Systematic review on the efficacy of fexofenadine in seasonal allergic rhinitis: a meta-analysis of randomized, double-blind, placebo-controlled clinical trials
Compalati E, Baena-Cagnani R, Penagos M, Badellino H, Braido F, Gómez RM, Canonica GW, Baena-Cagnani CE

CRD summary
The author’s conclusion that the evidence encouraged the use of fexofenadine for the treatment of seasonal allergic rhinitis reflected the evidence presented. This was a generally well conducted review, but the large unexplained discrepancy between the number of participants in the studies and the number included in the analysis means that the conclusion should be viewed with caution.

Authors' objectives
To assess the safety and efficacy of fexofenadine in the treatment of seasonal allergic rhinitis.

Searching
MEDLINE, EMBASE and the Web of Science were searched up to December 2007 for relevant English language publications. Search terms were reported. In addition, reference lists of retrieved articles and recent reviews were manually searched and abstracts of relevant meetings were scanned for further studies.

Study selection
Double-blind placebo-controlled randomised trials (RCTs) that assessed the safety and efficacy of fexofenadine (any regimen) compared with placebo in patients with allergic rhinitis, were eligible for inclusion. Eligible patients could have co-morbid allergic asthma and/or conjunctivitis and IgE sensitisation proven by skin prick tests and/or specific IgE assays. The outcomes of interest were the reduction in total and individual symptom scores. Cross-over RCTs that did not directly compare fexofenadine and placebo were excluded.

Most trials included patients aged 12 to 84 years, with one trial in children aged five to 12 years. All patients had seasonal allergic rhinitis. Doses of fexofenadine were 30mg twice daily, 120mg once or twice daily or 180mg once daily. Control patients received placebo, with or without loratadine 10mg, cetirizine 10mg, butterbur Ze339, or desloratadine 5mg. The median duration of treatment was 14 or 15 days. The primary outcomes were 12 to 24 hour reflective total symptoms scores, sum of sneezing, rhinorrhea, itchy nose/palate and itchy/watery/red eyes (excluding nasal congestion). Secondary outcomes included morning instantaneous total symptoms scores, reflective individual nasal symptom scores (rhinorrhea, sneezing, itching and nasal obstruction) and adverse events.

Two reviewers independently screened studies for inclusion. Screening was checked by the principal reviewer, and discrepancies were resolved by consensus.

Assessment of study quality
Two reviewers independently assessed trial quality using the Jadad scale, and risk of bias using the Cochrane Collaboration tool. Trials were assessed on sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and other sources of bias. Each criterion was graded as low risk of bias (A), unclear risk of bias (B) and high risk of bias (C) and an overall grade was allocated to each trial.

Data extraction
Two reviewers independently extracted post-treatment means and standard deviations (SDs) on an intention-to-treat basis to calculate mean differences for primary and secondary outcomes. Primary authors were contacted for further information. Where data were not available, graphics were digitised and the SD was estimated using an imputation method. Where trials included treatment arms with different doses of fexofenadine, the dose considered most effective and safe by the primary author was assessed. Adverse event data were extracted to calculate odds ratios (ORs) and 95% confidence intervals (CIs). Any discrepancies between reviewers were resolved by discussion.

Methods of synthesis
A fixed-effect model was used (or a random-effects model where there was evidence of statistical heterogeneity) to
pool mean differences to calculate standardised mean differences (SMDs) and 95% confidence intervals. Odds ratios and their 95% confidence intervals were also combined. Statistical heterogeneity was assessed using Cochran’s Q and I² statistics.

Sensitivity analysis was planned to assess different treatment durations, fexofenadine dosages (≤120 mg versus >120 mg), and data synthesis using random-effects versus fixed-effect models. Sensitivity analysis was also performed to exclude trials that estimated data using imputation methods.

Publication bias was assessed through visual inspection of a funnel plot.

Results of the review
Eight RCTs (total number of participants 5,545, total number included in analysis 3,535) were included in the review. One RCT had low risk of bias while the remaining eight had medium risk of bias as allocation concealment and blinding were unclear. Drop-out rates ranged from 1.2% to 14%.

Fexofenadine compared with placebo significantly reduced 12-hour reflective total symptoms scores (SMD -0.42, 95% CI -0.51 to -0.34, five RCTs) and 24-hours reflective total symptoms scores (SMD -0.41, 95% CI -0.51 to -0.30, three RCTs). There was no evidence of significant statistical heterogeneity (I²=0% and I²=35% respectively). Morning instantaneous total symptoms scores was also statistically significantly reduced with fexofenadine (SMD -0.28, 95% CI -0.36 to -0.21, I²=26%, seven RCTs).

Seven RCTs showed that fexofenadine statistically significantly reduced nasal stuffiness/congestion (SMD -0.17, 95% CI -0.24 to -0.10), rhinorrhea (SMD -0.24, 95% CI -0.31 to -0.17), sneezing (SMD -0.37, 95% CI -0.44 to -0.30) and nasal itching (SMD -0.31, 95% CI -0.38 to -0.24). There was no evidence of statistical heterogeneity.

Adverse events were similar between treatment groups and there was no evidence of statistical heterogeneity.

Sensitivity analyses could not be performed for treatment durations, but other analyses did not significantly alter the results. Findings in children from indirect evidence were reported in the review.

Funnel plots showed no evidence of publication bias, but did indicate potential lack of unpublished small studies.

Authors’ conclusions
The evidence encourages the use of fexofenadine for the treatment of seasonal allergic rhinitis.

CRD commentary
The review question and supporting inclusion criteria were clearly stated. Several sources were searched for relevant studies, but were hampered by potential language and publication bias. The authors acknowledged this, and formal assessment of publication bias indicated potential gaps in the evidence. Trial quality and risk of bias were assessed using previously published criteria and most trials indicated moderate risk of bias. The authors acknowledged the limitations in trial quality. Each stage of the review process was conducted in duplicate, which reduced the potential for reviewer error and bias.

There was evidence of clinical and methodological heterogeneity across studies in terms of fexofenadine dose, type of placebo and outcome scoring systems. The authors went some way to account for this, but there were some uncertainties that related to whether the different types of placebo may have impacted on the results, and whether patients suffered from additional allergic conditions. This was a generally well conducted review and the conclusions reflected the evidence presented. Large unexplained discrepancy between the number of participants in the studies and the number of participants included in the analysis means that these conclusions should be viewed with some caution, particularly as an intention-to-treat analysis was reported to have been undertaken.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that well conducted RCTs were needed to assess the long-term safety and efficacy of fexofenadine in patients, particularly children, with both seasonal and perennial allergic rhinitis. The effects of
fexofenadine on patients’ reported outcomes were also required.

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