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

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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.

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 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

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

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 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 5 mg OD for children 6-12 years old, 1.25 mg twice daily (BD) for children 1-5 years old, 0.125mg/kg OD for children 1-2 years old and 1.25 mg OD for children 6-11 months 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 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 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, 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

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^2LEN) 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 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 and used patient-reported AEs, through either interviews at trial visits or diary cards. A definition of serious adverse events and data on concomitant medications were generally not reported. 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 antihistamines due to the paucity of head-to-head RCTs. Of clinical importance in pediatrics, other factors that may not affect adults 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 DCPN	1.25-2.5mg po OD 1-2mg po TD	1	105 105	ND	45 46
Nayak et al., 2017 (14)	USA	SAR (6-11 years)	CTZ LRD placebo	10mg po OD 10mg po OD	2	228 220 219	8.6 8.9 8.9	42.5 42.2 46.3

Study, Year (Reference)	Region	Disease type (age range)	Treatment groups	Treatment dose	Treatment duration, weeks	Patients, n	Age, years++	Female, %
Novak et al., 2016 (15)	Europe, S. America	Allergic rhinoconjuctivitis or chronic urticarial (2-12 years)	BLN placebo	10 mg po OD	12	260 249	7.5 7.4	27.3 27.8
Potter et al., 2016 (16)	Europe	Chronic spontaneous urticaria (2-11 years)	RPD [3]DLRD placebo	2.5mg po OD (10-25kg), 5mg po OD (>25kg) standard dose OD	6	66 [3]71 69	5.6 [3]6.1 6.1	56.1 [3] 42
Potter et al. 2013 (17)	Europe Africa S. America	PAR (6-11 years)	RPD placebo	2,5mg po OD (<25kg), 5mg po OD ([?]25kg)	6	180 180	8.7 8.8	41.1 38.3
Wu et al., 2012 (18)	Asia	PAR (2-12 years)	LRD CPHD	5-10mg po OD (<30kg,>30kg) 2-4mg po TD (<30kg,>30kg)	2	30 30	5.8 6.6	61.5 34.
Marcucci et al., 2011 (19)	Europe	PAR (6-12 years)	LCTZ placebo	ND	12	30 30	9.73 (total)	60.0 (total)
Hampel et al., 2010 (20)	USA	AR or Chronic urticaria (6-11 months)	LCTZ placebo	1.25mg po OD	2	45 24	8.87 months 9.03 months	37.8 54.2
		AR or Chronic urticaria (1-5 years)	LCTZ placebo	1.25mg po BD	2	114 59	3.78 3.75	57.0 61.0
Lee et al., 2009 (21)	Europe	PAR (6-12 years)	CTZ LCTZ placebo	10mg po OD 5mg po OD	12	27 26 27	8.19 8.79 8.12	58.0 62.5 54.0

Study, Year (Reference)	Region	Disease type (age range)	Treatment groups	Treatment dose	Treatment duration, weeks	Patients, n	Age, years++	Female, %
Ngamphaiboon et al., 2009 (22)	Asia	Recurrent wheezing (<6 years)	LRD KTF placebo	0.25ml/kg po OD 0.25ml/kg po OD	16	27 25 26	3.2 2.9 2.9	29.6 52.0 34.6
Hampel et al., 2007 (23)	USA	AR (6-12 months)	FXD FXD placebo	15mg po OD 30mg po OD	8	58 5 69	8.8 months 10.4 months ND	43.1 40.0 46.3
		AR (1-2 years)	FXD FXD placebo	15mg po OD 30mg po OD	8	27 103 131	16.1 months 17.9 months ND	48.1 39.8 38.5
Milgrom et al., 2007 (24)	USA	AR (2-5 years)	FXD placebo	30mg po OD	2	222 231	3.6 3.6	44.6 44.9
Simons et al., 2007 (25)	Canada	AD (12-24 months)	LCTZ placebo	0.125mg/kg po OD	72	255 255	19.3 19.4	39.2 35.7
Chen et al., 2006 (26)	Taiwan	PAR (2-6 years)	CTZ MLK placebo	5mg po OD 4mg po OD	12	20 20 20	4.5 4.5 4.4	40.0 45. 55.0
Prenner et al., 2006 (27)	USA, S. America, S. Africa	ND (6-24 months)	DLRD placebo	1.0mg po OD (<1 yr) 1.25mg po OD (1-2 yrs)	2	131 129	12.6 months 13.3 months	44.0 53.0
de Blic et al., 2005 (28)	Europe	SAR (6-12 years)	LCTZ placebo	5mg po OD	6	89 88	9.9 9.9	29.2 38.6
Potter et al., 2005 (29)	Africa	PAR (6-12 years)	LCTZ placebo	5mg po OD	4	154 152	9.9 9.9	35.7 42.8
Bloom et al., 2004 (30)	USA	AR or CIU (2-5 years)	DLRD placebo	1.25mg po OD	2	55 56	3.5 3.4	44.0 45.0
		AR or CIU (6-11 years)	DLRD placebo	2.5mg po OD	2	60 60	7.9 8.5	48.0 65.0

Study, Year (Reference)	Region	Disease type (age range)	Treatment groups	Treatment dose	Treatment duration, weeks	Patients, n	Age, years++	Female, %
Grimfeld et al., 2004 (31)	Europe, S. Africa, Asia, C. and S. America	Rhinitis, rhinopharyngitis, acute otitis media, laryngitis or bronchitis (12-30 months)	LRD placebo	2.5mg po OD ([?]2 yrs) 5mg po OD (>2 yrs)	52	204 208	23.9 months 24 months	35.8 42.0
Hsieh et al., 2004 (32)	Taiwan	PAR (6-12 years)	CTZ MLK placebo	10mg po OD 5mg po OD	12	21 21 22	8.1 8.2 8.1	40.0 35.0 45.0
Wahn et al., 2003 (33)	Europe, Africa, USA, Australia	SAR (6-11 years)	FXD placebo	30mg po BD	2	464 471	8.8 8.8	40.0 33.5
Segal et al., 2003 (34)	USA	SAR (6-11 years)	CTZ placebo	5mg po OD (<25kg), 10mg po OD ([?]25kg)	2	86 86	9.2 9.1	35.8 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 placebo	0.25mg/kg po BD	1	42 43	8.5 months (male), 7.9 months (female) 8.0 months (male), 7.2 months (female)	50.0 53.5
Lai et al., 2002 (36)	Asia	PAR (6-12 years)	CTZ OXD KTF placebo	10mg po OD 1mg po OD 1mg po OD	12	20 20 20 20	8.2 8.3 7.4 8.3	58.7 56.6 56.2 56.2

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 placebo	5ml po OD ([?]30kg) 10ml po OD (>30kg)	2	24 24	71.0 months 76.3 months	54.0 50.0
La Rosa et al., 2001 (38)	Europe	Chronic urticaria (2-6 years)	OXD CTZ	25mg po OD 5mg po OD	4	31 31	ND ND	ND ND
Yang et al., 2001 (39)	Asia	AR (3-12 years)	LRD placebo	5mg po OD (<30kg), 10mg po OD ([?]30kg)	3	30 30	6.0 6.6	36.4 50.0
Ciprandi et al., 2001 (40)	Europe	Perennial rhinoconjunctivitis, mild intermittent asthma (3-10 years)	CTZ placebo	5mg po OD	24	10 10	6.2 6.7	30.0 20.0
Graft et al., 2001 (41)	USA, Canada	SAR (6-11 years)	FXD FXD FXD placebo	15mg po BD 30mg po BD 60mg po BD	2	223 208 212 229	9.1 9.1 9.0 9.2	37.0 41. 47.0 39.
Salmun et al., 2000 (42)	USA	AR or CIU (2-5 years)	LRD placebo	5mg po OD	2	60 61	3.7 3.5	55.0 55.7
Simons et al., 1999 (43) *and* Wahn et al., 1998 (44) [+]	N. America	AD (1-2 years)	CTZ placebo	0.25mg/kg po BD	72	399 396	16.8 months 17.2 months	38.1 37.6
Sienra-Monge et al., 1999 (45)	C. America	AR (2-6 years)	CTZ LRD	0.2mg/kg po OD 0.2mg/kg po OD	4	40 40	4.3 4.4	40.0 35.

Study, Year (Reference)	Region	Disease type (age range)	Treatment groups	Treatment dose	Treatment duration, weeks	Patients, n	Age, years[++]	Female, %
Serra et al., 1998 (46)	Argentina	SAR (3-15 years)	LRD-PSD placebo	0.2mg/kg po BD	2	20 20	ND ND	60.0 60.0
Delgado et al., 1998 (47)	Brazil	PAR, Sinusitis (5-12 years)	LRD LRD CTZ CTZ	5mg po OD (<30kg), 10mg po OD ([?]30kg) 10mg po OD	2	10 10 10 10	7.2 9.3	50.0 50.0 50.0 50.0
	USA	AR (6-11 years)	CTZ CTZ placebo	5mg po OD 10mg po OD	4	69 72 68	9.1 8.6 8.8	33.3 27.1 36.8
Winder et al., 1996 (49) [+]								
Ciprandi et al. 1997 (50)	Europe	Allergic rhinoconjunctivitis (6-15 years)	CTZ placebo	0.15mg/kg po OD	4	10 10	8.5 (total)	55.0 (total)
deBenedictis et al., 1997 (51)	Europe	PAR (2-6 years)	CTZ OXD	5mg po OD 12mg po BD	10 d	53 52	4.6 4.8	34.0 40.0
Tinkelman et al. 1996 (52)	USA	SAR (6-11 years)	CTZ CTZ CPN	5mg po OD (<25kg), 10mg po OD ([?]25kg) 2.5mg po BD (<25kg), 5mg po BD ([?]25kg) 2mg po TD	2	63 62 63	8.6 9.1 8.7	35.5 29.5 30.2
Fasce et al., 1996 (53)	Europe	Mite allergic asthma (5-14 years)	CTZ placebo	5mg po OD	2	10 10	8.3 (total)	ND ND

Study, Year (Reference)	Region	Disease type (age range)	Treatment groups	Treatment dose	Treatment duration, weeks	Patients, n	Age, years++	Female, %
LaRosa et al., 1994 (54)	Europe	AD (6-12 years)	CTZ placebo	5mg po OD ([?]30kg), 10mg po OD (>30kg)	8	12 11	7.0 (total)	41.6 63.6
Jobst et al., 1994 (55)	Europe	PAR (6-12 years)	CTZ CTZ CTZ placebo	2.5mg po OD 5mg po OD 10mg po OD	2	84 85 76 83	8.6 9.2 9.3 8.9	45.2 29.4 42.1 45.8
Allegra et al., 1993 (56)	Europe	SAR (2-6 years)	CTZ placebo	5mg po OD	2	54 53	4.6 4.3	33.3 28.3
Masi et al., 1993 (57)	Europe	Seasonal allergic rhinoconjunctivitis (6-12 years)	CTZ placebo	5mg po BD	2	63 61	10.1 10.2	39.7 37.7
Baelde et al., 1992 (58)	Europe	PAR (2-14 years)	CTZ CTZ placebo	5mg po BD 2.5mg po BD	2	46 46 46	8.8 8.5 8.6	30.4 30.4 39.1
Boner et al., 1989 (59)	Europe	SAR (4-12 years)	LRD DCPN	5mg po OD ([?]20kg or [?]6 yrs), 2.5mg po OD (<20kg or <6yrs) 1mg po TD ([?]20kg or [?]6 yrs), 0.5mg po TD (<20kg or <6yrs)	2	21 19	7.6 7.8	33.3 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; 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.

