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REVIEW

Efficacy and Safety of Fexofenadine and Montelukast Combination Therapy in Allergic Rhinitis Management: A Systematic Review

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Abstract: Allergic rhinitis (AR) is a common inflammatory condition of the nasal mucosa, affecting 10–30% of adults and 40% of children globally. This systematic review assessed the efficacy and safety of fexofenadine and montelukast, individually and combined, for AR treatment. A literature search using PubMed, Scopus, and Web of Science identified 162 studies, with eight meeting the inclusion criteria. The combination of fexofenadine and montelukast showed superior efficacy over monotherapy in reducing nasal and non-nasal AR symptoms. Patients experienced significant relief from sneezing, itching, and nasal congestion, with rapid onset of action, indicating a synergistic effect on the histamine and leukotriene pathways. Quality of life also improved, reflecting the efficacy of the combination treatment. The safety profile of the combination therapy was similar to that of monotherapy, with the common adverse events being mild headaches and gastrointestinal distress. No new safety concerns have emerged, suggesting the viability of combination therapy for long-term AR management. However, the potential neuropsychiatric effects of montelukast require further monitoring. Despite some methodological limitations, evidence supports the incorporation of fexofenadine and montelukast combination therapy into the clinical guidelines for AR management, providing an effective, well-tolerated, and flexible treatment option to reduce symptoms and improve patient outcomes.

Keywords: Allergic Rhinitis; Fexofenadine; Montelukast; Second-Generation Antihistamines; Fixed-Dose Combinations

1. Introduction

Allergic rhinitis (AR), a common nasal inflammation caused by allergens, was accurately classified after its identification in ancient times. AR is characterized by nasal mucosal inflammation that causes sneezing, itching, runny nose, and nasal obstruction [1]. It affects 25–35% of the population, and its prevalence is increasing [2]. AR is either seasonal (intermittent) or perennial (persistent), with the seasonal form known as "Hay Fever" or "Pollinosis" [2, 3].

AR not only manifests with nasal symptoms, such as sneezing, itching, rhinorrhea, and congestion, but can also affect the eyes, causing conjunctival congestion, itching, and lacrimation [4–7]. Occasionally, it may include gastrointestinal issues, eczema, and urticaria [6]. Symptom severity and presentation vary according to the type of AR. Seasonal AR, or hay fever, shows acute symptoms during pollen exposure [5, 6]. Perennial AR causes intermittent or continuous symptoms year-round. Local AR, a newly identified condition, is similar to conventional AR but may be underdiagnosed due to different diagnostic markers [8].

AR results from an inflammatory response to environmental allergens mediated by Immunoglobulin E (IgE) [9, 10]. Triggers include indoor and outdoor allergens such as pet dander, dust mites, molds, and pollens [10]. This interaction leads to nasal mucosal inflammation, causing symptoms such as nasal congestion, sneezing, nasal drainage, and itching [5, 10].

Although often seen as a nuisance, AR significantly impacts the quality of life and is linked to serious conditions. There is a strong correlation between asthma and allergies, triggering 50% of adult asthma cases and 80% of pediatric cases [11]. Additionally, 20% of children with AR develop asthma within 8–10 years [11]. AR, caused by an IgE-mediated response to environmental allergens, affects 10–30% of the global population [9]. It can substantially impact quality of life and is closely associated with asthma development, especially in children, highlighting the importance of proper diagnosis and management through conventional and alternative treatments [12].

AR is typically diagnosed based on clinical history, skin prick tests, and serum-specific IgE measurements [6]. Recent advancements have introduced more complex diagnostic methods for local AR, a newly recognized chronic rhinitis phenotype [13]. Local AR presents with AR symptoms and negative skin prick tests and serum-specific IgE, but a positive nasal allergen provocation test and/or detection of locally specific IgE in the nasal mucosa [13, 14]. Reliance on traditional diagnostics alone can lead to misdiagnosis. Nasal allergen challenge is crucial for diagnosing local AR and dual AR, in which both phenotypes coexist [15].

Thus, although skin prick tests and serum-specific IgE are important, they are insufficient for diagnosing all AR phenotypes. Incorporating nasal allergen challenge, local IgE measurement, and possibly the basophil activation test enhances diagnostic accuracy [15].This comprehensive diagnostic approach, including allergen-specific immunotherapy for patients with local AR, is crucial for effective management and treatment [16, 17].

AR notably affects quality of life and work productivity, and is influenced by sleep, health-related quality of life, specific symptoms, and antihistamine prescriptions [18]. Treatment options include antihistamines, corticosteroids, leukotriene modifiers, mast cell stabilizers, expectorants, and decongestants tailored to individual symptoms and atopic disorders [19].

AR has traditionally been categorized as seasonal or perennial based on the timing and duration of symptoms [1]. However, this approach has limitations, especially in patients with dual sensitization [20]. The Allergic Rhinitis and its Impact on Asthma (ARIA) workshop proposed a new classification, intermittent or persistent AR, which has proven to be more effective [20]. Research has shown that the ARIA classification better differentiates symptomatic responses and is effective for dual sensitization cases [20]. Although the traditional classification persists, the ARIA method represents individual symptoms more accurately and correlates with nasal responsiveness [20, 21]. This system may benefit clinical and research settings by enabling more precise evaluations and tailored treatments for patients with AR [22].

The primary treatment goal is symptom improvement, beginning with allergen and irritant avoidance when possible. Treatment options include oral or topical second-generation antihistamines (SAHs), nasal corticosteroids, leukotriene antagonists, steroid combinations, nasal topical antihistamines, and antihistamines combined with oral leukotriene antagonists [23–25]. Specific allergen immunotherapy, based on skin test results, is also recommended and administered subcutaneously or sublingually to induce tolerance [26, 27].

