PICO Search Assignment Worksheet **Name Melinda Chiu**

58yo F with PMH of asthma x 12 years, presenting with cough x 2 days. Admits to having a progressively difficult time breathing starting this morning, with a productive cough and wheezing, and says she ran out of her inhaler medication last week and has not gone to get refills due to the weather. Pt denies getting the influenza vaccine this year, sick contacts, fever, chills, runny/stuffy nose, NVD, C/P nor palpitations.

At the Ambulatory Medicine rotation, many patients come in with "cold-like symptoms" this time of the year. It is surprising how many patients also admit that they have a history of asthma. An important thing to do is to rule out influenza by doing a rapid swab test. We also pay a lot of attention to with Pulse Oximetry, where we want the value to be over 95%. If all signs suggest a possible asthma exacerbation we give these patients a treatment of DuoNeb, a combination of Ipratropium Bromide and Albuterol Sulfate. I am familiar with asthma patients commonly using Albuterol to control their asthma symptoms. I want to know if we solely gave nebulized Albuterol, would it be as effective as giving DuoNeb?

Search Question: In asthma patients with exacerbations, is nebulized Albuterol as effective as DuoNeb at relieving symptoms?

Question Type: What kind of question is this?
☐Prevalence ☐Screening ☐Diagnosis ☒Prognosis ☒Treatment ☐Harms

Preferred Study Type: Meta-analysis, Systematic review, RCT

PICO search terms:

P	I	C	O
asthma patients	*DuoNeb* (ipratropium bromide + albuterol sulfate)	nebulized Albuterol	resolution of sx
asthmatics	*Combivent* (ipratropium bromide + albuterol sulfate)	monotherapy Albuterol	improvement of sx
asthma exacerbation	*Berodual* (ipratropium bromide + fenoterol hydrobromide)	monotherapy SABA	alleviation of asthma exacerbation
acute asthma		Salbutamol	

Search tools and strategy used:

Cochrane
- asthma nebulize → 23 results
  - Filters: none

PubMed
- Combivent + asthma → 8 results
  - Filters: Review, 10 years
- DuoNeb + asthma → 44 results
  - Filters: Review, 10 years, Free full text

Google Scholar
- asthma ipratropium bromide + albuterol sulfate→ 8.5k results
  - Filters: none
- asthma ipratropium bromide + albuterol sulfate→ 1.5k results

- Filters: Since 2016

I chose these studies since they referred to the use of Albuterol or SABAs, along with anticholinergics like Ipratropium bromide. I was surprised at how difficult it was to find relevant articles; probably because I was very specific in what I wanted to find. Most of the studies included in the articles did include the use of *nebulized* treatment, but I had to be open to the use of *inhaled* administration since that was such a common route. I also had to be very careful to find articles specifically involving SABAs like Albuterol, since there is a lot of research out there regarding the use of LABAs with potential increased mortality in its use. Some difficulties also presented since COPD has been studied with these medications, and it was a common finding throughout my searches. I also made sure the articles were published in the past 10 years, and were indexed for MEDLINE. In all, I have 1 meta analysis, 1 systematic review, and 2 RCTs which all covered the topics and requirements I was looking for.

Search results:

Citation
Cochrane Database Syst Rev. 2017 Jan 11;1:CD001284. doi: 10.1002/14651858.CD001284.pub2.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6465060/

Title and Authors
Combined inhaled beta-agonist and anticholinergic agents for emergency management in adults with asthma.
Kirkland SW, Vandenberghe C, Voaklander B, Nikel T, Campbell S, Rowe BH

