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Article type : Original Article

**Title:** Newer-generation antihistamines and the risk of adverse events in children: a systematic review

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**Running title:** Antihistamines and risk of adverse events

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/PAI.13522

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Accepted Article

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**Word count:** 2704

**# Figures:** 1

**# Tables:** 4

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**Potential conflict of interests related to the manuscript content:** None to declare

**Financial support:** None

## Abstract

**Background:** H1-antihistamines (AHs) are widely used for the treatment of allergic diseases, being one of the most commonly prescribed classes of medications in pediatrics. Newer-generation AHs are associated with fewer adverse effects compared to first-generation. However, their relative harms in the pediatric population still need scrutiny.

**Methods:** We performed a systematic review of randomized controlled trials (RCTs) which included comparisons of safety parameters between an orally administered newer-generation AH with another AH (first- or second- generation), montelukast or placebo in children aged≤12 years. We searched MEDLINE and CENTRAL, independently extracted data on study population, interventions, adverse events (AEs) and treatment discontinuations, and assessed the methodological quality of the included RCTs using the Cochrane's risk of bias tool.

**Results:** Fourty-five RCTs published between 1989 and 2017 met eligibility criteria. The majority of RCTs included school-aged children with allergic rhinitis and had a follow-up period of up to a month. Four RCTs reported serious AEs in patients receiving a newer-generation AH, but only two patients experienced a possibly drug-related serious AE. The occurrence of AEs, drug-related AEs and treatment discontinuations due to AEs varied between RCTs. Most AEs reported were of mild intensity. Indirect evidence indicates that cetirizine is more sedating than the other newer-generation AHs.

**Conclusion:** Our findings confirm that newer-generation AHs have a favorable safety and tolerability profile. However, we could not draw firm conclusions regarding the comparative safety profile of the newer-generation AHs due to the paucity of head-to-head RCTs, variation in definitions and reporting of AEs, and short follow-up duration.

**Keywords:** antihistamines, children, pediatrics, adverse events, systematic review

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**Key Message:** This comprehensive systematic review examines the state of evidence regarding the relative harms of newer-generation antihistamines in children ≤ 12 years old. Although in general no clinically meaningful differences in the occurrence of AEs were observed in the majority of RCTs, the existing evidence indicates that there are intra-class differences, which need to be taken into account in the selection of the most appropriate agent for each patient.

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# Introduction

Allergic conditions affect a large number of children worldwide and have considerable socioeconomic burdens for both the children and their families[1]. It is estimated that approximately 40% of children suffer from allergic rhinitis, whereas almost half of the school-age population is sensitized to one or more common allergens, and these numbers are expected to rise following a steady upward trend in the last decades[1,2].

$H_1$-antihistamines are widely used for the treatment of allergic diseases, being one of the most commonly prescribed classes of medications in the pediatric population[3]. They mainly act in the respiratory, gastrointestinal and vascular smooth muscle tissues by preventing their constriction and in the salivary and lacrimal gland tissues by decreasing the histamine induced secretion[4]. More than 45 antihistamines are currently available[5] and they are generally subdivided into two groups: first- and newer-generation antihistamines. First-generation antihistamines are still widely used in clinical practice worldwide despite the relative paucity of data regarding their use in children. Newer-generation antihistamines are generally associated with fewer adverse effects (i.e., behavioral changes, anticholinergic properties, cardiotoxicity/QT prolongation) compared to first-generation antihistamines due to their higher selectivity for the H1-receptor and their limited blood-brain barrier passage and therefore are the preferred medications for the treatment of allergic diseases[6,7]. In adults, cetirizine and levocetirizine seem to be more sedating than loratadine, desloratadine and fexofenadine[8], whereas in a review of inter-drug differences using proportional impairment ratios, minor differences were observed in the likely impairing potential of newer-generation antihistamines[9]. In children, some newer-generation antihistamines are approved from the age of 6 months and most of them from the age of 2 years[10]. However, the relative harms of the newer-generation antihistamines have not been established in the pediatric population.

Therefore, we did a systematic review of randomized controlled trials (RCTs) that compared the safety of newer antihistamines with any other antihistamine, montelukast or placebo in children ≤12 years old.

# Methods

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## Data sources and search

We searched MEDLINE and CENTRAL from inception through September 2020. Our search strategy included terms suggestive of the intervention of interest (newer-generation antihistamines) and the age group of interest (pediatric patients ≤ 12 years old). Details of our search strategy can be found in the Appendix.

## Study selection

We included peer-reviewed publications of RCTs if they fulfilled all of the following criteria: comparison of a newer-generation antihistamine (bilastine, cetirizine, desloratadine, fexofenadine, levocetirizine, loratadine and rupatadine) with another antihistamine (first- or newer- generation, except for terfenadine/astemizole), montelukast or placebo, in children aged ≤ 12 years; oral administration of the interventions in any dose and for at least one week (single-dose and provocation challenge studies were excluded in order to better reflect everyday clinical practice); reporting of adverse events; and English-language publication.. The primary outcome of interest was the number of patients with at least one adverse event. Secondary outcomes of interest comprised the type of adverse events, adverse events related to study medication according to the original investigators, serious adverse events and treatment discontinuations due to adverse events. Two investigators (M.D. and E.S.) independently screened the titles and abstracts of the citations for potentially relevant publications using Abstrackr[11]. The same two investigators retrieved and screened the full-text of potentially relevant articles. Any disagreement was resolved with the assistance of a third investigator (M.M.).

## Data extraction

Two investigators (M.D. and E.S.) independently extracted data from the included publications. Any disagreement was resolved by a third investigator (M.M.). We extracted data on study design and methods, patient characteristics, interventions, comparators, concomitant medications, adverse events and treatment discontinuations using a standardized extraction form in an Excel® spreadsheet.

## Quality assessment

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We assessed the methodological quality of the included publications using the Cochrane's Collaboration risk of bias tool for RCTs[12]. We assigned a judgement of 'low', 'high' or 'unclear' to every item included in the tool (sequence generation, allocation concealment, patients' blinding, caregivers' blinding, outcome assessors' blinding, attrition, and selective outcome reporting). Studies that reported sufficient information about the implementation of blinding (such as double-blinding and matching capsules) were considered low risk of bias for this specific item, whereas studies that reported only phrases such as "double-blind" had unclear risk of bias. In double-blind studies, the blinding of the outcome assessors was considered adequate if patients reported the occurrence of adverse events. We compared the proportion of patients who discontinued treatment in each group by the chi-square test and a p-value less than 0.1 was indicative of differential loss-to-follow-up and the study was assigned a judgement of 'high risk of bias' for this specific item. Two of three authors (N.T., I.M. and J.P.) independently completed the assessments. Any disagreements were resolved by the addition of a third author (M.M.).

# Results

## Literature search

Figure 1 summarizes our search yield. We screened 2358 citations, we excluded 2249 as irrelevant, and 109 articles were retrieved for full-text review. Finally, we included 45 randomized controlled trials[13-59]. There were two RCTs with data reported in two separate publications each[43&44,48&49].

## Study characteristics

Table 1 summarizes the characteristics of the included studies that were published between 1989 - 2017.

The majority of studies were conducted in Europe and USA. The RCTs included children 6 months to 15 years old with an overall male predominance. Most studies included school-aged children and seven publications included children ≤24 months-old[20,25,27,31,35,43&44]. The most frequent type of condition that required the use of antihistamines was allergic rhinitis[13,14,15, 17-21,,23,24,26,28-30,32-36,39-42,45-52,55-58], followed by chronic idiopathic urticaria[15,20,30,35,38,42] and atopic dermatitis[25,35,37,43,44,54]. The majority of studies did not provide any evidence regarding concomitant medications and ten studies

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reported inclusion of patients with concomitant asthma[16,17,28,33,34,40,47,52-54]. Cetirizine was administered in 22 studies[14,21,26,32,34-36,38,40,45,47-58], loratadine in 10 studies[14,18,31,37,39,42,46-47,59], levocetirizine in 6 studies[19-21,25,28,29], fexofenadine in 4 studies[23,24,33,41], desloratadine in 4 studies[13,16,27,30], rupatadine in 2 studies[16,17] and bilastine in 1 study[15]. In most studies the dose of cetirizine was 0.2 mg/kg twice daily for children less than 2 years old, 2.5 to 5 mg once daily (OD) for children 2-6 years old and 10 mg OD for children 6-12 years old. Loratadine dosing was generally weight-based in the included studies (5 mg OD in children ≤ 30kg and 10 mg OD in children > 30kg). Levocetirizine dose was 1.25 mg OD for children 6-11 months old, 0.125mg/kg OD for children 1-2 years old, 1.25 mg twice daily (BD) for children 1-5 years old and 5 mg OD for children 6-12 years old., The dose of fexofenadine ranged from 15 mg to 60 mg OD, based on age. Desloratadine was administered at a dose of 1mg OD in infants, 1.25 mg OD in children 1-5 years old and 2.5 mg OD in children 6-11 years old. Rupatadine dosing was weight-based, i.e., 2.5 mg OD for children 10-25 kg and 5mg OD for children > 25 kg. Bilastine dose was 10 mg OD for children 2-12 years old. The duration of treatment varied among studies (1-72 weeks). The majority of studies lasted less than a month.

**Assessment of risk of bias**

Table 2 summarizes our risk of bias assessment. Generation of a randomized sequence and allocation concealment were not clearly reported in most RCTs. All but two RCTs reported double-blinding. The other RCTs were open-label[18] and investigator-blinded[59]. One RCT had differential loss to follow-up[24]. One crossover RCT had a washout period of 7 days[34].

**Adverse events and tolerability**

The proportions of patients with adverse events in each RCT are shown in Table 3. Four RCTs did not provide numerical data regarding adverse events[13,22,48&49,53].

**Serious adverse events**

Thirteen RCTs provided data regarding the occurrence of serious adverse events[14,15,19,21,25-29,32,33,36,43&44]. Four RCTs reported serious adverse events in patients receiving a newer-generation antihistamine[15,25,33,43&44], but only two patients experienced a possibly drug-related serious adverse

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event. The first patient received fexofenadine (30mg BD) for 14 days and he experienced mild asymptomatic transient neutropenia, which could also be associated with subclinical infections, according to study authors[33]. The second patient, a 14-month-old toddler, had slightly elevated baseline transaminases levels and 5 weeks after the initiation of cetirizine, the investigators observed a 10-fold increase (AST and ALT >1000 UI/ml)[43&44]. The toddler remained asymptomatic throughout the study period and the transaminases levels returned to normal a month after treatment discontinuation.

**Newer-generation antihistamines in head-to-head RCTs**

Only five RCTs directly compared newer-generation antihistamines[14,17,22,45,47]. In a large RCT[14], the (drug-related) AEs rates were similar in cetirizine and loratadine groups. However, more patients who received loratadine discontinued treatment due to AEs. Cetirizine and loratadine were also compared in a small RCT[47]; no patient experienced a drug-related AE or discontinued treatment. Patients on rupatadine experienced fewer (drug-related) AEs compared to patients on desloratadine; no data were reported regarding treatment discontinuations[16].

**Newer-generation antihistamines *vs.* placebo**

Across all placebo-controlled trials, the proportions of patients with AEs varied. Cetirizine was compared with placebo in 16 RCTs[14,21,26,32,34-36,40,43&44,48&49,50,53,54,56-58]. Overall, the occurrence of adverse events was generally similar in both groups. Half of the RCTs provided information regarding drug-related adverse events[14,26,35,40,43&44,54,56,57]. Drug-related AEs occurred in similar frequencies in treatment groups and in less than 5% of the included patients in RCTs with a large sample size[14,43&44]. The tolerability of cetirizine was comparable to placebo and in eight RCTs no patient discontinued treatment due to AEs in both treatment groups. Loratadine was compared with placebo in seven RCTs[14,22,31,37,39,42,46]. There were no clinically significant differences between groups in the proportion of patients with (drug-related) AEs or treatment discontinuations due to AEs. Levocetirizine and placebo were compared in six RCTs[19,21,23,25,28,29]. The proportions of patients with (drug-related) AEs or treatment discontinuations were similar between groups. Fexofenadine was compared with placebo in four studies[23,24,33,41]. None of them reported any clinically significant difference regarding AEs or treatment discontinuations. Three studies compared the use of desloratadine with placebo[16,27,30] and

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reported slightly lower rates of adverse events in the placebo group. In the largest RCT[27], more patients in the desloratadine group experienced drug-related AEs, but less than 1% of patients discontinued treatment. Rupatadine was compared with placebo in two studies[16,17]. In both studies, the proportions of patients with AEs were similar, however drug-related AEs occurred less frequently in the rupatadine group in one study[16]. No data were available regarding treatment discontinuations. In one RCT, there was no difference between bilastine and placebo in the frequency of AEs, drug-related AEs or discontinuations[15].