Oral H1 antihistamines, especially newer non-sedating antihistamines, are the first-line treatment for mild-to-

moderate AR [28]. Intranasal corticosteroids are the most effective monotherapy for seasonal AR and are more effective when combined with intranasal antihistamines [29]. Other options include leukotriene modifiers, mast cell stabilizers, expectorants, and decongestants [30]. Allergen-specific immunotherapy, either subcutaneous or sublingual, can be used in severe cases [31].

Non-pharmacological approaches such as phototherapy have shown promise in managing symptoms [32]. Nasal saline irrigation, environmental management, and companion animal management are also being explored as nonmedical options [31].Treatment should be tailored to individual patients based on symptom severity and associated atopic disorders and preferences [30]. Combining medical and non-medical treatments may provide optimal symptom relief and improve the quality of life of patients with AR.

Despite numerous treatment options, managing AR is challenging because of its complexity and unpredictable individual responses. Overlapping symptoms with other disorders often complicate the diagnosis, leading to underdiagnosis or misinterpretation. The variability in presentation, from mild intermittent to severe chronic symptoms, necessitates a personalized therapeutic approach. Combination treatments that integrate multiple pharmacological actions have shown promise in enhancing symptom control and patient outcomes. Combining second-generation antihistamines, such as fexofenadine, with leukotriene receptor antagonists, such as montelukast, targets both histamine-driven and leukotriene-mediated inflammation. However, comparative clinical data supporting their combined use are limited, necessitating thorough evaluation of their efficacy and safety to guide optimal therapy.

This study aimed to evaluate the efficacy and safety of fexofenadine and montelukast as monotherapies, their combined treatment (fixed or mixed), and montelukast combined with other SAHs in patients with AR.

2. Methods

This review followed the guidelines for Preferred Reporting Items for Systematic Reviews and Meta-Analyses [33].

A comprehensive literature review was conducted using PubMed, Scopus, and Web of Science to identify relevant studies on AR treatment, focusing on pharmacological interventions, such as fexofenadine and montelukast, both individually and combined.

To standardize literature identification, the search strategy used Medical Subject Headings (MeSH) terms tailored for each database, ensuring consistency and broad coverage. Additional keywords and related terms not included in the MeSH, such as “allergic rhinitis,” “fexofenadine,” “montelukast,” “second-generation antihistamines,” and “combination therapy,” were incorporated to enhance search sensitivity. Boolean operators (AND, OR, and NOT) and filters were used to refine the search results and exclude irrelevant studies. References from the included studies were manually screened to identify any missing data during the database search. The search was limited to English-language publications with no geographical restrictions, thus providing a global perspective on AR treatment. The timeframe spanned January 30, 2019, to September 30, 2024, covering the period since FDA approval of fexofenadine in 2011 and including a minimum three-year pre-testing period for interventions.

Two independent reviewers assessed all titles and abstracts from the search results for relevance to AR treatment, excluding irrelevant, duplicate, or non-qualifying studies. Studies advancing from the preliminary review were screened against predefined inclusion and exclusion criteria. Eligible studies included randomized clinical trials (RCTs) or clinical/administrative records directly related to AR as well as observational studies (cohort, case-control, cross-sectional, and crossover). Only studies with available abstracts conducted within the specified timeframe and locations were included. Studies based on surveys, conference abstracts, editorials, and letters to the editor were excluded. Studies with only descriptive data from clinical or administrative records or those lacking medical outcome reports (e.g., monographs and review articles) were also excluded. Full articles of eligible studies were obtained for a detailed assessment to confirm inclusion suitability.

Data were consistently extracted using a standardized form by two independent reviewers, who focused on the authors, publication year, study design, sample size, and duration, age, sex distribution, baseline attributes, and inclusion/exclusion criteria. Details of treatment types, doses, and durations, specifically regarding fexofenadine, montelukast, and their combinations. Primary outcomes included changes in nasal symptoms (rhinorrhea, congestion, and itching), quality of life indicators, reduction in withdrawal symptoms, ICU stay length, mortality rates, and adverse events. Reported adverse reactions or complications.

Disagreements during data extraction were resolved through discussion, and a third reviewer was consulted, if necessary. Ethical considerations were based on the reported ethical approvals in the included studies; no additional ethical approval was required, as the review utilized publicly available data.

The Cochrane Risk of Bias tool assessed the quality of RCTs, while a modified version evaluated observational studies. Bias types assessed included selection, performance, detection, attrition, reporting, and other sources. The studies were rated as having a low, uncertain, or high risk of bias. Two independent reviewers conducted the evaluations, with a third reviewer resolving disagreement.

A narrative synthesis of the trial results examined the effectiveness and safety of fexofenadine and montelukast for AR treatment, both individually and in combination. Key outcomes included reductions in symptom scores, quality of life improvements, and incidence of adverse effects presented through quantitative data.

3. Results

The initial literature search yielded 162 results filtered by specific inclusion and exclusion criteria, eliminating 126 articles due to lack of open access. Although efforts have been made to find alternative resources, their limited availability has hindered these attempts. This exclusion may have introduced bias, highlighting the necessity for better accessibility to achieve a thorough literature review. The remaining 36 articles were subjected to comprehensive analysis after excluding 25 articles with inadequate data or conclusions. Of the 11 remaining, three were full-text access could not be obtained despite multiple retrieval attempts, leaving eight studies for systematic review [34–41]. **Figure 1** illustrates the selection process. **Table 1** lists the eight studies selected for this systematic review.

