

# Effects of Inhaled Furosemide on Dyspnea and Pulmonary Function in COPD: A Systematic Review

Zeina Atwi, RRT

School of Health Sciences, Dalhousie University, Halifax, NS

## INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a highly prevalent disease throughout the world that is preventable and treatable. One of the most common and evident respiratory symptoms of COPD is dyspnea.<sup>1</sup> Dyspnea can be detrimental to the quality of life of patients with COPD; thus, finding ways to try to alleviate discomfort in breathing is clinically significant. Dyspnea is commonly measured using subjective means or through analyzing pulmonary function values. In patients with COPD, pulmonary function values such as forced vital capacity (FVC), forced expiratory volume in one second (FEV<sub>1</sub>), and peak expiratory flow rate (PEFR) are linked to the severity of symptoms and confirms the presence of airflow obstruction.<sup>9</sup> However, the correlation between pulmonary function values and symptoms is not strong thus assessment of patients' subjective dyspnea scores are still essential.<sup>1</sup> There is emerging evidence showing inhaled furosemide, a common loop diuretic, may be useful in relieving dyspnea in patients with COPD. The mechanism of action of this potential therapy is not yet fully understood, however, it has been suggested that inhaled furosemide has a bronchodilator effect on the airway epithelium, potentially improving patients' dyspneic levels and pulmonary function values.<sup>3</sup> There is no current systematic review that has examined the effects of inhaled furosemide specifically in people with COPD. This review presents the current evidence pertaining to the efficacy of inhaled furosemide as an approach to improving dyspnea and pulmonary function values in patients with COPD.

## QUESTION

Created with PICO method:

**Population** – Adult patients with Chronic Obstructive Pulmonary Disease (COPD)

**Intervention** – Inhaled furosemide

**Comparison** – The gold standard therapy for COPD

**Outcome** – Decreased perception of dyspnea and improved pulmonary function values

**“In people with COPD, does inhaled furosemide lead to decreased perception of dyspnea and improved pulmonary function values?”**

1. Dyspnea will be assessed using two methods: subjective data collected from patients as well as the pulmonary function values of patients.

