UNDERSTANDING THE CLINICAL OUTCOMES OF USING INHALERS COMPARING TO NEBULIZERS FOR TREATMENT OF ASTHMA IN PATIENT WITH HYPERTENSION.

ABSTRACT

Asthma and hypertension are common comorbidities, and managing these conditions concurrently presents unique challenges. This abstract provides a concise overview of clinical outcomes when using inhalers compared to nebulizers for asthma treatment in individuals with hypertension. Asthma is a prevalent respiratory condition, often coexisting with hypertension, a chronic cardiovascular condition. The choice of medication delivery device, whether inhalers or nebulizers, can significantly impact the clinical outcomes and safety of treatment for individuals dealing with both conditions. This abstract explores the implications of this choice. Studies comparing inhalers and nebulizers in asthma management for patients with coexisting hypertension were reviewed. Clinical effectiveness, safety, adherence, ease of use, and patient satisfaction were assessed. The findings suggest that both inhalers and nebulizers can effectively manage asthma symptoms in patients with hypertension. Safety profiles are generally comparable, with rare, mild adverse events. Adherence and ease of use may vary depending on individual patient abilities and preferences, emphasizing the need for patient education and training. Patient satisfaction is highly subjective, with no clear consensus. Individualized treatment plans that consider both asthma and hypertension are essential. Healthcare providers should prioritize patient education to ensure proper device use and maximize adherence. The choice between inhalers and nebulizers should align with individual patient needs. Shared decision-making and a holistic approach to treatment are crucial for optimizing clinical outcomes in this patient population. Further research may provide a deeper understanding of specific considerations for managing both conditions concurrently.

Keywords: - Inhaler, Nebulizer, Asthma treatment, Hypertension

INTRODUCTION

Asthma is a chronic respiratory condition that affects millions of individuals worldwide, characterized by airway inflammation, bronchoconstriction, and increased mucus production. Effective management and treatment of asthma are paramount to mitigate symptoms, improve quality of life, and reduce the risk of exacerbations. Inhalers and nebulizers are two commonly used devices for administering asthma medications, providing relief and controlling symptoms. Choosing the optimal delivery method is essential to ensure that patients receive the appropriate dosage of medication effectively and efficiently. This systematic review aims to comprehensively evaluate and compare the clinical outcomes of using inhalers versus nebulizers in the treatment of asthma, shedding light on their relative efficacy, safety, and patient preferences.

Background of the study

Asthma is a major public health concern, affecting approximately 235 million people globally (Global Asthma Network, 2018). The disease's prevalence continues to rise, necessitating continuous efforts to enhance asthma management strategies. The cornerstone of asthma treatment involves bronchodilators, which can be administered through various devices, such as inhalers and nebulizers. Inhalers, including metered-dose inhalers (MDIs) and dry powder inhalers (DPIs), have been widely used for decades, providing a convenient and portable option for patients to self-administer medication. On the other hand, nebulizers offer an alternative method of medication delivery, particularly suitable for individuals who struggle with coordination or have difficulty using inhalers effectively. It is essential to conduct a systematic review to comprehensively understand the clinical outcomes associated with using inhalers compared to nebulizers for the treatment of asthma in individuals with coexisting hypertension. This study aims to provide insights that can guide healthcare providers in making informed decisions regarding the selection of medication delivery devices, thereby optimizing clinical outcomes and patient quality of life in this specific population.

Rationale Of the study

This systematic review is essential to address the existing gaps in knowledge regarding the comparative effectiveness of inhalers and nebulizers for asthma treatment. By conducting a thorough examination of the available literature, we aim to provide evidence-based insights into the advantages and disadvantages of each delivery method (Payares-Salamanca JA, Castañeda-Orjuela CA, 2018). This information will assist healthcare professionals, patients, and policymakers in making informed decisions regarding the selection and use of inhalers or nebulizers for asthma management.

The rationale for this study lies in the need to address the specific challenges and considerations associated with managing both asthma and hypertension in the same individuals. By conducting a systematic review, we aim to provide a comprehensive understanding of the clinical outcomes associated with inhalers and nebulizers in this population, ultimately enhancing the quality of care for these patients.

Statement of the problem

This statement of problem highlights the need for a systematic review to comprehensively and rigorously compare the clinical outcomes of inhalers and nebulizers for asthma treatment.

1. What is the comparative effectiveness of inhalers and nebulizers for the treatment of asthma in hypertension?
2. What are the safety and tolerability profiles of inhalers and nebulizers?
3. What are the patient preferences for inhalers and nebulizers?

Research Objectives

Primary objective: To assess and compare the clinical outcomes of using inhalers and nebulizers for asthma treatment in individuals with coexisting hypertension.

Secondary objectives: To evaluate the safety profiles of inhalers and nebulizers in individuals with asthma and hypertension, focusing on adverse events and effects on blood pressure and cardiovascular function.

Scope & Delimitation

In this study, the scope is carefully delineated to ensure a focused investigation. We primarily concentrate on individuals who have been diagnosed with both asthma and hypertension. Our core objective is to compare the clinical outcomes resulting from the use of inhalers and nebulizers for asthma management within this specific population. The study encompasses an evaluation of clinical results, safety considerations, adherence levels, and patient satisfaction. This study does not evaluate the influence of specific medications but rather centers on the delivery devices themselves. Although the study considers various age groups, we do not conduct a separate analysis for pediatric and geriatric populations, as this would necessitate distinct research endeavors. Lastly, we do not differentiate between various types or stages of hypertension, focusing instead on the general coexistence of asthma and hypertension.

Review of related literature

The benefits of metered-dose inhalers with a spacer (MDI+S) have increasingly been recognized as an alternative method of albuterol administration for treating pediatric asthma exacerbations. (Wiley Periodicals LLC, 2020*)* The aim of this systematic review was to compare the response to albuterol delivered through nebulization (NEB) with albuterol delivered through MDI+S in pediatric patients with asthma exacerbations. We conducted an electronic search in MEDLINE/PubMed, EMBASE, Ovid, and Clinical Trials. To be included in the review, a study had to a randomized clinical trial comparing albuterol delivered via NEB versus MDI+S; and had to report the rate of hospital admission (primary outcome), or any of the following secondary outcomes: oxygen arterial saturation, heart rate (HR), respiratory rate (RR), the pulmonary index score (PIS), adverse effects, and need for additional treatment. Fifteen studies (n = 2057) met inclusion criteria. No significant differences were found between the two albuterol delivery methods in terms of hospital admission (relative risk, 0.89; 95% confidence interval [CI], 0.55-1.46; I^2 = 32%; p = .65). There was a significant

reduction in the PIS score (mean difference [MD], -0.63; 95% CI, -0.91 to -0.35; I^2 = 0%; p < .00001), and a significantly smaller increase in HR (better; MD -6.47; 95% CI, -11.69 to -1.25; I^2 = 0%; p = .02) when albuterol was delivered through MDI+S than when it was delivered through NEB. This review, an update of a previously published meta-analysis, showed a significant reduction in the PIS and a significantly smaller increase in HR when albuterol was delivered through MDI+S than when it was delivered through NEB.