Abstract
BACKGROUND:
Inhaled short-acting anticholinergics (SAAC) and short-acting beta$_2$-agonists (SABA) are effective therapies for adult patients with acute asthma who present to the emergency department (ED). It is unclear, however, whether the combination of SAAC and SABA treatment is more effective in reducing hospitalisations compared to treatment with SABA alone.
OBJECTIVES:
To conduct an up-to-date systematic search and meta-analysis on the effectiveness of combined inhaled therapy (SAAC + SABA agents) vs. SABA alone to reduce hospitalisations in adult patients presenting to the ED with an exacerbation of asthma.
SEARCH METHODS:
We searched MEDLINE, Embase, CINAHL, SCOPUS, LILACS, ProQuest Dissertations & Theses Global and evidence-based medicine (EBM) databases using controlled vocabulary, natural language terms, and a variety of specific and general terms for inhaled SAAC and SABA drugs. The search spanned from 1946 to July 2015. The Cochrane Airways Group provided search results from the Cochrane Airways Group Register of Trials which was most recently conducted in July 2016. An extensive search of the grey literature was completed to identify any other potentially relevant studies.
SELECTION CRITERIA:
Included studies were randomised or controlled clinical trials comparing the effectiveness of combined inhaled therapy (SAAC and SABA) to SABA treatment alone to prevent hospitalisations in adults with acute asthma in the emergency department. Two independent review authors assessed studies for inclusion using pre-determined criteria.
DATA COLLECTION AND ANALYSIS:
For dichotomous outcomes, we calculated individual and pooled statistics as risk ratios (RR) or odds ratios (OR) with 95% confidence intervals (CI) using a random-effects model and reporting heterogeneity (I^2). For continuous outcomes, we reported individual trial results using mean differences (MD) and pooled results as weighted mean differences (WMD) or standardised mean differences (SMD) with 95% CIs using a random-effects model.
MAIN RESULTS:
We included 23 studies that involved a total of 2724 enrolled participants. Most studies were rated at unclear or high risk of bias.Overall, participants receiving combination inhaled therapy were less likely to be hospitalised

(RR 0.72, 95% CI 0.59 to 0.87; participants = 2120; studies = 16; I^2 = 12%; moderate quality of evidence). An estimated 65 fewer patients per 1000 would require hospitalisation after receiving combination therapy (95% 30 to 95), compared to 231 per 1000 patients receiving SABA alone. Although combination inhaled therapy was more effective than SABA treatment alone in reducing hospitalisation in participants with severe asthma exacerbations, this was not found for participants with mild or moderate exacerbations (test for difference between subgroups P = 0.02).Participants receiving combination therapy were more likely to experience improved forced expiratory volume in one second (FEV_1) (MD 0.25 L, 95% CI 0.02 to 0.48; participants = 687; studies = 6; I^2 = 70%; low quality of evidence), peak expiratory flow (PEF) (MD 36.58 L/min, 95% CI 23.07 to 50.09; participants = 1056; studies = 12; I^2 = 25%; very low quality of evidence), increased percent change in PEF from baseline (MD 24.88, 95% CI 14.83 to 34.93; participants = 551; studies = 7; I^2 = 23%; moderate quality of evidence), and were less likely to return to the ED for additional care (RR 0.80, 95% CI 0.66 to 0.98; participants = 1180; studies = 5; I^2 = 0%; moderate quality of evidence) than participants receiving SABA alone. Participants receiving combination inhaled therapy were more likely to experience adverse events than those treated with SABA agents alone (OR 2.03, 95% CI 1.28 to 3.20; participants = 1392; studies = 11; I^2 = 14%; moderate quality of evidence). Among patients receiving combination therapy, 103 per 1000 were likely to report adverse events (95% 31 to 195 more) compared to 131 per 1000 patients receiving SABA alone.
AUTHORS' CONCLUSIONS:
Overall, combination inhaled therapy with SAAC and SABA reduced hospitalisation and improved pulmonary function in adults presenting to the ED with acute asthma. In particular, combination inhaled therapy was more effective in preventing hospitalisation in adults with severe asthma exacerbations who are at increased risk of hospitalisation, compared to those with mild-moderate exacerbations, who were at a lower risk to be hospitalised. A single dose of combination therapy and multiple doses both showed reductions in the risk of hospitalisation among adults with acute asthma. However, adults receiving combination therapy were more likely to experience adverse events, such as tremor, agitation, and palpitations, compared to patients receiving SABA alone.

Reason I chose it

- indexed for MEDLINE, published within the past 3 years
- covers all the topics I was looking for, and there is a large pool of subjects studied
- Meta analysis offers one of the highest levels of evidence, combing through different sources in order to produce statistical summary of their results.
- it is published in Cochrane Database of Systematic Reviews, which is a well known and trusted source.