**Newer-generation antihistamines *vs.* first generation antihistamines**

Seven studies compared a newer with a first generation antihistamine, i.e., oxatomide, ketotifen, chlorphenamine, dexchlorphenamine and cyproheptadine[18,22,36,38,51,52,59]. Across all RCTs, the proportions of patients with AEs were slightly lower in the newer-generation antihistamines group compared to the first generation antihistamines group. Only a few patients discontinued treatment in both groups.

**Newer-generation antihistamines *vs.* other drugs**

Cetirizine was compared with montelukast in two small RCTs[26,32]. No clinically meaningful differences regarding the occurrence of AEs were reported. No patient discontinued treatment in both RCTs.

**Newer-generation antihistamines in children ≤ 2 years old**

Seven RCTs[20,23,25,27,31,35,43&44] included infants (≥6 months old) or young toddlers. There was no difference in the proportion of patients with AEs between the active treatment and placebo groups (Table 3). However, in two RCTs with stratified randomization based on age, infants who received levocetirizine were more likely to experience an AE compared to children aged 1-5 years[20] and cetirizine-related AEs were generally more frequent in the 6-8 month- than the 9-11 month- age group[35].

**Commonly reported adverse events**

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Adverse events reported in the included RCTs are summarized in Table 4. The most frequently reported AEs included minor neurological, gastrointestinal and respiratory symptoms and specifically somnolence, headache, insomnia, abdominal pain, vomiting, diarrhea and upper respiratory tract infections. Of note, somnolence was more frequently reported by patients in the cetirizine compared with patients in the placebo groups, whereas no difference was observed between patients treated with cetirizine and first-generation antihistamines. In contrast, the other newer-generation antihistamines did not appear more sedating than placebo. In four head-to-head RCTs of cetirizine with loratadine or levocetirizine, the proportions of patients with somnolence were slightly higher in the cetirizine groups, but overall the observed proportions in these RCTs were low[14,21,45,47]. There were no significant differences regarding EEG parameters between any treatment groups in the included RCTs.

# Discussion

In children ≤ 12 years old who received newer-generation antihistamines, the occurrence of AEs, drug-related AEs and treatment discontinuations due to AEs varied between RCTs, though in general, no clinically meaningful differences were observed in the majority of RCTs. Importantly, only two patients experienced a possibly drug-related serious AE and most AEs reported in the RCTs were of mild intensity.

Several systematic reviews have examined the state of evidence regarding the use of antihistamines, but most of them included adults and/or antihistamines withdrawn from the market. International guidelines such as those published by the European Academy of Allergy and Clinical Immunology (EAACI), the Allergic Rhinitis and its Impact on Asthma (ARIA) group and the Global Allergy and Asthma European Network (GA$^2$LEN) recommend the use of newer-generation over first generation antihistamines in an attempt to avoid sedation and performance impairment associated with the latter type of antihistamines[60-62]. Carson and colleagues[8] assessed the efficacy and harms of newer-generation antihistamines in head-to-head, placebo-controlled or non-interventional trials in adults and children with allergic rhinitis or urticaria. They concluded that newer-generation antihistamines were well tolerated in children, with no clinically relevant differences regarding adverse events. However, the included studies in adults suggested that newer-generation antihistamines resulted in

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more sedation compared to placebo and both cetirizine and levocetirizine were more sedating than loratadine or desloratadine. In our study, due to the paucity of head-to-head RCTs, there is only indirect evidence that cetirizine is more sedating than the other newer-generation antihistamines; cetirizine-treated patients experienced somnolence more frequently than placebo-treated patients, whereas no such difference was observed between the remaining newer-generation antihistamines and placebo. In addition, although comparable proportions of patients aged ≤ 2 years treated with either a newer-generation antihistamine or placebo reported the occurrence of AEs, these AEs were more frequently reported in the younger age group.

Our systematic review has several limitations, which need to be considered when interpreting the results. At the individual trial level, most RCTs were not primarily designed to assess safety parameters and therefore no formal statistical comparisons were undertaken. The majority of RCTs had a short follow-up period, did not provide a definition of serious adverse events and used patient-reported AEs, through either interviews at trial visits or diary cards. In addition, data on concomitant medications ordiseases (e.g., asthma) were generally not reported and therefore the provided estimates of the frequency of AEs attributed to newer-generation antihistamines might not be accurate in all RCTs. Of note, the absence of a sufficient number of head-to-head RCTs provides only indirect evidence for the relative safety and tolerability of newer-generation antihistamines. Although the inclusion of RCTs only in the present systematic review provides the highest level of the available evidence, the exclusion of non-interventional studies which may better reflect everyday clinical practice in certain circumstances and have a longer follow-up period, limit our ability to increase the generalizability of our findings (e.g., reports of off-label use, up-dosing schemes or long-term administration). On the other hand, the exclusion of single-dose RCTs, which objectively measure the effect of antihistamines on alertness and psychomotor performance, may have restricted our ability to detect differences of clinical interest. Finally, the observed clinical and methodological heterogeneity (e.g., variation in definitions and monitoring of AEs, administration of antihistamines in patients with different diseases, limited use of validated tools) precluded the quantitative synthesis of the data.

This systematic review investigates the use of newer-generation antihistamines in children. Our findings suggest that these medications have a favorable safety and tolerability profile. However, we could not draw firm conclusions regarding the comparative safety profile of the newer-generation

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antihistamines due to the paucity of head-to-head RCTs. Therefore, in the absence of a compelling evidence base regarding inter-agent differences, other factors unique to pediatrics, should be taken into consideration in the selection of the desired antihistamine, such as taste preference, daily number of doses, volume of dose and safety in cases of overdosing. For example, cetirizine, fexofenadine and levocetirizine should be administered twice daily for optimum concentration in plasma, which may affect adherence compared to once daily dosing (10). Well-designed head-to-head RCTs of sufficient duration and with use of validated instruments to assess safety parameters important to patients may help with counselling parents on appropriate use, frequency, dosing and possible adverse effects of newer-generation antihistamines.

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**Table 1.** Trial characteristics

| Study, Year (Reference) | Region | Disease type (age range) | Treatment groups | Treatment dose | Treatment duration, weeks | Patients, n | Age, years‡ | Female, % |
|---|---|---|---|---|---|---|---|---|
| Wandalsen et al., 2017 (13) | S. America | PAR (2-12 years) | DLRD | 1.25-2.5mg po OD | 1 | 105 | ND | 45 |
| | | | DCPN | 1-2mg po TD | | 105 | | 46 |
| Nayak et al., 2017 (14) | USA | SAR (6-11 years) | CTZ | 10mg po OD | 2 | 228 | 8.6 | 42.5 |
| | | | LRD | 10mg po OD | | 220 | 8.9 | 42.2 |
| | | | placebo | | | 219 | 8.9 | 46.3 |
| Novak et al., 2016 (15) | Europe, S. America | Allergic rhinoconjuctivitis or chronic urticarial (2-12 years) | BLN | 10 mg po OD | 12 | 260 | 7.5 | 27.3 |
| | | | placebo | | | 249 | 7.4 | 27.8 |
| Potter et al., 2016 (16) | Europe | Chronic spontaneous urticaria (2-11 years) | RPD | 2.5mg po OD (10-25kg), 5mg po OD (>25kg) | 6 | 66 | 5.6 | 56.1 |
| | | | DLRD | standard dose OD | | 71 | 6.1 | 45.1 |
| | | | placebo | | | 69 | 6.1 | 42 |
| Potter et al. 2013 (17) | Europe Africa | PAR (6-11 years) | RPD | 2.5mg po OD (<25kg), 5mg po OD (≥25kg) | 6 | 180 | 8.7 | 41.1 |

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| Study, Year (Reference) | Region | Disease type (age range) | Treatment groups | Treatment dose | Treatment duration, weeks | Patients, n | Age, years‡ | Female, % |
|---|---|---|---|---|---|---|---|---|
| | S. America | | placebo | | | 180 | 8.8 | 38.3 |
| Wu et al., 2012 (18) | Asia | PAR (2-12 years) | LRD | 5-10mg po OD (<30kg,>30kg) | 2 | 30<br>30 | 5.8<br>6.6 | 61.5<br>34.7 |
| | | | CPHD | 2-4mg po TD (<30kg,>30kg) | | | | |
| Marcucci et al., 2011 (19) | Europe | PAR (6-12 years) | LCTZ<br>placebo | ND | 12 | 30<br>30 | 9.73 (total) | 60.0 (total) |
| Hampel et al., 2010 (20) | USA | AR or Chronic urticaria (6-11 months) | LCTZ<br>placebo | 1.25mg po OD | 2 | 45<br>24 | 8.87 months<br>9.03 months | 37.8<br>54.2 |
| | | AR or Chronic urticaria (1-5 years) | LCTZ<br>placebo | 1.25mg po BD | 2 | 114<br>59 | 3.78<br>3.75 | 57.0<br>61.0 |
| Lee et al., 2009 (21) | Europe | PAR (6-12 years) | CTZ<br>LCTZ<br>placebo | 10mg po OD<br>5mg po OD | 12 | 27<br>26<br>27 | 8.19<br>8.79<br>8.12 | 58.0<br>62.5<br>54.0 |
| Ngamphaiboon et al., 2009 (22) | Asia | Recurrent wheezing (<6 years) | LRD<br>KTF | 0.25ml/kg po OD<br>0.25ml/kg po OD | 16 | 27<br>25 | 3.2<br>2.9 | 29.6<br>52.0 |

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| Study, Year (Reference) | Region | Disease type (age range) | Treatment groups | Treatment dose | Treatment duration, weeks | Patients, n | Age, years‡ | Female, % |
|---|---|---|---|---|---|---|---|---|
| | | | placebo | | | 26 | 2.9 | 34.6 |
| Hampel et al., 2007 (23) | USA | AR (6-12 months) | FXD | 15mg po BD | 8 | 58 | 8.8 months | 43.1 |
| | | | FXD | 30mg po BD | | 5 | 10.4 months | 40.0 |
| | | | placebo | | | 69 | ND | 46.3 |
| | | AR (1-2 years) | FXD | 15mg po BD | 8 | 27 | 16.1 months | 48.1 |
| | | | FXD | 30mg po BD | | 103 | 17.9 months | 39.8 |
| | | | placebo | | | 131 | ND | 38.5 |
| Milgrom et al., 2007 (24) | USA | AR (2-5 years) | FXD | 30mg po OD | 2 | 222 | 3.6 | 44.6 |
| | | | placebo | | | 231 | 3.6 | 44.9 |
| Simons et al., 2007 (25) | Canada | AD (12-24 months) | LCTZ | 0.125mg/kg po OD | 72 | 255 | 19.3 | 39.2 |
| | | | placebo | | | 255 | 19.4 | 35.7 |
| Chen et al., 2006 (26) | Taiwan | PAR (2-6 years) | CTZ | 5mg po OD | 12 | 20 | 4.5 | 40.0 |
| | | | MLK | 4mg po OD | | 20 | 4.5 | 45.0 |
| | | | placebo | | | 20 | 4.4 | 55.0 |
| Prenner et al., 2006 (27) | USA, S. America, S. Africa | ND (6-24 months) | DLRD | 1.0mg po OD (<1 yr) 1.25mg po OD (1-2 yrs) | 2 | 131 | 12.6 months | 44.0 |
| | | | placebo | | | 129 | 13.3 months | 53.0 |

