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Update meta-analysis on the efficacy and safety issues of fexofenadine

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ABSTRACT

Background: Fexofenadine emerged as one of the most representative second generation histamine H1 antagonist drugs since the 1990s, with an outstanding efficacy and appreciable safety for the treatment of allergic patients. While allergic rhino-conjunctivitis represents the most frequent atopic disease globally, an update of fexofenadine efficacy and safety on this entity was proposed as a surrogate of allergic condition.

Methods: Double blind, placebo controlled, randomized clinical trials investigating the efficacy and safety of fexofenadine for the treatment of Allergic Rhinitis were searched in 5 major global databases. Eligibility criteria and characteristics, risk of bias, and validity assessment, data extraction and heterogeneity evaluation are described. Primary outcome selected corresponded to 12-reflective and instantaneous total symptom scores (TSS), besides morning instantaneous TSS and the frequency of reported adverse events (AEs); analysis was planned on the intention-to-treat population.
Standardized mean differences of scoring systems were analyzed, and Cochran's Q statistic test and the I^2 test were assessed for heterogeneity.

Results: From the initial 83 identified records, 12 eligible studies were selected. In the evaluated patients, individuals receiving fexofenadine (1910) showed a significant reduction of TSS compared with those who received placebo (1777), change from baseline: standardized mean difference (SMD) -0.33; 95% CI-0.47 to −0.18, $p < 0.0001$. Morning instantaneous TSS also demonstrated lower symptoms (change from baseline: SMS -1.42; 95% CI -2.22 to −0.62, $p = 0.0005$). Heterogeneity was found across selected studies.
Frequency of AEs was similar compared to placebo (OR = 1.04; 0.88–1.21), with no detection of heterogeneity across these 12 studies.

Conclusions: According to this new evidence, fexofenadine maintains its beneficial profile on signs and symptoms of patients with allergic conditions, as well as its attributes as one of the major candidates for an ideal antihistamine medication (including special conditions such as pregnancy and pre-school age), providing support to its over-the-counter condition in several countries.

Keywords: Histamine H1 antagonist, Non sedating, Safety, Efficacy, Fexofenadine

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INTRODUCTION

Allergic diseases have become prominent chronic conditions worldwide, with an important burden on quality of life and in health services utilization rates as well. The progression of their prevalence appears to be smoothened in some countries; however, the increasing trend is particularly notable in developing countries where health systems resources are limited, with the consequent inappropriate management of these conditions.[1-4]

Nevertheless, the chance of controlling its progression globally is elusive, while the origin and persistence of allergic diseases are conditioned by both genetics and epigenetics that might not be modelled according to individual or regional needs.

Management of allergic conditions includes identification and avoidance of sensitizing agents, which is not always feasible, therefore the availability of medications that interfere with the underlying allergic patho-mechanism taking advantage of a favorable safety/efficacy profile is a constant need. In this scenario, antihistamines (antiH1) are the first step management option, fulfilling these requirements in most patients. The second generation anti-H1 drugs progressively replaced those of the first-generation, owing to their higher affinity and selectivity for peripheral H1 receptors in respect to histaminergic and cholinergic receptors on the central nervous system, leading to maintained or even superior efficacy and reduced frequency of adverse effects such as sedation.[5-7]

Fexofenadine is one of the most representative second generation anti-H1 drugs, with abundant evidence regarding its efficacy and safety in allergic management. A former meta-analysis of 8 double-blind, placebo controlled, randomized trials up to December 2007 confirmed these statements.[8] A more recent systematic review[9] concluded that this drug has a positive antihistamine effect and a favorable safety profile, superior to first generation anti-H1 drugs; also, fexofenadine appears superior to other new generation anti-H1 drugs on sedative effects and on particular aspects of cognitive/psychomotor functions. Also, the experience of its routine use during this timeframe confirms the positive outcome. As such, fexofenadine has obtained regulatory agency authorization for its over-the-counter (OTC) access for some restricted dosages and population targets.[10] Since new literature is available, an update on the recent evidence of efficacy and safety emerged as needed.

METHODS

Search strategy

We searched ClinicalTrials.gov, International Clinical Trials Registry Platform (ICTRP), CENTRAL, PubMed, Embase, from January 1, 2008 to December 2021, for double-blind, randomized, placebo-controlled clinical trials investigating in humans the efficacy of fexofenadine in Allergic Rhinitis (AR), to update a previous systematic review including studies up to December 31, 2007.

