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Efficacy and Safety of Ensifentrine in Moderate to Severe COPD: A Systematic Review of Randomized Clinical Trials

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ABSTRACT

Chronic obstructive pulmonary disease is a lung condition that restricts airflow, causes ongoing inflammation, and results in frequent flare-ups. It has a significant impact on health and death rates around the world. Even with improved medications such as long-acting bronchodilators and inhaled corticosteroids, many patients still experience symptoms and are at risk for flare-ups. Ensifentrine is a new inhaled dual phosphodiesterase 3 and 4 (PDE3/PDE4) inhibitor. It provides a unique treatment by delivering both bronchodilation and anti-inflammatory effects through a single mechanism. This review evaluates randomized clinical trials published between 2020 and 2024 that studied the effectiveness and safety of ensifentrine. The results showed many benefits. Patients receiving ensifentrine had higher FEV_1 values, reported fewer symptoms, and experienced fewer exacerbations compared with those given a placebo. The results were even better when combined with standard bronchodilators. These findings show that ensifentrine could be a valuable addition to current COPD treatments. It offers benefits both when used alone and when combined with existing therapies. Its dual mechanism tackles key problems by targeting bronchoconstriction and airway inflammation at the same time. More long-term trials are required to confirm its lasting effectiveness and safety.

Keywords: Ensifentrine, Chronic Obstructive Pulmonary Disease, COPD, Severe Early-Onset, Lung Diseases

1. INTRODUCTION

Chronic obstructive pulmonary disease is a lung condition that causes ongoing airflow limitation, chronic inflammation, and flare-ups. These issues significantly impact a patient's health, lifespan, and quality of life. It also results in significant and growing financial and social burden, especially for older adults. There are

available therapies such as long-acting beta-agonists, long-acting muscarinic antagonists, inhaled corticosteroids and combination treatments, but many patients still experience severe symptoms and frequent flare-ups. It shows the need for new treatment approaches (Aamrah et al., 2025). Traditional drug treatments primarily focus on bronchodilation and controlling inflammation. However, using single therapies or even combinations of two or three drugs often does not fully address the disease's complexity. The airway inflammation in COPD is different from that in asthma. It usually involves neutrophils rather than eosinophils and is less responsive to corticosteroids. This difference has led to a strong effort to create drugs that target both bronchoconstriction and inflammation using different methods (Wright et al., 2024). Ensifentrine is the first of its kind. It is a dual inhibitor of phosphodiesterase (PDE) 3 and PDE4, designed for inhalation therapy. It works by blocking PDE3, which leads to direct bronchodilation through the relaxation of smooth muscles.

Inhibiting PDE4 provides anti-inflammatory benefits by regulating cyclic adenosine monophosphate (cAMP) signaling pathways in inflammatory cells. This dual-action mechanism offers a new treatment option that could support or enhance the effects of existing therapies (Hanania et al., 2025; Luigino et al., 2024).

It will also address safety outcomes, including adverse event profiles, tolerability, and treatment discontinuations. It presents the current evidence to explain ensifentrine's role in the changing landscape of COPD management and also points out areas that need further research (Mahler et al., 2024).