Asthma exacerbations can be frequent and range in severity from mild to life-threatening. (Rachel Knightly 1, Stephen J Milan, Rodney Hughes, Jennifer A Knopp-Sihota, Brian H Rowe, Rebecca Normansell, Colin Powell, 2017) The use of magnesium sulfate ($MgSO_4$) is one of numerous treatment options available during acute exacerbations. While the efficacy of intravenous $MgSO_4$ has been demonstrated, the role of inhaled $MgSO_4$ is less clear. To determine the efficacy and safety of inhaled $MgSO_4$ administered in acute asthma. To quantify the effects of inhaled $MgSO_4$ I) in addition to combination treatment with inhaled β_2-agonist and ipratropium bromide; ii) in addition to inhaled β_2-agonist; and iii) in comparison to inhaled β_2-agonist. We identified randomized controlled trials (RCTs) from the Cochrane Airways Group register of trials and online trials registries in September 2017. We supplemented these with searches of the reference lists of published studies and by contact with trialists. RCTs including adults or children with acute asthma were eligible for inclusion in the review. We included studies if patients were treated with nebulised $MgSO_4$ alone or in combination with β_2-agonist or ipratropium bromide or both and were compared with the same co-intervention alone or inactive control. Two review authors independently assessed trial selection, data extraction and risk of bias. We made efforts to collect missing data from authors. We present results, with their 95% confidence intervals (CIs), as mean differences (MDs) or standardized mean differences (SMDs) for pulmonary function, clinical severity scores and vital signs; and risk ratios (RRs) for hospital admission. We used risk differences (RDs) to analyze adverse events because events were rare. Twenty-five trials (43 references) of varying methodological quality were eligible; they included 2907 randomized patients (2777 patients

completed). Nine of the 25 included studies involved adults; four included adult and pediatric patients; eight studies enrolled pediatric patients; and in the remaining four studies the age of participants was not stated. The design, definitions, intervention and outcomes were different in all 25 studies; this heterogeneity made direct comparisons difficult. The quality of the evidence presented ranged from high to very low, with most outcomes graded as low or very low. This was largely due to concerns about the methodological quality of the included studies and imprecision in the pooled effect estimates. Inhaled magnesium sulfate in addition to inhaled β_2-agonist and ipratropium We included seven studies in this comparison. Although some individual studies reported improvement in lung function indices favoring the intervention group, results were inconsistent overall and the largest study reporting this outcome found no between-group difference at 60 minutes (MD -0.3 % predicted peak expiratory flow rate (PEFR), 95% CI -2.71% to 2.11%). Admissions to hospital at initial presentation may be reduced by the addition of inhaled magnesium sulfate (RR 0.95, 95% CI 0.91 to 1.00; participants = 1308; studies = 4; I^2 = 52%) but no difference was detected for re-admissions or escalation of care to ITU/HDU. Serious adverse events during admission were rare. There was no difference between groups for all adverse events during admission (RD 0.01, 95% CI -0.03 to 0.05; participants = 1197; studies = 2). Inhaled magnesium sulfate in addition to inhaled β_2-agonist We included 13 studies in this comparison. Although some individual studies reported improvement in lung function indices favoring the intervention group, none of the pooled results showed a conclusive benefit as measured by FEV1 or PEFR. Pooled results for hospital admission showed a point estimate that favored the combination of $MgSO_4$ and β_2-agonist, but the confidence interval includes the possibility of admissions increasing in the intervention group (RR 0.78, 95% CI 0.52 to 1.15; participants = 375; studies = 6; I^2 = 0%). There were no serious adverse events reported by any of the included studies and no between-group difference for all adverse events (RD -0.01, 95% CI -0.05 to 0.03; participants = 694; studies = 5). Inhaled magnesium sulfate versus inhaled β_2-agonist We included four studies in this comparison. The evidence for the efficacy of β_2-agonists in acute

asthma is well-established and therefore this could be considered a historical comparison. Two studies reported a benefit of β_2-agonist over $MgSO_4$ alone for PEFR and two studies reported no difference; we did not pool these results. Admissions to hospital were only reported by one small study and events were rare, leading to an uncertain result. No serious adverse events were reported in any of the studies in this comparison; one small study reported mild to moderate adverse events, but the result is imprecise. Treatment with nebulised $MgSO_4$ may result in modest additional benefits for lung function and hospital admission when added to inhaled β_2-agonists and ipratropium bromide, but our confidence in the evidence is low and there remains substantial uncertainty. The recent large, well-designed trials have generally not demonstrated clinically important benefits. Nebulised $MgSO_4$ does not appear to be associated with an increase in serious adverse events. Individual studies suggest that those with more severe attacks and attacks of shorter duration may experience a greater benefit but further research into subgroups is warranted. Despite including 24 trials in this review update we were unable to pool data for all outcomes of interest and this has limited the strength of the conclusions reached. A core outcome set for studies in acute asthma is needed. This is particularly important in pediatric studies where measuring lung function at the time of an exacerbation may not be possible. Placebo-controlled trials in patients not responding to standard maximal treatment, including inhaled β_2-agonists and ipratropium bromide and systemic steroids, may help establish if nebulised $MgSO_4$ has a role in acute asthma. However, the accumulating evidence suggests that a substantial benefit may be unlikely.