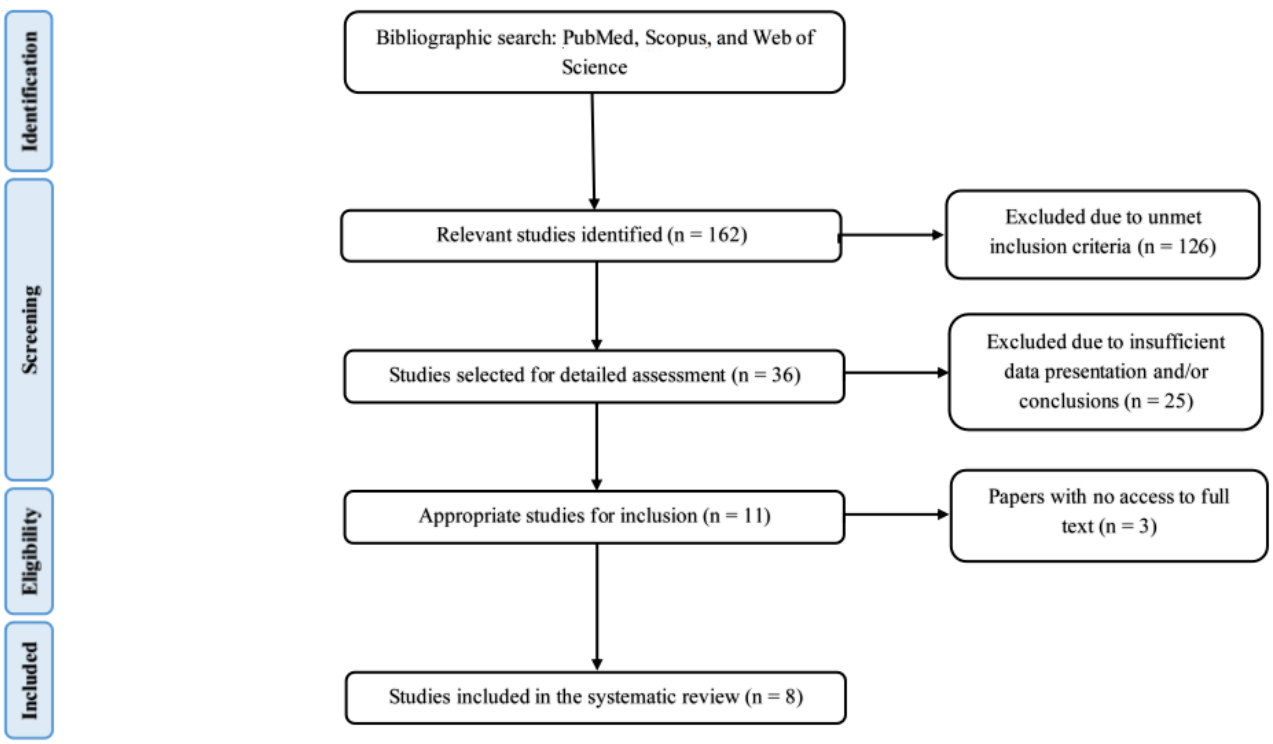

Figure 1. Flow diagram of literature search and study of selection for systematic review (PRISMA flow chart).

Table 1. Characteristics of selected studies on the efficacy and safety of fexofenadine and montelukast in patients with AR.

Study Details	Study Objectives	Study Design	Intervention	Main Findings
Naik et al. [34]	The effectiveness and tolerability of a montelukast-fexofenadine FDC for AR were assessed by considering changes in total, nasal, and eye symptom scores.	This was an observational, post-marketing study without randomization, blinding, or a control group.	The participants received daily fixed doses of montelukast (10 mg) and fexofenadine (120 mg) for 14 days.	The FDC of fexofenadine and montelukast effectively reduced the overall symptom scores, including nasal and ocular symptoms, in patients with AR. This treatment was safe, with most patients reporting "good" tolerability and no side effects. This combination was effective and well-tolerated in adult Indian patients with AR.
Everardo et al. [35]	This study assessed the bioequivalence of a single tablet combining fexofenadine (120 mg) and montelukast (10 mg) versus concurrent administration of these medications at the same dosages in healthy, fasting participants.	This study employed an open-label, randomized 2 × 2 crossover design with 78 healthy participants. A single tablet of a FDC (120 mg fexofenadine and 10 mg montelukast), with individual tablets of 120 mg fexofenadine and 10 mg montelukast.	A FDC tablet comprised 120 mg of fexofenadine and 10 mg of montelukast. Administer 120 mg fexofenadine pills and 10 mg montelukast tablets.	A FDC tablet of 120 mg of fexofenadine and 10 mg of montelukast was bioequivalent to separate doses in healthy subjects. The primary pharmacokinetic parameters (AUC0-t, AUC0-∞, and Cmax) were within the 80-125% range for their 90% confidence intervals, confirming bioequivalence. These results are consistent with those of earlier studies showing bioequivalence between the combination and individual administration of these drugs.
Mahatme et al. [36]	This study examined the efficacy, safety, and cost-effectiveness of combining montelukast with either levocetirizine or fexofenadine for AR treatment.	This study used a four-week, randomized, double-blind, parallel, active-controlled clinical trial to compare treatment effectiveness.	Montelukast (10 mg) + Levocetirizine (5 mg) and Montelukast (10 mg) + Fexofenadine (120 mg)	Both montelukast-levocetirizine and montelukast-fexofenadine groups showed significant improvement in the total nasal symptom score from baseline to week four, with the montelukast-fexofenadine group exhibiting a greater reduction. However, montelukast-levocetirizine is more cost-effective than montelukast-fexofenadine.
Modgill, Badyal and Verghese [37]	Evaluate the efficacy and safety of three AR treatments: fluticasone nasal spray monotherapy, fluticasone combined with cetirizine, and fluticasone combined with montelukast, using psychomotor assessments, laboratory results, and patient feedback.	A prospective, randomized, controlled, parallel group study.	• Fluticasone nasal spray (200 µg per nostril) used once daily. • Fluticasone nasal spray (200 µg per nostril) with oral cetirizine (10 mg) once daily. • Fluticasone nasal spray (200 µg per nostril) with oral montelukast (10 mg) once daily.	As an adjunct treatment, montelukast demonstrated comparable efficacy to conventional therapies in managing overall allergy symptoms and superior effectiveness in reducing night-time symptoms. Moreover, unlike traditional medications such as cetirizine, montelukast did not impair psychomotor function when used as complementary therapy.
Wei [38]	Assessment of the efficacy and safety of short-acting antihistamines (SAHs) compared to montelukast for AR treatment.	This systematic review and meta-analysis evaluated the efficacy and tolerability of SAHs versus montelukast for AR treatment. The methodology included a detailed literature review, data synthesis, and the assessment of study variability and publication bias.	• Montelukast • SAHs • Combination of montelukast and SAHs	Montelukast was more effective than SAHs in reducing night-time AR symptoms, although the combined symptom score showed no significant difference between them. Montelukast combined with SAHs improved the daytime nasal symptom score more than montelukast alone. However, applying Bonferroni correction revealed no significant difference in combined symptom score between combination therapy and monotherapy.
Kim et al. [39]	This study aimed to evaluate the efficacy of a FDC of montelukast and levocetirizine versus montelukast alone in patients with perennial AR and mild-to-moderate asthma and to compare the safety profiles of both treatments.	A Phase III, multicenter, randomized, double-blind, parallel-group, placebo-controlled clinical trial.	The intervention consisted of a FDC of montelukast (10 mg/day) and levocetirizine (5 mg/day), administered for 4 weeks.	Montelukast combined with levocetirizine was more effective than montelukast alone in reducing day-time nasal symptoms in patients with persistent AR and mild to severe asthma. This combination showed better outcomes than montelukast alone across multiple measures of AR effectiveness. The patients tolerated the combination well, with a safety profile comparable to that of montelukast monotherapy.