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| Study, Year (Reference) | Region | Disease type (age range) | Treatment groups | Treatment dose | Treatment duration, weeks | Patients, n | Age, years‡ | Female, % |
|---|---|---|---|---|---|---|---|---|
| de Blic et al., | Europe | SAR | LCTZ | 5mg po OD | 6 | 89 | 9.9 | 29.2 |
| 2005 (28) | | (6-12 years) | placebo | | | 88 | 9.9 | 38.6 |
| Potter et al., | Africa | PAR | LCTZ | 5mg po OD | 4 | 154 | 9.9 | 35.7 |
| 2005 (29) | | (6-12 years) | placebo | | | 152 | 9.9 | 42.8 |
| Bloom et al., | USA | AR or CIU | DLRD | 1.25mg po OD | 2 | 55 | 3.5 | 44.0 |
| 2004 (30) | | (2-5 years) | placebo | | | 56 | 3.4 | 45.0 |
| | | AR or CIU | DLRD | 2.5mg po OD | 2 | 60 | 7.9 | 48.0 |
| | | (6-11 years) | placebo | | | 60 | 8.5 | 65.0 |
| Grimfeld et al., | Europe, S. Africa, | Rhinitis, rhinopharyngitis, | LRD | 2.5mg po OD (≤2 yrs) | 52 | 204 | 23.9 months | 35.8 |
| 2004 (31) | Asia, | acute otitis media, | | 5mg po OD (>2 yrs) | | | | |
| | C. and S. America | laryngitis or bronchitis | | | | | | |
| | | (12-30 months) | | | | | | |
| | | | placebo | | | 208 | 24 months | 42.0 |
| Hsieh et al., | Taiwan | PAR | CTZ | 10mg po OD | 12 | 21 | 8.1 | 40.0 |
| 2004 (32) | | (6-12 years) | MLK | 5mg po OD | | 21 | 8.2 | 35.0 |
| | | | placebo | | | 22 | 8.1 | 45.0 |

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| Study, Year (Reference) | Region | Disease type (age range) | Treatment groups | Treatment dose | Treatment duration, weeks | Patients, n | Age, years‡ | Female, % |
|---|---|---|---|---|---|---|---|---|
| Wahn et al., 2003 (33) | Europe, Africa, USA, Australia | SAR (6-11 years) | FXD<br>placebo | 30mg po BD | 2 | 464<br>471 | 8.8<br>8.8 | 40.0<br>33.5 |
| Segal et al., 2003 (34) | USA | SAR (6-11 years) | CTZ<br><br>placebo | 5mg po OD (<25kg),<br>10mg po OD (≥25kg) | 2 | 86<br>86 | 9.2<br>9.1 | 35.8<br>37.3 |
| Simons et al., 2003 (35) | N. America | AR, urticaria, AD or other disorder that required treatment with $H_1$-antihistamines (6-11 months) | CTZ<br><br><br><br>placebo | 0.25mg/kg po BD | 1 | 42<br><br><br><br>43 | 8.5 months (male),<br>7.9 months (female)<br><br><br><br>8.0 months (male),<br>7.2 months (female) | 50.0<br><br><br><br>53.5 |
| Lai et al., 2002 (36) | Asia | PAR (6-12 years) | CTZ<br>OXD<br>KTF<br>placebo | 10mg po OD<br>1mg po OD<br>1mg po OD | 12 | 20<br>20<br>20<br>20 | 8.2<br>8.3<br>7.4<br>8.3 | 58.7<br>56.6<br>56.2<br>56.2 |

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| Study, Year (Reference) | Region | Disease type (age range) | Treatment groups | Treatment dose | Treatment duration, weeks | Patients, n | Age, years‡ | Female, % |
|---|---|---|---|---|---|---|---|---|
| Chunharas et al., 2002 (37) | Asia | AD (2-12 years) | LRD | 5ml po OD (≤30kg) 10ml po OD (>30kg) | 2 | 24 | 71.0 months | 54.0 |
| | | | placebo | | | 24 | 76.3 months | 50.0 |
| La Rosa et al., 2001 (38) | Europe | Chronic urticaria (2-6 years) | OXD | 25mg po OD | 4 | 31 | ND | ND |
| | | | CTZ | 5mg po OD | | 31 | ND | ND |
| Yang et al., 2001 (39) | Asia | AR (3-12 years) | LRD | 5mg po OD (<30kg), 10mg po OD (≥30kg) | 3 | 30 | 6.0 | 36.4 |
| | | | placebo | | | 30 | 6.6 | 50.0 |
| Ciprandi et al., 2001 (40) | Europe | Perennial rhinoconjunctivitis, mild intermittent asthma (3-10 years) | CTZ | 5mg po OD | 24 | 10 | 6.2 | 30.0 |
| | | | placebo | | | 10 | 6.7 | 20.0 |
| Graft et al., 2001 (41) | USA, Canada | SAR (6-11 years) | FXD | 15mg po BD | 2 | 223 | 9.1 | 37.0 |
| | | | FXD | 30mg po BD | | 208 | 9.1 | 41.0 |
| | | | FXD | 60mg po BD | | 212 | 9.0 | 47.0 |
| | | | placebo | | | 229 | 9.2 | 39.0 |
| Salmun et al., | USA | AR or | LRD | 5mg po OD | 2 | 60 | 3.7 | 55.0 |

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| Study, Year (Reference) | Region | Disease type (age range) | Treatment groups | Treatment dose | Treatment duration, weeks | Patients, n | Age, years‡ | Female, % |
|---|---|---|---|---|---|---|---|---|
| 2000 (42) | | CIU (2-5 years) | placebo | | | 61 | 3.5 | 55.7 |
| Simons et al., 1999 (43) *and* Wahn et al., 1998 (44) † | N. America | AD (1-2 years) | CTZ | 0.25mg/kg po BD | 72 | 399 | 16.8 months | 38.1 |
| | | | placebo | | | 396 | 17.2 months | 37.6 |
| Sienra-Monge et al., 1999 (45) | C. America | AR (2-6 years) | CTZ | 0.2mg/kg po OD | 4 | 40 | 4.3 | 40.0 |
| | | | LRD | 0.2mg/kg po OD | | 40 | 4.4 | 35.0 |
| Serra et al., 1998 (46) | Argentina | SAR (3-15 years) | LRD-PSD | 0.2mg/kg po BD | 2 | 20 | ND | 60.0 |
| | | | placebo | | | 20 | ND | 60.0 |
| Delgado et al., 1998 (47) | Brazil | PAR, Sinusitis (5-12 years) | LRD | 5mg po OD (<30kg), | 2 | 10 | 7.2 | 50.0 |
| | | | LRD-ER | 10mg po OD (≥30kg) | | 10 | | 50.0 |
| | | | CTZ | 10mg po OD | | 10 | 9.3 | 50.0 |
| | | | CTZ-ER | | | 10 | | 50.0 |
| Pearlman et a 1997 (48) | USA | AR (6-11 years) | CTZ | 5mg po OD | 4 | 69 | 9.1 | 33.3 |
| | | | CTZ | 10mg po OD | | 72 | 8.6 | 27.1 |

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| Study, Year (Reference) | Region | Disease type (age range) | Treatment groups | Treatment dose | Treatment duration, weeks | Patients, n | Age, years‡ | Female, % |
|---|---|---|---|---|---|---|---|---|
| *and* Winder et al., 1996 (49) † | | | placebo | | | 68 | 8.8 | 36.8 |
| Ciprandi et al. 1997 (50) | Europe | Allergic rhinoconjunctivitis (6-15 years) | CTZ<br>placebo | 0.15mg/kg po OD | 4 | 10<br>10 | 8.5 (total) | 55.0 (total) |
| deBenedictis et al., 1997 (51) | Europe | PAR (2-6 years) | CTZ<br>OXD | 5mg po OD<br>12mg po BD | 10 d | 53<br>52 | 4.6<br>4.8 | 34.0<br>40.0 |
| Tinkelman et al. 1996 (52) | USA | SAR (6-11 years) | CTZ<br><br>CTZ<br><br>CPN | 5mg po OD (<25kg), 10mg po OD (≥25kg)<br>2.5mg po BD (<25kg), 5mg po BD (≥25kg)<br>2mg po TD | 2 | 63<br><br>62<br><br>63 | 8.6<br><br>9.1<br><br>8.7 | 35.5<br><br>29.5<br><br>30.2 |
| Fasce et al., 1996 (53) | Europe | Mite allergic asthma (5-14 years) | CTZ<br>placebo | 5mg po OD | 2 | 10<br>10 | 8.3 (total) | ND<br>ND |
| LaRosa et al., 1994 (54) | Europe | AD (6-12 years) | CTZ<br><br>placebo | 5mg po OD (≤30kg), 10mg po OD (>30kg) | 8 | 12<br><br>11 | 7.0 (total) | 41.6<br><br>63.6 |

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| Study, Year (Reference) | Region | Disease type (age range) | Treatment groups | Treatment dose | Treatment duration, weeks | Patients, n | Age, years‡ | Female, % |
|---|---|---|---|---|---|---|---|---|
| Jobst et al., 1994 (55) | Europe | PAR (6-12 years) | CTZ | 2.5mg po OD | 2 | 84 | 8.6 | 45.2 |
| | | | CTZ | 5mg po OD | | 85 | 9.2 | 29.4 |
| | | | CTZ | 10mg po OD | | 76 | 9.3 | 42.1 |
| | | | placebo | | | 83 | 8.9 | 45.8 |
| Allegra et al., 1993 (56) | Europe | SAR (2-6 years) | CTZ | 5mg po OD | 2 | 54 | 4.6 | 33.3 |
| | | | placebo | | | 53 | 4.3 | 28.3 |
| Masi et al., 1993 (57) | Europe | Seasonal allergic rhinoconjunctivitis (6-12 years) | CTZ | 5mg po BD | 2 | 63 | 10.1 | 39.7 |
| | | | placebo | | | 61 | 10.2 | 37.7 |
| Baelde et al., 1992 (58) | Europe | PAR (2-14 years) | CTZ | 5mg po BD | 2 | 46 | 8.8 | 30.4 |
| | | | CTZ | 2.5mg po BD | | 46 | 8.5 | 30.4 |
| | | | placebo | | | 46 | 8.6 | 39.1 |

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| Study, Year (Reference) | Region | Disease type (age range) | Treatment groups | Treatment dose | Treatment duration, weeks | Patients, n | Age, years‡ | Female, % |
|---|---|---|---|---|---|---|---|---|
| Boner et al., 1989 (59) | Europe | SAR (4-12 years) | LRD | 5mg po OD (≥20kg or ≥6 yrs), 2.5mg po OD (<20kg or <6yrs) | 2 | 21 | 7.6 | 33.3 |
| | | | DCPN | 1mg po TD (≥20kg or ≥6 yrs), 0.5mg po TD (<20kg or <6yrs) | | 19 | 7.8 | 36.8 |

Abbreviations: AD = Atopic dermatitis; AR = Allergic rhinitis; BD = Bis in die (twice daily); BLN = Bilastine; CIU = Chronic idiopathic urticaria; CPHD = Cyproheptadine; CPN = Chlorpheniramine; CTZ = Cetirizine; DCPN = Dexchlorpheniramine; DLRD = Desloratadine; ER = Erythromycin; FXD = Fexofenadine; KTF = Ketotifen; LCTZ = Levocetirizine; LRD = Loratadine; MLK = Montelukast; ND = No data; OD = Omne in die (once daily); OXD = Oxotamide; PAR = Perennial allergic rhinitis; PO = Per os ; PSD = Pseudoephedrine; QD = Quater in die (four times daily); RPD = Rupatadine; SAR = Seasonal allergic rhinitis; TD = Ter in die (three times daily). CPHD= cyproeptadine

† Two publications of the same RCT.

‡ Data are mean years unless otherwise indicated.