People with asthma may experience exacerbations, or 'attacks', during which their symptoms worsen, and additional treatment is required. (Kayleigh M Kew 1, Ella Flemyng 2, Bradley S Quon 3, Clarus Leung, 2022) Written action plans sometimes advocate a short-term increase in the dose of inhaled corticosteroids (ICS) at the first sign of an exacerbation to reduce the severity of the attack and to prevent the need for oral steroids or hospital admission. To compare the clinical effectiveness and safety of increased versus stable doses of ICS as part of a patient-initiated action plan for the home management of exacerbations in children and adults

with persistent asthma. We searched the Cochrane Airways Group Specialized Register, which is derived from searches of the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, and CINAHL (Cumulative Index to Nursing and Allied Health Literature), and hand searched abstracts to 20 December 2021. We also searched major trial registries for ongoing trials. We included parallel and cross-over randomized controlled trials (RCTs) that allocated people with persistent asthma to take a blinded inhaler in the event of an exacerbation which either increased their daily dose of ICS or kept it stable (placebo). Two review authors independently selected trials, assessed quality, and extracted data. We reassessed the risk of bias for all studies at the result level using the revised risk of bias tool for RCTs (Risk of Bias 2) and employed the GRADE approach to assess our confidence in the synthesized effect estimates. The primary outcome was treatment failure, defined as the need for rescue oral steroids in the randomized population. Secondary outcomes were treatment failure in the subset who initiated the study inhaler (treated population), unscheduled physician visits, unscheduled acute care, emergency department or hospital visits, serious and non-serious adverse events, and duration of exacerbation. This review update added a new study that increased the number of people in the primary analysis from 1520 to 1774 and incorporates the most up-to-date methods to assess the likely impact of bias within the meta-analyses. The updated review now includes nine RCTs (1923 participants; seven parallel and two cross-over) conducted in Europe, North America, and Australasia and published between 1998 and 2018. Five studies evaluated adult populations (n = 1247; $\geqslant$ 15 years), and four studies evaluated child or adolescent populations (n = 676; < 15 years). All study participants had mild to moderate asthma. Studies varied in the dose of maintenance ICS, age, fold increase of ICS in the event of an exacerbation, criteria for initiating the study inhaler, and allowed medications. Approximately 50% of randomized participants initiated the study inhaler (range 23% to 100%), and the included studies reported treatment failure in a variety of ways, meaning assumptions were required to permit the combining of data. Participants randomized to increase

their ICS dose at the first signs of an exacerbation had similar odds of needing rescue oral corticosteroids to those randomized to a placebo inhaler (odds ratio (OR) 0.97, 95% confidence interval (CI) 0.76 to 1.25; 8 studies; 1774 participants; I2 = 0%; moderate quality evidence). We could draw no firm conclusions from subgroup analyses conducted to investigate the impact of age, time to treatment initiation, baseline dose, smoking history, and fold increase of ICS on the primary outcome. Results for the same outcome in the subset of participants who initiated the study inhaler were unchanged from the previous version, which provides a different point estimate with very low confidence due to heterogeneity, imprecision, and risk of bias (OR 0.84, 95% CI 0.54 to 1.30; 7 studies; 766 participants; I2 = 42%; random-effects model). Confidence was reduced due to risk of bias and assumptions that had to be made to include study data in the intention-to-treat and treated-population analyses. Sensitivity analyses that tested the impact of assumptions made for synthesis and to exclude cross-over studies, studies at overall high risk of bias, and those with commercial funding did not change our conclusions. Pooled effects for unscheduled physician visits, unscheduled acute care, emergency department or hospital visits, and duration of exacerbation made it very difficult to determine where the true effect may lie, and confidence was reduced by risk of bias. Point estimates for both serious and non-serious adverse events favored keeping ICS stable, but imprecision and risk of bias due to missing data and outcome measurement and reporting reduced our confidence in the effects (serious adverse events: OR 1.69, 95% CI 0.77 to 3.71; 2 studies; 394 participants; I^2 = 0%; non-serious adverse events: OR 2.15, 95% CI 0.68 to 6.73; 2 studies; 142 participants; I^2 = 0%). Evidence from double-blind trials of adults and children with mild to moderate asthma suggests there is unlikely to be an important reduction in the need for oral steroids from increasing a patient's ICS dose at the first sign of exacerbation. Other clinically important benefits and potential harms of increased doses of ICS compared with keeping the dose stable cannot be ruled out due to wide confidence intervals, risk of bias in the trials, and assumptions that had to be made for synthesis. Included studies conducted between 1998 and 2018 reflect evolving clinical practice and study methods, and the data do

not support thorough investigation of effect modifiers such as baseline dose, fold increase, asthma severity and timing. The review does not include recent evidence from pragmatic, unblinded studies showing benefits of larger dose increases in those with poorly controlled asthma. A systematic review is warranted to examine the differences between the blinded and unblinded trials using robust methods for assessing risk of bias to present the most complete view of the evidence for decision makers.

Asthma is a common chronic disease worldwide. Inhalers are often prescribed to help control asthma symptoms, improve quality of life and reduce the risk of exacerbations or flare-ups. (Rebecca Normansell 1, Kayleigh M Kew 1 2, Alexander G Mathioudakis, 2017) However, evidence suggests that many people with asthma do not use their inhaler correctly. It is therefore important to evaluate whether interventions aimed specifically at improving technique are effective and safe, and whether use of these interventions translates into improved clinical outcomes. To assess the impact of interventions to improve inhaler technique on clinical outcomes and safety in adults and children with asthma. We searched the Cochrane Airways Trials Register, which contains records compiled from multiple electronic and hand searched resources. We also searched trial registries and reference lists of primary studies. We conducted the most recent search on 23 November 2016. We included studies comparing a group of adults or children with asthma receiving an inhaler technique intervention versus a group receiving a control or alternative intervention. We included parallel and cluster-randomized trials of any duration conducted in any setting and planned to include only the first phase of any cross-over trials identified. We included studies reported as full-text articles, those published as abstracts only and unpublished data. Two review authors screened the search results for eligible studies. We extracted outcome data, assessed risk of bias in duplicate and resolved discrepancies by involving another review author. We grouped studies making similar comparisons by consensus (e.g. all those comparing enhanced inhaler technique education vs usual care) and conducted meta-analyses only if treatments, participants and the underlying clinical question were similar enough for pooling to make sense. We analyzed dichotomous

data as odds ratios, and continuous data as mean differences or standardized mean differences, all with random-effects models. We described skewed data narratively. We graded the results and presented evidence in the ‘Summary of findings' tables for each comparison. Primary outcomes were inhaler technique, asthma control and exacerbations requiring at least oral corticosteroids (OCS). This review includes 29 parallel randomized controlled trials (RCTs) (n = 2210), although not all reported relevant or usable data. All participants had asthma, and follow-up ranged from 2 to 26 weeks. Most studies were at low or unclear risk of selection and attrition biases and at high risk for biases associated with blinding. We considered most of the evidence to be of low-quality owing to these biases and to imprecision in the estimates of effect. We classified studies into three comparisons: enhanced face-to-face training session(s), multi-media-delivered inhaler training (e.g. DVD, computer app or game) and technique feedback devices. Differences between interventions, populations and outcome measures limited quantitative analyses, particularly for exacerbations, adverse events, unscheduled visits to a healthcare provider and absenteeism from work or school. Enhanced inhaler technique education and multi-media training improved technique in most studies immediately after the intervention and at follow-up, although the variety of checklists used meant that this was difficult to assess reliably. For both adults and children, how and when inhaler technique was assessed appeared to affect whether inhaler technique improved and by how much. Analyses of the numbers of people who demonstrated correct or 'good enough' technique were generally more useful than checklist scores. Adult studies of enhanced education showed benefit when this metric was used at 2 to 26 weeks' follow-up (odds ratio (OR) 5.00, 95% confidence interval (CI) 1.83 to 13.65; 258 participants; three studies; 31 per 100 with correct technique in the control group compared with 69 (95% CI 45 to 86) in the education group; moderate-quality evidence). A similar result was seen in studies looking at feedback devices at four weeks' follow-up (OR 4.80, 95% CI 1.87 to 12.33; 97 participants; one study; 51 per 100 with correct technique in the control group compared with 83 (95% CI 66 to 93) in the feedback group; low-quality evidence). However, the benefit of multi-media training for adults even