The search strategy included citations referring to the exploded topic heading "fexofenadine" combined with exploded topic headings describing the allergic disease (allergic rhinitis, rhino-conjunctivitis, and hay fever), focused on the intended population (human beings). The reference lists were screened for all retrieved articles and also from recent review articles to select additional studies. Only publications in English language were selected.

Eligibility criteria and characteristics

Included publications were only fully published, parallel group, double-blind, placebo-controlled, randomized clinical trials (DBPC RCT).

Target population corresponds to patients with AR diagnosis, with or without allergic asthma and/or conjunctivitis, and corroborated by IgE sensitization remarked by positive skin prick tests and/or specific IgE assays. There were neither restrictions on fexofenadine doses and treatment durations, nor on time of evolution of the disease. Post-challenge (or similar) studies were excluded from our selection. Crossover studies that do not directly compare fexofenadine and placebo were excluded. Comparisons including arms in which fexofenadine was associated to other drugs (ie, decongestants, nasal steroids, leukotriene

antagonists, or others) were not included to avoid confounded treatment effect.

Sources were initially selected through title and abstracts screening, then on the basis of full text eligibility evaluation.

Evaluation of validity and risk of bias assessment

Methodological quality and risk of bias of included studies were evaluated using the Cochrane Collaboration tool. Six parameters were evaluated: (a) sequence generation, (b) allocation concealment, (c) blinding of caregivers, personnel, and outcome assessors, (d) incomplete outcome data, (e) selective outcome reporting, and (f) other sources of bias. The grading of each item was as follows: (A) low risk of bias, (B) unclear risk of bias, and (C) high risk of bias. General conclusive assessment for each controlled trial used the same 3 criteria.

Data extraction

The following outcomes were evaluated: primary outcome was 12- or 24-h reflective total symptom scores (TSS), as sum of sneezing, rhinorrhea, itchy nose/palate, and itchy/watery/red eyes, excluding nasal congestion. Secondary outcomes corresponded to morning instantaneous TSS, and the reported frequency of adverse events (AEs). The assay was planned on the full-analysis-set as expression of the intention-to-treat population (ITT). If more than 1 dose of antihistamine was assessed in a study, the one described as more effective and safer was selected. When necessary, missing change-from-baseline standard deviation were derived from standard errors, confidence intervals or imputed using a correlation coefficient as described in Cochrane handbook. In case the results were not presented in tables and only available in graphics, they were digitalized and extrapolated to numbers using the DigitizeIt 1.5.7 program (DigitizeIt 2003; Bormann, Braunschweig, Germany).

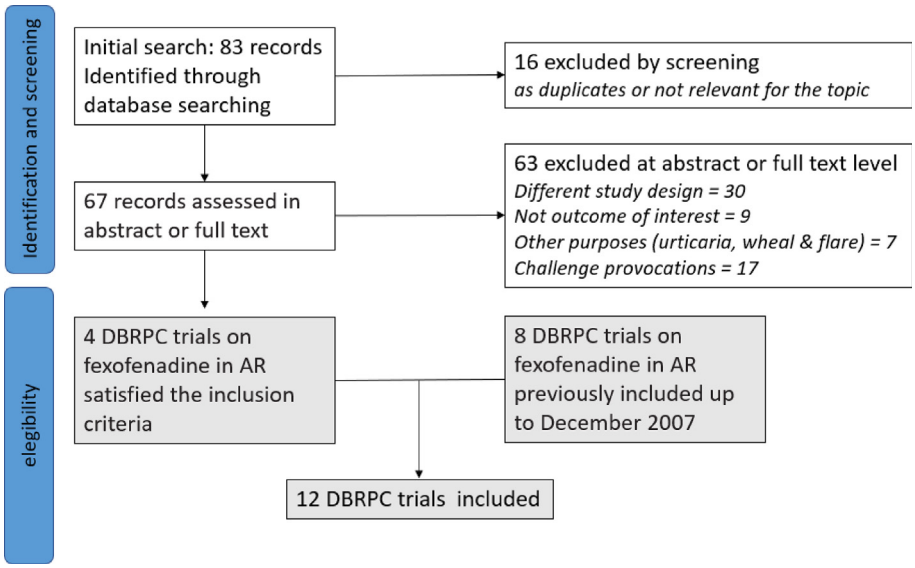
Assessment of heterogeneity and data synthesis