## SEARCH STRATEGY

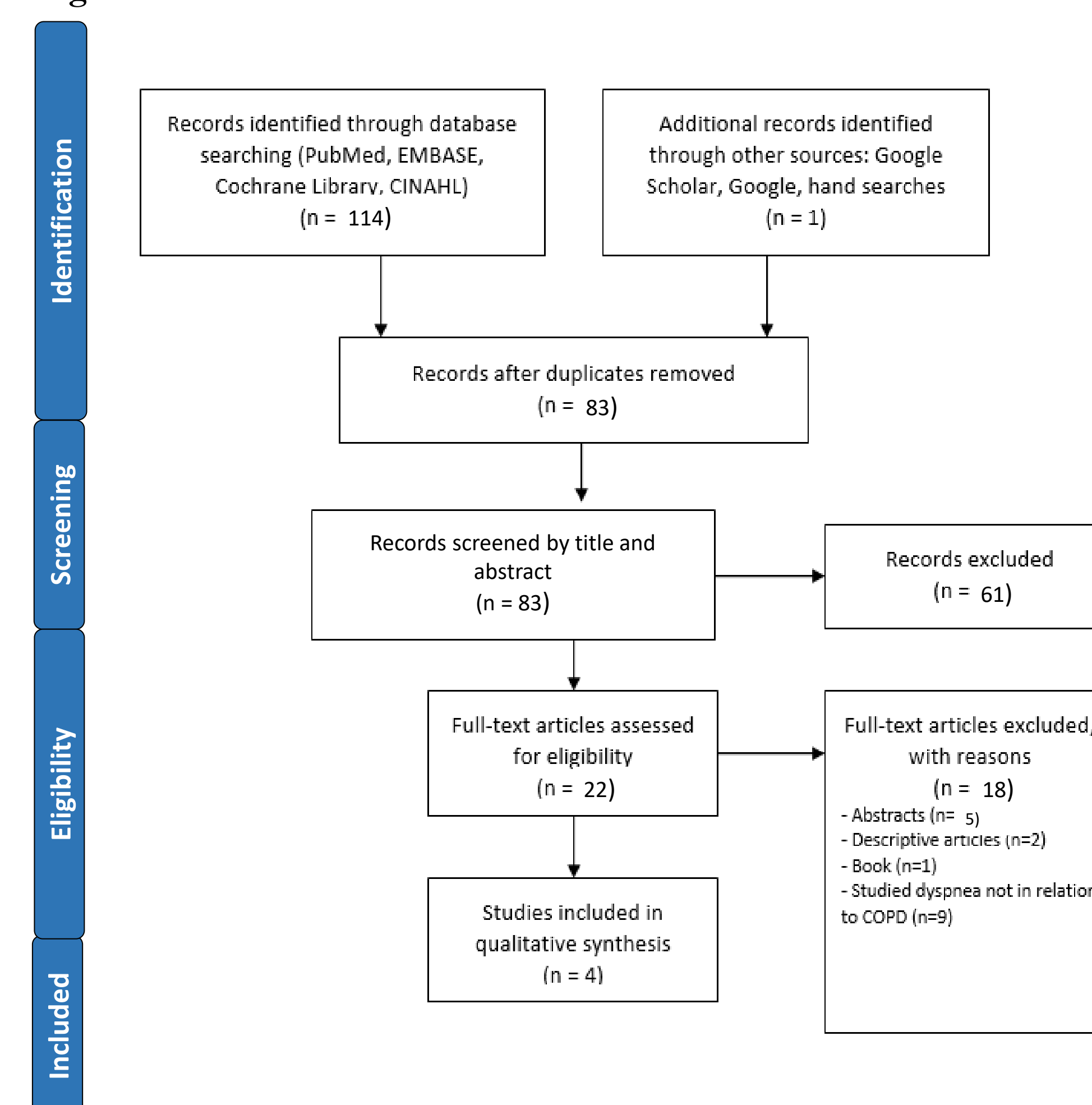
<b>Search Terminology</b>	Key Terms/ MeSH Terms <ul style="list-style-type: none"> <li>• Inhalation Administration</li> <li>• Aerosol</li> <li>• Furosemide</li> </ul>
<b>Database</b>	Cochrane Library, PubMed, EMBASE, CINAHL
<b>Publication Type</b>	Randomized controlled trial (RCT), Meta-analysis (MA), Systematic reviews (SR), practice guidelines
<b>Publication Date</b>	2010 – 2021
<b>Subjects</b>	Human
<b>Language</b>	English
<b>Age</b>	>19 years
<b>Sex</b>	Male and Female

CONSORT checklist, the Cochrane Handbook, and PRISMA were used to guide critical appraisal of the included studies. PRISMA was used to guide this review.