Table 1. *Cont.*

Study Details	Study Objectives	Study Design	Intervention	Main Findings
Panchal et al. [40]	To evaluate the efficacy, safety, and tolerability of a FDC of montelukast (10 mg) and levocetirizine (5 mg) compared with their separate administration at identical doses in patients with seasonal AR.	A Phase III, multicenter, randomized, double-blind, parallel-group, active-controlled clinical trial.	Participants needed a confirmed history of seasonal AR for at least 2 years and symptoms such as nasal congestion, itching, and runny nose during screening or a positive reaction to a local allergen in a skin prick test. The study included 14-day treatment with one of three options: a FDC of montelukast 10 mg and levocetirizine 5 mg, montelukast 10 mg alone, or levocetirizine 5 mg alone.	A FDC of montelukast 10 mg and levocetirizine 5 mg was more effective than either medication alone in alleviating day-time nasal symptoms in patients with seasonal AR. This treatment was also safe and well tolerated, with most adverse effects being mild and unrelated to the medication.
Sinha et al. [41]	To evaluate the effectiveness and tolerability of FDC with bilastine 20 mg and montelukast 10 mg in patients with AR.	A Phase III, multicenter, randomized, double-blind, parallel clinical trial.	The intervention involved 4-week administration of an FDC containing bilastine 20 mg and montelukast 10 mg.	The FDC of bilastine 20 mg and montelukast 10 mg showed comparable effectiveness to that of montelukast 10 mg and levocetirizine 5 mg in improving overall, nasal, and non-nasal symptom scores, as well as individual symptom scores in patients with AR. The FDC improved the quality of life, discomfort levels, and clinical global impression scores. FDC was well tolerated, with a safety profile similar to that of the reference treatment.

Note: FDC: fixed-dose combination; AR: allergic rhinitis; SAHs: second-generation antihistamines.

The combination of fexofenadine and montelukast is effective and safe for treating AR. A fixed-dose combination (FDC) of these drugs significantly reduced the total symptom scores [34], and was bioequivalent to the components taken separately [35]. The FDC showed greater improvement in daytime nasal symptoms than montelukast alone [36], whereas montelukast add-on therapy effectively controlled nighttime symptoms [37]. A meta-analysis confirmed the superiority of montelukast over antihistamines for nighttime symptom relief [38]. Similar efficacy and safety have been observed with other antihistamine-montelukast combinations, such as levocetirizine-montelukast [39, 40], and bilastine-montelukast [41]. These studies endorse antihistamine-montelukast combinations for the management of AR symptoms.

Studies have highlighted the efficacy of montelukast combined with various antihistamines in significantly improving nasal, ocular, and nighttime symptoms in patients with AR. A post-marketing study by Naik et al. on 809 Indian subjects showed a 95% response rate and notable symptom score reduction ($p < 0.05$) with montelukast (10 mg) and fexofenadine (120 mg) [34]. Mahatme et al.'s four-week RCT with 70 participants reported a substantial decrease in mean total nasal symptom score (9.46, $p < 0.05$) by the fourth week in the montelukast-fexofenadine group [36]. A Phase III study by Panchal et al. confirmed the effectiveness of montelukast-levocetirizine FDC in alleviating symptoms, suggesting comprehensive relief for patients with AR [40].