The post-treatment means and standard deviation (SD) values for both active and control groups were analyzed pooling together with the outcomes of a previous metanalysis (https://doi.org/10.1159/000321896) based on the same inclusion criteria and objective of research. Since in the selected papers, we observed different scoring systems in symptom evaluations; they were analyzed in terms of the standardized mean difference (SMD). Odds ratios were used for dichotomous outcomes (frequency of adverse effects). Cochran's Q statistic test and the I^2 test were adopted to assess inter-study heterogeneity. A fixed-effects model (FEM) was used when non-substantial heterogeneity among outcomes was found ($I^2 < 50\%$). A FEM utilizes the inverse-variance approach, and it assumes that all studies are representative of a common population; for $I^2 > 50\%$, a random-effects model (REM) was applied. All results have been presented with 95% confidence intervals (95% CI) and all p values are 2-sided. The analysis was conducted with RevMan 5 program (The Cochrane Collaboration, Oxford, UK).

RESULTS

Search results

The first step search identified 83 documents; an initial exclusion of 16 studies corresponded to duplicates or not related to the topic and remaining 67 abstract and full-text articles were reviewed for eligibility. Of those, 63 were not included because they were review articles, studies with different objectives or outcomes, were limited to safety evaluations, were not randomized studies, were open or single-blind studies, not placebo-controlled, or with different study design. Four clinical studies on fexofenadine in the treatment of AR were potentially pertinent, one published before 2007 and missed in the previous search (Kaiser et al), 1 on daytime symptoms of perennial rhinitis caused by house dust mites (Okubo et al) and 2 on nighttime symptom reduction in cedar and ragweed pollinosis respectively (Andrews et al). In the study by Kaiser et al, however, no sufficient information on outcome measurement was reported; therefore this study was not suitable for metanalysis. Eight eligible studies were previously identified in the period before December 2007 and were included in the metanalysis along with the 3 mentioned above.



Flowchart 1 From initial search to final eligible studies

Trial characteristics

Table 1 describes the specific features of the studies and participants included in the meta-analysis. Out of 12 eligible trials, eleven DBPC RCT which included a total of 7134 subjects were considered for the primary outcome and analytically included in this systematic review. All the selected trials were carried out to investigate the efficacy and the safety of fexofenadine in seasonal AR (SAR). Patients' age range was wide and included children, adolescents, adults, and elderly people. All but 1 study involved a mixed adult-pediatric population. Just 1 trial by Wahn et al studied only a pediatric population. All studies administered the study medication in form of oral tablets for a median duration of 2 weeks.

Methodological quality of the included studies

All the analyzed studies had randomized, parallel group, double blind, and placebo-controlled design. Patients' informed consent before enrolment was achieved by all investigators. All trials described dropouts and withdrawals, and evaluated participants who have completed the trial; the drop-out rate ranged from 1.2 to 14%. The global risk of bias assessment, obtained from the appraisal of allocation concealment, attrition, and detection bias, resulted in a moderate level (Table 2). A "moderate risk" study may indicate some bias but probably not enough to invalidate the results. If missing information emerges, it may be difficult to weight limitations and potential critical aspects (unclear risk).

Most of the studies incorporated in this review were conducted in an age when the requested standard for data reporting in clinical trials was less demanding and detailed. Notably, the procedures for treatment allocation and ensuring blinding were poorly or not described (score B). For the efficacy endpoints, few studies provided full outcome measurements but just p values or graphical presentation (score C). The Intention to treat approach was basically adopted in most cases.

As the moderate risk category is broad, studies with this rating may vary in strengths and weaknesses.

Data synthesis

The 12-h reflective total symptom severity score (TSS) was assessed in 8 studies. Out of 3687 patients, 1910 received fexofenadine and 1777 received placebo. Those patients receiving fexofenadine exhibited a significant reduction of TSS compared with the placebo group (change from baseline: SMD -0.33; 95% CI-0.47 to −0.18, $p < 0.0001$). A substantial heterogeneity was observed ($X^2 = 32.64$; $p < 0.001$, $I^2 = 79\%$). (Fig. 1a).