Table 2. Risk of bias in included trials

Study, Year (Reference)	Sequence generation	Allocation concealment	Blinding
Wandalsen et al., 2017 (13)	Unclear	Unclear	Low
Nayak et al., 2017 (14)	Unclear	Unclear	Unclear
Novak et al., 2016 (15)	Low	Unclear	Low
Potter et al., 2016 (16)	Unclear	Unclear	Low
Potter et al., 2013 (17)	Unclear	Unclear	Low
Wu et al., 2012 (18)	Unclear	High	High
Marucci et al., 2011 (19)	Unclear	Low	Unclear
Hampel et al., 2010 (20)	Unclear	Unclear	Low
Lee et al., 2009 (21)	Unclear	Unclear	Unclear
Ngamphaiboon et al., 2009 (22)	Unclear	Unclear	Unclear
Hampel et al., 2007 (23)	Unclear	Unclear	Unclear
Milgrom et al., 2007 (24)	Unclear	Unclear	Low
Simons et al., 2007 (25)	Unclear	Unclear	Low
Chen et al., 2006 (26)	Unclear	Unclear	Unclear
Prenner et al., 2006 (27)	Low	Unclear	Low
de Blic et al., 2005 (28)	Unclear	Unclear	Low
Potter et al., 2005 (29)	High	Low	Low
Bloom et al., 2004 (30)	Unclear	Unclear	Low
Grimfeld et al., 2004 (31)	Unclear	Unclear	Unclear
Hsieh et al., 2004 (32)	Low	Unclear	Unclear
Wahn et al., 2003 (33)	Unclear	Unclear	Low
Segal et al., 2003 (34)	Unclear	Unclear	Unclear
Simons et al., 2003 (35)	Unclear	Unclear	Low
Lai et al., 2002 (36)	Low	Unclear	Unclear
Chunharas et al., 2002 (37)	Unclear	Unclear	Unclear
La Rosa et al., 2001 (38)	Low	Low	Low
Yang et al., 2001 (39)	Unclear	Unclear	Unclear
Ciprandi et al., 2001 (40)	Low	Unclear	Low
Graft et al., 2001 (41)	Unclear	Unclear	Unclear
Salmun et al., 2000 (42)	Unclear	Unclear	Unclear
Simons et al., 1999 (43) *and* Wahn et al., 1998 (44)	Low	Low	Low
Sienra-Monge et al., 1999 (45)	Unclear	Unclear	Unclear
Serra et al., 1998 (46)	Unclear	Unclear	Unclear
Delgado et al., 1998 (47)	Unclear	Unclear	Unclear
Pearlman et al., 1997 (48) *and* Winder et al., 1996 (49)	Unclear	Unclear	Low
Ciprandi et al., 1997 (50)	Unclear	Unclear	Unclear
deBenedictis et al., 1997 (51)	Unclear	Unclear	Low
Tinkelman et al., 1996 (52)	Unclear	Low	High
Fasce et al., 1996 (53)	Unclear	Unclear	Unclear
La Rosa et al., 1994 (54)	Unclear	Unclear	Low

Study, Year (Reference)	Sequence generation	Allocation concealment	Blinding
Jobst et al., 1994 (55)	Low	Unclear	Low
Allegra et al., 1993 (56)	Low	Unclear	Low
Masi et al., 1993 (57)	Unclear	Unclear	Low
Baelde et al., 1992 (58)	Low	Unclear	Low
Boner et al. 1989 (59)	Unclear	Unclear	High

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 DCPN	105 105	ND ND	ND ND	ND ND	0.9 1.9	Six patients in the DLRD group and 11 in the DCPN group presented ECG changes at the end of the study
Nayak et al., 2017 (14)	CTZ LRD placebo	228 220 219	0 0 0	19.7 21.8 22.7	4.8 4.5 2.6	2.6 5.6 3.9	
Novak et al, 2016 (15)	BLN placebo	260 249	0.7 3.6	68.5 67.5	5.8 8.0	1.1 0.8	No clinically and/or statistically relevant differences between bilastine and placebo for vital signs, clinical laboratory values, ECG parameters or physical examination
Potter et al., 2016 (16)	RPD DLRD placebo	66 71 69	ND ND ND	61.0 65.0 54.0	1.5 5.6 7.2	ND ND ND	
Potter et al., 2013 (17)	RPD placebo	180 180	ND ND	37.2 30.0	6.1 5.5	ND ND	

Wu et al., 2012 (18)	LRD CPHD	30 30	ND ND	0 13.0	0 13.0	0 0	
Marucci et al., 2011 (19)	LCTZ placebo	30 30	0 0	14.3 10.5	ND ND	ND ND	
Hampel et al., 2010 (20)	LCTZ placebo [6-11 months]	45 24	ND ND	64.4 70.8	11.1 4.2	6.7 0	No clinically relevant changes or trends in vital signs, laboratory tests, or ECG parameters were noted
	LCTZ placebo [1-5 years]	114 59	ND ND	35.1 35.6	7.0 11.9	0 0	
Lee et al., 2009 (21)	CTZ LCTZ placebo	27 26 27	0 0 0	3.7 3.8 0	ND ND ND	0 0 0	
Ngamphaiboon et l., 2009 (22)	LRD KTF placebo	27 25 26	ND ND ND	ND ND ND	ND ND ND	ND ND ND	A few patients had mild AEs in all groups.
Hampel et al., 2007 (23)	FXD FXD placebo [6-11 months]	58 5 69	ND ND ND	39.7 40 40.6	8.8 (in total for FXD in both studies) 9.5 (in total for placebo in both studies)	3.2 4.3	No clinical differences were observed between the fexofenadine treatment groups and placebo for any vital sign or any ECG variable.
	FXD FXD placebo [1-2 years]	27 103 131	ND ND ND	40.7 35.0 52.3		3.1 5.3	
Milgrom et al., 2007 (24)	FXD placebo	222 231	ND ND	50.0 50.2	9.5 8.2	ND ND	No clinically relevant ECG changes.

Simons et al., 2007 (25)	LCTZ placebo	255 255	12.2 14.5	96.9 95.7	5.1 6.3	2.0 1.2	There were no significant differences between levocetirizine- and placebo-treated children with respect to laboratory test results.
Chen et al., 2006 (26)	CTZ MLK placebo	20 20 20	0 0 0	10.0 0 0	10.0 0 0	0 0 0	
Prenner et al., 2006 (27)	DLRD placebo	131 129	0 0.8	67.2 58.9	26 21.8	0.8 1.6	No statistically significant or clinically relevant differences in ECG parameters.
de Blic et al., 2005 (28)	LCTZ placebo	89 88	0 0	33.7 30.7	5.6 5.6	0 1.0	
Potter et al., 2005 (29)	LCTZ placebo	154 152	0 0	55.2 52.6	7.8 5.9	1.3 1.3	

Bloom et al., 2004 (30)	DLRD placebo	55 56	ND ND	12.7 10.7	3.6 0	0 0	No clinically relevant changes were noted in median clinical laboratory test values or mean vital signs. Increase in heart rate was observed in the study of subjects aged 2 years–5 years, but the incidence was similar in the deslo-ratadine and placebo groups.
	DLRD placebo	60 60	ND ND	1.7 10.0	0 0	0 0	
Grimfeld et al., 2004 (31)	LRD placebo	204 208	ND ND	80.9 85.0	ND ND	0 0.5	There was no difference between groups regarding ECG or laboratory parameters.
Hsieh et al., 2004 (32)	CTZ MLK placebo	21 21 22	0 0 0	5.0 5.0 10.0	ND ND ND	0 0 0	

Wahn et al., 2003 (33)	FXD placebo	464 471	0.2 ND	18.3 18.7	2.3 3.0	0.6 0	There were no significant differences in changes in clinical laboratory and vital signs results between the fexofenadine- and placebo-treated groups.
Segal et al., 2003 (34)	CTZ placebo	86 86	ND ND	32.1 20.9	ND ND	0 0	
Simons et al., 2003 (35)	CTZ placebo	42 43	ND ND	73.8 88.4	45.2 62.8	7.1 6.9	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 group.
Lai et al. 2002 (36)	CTZ OXD KTF placebo	20 20 20 20	0 0 0 0	15.8 16.7 12.5 12.5	ND ND ND ND	ND ND ND ND	
Chunharas et al., 2002 (37)	LRD placebo	24 24	ND ND	12.5 8.0	ND ND	4.2 0	

La Rosa et al., 2001 (38)	CTZ OXT	31 31	ND ND	0 3.2	0 3.2	0 3.2	The hematologic, hematochemical, and urinary tests were within the normal limits in all patients before and at the end of the treatment.
Yang et al., 2001 (39)	LRD placebo	30 30	ND ND	0 0	0 0	ND ND	
Ciprandi et al., 2001 (40)	CTZ placebo	10 10	ND ND	0 0	0 0	0 0	
Graft et al., 2001 (41)	FXD FXD FXD placebo	223 208 212 229	ND ND ND ND	35.3 36.8 34.7 36.2	ND ND ND ND	0.40 1.40 0.50 2.20	Lab - ECG changes unremarkable, vital signs consistent among groups.

Salmun et al., 2000 (42)	LRD placebo	60 61	ND ND	32.0 41.0	ND ND	0 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.
Simons et al., 1999 (43) *and* Wahn et al., 1998 (44)	CTZ placebo	399 396	9.3 13.6	98.5 98.7	0.5 1.8	2.8 3.8	There were no statistically significant differences between groups in QTc interval or behavioral/developm assessments.
Sienra-Monge et al.,1999 (45)	CTZ LRD	40 40	ND ND	5.0 0	ND ND	5.0 ND	
Serra et al., 1998 (46)	LRD-PSD placebo	20 20	ND ND	5.0 0	ND 0	0 0	No changes in vital signs or lab tests.