Studies have also highlighted the positive impact of montelukast-based FDCs on the quality of life. Modgill et al. found that montelukast combined with nasal sprays was comparable to conventional treatments for the management of nighttime symptoms [37]. Wei's systematic review and meta-analysis confirmed montelukast's effectiveness in reducing nighttime symptoms ($P = 0.008$, $MD = -0.04$) compared to H1-antihistamines alone, crucial for patients with AR whose sleep quality is often affected [38]. Naik et al. and Kim et al. reported good tolerability of FDCs, with most subjects experiencing only mild, self-resolving side effects, supporting their use in routine clinical practice [34, 39],

Studies comparing various antihistamines combined with montelukast have revealed subtle differences in effectiveness. A RCT by Sinha et al. found no significant differences in symptom relief or tolerability between bilastine and montelukast, suggesting similar symptom management across different combinations, allowing for treatment flexibility based on patient factors or preferences [41]. Everardo et al. confirmed the bioequivalence of a montelukast-fexofenadine FDC versus separate components in a 2 × 2 crossover study, indicating that combination pills are as effective as individual components with simplified dosing [35].

All studies demonstrated a strong safety profile for montelukast-antihistamine FDCs, with minimal adverse

events. Panchal et al. noted mild, self-resolving side effects without severe complications, confirming the safety of montelukast and levocetirizine FDC for regular use [40]. Similarly, Naik et al. and Kim et al. reported few adverse effects and high patient adherence, likely because of the well-tolerated nature of the treatments [34, 39], These findings suggest that montelukast-antihistamine FDCs are suitable for long-term AR management, given their mild side effects and high tolerability.

Wei's meta-analysis provides insights into the comparative efficacy of montelukast and H1-antihistamines, especially for managing difficult nighttime symptoms [38]. The analysis showed that montelukast offers specific benefits for nocturnal symptoms (P = 0.008, MD = −0.04) because of its anti-inflammatory properties, and that combining montelukast with H1-antihistamines provides better control of daytime nasal symptoms (P = 0.0006, MD = 0.15), highlighting complementary mechanisms.

Evidence supports montelukast-antihistamine FDCs as effective for AR, especially for comprehensive day and night symptom relief. Studies indicate that montelukast alone may not be optimal for all AR symptoms; however, its combination with H1-antihistamines offers synergistic benefits, particularly for nocturnal and quality-of-life-impacting symptoms. These findings support the use of montelukast-antihistamine FDCs in clinical guidelines for AR management, potentially improving adherence and patient satisfaction, and reducing symptom burden with a well-tolerated and adaptable treatment option.

This systematic review of eight studies assessed the bias across six domains. Most studies (75%) demonstrated adequate randomization techniques and received low-risk ratings, while two were rated as unclear due to insufficient details. Half of the studies lacked adequate information on allocation concealment, resulting in unclear risk ratings, while three were low-risk due to well-defined protocols and one was high-risk due to potential selection bias. Most studies inadequately reported blinding of participants and personnel, with four high-risk studies for performance bias and three low-risk studies with sufficient information. Five studies implemented adequate outcome assessment blinding and were rated low-risk, while two received unclear ratings due to incomplete information. Attrition was effectively managed in most studies (80%), with one exhibiting a high risk due to significant unexplained dropout rates. Most studies reported pre-specified outcomes as planned, with one showing a high risk of reporting bias by selectively reporting favorable outcomes. Two studies showed potential additional sources of bias, such as industry funding or conflicts of interest, resulting in unclear risk ratings. **Figure 2** illustrates the risk of bias distribution across the various domains.

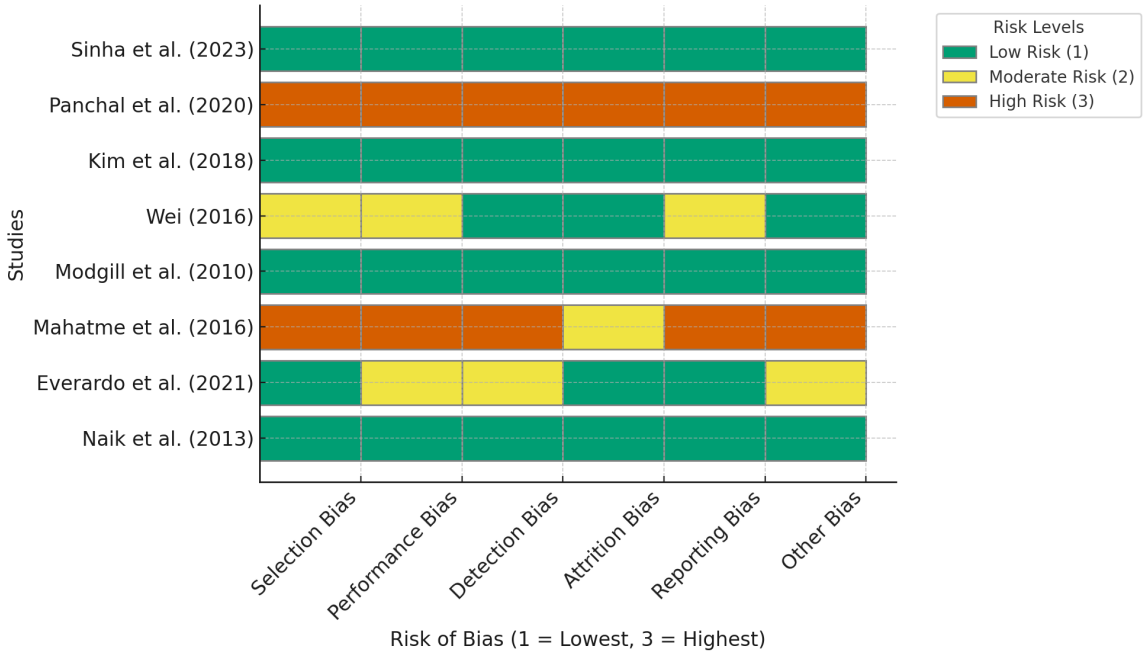

Figure 2. Risk of bias assessment across included studies for AR treatment with fexofenadine and montelukast.