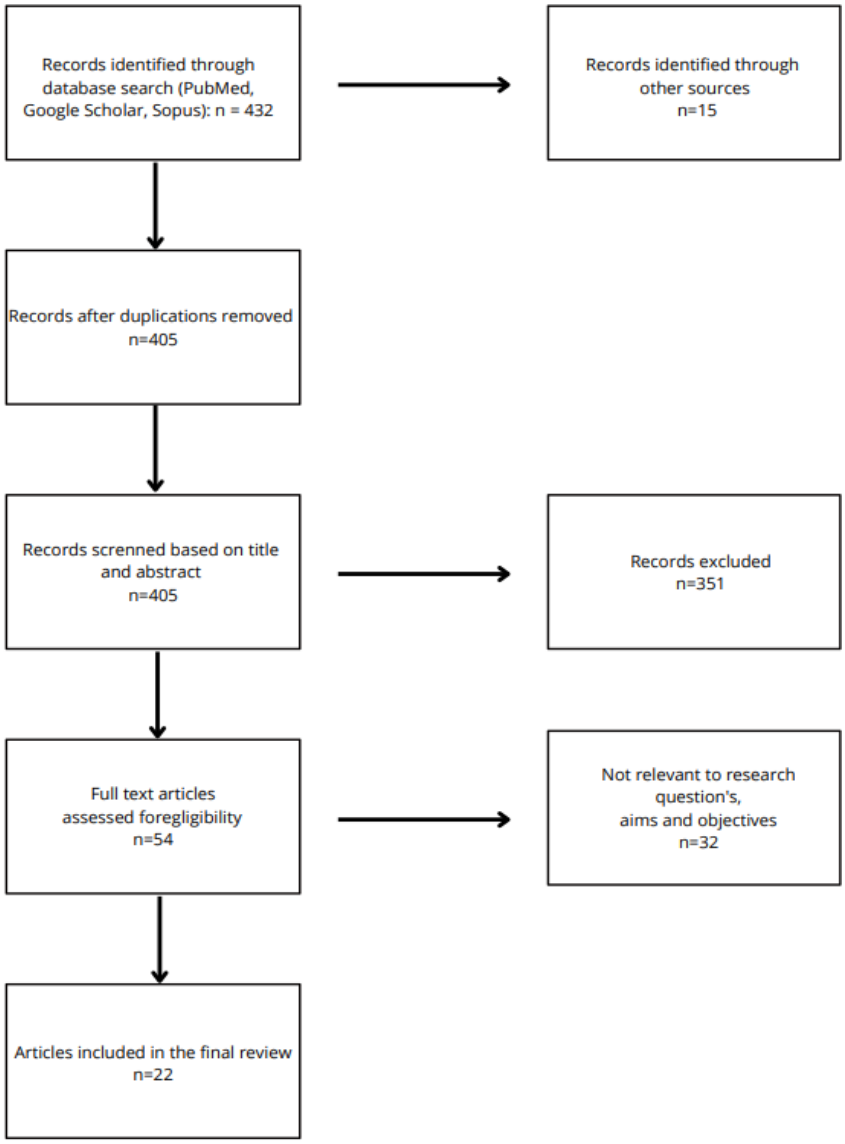

Figure 1. PRISMA flow diagram

2. REVIEW METHODS

The literature was gathered from the PubMed and Google Scholar. The articles were published from January 2020 to June 2025. The review focused on randomized controlled clinical trials. Inclusion criteria depended on the topic of the clinical studies, the publication dates, and specific keywords. The selection of articles followed the PRISMA guidelines (Figure 1).

Inclusion Criteria:

- Articles reporting randomized controlled trials, clinical trials and cohort studies.
- Articles published from 2020 to 2024.
- Adult patients (≥18 years) diagnosed with moderate to severe COPD.
- Studies with a comparator group (placebo).

Exclusion Criteria:

- Studies involving mixed populations (e.g., COPD and asthma) without separate data for COPD patients.
- Articles lacking data on either the efficacy or safety of ensifentrine.
- Articles published in languages other than English, unless a full official English version is available.

3. RESULTS AND DISCUSSION

Ensifentrine is inhaled through nebulization, which is helpful for patients with severe COPD. For these patients it is hard to create the strong inhalation required for dry powder inhalers. Thanks to nebulized delivery, the drug reaches the lower airways, no matter how hard the patient breathes. This approach can improve adherence and clinical results (Donohue et al., 2023).