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**Table 2.** Risk of bias in included trials

| Study, Year (Reference) | Sequence generation | Allocation concealment | Blinding/ Patients | Blinding/ Caregivers | Blinding/ Assessors | Attrition | Selective outcome | Comments |
|---|---|---|---|---|---|---|---|---|
| Wandalsen et al., 2017 (13) | Unclear | Unclear | Low | Low | Low | Low | Low | Patient-reported AEs (diary) |
| Nayak et al., 2017 (14) | Unclear | Unclear | Unclear | Unclear | Unclear | Low | Low | 5 patients not evaluated for safety; Observed or patient-reported AEs |
| Novak et al., 2016 (15) | Low | Unclear | Low | Low | Low | Low | Low | Detailed AE assessment and somnolence/sedation, in particular |
| Potter et al., 2016 (16) | Unclear | Unclear | Low | Low | Low | Unclear | Low | Patient-reported AEs (interview) |
| Potter et al., 2013 (17) | Unclear | Unclear | Low | Low | Low | Low | Low | Patient-reported AEs |
| Wu et al., 2012 (18) | Unclear | High | High | High | High | Low | Low | Not all patients evaluated for safety; patient-reported AEs (diary and interview) |
| Marucci et al., 2011 (19) | Unclear | Low | Unclear | Unclear | Unclear | Unclear | Low | 67% of the patients evaluated for safety; patient-reported AEs (diary) |
| Hampel et al., 2010 (20) | Unclear | Unclear | Low | Low | Low | Low | Low | Primarily designed to assess safety; patient-reported AEs and laboratory tests |
| Lee et al., 2009 (21) | Unclear | Unclear | Unclear | Unclear | Unclear | Low | Low | Not all patients evaluated for safety; patient-reported AEs (interview) |
| Ngamphaiboon | Unclear | Unclear | Unclear | Unclear | Unclear | Low | Low | Not all patients evaluated |

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| Study, Year (Reference) | Sequence generation | Allocation concealment | Blinding/ Patients | Blinding/ Caregivers | Blinding/ Assessors | Attrition | Selective outcome | Comments |
|---|---|---|---|---|---|---|---|---|
| et al., 2009 (22) | | | | | | | | for safety, number of patients with AEs per group not reported; patient-reported AEs |
| Hampel et al., 2007 (23) | Unclear | Unclear | Unclear | Unclear | Unclear | Low | Low | Primarily designed to assess safety; patient-reported AEs |
| Milgrom et al., 2007 (24) | Unclear | Unclear | Low | Low | Low | High | Low | Primarily designed to assess safety; AE recording at trial visits and through phone calls |
| Simons et al., 2007 (25) | Unclear | Unclear | Low | Low | Low | Low | Low | Primarily designed to assess safety; definitions of AEs, Patient-reported AEs (interviews), laboratory tests, assessment of psychomotor development |
| Chen et al., 2006 (26) | Unclear | Unclear | Unclear | Unclear | Unclear | Low | Low | Patient-reported AEs (interview) |
| Prenner et al., 2006 (27) | Low | Unclear | Low | Low | Low | Low | Low | Primarily designed to assess safety; patient-reported AEs (diary and interview) and laboratory tests |
| de Blic et al., 2005 (28) | Unclear | Unclear | Low | Low | Low | Low | Low | Patient-reported AEs (diary and interview) |
| Potter et al., 2005 (29) | High | Low | Low | Low | Low | Low | Low | Unclear how AEs were recorded |

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| Study, Year (Reference) | Sequence generation | Allocation concealment | Blinding/ Patients | Blinding/ Caregivers | Blinding/ Assessors | Attrition | Selective outcome | Comments |
|---|---|---|---|---|---|---|---|---|
| Bloom et al., 2004 (30) | Unclear | Unclear | Low | Low | Low | Low | Low | Primarily designed to assess safety; patient-reported AEs (diary and interview) |
| Grimfeld et al., 2004 (31) | Unclear | Unclear | Unclear | Unclear | Unclear | Low | Low | AEs reported for both treatment and follow-up phase, patient-reported AEs (diary) and assessment of psychomotor development |
| Hsieh et al., 2004 (32) | Low | Unclear | Unclear | Unclear | Unclear | Low | Low | 5 pts not evaluated for safety; patient-reported AEs |
| Wahn et al., 2003 (33) | Unclear | Unclear | Low | Low | Low | Low | Low | Patient-reported AEs (diary and interview) and laboratory tests |
| Segal et al., 2003 (34) | Unclear | Unclear | Unclear | Unclear | Unclear | Low | Low | Observed or patient-reported AEs and laboratory tests |
| Simons et al., 2003 (35) | Unclear | Unclear | Low | Low | Low | Low | Low | Primarily designed to assess safety; patient-reported AEs (diary and interview) and laboratory tests |
| Lai et al., 2002 (36) | Low | Unclear | Unclear | Unclear | Unclear | Low | Low | Not all patients evaluated for safety; patient-reported AEs (interview) |
| Chunharas et al., 2002 (37) | Unclear | Unclear | Unclear | Unclear | Unclear | Low | Low | Unclear how AEs were recorded |

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| Study, Year (Reference) | Sequence generation | Allocation concealment | Blinding/ Patients | Blinding/ Caregivers | Blinding/ Assessors | Attrition | Selective outcome | Comments |
|---|---|---|---|---|---|---|---|---|
| La Rosa et al., 2001 (38) | Low | Low | Low | Low | Low | Low | Low | Patient-reported AEs (interview) and laboratory tests |
| Yang et al., 2001 (39) | Unclear | Unclear | Unclear | Unclear | Unclear | Low | Low | Reasons of withdrawals not reported; patient-reported AEs (interview) |
| Ciprandi et al., 2001 (40) | Low | Unclear | Low | Low | Low | Low | Low | Unclear how AEs were recorded |
| Graft et al., 2001 (41) | Unclear | Unclear | Unclear | Unclear | Unclear | Low | Low | Primarily designed to assess safety; patient-reported AEs (diary) |
| Salmun et al., 2000 (42) | Unclear | Unclear | Unclear | Unclear | Unclear | Low | Low | Primarily designed to assess tolerability; patient-reported AEs (diary) |
| Simons et al., 1999 (43) *and* Wahn et al., 1998 (44) | Low | Low | Low | Low | Low | Low | Low | Primarily designed to assess safety; more active monitoring, over-reporting according to the authors; patient-reported AEs (diary and interview) |
| Sienra-Monge et al., 1999 (45) | Unclear | Unclear | Unclear | Unclear | Unclear | Unclear | Low | Protocol violators were replaced by other pts, patient-reported AEs (diary and interview) |
| Serra et al., 1998 (46) | Unclear | Unclear | Unclear | Unclear | Unclear | Low | Low | Patient-reported AEs |
| Delgado et al., 1998 (47) | Unclear | Unclear | Unclear | Unclear | Unclear | Low | Low | Patient-reported AEs |

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| Study, Year (Reference) | Sequence generation | Allocation concealment | Blinding/ Patients | Blinding/ Caregivers | Blinding/ Assessors | Attrition | Selective outcome | Comments |
|---|---|---|---|---|---|---|---|---|
| Pearlman et al., 1997 (48) *and* Winder et al., 1996 (49) | Unclear | Unclear | Low | Low | Low | Low | Low | Number of patients with AEs per group not reported; patient-reported AEs (diary and interview) |
| Ciprandi et al., 1997 (50) | Unclear | Unclear | Unclear | Unclear | Unclear | Low | Low | Unclear how AEs were recorded |
| deBenedictis et al., 1997 (51) | Unclear | Unclear | Low | Low | Low | Low | Low | 3 patients not evaluated for safety; number of patients with AEs per group not reported, patient-reported AEs (diary and interview) |
| Tinkelman et al., 1996 (52) | Unclear | Low | High | High | High | Low | Low | patient-reported AEs (diary) |
| Fasce et al., 1996 (53) | Unclear | Unclear | Unclear | Unclear | Unclear | Low | Low | Only reported that no important AEs were observed |
| La Rosa et al., 1994 (54) | Unclear | Unclear | Low | Low | Low | Low | Low | Differential use of concomitant drugs |
| Jobst et al., 1994 (55) | Low | Unclear | Low | Low | Low | Low | Low | Patient-reported AEs (diary) |
| Allegra et al., 1993 (56) | Low | Unclear | Low | Low | Low | Low | Low | Patient-reported AEs (diary and interview) |
| Masi et al., 1993 (57) | Unclear | Unclear | Low | Low | Low | Low | Low | Patient-reported AEs (diary and interview) |
| Baelde et al., 1992 (58) | Low | Unclear | Low | Low | Low | Low | Low | 4 pts not evaluated for safety; patient-reported AEs (diary and interview) |

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| Study, Year (Reference) | Sequence generation | Allocation concealment | Blinding/ Patients | Blinding/ Caregivers | Blinding/ Assessors | Attrition | Selective outcome | Comments |
|---|---|---|---|---|---|---|---|---|
| Boner et al. 1989 (59) | Unclear | Unclear | High | High | Unclear | Low | Low | Patient-reported AEs (diary and interview) |

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**Table 3.** Adverse events and treatment discontinuations

| Study, Year (Reference) | Treatment groups (n) | Patients, n | Patients with serious AEs, % | Patients with ≥1 AE, % | Patients with AEs related to study drug, %† | Treatment discontinuations due to AEs, % | Comments in original trials |
|---|---|---|---|---|---|---|---|
| Wandalsen et al., 2017 (13) | DLRD | 105 | ND | ND | ND | 0.9 | Six patients in the DLRD group and 11 in the DCPN group presented ECG changes at the end of the study |
| | DCPN | 105 | ND | ND | ND | 1.9 | |
| Nayak et al., 2017 (14) | CTZ | 228 | 0 | 19.7 | 4.8 | 2.6 | |
| | LRD | 220 | 0 | 21.8 | 4.5 | 5.6 | |
| | placebo | 219 | 0 | 22.7 | 2.6 | 3.9 | |
| Novak et al, 2016 (15) | BLN | 260 | 0.7 | 68.5 | 5.8 | 1.1 | No clinically and/or statistically relevant differences between bilastine and placebo for vital signs, clinical laboratory values, ECG parameters or physical examination |
| | placebo | 249 | 3.6 | 67.5 | 8.0 | 0.8 | |
| Potter et al., 2016 (16) | RPD | 66 | ND | 61.0 | 1.5 | ND | |
| | DLRD | 71 | ND | 65.0 | 5.6 | ND | |

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| Study, Year (Reference) | Treatment groups (n) | Patients, n | Patients with serious AEs, % | Patients with ≥1 AE, % | Patients with AEs related to study drug, %† | Treatment discontinuations due to AEs, % | Comments in original trials |
|---|---|---|---|---|---|---|---|
| | placebo | 69 | ND | 54.0 | 7.2 | ND | |
| Potter et al., 2013 | RPD | 180 | ND | 37.2 | 6.1 | ND | |
| (17) | placebo | 180 | ND | 30.0 | 5.5 | ND | |
| Wu et al., 2012 (18) | LRD | 30 | ND | 0 | 0 | 0 | |
| | CPHD | 30 | ND | 13.0 | 13.0 | 0 | |
| Marucci et al., 2011 | LCTZ | 30 | 0 | 14.3 | ND | ND | |
| (19) | placebo | 30 | 0 | 10.5 | ND | ND | |
| Hampel et al., 2010 | LCTZ | 45 | ND | 64.4 | 11.1 | 6.7 | No clinically relevant changes or |
| (20) | placebo | 24 | ND | 70.8 | 4.2 | 0 | trends in vital signs, laboratory |
| | [6-11 months] | | | | | | tests, or ECG parameters were noted |
| | LCTZ | 114 | ND | 35.1 | 7.0 | 0 | |
| | placebo | 59 | ND | 35.6 | 11.9 | 0 | |
| | [1-5 years] | | | | | | |
| Lee et al., 2009 (21) | CTZ | 27 | 0 | 3.7 | ND | 0 | |
| | LCTZ | 26 | 0 | 3.8 | ND | 0 | |
| | placebo | 27 | 0 | 0 | ND | 0 | |