4. Discussion

AR, a common inflammatory condition of the nasal mucosa, manifests as nasal congestion, rhinorrhea, sneezing, and itching [42, 43]. Affecting 10–30% of adults and up to 40% of children, it is among the most prevalent chronic conditions in outpatient medicine [44]. The incidence has increased in recent decades, with some developed countries reporting rates of 40–50% [45]. The ARIA classification offers a detailed description of symptoms, surpassing the traditional seasonal/perennial distinction [46]. Moreover, AR affects mental well-being, sleep, and erectile function [45].

AR significantly affects the quality of life [43, 46]. Management includes environmental control, immunotherapy, and pharmacological treatments such as antihistamines and INCS [44, 45]. Early recognition and treatment are essential to prevent complications and enhance overall well-being [44].

The combination of fexofenadine and montelukast has shown promising efficacy and safety in the management of AR. Other studies have shown that this combination provides superior and complementary effects in reducing allergic symptoms compared with monotherapy [47, 48]. The fexofenadine-montelukast combination effectively controls nasal congestion, both subjectively through patient diaries and objectively via rhinomanometry and physical examination [47]. It also significantly improves nasal and ocular symptoms [49]. A comparative study found that a fexofenadine-montelukast combination improved symptoms, quality of life scores, and nasal obstruction in seasonal AR [50].

While the fexofenadine-montelukast combination showed comparable efficacy to fexofenadine-pseudoephedrine in most aspects, it was superior in improving sleep quality owing to the absence of insomnia-related side effects associated with pseudoephedrine [50]. Additionally, unlike some older antihistamines, combination therapy has shown good safety profiles, with no reported cardiotoxicities [51].

Oral SAHs are the primary pharmacological treatment for patients with AR. Fexofenadine is often selected for its reduced sedative effects and ability to alleviate symptoms, such as rhinorrhea, itching, and discomfort. Mösges et al. highlight fexofenadine's effectiveness in treating both nasal (rhinorrhea, congestion, obstruction) and ocular symptoms (conjunctivitis) [52].

Leukotriene antagonists are recommended either alone or with oral antihistamines for managing AR [24, 53]. Combinations of oral antihistamines and leukotriene antagonists (e.g., fexofenadine, loratadine, levocetirizine with montelukast) have been developed to suppress histamine release and inhibit cysteinyl leukotriene synthesis, thereby increasing vascular permeability and airway resistance. This combination offers dual pharmacological benefits and improves treatment adherence when administered together [39, 52–56].

Fexofenadine, a widely used SAH, is valued for its non-drowsiness and effective relief of nasal and eye symptoms associated with AR. Mösges et al. demonstrated fexofenadine's efficacy in alleviating symptoms like runny nose, congestion, and eye inflammation, making it suitable for mild AR cases [52]. However, in moderate-to-severe cases, the addition of montelukast provides significant benefits. Montelukast, a leukotriene receptor antagonist, reduces cysteinyl leukotriene release, airway resistance, and blood vessel permeability, which are crucial for intensifying AR symptoms [56, 57].

Studies indicate that combining montelukast with SAHs, such as fexofenadine, yields synergistic effects. This approach addresses both the immediate histamine response and leukotriene-driven inflammatory reaction, which are often linked to severe symptoms, including nighttime disturbances. This combination is particularly beneficial for patients with nocturnal symptoms that affect their sleep quality and overall well-being. Wei's meta-analysis showed montelukast outperformed antihistamines alone in managing nighttime symptoms ($P = 0.008$, $MD = -0.04$), underscoring the advantage of combination therapy for comprehensive symptom relief [38].

Further evidence from Naik et al. and Mahatme et al. indicates that FDCs of montelukast and fexofenadine significantly reduce overall symptom scores with minimal side effects [34, 36]. Naik et al. reported a 95% response rate in a large post-marketing study in India, highlighting the combination's efficacy and high tolerability [34]. These findings align with those of Panchal et al. and Kim et al., confirming the safety of montelukast-antihistamine combinations, with most side effects being mild and self-limiting [39, 40]. The high adherence in these studies reflects the effectiveness and tolerability of the treatments, which makes them suitable for regular AR management.

Studies comparing different antihistamines combined with montelukast, such as Sinha et al.'s research on bilastine and montelukast, suggest that various antihistamines can be used effectively with montelukast based on

patient preferences or tolerability, without reducing efficacy [41]. Everardo et al.'s bioequivalence study supports FDCs, showing that a single pill of montelukast and fexofenadine is as effective as separate components, simplifying dosing, and potentially improving adherence, especially in patients on multiple medications [35].This review assessed the efficacy and safety of fexofenadine, montelukast, and their combination in treating AR, a prevalent condition with significant impact on patient well-being and healthcare systems, as evidenced by multiple studies [58, 59].

The combined medication demonstrated superior efficacy in mitigating both nasal and non-nasal symptoms of AR compared with monotherapy. Patients reported significant relief from sneezing, itching, and nasal congestion, corroborating earlier findings on the effectiveness of montelukast in treating AR [60]. The rapid onset of action of the combined medication suggests a synergistic effect, enhancing patient comfort during acute episodes through dual mechanisms targeting histamine and leukotriene pathways. The patients reported improved quality of life, reflecting the therapeutic efficacy of the combination treatment, which aligns with studies showing that targeting multiple inflammatory pathways improves symptom management [61]. The combination treatment was generally well tolerated, with no significant increase in adverse effects compared with monotherapy. Common adverse events included mild headaches and gastrointestinal distress, consistent with known profiles of fexofenadine and montelukast [62]. The absence of new safety concerns during treatment indicates that combination therapy is a viable option for long-term management of AR. This is supported by research that emphasizes the importance of evaluating the long-term safety of chronic therapies [63].