In 10 studies (2154 patients who received fexofenadine and 2022 placebo) morning instantaneous TSS were reported. A significant decrement

Study features				Subjects		
Active FEX dose analyzed in this review	Control group	Median duration (days)	ITT analysis (active/ placebo)	Population	Mean age (range) years	Disease classification as reported by the author
30 mg/b.i.d.	Placebo	15	935 (464/ 471)	children	8.8 ± 1.6 (5-12)	SAR
120 mg/b.i.d.	Placebo	14	589 (137/ 138)	children and adults	34 ± 10 (12-65)	SAR
180 mg/o.d.	Placebo	14	864 (282/ 292)	children and adults	33 ± 12 (12-65)	SAR
120 mg/o.d.	Placebo, Loratadine 10 mg	14	688 (232/ 225)	children and adults	30.9 ± 11.51 (12–75)	SAR
120 mg/b.i.d.	Placebo	14	575 (144/ 141)	children and adults	32 ± 10 (12-65)	SAR
180 mg/o.d.	Placebo, Cetirizine 10 mg	14	842 (202/ 201)	children and adults	33 (13–66)	SAR
180 mg/o.d.	Placebo	14	330 (113/ 107)	adults	38.6 ± 14 (18–80)	SAR
180 mg/o.d.	Placebo, Desloratadine 5 mg	15	722 (288/ 244)	children and adults	34.5 ± 14.09 (12–84)	SAR
180 mg/o.d.	Placebo, Fluticasone furoate	14	624 (311/ 313)	adults and adolescents	38.7 ± 14.5	SAR
180 mg/o.d.	Placebo, Fluticasone furoate	14	456 (227/ 229)	adults and adolescents	34.55 ± 13.2	SAR
60 mg/t.d.	Placebo, Bilastine 20 mg	14	509 (254/ 255)	adults	35.25 ± 10.2	PAR
60 mg/t.d.	Placebo, Loratadine 10 mg	7	479 (360/ 119)	adults and adolescents	33 (12–60)	SAR

Table 1. Characteristics of the studies and subjects included in the meta-analysis

in symptoms scores was evidenced in the fexofenadine group (change from baseline: SMS -1.42; 95% CI -2.22 to −0.62, $p = 0.0005$). A substantial heterogeneity was observed ($X^2 = 12140.7$; $p < 0.00001$, $I^2 = 99\%$). (Fig. 1a).

No treatment duration comparisons were carried out because of the limited number of trials included in the present analysis.

For the outcome change from baseline in 12-h reflective TSS, the funnel plots apparently did not indicate substantial asymmetry; however, a possible publication bias cannot be ruled out, given the low number of trials included (Fig. 1b). The observed gap in the 2 bottom corners of the graphs, considering all outcomes of interest, but especially for instantaneous TSS, may indicate unpublished small studies.

Reference	Study	Random sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Selective reporting	Quality score - Jadad	Dropout	Overall quality assessment (risk of bias)	Experimental intervention
Wahn	2 arms	B	B	B	C	B	3/5	3.7	Unclear risk	FEX 30
Bronsky	4 arms	B	B	B	C	B	3/5	6	Unclear risk	FEX 40/60/120
Casale et	3 arms	B	B	B	C	B	3/5	1.2	Unclear risk	FEX 180/120
Van Cauwenberge	3 arms	B	B	B	C	B	3/5	3.9	Unclear risk	FEX 120
Bernstein	4 arms	B	B	B	C	B	3/5	9	Unclear risk	FEX 60/120/ 240
Howarth	4 arms	B	B	B	C	B	3/5	14	Unclear risk	FEX 120/180
Schapowal	3 arms	A	B	B	A	B	3/5	8.2	Unclear risk	FEX 180
Berger	3 arms	A	B	A	A	B	5/5	3.4	Low risk	FEX 180
Andrews[1]	3 arms	B	B	A	A	B	3/5	7.5	Lowrisk	FEX 180
Andrews[2]	3 arms	B	B	A	A	B	3/5	5	Unclear risk	FEX 180
Okubo	3 arms	B	B	B	A	B	4/5	2	Low risk	FEX 60
Kaiser	3 arms	A	B	B	C	C	4/5	3	Unclear risk	FEX 60