immediately after the intervention was uncertain (OR 2.15, 95% CI 0.84 to 5.50; 164 participants; two studies; I^2 = 49%; 30 per 100 in the control group with correct technique compared with 47 (95% CI 26 to 70) in the multi-media group; moderate-quality evidence). Evidence tended to be less clear for children, usually because results were based on fewer and smaller studies. Some studies did not report exacerbations in a way that allowed meta-analysis; others provided inconclusive results. Inhaler technique interventions provided some benefit for asthma control and quality of life but generally did not lead to consistent or important clinical benefits for adults or children. Confidence intervals included no difference or did not reach a threshold that could be considered clinically important. Responder analyses sometimes showed improvement among more people in the intervention groups, even though the mean difference between groups was small. We found no evidence about harms. Although interventions to improve inhaler technique may work in some circumstances, the variety of interventions and measurement methods used hampered our ability to perform meta-analyses and led to low to moderate confidence in our findings. Most included studies did not report important improvement in clinical outcomes. Guidelines consistently recommend that clinicians check regularly the inhaler technique of their patients; what is not clear is how clinicians can most effectively intervene if they find a patient's technique to be inadequate, and whether such interventions will have a discernible impact on clinical outcomes.

Asthma affects 350 million people worldwide including 45% to 70% with mild disease. (Iain Crossingham 1, Sally Turner 1, Sanjay Ramakrishnan 2 3 4, Anastasia Fries 2, Matthew Gowell 5, Farhat Yasmin 6, Rebekah Richardson 1, Philip Webb 1, Emily O'Boyle 5, Timothy Sc Hinks, 2021). Treatment is mainly with inhalers containing beta$_2$-agonists, typically taken as required to relieve bronchospasm, and inhaled corticosteroids (ICS) as regular preventive therapy. Poor adherence to regular therapy is common and increases the risk of exacerbations, morbidity and mortality. Fixed-dose combination inhalers containing both a steroid and a fast-acting beta$_2$-agonist (FABA) in the same device simplify inhalers regimens and ensure symptomatic relief is accompanied by preventative therapy. Their use is established in

moderate asthma, but they may also have potential utility in mild asthma. To evaluate the efficacy and safety of single combined (fast-onset beta$_2$-agonist plus an inhaled corticosteroid (ICS)) inhaler only used as needed in people with mild asthma. We searched the Cochrane Airways Trials Register, Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE and Embase, ClinicalTrials.gov and the World Health Organization (WHO) trials portal. We contacted trial authors for further information and requested details regarding the possibility of unpublished trials. The most recent search was conducted on 19 March 2021. We included randomized controlled trials (RCTs) and cross-over trials with at least one week washout period. We included studies of a single fixed-dose FABA/ICS inhaler used as required compared with no treatment, placebo, short-acting beta agonist (SABA) as required, regular ICS with SABA as required, regular fixed-dose combination ICS/long-acting beta agonist (LABA), or regular fixed-dose combination ICS/FABA with as required ICS/FABA. We planned to include cluster-randomized trials if the data had been or could be adjusted for clustering. We excluded trials shorter than 12 weeks. We included full texts, abstracts and unpublished data. Two review authors independently extracted data. We analyzed dichotomous data as odds ratios (OR) or rate ratios (RR) and continuous data as mean difference (MD). We reported 95% confidence intervals (CIs). We used Cochrane's standard methodological procedures of meta-analysis. We applied the GRADE approach to summarize results and to assess the overall certainty of evidence. Primary outcomes were exacerbations requiring systemic steroids, hospital admissions/emergency department or urgent care visits for asthma, and measures of asthma control. We included six studies of which five contributed results to the meta-analyses. All five used budesonide 200 μg and formoterol 6 μg in a dry powder formulation as the combination inhaler. Comparator fast-acting bronchodilators included terbutaline and formoterol. Two studies included children aged 12+ and adults; two studies were open-label. A total of 9657 participants were included, with a mean age of 36 to 43 years. 2.3% to 11% were current smokers. FABA / ICS as required versus FABA as required Compared with as-required FABA alone, as-required FABA/ICS reduced exacerbations

requiring systemic steroids (OR 0.45, 95% CI 0.34 to 0.60, 2 RCTs, 2997 participants, high-certainty evidence), equivalent to 109 people out of 1000 in the FABA alone group experiencing an exacerbation requiring systemic steroids, compared to 52 (95% CI 40 to 68) out of 1000 in the FABA/ICS as-required group. FABA/ICS as required may also reduce the odds of an asthma-related hospital admission or emergency department or urgent care visit (OR 0.35, 95% CI 0.20 to 0.60, 2 RCTs, 2997 participants, low-certainty evidence). Compared with as-required FABA alone, any changes in asthma control or spirometry, though favoring as-required FABA/ICS, were small and less than the minimal clinically important differences. We did not find evidence of differences in asthma-associated quality of life or mortality. For other secondary outcomes FABA/ICS as required was associated with reductions in fractional exhaled nitric oxide, probably reduces the odds of an adverse event (OR 0.82, 95% CI 0.71 to 0.95, 2 RCTs, 3002 participants, moderate-certainty evidence) and may reduce total systemic steroid dose (MD -9.90, 95% CI -19.38 to -0.42, 1 RCT, 443 participants, low-certainty evidence), and with an increase in the daily inhaled steroid dose (MD 77 μg beclomethasone equiv./day, 95% CI 69 to 84, 2 RCTs, 2554 participants, moderate-certainty evidence). FABA/ICS as required versus regular ICS plus FABA as required There may be little or no difference in the number of people with asthma exacerbations requiring systemic steroid with FABA/ICS as required compared with regular ICS (OR 0.79, 95% CI 0.59 to 1.07, 4 RCTs, 8065 participants, low-certainty evidence), equivalent to 81 people out of 1000 in the regular ICS plus FABA group experiencing an exacerbation requiring systemic steroids, compared to 65 (95% CI 49 to 86) out of 1000 FABA/ICS as required group. The odds of an asthma-related hospital admission or emergency department or urgent care visit may be reduced in those taking FABA/ICS as required (OR 0.63, 95% CI 0.44 to 0.91, 4 RCTs, 8065 participants, low-certainty evidence). Compared with regular ICS, any changes in asthma control, spirometry, peak flow rates (PFR), or asthma-associated quality of life, though favouring regular ICS, were small and less than the minimal clinically important differences (MCID). Adverse events, serious adverse events, total systemic corticosteroid dose and mortality were similar between

