[149]			10% vs. fluticasone 16%[103] 18.8% vs. 18.1%, NSD[155]
OTHER					
MAJOR	Accidental overdose	2 children vs. 8 placebo[117, 147]			
MINOR	Rash	3.2% vs. placebo 0%[98] 1/40 patients withdrew due to rash[110]			
	Mean increase height and weight	NSD vs. placebo[117, 147]			
	Fever		5.5 vs. placebo 5.4% (2-5 years)[156] 5.5 vs. placebo 5.4% (6-11 years)[156]		3% vs. placebo 5%, NSD[169]

[a] Only fair- and good-quality studies are presented in the table. Poor-quality studies are listed in Appendix F.
Abbreviations: NSD, no significant difference; QT, cardiac output; QTc, corrected QT interval for heart rate.

Appendix F. Poor-quality studies

Original Report and Update 1

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

Abbreviations: bid, twice daily; CIU, chronic idiopathic urticaria; db, double blind; PAR, perennial allergic rhinitis; pts, patients; qd, once daily; QoL, quality-of-life; mc, SAR, seasonal allergic rhinitis; tid; 3 times daily; wks, weeks.

Update 2

Amat P, Novella A, Roma J, Valero A, Lluch M, Malet A. Treatment of perennial allergic rhinitis with cetirizine. *Allergol Immunopathol.* 1992;20(4):139-143.
Berlin JM, Golden SJ, Teets S, Lehman EB, Lucas T, Craig TJ. Efficacy of a steroid nasal spray compared with an antihistamine nasal spray in the treatment of perennial allergic rhinitis. *J Am Osteopath Assoc.*2000;100(7 Suppl):S8-13.
Bruttmann G, Arendt C, Bernheim J. Double-blind, placebo controlled comparison of cetirizine 2HC1 and terfenadine in atopic perennial rhinitis. *Acta Therapeutica.*1989;15(1):99-109.
Ciprandi G, Cirillo I, Vizzaccaro A, et al. Desloratadine and levocetirizine improve nasal symptoms, airflow, and allergic inflammation in patients with perennial allergic rhinitis: a pilot study. *International Immunopharmacology.*2005;5(13-14):1800-1808.
Dorow P, Aurich R, Petzold U. Efficacy and tolerability of azelastine nasal spray in patients with allergic

rhinitis compared to placebo and budesonide. *Arzneimittelforschung.*1993;43(8):909-912.

Hampel FC, Jr., Ratner PH, Amar NJ, et al. Improved quality of life among seasonal allergic rhinitis patients treated with olopatadine HCl nasal spray 0.4% and olopatadine HCl nasal spray 0.6% compared with vehicle placebo. *Allergy Asthma Proc.*2006;27(3):202-207.

Mahmoud F, Arifhodzic N, Haines D, Novotney L. Levocetirizine modulates lymphocyte activation in patients with allergic rhinitis. *Journal of Pharmacological Sciences.*2008;108(2):149-156.

Potter PC, Paediatric Levocetirizine Study G. Efficacy and safety of levocetirizine on symptoms and health-related quality of life of children with perennial allergic rhinitis: a double-blind, placebo-controlled randomized clinical trial. *Ann Allergy Asthma Immunol.*2005;95(2):175-180.