Table 2. Features of the studies included in the meta-analysis

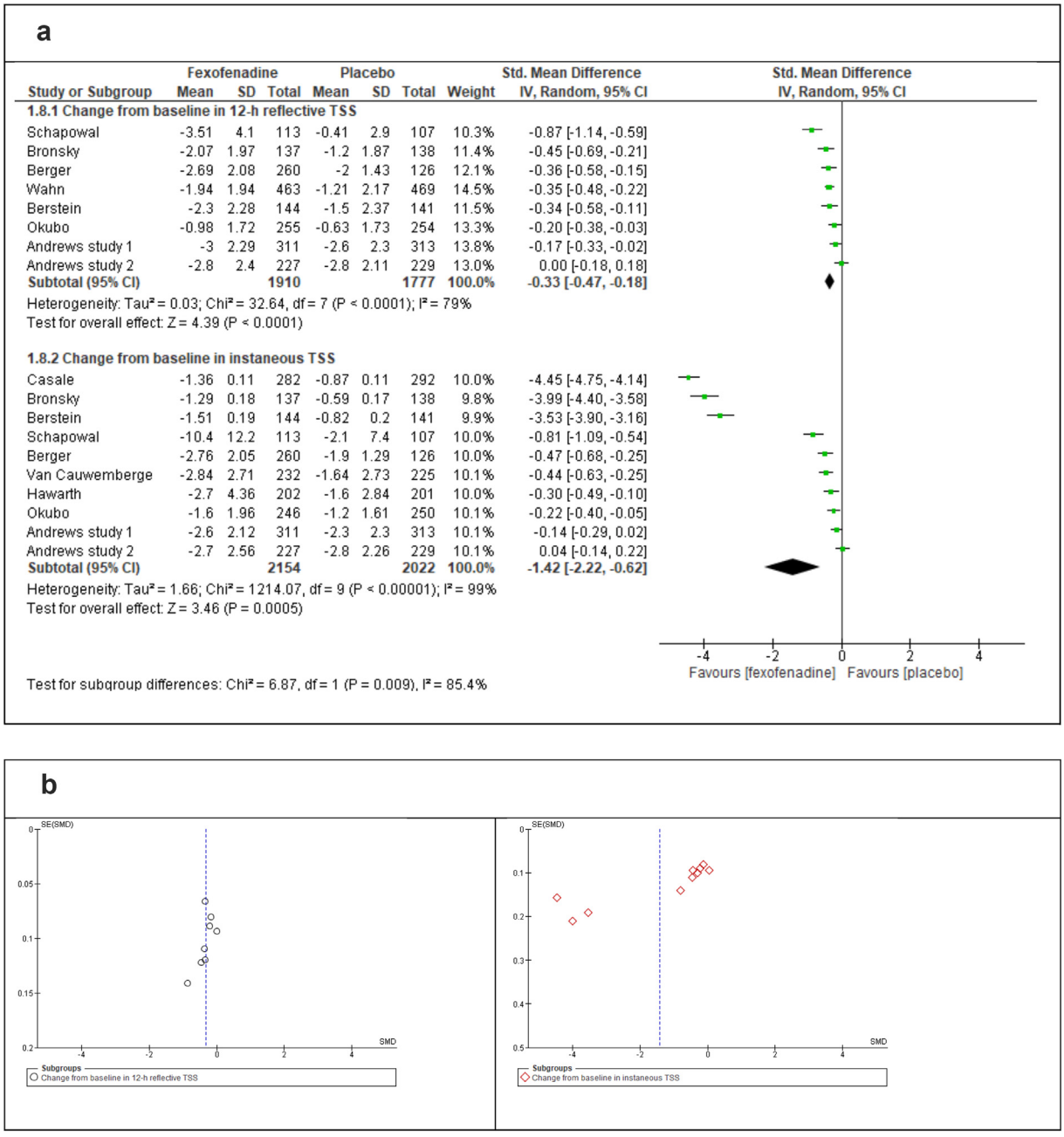


Fig. 1 (a) Change from baseline in the 12-h reflective TSS and Change from baseline in daily instantaneous TSS. (b) Funnel plots for reflective and instantaneous TSS

The study by Kaiser et al was excluded from the data synthesis despite the efficacy outcome was a suitable change from baseline in TSS based on reflective and instantaneous scores on a 4-point scale. Fexofenadine orally administered twice daily for 1 week (1 dose in the morning and another 1 dose 12 h later), exhibited significantly greater reductions in reflective TSS versus placebo at the final time-point (day 7:00 PM, $p = 0.018$). The change from baseline was −19% even at the first analysis after the first dose (day 1:00 PM reflective). No dispersion measures were reported in the article for baseline TSS or final values or changes from baseline; measures of improvement were reported only graphically day by day.