A growing number of studies from randomized clinical trials have examined how effective and safe ensifentrine is for patients with moderate to severe COPD. Phase II and III studies have shown encouraging results. They indicate improvements in lung function, symptoms, and quality of life. There were also reductions in exacerbation rates, and the tolerability was like that of a placebo Faruqi and Khan, 2024. However, researchers are still actively studying the extent of the benefits, the consistency across different patient groups, and how it fits into current treatment approaches (Table 1).

Table 1. Summary of current treatment approaches

Study	Sample Size	Intervention	Duration	Primary Outcome	Key Findings
Anzueto et al., 2023	1,549	Ensifentrine 3 mg BID vs. Placebo	24 weeks	Change in FEV_1	Significant improvement in FEV_1 and reduction in exacerbations with a safety profile comparable to placebo
Sciurba et al., 2024	1,649	Ensifentrine 3 mg BID vs. Placebo	24 weeks	Exacerbation rate	Notable reduction in moderate to severe exacerbations; well-tolerated treatment.
Dransfield et al., 2025	757 (485 on LAMA, 272 on LABA+ICS)	Ensifentrine 3 mg BID vs. Placebo	24 weeks	FEV_1 improvement Exacerbation rate	Ensifentrine led to significant improvements in lung function. It also reduced exacerbation rates by 48 to 51%, with a safety profile similar to placebo.

Ferguson et al., 2021	416	Ensifentrine 0.375–3 mg BID + Tiotropium vs. Tiotropium alone	4 weeks	FEV_1 improvement	Enhanced bronchodilation when combined with tiotropium; favorable safety profile.
Watz et al., 2020	405	Ensifentrine 0.75–6 mg BID vs. Placebo	4 weeks	Symptom scores	Significant symptom relief and improved quality of life measures.

The studies show clear evidence that ensifentrine is effective and safe for patients with chronic obstructive pulmonary disease (COPD). In randomized controlled trials, ensifentrine has been shown to significantly improve lung function. This was shown by increases in FEV1 when compared to a placebo (Anzueto et al., 2023; Dransfield et al., 2025; Ferguson et al., 2021). Improvements in symptom scores, such as dyspnea and health-related quality of life, were also seen (Watz et al., 2020). In the ENHANCE trials (Anzueto et al., 2023), both ensifentrine monotherapy and its combination with standard bronchodilators resulted in significant reductions in COPD exacerbation rates. The treatment was well tolerated. The rates of side effects were similar to those of the placebo, and no new safety problems were found (Dransfield et al., 2025; Anzueto et al., 2023).

Ensifentrine is a new, first-of-its-kind inhaled drug that inhibits two enzymes: phosphodiesterase 3 (PDE3) and phosphodiesterase 4 (PDE4). By blocking these enzymes, ensifentrine raises the levels of cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) inside cells. This action results in bronchodilation and reduces inflammation in the respiratory system (Luigino et al., 2024).

Ensifentrine's dual inhibition mechanism targets both airway smooth muscle relaxation and inflammatory pathways. This provides a well-rounded approach to managing COPD. The enhance trials (Anzueto et al., 2023) showed strong evidence of improved lung function and fewer exacerbations over 24 weeks. Short-term studies supported these findings. They noted a quick onset of action and relief from symptoms (Ferguson et al., 2021; Watz et al., 2020).

Inhaled ensifentrine can cause bronchodilation thanks to it dual inhibition of phosphodiesterase 3 and 4. It also has anti-inflammatory effects, which contribute to reductions in the frequency of exacerbations (Sciurba et al., 2025; Dransfield et al., 2025). Improvements in patient-reported outcomes and lasting benefits over time show the value of ensifentrine. These findings show that ensifentrine can be used as both an add-on and a standalone treatment option.

The inhibition of PDE3 causes the relaxation of airway smooth muscle cells. This leads to easier airflow and less bronchoconstriction. Inhibiting PDE4 reduces the release of pro-inflammatory cytokines and chemokines from immune cells. It helps to decrease airway inflammation (Bolger, 2023). Combining ensifentrine with existing therapies, such as tiotropium, may provide additive benefits (Ferguson et al., 2021). The positive safety profile seen in studies shows that ensifentrine is well-tolerated.