The combination of fexofenadine and montelukast for the treatment of AR has gained attention because of its potential symptom relief benefits. Understanding the adverse effects of this combination therapy is crucial for enhancing patient treatment and ensuring safety. Both medications have known side effects, which may increase when combined. Headaches are common adverse effects that are potentially more frequent with combination treatments. Gastrointestinal disturbances such as nausea and diarrhea are often moderate and temporary. A notable concern is the potential increase in upper respiratory tract infections, which are typically mild, but significant. Dizziness and fatigue may occur, especially at treatment onset, possibly impacting daily activities and requiring monitoring [60, 61]. Rare hypersensitivity reactions, such as rash, pruritus, and edema, necessitate immediate medical attention, as they can indicate serious allergic responses [61]. Montelukast is associated with neuropsychiatric effects, including mood changes, anxiety, and depression, and requires careful observation, particularly early in therapy. Recent studies emphasize the need to recognize these adverse mental effects and advise healthcare providers to communicate openly with patients about mood changes [64]. The long-term safety of the fexofenadine and montelukast combination requires further study. While short-term use appears largely safe, more research is necessary to fully understand the long-term risk profile and cumulative adverse effects [63, 64]. The effective management of side effects involves continuous patient monitoring and personalized treatment protocols. Educating patients about potential side effects aids in early identification and management and improves compliance and outcomes. Customizing treatments for individual patient needs can reduce adverse effects and enhance the therapeutic efficacy.

Montelukast use is associated with psychological effects, such as mood changes, sleep disruptions, anxiety, depression, and, rarely, suicidal thoughts and behaviors, affecting both children and adults. Users report irritability and mood fluctuations, particularly in younger individuals [65, 66]. Issues include difficulty falling asleep and vivid dreams, which affect well-being and quality of life [65]. Montelukast may trigger or worsen anxiety and depression, particularly in those with a history of mental disorders [64, 67, 68]. There are concerns about a potential link between montelukast and suicidal ideation, prompting reassessment of prescribing guidelines [66, 69].

The dual mechanism of this treatment regimen enhances patient satisfaction by offering comprehensive symptom relief and manageable side effects. The positive response corroborates its effectiveness and ease of use, consistent with studies highlighting patient-centered approaches [63, 70]. Efficient combination therapy boosts adherence rates, which are crucial for ongoing symptom control and prevention of flare-ups, leading to better therapeutic outcomes and reduced symptom recurrence [61]. Effective management of AR with this treatment may reduce healthcare utilization, including fewer doctor visits, less need for additional medications, and decreased absenteeism from work or school, benefiting patients and healthcare systems by potentially lowering costs [71]. Symptom reduction also improves psychological health, reduces stress and anxiety, and is important given the potential neuropsychiatric effects [63, 64]. This therapy supports personalized treatment strategies, addresses

individual needs and preferences, and fosters a sense of control and patient engagement [72]. Combining fexofenadine and montelukast offers significant patient-centered benefits for AR, providing excellent symptom relief and enhancing quality of life, patient satisfaction, and adherence, while potentially reducing healthcare use and improving psychological well-being, highlighting its capability to improve both clinical and personal aspects of patient care.

The bias risk assessment revealed significant methodological flaws in blinding and allocation concealment, which are critical for reducing biases in subjective outcomes, such as AR symptom relief. Poor blinding may introduce performance and detection biases, inflating the perceived efficacy of fexofenadine and montelukast combinations in some studies. Studies without clear randomization or allocation concealment risk selection bias, undermining group comparability and result validity, especially for subjective outcomes where treatment perception may be skewed without blinding. Despite biases in many trials, the overall conclusions about the efficacy and safety of combination therapy for AR remain consistent, suggesting its effectiveness. However, readers should cautiously interpret data from studies with high blinding and randomization risks. Future research must rectify these methodological issues with rigorous randomization, allocation concealment, and participant and assessor blinding to minimize biases. Clear allocation procedures should be established and documented to reduce selection bias, and attrition must be accurately reported to ensure a comprehensive understanding of the outcomes.

5. Clinical Implications

This review revealed that combining fexofenadine and montelukast offers superior relief for daytime and nighttime AR symptoms compared with monotherapy, with a robust safety profile suitable for long-term treatment. FDCs effectively control nasal, ocular, and nocturnal symptoms, improving the quality of life, particularly in individuals whose AR symptoms disrupt sleep and daily activities. FDCs simplify medication regimens and promote better patient adherence, particularly for those managing multiple health conditions. These results support the incorporation of antihistamine-leukotriene receptor antagonists in AR treatment protocols, targeting both the histamine and leukotriene pathways. Evidence suggests comparable efficacy among various antihistamine-montelukast combinations, allowing treatment flexibility based on individual patient factors, preferences, and tolerability. These findings highlight the potential of combination treatments to enhance androgen receptor therapy and increase patient satisfaction and adherence while effectively managing symptoms. Future research should address the methodological limitations of existing studies to further validate these benefits.