Safety

Regarding Adverse Events, 12 studies described the occurrence of adverse events (patients: 3018 fexofenadine/2640 placebo). The frequency of AEs was comparable between groups (OR = 1.04; 0.88–1.21). There was no heterogeneity across the studies (I2 = 0%) (Fig. 2). The relative incidence of AE registered, related or not to drug intake, is detailed in Table 3.

DISCUSSION

This updated systematic review confirmed with new original data the efficacy and safety profile of fexofenadine as a highly selective antihistamine of second-generation able to alleviate symptoms of AR in comparison with placebo involving more than 4000 patients. Four additional large studies were included providing evidence from 2068 new subjected treated (1152 treated with fexofenadine and 916 with placebo).

In respect to the previous meta-analysis, the evaluation was subordinated to changes from baseline, being considered more powerful and valuable in respect to comparison of final values because a component of between-person variability from the analysis is more properly controlled. On the other hand, calculation of a change score demands a collection and an evaluation of outcome at least twice and may be less appropriate for outcomes where measurement error may be wider than the true between-person variability at baseline. In addition, change-from-baseline outcomes may be preferred when they have a less skewed distribution in respect to final measurement outcomes, but this seems to be not the case for the instantaneous TSS since a particular pattern is observable, with 3 studies showing a very large SMD in respect to the remaining seven (must be taken with caution). On the other hand, this might be linked to the imputed missing values using a correlation coefficient from available data. A sensitivity analysis excluding these 3 studies generated an SMD of −0.63; 95% CI -1.19 to −0.07; p = 0.03. It is noteworthy due to the poor reporting in original source documents, several imputation techniques were necessary to enable combination with other studies for which full data were available. These involved making assumptions about unknown statistics and introduced a sort of approximation.

Regarding to the effect size of efficacy observed in this analysis, for the 12-h reflective TSS and the Morning instantaneous TSS, a moderate and large level was found respectively according to the common Cohen's scale.

A week point of this analysis is related to the high rate of interstudy heterogeneity, despite that most of the studies included investigated similar treatment durations with a median duration of 2

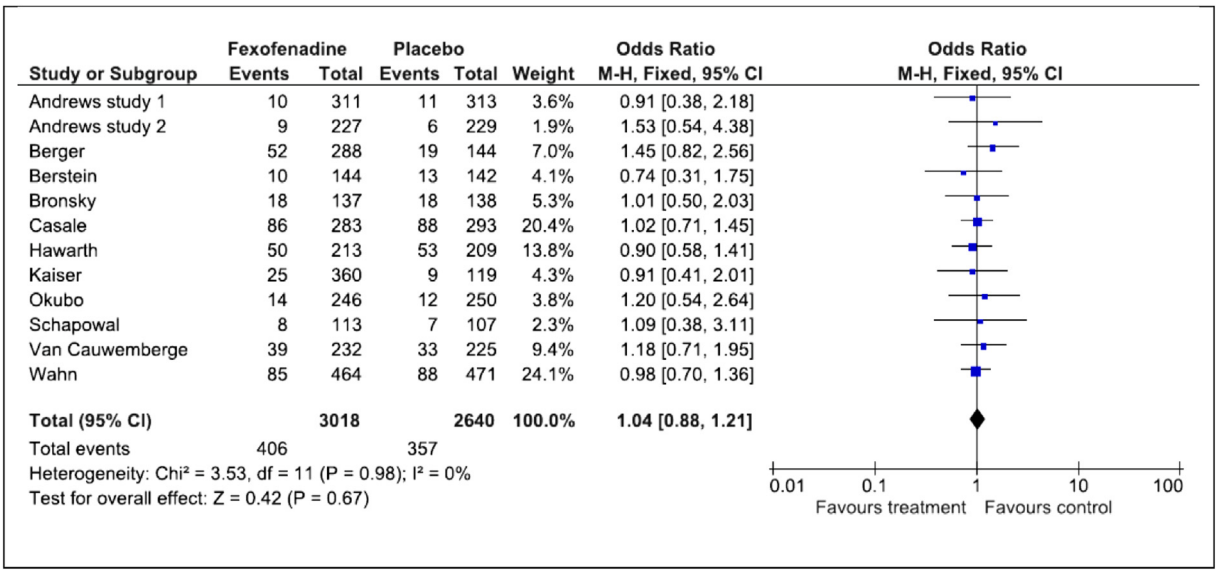


Fig. 2 Frequency of reported AE in subjects treated with fexofenadine compared to placebo (outcome: AE frequency)

