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Comparative Efficacy, Safety, and Healthcare Resource Utilization of Levosalbutamol Versus Racemic Salbutamol in Asthma and Wheezing: A Systematic Review of Physiological, Clinical, and Management Outcomes

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Abstract

Levosalbutamol (LEV), the active R-enantiomer of salbutamol, has been proposed as an alternative to racemic salbutamol (RAC), potentially providing comparable bronchodilation with fewer systemic adverse effects. However, evidence regarding its comparative efficacy, safety, and healthcare resource utilization remains variable.

The aim of this study was to systematically review the available evidence on the efficacy, safety, tolerability, and healthcare resource utilization associated with LEV compared with RAC in patients with asthma and wheezing.

A systematic literature search was conducted in PubMed, Embase, Scopus, and the Cochrane Library from database inception through July 2026. Eligible randomized controlled trials and observational studies evaluating LEV in patients with asthma, wheezing, or related respiratory conditions were included. Two reviewers independently screened studies and extracted relevant data. Risk of bias was assessed using the Cochrane Risk of Bias 2 (RoB 2) tool, Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I), and the Joanna Briggs Institute checklist, according to study design. Because of clinical and methodological heterogeneity, findings were synthesized narratively without quantitative meta-analysis.

Eleven studies involving 2,701,152 participants met the inclusion criteria. Five randomized studies involving 334 participants directly compared LEV with RAC, while the remaining studies evaluated alternative delivery techniques, clinical effectiveness, or epidemiological and healthcare utilization outcomes. Direct comparative studies generally reported similar improvements in forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) between treatments. One study demonstrated greater improvement in peak expiratory flow rate with LEV (19.71 ± 7.23% vs. 15.57 ± 7.48%; p = 0.008). Two of three studies assessing symptom scores reported significantly lower post-treatment scores with LEV, whereas one found no significant difference. Safety findings were inconsistent: some comparative studies reported smaller increases in heart rate, better preservation of serum potassium, or fewer adverse events with LEV, while others found comparable safety outcomes. Observational and epidemiological studies provided additional information on clinical outcomes and healthcare utilization but did not establish comparative treatment benefits.

Available comparative evidence suggests that LEV provides bronchodilator effects broadly similar to RAC, including in studies using lower doses of LEV. Some studies indicate potential benefits in symptom control and selected cardiovascular or metabolic safety outcomes; however, these findings are not consistent enough to establish overall safety superiority. Larger, adequately powered comparative trials using standardized dosing and longer follow-up are needed to clarify its clinical advantages and cost-effectiveness.

Categories: Emergency Medicine, Pulmonology
Keywords: asthma, levosalbutamol, racemic salbutamol, systematic review, wheezing

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Introduction And Background

Asthma is a chronic inflammatory airway disease characterized by recurrent episodes of wheezing, cough, chest tightness, and shortness of breath, accompanied by variable expiratory airflow limitation. It affects individuals of all ages and remains a major global public health concern. In 2021, approximately 260 million people worldwide were living with asthma, contributing substantially to disease-related disability and healthcare needs. Despite advances in diagnosis and treatment, asthma continues to cause considerable morbidity, impaired quality of life, and healthcare utilization, including emergency department visits and hospital admissions. The burden is particularly concerning in low- and middle-income countries, where underdiagnosis and inadequate access to effective treatment remain important challenges [1-3].

The Global Initiative for Asthma (GINA) [2] recommends immediate relief of bronchoconstriction and long-term management of inflammation to optimize asthma control and minimize exacerbations. Because of their rapid onset of bronchodilatory activity, short-acting β_2-agonists (SABAs) are a vital part of acute symptom treatment, and racemic salbutamol has been used for many years; it is a mixture of the pharmacologically active (R)-salbutamol and (S)-salbutamol enantiomers. Experimental studies indicate that the (R)-isomer is the major bronchodilator, while the (S)-isomer offers little therapeutic value and is thought to cause some undesirable physiological effects, such as airway hyperresponsiveness and undesirable systemic effects mediated by β_2-receptors [4,5].

Levosalbutamol (LEV) is the pharmacologically active (R)-enantiomer of salbutamol and is used as a bronchodilator for the management of reversible airway obstruction. It has been proposed as an alternative to racemic salbutamol, with the potential to provide effective bronchodilation while reducing adverse effects such as tachycardia, tremor, and hypokalemia. Clinical studies have evaluated LEV and racemic salbutamol in both adult and pediatric populations with asthma and wheezing. However, the available evidence varies in terms of patient characteristics, dosing regimens, routes of administration, and reported outcomes, making comparisons across studies challenging. Furthermore, the comparative effectiveness and safety of these treatments, including their impact on healthcare utilization in routine clinical practice, require further evaluation [6,7].

Thus, this systematic review aims to critically assess and synthesize current evidence comparing LEV with racemic salbutamol in asthma and wheezing to provide evidence-based recommendations for clinical decision-making regarding efficacy, safety, tolerability, and healthcare resource utilization.

Review

Methods

Study Design

This systematic review was conducted to evaluate the efficacy, safety, tolerability, and healthcare resource utilization (HCRU) associated with LEV and racemic salbutamol (RAC) in patients with asthma and wheezing. The review was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines [8]. The review protocol was registered under the identifier CRD420261465698. The primary objective was to synthesize direct comparative evidence evaluating LEV versus RAC, while additional eligible studies reporting clinical effectiveness, treatment delivery, epidemiological characteristics, or HCRU were included to provide a broader overview of the available evidence.

Search Strategy

A comprehensive literature search was conducted in PubMed, Embase, Scopus, and the Cochrane Library from database inception through July 2026. The search strategy incorporated Medical Subject Headings (MeSH), database-specific controlled vocabulary, and free-text terms related to LEV, racemic salbutamol, asthma, and wheezing. Search terms were combined using Boolean operators, with synonyms grouped using OR and the main concepts combined using AND. The principal search concepts included "levosalbutamol," "levalbuterol," "R-salbutamol," "racemic salbutamol," "albuterol," "asthma," "bronchial asthma," and "wheezing." The search strategy was adapted to the syntax and indexing requirements of each database and is provided in the Appendices. Additionally, the reference lists of eligible studies were manually screened to identify potentially relevant publications not retrieved through the electronic searches.

Eligibility Criteria

Studies were selected according to the Population, Intervention, Comparison, Outcomes, and Study Design (PICOS) framework. To accommodate the complementary objectives of this review, eligibility was considered across two evidence categories: (1) direct comparative studies evaluating LEV against RAC and (2) studies providing additional clinical, safety, treatment-delivery, epidemiological, or HCRU information relevant to LEV use or the target respiratory populations. Findings from the second category were considered supportive evidence and were not interpreted as direct comparative treatment effects.

Inclusion Criteria

Studies were eligible for inclusion if they met the following criteria:

Population: Pediatric or adult patients with bronchial asthma, including stable asthma or acute exacerbations, wheezing, or other obstructive respiratory presentations relevant to the review. Studies involving infants and children presenting with productive cough accompanied by bronchospasm were also considered.