Delgado et al., 1998 (47)	LRD CTZ LRD CTZ	10 10 10 10	ND ND ND ND	0 0 0 0	0 0 0 0	0 0 0 0	The ECG parameters remained within normal limits following treatment, and all children presented with sinusal rhythm at the follow-up evaluation.
Pearlman et al., 1997 (48) *and* Winder et al., 1996 (49)	CTZ CTZ placebo	69 72 68	ND ND ND	ND ND ND	ND ND ND	ND ND ND	No pronounced differences in the incidence of AEs between cetirizine groups, no statistically significant difference with placebo.
Ciprandi et al., 1997 (50)	CTZ placebo	10 10	ND	10.0 20.0	ND	0 0	
Benedictis et al., 1997 (51)	CTZ OXD	53 52	ND ND	8.0 7.7	ND ND	0 0	No clinically significant changes in laboratory tests were found except for one oxatomide patient.
Tinkelman et al., 1996 (52)	CTZ CTZ CPN	63 62 63	ND ND ND	33.6 38.1	ND ND ND	0 0 0	

Fasce et al., 1996 (53)	CTZ placebo	10 10	ND ND	ND ND	ND ND	0 0	No important adverse reactions reported.
La Rosa et al., 1994 (54)	CTZ placebo	12 11	ND ND	0 ND	0 ND	ND ND	
Jobst et al., 1994 (55)	CTZ CTZ CTZ placebo	84 85 76 83	ND ND ND ND	25.0 14.0 22.4 18.4	ND ND ND ND	4.8 2.9 1.3 1.2	
Allegra et al.,1993 (56)	CTZ placebo	54 53	ND ND	24.1 20.7	5.6 0	1.8 3.8	Minor changes in clinical laboratory tests were carefully reviewed and considered not to be clinically relevant.
Masi et al., 1993 (57)	CTZ placebo	63 61	ND ND	22.2 22.9	ND ND	3.2 1.6	Minor changes in clinical laboratory tests were considered not to be clinically relevant.

Baelde et al., 1992 (58)	CTZ CTZ Placebo	46 46 46	ND ND ND	6.5 17.3 13.0	ND ND ND	0 0 0	Leucocytosis 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.
Boner et al., 1989 (59)	LRD DCPN	21 19	ND	19.0 31.5	ND	4.7 0	Hematological counts and bio-chemical analysis showed that loratadine and dexchlor-pheni-ramine at the dosages used were devoid of toxic effects.

Abbreviations: AE = Adverse event; BLN = Bilastine; CPHD = Cyproheptadine; CPN = Chlorpheniramine;

CTZ = Cetirizine; DCPN = Dexchlorpheniramine; DLRD = Desloratadine; FXD = Fexofenadine; KTF = Ketotifen; LCTZ = Levocetirizine; LRD = Loratadine; MLK = Montelukast; ND = No data; OXD = Oxotamide; PSD = Pseudoephedrine; RPD = Rupatadine; + Relation to study drug was assessed by the authors of each trial.

Table 4. Adverse events reported in included RCTs

Study, Year (Reference)	Patients with Adverse Events (%) per treatment group	Patients with Adverse Events (%) per treatment group	Patients with Adverse Events (%) per treatment group	Patients with Adverse Events (%) per treatment group	Patients with Adverse Events (%) per treatment group	Patients with Adverse Events (%) per treatment group	Patients with Adverse Events (%) per treatment group	Patients with Adverse Events (%) per treatment group	Patients with Adverse Events (%) per treatment group	Patients with Adverse Events (%) per treatment group	Patients with Adverse Events (%) per treatment group	Patients with Adverse Events (%) per treatment group	Patients with Adverse Events (%) per treatment group	Patients with Adverse Events (%) per treatment group	Patients with Adverse Events (%) per treatment group	Patients with Adverse Events (%) per treatment group	Pati with Ad- verse Eve (%) per trea men grou
Wandalsen et al., 2017 (13)	DLRD	DLRD	DLRD	DLRD	DLRD	DLRD	DCPN	DCPN	DCPN	DCPN	DCPN	DCPN						

	Somnolence	8.6	8.6	8.6	8.6	Somnolence	Somnolence	17.1	17.1	17.1	17.1					
	Cough	6.6	6.6	6.6	6.6	ECG	ECG	11.3	11.3	11.3	11.3					
	ECG	6.1	6.1	6.1	6.1	changes	changes	4.8	4.8	4.8	4.8					
	changes	2.9	2.9	2.9	2.9	In-	In-	4.8	4.8	4.8	4.8					
	Epis-	2.9	2.9	2.9	2.9	creased	creased	3.8	3.8	3.8	3.8					
	taxis	2.9	2.9	2.9	2.9	ap-	ap-	2.9	2.9	2.9	2.9					
	In-	1.9	1.9	1.9	1.9	petite	petite	2.9	2.9	2.9	2.9					
	som-	1.9	1.9	1.9	1.9	Cough	Cough	2.9	2.9	2.9	2.9					
	nia	1.9	1.9	1.9	1.9	Fever	Fever	1.9	1.9	1.9	1.9					
	Vomit	1.9	1.9	1.9	1.9	Headache	Headache	1.9	1.9	1.9	1.9					
	In-	1.9	1.9	1.9	1.9	Di-	Di-	1.9	1.9	1.9	1.9					
	creased	0.9	0.9	0.9	0.9	ar-	ar-	1.9	1.9	1.9	1.9					
	ap-	0.9	0.9	0.9	0.9	rhea	rhea	1.9	1.9	1.9	1.9					
	petite	0.9	0.9	0.9	0.9	Ab-	Ab-	1.9	1.9	1.9	1.9					
	Heart	0	0	0	0	dom-	dom-	1.9	1.9	1.9	1.9					
	burn	0	0	0	0	i-	i-	0.9	0.9	0.9	0.9					
	Di-	0	0	0	0	nal	nal	0	0	0	0					
	ar-	0	0	0	0	pain	pain	0	0	0	0					
	rhea					Ex-	Ex-									
	Pain					cite-	cite-									
	Ab-					ment	ment									
	dom-					Breath-	Breath-									
	i-					less-	less-									
	nal					ness	ness									
	pain					In-	In-									
	Ex-					som-	som-									
	cite-					nia	nia									
	ment					Ir-	Ir-									
	Ir-					ri-	ri-									
	ri-					tabil-	tabil-									
	tabil-					ity	ity									
	ity					Nau-	Nau-									
	Dizzi-					sea	sea									
	ness					Dizzi-	Dizzi-									
	Headache					ness	ness									
	Breath-					Vomit	Vomit									
	less-					Heart	Heart									
	ness					burn	burn									
	Fever					Epis-	Epis-									
	Nausea					taxis	taxis									
						Pain	Pain									
Nayak et al., 2017 (14)	CTZ	CTZ	CTZ	CTZ	CTZ	CTZ	LRD	LRD	LRD	LRD	LRD	LRD	Placebo	Placebo	Placebo	Placebo	Plac

Novak et al., 2016 (15)	BLN	Treatment-related: Headache Pharyngitis Fever Vomiting Sinusitis Somnolence Lymphadenopathy Asthma	BLN	Treatment-related: Headache Pharyngitis Fever Vomiting Sinusitis Somnolence Lymphadenopathy Asthma	BLN	Treatment-related: Headache Pharyngitis Fever Vomiting Sinusitis Somnolence Lymphadenopathy Asthma	3.5 1.8 1.3 1.3 0.4 0.4	3.5 1.8 1.3 1.3 0.4 0.4	3.5 1.8 1.3 1.3 0.4 0.4	Placebo	Treatment-related: Headache Pharyngitis Vomiting Sinusitis Lymphadenopathy Nausea Epistaxis Fever Asthma	Placebo	Treatment-related: Headache Pharyngitis Vomiting Sinusitis Lymphadenopathy Nausea Epistaxis Fever Asthma	Placebo	Treatment-related: Headache Pharyngitis Vomiting Sinusitis Lymphadenopathy Nausea Epistaxis Fever Asthma	3.6 2.7 2.7 1.8 1.8 1.4 0.9 0.5	3.6 2.7 2.7 1.8 1.8 1.8 1.4 0.9 0.5	Placebo	Treatment-related: Headache Pharyngitis Sinusitis Asthma Bronchitis Fever Vomiting Nausea Epistaxis	3.1 3.5 1.7 1.3 1.3 0.9 0.9 0.9 0.9	3.1 3.5 1.7 1.3 1.3 0.9 0.9 0.9 0.9

	Headache	Headache	Headache	11.5	11.5	11.5	Headache	Headache	Headache	Headache	10.4	10.4										
	Cough	Cough	Cough	8.8	8.8	8.8	Cough	Cough	Cough	Cough	8.8	8.8										
	Pharyngitis	Pharyngitis	Pharyngitis	9.6	9.6	9.6	Pharyngitis	Pharyngitis	Pharyngitis	Pharyngitis	6.4	6.4										
	Allergic conjunctivitis	Allergic conjunctivitis	Allergic conjunctivitis	9.2	9.2	9.2	Allergic conjunctivitis	Allergic conjunctivitis	Allergic conjunctivitis	Allergic conjunctivitis	7.6	7.6										
	Nasopharyngitis	Nasopharyngitis	Nasopharyngitis	9.2	9.2	9.2	Nasopharyngitis	Nasopharyngitis	Nasopharyngitis	Nasopharyngitis	6.8	6.8										
	Pyrexia	Pyrexia	Pyrexia	6.2	6.2	6.2	Pyrexia	Pyrexia	Pyrexia	Pyrexia	9.2	9.2										
	Allergic rhinitis	Allergic rhinitis	Allergic rhinitis	5.0	5.0	5.0	Allergic rhinitis	Allergic rhinitis	Allergic rhinitis	Allergic rhinitis	8.4	8.4										
	Bronchitis	Bronchitis	Bronchitis	3.8	3.8	3.8	Bronchitis	Bronchitis	Bronchitis	Bronchitis	5.6	5.6										
	Viral infection	Viral infection	Viral infection	3.8	3.8	3.8	Viral infection	Viral infection	Viral infection	Viral infection	6.4	6.4										
Potter et al., 2016 (16)	RPD	RPD	RPD	RPD	RPD	RPD	DSLRD	DSLRD	DSLRD	DSLRD	DSLRD	DSLRD	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo				
	Treatment-related: Headache	Treatment-related: Headache	Treatment-related: Headache	1.5	1.5	1.5	Treatment-related: Decreased appetite	Treatment-related: Decreased appetite	Treatment-related: Decreased appetite	Treatment-related: Decreased appetite	1.4	1.4	Treatment-related: Increased ALP	Treatment-related: Increased ALP	Treatment-related: Increased ALP	1.4	1.4					
							Dizziness	Dizziness	Dizziness	Dizziness	1.4	1.4	Abdominal pain upper	Abdominal pain upper	Abdominal pain upper	1.4	1.4					
							Headache	Headache	Headache	Headache	1.4	1.4	Abdominal pain	Abdominal pain	Abdominal pain	1.4	1.4					
							Constipation	Constipation	Constipation	Constipation	1.4	1.4	Constipation	Constipation	Constipation	1.4	1.4					
							Nausea	Nausea	Nausea	Nausea	1.4	1.4										