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| Study, Year (Reference) | Treatment groups (n) | Patients, n | Patients with serious AEs, % | Patients with ≥1 AE, % | Patients with AEs related to study drug, %† | Treatment discontinuations due to AEs, %‡ | Comments in original trials |
|---|---|---|---|---|---|---|---|
| Ngamphaiboon et l., 2009 (22) | LRD | 27 | ND | ND | ND | ND | A few patients had mild AEs in all groups. |
| | KTF | 25 | ND | ND | ND | ND | |
| | placebo | 26 | ND | ND | ND | ND | |
| Hampel et al., 2007 (23) | FXD (15mg BD) | 58 | ND | 39.7 | 8.8 (in total for FXD in both studies) | 3.2 | No clinical differences were observed between the fexofenadine treatment groups and placebo for any vital sign or any ECG variable. |
| | FXD (30mg BD) | 5 | ND | 40 | | | |
| | placebo | 69 | ND | 40.6 | 9.5 (in total for placebo in both studies) | 4.3 | |
| | [6-11 months] | | | | | | |
| | FXD (15mg BD) | 27 | ND | 40.7 | | 3.1 | |
| | FXD (30mg BD) | 103 | ND | 35.0 | | | |
| | placebo | 131 | ND | 52.3 | | 5.3 | |
| | [1-2 years] | | | | | | |
| Milgrom et al., 2007 (24) | FXD | 222 | ND | 50.0 | 9.5 | ND | No clinically relevant ECG changes. |
| | placebo | 231 | ND | 50.2 | 8.2 | ND | |
| Simons et al., 2007 (25) | LCTZ | 255 | 12.2 | 96.9 | 5.1 | 2.0 | There were no significant differences between levocetirizine- and placebo-treated children with |
| | placebo | 255 | 14.5 | 95.7 | 6.3 | 1.2 | |

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| Study, Year (Reference) | Treatment groups (n) | Patients, n | Patients with serious AEs, % | Patients with ≥1 AE, % | Patients with AEs related to study drug, %† | Treatment discontinuations due to AEs, % | Comments in original trials |
|---|---|---|---|---|---|---|---|
| | | | | | | | respect to laboratory test results. |
| Chen et al., 2006 | CTZ | 20 | 0 | 10.0 | 10.0 | 0 | |
| (26) | MLK | 20 | 0 | 0 | 0 | 0 | |
| | placebo | 20 | 0 | 0 | 0 | 0 | |
| Prenner et al., 2006 | DLRD | 131 | 0 | 67.2 | 26 | 0.8 | No statistically significant or |
| (27) | placebo | 129 | 0.8 | 58.9 | 21.8 | 1.6 | clinically relevant differences in ECG parameters. |
| de Blic et al., 2005 | LCTZ | 89 | 0 | 33.7 | 5.6 | 0 | |
| (28) | placebo | 88 | 0 | 30.7 | 5.6 | 1.0 | |
| Potter et al., 2005 | LCTZ | 154 | 0 | 55.2 | 7.8 | 1.3 | |
| (29) | placebo | 152 | 0 | 52.6 | 5.9 | 1.3 | |
| Bloom et al., 2004 | DLRD | 55 | ND | 12.7 | 3.6 | 0 | No clinically relevant changes |
| (30) | placebo | 56 | ND | 10.7 | 0 | 0 | were noted in median clinical |
| | [2-5 years] | | | | | | laboratory test values or mean vital |
| | DLRD | 60 | ND | 1.7 | 0 | 0 | signs. Increase in heart rate was |
| | placebo | 60 | ND | 10.0 | 0 | 0 | observed in the study of subjects |
| | [6-11 years] | | | | | | aged 2 years–5 years, but the incidence was similar in the |

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| Study, Year (Reference) | Treatment groups (n) | Patients, n | Patients with serious AEs, % | Patients with ≥1 AE, % | Patients with AEs related to study drug, %† | Treatment discontinuations due to AEs, % | Comments in original trials |
|---|---|---|---|---|---|---|---|
| | | | | | | | desloratadine and placebo groups. |
| Grimfeld et al., 2004 (31) | LRD | 204 | ND | 80.9 | ND | 0 | There was no difference between groups regarding ECG or laboratory parameters. |
| | placebo | 208 | ND | 85.0 | ND | 0.5 | |
| Hsieh et al., 2004 (32) | CTZ | 21 | 0 | 5.0 | ND | 0 | |
| | MLK | 21 | 0 | 5.0 | ND | 0 | |
| | placebo | 22 | 0 | 10.0 | ND | 0 | |
| Wahn et al., 2003 (33) | FXD | 464 | 0.2 | 18.3 | 2.3 | 0.6 | There were no significant differences in changes in clinical laboratory and vital signs results between the fexofenadine- and placebo-treated groups. |
| | placebo | 471 | ND | 18.7 | 3.0 | 0 | |
| Segal et al., 2003 (34) | CTZ | 86 | ND | 32.1 | ND | 0 | |
| | placebo | 86 | ND | 20.9 | ND | 0 | |
| Simons et al., 2003 (35) | CTZ | 42 | ND | 73.8 | 45.2 | 7.1 | All cause and treatment related AEs were generally more frequent in the 6- to 8- month age group than in the 9 to 11-month age |
| | placebo | 43 | ND | 88.4 | 62.8 | 6.9 | |

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| Study, Year (Reference) | Treatment groups (n) | Patients, n | Patients with serious AEs, % | Patients with ≥1 AE, % | Patients with AEs related to study drug, %† | Treatment discontinuations due to AEs, % | Comments in original trials |
|---|---|---|---|---|---|---|---|
| | | | | | | | group. |
| Lai et al. 2002 (36) | CTZ | 20 | 0 | 15.8 | ND | ND | |
| | OXD | 20 | 0 | 16.7 | ND | ND | |
| | KTF | 20 | 0 | 12.5 | ND | ND | |
| | placebo | 20 | 0 | 12.5 | ND | ND | |
| Chunharas et al., 2002 (37) | LRD | 24 | ND | 12.5 | ND | 4.2 | |
| | placebo | 24 | ND | 8.0 | ND | 0 | |
| La Rosa et al., 2001 (38) | CTZ | 31 | ND | 0 | 0 | 0 | The hematologic, hematochemical, and urinary tests were within the normal limits in all patients before and at the end of the treatment. |
| | OXT | 31 | ND | 3.2 | 3.2 | 3.2 | |
| Yang et al., 2001 (39) | LRD | 30 | ND | 0 | 0 | ND | |
| | placebo | 30 | ND | 0 | 0 | ND | |
| Ciprandi et al., 2001 (40) | CTZ | 10 | ND | 0 | 0 | 0 | |
| | placebo | 10 | ND | 0 | 0 | 0 | |
| Graft et al., 2001 (41) | FXD (15mg BD) | 223 | ND | 35.3 | ND | 0.40 | Lab - ECG changes unremarkable, vital signs consistent among |
| | FXD (30mg BD) | | | | | | |

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| Study, Year (Reference) | Treatment groups (n) | Patients, n | Patients with serious AEs, % | Patients with ≥1 AE, % | Patients with AEs related to study drug, %† | Treatment discontinuations due to AEs, % | Comments in original trials |
|---|---|---|---|---|---|---|---|
| | FXD (60mg BD) | 208 | ND | 36.8 | ND | 1.40 | groups. |
| | placebo | 212 | ND | 34.7 | ND | 0.50 | |
| | | 229 | ND | 36.2 | ND | 2.20 | |
| Salmun et al., 2000 (42) | LRD | 60 | ND | 32.0 | ND | 0 | There were no significant differences between groups in any ECG variable. There were no clinically relevant changes in laboratory values, physical findings, or vital signs in either group. |
| | placebo | 61 | ND | 41.0 | ND | 0 | |
| Simons et al., 1999 (43) *and* Wahn et al., 1998 (44) | CTZ | 399 | 9.3 | 98.5 | 0.5 | 2.8 | There were no statistically significant differences between groups in QTc interval or behavioral/developmental assessments. |
| | placebo | 396 | 13.6 | 98.7 | 1.8 | 3.8 | |
| Sienra-Monge et al.,1999 (45) | CTZ | 40 | ND | 5.0 | ND | 5.0 | |
| | LRD | 40 | ND | 0 | ND | ND | |
| Serra et al., 1998 | LRD-PSD | 20 | ND | 5.0 | ND | 0 | No changes in vital signs or lab |

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| Study, Year (Reference) | Treatment groups (n) | Patients, n | Patients with serious AEs, % | Patients with ≥1 AE, % | Patients with AEs related to study drug, %† | Treatment discontinuations due to AEs, % | Comments in original trials |
|---|---|---|---|---|---|---|---|
| (46) | placebo | 20 | ND | 0 | 0 | 0 | tests. |
| Delgado et al., 1998 (47) | LRD | 10 | ND | 0 | 0 | 0 | The ECG parameters remained within normal limits following treatment, and all children presented with sinusal rhythm at the follow-up evaluation. |
| | CTZ | 10 | ND | 0 | 0 | 0 | |
| | LRD-ER | 10 | ND | 0 | 0 | 0 | |
| | CTZ-ER | 10 | ND | 0 | 0 | 0 | |
| Pearlman et al., 1997 (48) *and* Winder et al., 1996 (49) | CTZ(5mg OD) | 69 | ND | ND | ND | ND | No pronounced differences in the incidence of AEs between cetirizine groups, no statistically significant difference with placebo. |
| | CTZ(10mg OD) | 72 | ND | ND | ND | ND | |
| | placebo | 68 | ND | ND | ND | ND | |
| Ciprandi et al., 1997 (50) | CTZ | 10 | ND | 10.0 | ND | 0 | |
| | placebo | 10 | | 20.0 | | 0 | |
| Benedictis et al., 1997 (51) | CTZ | 53 | ND | 8.0 | ND | 0 | No clinically significant changes in laboratory tests were found except for one oxatomide patient. |
| | OXD | 52 | ND | 7.7 | ND | 0 | |
| Tinkelman et al., 1996 (52) | CTZ(2.5-5mg BD) | 63 | ND | 33.6 | ND | 0 | |
| | | | | | | 0 | |

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| Study, Year (Reference) | Treatment groups (n) | Patients, n | Patients with serious AEs, % | Patients with ≥1 AE, % | Patients with AEs related to study drug, %† | Treatment discontinuations due to AEs, % | Comments in original trials |
|---|---|---|---|---|---|---|---|
| | CTZ(5-10mg OD) | 62 | ND | | ND | 0 | |
| | CPN | 63 | ND | 38.1 | ND | | |
| Fasce et al., 1996 (53) | CTZ | 10 | ND | ND | ND | 0 | No important adverse reactions reported. |
| | placebo | 10 | ND | ND | ND | 0 | |
| La Rosa et al., 1994 (54) | CTZ | 12 | ND | 0 | 0 | ND | |
| | placebo | 11 | ND | ND | ND | ND | |
| Jobst et al., 1994 (55) | CTZ(2.5mg OD) | 84 | ND | 25.0 | ND | 4.8 | |
| | CTZ(5mg OD) | 85 | ND | 14.0 | ND | 2.9 | |
| | CTZ(10mg OD) | 76 | ND | 22.4 | ND | 1.3 | |
| | placebo | 83 | ND | 18.4 | ND | 1.2 | |
| Allegra et al.,1993 (56) | CTZ | 54 | ND | 24.1 | 5.6 | 1.8 | Minor changes in clinical laboratory tests were carefully reviewed and considered not to be clinically relevant. |
| | placebo | 53 | ND | 20.7 | 0 | 3.8 | |
| Masi et al., 1993 (57) | CTZ | 63 | ND | 22.2 | ND | 3.2 | Minor changes in clinical laboratory tests were considered not to be clinically relevant. |
| | placebo | 61 | ND | 22.9 | ND | 1.6 | |

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| Study, Year (Reference) | Treatment groups (n) | Patients, n | Patients with serious AEs, % | Patients with ≥1 AE, % | Patients with AEs related to study drug, %† | Treatment discontinuations due to AEs, % | Comments in original trials |
|---|---|---|---|---|---|---|---|
| Baelde et al., 1992 (58) | CTZ(10mg OD) | 46 | ND | 6.5 | ND | 0 | Leukocytosis that occurred in some patients in the three groups was not considered clinically relevant, a slight and clinically unimportant increase in AST levels with no effect on the liver's function occurred in some patients in the three groups, no clinically significant changes in blood urea or creatinine levels. |
| | CTZ(5mg OD) | 46 | ND | 17.3 | ND | 0 | |
| | Placebo | 46 | ND | 13.0 | ND | 0 | |
| Boner et al., 1989 (59) | LRD | 21 | ND | 19.0 | ND | 4.7 | Hematological counts and biochemical analysis showed that loratadine and dexchlorpheniramine at the dosages used were devoid of toxic effects. |
| | DCPN | 19 | | 31.5 | | 0 | |

Abbreviations: AE = Adverse event; BLN = Bilastine; CPHD = Cyproheptadine; CPN = Chlorpheniramine; CTZ = Cetirizine; DCPN = Dexchlorpheniramine; DLRD = Desloratadine; ER = Erythromycin; FXD = Fexofenadine; KTF = Ketotifen; LCTZ = Levocetirizine; LRD = Loratadine;

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MLK = Montelukast; ND = No data; OXD = Oxotamide; PSD = Pseudoephedrine; RPD = Rupatadine;

† Relation to study drug was assessed by the authors of each trial.