groups, although deaths were rare, so confidence intervals for this analysis were wide. We found moderate-certainty evidence from four trials involving 7180 participants that FABA/ICS as required was likely associated with less average daily exposure to inhaled corticosteroids than those on regular ICS (MD -154.51 μg/day, 95% CI -207.94 to -101.09). We found FABA/ICS as required is clinically effective in adults and adolescents with mild asthma. Their use instead of FABA as required alone reduced exacerbations, hospital admissions or unscheduled healthcare visits and exposure to systemic corticosteroids and probably reduces adverse events. FABA/ICS as required is as effective as regular ICS and reduced asthma-related hospital admissions or unscheduled healthcare visits, and average exposure to ICS, and is unlikely to be associated with an increase in adverse events. Further research is needed to explore use of FABA/ICS as required in children under 12 years of age, use of other FABA/ICS preparations, and long-term outcomes beyond 52 weeks.

With increasing choice of medications and devices for asthma and chronic obstructive pulmonary disease (COPD) treatment, comparative evidence may inform treatment decisions. (Shiyuan Zhang 1, Denise King 2, Virginia M Rosen 3, Afisi S Ismaila, 2020) This systematic literature review assessed clinical and economic evidence for using a single combination inhaler versus multiple inhalers to deliver the same medication for patients with asthma or COPD. In 2016, Embase, PubMed and the Cochrane library were searched for publications reporting studies in asthma or COPD comparing a single-inhaler combination medicine with multiple inhalers delivering the same medication. Publications included English-language articles published since 1996 and congress abstracts since 2013. Clinical, economic and adherence endpoints were assessed. Of 2031 abstracts screened, 18 randomized controlled trials (RCTs) in asthma and four in COPD, nine retrospective and three prospective observational studies in asthma, and four observational studies in COPD were identified. Of these, five retrospective and one prospective study in asthma, and two retrospective studies in COPD reported greater adherence with a single inhaler than multiple inhalers. Nine observational studies reported significantly (n=7) or numerically (n=2) higher rates of

adherence with single- versus multiple-inhaler therapy. Economic analyses from retrospective and prospective studies showed that use of single-inhaler therapies was associated with reduced healthcare resource use (n=6) and was cost-effective (n=5) compared with multiple-inhaler therapies. Findings in 18 asthma RCTs and one prospective study reporting lung function, and six RCTs reporting exacerbation rates, showed no significant differences between a single inhaler and multiple inhalers. This was in contrast to several observational studies reporting reductions in healthcare resource use or exacerbation events with single-inhaler treatment, compared with multiple inhalers. Retrospective and prospective studies showed that single-inhaler use was associated with decreased healthcare resource utilization and improved cost-effectiveness compared with multiple inhalers. Lung function and exacerbation rates were mostly comparable in the RCTs, possibly due to study design.

About 10% of adults have suffered an attack of asthma, and up to 5% of these have severe disease that responds poorly to treatment (Ruth H Green, 2016). Patients with severe disease have an increased risk of death, but patients with mild to moderate disease are also at risk of exacerbations. Most guidelines about the management of asthma follow stepwise protocols. This overview does not endorse or follow any particular protocol, but presents the evidence about a specific intervention, magnesium sulfate. We conducted a systematic overview, aiming to answer the following clinical question: What are the effects of magnesium sulfate for acute asthma? We searched: Medline, Embase, The Cochrane Library, and other important databases up to November 2014 (Clinical Evidence overviews are updated periodically; please check our website for the most up-to-date version of this overview). At this update, searching of electronic databases retrieved 50 studies. After deduplication and removal of conference abstracts, 24 records were screened for inclusion in the overview. Appraisal of titles and abstracts led to the exclusion of 10 studies and the further review of 14 full publications. Of the 14 full articles evaluated, one systematic review was updated and one systematic review was added at this update. We performed a GRADE evaluation for five PICO combinations. In this systematic overview, we categorized the efficacy for two comparisons

based on information about the effectiveness and safety of magnesium sulfate (iv) versus placebo and magnesium sulfate (nebulised) plus short-acting beta2 agonists (inhaled) versus short-acting beta2 agonists (inhaled) alone.

The effect of heliox as a nebulizer β2-agonist driving gas in acute asthma remains controversial. (Gustavo J Rodrigo 1, Jose A Castro-Rodriguez, 2018) To perform a systematic review with a meta-analysis of randomized trials designed to evaluate the efficacy of heliox versus oxygen in driving β2-agonist nebulization in patients with acute asthma. A search was conducted of all randomized controlled trials published before August 2013. Primary outcomes were change in spirometric measurements and severity composite score (pediatric studies); secondary outcomes were hospitalizations and serious adverse effects. Eleven trials from 10 studies (697 participants) met the inclusion criteria (7 included adults and 3 included children). The mean duration of heliox therapy was 120 minutes and the most common helium-oxygen mixture used was 70:30. Patients receiving heliox presented a statistically significant difference for mean percentage of change in peak expiratory flow (17.2%; 95% confidence interval 5.2-29.2, P = .005). Post hoc subgroup analysis showed that patients with severe and very severe asthma showed a significant improvement in peak expiratory flow compared with those with mild to moderate acute asthma. Heliox-driven nebulization also produced significant decreases in the risk of hospitalizations (odds ratio 0.49, 95% confidence interval 0.31-0.79, P = .003) and severity of exacerbations (pediatric studies; standard mean difference -0.74, 95%% confidence interval -1.45 to -0.03, P = .04). There were no group differences for serious adverse effects. This review suggests that heliox benefits in airflow limitation and hospital admissions could be considered clinically significant. Data supports the use of heliox as a nebulizing β2-agonist driving gas in the routine care of patients with acute asthma.