Intervention: Administration of LEV (the active R-enantiomer of salbutamol) through nebulization, pressurized metered-dose inhaler (pMDI), oral administration, or combination treatment.

Comparison: Racemic salbutamol was the principal comparator for studies assessing comparative treatment efficacy and safety. Studies evaluating alternative inhalation devices or delivery techniques, placebo-controlled interventions, or relevant clinical and epidemiological outcomes without a direct LEV-versus-RAC comparison were also eligible for the broader evidence synthesis.

Outcomes: Studies were required to report at least one relevant efficacy, safety, tolerability, or HCRU outcome. Efficacy outcomes included forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), peak expiratory flow rate (PEFR), area under the curve (AUC), symptom scores, asthma control, and clinical response. Safety outcomes included adverse events, heart rate, serum potassium concentration, hypokalemia, tremor, and palpitations. HCRU outcomes included emergency department attendance, hospitalization, recurrent hospital admissions, and intensive care unit (ICU) or pediatric intensive care unit (PICU) admissions.

Study design: Randomized controlled trials, including parallel-group, crossover, and non-inferiority trials; prospective observational studies; cross-sectional studies; and phase IV clinical studies.

Publication characteristics: Only full-text articles published in English were considered eligible.

Exclusion Criteria

Studies were excluded if they were narrative reviews, systematic reviews, meta-analyses, editorials, commentaries, letters to the editor, case reports, case series, or animal studies. Studies that did not evaluate LEV or RAC and did not provide relevant clinical, safety, treatment-delivery, epidemiological, or HCRU information within the scope of the review were also excluded. Studies reporting exclusively pharmacokinetic, pharmacodynamic, or laboratory findings without relevant clinical outcome data were excluded, as were duplicate publications or secondary analyses of an already included study population without additional relevant outcome data. Conference abstracts without an accessible full-text publication and articles published in languages other than English were also excluded.

Study Selection and Screening Process

All records retrieved through the electronic database searches were imported into Zotero for reference management and duplicate removal. Following deduplication, two reviewers independently screened the titles and abstracts of the retrieved records using Rayyan against the predefined eligibility criteria. Records considered potentially relevant were advanced to full-text assessment. The full-text reports were evaluated against the prespecified inclusion and exclusion criteria to determine their eligibility for the review. Studies that did not meet the eligibility requirements were excluded, and the reasons for exclusion were documented and categorized.

Any disagreements arising during the study selection process were resolved through discussion and consensus between the two reviewers. The selection process, including the number of records identified, duplicates removed, records screened, full-text reports assessed, and studies included, is presented in the PRISMA 2020 flow diagram. The included studies were subsequently classified into direct comparative studies evaluating LEV versus RAC and additional studies providing relevant clinical, treatment-delivery, epidemiological, or HCRU evidence. This classification was maintained during data synthesis to ensure that findings from studies without a direct drug comparison were not interpreted as evidence of comparative treatment effectiveness.

Data Extraction

Data were extracted using a standardized Microsoft Excel extraction sheet (Microsoft Corporation, Redmond, Washington). Extracted information included study characteristics, such as author, publication year, country, study design, and clinical setting; participant characteristics, including age, sex, sample size, and baseline clinical characteristics; and intervention details, including treatment group, comparator, route of administration, dosage, and duration of treatment. Outcome data were organized into three prespecified

domains: efficacy, safety and tolerability, and healthcare resource utilization. Efficacy data included pulmonary function measurements (FEV_1, FVC, and PEFR), AUC, symptom scores, onset and duration of bronchodilation, asthma control, and clinical response. Safety data included overall adverse events, heart rate, serum potassium concentration, hypokalemia, tremor, and palpitations. HCRU data included emergency department visits, hospitalization, recurrent hospital admissions, and ICU/PICU admissions. Where available, numerical results, including group-specific means and standard deviations, event counts, percentages, effect estimates, confidence intervals, and p-values, were extracted. Outcome assessment time points were recorded as reported in the original studies rather than assuming a common follow-up time across studies. Baseline characteristics were also extracted to assess the comparability of treatment groups. When numerical information was available only in tables or figures, the relevant data were obtained from the original publications.

Outcome Measures

The review evaluated outcomes across three main domains: efficacy, safety and tolerability, and healthcare resource utilization.

Efficacy outcomes included pulmonary function parameters (FEV_1, FVC, and PEFR), AUC, asthma symptom scores, onset and duration of bronchodilation, asthma control, and clinical response. Safety and tolerability outcomes included overall adverse events, heart rate, serum potassium concentration, hypokalemia, tremor, and palpitations. Healthcare resource utilization outcomes included emergency department attendance, hospitalization, recurrent hospitalization, and ICU/PICU admission.

For direct comparative studies, outcomes were interpreted in relation to the LEV and RAC treatment groups. Findings from studies without a direct LEV-versus-RAC comparison were summarized separately and were not used to infer comparative treatment effects.

Risk-of-Bias Assessment

Methodological quality was assessed according to study design. The Cochrane Risk of Bias 2 (RoB 2) tool [9] was used to evaluate RCTs. Non-randomized interventional studies were assessed using the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool [10]. Cross-sectional studies were appraised using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Analytical Cross-Sectional Studies [11]. Two reviewers independently performed the assessments, and disagreements were resolved through discussion and consensus. The domain-level and overall judgments were summarized separately according to the applicable assessment tool.

Data Synthesis and Statistical Analysis

Given the substantial clinical and methodological heterogeneity among the included studies, particularly differences in patient populations, study designs, interventions, dosing regimens, routes of administration, comparator groups, and outcome measures, quantitative meta-analysis was considered inappropriate. Therefore, a narrative synthesis was performed to summarize and interpret the available evidence. The extracted data were organized into three prespecified outcome domains: (1) efficacy, (2) safety and tolerability, and (3) HCRU. Continuous outcomes, including FEV_1, FVC, PEFR, heart rate, serum potassium levels, and symptom scores, were summarized using reported means and standard deviations, mean changes from baseline, or between-group mean differences, where available. Dichotomous outcomes, including adverse events, hospital admissions, emergency department visits, and clinical response rates, were summarized using frequencies and percentages. For comparative studies, between-group differences were interpreted using the effect estimates, 95% confidence intervals, and p-values reported in the original publications. Statistical significance was considered at $p < 0.05$ when reported by the individual studies. For studies without a comparator group, findings were summarized descriptively using the reported frequencies, percentages, and changes from baseline. No additional pooled effect estimates or statistical tests were calculated because of the heterogeneity of the available data. Results were presented in summary tables and synthesized narratively according to outcome domains, study characteristics, and intervention types. Differences in study design and risk of bias were considered when interpreting the findings. No statistical assessment of between-study heterogeneity or publication bias was performed because quantitative meta-analysis was not undertaken.

Results

Study Selection Process

We identified 573 records through searches of four electronic databases. After removing 211 duplicate records, 362 records were screened, of which 106 were excluded based on title and abstract screening. Full texts of 256 reports were sought, and 253 were assessed for eligibility after excluding three unretrieved reports. Following full-text assessment, 242 studies were excluded for wrong population (n = 134), wrong intervention (n = 56), wrong outcomes (n = 49), or conference abstracts (n = 3), leaving 11 studies for

inclusion in the systematic review.