Potter et al., 2013 (17)	RPD	RPD	RPD	RPD	RPD	RPD	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo
	Headache, Cough, Abdominal pain, Epistaxis, Eczema, Influenza Somnolence	Headache, Cough, Abdominal pain, Epistaxis, Eczema, Influenza Somnolence	Headache, Cough, Abdominal pain, Epistaxis, Eczema, Influenza Somnolence	12.8 <4.0 1.1	12.8 <4.0 1.1	12.8 <4.0 1.1	Headache, Cough, Abdominal pain, Epistaxis, Eczema, Influenza	Headache, Cough, Abdominal pain, Epistaxis, Eczema, Influenza	5.6 <4.0	5.6 <4.0	5.6 <4.0	5.6 <4.0
Wu et al., 2012 (18)	LRD	LRD	LRD	LRD	LRD	LRD	CPHD	CPHD	CPHD	CPHD	CPHD	CPHD
	No AEs	No AEs	No AEs	No AEs	No AEs	No AEs	Increased appetite Increased drowsiness	Increased appetite Increased drowsiness	8.7 4.3	8.7 4.3	8.7 4.3	8.7 4.3
Marucci et al., 2011 (19)	LCTZ	LCTZ	LCTZ	LCTZ	LCTZ	LCTZ	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo
	Headache	Headache	Headache	Headache	14.3	14.3	Headache Abdominal pain	Headache Abdominal pain	10.5 5.3	10.5 5.3	10.5 5.3	10.5 5.3
Hampel et al., 2010 (20)	LCTZ (1.25 mg OD)	LCTZ (1.25 mg OD)	LCTZ (1.25 mg OD)	LCTZ (1.25 mg OD)	LCTZ (1.25 mg OD)	LCTZ (1.25 mg OD)	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo

	Diarrhea Teething Constipation Pyrexia Irritability URTI Sinusitis Otitis media Viral URTI Somnolence Cough Skin and subcutaneous tissue disorders	Diarrhea Teething Constipation Pyrexia Irritability URTI Sinusitis Otitis media Viral URTI Somnolence Cough Skin and subcutaneous tissue disorders	Diarrhea Teething Constipation Pyrexia Irritability URTI Sinusitis Otitis media Viral URTI Somnolence Cough Skin and subcutaneous tissue disorders	Diarrhea Teething Constipation Pyrexia Irritability URTI Sinusitis Otitis media Viral URTI Somnolence Cough Skin and subcutaneous tissue disorders	13.3 6.7 6.7 15.6 2.2 4.4 2.2 4.4 2.2 4.4 2.2 13.3	13.3 6.7 6.7 15.6 2.2 4.4 2.2 4.4 2.2 13.3	Diarrhea Constipation Pyrexia Irritability Otitis media Somnolence Cough Skin and subcutaneous tissue disorders	Diarrhea Constipation Pyrexia Irritability Otitis media Somnolence Cough Skin and subcutaneous tissue disorders	Diarrhea Constipation Pyrexia Irritability Otitis media Somnolence Cough Skin and subcutaneous tissue disorders	4.2 4.2 16.7 12.5 8.3 4.2 8.3 29.2	4.2 4.2 16.7 12.5 8.3 4.2 8.3 29.2	4.2 4.2 16.7 12.5 8.3 4.2 8.3 29.2	4.2 4.2 16.7 12.5 8.3 4.2 8.3 29.2
Hampel et al., 2010 (20)	LCTZ (1.25 mg BD)	LCTZ (1.25 mg BD)	LCTZ (1.25 mg BD)	LCTZ (1.25 mg BD)	LCTZ (1.25 mg BD)	LCTZ (1.25 mg BD)	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo			

	Diarrhea	Diarrhea	Diarrhea	Diarrhea	3.5	3.5	Diarrhea	Diarrhea	Diarrhea	3.4	3.4	3.4	3.4							
	Teething	Teething	Teething	Teething	1.8	1.8	Pyrexia	Pyrexia	Pyrexia	1.7	1.7	1.7	1.7							
	Constipation	Constipation	Constipation	Constipation	0.9	0.9	URTI	URTI	URTI	3.4	3.4	3.4	3.4							
					4.4	4.4	Sinusitis	Sinusitis	Sinusitis	3.4	3.4	3.4	3.4							
					2.6	2.6				3.4	3.4	3.4	3.4							
					0.9	0.9				3.4	3.4	3.4	3.4							
	Pyrexia	Pyrexia	Pyrexia	Pyrexia	2.6	2.6	Viral	Viral	Viral	5.1	5.1	5.1	5.1							
	URTI	URTI	URTI	URTI	0.9	0.9				8.5	8.5	8.5	8.5							
	Sinusitis	Sinusitis	Sinusitis	Sinusitis	0.9	0.9	URTI	URTI	URTI	1.7	1.7	1.7	1.7							
					3.5	3.5	Somnolence	Somnolence	Somnolence											
					4.4	4.4														
	Otitis media Viral	Otitis media Viral	Otitis media Viral	Otitis media Viral			Psychomotor hyperactivity	Psychomotor hyperactivity	Psychomotor hyperactivity											
	URTI	URTI	URTI	URTI																
	Somnolence	Somnolence	Somnolence	Somnolence																
	Cough	Cough	Cough	Cough			Cough	Cough	Cough											
	Skin and subcutaneous tissue disorders	Skin and subcutaneous tissue disorders	Skin and subcutaneous tissue disorders	Skin and subcutaneous tissue disorders			Skin and subcutaneous tissue disorders	Skin and subcutaneous tissue disorders	Skin and subcutaneous tissue disorders											
Lee et al., 2009 (21)	CTZ	CTZ	CTZ	CTZ	CTZ	CTZ	LCTZ	LCTZ	LCTZ	LCTZ	LCTZ	LCTZ	Placebo	Placebo	Placebo	Placebo	Plac			
	Mild sedation	Mild sedation	Mild sedation	Mild sedation	3.7	3.7	Mild fatigue	Mild fatigue	Mild fatigue	3.8	3.8	3.8	3.8	No AEs						
Ngamphaiboon et al., 2009 (22)	LRD	LRD	LRD	LRD	LRD	LRD	KTF	KTF	KTF	KTF	KTF	KTF	Placebo	Placebo	Placebo	Placebo	Plac			
	Irritability Somnolence	Irritability Somnolence	Irritability Somnolence	Irritability Somnolence	ND	ND	Irritability Somnolence	Irritability Somnolence	Irritability Somnolence	ND	ND	ND	ND	Irritability Somnolence	ND	ND	ND			
Hampel et al., 2007 (23)	FXD HCL (15 mg BD)	FXD HCL (15 mg BD)	FXD HCL (15 mg BD)	FXD HCL (15 mg BD)	FXD HCL (15 mg BD)	FXD HCL (15 mg BD)	FXD HCL (30 mg BD)	FXD HCL (30 mg BD)	FXD HCL (30 mg BD)	FXD HCL (30 mg BD)	FXD HCL (30 mg BD)	FXD HCL (30 mg BD)	Placebo	Placebo	Placebo	Placebo	Plac			

	Digestive system Vomiting Diarrhea Gastroenteritis *Respiratory system* Cough increased URTI Rhinitis Fever Infection Otitis media *Skin and appendages*	*Digestive system* Vomiting Diarrhea Gastroenteritis *Respiratory system* Cough increased URTI Rhinitis Fever Infection Otitis media *Skin and appendages*	*Digestive system* Vomiting Diarrhea Gastroenteritis *Respiratory system* Cough increased URTI Rhinitis Fever Infection Otitis media *Skin and appendages*	*Digestive system* Vomiting Diarrhea Gastroenteritis *Respiratory system* Cough increased URTI Rhinitis Fever Infection Otitis media *Skin and appendages*	25.9 15.5 5.2 3.4 12.2 1.7 1.7 3.4 1.7 3.4 1.7 6.9	25.9 15.5 5.2 3.4 12.2 1.7 1.7 3.4 1.7 3.4 1.7 6.9	*Digestive system* Vomiting *Respiratory system* URTI	*Digestive system* Vomiting *Respiratory system* URTI	*Digestive system* Vomiting *Respiratory system* URTI	20 20 20 20 20 20 20	20 20 20 20 20 20 20	20 20 20 20 20 20 20	20 20 20 20 20 20 20	*Digestive system* Vomiting Diarrhea *Respiratory system* URTI Fever Unintentional injury Infection Otitis media *Skin and appendages*	15.9 14.5 1.4 10.1 5.8 5.8 1.4 2.9 7.2 1.4	15.9 14.5 1.4 10.1 5.8 5.8 1.4 2.9 7.2 1.4	15.9 14.5 1.4 10.1 5.8 5.8 1.4 2.9 7.2 1.4
Hampe et al.,2007 (23)	FXD HCL (15 mg BD)	FXD HCL (15 mg BD)	FXD HCL (15 mg BD)	FXD HCL (15 mg BD)	FXD HCL (15 mg BD)	FXD HCL (15 mg BD)	FXD HCL (30 mg BD)	FXD HCL (30 mg BD)	FXD HCL (30 mg BD)	FXD HCL (30 mg BD)	FXD HCL (30 mg BD)	FXD HCL (30 mg BD)	Placebo	Placebo	Placebo	Placebo	Plac

	Digestive system Vomiting Diarrhea Gastroenteritis *Respiratory system* Cough increased URTI Fever Unintentional injury Otitis media Ophthalmitis Ear disorder Skin and appendages	*Digestive system* Vomiting Diarrhea Gastroenteritis *Respiratory system* Cough increased URTI Fever Unintentional injury Otitis media Ophthalmitis Ear disorder Skin and appendages	*Digestive system* Vomiting Diarrhea Gastroenteritis *Respiratory system* Cough increased URTI Fever Unintentional injury Otitis media Ophthalmitis Ear disorder Skin and appendages	*Digestive system* Vomiting Diarrhea Gastroenteritis *Respiratory system* Cough increased URTI Fever Unintentional injury Otitis media Ophthalmitis Ear disorder Skin and appendages	18.5 11.1 3.7 3.7 7.4 3.7 3.7 3.7 3.7 7.4 3.7 3.7 3.7	18.5 11.1 3.7 3.7 7.4 3.7 3.7 3.7 3.7 7.4 3.7 3.7 3.7	*Digestive system* Vomiting Diarrhea Gastroenteritis Flatulence *Respiratory system* Cough increased URTI Rhinitis Fever Unintentional injury Infection Otitis media Skin and appendages	*Digestive system* Vomiting Diarrhea Gastroenteritis Flatulence *Respiratory system* Cough increased URTI Rhinitis Fever Unintentional injury Infection Otitis media Skin and appendages	*Digestive system* Vomiting Diarrhea Gastroenteritis Flatulence *Respiratory system* Cough increased URTI Rhinitis Fever Unintentional injury Infection Otitis media Skin and appendages	15.5 4.9 5.8 1.0 1.0 11.7 3.9 3.9 2.9 4.9 1.0 1.9 6.8 3.9	15.5 4.9 5.8 1.0 1.0 11.7 3.9 3.9 2.9 4.9 1.0 1.9 6.8 3.9	15.5 4.9 5.8 1.0 1.0 11.7 3.9 3.9 2.9 4.9 1.0 1.9 6.8 3.9	15.5 4.9 5.8 1.0 1.0 11.7 3.9 3.9 2.9 4.9 1.0 1.9 6.8 3.9	*Digestive system* Vomiting Diarrhea Gastroenteritis Flatulence *Respiratory system* Cough increased URTI Rhinitis Fever Infection Otitis media Ear disorder Skin and appendages	20.8 13.1 2.3 1.5 3.1 18.5 6.2 6.2 6 10.8 6.2 4.6 2.3 5.4	20.8 13.1 2.3 1.5 3.1 18.5 6.2 6.2 6 10.8 6.2 4.6 2.3 5.4	20.8 13.1 2.3 1.5 3.1 18.5 6.2 6.2 6 10.8 6.2 4.6 2.3 5.4
Milgrom et al., 2007 (24)	FXD HCL	FXD HCL	FXD HCL	FXD HCL	FXD HCL	FXD HCL	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo					