Reference	No. of patients reporting adverse events (active/placebo)	
	Tot. Patients	Most commonly reported specific adverse events
Wahn et al	85/88	Headache (23/13), Epistaxis (7/5), Upper respiratory infection (11/5), Pharyngitis (6/1), Sinusitis (6/0), Nausea (5/1), Rash (5/3), Accidental injury (4/6), Asthma (3/9), Infection (1/5), Gastro-intestinal pain (1/5), Leukopenia (1/0)
Bronsky et al	18/18	Headache (3/4)
Casale et al	86/88	Upper respiratory infection (9/9), Pharyngitis 6/9, Back pain (8/4)
Van Cauwemberge et al	39/33	Headache (7/5), Sedation (4/3), Asthenia (1/1), Pharyngitis (3/1), Diarrhea (4/0), Nausea (1/3)
Berstein et al	10/13	Headache (6/4), Pharyngitis (1/2), Dry mouth (0/2), Cough (0/2), Leukopenia (1/1)
Howarth et al	50/53	Headache (8/15), Asthenia (3/2), Drowsiness (14/7)
Schapowal et al	8/7	Headache (0/1), Sedation (6/3), Upper respiratory infection (1/2), Sinusitis (1/2), Nausea (1/2)
Berger et al	52/19	Headache (11/2), Sedation (3/0), Nausea (3/0), Upper respiratory infection (3/1)
Andrews et al[1]	10/11	Headache (10/11)
Andrews et al[2]	9/6	Headache (9/6)
Okubo et al	14/12	Headaches (2/0), dizziness (1/0), somnolence (1/0)
Kaiser et al	25/9	Headache (16/8)

Table 3. Reported AE in the active and placebo treatment patients included in the safety evaluation

weeks and involved adults, adolescents, and children mainly with seasonal allergic rhinitis. This is likely related to the different dose administered (for each trial the highest dose in a single tablet currently available on the market), to the different outcome assessments adopted or simply to defects in data reporting. To control for the heterogeneity of scoring systems, SMD was used as a robust measure, independent from the scale of measurement, and providing the effect size of the intervention in SD units. A random effect analytical model was applied involving the assumption that effects being tested are not identical but follow a distribution.

A consequence of the weaknesses in data reporting and outcome selection is the unclear risk of bias observed in 9 out of 12 studies. In addition, as for the previous systematic review, the lack of concealment of allocation and blinding procedures description together with the power calculation represents the major deficiencies of the selected RCT. The dropout rate, on the other hand, was very low (raging 2–14%) despite that the attrition bias is an important element that may generate uncertainty in the interpretation of study results, but it can be concluded that this was not the case in this review.

The language and electronic database restrictions may have introduced publication bias, since it is plausible that not all the relevant studies have been considered. On the opposite, total population analyzed in this review is huge, and the individual size of studies is high enough on average, therefore limiting the risk of small studies

with outlier outcome in influencing the overall results.

Fexofenadine, in this review, has been confirmed to be a well-tolerated treatment, with low frequency of sedating effects attributable to a scarcely blood-brain barrier permeability, and devoid of cardiovascular side effects. The frequency of AEs was similar between active (406) and control groups (357) when 5650 subjects were treated with fexofenadine or placebo, where headache was the most commonly reported AE. No cardiovascular adverse events were reported. This evidence is largely confirmed in literature. In a systematic review by Iriarte Sotés P et al, which included 6 trials on fexofenadine (maximum dose, 720 mg), only 5 studies —3 on fexofenadine— were placebo-controlled. Again, headache was the most frequently reported treatment-related adverse event, with no subjects complaining of drowsiness.[11]