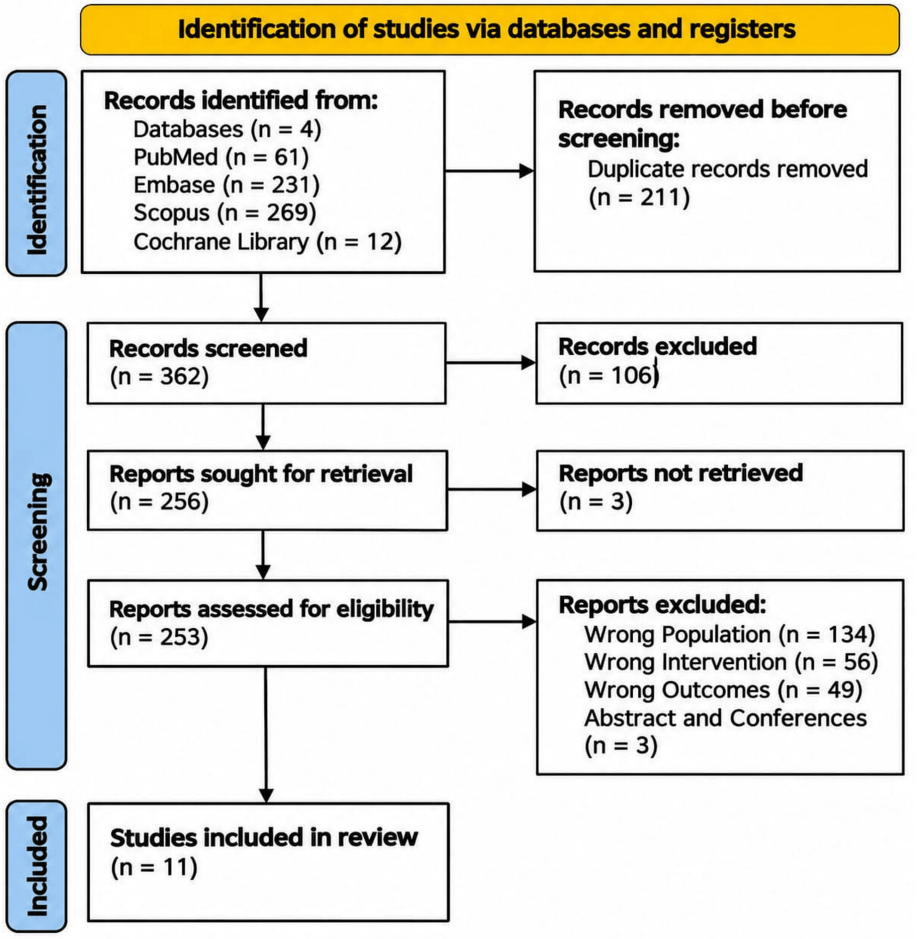


FIGURE 1: PRISMA flow diagram

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Baseline Characteristics and Patient Demographics

We included 11 studies [12-22], comprising a total of 2,701,152 participants. The nationwide cross-sectional study by Aksu et al. (2026) [21] contributed the majority of participants, including 2,700,183 adults with asthma, and provided epidemiological data on disease burden and healthcare resource utilization rather than evaluating LEV treatment. The remaining 10 studies included 969 participants across clinical, observational, and epidemiological populations. The included populations encompassed both pediatric and adult patients, with pediatric ages ranging from infancy to 14 years and adult mean ages ranging from 44.8 to 55.7 years. Among the randomized trials, baseline pulmonary function parameters, including FEV_1, FVC, and PEFR, were generally comparable between treatment groups. Jantikar et al. (2007) [12] reported no significant baseline difference in FEV_1 ($p = 0.28$), while Kurbacheva et al. (2024) [13] reported comparable baseline FEV_1 values ($p > 0.05$). Similarly, Sharma et al. (2019) [14] found no significant baseline differences in PEFR ($p = 0.90$) or asthma symptom scores ($p = 0.66$). Studies evaluating pediatric nebulization by Rahman et al. (2012) [15] and Punj et al. (2009) [16] also reported generally comparable baseline demographic and clinical characteristics (all $p > 0.05$). However, some differences in sex distribution and baseline disease severity were observed between treatment groups, with relatively more males and patients with greater disease severity in the racemic salbutamol groups and more females and patients with milder disease in the LEV groups. Although these differences were not statistically significant, they may represent clinically relevant baseline imbalances that could influence symptom-score assessments. Therefore, differences in symptom outcomes between treatments should be interpreted cautiously, particularly because the potential influence of sex and baseline disease severity was not consistently addressed through adjusted analyses. The epidemiological studies by Aksu et al. [21] and Zala et al. [22] additionally provided information on the demographic characteristics and healthcare burden of adult asthma and pediatric wheezing populations. Detailed baseline characteristics and study populations are presented in Table *1*.