Hypertonic saline enhances mucociliary clearance and may lessen the destructive inflammatory process in the airways. (Peter Wark 1, Vanessa M McDonald 2, Sherie Smith, 2023) This is an update of a previously published review. To investigate efficacy and tolerability of nebulised hypertonic saline treatment in people with cystic fibrosis (CF)

compared to placebo or other treatments that enhance mucociliary clearance. We searched the Cochrane Cystic Fibrosis and Genetic Disorders Group's Cystic Fibrosis Trials Register, comprising references identified from comprehensive electronic database searches, handsearches of relevant journals and abstract books of conference proceedings. We also searched ongoing trials databases. Most recent search: 25 April 2022. We included randomised and quasi-randomised controlled trials assessing hypertonic saline compared to placebo or other mucolytic therapy, for any duration or dose regimen in people with CF (any age or disease severity). Two authors independently reviewed all identified trials and data, and assessed trial quality. We assessed the certainty of the evidence using GRADE. For cross-over trials we stipulated a one-week washout period. We planned to use results from a paired analysis in the review, but this was only possible in one trial. For other cross-over trials, we chose to treat the trials as if they were parallel. We included 24 trials (1318 participants, aged one month to 56 years); we excluded 29 trials, two trials are ongoing and six are awaiting classification. We judged 15 of the 24 included trials to have a high risk of bias due to participants' ability to discern the taste of the solutions. Hypertonic saline 3% to 7% versus placebo (stable disease) We are uncertain whether the regular use of nebulised hypertonic saline in stable lung disease leads to an improvement in forced expiratory volume in one second (FEV1) % predicted at four weeks, (mean difference (MD) 3.30%, 95% confidence interval (CI) 0.71 to 5.89; 4 trials, 246 participants; very low-certainty evidence). In preschool children we found no difference in lung clearance index (LCI) at four weeks, but a small improvement after 48 weeks of treatment with hypertonic saline compared to isotonic saline (MD -0.60, 95% CI -1.00 to -0.19; 2 trials, 192 participants). We are also uncertain whether hypertonic saline made a difference to mucociliary clearance, pulmonary exacerbations or adverse events compared to placebo. Hypertonic saline versus control (acute exacerbation) Two trials compared hypertonic saline to control, but only one provided data. There may be little or no difference in lung function measured by FEV1 % predicted after hypertonic saline compared to isotonic saline (MD 5.10%, 95% CI -14.67 to 24.87; 1 trial, 130 participants). Neither trial reported any deaths or

measures of sputum clearance. There were no serious adverse events. Hypertonic saline versus rhDNase Three trials compared a similar dose of hypertonic saline to recombinant deoxyribonuclease (rhDNase); two trials (61 participants) provided data for inclusion in the review. We are uncertain whether there was an effect of hypertonic saline on FEV1 % predicted after three weeks (MD 1.60%, 95% CI -7.96 to 11.16; 1 trial, 14 participants; very low-certainty evidence). At three months, rhDNase may lead to a greater increase in FEV1 % predicted than hypertonic saline (5 mL twice daily) at 12 weeks in participants with moderate to severe lung disease (MD 8.00%, 95% CI 2.00 to 14.00; low-certainty evidence). We are uncertain whether adverse events differed between the two treatments. No deaths were reported. Hypertonic saline versus amiloride One trial (12 participants) compared hypertonic saline to amiloride but did not report on most of our outcomes. The trial found that there was no difference between treatments in measures of sputum clearance (very low-certainty evidence). Hypertonic saline compared with sodium-2-mercaptoethane sulphonate (Mistabron®) One trial (29 participants) compared hypertonic saline to sodium-2-mercaptoethane sulphonate. The trial did not measure our primary outcomes. There was no difference between treatments in any measures of sputum clearance, courses of antibiotics or adverse events (very low-certainty evidence). Hypertonic saline versus mannitol One trial (12 participants) compared hypertonic saline to mannitol, but did not report lung function at relevant time points for this review; there were no differences in sputum clearance, but mannitol was reported to be more 'irritating' (very low-certainty evidence). Hypertonic saline versus xylitol Two trials compared hypertonic saline to xylitol, but we are uncertain whether there is any difference in FEV1 % predicted or median time to exacerbation between groups (very low-certainty evidence). No other outcomes were reported in the review. Hypertonic saline 7% versus hypertonic saline 3% We are uncertain whether there was an improvement in FEV1 % predicted after treatment with 7% hypertonic saline compared with 3% (very low-certainty evidence). We are very uncertain if regular use of nebulised hypertonic saline by adults and children over the age of 12 years with CF results in an improvement in lung function after four weeks (three trials; very low-certainty evidence);

there was no difference seen at 48 weeks (one trial; low-certainty evidence). Hypertonic saline improved LCI modestly in children under the age of six years. Evidence from one small cross-over trial in children indicates that rhDNase may lead to better lung function than hypertonic saline at three months; qualifying this, we highlight that while the study did demonstrate that the improvement in FEV1 was greater with daily rhDNase, there were no differences seen in any of the secondary outcomes. Hypertonic saline does appear to be an effective adjunct to physiotherapy during acute exacerbations of lung disease in adults. However, for the outcomes assessed, the certainty of the evidence ranged from very low to low at best, according to the GRADE criteria. The role of hypertonic saline in conjunction with cystic fibrosis transmembrane conductance regulator (CFTR) modulator therapy now needs to be considered, and future research needs to focus on this aspect.

Inhaled anticholinergics given in addition to β2-agonists are effective in reducing hospital admissions in children presenting to the emergency department with a moderate to severe asthma exacerbation. It seems logical to assume a similar beneficial effect in children hospitalized for an acute asthma exacerbation. To assess the efficacy and safety of anticholinergics added to β2-agonists as inhaled or nebulised therapy in children hospitalized for an acute asthma exacerbation. To investigate the characteristics of patients or therapy, if any, that would influence the magnitude of response attributable to the addition of anticholinergics. We identified trials from the Cochrane Airways Group Specialized Register of trials (CAGR), which is derived through systematic searches of bibliographic databases including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, CINAHL, AMED and PsycINFO and through handsearching of respiratory journals and meeting abstracts. The search is current to November 2013. Randomized trials comparing the combination of inhaled or nebulised anticholinergics and short-acting β2-agonists versus short-acting β2-agonists alone in children one to 18 years of age hospitalized for an acute asthma exacerbation were eligible. Two review authors independently assessed the methodological quality of trials and extracted data; disagreement was resolved by consensus