	Respiratory system	*Respiratory system*	*Respiratory system*	*Respiratory system*	*Respiratory system*	20.3	20.3	*Respiratory system*	*Respiratory system*	*Respiratory system*	*Respiratory system*	17.3	17.3	17.3	17.3
	System	System	System	System	4.5	4.5	System	System	System	3.0	3.0	3.0	3.0	
	system	*system*	*system*	*system*	4.1	4.1	*system*	*system*	*system*	6.9	6.9	6.9	6.9	
	Cough	Cough	Cough	Cough	4.1	4.1	Cough	Cough	Cough	2.6	2.6	2.6	2.6	
	increased	increased	increased	increased	2.7	2.7	increased	increased	increased	0.9	0.9	0.9	0.9	
	URTI	URTI	URTI	URTI	5.9	5.9	URTI	URTI	URTI	5.6	5.6	5.6	5.6	
	Rhinitis	Rhinitis	Rhinitis	Rhinitis	4.5	4.5	Rhinitis	Rhinitis	Rhinitis	3.0	3.0	3.0	3.0	
	Pharyngitis	Pharyngitis	Pharyngitis	Pharyngitis	3.6	3.6	Pharyngitis	Pharyngitis	Pharyngitis	6.1	6.1	6.1	6.1	
	Fever	Fever	Fever	Fever	5.0	5.0	Fever	Fever	Fever	4.8	4.8	4.8	4.8	
	Accidental injury	Accidental injury	Accidental injury	Accidental injury	2.7	2.7	Accidental injury	Accidental injury	Accidental injury	2.6	2.6	2.6	2.6	
	Infection	Infection	Infection	Infection	2.3	2.3	Infection	Infection	Infection	3.0	3.0	3.0	3.0	
	Vomiting	Vomiting	Vomiting	Vomiting	3.2	3.2	Vomiting	Vomiting	Vomiting	3.9	3.9	3.9	3.9	
	GI pain	GI pain	GI pain	GI pain	3.6	3.6	GI pain	GI pain	GI pain	1.3	1.3	1.3	1.3	
	Diarrhea	Diarrhea	Diarrhea	Diarrhea	1.4	1.4	Diarrhea	Diarrhea	Diarrhea	2.6	2.6	2.6	2.6	
	Headache	Headache	Headache	Headache	5.9	5.9	Headache	Headache	Headache	5.6	5.6	5.6	5.6	
	Otitis media	Otitis media	Otitis media	Otitis media			Otitis media	Otitis media	Otitis media					
	Ear pain	Ear pain	Ear pain	Ear pain			Ear pain	Ear pain	Ear pain					
	Special senses	Special senses	Special senses	Special senses			Special senses	Special senses	Special senses					
Simons et al.,2007 (25)	LCTZ	LCTZ	LCTZ	LCTZ	LCTZ	LCTZ	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo		

Serious AEs: Wheezing	Serious AEs: Wheezing	Serious AEs: Wheezing	Serious AEs: Wheezing	4.7	4.7
Dermatitis	Dermatitis	Dermatitis	Dermatitis	1.2	1.2
atopic	atopic	atopic	atopic	0.8	0.8
Gastroenteritis	Gastroenteritis	Gastroenteritis	Gastroenteritis	1.6	1.6
Cough	Cough	Cough	Cough	2.0	2.0
Bronchopneumonia	Bronchopneumonia	Bronchopneumonia	Bronchopneumonia	0.4	0.4
Febrile convulsion	Febrile convulsion	Febrile convulsion	Febrile convulsion	1.2	1.2
Urticaria	Urticaria	Urticaria	Urticaria	0.4	0.4
Neurologic/behavioral events:	Neurologic/behavioral events:	Neurologic/behavioral events:	Neurologic/behavioral events:	0.4	0.4
Abnormal behavior	Abnormal behavior	Abnormal behavior	Abnormal behavior		
Agitation	Agitation	Agitation	Agitation		
Bronchopneumonia	Bronchopneumonia	Bronchopneumonia	Bronchopneumonia		
Convulsions	Convulsions	Convulsions	Convulsions		
Epilepsy	Epilepsy	Epilepsy	Epilepsy		
Febrile convulsions	Febrile convulsions	Febrile convulsions	Febrile convulsions		
Headache	Headache	Headache	Headache		
Insomnia	Insomnia	Insomnia	Insomnia		
Nervousness	Nervousness	Nervousness	Nervousness		
Sleep disorder	Sleep disorder	Sleep disorder	Sleep disorder		

Serious AEs: Wheezing	Serious AEs: Wheezing	Serious AEs: Wheezing	7.5	7.5	7.5	7.5
Dermatitis	Dermatitis	Dermatitis	2.4	2.4	2.4	2.4
atopic	atopic	atopic	2.0	2.0	2.0	2.0
Gastroenteritis	Gastroenteritis	Gastroenteritis	0.8	0.8	0.8	0.8
Cough	Cough	Cough	0.4	0.4	0.4	0.4
Bronchopneumonia	Bronchopneumonia	Bronchopneumonia	1.2	1.2	1.2	1.2
Urticaria	Urticaria	Urticaria	1.2	1.2	1.2	1.2
Bronchitis	Bronchitis	Bronchitis	1.2	1.2	1.2	1.2
chronic	chronic	chronic	0.4	0.4	0.4	0.4
Neurologic/behavioral events:	Neurologic/behavioral events:	Neurologic/behavioral events:	0.4	0.4	0.4	0.4
Abnormal behavior	Abnormal behavior	Abnormal behavior	0.4	0.4	0.4	0.4
Aggression	Aggression	Aggression	0.4	0.4	0.4	0.4
Anxiety	Anxiety	Anxiety	0.4	0.4	0.4	0.4
Burning sensation	Burning sensation	Burning sensation	0.4	0.4	0.4	0.4
Febrile convulsions	Febrile convulsions	Febrile convulsions	0.4	0.4	0.4	0.4
Headache	Headache	Headache	0.4	0.4	0.4	0.4
Insomnia	Insomnia	Insomnia	0.4	0.4	0.4	0.4
Irritability	Irritability	Irritability	0.4	0.4	0.4	0.4
Nightmare	Nightmare	Nightmare	0.4	0.4	0.4	0.4
Sleep	Sleep	Sleep	0.4	0.4	0.4	0.4
Urticaria	Urticaria	Urticaria	0.4	0.4	0.4	0.4
Bronchitis	Bronchitis	Bronchitis				
chronic	chronic	chronic				
Neurologic/behavioral events:	Neurologic/behavioral events:	Neurologic/behavioral events:				
Abnormal behavior	Abnormal behavior	Abnormal behavior				
Aggression	Aggression	Aggression				
Anxiety	Anxiety	Anxiety				
Burning sensation	Burning sensation	Burning sensation				
Febrile convulsions	Febrile convulsions	Febrile convulsions				
Headache	Headache	Headache				
Insomnia	Insomnia	Insomnia				
Irritability	Irritability	Irritability				
Nightmare	Nightmare	Nightmare				
Sleep	Sleep	Sleep				

Chen et al., 2006 (26)	CTZ	CTZ	CTZ	CTZ	CTZ	CTZ	MLK	MLK	MLK	MLK	MLK	MLK	Placebo	Placebo	Placebo	Placebo	Plac	
	Mild medication induced sedation	Mild medication induced sedation	Mild medication induced sedation	Mild medication induced sedation	10.0	10.0	No AEs	No AEs	No AEs					No AEs				
Prenner et al., 2006 (27)	DLRD	DLRD	DLRD	DLRD	DLRD	DLRD	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo						

	Treatment-related: Anorexia	Treatment-related: Increased appetite	Treatment-related: Fever	Treatment-related: Somnolence	Treatment-related: Diarrhea	3.1	3.1	Treatment-related: Anorexia	Treatment-related: Increased appetite	Treatment-related: Fever	Treatment-related: Somnolence	1.6	1.6	1.6
					Insomnia	2.3	2.3					2.4	2.4	2.4
					Irritability	3.1	3.1					0.8	0.8	0.8
					Bronchitis	5.3	5.3					7.3	7.3	7.3
					Coughing	6.1	6.1					2.4	2.4	2.4
					Epistaxis	2.3	2.3					5.6	5.6	5.6
					Mild-to-moderate infection (unrelated)	6.9	6.9					1.6	1.6	1.6
						0.8	0.8					1.6	1.6	1.6
						1.5	1.5					0.8	0.8	0.8
						0.8	0.8							
						0.8	0.8							
de Blic et al., 2005 (28)	LCTZ	LCTZ	LCTZ	LCTZ	LCTZ	LCTZ	LCTZ	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo
	Headache	Headache	Headache	Headache	Headache	4.5	4.5	Headache	Headache	Headache	Headache	9.1	9.1	9.1
	Epistaxis	Epistaxis	Epistaxis	Epistaxis	Epistaxis	5.6	5.6	Epistaxis	Epistaxis	Epistaxis	Epistaxis	1.1	1.1	1.1
	Somnolence	Somnolence	Somnolence	Somnolence	Somnolence	1.1	1.1							

Potter et al., 2005 (29)	LCTZ	LCTZ	LCTZ	LCTZ	LCTZ	LCTZ	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo	
	Headache	Headache	Headache	Headache	12.3	12.3	Headache	Headache	Headache	11.2	11.2	11.2	11.2
	URTI	URTI	URTI	URTI	8.4	8.4	URTI	URTI	URTI	11.8	11.8	11.8	11.8
	Influenza	Influenza	Influenza	Influenza	5.2	5.2	Influenza	Influenza	Influenza	9.2	9.2	9.2	9.2
Bloom et al., 2004 (30)	DLRD	DLRD	DLRD	DLRD	DLRD	DLRD	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo	
	Fever	Fever	Fever	Fever	5.5	5.5	Fever	Fever	Fever	5.4	5.4	5.4	5.4
	Headache	Headache	Headache	Headache	1.8	1.8	Headache	Headache	Headache	5.4	5.4	5.4	5.4
	Viral infection	Viral infection	Viral infection	Viral infection	1.8	1.8	Viral infection	Viral infection	Viral infection	1.8	1.8	1.8	1.8
	Varicella Rash	Varicella Rash	Varicella Rash	Varicella Rash	3.6	3.6	Otitis media	Otitis media	Otitis media	1.8	1.8	1.8	1.8
	Urinary tract infection	Urinary tract infection	Urinary tract infection	Urinary tract infection	3.6	3.6							
Bloom et al., 2004 (30)	DLRD	DLRD	DLRD	DLRD	DLRD	DLRD	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo	
	Headache	Headache	Headache	Headache	1.7	1.7	Headache	Headache	Headache	6.7	6.7	6.7	6.7
							Gastroenteritis	Gastroenteritis	Gastroenteritis	3.3	3.3	3.3	3.3
							Vomiting	Vomiting	Vomiting	3.3	3.3	3.3	3.3
Grimfeld et al., 2004 (31)	LRD	LRD	LRD	LRD	LRD	LRD	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo	