Study (Author, Year)	Country and Study Design	Population/Sample Size	Intervention/Exposure	Comparator/Control	Age	Sex (Male/Female)	Baseline Clinical Characteristics	Baseline Equivalence/Statistical Comparison
Jantikar et al. (2007) [12]	India; Randomized, double-blind, crossover trial	Stable asthmatics (n=30)	Levosalbutamol 100 µg via pMDI	Racemic salbutamol 200 µg via pMDI + placebo	44.8 ± 11.0 years	17/13	FEV_1: 1.70 ± 0.55 L; FVC: 2.73 ± 0.86 L; FEV_1/FVC: 70.54 ± 5.73%; reversibility: 17.61 ± 4.87%	Baseline FEV_1: p=0.28
Kurbacheva et al. (2024) [13]	Russia; Multicenter randomized crossover trial	Mild-to-moderate asthmatics (n=91)	Levosalbutamol 90 µg via MDI	Racemic salbutamol 180 µg via MDI + placebo	47.2 ± 13.3 years	28/63	BMI: 27.1 ± 5.3 kg/m²; baseline FEV_1: 2.00 ± 0.51 L (64.9% predicted)	Baseline FEV_1: p>0.05
Sharma et al. (2019) [14]	India; Randomized controlled trial	Persistent asthmatic children (n=93)	Levosalbutamol 100 µg (2 puffs) via MDI (n=48)	Racemic salbutamol 200 µg (2 puffs) via MDI (n=45)	6–14 years	Not specified	PEF%: 69.6 ± 7.5 vs 69.8 ± 7.1; FEV_1%: ~65.2; Asthma Symptom Score: 16.8 vs 17.3	PEF%: p=0.90; Symptom score: p=0.66
Rahman et al. (2012) [15]	Bangladesh; Randomized double-blind trial	Acute asthmatic children (n=60)	Levosalbutamol 0.63 mg via nebulizer (n=30)	Racemic salbutamol 2.5 mg via nebulizer (n=30)	10.6 ± 3.8 years	33/27	Baseline FEV_1: 50.5 ± 10.1% vs 51.1 ± 10.9%; Asthma score: 7.8 vs 8.4	All baseline characteristics: p>0.05
Punj et al. (2009) [16]	India; Randomized double-blind trial	Acute asthmatic children (n=60)	Levosalbutamol 0.63 mg via nebulizer (n=30)	Racemic salbutamol 2.5 mg via nebulizer (n=30)	10.2 ± 3.8 years	34/26	PEFR: 195.3 ± 29.8 vs 196 ± 30.5 L/min; SpO_2 ~95%; Asthma score: 7.3 vs 9.2	All parameters: p>0.05
Perumal et al. (2023) [17]	India; Randomized clinical trial	Acute asthmatic children (n=58)	Levosalbutamol via MDI-spacer (n=29)	Levosalbutamol via nebulizer (n=29)	Median 9 vs 8 years	34/24	Pulmonary Index Score: 6.2 ± 1.6 vs 6.8 ± 2.1; median wheeze onset: 5 years	Age: p=0.420; PIS: p>0.05
Das et al. (2025) [18]	India; Randomized open-label trial	Persistent asthmatic children (n=82)	Breath-holding technique (n=41)	Tidal breathing technique (n=41)	8.64 ± 2.9 years	46/36	FEV_1: 0.94 ± 0.36 L; ACT score: 18.43 vs 19.05; rural residence: 58.5%	Age: p=0.22; ACT: p=0.32; FEV_1: p=0.52
Hadia et al. (2026) [19]	India; Prospective observational study	COPD/asthma/TOPD patients (n=73)	Nebulized Duolin (levosalbutamol + ipratropium)	Single-arm cohort	55.72 ± 14 years	57/16	Breathlessness at baseline: 93.15%; COPD: 60%; asthma: 30%; TOPD: 10%	Not applicable (observational study)
Kiran et al. (2017) [20]	India; Phase IV clinical trial	Productive cough cases (n=325)	Oral triple therapy (levosalbutamol + ambroxol + guaifenesin)	Single-arm trial	2.89 years	189/136	Baseline cough severity score: 6.624; age <1 year: 54.15%; weight up to 48 kg	Not applicable
Aksu et al. (2026) [21]	Türkiye; Nationwide cross-sectional study	Adult asthma population (n=2,700,183)	Asthma population assessment	Epidemiological cohort	45.70 ± 15.87 years	689,000/2,011,000	Rhinitis: 84.6%; hypertension: 53%; diabetes: 37%	Not applicable (descriptive population study)
Zala et al. (2026) [22]	India; Hospital-based cross-sectional study	Wheezing children <5 years (n=97)	Clinical profile assessment	Clinical cohort	Median 17 months	59/38	Rural residence: 81.4%; preterm birth: 12.4%; NICU history: 16.5%; exclusive breastfeeding: 86.6%	Rural association: p<0.05

TABLE 1: Study Characteristics, Patient Demographics, and Baseline Characteristics of Included Studies

ACT, Asthma Control Test; ASS, Asthma Symptom Score; BMI, body mass index; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; LEV, levosalbutamol; MDI, metered-dose inhaler; NICU, neonatal intensive care unit; PEFR, peak expiratory flow rate; PIS, Pulmonary Index Score; pMDI, pressurized metered-dose inhaler; RAC, racemic salbutamol; SpO_2, peripheral oxygen saturation; TOPD, asthma-COPD overlap phenotype.

The Risk-of-Bias Assessment Using ROB 2.0

We used the Cochrane Risk of Bias 2 (RoB 2) tool to evaluate the methodological quality of the seven RCTs. There were five studies with low risk of bias on all domains: Jantikar et al. (2007) [12]; Kurbacheva et al. (2024) [13]; Rahman et al. (2012) [15]; Punj et al. (2009) [16]; and Das et al. (2025) [18]. Sharma et al. (2019) [14] had some overall concerns, although none of the domains were identified as high risk. Perumal et al. (2023) [17] was assessed as having an overall high risk of bias, with a high risk of bias from deviations from intended interventions. Overall, all studies had low risk of bias for randomization, missing outcome data, outcome measurement, and selection of reported results; 14.3% (1/7) of studies had high risk of bias for deviations from intended interventions. (Figure *2* and Figure *3*)

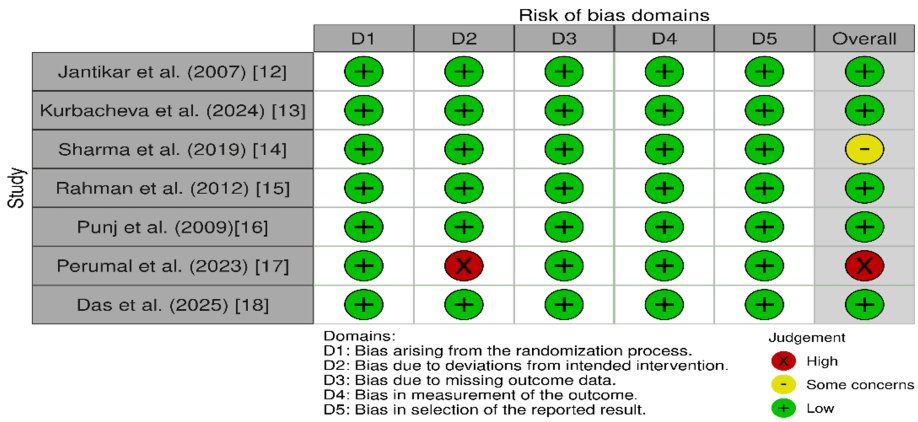


FIGURE 2: Traffic Light Plot OF Domains Showing Risk of Bias for Included Studies Using ROB 2

ROB 2: Cochrane Risk of Bias 2.

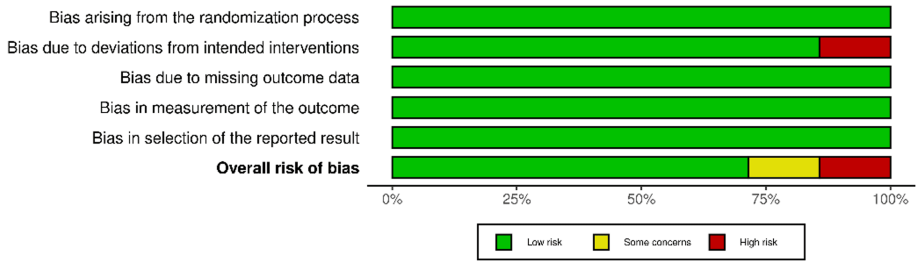


FIGURE 3: Traffic Light Plot Summary for Included Studies Using RoB 2

RoB 2, Revised Cochrane Risk of Bias Tool for Randomized Trials; D1, randomization process; D2, deviations from intended interventions; D3, missing outcome data; D4, measurement of the outcome; D5, selection of the reported result.

Assessment interpretation: Low = low concern of bias; Some Concerns = moderate concern regarding potential bias; High = great concern of bias.