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**Table 4.** Adverse events reported in included RCTs

| **Study, Year (Reference)** | **Patients with Adverse Events (%) per treatment group** | | | | |
|---|---|---|---|---|---|
| Wandalsen et al., 2017 (13) | DLRD | | DCPN | | |
| | Somnolence | 8.6 | Somnolence | 17.1 | |
| | Cough | 6.6 | ECG changes | 11.3 | |
| | ECG changes | 6.1 | Increased appetite | 4.8 | |
| | Epistaxis | 2.9 | Cough | 4.8 | |
| | Insomnia | 2.9 | Fever | 3.8 | |
| | Vomit | 2.9 | Headache | 2.9 | |
| | Increased appetite | 1.9 | Diarrhea | 2.9 | |
| | Heart burn | 1.9 | Abdominal pain | 2.9 | |
| | Diarrhea | 1.9 | Excitement | 1.9 | |
| | Pain | 1.9 | Breathlessness | 1.9 | |
| | Abdominal pain | 1.9 | Insomnia | 1.9 | |
| | Excitement | 0.9 | Irritability | 1.9 | |
| | Irritability | 0.9 | Nausea | 1.9 | |
| | Dizziness | 0.9 | Dizziness | 1.9 | |
| | Headache | 0 | Vomit | 1.9 | |
| | Breathlessness | 0 | Heart burn | 0.9 | |
| | Fever | 0 | Epistaxis | 0 | |
| | Nausea | 0 | Pain | 0 | |
| Nayak et al., 2017 | CTZ | | LRD | | Placebo |

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| **Study, Year (Reference)** | **Patients with Adverse Events (%) per treatment group** | | | | | |
|---|---|---|---|---|---|---|
| (14) | | | | | | |
| | Treatment-related: | | Treatment-related: | | Treatment-related: | |
| | Headache | 3.5 | Headache | 3.6 | Headache | 3.1 |
| | Pharyngitis | 3.5 | Pharyngitis | 2.7 | Pharyngitis | 3.5 |
| | Fever | 1.8 | Vomiting | 2.7 | Sinusitis | 1.7 |
| | Vomiting | 1.3 | Sinusitis | 1.8 | Asthma | 1.3 |
| | Sinusitis | 1.3 | Lymphadenopathy | 1.8 | Bronchitis | 1.3 |
| | Somnolence | 1.3 | Nausea | 1.8 | Fever | 0.9 |
| | Lymphadenopathy | 0.4 | Epistaxis | 1.4 | Vomiting | 0.9 |
| | Asthma | 0.4 | Fever | 0.9 | Nausea | 0.9 |
| | | | Asthma | 0.5 | Epistaxis | 0.9 |
| Novak et al., 2016 (15) | BLN | | Placebo | | | |
| | Headache | 11.5 | Headache | 10.4 | | |
| | Cough | 8.8 | Cough | 8.8 | | |
| | Pharyngitis | 9.6 | Pharyngitis | 6.4 | | |
| | Allergic conjunctivitis | 9.2 | Allergic conjunctivitis | 7.6 | | |
| | Nasopharyngitis | 9.2 | Nasopharyngitis | 6.8 | | |
| | Pyrexia | 6.2 | Pyrexia | 9.2 | | |
| | Allergic rhinitis | 5.0 | Allergic rhinitis | 8.4 | | |
| | Bronchitis | 3.8 | Bronchitis | 5.6 | | |

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| Study, Year (Reference) | Patients with Adverse Events (%) per treatment group | | | | | |
|---|---|---|---|---|---|---|
| | Viral infection | 3.8 | Viral infection | 6.4 | | |
| Potter et al., 2016 (16) | RPD | | DSLRD | | Placebo | |
| | Treatment-related: | | Treatment-related: | | Treatment-related: | |
| | Headache | 1.5 | Decreased appetite | 1.4 | Increased ALP | 1.4 |
| | | | Dizziness | 1.4 | Abdominal pain upper | 1.4 |
| | | | Headache | 1.4 | Abdominal pain | 1.4 |
| | | | Constipation | 1.4 | Constipation | 1.4 |
| | | | Nausea | 1.4 | | |
| Potter et al., 2013 (17) | RPD | | Placebo | | | |
| | Headache | 12.8 | Headache | 5.6 | | |
| | Cough, | | Cough, | | | |
| | Abdominal pain, | | Abdominal pain, | | | |
| | Epistaxis, | | Epistaxis, | | | |
| | Eczema, | | Eczema, | | | |
| | Influenza | <4.0 | Influenza | <4.0 | | |
| | Somnolence | 1.1 | | | | |
| Wu et al., 2012 | LRD | | CPHD | | | |

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| Study, Year (Reference) | Patients with Adverse Events (%) per treatment group | | | |
|---|---|---|---|---|
| (18) | | | | |
| | No AEs | | Increased appetite | 8.7 |
| | | | Increased drowsiness | 4.3 |
| Marucci et al., 2011 (19) | LCTZ | | Placebo | |
| | Headache | 14.3 | Headache | 10.5 |
| | | | Abdominal pain | 5.3 |
| Hampel et al., 2010 (20) | LCTZ (1.25 mg OD) | | Placebo | |
| | Diarrhea | 13.3 | Diarrhea | 4.2 |
| | Teething | 6.7 | Constipation | 4.2 |
| | Constipation | 6.7 | Pyrexia | 16.7 |
| | Pyrexia | 15.6 | Irritability | 12.5 |
| | Irritability | 2.2 | Otitis media | 8.3 |
| | URTI | 4.4 | Somnolence | 4.2 |
| | Sinusitis | 2.2 | Cough | 8.3 |
| | Otitis media | 4.4 | Skin and subcutaneous | |
| | Viral URTI | 2.2 | tissue disorders | 29.2 |
| | Somnolence | 4.4 | | |

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| Study, Year (Reference) | Patients with Adverse Events (%) per treatment group | | | | |
|---|---|---|---|---|---|
| | Cough | 2.2 | | | |
| | Skin and subcutaneous tissue disorders | 13.3 | | | |
| Hampel et al., 2010 (20) | LCTZ (1.25 mg BD) | | Placebo | | |
| | Diarrhea | 3.5 | Diarrhea | 3.4 | |
| | Teething | 1.8 | Pyrexia | 1.7 | |
| | Constipation | 0.9 | URTI | 3.4 | |
| | Pyrexia | 4.4 | Sinusitis | 3.4 | |
| | URTI | 2.6 | Viral URTI | 3.4 | |
| | Sinusitis | 0.9 | Somnolence | 3.4 | |
| | Otitis media | 2.6 | Psychomotor | | |
| | Viral URTI | 0.9 | hyperactivity | 5.1 | |
| | Somnolence | 0.9 | Cough | 8.5 | |
| | Cough | 3.5 | Skin and subcutaneous | | |
| | Skin and subcutaneous tissue disorders | 4.4 | tissue disorders | 1.7 | |
| Lee et al., 2009 (21) | CTZ | | LCTZ | | Placebo |

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| **Study, Year (Reference)** | **Patients with Adverse Events (%) per treatment group** | | | | | |
|---|---|---|---|---|---|---|
| | Mild sedation | 3.7 | Mild fatigue | 3.8 | No AEs | |
| Ngamphaiboon et al., 2009 (22) | LRD | | KTF | | Placebo | |
| | Irritability | ND | Irritability | ND | Irritability | ND |
| | Somnolence | | Somnolence | | Somnolence | |
| Hampel et al., 2007 (23) | FXD HCL (15 mg BD) | | FXD HCL (30 mg BD) | | Placebo | |
| | *Digestive system* | 25.9 | *Digestive system* | 20 | *Digestive system* | 15.9 |
| | Vomiting | 15.5 | Vomiting | 20 | Vomiting | 14.5 |
| | Diarrhea | 5.2 | *Respiratory system* | 20 | Diarrhea | 1.4 |
| | Gastroenteritis | 3.4 | URTI | 20 | *Respiratory system* | 10.1 |
| | *Respiratory system* | 12.2 | | | URTI | 5.8 |
| | Cough increased | 1.7 | | | Fever | 5.8 |
| | URTI | 1.7 | | | Unintentional injury | 1.4 |
| | Rhinitis | 3.4 | | | Infection | 2.9 |
| | Fever | 1.7 | | | Otitis media | 7.2 |
| | Infection | 3.4 | | | *Skin and appendages* | 1.4 |
| | Otitis media | 1.7 | | | | |

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| **Study, Year (Reference)** | **Patients with Adverse Events (%) per treatment group** | | | | | |
|---|---|---|---|---|---|---|
| | *Skin and appendages* | 6.9 | | | | |
| Hampel et al.,2007 (23) | FXD HCL (15 mg BD) | | FXD HCL (30 mg BD) | | Placebo | |
| | *Digestive system* | 18.5 | *Digestive system* | 15.5 | *Digestive system* | 20.8 |
| | Vomiting | 11.1 | Vomiting | 4.9 | Vomiting | 13.1 |
| | Diarrhea | 3.7 | Diarrhea | 5.8 | Diarrhea | 2.3 |
| | Gastroenteritis *Respiratory* | 3.7 | Gastroenteritis | 1.0 | Gastroenteritis | 1.5 |
| | *system* | 7.4 | Flatulence | 1.0 | Flatulence | 3.1 |
| | Cough increased | 3.7 | *Respiratory system* | 11.7 | *Respiratory system* | 18.5 |
| | URTI | 3.7 | Cough increased | 3.9 | Cough increased | 6.2 |
| | Fever | 3.7 | URTI | 3.9 | URTI | 6.2 |
| | Unintentional injury | 3.7 | Rhinitis | 2.9 | Rhinitis | 6 |
| | Otitis media | 7.4 | Fever | 4.9 | Fever | 10.8 |
| | Ophthalmitis | 3.7 | Unintentional injury | 1.0 | Infection | 6.2 |
| | Ear disorder | 3.7 | Infection | 1.9 | Otitis media | 4.6 |
| | Skin and appendages | 3.7 | Otitis media | 6.8 | Ear disorder | 2.3 |
| | | | Skin and appendages | 3.9 | Skin and appendages | 5.4 |
| Milgrom et al., 2007 (24) | FXD HCL | | Placebo | | | |