	Pharyngitis	Pharyngitis	Pharyngitis	Pharyngitis	18.8	18.8	Pharyngitis	Pharyngitis	Pharyngitis	18.1	18.1	18.1	18.1						
	Bronchitis	Bronchitis	Bronchitis	Bronchitis	15.8	15.8	Bronchitis	Bronchitis	Bronchitis	13.0	13.0	13.0	13.0						
	Otitis media	Otitis media	Otitis media	Otitis media	9.1	9.1	Otitis media	Otitis media	Otitis media	13.0	13.0	13.0	13.0						
	Gastroenteritis	Gastroenteritis	Gastroenteritis	Gastroenteritis	7.9	7.9	Gastroenteritis	Gastroenteritis	Gastroenteritis	7.9	7.9	7.9	7.9						
	Rhinitis	Rhinitis	Rhinitis	Rhinitis	7.9	7.9	Rhinitis	Rhinitis	Rhinitis	7.3	7.3	7.3	7.3						
	Fever	Fever	Fever	Fever	6.7	6.7	Fever	Fever	Fever	7.3	7.3	7.3	7.3						
	Varicella	Varicella	Varicella	Varicella	8.5	8.5	Varicella	Varicella	Varicella	4.5	4.5	4.5	4.5						
	Coughing	Coughing	Coughing	Coughing	7.3	7.3	Coughing	Coughing	Coughing	5.1	5.1	5.1	5.1						
	Tonsillitis	Tonsillitis	Tonsillitis	Tonsillitis	5.5	5.5	Tonsillitis	Tonsillitis	Tonsillitis	5.1	5.1	5.1	5.1						
	Viral infection	Viral infection	Viral infection	Viral infection	5.5	5.5	Viral infection	Viral infection	Viral infection	4.5	4.5	4.5	4.5						
	Vomiting	Vomiting	Vomiting	Vomiting	5.5	5.5	Vomiting	Vomiting	Vomiting	3.4	3.4	3.4	3.4						
Hsieh et al.,2004 (32)	CTZ	CTZ	CTZ	CTZ	CTZ	CTZ	MLK	MLK	MLK	MLK	MLK	MLK	Placebo	Placebo	Placebo	Placebo	Plac		
	Sedation	Sedation	Sedation	Sedation	5.0	5.0	Headache	Headache	Headache	5.0	5.0	5.0	5.0	Headache	5.0	5.0	5.0		
														Fatigue	5.0	5.0	5.0		
Wahn et al.,2003 (33)	FXD HCL	FXD HCL	FXD HCL	FXD HCL	FXD HCL	FXD HCL	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo							

	Headache	Headache	Headache	Headache	5.0	5.0	Headache	Headache	Headache	2.8	2.8	2.8	2.8
	Epistaxis	Epistaxis	Epistaxis	Epistaxis	1.5	1.5	Epistaxis	Epistaxis	Epistaxis	1.1	1.1	1.1	1.1
	URTI	URTI	URTI	URTI	1.3	1.3	URTI	URTI	URTI	0.2	0.2	0.2	0.2
	Pharyngitis	Pharyngitis	Pharyngitis	Pharyngitis	1.1	1.1	Pharyngitis	Pharyngitis	Pharyngitis	0.6	0.6	0.6	0.6
	Sinusitis	Sinusitis	Sinusitis	Sinusitis	0.9	0.6	Nausea	Nausea	Nausea	1.9	1.9	1.9	1.9
	Nausea	Nausea	Nausea	Nausea	0.6	0.2	Rash	Rash	Rash	1.1	1.1	1.1	1.1
	Rash	Rash	Rash	Rash	0.2	0.2	Accidental injury	Accidental injury	Accidental injury	1.1	1.1	1.1	1.1
	Accidental injury	Accidental injury	Accidental injury	Accidental injury			Asthma	Asthma	Asthma				
	Asthma	Asthma	Asthma	Asthma			Infection	Infection	Infection				
	Infection	Infection	Infection	Infection			Gastrointestinal pain	Gastrointestinal pain	Gastrointestinal pain				
	Gastrointestinal pain	Gastrointestinal pain	Gastrointestinal pain	Gastrointestinal pain									
	Neutropenia (severe)	Neutropenia (severe)	Neutropenia (severe)	Neutropenia (severe)									
Segal et al., 2003 (34)	CTZ	CTZ	CTZ	CTZ	CTZ	CTZ	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo	

	Headache	Headache	Headache	Headache	8.3	8.3	Headache	Headache	Headache	9.3	9.3	9.3	9.3
	Somnolence	Somnolence	Somnolence	Somnolence	9.1	9.1	Somnolence	Somnolence	Somnolence	1.2	1.2	1.2	1.2
	Rash	Rash	Rash	Rash	3.6	3.6				1.2	1.2	1.2	1.2
	Nausea	Nausea	Nausea	Nausea	3.6	3.6	Nausea	Nausea	Nausea	2.3	2.3	2.3	2.3
	Nervousness	Nervousness	Nervousness	Nervousness	2.4	2.4	Nervousness	Nervousness	Nervousness				
	Abdominal pain	Abdominal pain	Abdominal pain	Abdominal pain	2.4	2.4							
Simons et al., 2003 (35)	CTZ	CTZ	CTZ	CTZ	CTZ	CTZ	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo	
	Nervousness	Nervousness	Nervousness	Nervousness	28.6	28.6	Nervousness	Nervousness	Nervousness	44.2	44.2	44.2	44.2
	Insomnia	Insomnia	Insomnia	Insomnia	23.8	23.8	Insomnia	Insomnia	Insomnia	44.2	44.2	44.2	44.2
	Somnolence	Somnolence	Somnolence	Somnolence	21.4	21.4	Somnolence	Somnolence	Somnolence	30.2	30.2	30.2	30.2
	Toothache+	Toothache+	Toothache+	Toothache+	9.5	9.5	Toothache+	Toothache+	Toothache+	9.3	9.3	9.3	9.3
	Diarrhea	Diarrhea	Diarrhea	Diarrhea	7.1	7.1	Diarrhea	Diarrhea	Diarrhea	9.3	9.3	9.3	9.3
	Otitis media	Otitis media	Otitis media	Otitis media	7.1	7.1	Otitis media	Otitis media	Otitis media	4.7	4.7	4.7	4.7
	URTI	URTI	URTI	URTI	7.1	7.1	URTI	URTI	URTI	2.3	2.3	2.3	2.3
	Agitation	Agitation	Agitation	Agitation	4.8	4.8	Agitation	Agitation	Agitation	16.3	16.3	16.3	16.3
	Tremor	Tremor	Tremor	Tremor	4.8	4.8	Tremor	Tremor	Tremor	4.7	4.7	4.7	4.7
	Fever	Fever	Fever	Fever	4.8	4.8	Fever	Fever	Fever	4.7	4.7	4.7	4.7
	Pharyngitis	Pharyngitis	Pharyngitis	Pharyngitis	4.8	4.8	Cough	Cough	Cough	4.7	4.7	4.7	4.7
	Rhinitis	Rhinitis	Rhinitis	Rhinitis	4.8	4.8	Rhinitis	Rhinitis	Rhinitis	4.7	4.7	4.7	4.7
	Rash	Rash	Rash	Rash	2.4	2.4	Rash	Rash	Rash				

Lai et al., 2002 (36)	CTZ	CTZ	CTZ	CTZ	CTZ	CTZ	OXD	OXD	OXD	OXD	OXD	OXD	KTF	KTF	KTF	KTF	KTF
	Sedation Fatigue	Sedation Fatigue	Sedation Fatigue	Sedation Fatigue	10.5 5.3	10.5 5.3	Sedation Fatigue	Sedation Fatigue	Sedation Fatigue	11.1 5.6	11.1 5.6	11.1 5.6	11.1 5.6	Sedation Nausea	6.3 6.3	6.3 6.3	6.3 6.3
Chunchanur et al., 2002 (37)	LRD	LRD	LRD	LRD	LRD	LRD	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo					
	Dizziness Nausea Impetigo	Dizziness Nausea Impetigo	Dizziness Nausea Impetigo	Dizziness Nausea Impetigo	4.2 4.2 4.2	4.2 4.2 4.2	Dizziness Anorexia	Dizziness Anorexia	Dizziness Anorexia	4.2 4.2	4.2 4.2	4.2 4.2	4.2 4.2				
La Rosa et al., 2001 (38)	OXD	OXD	OXD	OXD	OXD	OXD	CTZ	CTZ	CTZ	CTZ	CTZ	CTZ					
	Moderate peri-oral allergic reaction	Moderate peri-oral allergic reaction	Moderate peri-oral allergic reaction	Moderate peri-oral allergic reaction	3.2	3.2	ND	ND	ND								
Yang et al., 2001 (39)	LRD	LRD	LRD	LRD	LRD	LRD	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo					
	No AEs	No AEs	No AEs	No AEs			No AEs	No AEs	No AEs								
Ciprandi et al., 2001 (40)	CTZ	CTZ	CTZ	CTZ	CTZ	CTZ	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo					
	No AEs	No AEs	No AEs	No AEs			No AEs	No AEs	No AEs								
Graft et al., 2001 (41)	FXD (15 mg BD)	FXD (15 mg BD)	FXD (15 mg BD)	FXD (15 mg BD)	FXD (15 mg BD)	FXD (15 mg BD)	FXD (30 mg BD)	FXD (30 mg BD)	FXD (30 mg BD)	FXD (30 mg BD)	FXD (30 mg BD)	FXD (30 mg BD)	FXD (60 mg BD)	FXD (60 mg BD)	FXD (60 mg BD)	FXD (60 mg BD)	FXD (60 mg BD)