Risk-of-Bias Assessment By ROBINS-I

Using the ROBINS-I tool, the risk-of-bias assessment of the two included studies (Hadia et al., 2026 [19]; Kiran et al., 2017 [20]) concluded that both had an overall serious risk of bias, mainly because of confounding present in both studies. Both studies showed low risk of bias for participant selection, classification of interventions, deviations from intended interventions, and selection of the reported results domains. Hadia et al. (2026) [19] had a moderate risk of bias for measuring outcomes, and Kiran et al. (2017) [20] had a moderate risk of bias for missing outcome data and for measuring outcomes. Furthermore, the risk-of-bias assessment of the 2 studies indicated that 50% of them had moderate risk related to missing data and 100% had moderate risk related to outcome measurement. The evidence was generally weak, leading to a high overall risk of bias for both studies. As mentioned in Figure *4* and Figure *5*.

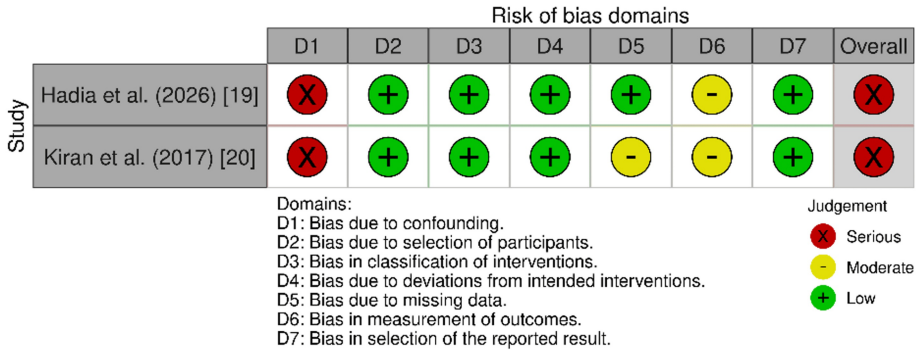


FIGURE 4: Traffic Light Plot OF Domains Showing Risk of Bias for Included Studies Using ROBINS-I

ROBINS-I: Risk of Bias in Non-randomized Studies of Interventions.

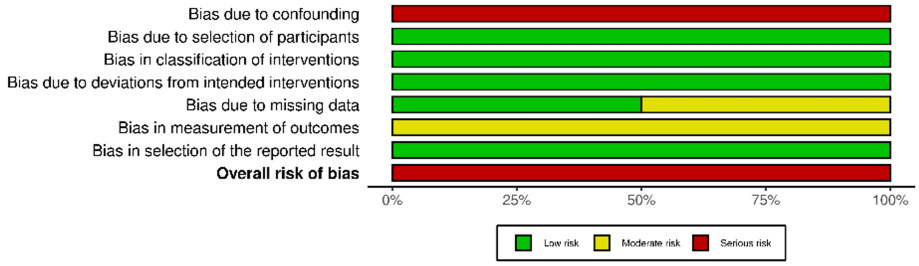


FIGURE 5: Traffic Light Plot Summary for Included Studies Using ROBINS-I

ROBINS-I, Risk Of Bias In Non-randomized Studies of Interventions; D1, bias due to confounding; D2, bias in selection of participants into the study; D3, bias in classification of interventions; D4, bias due to deviations from intended interventions; D5, bias due to missing data; D6, bias in measurement of outcomes; D7, bias in selection of the reported result.

Risk interpretation: Low = low concern of bias; Moderate = moderate concern of bias; Serious = serious concern of bias; Critical = critical concern of bias.

Methodological Quality Assessment Using the JBI Checklist

Based on the JBI Critical Appraisal Checklist, Zala et al. (2026) [22] demonstrated high methodological quality, fulfilling all eight appraisal criteria (8/8). Aksu et al. (2026) [21] achieved a score of 6/8, with limitations in identifying and addressing potential confounding factors. Overall, both studies were considered to be of moderate to high methodological quality, with a low risk of methodological bias (Table *2*).

Study (Author, Year)	Inclusion Criteria Clearly Defined	Subjects and Setting Described	Exposure Measured Validly and Reliably	Objective and Standard Criteria Used	Confounding Factors Identified	Strategies to Address Confounding	Outcomes Measured Validly and Reliably	Appropriate Statistical Analysis	Overall Methodological Quality Score
Aksu et al. (2026) [21]	Yes	Yes	Yes	Yes	No	No	Yes	Yes	6/8
Zala et al. (2026) [22].	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/8

TABLE 2: Critical Appraisal of Included Cross-Sectional Studies Using the Joanna Briggs Institute (JBI) Checklist

Quality interpretation: Scores represent the number of fulfilled criteria from the JBI Critical Appraisal Checklist for Analytical Cross-Sectional Studies; higher scores indicate better methodological quality.

Systematic Review of Efficacy and Safety Outcomes

Efficacy outcomes: Eleven studies [12-22] assessed efficacy outcomes. Six studies directly compared LEV with racemic salbutamol; five studies evaluated clinical effectiveness, inhalation techniques, combination therapy, or disease burden. Pulmonary function (FEV_1, FVC, and PEFR), asthma symptom scores, onset of bronchodilation, asthma control, hospitalization, and clinical response were considered as outcomes. These outcomes are presented in Table *3*.

Outcome Domain	Study (Author, Year)	Outcome Measure	LEV/Intervention	RAC/Control	Statistical Significance	Interpretation
Bronchodilator efficacy	Jantikar et al. (2007) [12]	FEV_1 AUC (0–6 h)	7486.3	7493.6	p > 0.05	Comparable bronchodilator efficacy
Bronchodilator efficacy	Jantikar et al. (2007) [12]	Maximum FEV_1 change (mL)	537	538	p > 0.05	No significant difference
Bronchodilator efficacy	Jantikar et al. (2007) [12]	Maximum FVC change (mL)	456	417	p > 0.05	Comparable improvement
Onset of bronchodilation	Jantikar et al. (2007) [12]	Onset of action (min)	12	18	Not significant	Faster numerical onset with LEV
Clinical effectiveness	Hadia et al. (2026) [19]	Baseline breathlessness	68/73 (93.2%)	—	Descriptive	Most patients presented with breathlessness
Clinical effectiveness	Hadia et al. (2026) [19]	Clinical success	58/73 (79.5%)	—	Descriptive	High treatment success
Bronchodilator efficacy	Kurbacheva et al. (2024) [13]	Adjusted FEV_1 AUC (L×h)	2.31	2.29	p = 0.595	Equivalent efficacy
Bronchodilator efficacy	Kurbacheva et al. (2024) [13]	Peak FEV_1 (L)	2.53 ± 0.51	2.54 ± 0.63	p = 0.643	No significant difference
Bronchodilator efficacy	Kurbacheva et al. (2024) [13]	Peak FVC (L)	3.58 ± 0.81	3.61 ± 0.86	p = 0.511	Comparable improvement
Duration of bronchodilation	Kurbacheva et al. (2024) [13]	Patients with FEV_1 increase ≥12% at 360 min	42.2%	36.3%	No formal statistical comparison reported	Trend toward longer bronchodilator duration with LEV
Healthcare utilization	Perumal et al. (2023) [17]	Pulmonary Index Score	6.2 ± 1.6	6.8 ± 2.1	p = 0.18	Comparable clinical severity
Healthcare utilization	Perumal et al. (2023) [17]	Hospital admission	4/29 (13.8%)	4/29 (13.8%)	p > 0.05	No significant difference