or with the input of a third review author, when needed. Primary outcomes were duration of hospital stay and serious adverse events. Secondary outcomes included admission and duration of stay in the intensive care unit (ICU), ventilation assistance, time to short-acting β2-agonists spaced at four hours or longer, supplemental asthma therapy, duration of supplemental oxygen, change from baseline in asthma severity, relapse after discharge, adverse health effects and withdrawals. Seven randomized trials were included, four of which reported usable data on 472 children with asthma one to 18 years of age who were admitted to pediatric wards. No trials included patients admitted to the ICU. The anticholinergic used, ipratropium bromide 250 μg, was given every one to eight hours over a period from four hours to the entire length of the hospital stay. Two of four trials (50%) contributing data were deemed of high methodological quality. The addition of anticholinergics to β2-agonists showed no evidence of effect on the duration of hospital admission (mean difference (MD) -0.28 hours, 95% confidence interval (CI) -5.07 to 4.52, 3 studies, 327 participants, moderate quality evidence) and no serious or non-serious adverse events were reported in any included trials. As a result of the similarity of trials, we could not explore the influence of age, admission site, intensity of anticholinergic treatment and co-interventions on primary outcomes. No statistically significant group difference was noted in other secondary outcomes, including the need for supplemental asthma therapy, time to short-acting β2-agonists spaced at four hours or longer, asthma clinical scores, lung function and overall withdrawals for any reason. In children hospitalized for an acute asthma exacerbation, no evidence of benefit for length of hospital stay and other markers of response to therapy was noted when nebulised anticholinergics were added to short-acting β2-agonists. No adverse health effects were reported, yet the small number of trials combined with inadequate reporting prevent firm reassurance regarding the safety of anticholinergics. In the absence of trials conducted in ICUs, no conclusion can be drawn regarding children with impending respiratory failure. These findings support current national and international recommendations indicating that healthcare practitioners should refrain from using anticholinergics in children hospitalized for acute asthma.

Research Methods

Research objectives

The authors used PubMed as the main database to search for systematic reviews on asthma management, inhalers and nebulizers, and hypertension published in the last 10 years. The authors considered PubMed as the main database. PubMed is a free database of biomedical and life sciences literature maintained by the National Center for Biotechnology Information (NCBI). It is one of the most comprehensive databases of biomedical literature in the world and is often used for academic research. In the PubMed database the following search strategy was performed with a search filter considering articles published in the last 10 years and were Systematic Review. Asthma management refers to the treatment and prevention of asthma symptoms and exacerbations. It typically involves a combination of lifestyle changes, medications, and patient education. Inhalers and nebulizers are two common methods for delivering asthma medications to the lungs. Inhalers are portable devices that allow patients to self-administer their medication. Nebulizers are machines that convert liquid medication into a mist that can be inhaled. Hypertension is also known as high blood pressure. It is a condition in which the force of blood against the artery walls is too high. Hypertension is a major risk factor for heart disease, stroke, and other cardiovascular diseases. Asthma management, Inhalers and nebulizers, hypertension are keywords which are inserted in search bar for the research.

Search	Query	Results
#1	Inhaler, Nebulizer, Asthma management, hypertension Filters: Full text, RCT, Last 10 years	38

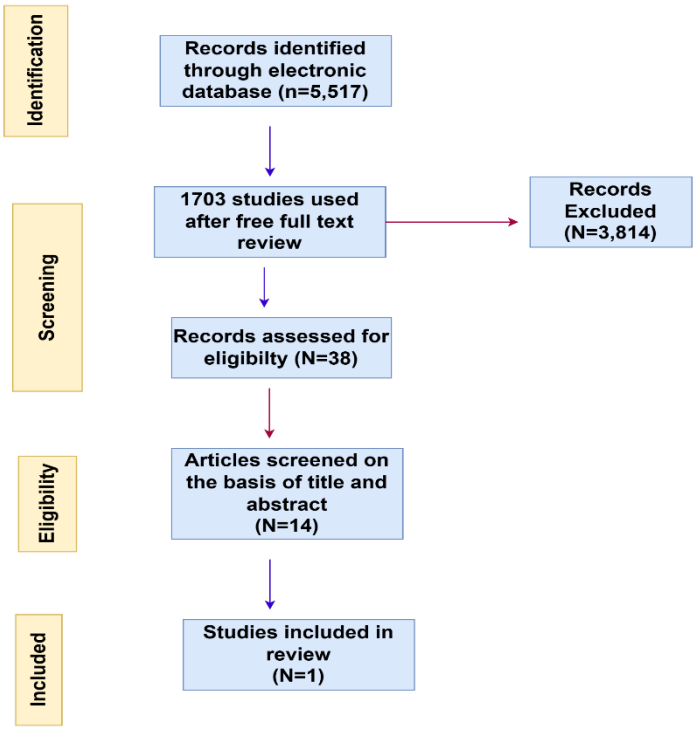
Study selection

The authors started with 5,517 articles that were identified through electronic search using PubMed. They then applied the following filters: Free full text articles: 1703 articles, Systematic articles: 65 articles, Last 10 years: 38 articles. A total of 5,517 articles were identified through electronic search using PubMed. After adding free full text articles left with filter are 1703.After adding filter Systematic articles left with filters are 65. After adding filter of Last 10 years articles left with filter are 38. The remaining 38 articles were examined for eligibility and relevant to our topic and only 1 article met the criteria. The inclusion criteria were included in the Quantitative analysis. A PRISMA diagram is presented below to illustrate the screened, excluded and included studies. This left them with 38 articles to be screened for eligibility. After screening, they identified only 1 article that met all the inclusion criteria. This article was then included in the quantitative analysis.

PRISMA FLOW CHART

A PRISMA diagram is a flowchart that shows the flow of information through the different stages of a systematic review. It is a useful tool for documenting the study selection process and for ensuring that the review is transparent and reproducible. The following is a simplified explanation of the PRISMA diagram presented in the paragraph: Total records identified: 5,517 articles Records after duplicates removed: 1703 articles Records screened: 38 articles

Records excluded: 37 articles Records included in study: 1 article The 37 articles that were excluded were likely excluded because they did not meet one or more of the inclusion criteria.



CRITERIA

Inclusion Criteria:-

Patients with age group of both children and adults with the hypertension diagnosis: This ensures that the review will include studies that are relevant to a wide range of patients.

Comparison of hypertensive patients using Nebulizers and inhalers: This ensures that the review will focus on the primary question of interest, which is to compare the effectiveness and safety of nebulizers and inhalers for the treatment of hypertension. Outcomes Efficiency, safety, cost effectiveness and Availability: These are all important outcomes to consider. when evaluating the effectiveness of different treatments.

Test available in English language and free full text: This ensures that the review will be accessible to a wide range of readers.