	URTI Pharyngitis Cough-ing In-jury ac-ci-dent Ab-dom-i-nal pain Fever Headache	URTI Pharyngitis Cough-ing In-jury ac-ci-dent Ab-dom-i-nal pain Fever Headache	URTI Pharyngitis Cough-ing In-jury ac-ci-dent Ab-dom-i-nal pain Fever Headache	URTI Pharyngitis Cough-ing In-jury ac-ci-dent Ab-dom-i-nal pain Fever Headache	4.9 4.0 1.3 1.8 2.7 1.8 8.0	4.9 4.0 1.3 1.8 2.7 1.8 8.0	URTI Pharyngitis Cough-ing In-jury ac-ci-dent Ab-dom-i-nal pain Fever Headache Somnolence (unrelated to treatment)	URTI Pharyngitis Cough-ing In-jury ac-ci-dent Ab-dom-i-nal pain Fever Headache Somnolence (unrelated to treatment)	URTI Pharyngitis Cough-ing In-jury ac-ci-dent Ab-dom-i-nal pain Fever Headache Somnolence (unrelated to treatment)	4.3 2.9 3.8 2.9 1.9 2.4 7.2 0.5	4.3 2.9 3.8 2.9 1.9 2.4 7.2 0.5	4.3 2.9 3.8 2.9 1.9 2.4 7.2 0.5	4.3 2.9 3.8 2.9 1.9 2.4 7.2 0.5	URTI Pharyngitis Cough-ing In-jury ac-ci-dent Ab-dom-i-nal pain Fever Headache	1.4 2.8 2.3 4.2 2.3 1.9 9.4	1.4 2.8 2.3 4.2 2.3 1.9 9.4	1.4 2.8 2.3 4.2 2.3 1.9 9.4
Salmun et al., 2000 (42)	LRD	LRD	LRD	LRD	LRD	LRD	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo						
	Coughing Drowsiness Dyspepsia Fever Vomiting	Coughing Drowsiness Dyspepsia Fever Vomiting	Coughing Drowsiness Dyspepsia Fever Vomiting	Coughing Drowsiness Dyspepsia Fever Vomiting	3.0 7.0 2.0 7.0 5.0	3.0 7.0 2.0 7.0 5.0	Coughing Drowsiness Dyspepsia Fever Headache Vomiting	Coughing Drowsiness Dyspepsia Fever Headache Vomiting	Coughing Drowsiness Dyspepsia Fever Headache Vomiting	5.0 7.0 7.0 8.0 7.0 5.0	5.0 7.0 7.0 8.0 7.0 5.0	5.0 7.0 7.0 8.0 7.0 5.0	5.0 7.0 7.0 8.0 7.0 5.0					
Simons et al., 1999 (43)	CTZ	CTZ	CTZ	CTZ	CTZ	CTZ	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo						

Rhinitis	Rhinitis	Rhinitis	Rhinitis	79.0	79.0	Rhinitis	Rhinitis	Rhinitis	77.0	77.0	77.0	77.0
URTI	URTI	URTI	URTI	58.0	58.0	URTI	URTI	URTI	62.0	62.0	62.0	62.0
Fever	Fever	Fever	Fever	38.0	38.0	Fever	Fever	Fever	42.0	42.0	42.0	42.0
Di-	Di-	Di-	Di-	29.0	29.0	Di-	Di-	Di-	28.0	28.0	28.0	28.0
ar-	ar-	ar-	ar-	28.0	28.0	ar-	ar-	ar-	27.0	27.0	27.0	27.0
rhea	rhea	rhea	rhea	21.0	21.0	rhea	rhea	rhea	22.0	22.0	22.0	22.0
Gas-	Gas-	Gas-	Gas-	24.0	24.0	Gas-	Gas-	Gas-	28.0	28.0	28.0	28.0
troen-	troen-	troen-	troen-	23.0	23.0	troen-	troen-	troen-	22.0	22.0	22.0	22.0
teri-	teri-	teri-	teri-	6.0	6.0	teri-	teri-	teri-	16.0	16.0	16.0	16.0
tis	tis	tis	tis	9.0	9.0	tis	tis	tis	14.0	14.0	14.0	14.0
Vom-	Vom-	Vom-	Vom-	8.0	8.0	Vom-	Vom-	Vom-	9.0	9.0	9.0	9.0
it-	it-	it-	it-	6.0	6.0	it-	it-	it-	7.0	7.0	7.0	7.0
ing	ing	ing	ing	7.0	7.0	ing	ing	ing	6.0	6.0	6.0	6.0
Pharyn	Pharyn	Pharyn	Pharyn	0.7	0.7	Pharyn	Pharyn	Pharyn	0.7	0.7	0.7	0.7
gi-	gi-	gi-	gi-	0.2	0.2	gi-	gi-	gi-	0.2	0.2	0.2	0.2
tis	tis	tis	tis	0.5	0.5	tis	tis	tis	0.2	0.2	0.2	0.2
Vari-	Vari-	Vari-	Vari-	0.5	0.5	Vari-	Vari-	Vari-	0.2	0.2	0.2	0.2
cella	cella	cella	cella	3.2	3.2	cella	cella	cella	0.5	0.5	0.5	0.5
Ur-	Ur-	Ur-	Ur-	1.2	1.2	Ur-	Ur-	Ur-	1.0	1.0	1.0	1.0
ticaria	ticaria	ticaria	ticaria	1.2	1.2	ticaria	ticaria	ticaria	1.3	1.3	1.3	1.3
Al-	Al-	Al-	Al-	8.8	8.8	Al-	Al-	Al-	1.5	1.5	1.5	1.5
ler-	ler-	ler-	ler-	1.2	1.2	ler-	ler-	ler-	2.3	2.3	2.3	2.3
gic	gic	gic	gic	2.2	2.2	gic	gic	gic	5.3	5.3	5.3	5.3
re-	re-	re-	re-			re-	re-	re-	1.8	1.8	1.8	1.8
ac-	ac-	ac-	ac-			ac-	ac-	ac-	2.0	2.0	2.0	2.0
tion	tion	tion	tion			tion	tion	tion				
Toothache	Toothache	Toothache	Toothache			Toothache	Toothache	Toothache				
In-	In-	In-	In-			In-	In-	In-				
fluenza	fluenza	fluenza	fluenza			fluenza	fluenza	fluenza				
like	like	like	like			like	like	like				
symp-	symp-	symp-	symp-			symp-	symp-	symp-				
toms	toms	toms	toms			toms	toms	toms				
Other	Other	Other	Other			Other	Other	Other				
vi-	vi-	vi-	vi-			vi-	vi-	vi-				
ral	ral	ral	ral			ral	ral	ral				
in-	in-	in-	in-			in-	in-	in-				
fec-	fec-	fec-	fec-			fec-	fec-	fec-				
tion	tion	tion	tion			tion	tion	tion				
Im-	Im-	Im-	Im-			Im-	Im-	Im-				
mu-	mu-	mu-	mu-			mu-	mu-	mu-				
niza-	niza-	niza-	niza-			niza-	niza-	niza-				
tion	tion	tion	tion			tion	tion	tion				
com-	com-	com-	com-			com-	com-	com-				
pli-	pli-	pli-	pli-			pli-	pli-	pli-				
ca-	ca-	ca-	ca-			ca-	ca-	ca-				
tion	tion	tion	tion			tion	tion	tion				
Heart	Heart	Heart	Heart			Mur-	Mur-	Mur-				
mur-	mur-	mur-	mur-			mur	mur	mur				
mur	mur	mur	mur			Tachy-	Tachy-	Tachy-				
Syn-	Syn-	Syn-	Syn-			car-	car-	car-				
cope	cope	cope	cope			dia	dia	dia				
af-	af-	af-	af-			Other	Other	Other				
ter	ter	ter	ter			ar-	ar-	ar-				
in-	in-	in-	in-			rhyth-	rhyth-	rhyth-				
jury	jury	jury	jury			mia	mia	mia				
Ataxia	Ataxia	Ataxia	Ataxia			Ex-	Ex-	Ex-				
Febrile	Febrile	Febrile	Febrile			trasys-	trasys-	trasys-				
con-	con-	con-	con-			tole	tole	tole				
vul-	vul-	vul-	vul-			Ataxia	Ataxia	Ataxia				
sions	sions	sions	sions			Febrile	Febrile	Febrile				

Wahn et al., 1998 (44)	CTZ	CTZ	CTZ	CTZ	CTZ	CTZ	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo	

Abdominal pain	Abdominal pain	Abdominal pain	Abdominal pain	4.3	4.3	Abdominal pain	Abdominal pain	Abdominal pain	4.3	4.3	4.3	4.3
Agitation	Agitation	Agitation	Agitation	0.3	0.3	Agitation	Agitation	Agitation	0.5	0.5	0.5	0.5
Allergic reaction	Allergic reaction	Allergic reaction	Allergic reaction	9.1	9.1	Allergic reaction	Allergic reaction	Allergic reaction	13.4	13.4	13.4	13.4
Anorexia	Anorexia	Anorexia	Anorexia	3.3	3.3	Anorexia	Anorexia	Anorexia	4.0	4.0	4.0	4.0
Appetite increased	Appetite increased	Appetite increased	Appetite increased			Appetite increased	Appetite increased	Appetite increased	0.3	0.3	0.3	0.3
Fatigue	Fatigue	Fatigue	Fatigue			ECG abnormalities	ECG abnormalities	ECG abnormalities	0.3	0.3	0.3	0.3
Hepatic enzymes increased	Hepatic enzymes increased	Hepatic enzymes increased	Hepatic enzymes increased			Fatigue	Fatigue	Fatigue	1.3	1.3	1.3	1.3
Hyperkinesia	Hyperkinesia	Hyperkinesia	Hyperkinesia			Hepatic enzymes increased	Hepatic enzymes increased	Hepatic enzymes increased	1.8	1.8	1.8	1.8
Insomnia	Insomnia	Insomnia	Insomnia			Hyperkinesia	Hyperkinesia	Hyperkinesia	2.5	2.5	2.5	2.5
Laryngitis	Laryngitis	Laryngitis	Laryngitis			Insomnia	Insomnia	Insomnia	5.3	5.3	5.3	5.3
Somnolence	Somnolence	Somnolence	Somnolence			Laryngitis	Laryngitis	Laryngitis	9.3	9.3	9.3	9.3
Urticaria	Urticaria	Urticaria	Urticaria			Somnolence	Somnolence	Somnolence	2.0	2.0	2.0	2.0
Vaccination complication	Vaccination complication	Vaccination complication	Vaccination complication			Urticaria	Urticaria	Urticaria	16.1	16.1	16.1	16.1
						Vaccination complication	Vaccination complication	Vaccination complication	5.5	5.5	5.5	5.5