Disease burden	Aksu et al. (2026) [21]	Emergency department visits	334,256/2,700,183 (12.4%)	—	Descriptive	High healthcare utilization
Disease burden	Aksu et al. (2026) [21]	Hospitalization	149,868/2,700,183 (5.6%)	—	Descriptive	Moderate hospitalization burden
Disease burden	Aksu et al. (2026) [21]	ICU admission	3,764/2,700,183 (0.1%)	—	Descriptive	Rare ICU admission
Disease burden	Zala et al. (2026) [22]	Wheezing prevalence	97/1220 (7.95%)	—	Descriptive	Community prevalence
Disease burden	Zala et al. (2026) [22]	Recurrent hospitalization	77/97 (79.4%)	—	$p < 0.05$	Higher burden among rural children
Disease burden	Zala et al. (2026) [22]	Subsequent admissions	49/97 (50.5%)	—	Descriptive	High readmission burden
Asthma control	Das et al. (2025) [18]	FEV_1 at 8 weeks (L)	1.17 ± 0.29	1.16 ± 0.31	$p = 0.71$	Comparable lung function
Asthma control	Das et al. (2025) [18]	PEFR at 8 weeks (L/s)	2.79 ± 0.78	2.71 ± 0.77	$p = 0.53$	No significant difference
Asthma control	Das et al. (2025) [18]	ACT score at 8 weeks	25.17 ± 3.60	25.08 ± 3.50	$p = 0.77$	Similar asthma control
Bronchodilator efficacy	Sharma et al. (2019) [14]	Mean PEFR change (%)	19.71 ± 7.23	15.57 ± 7.48	$p = 0.008$	Significantly greater improvement with LEV
Bronchodilator efficacy	Sharma et al. (2019) [14]	Mean FEV_1 change (%)	11.76 ± 6.80	8.67 ± 4.06	$p > 0.05$	Comparable bronchodilator efficacy
Symptom improvement	Sharma et al. (2019) [14]	Asthma symptom score	13.95 ± 4.60	12.93 ± 5.60	$p = 0.341$	No significant difference
Bronchodilator efficacy	Rahman et al. (2012) [15]	Post-treatment FEV_1 (%)	69.80 ± 12.50	68.99 ± 13.12	Improved from baseline ($p < 0.05$)	Both groups showed significant improvement
Oxygenation	Rahman et al. (2012) [15]	Post-treatment SpO_2 (%)	98.43 ± 11.12	98.12 ± 7.20	Improved from baseline ($p < 0.05$)	Comparable oxygenation
Symptom improvement	Rahman et al. (2012) [15]	Post-treatment asthma score	5.60 ± 0.79	6.26 ± 0.71	$p < 0.05$	LEV produced significantly lower asthma scores
Bronchodilator efficacy	Punj et al. (2009) [16]	Post-treatment PEFR (L/min)	275 ± 32.61	273 ± 30.38	Improved from baseline ($p < 0.05$)	Comparable pulmonary improvement
Oxygenation	Punj et al. (2009) [16]	Post-treatment SpO_2 (%)	98.23 ± 11.01	97.73 ± 7.22	Improved from baseline ($p < 0.05$)	Comparable oxygenation
Symptom improvement	Punj et al. (2009) [16]	Post-treatment asthma score	5.20 ± 0.73	6.70 ± 0.69	$p < 0.01$	LEV produced significantly lower asthma scores
Clinical effectiveness	Kiran et al. (2017) [20]	Cough severity reduction (Day 5)	84.18% reduction from baseline	—	Descriptive	Marked reduction in cough severity
Clinical effectiveness	Kiran et al. (2017) [20]	Complete symptom relief	128/325 (39.4%)	—	Descriptive	Good clinical response

TABLE 3: Summary of Efficacy Outcomes of Included Studies

ACT, Asthma Control Test; AUC, area under the curve; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; ICU, intensive care unit; LEV, levosalbutamol; L, liter; L×h, liter-hour; min, minutes; PEFR, peak expiratory flow rate; RAC, racemic salbutamol; SpO_2, peripheral oxygen saturation.

Bronchodilator response (FEV_1, FVC, and PEFR): Five randomized comparative studies compared the effects of LEV and racemic salbutamol on pulmonary function. In general, the bronchodilator efficacy of LEV at about half the dose of racemic salbutamol was equivalent. Jantikar et al. (2007) [12] demonstrated comparable FEV_1 AUC over 0-6 hours between LEV 100 µg and RAC 200 µg (7486.3 vs. 7493.6%; $p > 0.05$). Maximum FEV_1 improvement (537 vs. 538 mL; $p > 0.05$) and maximum FVC improvement (456 vs. 417 mL; p

> 0.05) were also similar. Likewise, Kurbacheva et al. (2024) [13] reported no significant differences in adjusted FEV_1 AUC (2.31 vs. 2.29 L × h; p = 0.595), peak FEV_1 (2.53 ± 0.51 vs. 2.54 ± 0.63 L; p = 0.643), or peak FVC (3.58 ± 0.81 vs. 3.61 ± 0.86 L; p = 0.511). More patients treated with LEV had an improvement in FEV_1 of ⩾12% after 360 minutes than those in the other groups (42.2% vs. 36.3%), indicating a tendency toward extended bronchodilation. Sharma et al. (2019) [14] observed significantly greater improvement in PEFR with LEV than with racemic salbutamol (19.71 ± 7.23% vs. 15.57 ± 7.48%; p = 0.008), whereas improvement in FEV_1 remained comparable between treatments (p > 0.05). Compared with racemic salbutamol, LEV was found to significantly increase PEFR by 19.71 ± 7.23% versus 15.57 ± 7.48% (p = 0.008), while FEV_1 improvement was similar (p > 0.05) between the two groups. Rahman et al. (2012) [15] and Punj et al. (2009) [16] also noted significant improvements in both FEV_1 and PEFR from baseline in both treatment groups; however, they found no clinically meaningful difference between LEV and RAC in pulmonary function.

Clinical symptom improvement: Three comparative studies examined improvement in asthma symptoms. Rahman et al. (2012) [15] showed significantly better post-treatment asthma scores with LEV than with racemic salbutamol (5.6 ± 0.79 vs. 6.26 ± 0.71; p < 0.05). Punj et al. (2009) [16] reported similar findings, with LEV achieving lower asthma scores than RAC (5.2 ± 0.73 vs. 6.7 ± 0.69; p < 0.01). Sharma et al. (2019) [14] found no statistically significant difference in asthma symptom scores between treatment groups (13.95 ± 4.60 vs. 12.93 ± 5.60; p = 0.341).

Onset and duration of bronchodilation: Only two studies assessed the onset and duration of the bronchodilator effect. Jantikar et al. (2007) [12] found a numerically quicker onset of action for LEV than for racemic salbutamol (12 versus 18 minutes), but the difference was not statistically significant. Kurbacheva et al. (2024) [13] found more patients with clinically meaningful bronchodilation (FEV_1 increase ⩾12%) six hours after LEV treatment, indicating a longer duration of action.