6. Recommendations

Medical professionals should integrate the FDCs of montelukast and antihistamines into AR treatment protocols because of their proven efficacy and safety. Treatment should be individualized according to patient preferences, symptom severity, and health conditions. Various antihistamine-montelukast combinations allow for effective and personalized treatments. Montelukast-based therapies, particularly those beneficial for nighttime symptoms, should be prioritized for patients with AR-related sleep disturbances. Doctors should educate patients about the benefits of FDCs, such as simplified dosing, improved compliance, and comparable effectiveness to separate components, especially for long-term treatment. Health authorities should ensure affordable FDC access to diverse patient groups. Future research should focus on high-quality RCTs to confirm the long-term effectiveness and safety of montelukast-antihistamine combinations, addressing the current limitations. Despite the strong safety profiles of FDCs, the ongoing monitoring of rare side effects is crucial. General practitioners should consider combination therapy as the first-line treatment for moderate-to-severe AR, emphasizing adherence and symptom control. Clinicians should use FDCs to target both nasal and ocular symptoms and provide comprehensive care to patients with AR. Implementing these guidelines will enhance AR management and improve patient outcomes and satisfaction.

7. Limitations

The reliability and applicability of this systematic review were limited by several factors. The exclusion of 126 articles due to accessibility issues likely introduced bias, narrowing the analysis and omitting valuable research. Heterogeneity in study design, participant characteristics, intervention methods, and outcome measures complicates result consistency and comparability, hindering definitive conclusions. Methodological flaws, such as unclear randomization, inadequate allocation concealment, and insufficient blinding, increase the risk of performance and

detection biases, potentially exaggerating the effectiveness and safety of combination therapy. Short follow-up periods impede the assessment of long-term efficacy and safety for chronic conditions such as AR. The predominance of region-specific studies limits generalizability, and the exclusion of non-English studies and those behind paywalls raises concerns regarding publication bias. While the included studies generally reported positive safety profiles, the inadequate reporting of adverse events may underestimate potential risks, affecting the accuracy of the safety assessment, especially for rare or long-term adverse effects.

8. Future Prospects

Robust, multicenter RCTs with standardized reporting are necessary to address the limitations identified in this systematic review and strengthen the evidence for fexofenadine and montelukast combination therapies. Long-term follow-up is essential to evaluate the effectiveness, safety, and sustainability of these treatments for AR considering its chronic nature. Longitudinal studies can offer valuable insights into treatment adherence, cumulative effects on patient outcomes, quality of life, work productivity, healthcare use, and prevention of AR-related complications, such as asthma exacerbations.

Eligibility criteria should incorporate diverse populations and settings, including non-English language studies and those from low- to middle-income countries, to improve the understanding of the global effectiveness and safety of AR management. Advancements in personalized medicine should identify genetic and proteomic markers to predict treatment outcomes and optimize results while minimizing adverse effects. Future research should explore novel therapeutic combinations, such as fexofenadine and montelukast, with biologics, and integrate pharmacological and non-pharmacological approaches, including environmental controls and digital health tools, for comprehensive patient management.

The safety, efficacy, and optimal dosing of montelukast-fexofenadine in pediatric and geriatric populations require investigation to address unique challenges in these vulnerable groups and ensure comprehensive care. Enhancing treatment accessibility through policies that support affordable generic formulations and FDCs, along with educational initiatives for healthcare providers and patients, is crucial for improving adherence and outcomes. Addressing these research areas will facilitate evidence-based, patient-centered AR management strategies, leading to better health outcomes and quality of life globally.

9. Conclusions

This review highlights the effectiveness and safety of combining fexofenadine and montelukast for the treatment of AR. FDCs of these drugs significantly alleviated nasal and ocular symptoms (rhinorrhea, sneezing, and itching) and improved the quality of life compared to single-drug therapies. By targeting the histamine and leukotriene pathways, this dual-action approach provides superior, round-the-clock symptom relief.

Studies have noted the rapid onset and sustained effectiveness of combination therapy, aligning with the goals of comprehensive symptom control and minimal side effects. With consistent tolerability and few mild, self-resolving adverse reactions, this combination appears suitable for long-term use across various patient groups. Additionally, it offers practical benefits such as simplified dosing regimens and improved patient compliance, particularly for those with multiple chronic conditions.

However, limitations, such as variability in study designs, sample sizes, and methodologies, along with the exclusion of non-English studies and those behind paywalls, introduce potential selection bias and affect the comprehensiveness of this review. Large-scale, high-quality RCTs are needed to validate outcomes and explore long-term safety and efficacy in both pediatric and adult populations.

Future research should investigate combining fexofenadine and montelukast with other treatments, such as biologics and non-pharmacological interventions, for resistant or severe AR. Expanding studies to include diverse and underserved populations will provide a better understanding of the applicability of this therapy. Additionally, exploring personalized medical approaches, such as biomarkers for treatment response, could enhance AR management precision.

This review supports the incorporation of fexofenadine and montelukast combinations into the clinical guidelines for AR management. These combinations not only mitigate symptoms but also improve patient satisfaction, adherence, and quality of life, contributing to better healthcare outcomes. Given the global prevalence of AR, ad-

vancing effective, patient-centered treatments, such as this combination therapy, is essential for improving clinical and personal outcomes.

Author Contributions

Conception: W.A., L.A. (Leen Abdullah), K.A., M.K.; Design of the work: H.A., Z.A., L.A. (Layaly Allwaish), N.A., E.A.; Data acquisition: T.A., R.A. (Riyadh Alharbi), A.A. (Abdulrahman Akshah), R.A. (Refal Aljali), Y.A.; Data synthesis: H.A., Z.A., L.A. (Layaly Allwaish), R.A. (Refal Aljali), Y.A.; Manuscript drafting: R.A. (Riyadh Alharbi), A.A. (Abdulrahman Akshah), N.A., E.A., M.K.; Manuscript review: A.A. (Awatif Alnami), A.A. (Abdullah Alzahrani), L.A. (Leen Abdullah), K.A., M.K.

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