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| **Study, Year (Reference)** | **Patients with Adverse Events (%) per treatment group** | | | |
|---|---|---|---|---|
| | *Respiratory system* | 20.3 | *Respiratory system* | 17.3 |
| | Cough increased | 4.5 | Cough increased | 3.0 |
| | URTI | 4.1 | URTI | 6.9 |
| | Rhinitis | 4.1 | Rhinitis | 2.6 |
| | Pharyngitis | 2.7 | Pharyngitis | 0.9 |
| | Fever | 5.9 | Fever | 5.6 |
| | Accidental injury | 4.5 | Accidental injury | 3.0 |
| | Infection | 3.6 | Infection | 6.1 |
| | Vomiting | 5.0 | Vomiting | 4.8 |
| | GI pain | 2.7 | GI pain | 2.6 |
| | Diarrhea | 2.3 | Diarrhea | 3.0 |
| | Headache | 3.2 | Headache | 3.9 |
| | Otitis media | 3.6 | Otitis media | 1.3 |
| | Ear pain | 1.4 | Ear pain | 2.6 |
| | Special senses | 5.9 | Special senses | 5.6 |
| Simons et al.,2007 (25) | LCTZ | | Placebo | |
| | Serious AEs: | | Serious AEs: | |
| | Wheezing | 4.7 | Wheezing | 7.5 |
| | Dermatitis atopic | 1.2 | Dermatitis atopic | 2.4 |
| | Gastroenteritis | 0.8 | Gastroenteritis | 2.0 |
| | Cough | 1.6 | Cough | 0.8 |

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| Study, Year (Reference) | Patients with Adverse Events (%) per treatment group | | | | |
|---|---|---|---|---|---|
| | Bronchopneumonia | 1.6 | Bronchopneumonia | 0.4 | |
| | Febrile convulsion | 1.6 | Urticaria | 1.2 | |
| | Urticaria | 0.4 | Bronchitis chronic | 1.2 | |
| | Neurologic/behavioral events: | | Neurologic/behavioral events: | | |
| | Abnormal behavior | 0.8 | Abnormal behavior | 1.2 | |
| | Agitation | 0.4 | Aggression | 0.4 | |
| | Bronchopneumonia | 1.6 | Anxiety | 0.4 | |
| | Convulsions | 0.4 | Burning sensation | 0.4 | |
| | Epilepsy | 0.4 | Febrile convulsions | 0.4 | |
| | Febrile convulsions | 2.0 | Headache | 1.6 | |
| | Headache | 0.4 | Insomnia | 0.8 | |
| | Insomnia | 1.2 | Irritability | 1.6 | |
| | Nervousness | 0.4 | Nightmare | 0.4 | |
| | Sleep disorder | 0.4 | Sleep disorder | 0.4 | |
| | | | Somnolence | 0.4 | |
| | | | Syncope | 0.4 | |
| Chen et al., 2006 (26) | CTZ | | MLK | | Placebo |

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| Study, Year (Reference) | Patients with Adverse Events (%) per treatment group | | | |
|---|---|---|---|---|
| | Mild medication induced sedation | 10.0 | No AEs | No AEs |
| Prenner et al., 2006 (27) | DLRD | | Placebo | |
| | Treatment-related: | | Treatment-related: | |
| | Anorexia | 3.1 | Anorexia | 1.6 |
| | Increased appetite | 2.3 | Increased appetite | 2.4 |
| | Fever | 3.1 | Fever | 0.8 |
| | Somnolence | 5.3 | Somnolence | 7.3 |
| | Diarrhea | 6.1 | Diarrhea | 2.4 |
| | Insomnia | 2.3 | Irritability | 5.6 |
| | Irritability | 6.9 | Coughing | 1.6 |
| | Bronchitis | 0.8 | Mild-to-moderate | |
| | Coughing | 1.5 | infection (unrelated) | 1.6 |
| | Epistaxis | 0.8 | Mild viral bronchiolitis | |
| | Mild-to-moderate infection | | (unrelated) | 0.8 |
| | (unrelated) | 0.8 | | |
| de Blic et al., 2005 (28) | LCTZ | | Placebo | |

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| Study, Year (Reference) | Patients with Adverse Events (%) per treatment group | | | |
|---|---|---|---|---|
| | Headache | 4.5 | Headache | 9.1 |
| | Epistaxis | 5.6 | Epistaxis | 1.1 |
| | Somnolence | 1.1 | | |
| Potter et al., 2005 (29) | LCTZ | | Placebo | |
| | Headache | 12.3 | Headache | 11.2 |
| | URTI | 8.4 | URTI | 11.8 |
| | Influenza | 5.2 | Influenza | 9.2 |
| Bloom et al., 2004 (30) | DLRD | | Placebo | |
| | Fever | 5.5 | Fever | 5.4 |
| | Headache | 1.8 | Headache | 5.4 |
| | Viral infection | 1.8 | Viral infection | 1.8 |
| | Varicella | 3.6 | Otitis media | 1.8 |
| | Rash | 3.6 | | |
| | Urinary tract infection | 3.6 | | |
| Bloom et al., 2004 (30) | DLRD | | Placebo | |

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| Study, Year (Reference) | Patients with Adverse Events (%) per treatment group | | | | | |
|---|---|---|---|---|---|---|
| | Headache | 1.7 | Headache | 6.7 | | |
| | | | Gastroenteritis | 3.3 | | |
| | | | Vomiting | 3.3 | | |
| Grimfeld et al., 2004 (31) | LRD | | Placebo | | | |
| | Pharyngitis | 18.8 | Pharyngitis | 18.1 | | |
| | Bronchitis | 15.8 | Bronchitis | 13.0 | | |
| | Otitis media | 9.1 | Otitis media | 13.0 | | |
| | Gastroenteritis | 7.9 | Gastroenteritis | 7.9 | | |
| | Rhinitis | 7.9 | Rhinitis | 7.3 | | |
| | Fever | 6.7 | Fever | 7.3 | | |
| | Varicella | 8.5 | Varicella | 4.5 | | |
| | Coughing | 7.3 | Coughing | 5.1 | | |
| | Tonsillitis | 5.5 | Tonsillitis | 5.1 | | |
| | Viral infection | 5.5 | Viral infection | 4.5 | | |
| | Vomiting | 5.5 | Vomiting | 3.4 | | |
| Hsieh et al.,2004 (32) | CTZ | | MLK | | Placebo | |
| | Sedation | 5.0 | Headache | 5.0 | Headache | 5.0 |
| | | | | | Fatigue | 5.0 |

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| **Study, Year (Reference)** | **Patients with Adverse Events (%) per treatment group** | | | |
|---|---|---|---|---|
| Wahn et al.,2003 (33) | FXD HCL | | Placebo | |
| | Headache | 5.0 | Headache | 2.8 |
| | Epistaxis | 1.5 | Epistaxis | 1.1 |
| | URTI | 1.5 | URTI | 1.1 |
| | Pharyngitis | 1.3 | Pharyngitis | 0.2 |
| | Sinusitis | 1.3 | Nausea | 0.2 |
| | Nausea | 1.1 | Rash | 0.6 |
| | Rash | 1.1 | Accidental injury | 1.3 |
| | Accidental injury | 0.9 | Asthma | 1.9 |
| | Asthma | 0.6 | Infection | 1.1 |
| | Infection | 0.2 | Gastrointestinal pain | 1.1 |
| | Gastrointestinal pain | 0.2 | | |
| | Neutropenia (severe) | 0.2 | | |
| Segal et al., 2003 (34) | CTZ | | Placebo | |
| | Headache | 8.3 | Headache | 9.3 |
| | Somnolence | 9.1 | Somnolence | 1.2 |
| | Rash | 3.6 | Nausea | 1.2 |
| | Nausea | 3.6 | Nervousness | 2.3 |
| | Nervousness | 2.4 | | |
| | Abdominal pain | 2.4 | | |

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| **Study, Year (Reference)** | **Patients with Adverse Events (%) per treatment group** | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Simons et al., 2003 (35) | CTZ | | Placebo | | | | | |
| | Nervousness | 28.6 | Nervousness | 44.2 | | | | |
| | Insomnia | 23.8 | Insomnia | 44.2 | | | | |
| | Somnolence | 21.4 | Somnolence | 30.2 | | | | |
| | Toothache† | 9.5 | Toothache† | 9.3 | | | | |
| | Diarrhea | 7.1 | Diarrhea | 9.3 | | | | |
| | Otitis media | 7.1 | Otitis media | 4.7 | | | | |
| | URTI | 7.1 | URTI | 2.3 | | | | |
| | Agitation | 4.8 | Agitation | 16.3 | | | | |
| | Tremor | 4.8 | Tremor | 4.7 | | | | |
| | Fever | 4.8 | Fever | 4.7 | | | | |
| | Pharyngitis | 4.8 | Cough | 4.7 | | | | |
| | Rhinitis | 4.8 | Rhinitis | 4.7 | | | | |
| | Rash | 2.4 | Rash | 4.7 | | | | |
| Lai et al., 2002 (36) | CTZ | | OXD | | KTF | | Placebo | |
| | Sedation | 10.5 | Sedation | 11.1 | Sedation | 6.3 | Headache | 6.3 |
| | Fatigue | 5.3 | Fatigue | 5.6 | Nausea | 6.3 | Sedation | 6.3 |
| Chuncharas et al., 2002 (37) | LRD | | Placebo | | | | | |

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| **Study, Year (Reference)** | **Patients with Adverse Events (%) per treatment group** | | | | | |
|---|---|---|---|---|---|---|
| | Dizziness | 4.2 | Dizziness | 4.2 | | |
| | Nausea | 4.2 | Anorexia | 4.2 | | |
| | Impetigo | 4.2 | | | | |
| La Rosa et al., 2001 (38) | OXD | | CTZ | | | |
| | Moderate perioral allergic reaction | 3.2 | ND | | | |
| Yang et al., 2001 (39) | LRD | | Placebo | | | |
| | No AEs | | No AEs | | | |
| Ciprandi et al., 2001 (40) | CTZ | | Placebo | | | |
| | No AEs | | No AEs | | | |
| Graft et al., 2001 (41) | FXD (15 mg BD) | | FXD (30 mg BD) | | FXD (60 mg BD) | Placebo |

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| Study, Year (Reference) | Patients with Adverse Events (%) per treatment group | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | URTI | 4.9 | URTI | 4.3 | URTI | 1.4 | URTI | 1.7 |
| | Pharyngitis | 4.0 | Pharyngitis | 2.9 | Pharyngitis | 2.8 | Pharyngitis | 1.9 |
| | Coughing | 1.3 | Coughing | 3.8 | Coughing | 2.3 | Coughing | 1.3 |
| | Injury accident | 1.8 | Injury accident | 2.9 | Injury accident | 4.2 | Injury accident | 1.3 |
| | Abdominal pain | 2.7 | Abdominal pain | 1.9 | Abdominal pain | 2.3 | Abdominal pain | 3.5 |
| | Fever | 1.8 | Fever | 2.4 | Fever | 1.9 | Fever | 0.9 |
| | Headache | 8.0 | Headache | 7.2 | Headache | 9.4 | Headache | 6.6 |
| | | | Somnolence (unrelated to treatment) | 0.5 | | | Somnolence | 0.9 |
| Salmun et al., 2000 (42) | LRD | | Placebo | | | | | |
| | Coughing | 3.0 | Coughing | 5.0 | | | | |
| | Drowsiness | 7.0 | Drowsiness | 7.0 | | | | |
| | Dyspepsia | 2.0 | Dyspepsia | 7.0 | | | | |
| | Fever | 7.0 | Fever | 8.0 | | | | |
| | Vomiting | 5.0 | Headache | 7.0 | | | | |
| | | | Vomiting | 5.0 | | | | |
| Simons et al., 1999 (43) | CTZ | | Placebo | | | | | |
| | Rhinitis | 79.0 | Rhinitis | 77.0 | | | | |
| | URTI | 58.0 | URTI | 62.0 | | | | |
| | Fever | 38.0 | Fever | 42.0 | | | | |