Asthma Control and Alternative Delivery Techniques

Two studies focused on inhalation technique rather than bronchodilator type. There were no significant differences between MDI-spacer and nebulized LEV for pulmonary index score (6.2 ± 1.6 vs. 6.8 ± 2.1; p = 0.18) or hospital admission rates (13.8% in both groups; p > 0.05), according to Perumal et al. (2023) [17]. Likewise, Das et al. (2025) [18] observed similar improvements in asthma control with both breath-holding and tidal breathing after 8 weeks, but the differences were not significant for FEV_1 (p = 0.71), PEFR (p = 0.53), or Asthma Control Test (p = 0.77).

Real-World Clinical Effectiveness

Four observational studies assessed treatment efficacy in routine practice. According to Hadia et al. (2026) [19], 79.5% of patients receiving nebulized ipratropium + LEV experienced satisfactory symptom management. After five days of oral LEV combination therapy, Kiran et al. (2017) [20] showed an 84.18% decrease in cough intensity, with 39.4% of children experiencing total symptom alleviation. Large epidemiological studies by Aksu et al. (2026) [21] and Zala et al. (2026) [22] described the burden of asthma and wheezing. They found that 12.4% of adults with asthma visited the emergency room, 5.6% were hospitalized, 0.1% were admitted to the ICU, and 79.4% of children with wheezing were hospitalized repeatedly.

Discussion

Summary of Principal Findings

This systematic review pooled data on physiological, clinical, and healthcare utilization outcomes from 11 studies comparing LEV with racemic salbutamol (RAC) in asthma and wheezing. Overall, LEV is as effective as RAC at approximately half the dose for bronchodilation (as reflected by FEV_1, FVC, and PEFR) and has a more favorable cardiovascular and metabolic safety profile. In terms of clinical efficacy, LEV was associated with a numerically earlier onset and a longer duration of action. It was superior in two of three comparative studies for asthma symptom scores. Regarding safety, individual studies reported differences in post-treatment heart rate, serum potassium levels, and adverse event frequency between LEV and RAC. Some findings favored LEV, including smaller increases in heart rate, better preservation of serum potassium, and fewer reported adverse events in certain comparisons. However, these findings were not sufficient to establish an overall safety advantage of LEV, particularly given the limited number of comparative studies and the variability in reported safety outcomes. Therefore, the possibility of a more favorable safety profile with LEV should be interpreted cautiously and requires confirmation in further comparative studies.

Comparison With Previous Literature

Our results confirm and build on the evidence on the enantiomeric selectivity of β_2-agonists. LEV's benefit is based on the racemate ratio used (50:50 (R)- and (S)-salbutamol). Presently, the (R)-enantiomer (LEV) is the active bronchodilator, and (S)-salbutamol was long believed to be inactive. However, growing evidence suggests that (S)-salbutamol is pro-inflammatory and bronchoconstrictive, which can amplify adverse

effects and offset the therapeutic effect of the R-isomer [23]. This gives a mechanistic explanation for the "dose-sparing" effect we found in our review; LEV is equally effective at 50% of the dose. In terms of clinical efficacy, LEV was associated with a numerically earlier onset and a potentially longer duration of action. Regarding symptom control, two of the three comparative studies (Rahman et al. [15] and Punj et al. [16]) reported significantly lower post-treatment asthma symptom scores with LEV compared with RAC ($p < 0.05$ and $p < 0.01$, respectively). In contrast, Sharma et al. [14] found no statistically significant difference between the treatment groups ($p = 0.341$). Thus, the available evidence suggests a potential advantage of LEV in symptom improvement, although this finding was not consistent across all comparative studies.

Furthermore, our findings are consistent with the seminal meta-analysis [23], which included seven RCTs and reported no differences in overall efficacy between LEV and RAC in acute asthma. Our review adds nuance, however, because the lack of superiority in efficacy does not necessarily imply equivalence in safety. The marked reduction in tachycardia and hypokalemia with LEV reported by Rahman et al. (2012) [15] and Punj et al. (2009) [16] is in line with the meta-analysis by Shebli et al. (2024) [24], which showed that LEV significantly reduced heart rate, with a mean difference of -5.97 bpm ($p = 0.02$), when compared with RAC at a dose ratio of LEV:RAC 1:4 (half-dose LEV). Furthermore, the same meta-analysis found that the protective effect on the heart is removed when doses are equal (1:2 ratio), supporting our interpretation that the safety benefit is dose-dependent [24].

The clinical efficacy of LEV in symptom control, as demonstrated in two of the studies included here, is corroborated by Maiti et al. (2011) [25], who reported that patients with mild persistent asthma who received LEV had significantly better scores for asthma symptoms, quality of life, and percentage change in FEV_1, FVC, and PEFR than those who received RAC. Our review did not show consistent superiority across all studies, but this may reflect differences in disease severity, dosage, or outcome measures. Some included studies involved both acute exacerbations and stable asthma. In contrast, Maiti et al. included only mild persistent asthma, where the negative aspects of (S)-salbutamol use might have been more evident over the long term.

Additionally, our metabolic safety results (potassium preservation) with LEV are well supported by Punj et al. (2009) [16], who showed that both drugs were effective in stabilizing clinical parameters. However, LEV did not affect serum potassium, whereas RAC caused severe tachycardia and hypokalemia. This has significant clinical implications because hypokalemia can cause arrhythmias, especially in those with underlying cardiac disease and/or when used with other corticosteroids or theophylline. In children, Ralston et al. (2005) [26] demonstrated that nebulized LEV was associated with a significantly lower increase in heart rate than RAC combined with ipratropium (9% vs. 26%, $p < 0.001$), suggesting a lower propensity for tachycardia with LEV in acute pediatric asthma.

The crossover placebo-controlled study by Kurbacheva et al. (2024) [13] also confirmed the dose-sparing and safety advantages of LEV 90 μg compared with RAC 180 μg, with twice as few adverse reactions. An important clinical takeaway is that adverse effects are dose-related and that the same bronchodilation can be obtained with half the dose of LEV for fewer systemic effects. The prior study noted above [27] showed similar efficacy and no heart rate or potassium differences with 100 μg LEV vs. 200 μg RAC, the 1:2 ratio in which Shebli et al. found no heart rate or potassium differences. This highlights the need to consider dose when comparing studies [24].

Finally, Gupta and Singh (2007) [27] provide a broader perspective on the clinical utility of LEV by reviewing the evidence and concluding that LEV has a favorable risk-benefit profile, especially for patients with cardiovascular risk factors. In resource-limited settings, they also noted that LEV's cost-effectiveness is a concern, which we echo in our clinical implications. Overall, our review agrees with previous publications and confirms that LEV is not a more potent bronchodilator but a safer and more efficient bronchodilator when administered at half the dose, since the (S)-salbutamol side effects are removed [27].

Strengths

The systematic review has several strengths. It provides a comprehensive overview of evidence from a range of study designs, including RCTs, observational studies, and cross-sectional epidemiological studies, and covers both efficacy and effectiveness. Including healthcare resource utilization outcomes adds practical value for clinicians and policymakers. The review followed PRISMA 2020 guidelines and used validated risk-of-bias assessment tools (RoB 2, ROBINS-I, and the JBI Checklist). Including pediatric and adult patients across diverse clinical contexts increases generalizability. Detailed information on dosing, timing, and safety parameters enabled a more nuanced interpretation of dose-related effects, and comprehensive nationwide epidemiological studies provided robust real-world evidence on disease burden.