Sienra-Monge et al., 1999 (45)	CTZ	CTZ	CTZ	CTZ	CTZ	CTZ	LRD	LRD	LRD	LRD	LRD	LRD						
	Somnolence and mild irritability Generalized rash	Somnolence and mild irritability Generalized rash	Somnolence and mild irritability Generalized rash	Somnolence and mild irritability Generalized rash	2.5	2.5	No AEs	No AEs	No AEs									
Serra et al., 1998 (46)	LRD-PSD.	LRD-PSD.	LRD-PSD.	LRD-PSD.	LRD-PSD.	LRD-PSD.	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo						
	Slight transient insomnia	Slight transient insomnia	Slight transient insomnia	Slight transient insomnia	5.0	5.0	No AEs	No AEs	No AEs									
Delgado et al., 1998 (47)	LRD (5 mg or 10 mg OD)	LRD (5 mg or 10 mg OD)	LRD (5 mg or 10 mg OD)	LRD (5 mg or 10 mg OD)	LRD (5 mg or 10 mg OD)	LRD (5 mg or 10 mg OD)	CTZ (10 mg OD)	CTZ (10 mg OD)	CTZ (10 mg OD)	CTZ (10 mg OD)	CTZ (10 mg OD)	CTZ (10 mg OD)	LRD (5 mg or 10 mg OD)	LRD (5 mg or 10 mg OD)	LRD (5 mg or 10 mg OD)	LRD (5 mg or 10 mg OD)	LRD (5 mg or 10 mg OD)	
	No AEs	No AEs	No AEs	No AEs			No AEs	No AEs	No AEs					No AEs				
Pearlman et al.,1997 (48) *and* Winder et al.,1996 (49)	CTZ (10 mg OD)	CTZ (10 mg OD)	CTZ (10 mg OD)	CTZ (10 mg OD)	CTZ (10 mg OD)	CTZ (10 mg OD)	CTZ (5 mg OD)	CTZ (5 mg OD)	CTZ (5 mg OD)	CTZ (5 mg OD)	CTZ (5 mg OD)	CTZ (5 mg OD)	Placebo	Placebo	Placebo	Placebo	Plac	

	Headache Pharyngitis Abdominal pain Epistaxis	Headache Pharyngitis Abdominal pain Epistaxis	Headache Pharyngitis Abdominal pain Epistaxis	Headache Pharyngitis Abdominal pain Epistaxis	Headache Pharyngitis Abdominal pain Epistaxis	Headache Pharyngitis Abdominal pain Epistaxis	Headache Pharyngitis Abdominal pain Epistaxis	Headache Pharyngitis Abdominal pain Epistaxis	Headache Pharyngitis Abdominal pain Epistaxis	15.1 10.1 9.4 7.1	15.1 10.1 9.4 7.1	15.1 10.1 9.4 7.1	15.1 10.1 9.4 7.1	Headache Pharyngitis Abdominal pain Epistaxis	19.7 13.6 4.5 4.3	19.7 13.6 4.5 4.3	19.7 13.6 4.5 4.3
Ciprandi et al., 1997 (50)	CTZ	CTZ	CTZ	CTZ	CTZ	CTZ	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo						
Benedict et al., 1997 (51)	Headache CTZ	Headache CTZ	Headache CTZ	Headache CTZ	Headache 10.0 CTZ	10.0 CTZ	Headache OXD	Headache OXD	Headache OXD	Headache 20.0 OXD	20.0 OXD	20.0 OXD	20.0					
	Sleepiness 8.0	Sleepiness	Sleepiness	Sleepiness	8.0	8.0	Sleepiness Slightly increased SGPT	Sleepiness Slightly increased SGPT	Sleepiness Slightly increased SGPT	7.7 1.9	7.7 1.9	7.7 1.9	7.7 1.9					
Tinkelman et al., 1996 (52)	CTZ (5-10 mg OD)	CTZ (5-10 mg OD)	CTZ (5-10 mg OD)	CTZ (5-10 mg OD)	CTZ (5-10 mg OD)	CTZ (5-10 mg OD)	CTZ (2.5-5 mg OD)	CTZ (2.5-5 mg OD)	CTZ (2.5-5 mg OD)	CTZ (2.5-5 mg OD)	CTZ (2.5-5 mg OD)	CTZ (2.5-5 mg OD)	CPN	CPN	CPN	CPN	CPN	
	Abdominal pain Somnolence Fatigue Nausea and headache	Abdominal pain Somnolence Fatigue Nausea and headache	Abdominal pain Somnolence Fatigue Nausea and headache	Abdominal pain Somnolence Fatigue Nausea and headache	Abdominal pain Somnolence Fatigue Nausea and headache	Abdominal pain Somnolence Fatigue Nausea and headache	Abdominal pain Somnolence Fatigue Nausea and headache	Abdominal pain Somnolence Fatigue Nausea and headache	Abdominal pain Somnolence Fatigue Nausea and headache	Abdominal 9.6 8.0 4.0 3.2	9.6 8.0 4.0 3.2	9.6 8.0 4.0 3.2	9.6 8.0 4.0 3.2	Abdominal pain Somnolence Fatigue Nausea Headache	4.8 7.9 6.3 1.6 6.3	4.8 7.9 6.3 1.6 6.3	4.8 7.9 6.3 1.6 6.3
Fasce et al.,1996 (53)	CTZ	CTZ	CTZ	CTZ	CTZ	CTZ	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo						
	ND	ND	ND	ND			ND	ND	ND									

La Rosa et al.,1994 (54)	CTZ	CTZ	CTZ	CTZ	CTZ	CTZ	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo						
	No AEs	No AEs	No AEs	No AEs			ND	ND	ND									
Jobst et al.,1994 (55)	CTZ (2.5 mg OD) ND	CTZ (2.5 mg OD) ND	CTZ (2.5 mg OD) ND	CTZ (2.5 mg OD) ND	CTZ (2.5 mg OD)	CTZ (2.5 mg OD)	CTZ (5 mg OD) ND	CTZ (5 mg OD) ND	CTZ (5 mg OD) ND	CTZ (5 mg OD)	CTZ (5 mg OD)	CTZ (5 mg OD)	CTZ (10 mg OD)	CTZ (10 mg OD) ND	CTZ (10 mg OD)	CTZ (10 mg OD)	CTZ (10 mg OD)	CTZ (10 mg OD)
Allegra et al.,1993 (56)	CTZ	CTZ	CTZ	CTZ	CTZ	CTZ	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo						
	Number of events: Headache Fever Abdominal pain Increased appetite Diarrhea Somnolence Nervousness Insomnia Respiratory tract	Number of events: Headache Fever Abdominal pain Increased appetite Diarrhea Somnolence Nervousness Insomnia Respiratory tract	Number of events: Headache Fever Abdominal pain Increased appetite Diarrhea Somnolence Nervousness Insomnia Respiratory tract	Number of events: Headache Fever Abdominal pain Increased appetite Diarrhea Somnolence Nervousness Insomnia Respiratory tract	1 2 1 1 3 2 1 3	1 2 1 1 3 2 1 3	Number of events: Headache Abdominal pain Diarrhea Vomiting Nervousness Insomnia Depression Respiratory tract	Number of events: Headache Abdominal pain Diarrhea Vomiting Nervousness Insomnia Depression Respiratory tract	Number of events: Headache Abdominal pain Diarrhea Vomiting Nervousness Insomnia Depression Respiratory tract	1 2 1 1 1 1 7	1 2 1 1 1 1 7	1 2 1 1 1 1 7	1 2 1 1 1 1 7						
Masi et al.,1993 (57)	CTZ	CTZ	CTZ	CTZ	CTZ	CTZ	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo						

	Somnolence	Somnolence	Somnolence	Somnolence	9.5	9.5	Somnolence	Somnolence	Somnolence	3.3	3.3	3.3	3.3							
	Headache	Headache	Headache	Headache	3.2	3.2	Headache	Headache	Headache	1.6	1.6	1.6	1.6							
	Vertigo	Vertigo	Vertigo	Vertigo	1.6	1.6	Nausea	Nausea	Nausea	4.9	4.9	4.9	4.9							
	Rash	Rash	Rash	Rash	3.2	3.2	-	-	-	1.6	1.6	1.6	1.6							
	Increased appetite	Increased appetite	Increased appetite	Increased appetite	1.6	1.6	vomiting	vomiting	vomiting	4.9	4.9	4.9	4.9							
	Dry mouth	Dry mouth	Dry mouth	Dry mouth	1.6	1.6	Anorexia	Anorexia	Anorexia											
	Abdominal pain	Abdominal pain	Abdominal pain	Abdominal pain			Abdominal pain	Abdominal pain	Abdominal pain											
	Increased cough	Increased cough	Increased cough	Increased cough			Increased cough	Increased cough	Increased cough											
	Pharyngitis	Pharyngitis	Pharyngitis	Pharyngitis			Pharyngitis	Pharyngitis	Pharyngitis											
Baelde et al., 1992 (58)	CTZ (10mg OD)	CTZ (10mg OD)	CTZ (10mg OD)	CTZ (10mg OD)	CTZ (10mg OD)	CTZ (10mg OD)	CTZ (5mg OD)	CTZ (5mg OD)	CTZ (5mg OD)	CTZ (5mg OD)	CTZ (5mg OD)	CTZ (5mg OD)	Placebo	Placebo	Placebo	Placebo	Plac			
	Tiredness	Tiredness	Tiredness	Tiredness	2.2	2.2	Tiredness	Tiredness	Tiredness	2.2	2.2	2.2	2.2	Tiredness	2.2	2.2	2.2			
	Mood change	Mood change	Mood change	Mood change	2.2	2.2	Sleepiness/difficulty waking	Sleepiness/difficulty waking	Sleepiness/difficulty waking	[2]6.5	[2]6.5	[2]6.5	[2]6.5	Sleepiness/difficulty waking	[2]4.3	[2]4.3	[2]4.3			
	Appetite increase	Appetite increase	Appetite increase	Appetite increase	2.2	2.2				2.2	2.2	2.2	2.2							
	Abdominal pain/diarrhea	Abdominal pain/diarrhea	Abdominal pain/diarrhea	Abdominal pain/diarrhea						[2]2.2	[2]2.2	[2]2.2	[2]2.2							
										2.2	2.2	2.2	2.2	Headache						
														Abdominal pain/diarrhea other						
							Mood change	Mood change	Mood change	2.2	2.2	2.2	2.2							
							Appetite increase	Appetite increase	Appetite increase											
							Abdominal pain/diarrhea other	Abdominal pain/diarrhea other	Abdominal pain/diarrhea other											
Boner et al.,1989 (59)	LRD	LRD	LRD	LRD	LRD	LRD	DCPN	DCPN	DCPN	DCPN	DCPN	DCPN								

Moderate epistaxis Nausea, vomiting and Lipothymia	Moderate epistaxis Nausea, vomiting and Lipothymia	Moderate epistaxis Nausea, vomiting and Lipothymia	Moderate epistaxis Nausea, vomiting and Lipothymia	14.2 4.7	14.2 4.7	Somnolence Mild epistaxis	Somnolence Mild epistaxis	Somnolence Mild epistaxis	21.0 10.5	21.0 10.5	21.0 10.5	21.0 10.5

Abbreviations: AE = Adverse events; BD = bis in die (twice daily); BLN = Bilastine; CTZ = Cetirizine; CPN = Clorpheniramine; CPHD = Cyproheptadine; DLRD = Desloratadine; DCPN = Dexchlorpheniramine; 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.

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.

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)