Cardiovascular events have been a major concern on anti-H1 safety, particularly alterations on heart rate, PR interval, QRS width, QT interval, or QTc (corrected QT interval). Cardiac safety index (CSI) has been proposed as the arrhythmogenic potential of anti-H1 drugs, provided by the ratio between the hERG IC50 (concentration of a drug provoking a 50% decrease in the current carried by hERG channels) and EC50 (concentration of drug provoking 50% anti-allergic effect). Peak concentrations of fexofenadine need to be more than ten times higher for a potential effect on the IC50 for human hERG channels, and its Cmax was even 20 times lower than hERG IC50 following a unique dose of 800 mg or after repeated doses of 690 mg twice a day, considering the licensed daily doses of 120 and 180 mg for allergic rhinitis and urticaria respectively. Above two thousand ECGs and six thousand clinical histories were revised without any evidence of cardiac arrythmia, even with the highest doses of fexofenadine.[12]

The therapeutic range of fexofenadine in adolescents was investigated up to 240 mg, with scarce unwanted effects and headache was reported similarly to adults. He same safety pattern was seen in 6–24 month-old children having AR at 15 mg and 30 mg BID. No cardiac relevant findings were reported from children aged 2–5 years taking 30 mg fexofenadine BID, or children (6–11 years) taking either 15, 30, or 60 mg of fexofenadine BID. Another relevant safety issue corresponds to cognitive and psychomotor function, with alteration of rapid eye movement (REM) sleep associated to first generation antihistamines and no impairment related to the second generation anti-H1 fexofenadine and others of its kind. This unwanted sleep effect of the former has a direct impact on attention, with the consequent impaired working in adults and learning performance in children.[13]

Recent research investigated for any major birth defects and spontaneous abortions as a primary analysis, without overlooking other aspects such as subgroups of birth defects, stillbirth, preterm birth, and small size for gestational age (SGA), as secondary items. The statistical analysis (considering potential confounders) evidenced no association of fexofenadine with a superior risk of adverse outcomes compared to loratadine and cetirizine, both considered to be safe in pregnancy.[14,15]

In conclusion, although this review did not include any preference analysis or patient-reported outcome evaluations, the emerging information suggests a favorable risk/benefit ratio for fexofenadine treatment. Most trials included in this review were based on short-term treatment of subjects with seasonal AR caused by natural exposure to pollens. Only 1 study involved subjects with perennial disease related to house dust mites' sensitivity. Further clinical trials are needed to extend the judgments of current review on safety and efficacy for fexofenadine to perennial rhinitis and longer treatment courses.

Availability of data and materials

Presented as Appendices 1 & 2.

Contribution

RMG & PM contributed on proposal, search of material, discussion of results and manuscript development.
EC contributed on search of material, methodology, guidance on the analysis of data, discussion of results and manuscript development.
GWC & IJA contributed on discussion of results, manuscript development and final edition.

Ethics approval

This was a study of the literature. There was no testing of human subjects. The present meta-analysis is based on

published data from clinical trials, all of them having their respective ethics evaluation and approvals.

Declaration of competing interest

Authors declare to have no conflict of interest regarding the present publication.

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Abbreviations

AEs, adverse events; anti H1, Anti Histamines (Receptor H1); AR, Allergic Rhinitis; BID, bis in die, equals twice a day; Cmax, maximum concentration of drug in organism system; CSI, Cardiac safety index; DBPC RCT, double-blind, placebo-controlled, randomized clinical trials; EC50, concentration of drug provoking 50% anti-allergic effect; ECG, ElectroCardioGram; FEM, fixed-effects model; hERG, human ether-a-go-go related gene encoding the pore-forming subunit of the rapid component of the delayed rectifier potassium (K+) channel; hERG IC50, concentration of drug provoking a 50% decrease in the current carried by hERG channels; ICTRP, International Clinical Trials Registry Platform; IgE, Immunoglobulin E; ITT, intention-to-treat population; OR, Odds ratio; OTC, over the counter; PAR, Perennial Allergic Rhinitis; PR interval, cardiac ECG measurement; QRS width, cardiac ECG measurement; QT interval, cardiac ECG measurement; QTc, corrected QT interval; REM, random-effects model; SAR, Seasonal Allergic Rhinitis; SD, standard deviation; SGA, small size for gestational age; SMD, standardized mean differences; TSS, total symptom score.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.waojou.2023.100795.

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