Limitations

Several points warrant attention. Because of large clinical and methodological variability across studies, quantitative meta-analysis was not possible, limiting the ability to pool effect sizes. Most randomized trials were small, reducing power to detect rare adverse events. Causal inferences were at moderate to serious risk

of bias in observational and cross-sectional studies because of confounding and the absence of comparator groups. Most trials were short, reducing the ability to assess safety and efficacy outcomes at long-term follow-up. Furthermore, publication bias cannot be ruled out, and language bias may have been introduced by including only English-language publications. Different dose ratios across studies make comparisons and conclusions about safety differences difficult.

Future Implications

Large-scale, long-term, head-to-head RCTs with standardized dosing ratios are needed to establish safety benefits and measure effects over longer time periods. Specific pharmacoeconomic evaluations are needed to determine whether the costs of adverse event management and length of hospital stay offset the acquisition cost of LEV. Further research is needed to specifically include high-risk groups, such as those with cardiovascular diseases, elderly patients, and children, to provide definitive guidelines for the preferential use of LEV. Future studies should focus on LEV use in chronic asthma care and in combination therapies. Studies using prospective real-world data collection should complement the results of controlled trials, and public health initiatives aimed at early diagnosis and selection of appropriate bronchodilators in resource-limited environments should be emphasized.

Conclusions

This systematic review synthesized evidence from 11 studies evaluating the physiological, clinical, safety, and healthcare resource utilization outcomes associated with LEV in asthma and wheezing. However, only five randomized studies, involving 334 participants, directly compared LEV with RAC; therefore, the overall population of 2,701,152 participants should not be interpreted as the sample size supporting the direct treatment comparison. Findings from the head-to-head trials suggest that LEV may provide bronchodilator effects comparable to RAC at lower doses, although formal equivalence or non-inferiority has not been established. Some studies reported smaller increases in heart rate, better preservation of serum potassium, or fewer adverse events with LEV, particularly at certain dose ratios. However, these findings were not consistent across all studies, and a definitive cardiovascular or metabolic safety advantage cannot be established from the available evidence. The proposed pharmacological explanation involving the removal of the (S)-enantiomer should also be interpreted as a potential mechanism rather than a proven explanation for the observed clinical differences. Furthermore, the available evidence does not establish LEV as the preferred treatment for specific high-risk populations, including patients with cardiovascular disease, older adults, or children.

The epidemiological studies included in this review highlight the substantial healthcare burden associated with asthma and wheezing but do not provide direct evidence of comparative treatment effectiveness. Although acquisition cost may influence treatment selection, the available evidence is insufficient to determine whether potential reductions in adverse events offset the higher cost of LEV. Overall, LEV may represent an alternative to RAC in selected clinical settings; however, its comparative efficacy, safety, dose equivalence, and cost-effectiveness require confirmation through larger, adequately powered trials with standardized dosing, longer follow-up, and population-specific analyses.

Appendices

PubMed=61	Embase = 231	Scopus = 269	Cochrane = 12
("Asthma"[MeSH Terms] OR ("Asthma"[MeSH Terms] OR "Asthma"[All Fields] OR "asthmas"[All Fields] OR "asthma s"[All Fields]) OR ("respiratory sounds"[MeSH Terms] OR ("respiratory"[All Fields] AND "sounds"[All Fields]) OR "respiratory sounds"[All Fields] OR "wheeze"[All Fields] OR "wheezes"[All Fields] OR "wheezing"[All Fields] OR "wheezed"[All Fields]) OR "Bronchial Asthma"[All Fields]) AND ("Levalbuterol"[MeSH Terms] OR ("Levalbuterol"[Supplementary Concept] OR "Levalbuterol"[All Fields] OR "Levalbuterol"[MeSH Terms]) OR ("Levalbuterol"[Supplementary Concept] OR "Levalbuterol"[All Fields] OR "levosalbutamol"[All Fields] OR "Levalbuterol"[MeSH Terms]) OR "R-salbutamol"[All Fields]) AND ("Albuterol"[MeSH Terms] OR ("Levalbuterol"[Supplementary Concept] OR "Levalbuterol"[All Fields] OR "Albuterol"[All Fields] OR "Albuterol"[Supplementary Concept] OR "Levalbuterol"[MeSH Terms] OR "Albuterol"[MeSH Terms] OR "salbutamol"[All Fields]) OR ("Levalbuterol"[Supplementary Concept] OR "Levalbuterol"[All Fields] OR "Albuterol"[All Fields] OR "Albuterol"[Supplementary Concept] OR "Levalbuterol"[MeSH Terms] OR "Albuterol"[MeSH Terms] OR "salbutamol"[All Fields]) OR "racemic salbutamol"[All Fields]) AND ("Randomized Controlled Trial"[Publication Type] OR "Clinical Trial"[All Fields] OR "observational"[All Fields] OR "cross-sectional"[All Fields] OR "cohort"[All Fields] OR ("clinical trials as topic"[MeSH Terms] OR ("clinical"[All Fields] AND "trials"[All Fields] AND "topic"[All Fields]) OR "clinical trials as topic"[All Fields] OR "trial"[All Fields] OR "trial s"[All Fields] OR "trialed"[All Fields] OR "trialing"[All Fields] OR "trials"[All Fields]))	('asthma'/exp OR asthma:ti,ab OR wheezing:ti,ab OR 'bronchial asthma':ti,ab) AND ('levalbuterol'/exp OR levosalbutamol:ti,ab OR levalbuterol:ti,ab OR 'r-salbutamol':ti,ab) AND ('salbutamol'/exp OR salbutamol:ti,ab OR albuterol:ti,ab OR 'racemic salbutamol':ti,ab) AND ('randomized controlled trial'/exp OR 'clinical trial'/exp OR observational:ti,ab OR 'cross-sectional study'/exp OR cohort:ti,ab)	TITLE-ABS-KEY ((asthma OR wheezing OR "bronchial asthma") AND (levosalbutamol OR levalbuterol OR "R-salbutamol") AND (salbutamol OR albuterol OR "racemic salbutamol") AND ("randomized controlled trial" OR trial OR observational OR cohort OR "cross-sectional"))	Search No. Search Strategy #1 MeSH descriptor: [Asthma] explode all trees #2 asthma OR wheezing OR "bronchial asthma":ti,ab,kw #3 #1 OR #2 #4 MeSH descriptor: [Albuterol] explode all trees #5 levalbuterol OR levosalbutamol OR "R-salbutamol" OR salbutamol OR albuterol OR "racemic salbutamol":ti,ab,kw #6 #4 OR #5 #7 #3 AND #6 Limits Trials; Humans; English language

TABLE 4: Search Strategy

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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Syeda Aisha Zaheer and Adnan Bin Rafiq Chaudhry contributed equally and should be considered co-first

authors.

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