**Table 1: Comparison of studies included in this review**

Study	Methodology	Outcome/Intervention	Results	Limitations
Sheikh et al. (2013)	5-month randomized double blinded clinical trial (n = 100)	The primary outcomes are dyspnea severity (measured with a visual analog scale), and FEV <sub>1</sub> . The intervention group of the study was given 40 mg nebulized furosemide while the control group received a placebo as an adjunct to the conventional treatments.	Dyspnea and FEV <sub>1</sub> improved in both intervention and placebo groups, but the improvement was significantly greater in the intervention group (p<0.001 which is less than 0.5 alpha level).	The study did not discuss outcomes such as eventual ICU admission, need for invasive/ noninvasive ventilation, or mortality rates. Additionally, noninvasive, as a standard of care for COPD exacerbations, was not used therefore, an adequate comparison was lacking.
Saba, Davoodabadi, Ghaffari, Gilasi, & Haghpanah (2020)	Randomized double blind controlled trial (n=69)	Participants were divided into two groups. The first group received salbutamol in their first episode while the second group received inhaled furosemide in their first episode. The treatments for the two groups were subsequently reversed. Spirometry values (FEV <sub>1</sub> , FVC, and FEV <sub>1</sub> /FVC) and dyspnea scores (mMRC and BORG scales) were assessed between episodes and after the second episode in both groups.	The primary outcomes improved in both groups after the first episode however only the Borg scale significantly improved after the first episode (p-value< 0.001). However, all outcomes improved significantly after the second episode in both groups (p value <0.001). The sequence of drug administration did not cause a significant effect as the two groups did not have significantly different reactions.	The Cochrane Risk of Bias Assessment Tool (Table 2) demonstrates unclear risk for the blinding process due to insufficient details. Another limitation is that all patients were stable at the time of the intervention, therefore when considering patients experiencing COPD exacerbations, optimal interventional therapy may differ.
Masoumi et al., (2014)	Randomized, double blind, clinical trial (n= 90)	Participants were patients admitted to the emergency department with an acute exacerbation of reactive airway disease symptoms. For the study they received 5 mg of nebulized salbutamol and 40 mg of nebulized furosemide in the intervention group. 5 mg of nebulized salbutamol were given alone in the control group. PEFR was estimated before treatment and at specific intervals after.	The difference between the mean PEFR of the two groups was significant at the end of the trial (p= 0.0001). Post-intervention, the severity of dyspnea was noted to be worse in the salbutamol group than the furosemide group.	As noted in the study, a recorded formal diagnosis of asthma or COPD were considered an exclusion criteria therefore the sample may be compromised and may not be indicative of the general COPD population.
Boyden et al. (2015)	Literature Review (39 publications)	4 of the studies in this review specifically looked at inhaled furosemide use with COPD participants.	<ul style="list-style-type: none"> <li>• A potential benefit was suggested for nebulized furosemide.</li> <li>• Included studies indicated significant improvements in FEV1, FVC, and dyspnea relief with inhaled furosemide.</li> </ul>	This review included studies from 1989 to 2013 – therefore newer research is not included and not considered.

**Figure 1: PRISMA Flowsheet**



**Table 2: Cochrane Risk of Bias Assessment Tool for included RCTs**

Study	Sheikh et al. (2013)	Saba, Davoodabadi, Ghaffari, Gilasi, & Haghpanah (2020)	Masoumi et al. (2014)
Random Sequence Generation	Low risk	Low risk	Low risk
Allocation Concealment	Low risk	Low risk	Low risk
Blinding – Participants and Personnel	Low risk	Unclear risk	Unclear risk
Blinding – Outcome Assessment	Low risk	Unclear risk	Low risk
Incomplete Outcome Data	Low risk	Low risk	Low risk
Selective Reporting	Low risk	Low risk	Low risk
Other bias	High risk of baseline imbalance. Baseline FEV <sub>1</sub> was higher in the furosemide group.	Low risk	Low risk

## DISCUSSION

The articles included in this systematic review present a potentially significant effect of inhaled furosemide on dyspnea, and on pulmonary function values in individuals with COPD. While inhaled furosemide seems to benefit dyspnea and pulmonary function values in COPD patients, more research is needed to support firm recommendations for its use. Additionally, further research is needed to consider the long-term impact and mechanism of action of inhaled furosemide. Two notable RCTs were not included in this review as they exceeded the ten-year limitation; however, they should be considered when discussing this topic due to their significant impact. Both examined the efficacy of inhaled furosemide in COPD patients. The first RCT concluded that inhaled furosemide provides relief for induced dyspnea, bronchodilation and a significant improvement in mean FEV<sub>1</sub> and FVC after intervention with inhaled furosemide.<sup>8</sup> The second RCT reported statistically significant alleviation of exercise-induced dyspnea in people with COPD following inhaled furosemide therapy.<sup>6</sup> Future iterations of clinical practice guidelines will help improve patient outcomes/ quality of life and guidelines for best practice.

## CONCLUSION

Currently inhaled furosemide is not a standard therapy for dyspnea relief and improvement of pulmonary function values in people with COPD. There needs to be more evidence-based research in order to validate current findings and assist in determining the best way to integrate this research into current practice. To date, while inhaled furosemide therapy is promising for dyspnea relief and the improvement of pulmonary function values in individuals with COPD, there is still insufficient data to draw a definitive conclusion regarding the effectiveness of inhaled furosemide. Researchers and clinicians should consider the use of inhaled furosemide in conjunction with current best practice interventions for COPD since it has been shown to demonstrate clinically significant improvements. Determining the best way to integrate this research into current practice is essential for improving the physical burdens of these patients.

## ACKNOWLEDGEMENTS

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