Exclusion Criteria: -

Studies that include participants with other chronic lung diseases, such as chronic obstructive pulmonary disease (COPD): This exclusion criterion is necessary because COPD can affect the response to treatment for hypertension. Studies that do not report clinical

outcomes of interest: This exclusion criterion is necessary because the review is focused on evaluating the clinical effectiveness and safety of different treatments.

METHOD EXTRACTION

Data extraction is the process of collecting relevant information from the included studies in a systematic and standardized way. The data extraction process is important because ensures that the data are collected in a way that is unbiased and reproducible. The paragraph states that two reviewers will independently extract data from the studies included using a standardized data extraction form. This is good practice because it helps to reduce the risk of bias. If two reviewers independently extract the same data and come up with different results, then the authors of the systematic review can discuss the discrepancy and resolve it.

The paragraph also lists the specific data that will be extracted from the included studies. This data includes information on the study design, participant characteristics, interventions, and outcomes. Here is a more detailed explanation of each data item that will be extracted:

Study characteristics: This includes information such as the author, publication year, study design, and sample size. This information is important for understanding the quality of the study and the generalizability of the findings. Hypertensive patient characteristics: This includes information such as age, sex, and asthma severity. This information is important for understanding the characteristics of the study population and for identifying potential subgroups of patients who may benefit from different treatments. Intervention: This includes information on the type of inhaler or nebulizer and the medication dose. This information is important for understanding the treatment that was being evaluated in the study. Comparison: This includes information on the type of inhaler or nebulizer and the medication dose of the comparator group. This information is important for understanding the treatment that was being compared to the intervention of interest. Outcomes: This includes information on asthma symptoms, exacerbations, lung function, and quality of life. These are all important outcomes to consider when evaluating the effectiveness of different treatments.

Results

Table no. 1

INTERVENTIONS	RESULT
To study had to a randomized clinical trial comparing albuterol delivered via NEB versus MDI+S	significant reduction in the PIS (pulmonary index score) and a significantly smaller increase in heart rate when albuterol was delivered through MDI+S than when it was delivered through NEB

Summary

This study investigates the clinical outcomes of utilizing inhalers compared to nebulizers for asthma treatment in individuals concurrently diagnosed with hypertension. The research considers the coexistence of two prevalent chronic conditions and their management challenges. The scope encompasses a comprehensive review of clinical outcomes, safety profiles, adherence, and patient satisfaction associated with these two delivery devices. The findings suggest that both inhalers and nebulizers can effectively manage asthma symptoms in individuals with hypertension. Safety profiles are generally comparable with rare, mild adverse events. Adherence and ease of use may vary depending on the individual patient's abilities and preferences. Patient satisfaction is highly subjective, with no clear consensus. The study highlights the importance of individualized treatment plans, patient education, and shared decision-making in optimizing care for this population.

Conclusion

In conclusion, the clinical outcomes of using inhalers compared to nebulizers for asthma treatment in individuals with coexisting hypertension are encouraging. Both delivery devices offer effective asthma symptom management with comparable safety profiles. However, the choice between these devices should align with individual patient needs,

preferences, and abilities. Adherence and patient satisfaction may vary, emphasizing the significance of patient education and shared decision-making. Healthcare providers should prioritize these aspects in their care plans to optimize clinical outcomes and enhance patient-centered care for this specific population. Patients using inhalers have slight increase in hypertension.

Recommendations

- Healthcare providers should adopt an individualized approach to treatment, considering the specific needs and abilities of patients with both asthma and hypertension.
- Patient education and training on the proper use of inhalers and nebulizers are crucial for optimizing treatment outcomes. Healthcare providers should prioritize these aspects in patient care.
- Regular follow-up assessments are essential to evaluate treatment response, adherence, and device-specific challenges in individuals with concurrent asthma and hypertension.
- Patient preferences should be considered, involving patients in shared decision-making regarding their treatment plans.
- Further research should focus on specific subpopulations, such as pediatric and geriatric patients, to better understand their unique needs and preferences.
- While cost-effectiveness was not within the scope of this study, healthcare providers and patients should also consider the cost of medications and devices when making treatment choices.

References

- National Asthma Education and Prevention Program. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. Bethesda, MD: National Institutes of Health; 2007.
- Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. 2023. Available at: https://ginasthma.org/
- Gibson PG, Barnes PJ, Brusselle GG, et al. Asthma management and prevention: A new consensus statement. Lancet Respir Med. 2014;2(11):734-753.
- GINA. Global Strategy for Asthma Management and Prevention. Available at: https://ginasthma.org/
- Payares-Salamanca JA, Castañeda-Orjuela CA, Hernández-Gutiérrez CA, Pérez-Gutiérrez R. Inhalers versus nebulizers for acute asthma in children: a systematic review with meta-analysis. J Asthma. 2018;55(11):1173-1182.
- Newman KB, Rothman RE, Camargo CA Jr, Weinberger M. A comparison of albuterol administered by metered-dose inhaler and spacer with albuterol by nebulizer in adults presenting to an urban emergency department with acute asthma. Chest. 2002;121(4):1036-1041.
- Cates CJ, Welsh EJ, Rowe BH. Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma. Cochrane Database Syst Rev. 2013;9:CD000052.
- https://pubmed.ncbi.nlm.nih.gov/32940961/
- https://pubmed.ncbi.nlm.nih.gov/29182799/
- https://pubmed.ncbi.nlm.nih.gov/36161875/
- https://pubmed.ncbi.nlm.nih.gov/28288272/
- https://pubmed.ncbi.nlm.nih.gov/33945639/
- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8993836/
- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6776421/

europepmc.org/articles/pmc5353274/bin/bmjopen-2016-013588supp_appendix3.pdf

Ahmad, R., Khan, S., & Naeem, Z. (2020). A systematic review of randomized controlled trials comparing the effectiveness of inhalers and nebulizers in the treatment of adult asthma. Frontiers in pharmacology, 11, 575111.

- Gibson, P. G., Powell, H., & Ducharme, F. M. (2014). Nebulizers for asthma in adults. Cochrane Database of Systematic Reviews, (7).
- O'Byrne, P., Bateman, E. D., Bousquet, J., Global Initiative for Asthma (GINA) Program Committee. (2023). Global strategy for asthma management and prevention (2023 update). European respiratory journal, 61(2), 20220166.
- Rowe, J. M., & Barnes, P. J. (2022). Asthma. Lancet (London, England), 399(10338), 1807-1817.
- Tinkelman, D. G., & Drazen, J. M. (2016). Asthma. In Harrison's principles of internal medicine (19th ed., pp. 1994-1995). New York: McGraw-Hill Education
- search.proquest.com/openview/9ab1653846cc4b3a68932e9c1ea531d2/1?pq-origsite=gscholar&cbl=2041043