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| Study, Year (Reference) | Patients with Adverse Events (%) per treatment group | | | |
|---|---|---|---|---|
| | Diarrhea | 29.0 | Diarrhea | 28.0 |
| | Gastroenteritis | 28.0 | Gastroenteritis | 27.0 |
| | Vomiting | 21.0 | Vomiting | 22.0 |
| | Pharyngitis | 24.0 | Pharyngitis | 28.0 |
| | Varicella | 23.0 | Varicella | 22.0 |
| | Urticaria | 6.0 | Urticaria | 16.0 |
| | Allergic reaction | 9.0 | Allergic reaction | 14.0 |
| | Toothache | 8.0 | Toothache | 9.0 |
| | Influenza like symptoms | | Influenza like | |
| | Other viral infection | 6.0 | symptoms | 7.0 |
| | Immunization complication | 7.0 | Other viral infection | |
| | Heart murmur | 0.7 | Immunization | 6.0 |
| | Syncope after injury | 0.2 | complication | 0.7 |
| | Ataxia | 0.5 | Murmur | 0.2 |
| | Febrile convulsions | 0.5 | Tachycardia | 0.2 |
| | Fatigue | 3.2 | Other arrhythmia | 0.2 |
| | Emotional lability | 1.2 | Extrasystole | 0.5 |
| | Hyperkinesia | 1.2 | Ataxia | 1.0 |
| | Insomnia | 8.8 | Febrile convulsions | 1.3 |
| | Nervousness | 1.2 | Fatigue | 1.5 |
| | Somnolence | 2.2 | Emotional lability | 2.3 |
| | | | Hyperkinesia | 5.3 |

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| Study, Year (Reference) | Patients with Adverse Events (%) per treatment group | | | |
|---|---|---|---|---|
| | | | Insomnia Nervousness | 1.8 |
| | | | Somnolence | 2.0 |
| Wahn et al., 1998 (44) | CTZ | | Placebo | |
| | Abdominal pain | 4.3 | Abdominal pain | 4.3 |
| | Agitation | 0.3 | Agitation | 0.5 |
| | Allergic reaction | 9.1 | Allergic reaction | 13.4 |
| | Anorexia | 3.3 | Anorexia | 4.0 |
| | Appetite increased | 0.5 | Appetite increased | 0.3 |
| | Fatigue | 3.3 | ECG abnormalities | 0.3 |
| | Hepatic enzymes increased | 1.3 | Fatigue | 1.3 |
| | Hyperkinesia | 1.3 | Hepatic enzymes | |
| | Insomnia | 8.8 | increased | 1.8 |
| | Laryngitis | 7.3 | Hyperkinesia | 2.5 |
| | Somnolence | 2.3 | Insomnia | 5.3 |
| | Urticaria | 5.8 | Laryngitis | 9.3 |
| | Vaccination complication | 3.3 | Somnolence | 2.0 |
| | | | Urticaria | 16.1 |
| | | | Vaccination | |
| | | | complication | 5.5 |
| Sienra-Monge et | CTZ | | LRD | |

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| **Study, Year (Reference)** | **Patients with Adverse Events (%) per treatment group** | | | |
|---|---|---|---|---|
| al., 1999 (45) | | | | |
| | Somnolence and mild irritability 2.5<br>Generalized rash 2.5 | No AEs | | |
| Serra et al., 1998 (46) | LRD-PSD. | Placebo | | |
| | Slight transient insomnia 5.0 | No AEs | | |
| Delgado et al., 1998 (47) | LRD (5 mg or 10 mg OD) | CTZ (10 mg OD) | LRD-ER (5 mg or 10 mg OD) | CTZ-ER (10 mg OD) |
| | No AEs | No AEs | No AEs | No AEs |
| Pearlman et al.,1997 (48) *and* Winder et al.,1996 (49) | CTZ (10 mg OD) | CTZ (5 mg OD) | Placebo | |

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| Study, Year (Reference) | Patients with Adverse Events (%) per treatment group | | | | | |
|---|---|---|---|---|---|---|
| | Headache | | | 15.1 | Headache | 19.7 |
| | Pharyngitis | | | 10.1 | Pharyngitis | 13.6 |
| | Abdominal pain | | | 9.4 | Abdominal pain | 4.5 |
| | Epistaxis | | | 7.1 | Epistaxis | 4.3 |
| Ciprandi et al., 1997 (50) | CTZ | | Placebo | | | |
| | Headache | 10.0 | Headache | 20.0 | | |
| Benedictis et al., 1997 (51) | CTZ | | OXD | | | |
| | Sleepiness | 8.0 | Sleepiness | 7.7 | | |
| | | | Slightly increased SGPT | 1.9 | | |
| Tinkelman et al., 1996 (52) | CTZ (5-10 mg OD) | | CTZ (2.5-5 mg BD) | | CPN | |
| | Abdominal pain | | | 9.6 | Abdominal pain | 4.8 |
| | Somnolence | | | 8.0 | Somnolence | 7.9 |
| | Fatigue | | | 4.0 | Fatigue | 6.3 |
| | Nausea and headache | | | 3.2 | Nausea | 1.6 |

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| **Study, Year (Reference)** | **Patients with Adverse Events (%) per treatment group** | | | | | |
|---|---|---|---|---|---|---|
| | | | | | Headache | 6.3 |
| Fasce et al.,1996 (53) | | CTZ | | Placebo | | |
| | ND | | ND | | | |
| La Rosa et al.,1994 (54) | | CTZ | | Placebo | | |
| | No AEs | | ND | | | |
| Jobst et al.,1994 (55) | | CTZ (2.5 mg OD) | | CTZ (5 mg OD) | CTZ (10 mg OD) | Placebo |
| | ND | | ND | | ND | ND |
| Allegra et al.,1993 (56) | | CTZ | | Placebo | | |

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| **Study, Year (Reference)** | **Patients with Adverse Events (%) per treatment group** | | | | |
|---|---|---|---|---|---|
| | Number of events: | | Number of events: | | |
| | Headache | 1 | Headache | 1 | |
| | Fever | 2 | Abdominal pain | 2 | |
| | Abdominal pain | 1 | Diarrhea | 1 | |
| | Increased appetite | 1 | Vomiting | 1 | |
| | Diarrhea | 1 | Nervousness | 1 | |
| | Somnolence | 3 | Insomnia | 1 | |
| | Nervousness | 2 | Depression | 1 | |
| | Insomnia | 1 | Respiratory tract | 7 | |
| | Respiratory tract | 3 | | | |
| Masi et al.,1993 (57) | CTZ | | Placebo | | |
| | Somnolence | 9.5 | Somnolence | 3.3 | |
| | Headache | 3.2 | Headache | 1.6 | |
| | Vertigo | 1.6 | Nausea - vomiting | 4.9 | |
| | Rash | 3.2 | Anorexia | 1.6 | |
| | Increased appetite | 1.6 | Abdominal pain | 1.6 | |
| | Dry mouth | 1.6 | Increased cough | 4.9 | |
| | Abdominal pain Increased | 1.6 | Pharyngitis | 4.9 | |
| | cough | 1.6 | | | |
| | Pharyngitis | 1.6 | | | |
| Baelde et al., | CTZ (10mg OD) | | CTZ (5mg OD) | | Placebo |

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| Study, Year (Reference) | Patients with Adverse Events (%) per treatment group | | | | | |
|---|---|---|---|---|---|---|
| 1992 (58) | | | | | | |
| | Tiredness | 2.2 | Tiredness | 2.2 | Tiredness | 2.2 |
| | Mood change | 2.2 | Sleepiness/difficulty | | Sleepiness/difficulty | |
| | Appetite increase | 2.2 | waking | 6.5 | waking | 4.3 |
| | Abdominal pain/diarrhea | 2.2 | Mood change | 2.2 | Headache | 4.3 |
| | | | Appetite increase | 2.2 | Abdominal | 4.3 |
| | | | Abdominal | | pain/diarrhea | |
| | | | pain/diarrhea | 2.2 | other | 2.2 |
| | | | other | 2.2 | | |
| Boner et al.,1989 (59) | LRD | | DCPN | | | |
| | Moderate epistaxis | 14.2 | Somnolence | 21.0 | | |
| | Nausea, vomiting and | | Mild epistaxis | 10.5 | | |
| | Lipothymia | 4.7 | | | | |

Abbreviations: AE = Adverse events; BD = bis in die (twice daily); BLN = Bilastine; CTZ = Cetirizine; CPN = Clorpheniramine; CPHD = Cyproheptadine; DLRD = Desloratadine; DCPN = Dexchlorpheniramine; ER = Erythromycin; FXD = Fexofenadine; KTF = Ketotifen HCL; LRD = Loratadine; LCTZ = Levocetirizine; MLK = Montelukast; ND = No data; OD = omne in die (once daily); OXD = Oxotamide; PSD = Pseudoephedrine; RPD = Rupatadine; URTI = Upper respiratory tract infection.

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Figure Legends

**Figure 1.** Summary of evidence search and selection

* In total, 47 citations were included; there were two RCTs with data reported in two separate publications each.

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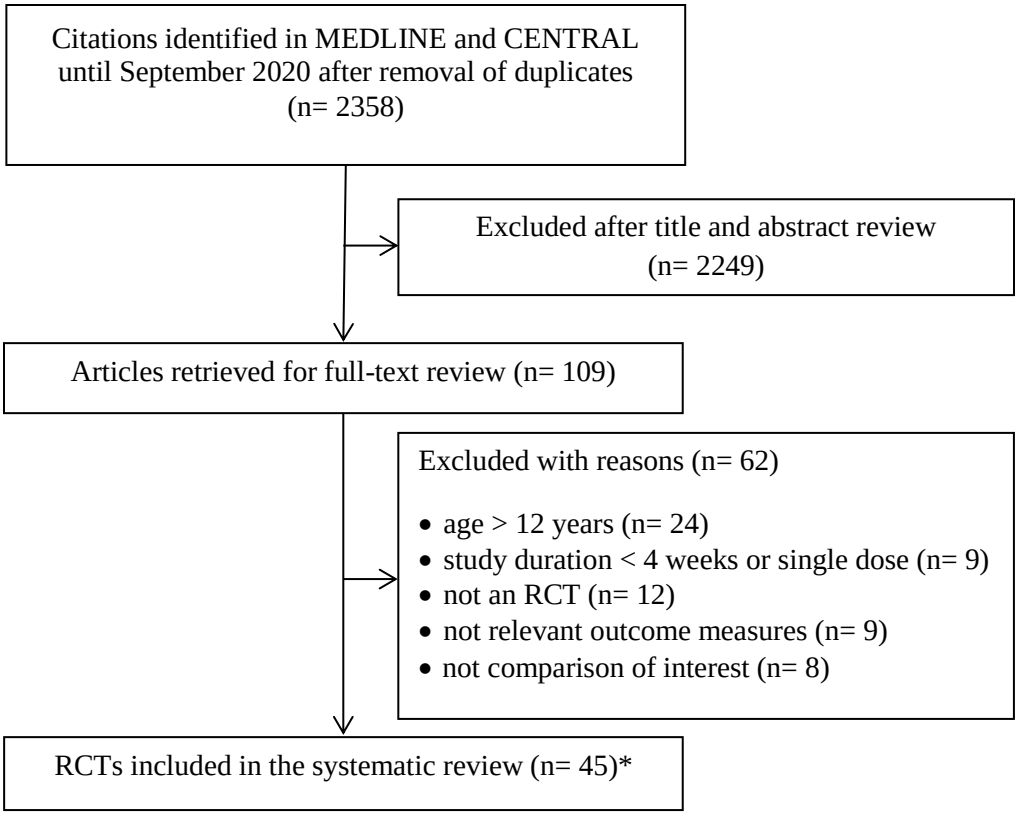
Appendix

**Ovid MEDLINE and CENTRAL search strategy**

(Histamine H1 Antagonists.sh OR antihistamin*.af OR Cetirizine.af OR Loratadine.af OR Fexofenadine.af OR Levocetirizine.af OR Desloratadine.af OR Rupatadine.af OR Bilastine.af) AND (child*.tw OR infant*.tw OR toddler*.tw OR newborn*.tw OR neonate*.tw OR pediatric*.tw OR paediatric*.tw)

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