Ensifentrine offers notable clinical benefits while causing few systemic side effects. This makes it a promising choice, especially for patients who do not respond well to standard bronchodilators. Safety data consistently showed that the treatment-emergent adverse event (TEAE) profile was similar to that of a placebo. There were no significant safety signals or dose-related side effects, even at the higher doses tested in Singh et al., (2023) study. Discontinuation rates due to adverse events stayed low. These findings support its long-term use (Hammadeh et al., 2025, Singh et al., 2023). The safety profile is very important because current PDE4 inhibitors like roflumilast often cause gastrointestinal side effects. Ensifentrine's dual PDE3/4 inhibition seems to keep its effectiveness while reducing systemic adverse effects (Al Matni et al., 2024).

While efficacy and safety are important, drug delivery also plays a key role in managing COPD, especially in patients with reduced inspiratory capacity. Recent expert opinion suggests that nebulized delivery of ensifentrine allows for reliable lung deposition, particularly for patients with severe airflow limitation. This method may provide an advantage over dry powder or metered dose inhalers (Fatima et al., 2024).

Clinically, ensifentrine is mainly being developed to treat chronic obstructive pulmonary disease (COPD). It has shown promise in improving lung function and reducing symptoms like shortness of breath. It may also lower the number of flare-ups.

Therapeutic Uses of Ensifentrine

Ensifentrine is well known in treating respiratory conditions, but it also shows potential in other groups of patients. At therapeutic doses, ENF has low cytotoxicity. When combined with antibiotics, it may help with drug penetration into biofilms and reduce local inflammation. This could make treatments more effective (Sajeevan et al., 2025).

Phosphodiesterase inhibitors have gained significant attention for treating various human diseases. Selective PDE4 inhibitors increase intracellular cAMP and are effective for inflammatory airway diseases. Roflumilast, for instance, is approved as a second-line treatment for chronic bronchitis in COPD and has also helped manage asthma. However, the clinical use of PDE4 inhibitors has faced limitations due to their side effects (Sherpa et al., 2025). There is still research to be conducted to find PDE4 inhibitors that are safer and more effective, including isoform-selective agents, inhalable forms, and combined PDE inhibitors. Among these, tanimilast and ensifentrine stand out as promising candidates for future asthma treatments.

4. CONCLUSION

Ensifentrine is an inhaled nebulized therapy currently in Phase III clinical development. It shows great promise as a new treatment for patients with moderate to severe COPD. It is the first dual inhibitor of phosphodiesterase 3 (PDE3) and phosphodiesterase 4 (PDE4) tested for COPD. This medication combines a bronchodilator and non-steroidal anti-inflammatory effects. Patients take it twice daily with a standard jet nebulizer. It is especially suitable for individuals who continue to experience symptoms despite trying standard treatments, such as inhaled bronchodilators, corticosteroids, oral antibiotics, or PDE4 inhibitors.

Data from the enhanced trials and other randomized controlled studies show consistent improvements in lung function and symptom control. These studies also report fewer flare-ups while maintaining a good safety and tolerability profile. These benefits occur both when used alone and when ensifentrine is added to existing treatments like long-acting muscarinic antagonists and long-acting beta agonists.

Ensifentrine may help improve mucociliary clearance. This could ease symptoms related to sputum production. Its dual therapeutic effects, along with the positive clinical outcomes, make it a promising addition to current treatments for COPD. Still, we need more long-term studies to better understand its lasting effectiveness and optimal role in treatment plans.

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Author's Contribution

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

Informed consent

Not applicable.

Ethical approval

Not applicable.

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Conflict of interest

The authors declare that there is no conflict of interest.

Data and materials availability

All data sets collected during this study are available upon reasonable request from the corresponding author.

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