Citation

Cochrane Database Syst Rev. 2013 Aug 21;(8):CD000060. doi: 10.1002/14651858.CD000060.pub2.
https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD000060.pub2/epdf/full

Title and Authors

Combined inhaled anticholinergics and short-acting beta2-agonists for initial treatment of acute asthma in children.

Griffiths B, Ducharme FM

Abstract

BACKGROUND:
There are several treatment options for managing acute asthma exacerbations (sustained worsening of symptoms that do not subside with regular treatment and require a change in management). Guidelines advocate the use of inhaled short acting beta2-agonists (SABAs) in children experiencing an asthma exacerbation. Anticholinergic agents, such as ipratropium bromide and atropine sulfate, have a slower onset of action and weaker bronchodilating effect, but may specifically relieve cholinergic bronchomotor tone and decrease mucosal edema and secretions. Therefore, the combination of inhaled anticholinergics with SABAs may yield enhanced and prolonged bronchodilation.
OBJECTIVES:

To determine whether the addition of inhaled anticholinergics to SABAs provides clinical improvement and affects the incidence of adverse effects in children with acute asthma exacerbations.
SEARCH METHODS:
We searched MEDLINE (1966 to April 2000), EMBASE (1980 to April 2000), CINAHL (1982 to April 2000) and reference lists of studies of previous versions of this review. We also contacted drug manufacturers and trialists. For the 2012 review update, we undertook an 'all years' search of the Cochrane Airways Group's register on the 18 April 2012.
SELECTION CRITERIA:
Randomized parallel trials comparing the combination of inhaled anticholinergics and SABAs with SABAs alone in children (aged 18 months to 18 years) with an acute asthma exacerbation.
DATA COLLECTION AND ANALYSIS:
Two review authors independently assessed trial quality and extracted data. We used the GRADE rating system to assess the quality of evidence for our primary outcome (hospital admission).
MAIN RESULTS:
Twenty trials met the review eligibility criteria, generated 24 study comparisons and comprised 2697 randomised children aged one to 18 years, presenting predominantly with moderate or severe exacerbations. Most studies involved both preschool-aged children and school-aged children; three studies also included a small proportion of infants less than 18 months of age. Nine trials (45%) were at a low risk of bias. Most trials used a fixed-dose protocol of three doses of 250 mcg or two doses of 500 mcg of nebulized ipratropium bromide in combination with a SABA over 30 to 90 minutes while three trials used a single dose and two used a flexible-dose protocol according to the need for SABA.The addition of an anticholinergic to a SABA significantly reduced the risk of hospital admission (risk ratio (RR) 0.73; 95% confidence interval (CI) 0.63 to 0.85; 15 studies, 2497 children, high-quality evidence). In the group receiving only SABAs, 23 out of 100 children with acute asthma were admitted to hospital compared with 17 (95% CI 15 to 20) out of 100 children treated with SABAs plus anticholinergics. This represents an overall number needed to treat for an additional beneficial outcome (NNTB) of 16 (95% CI 12 to 29).Trends towards a greater effect with increased treatment intensity and with increased asthma severity were observed, but did not reach statistical significance. There was no effect modification due to concomitant use of oral corticosteroids and the effect of age could not be explored. However, exclusion of the one trial that included infants (< 18 months) and contributed data to the main outcome, did not affect the results. Statistically significant group differences favoring anticholinergic use were observed for lung function, clinical score at 120 minutes, oxygen saturation at 60 minutes, and the need for repeat use of bronchodilators prior to discharge from the emergency department. No significant group difference was seen in relapse rates.Fewer children treated with anticholinergics plus SABA reported nausea and tremor compared with SABA alone; no significant group difference was observed for vomiting.
AUTHORS' CONCLUSIONS:
Children with an asthma exacerbation experience a lower risk of admission to hospital if they are treated with the combination of inhaled SABAs plus anticholinergic versus SABA alone. They also experience a greater improvement in lung function and less risk of nausea and tremor. Within this group, the findings suggested, but did not prove, the possibility of an effect modification, where intensity of anticholinergic treatment and asthma severity, could be associated with greater benefit.Further research is required to identify the characteristics of children that may benefit from anticholinergic use (e.g. age and asthma severity including mild exacerbation and impending respiratory failure) and the treatment modalities (dose, intensity, and duration) associated with most benefit from anticholinergic use better.

Reason I chose it

- indexed for MEDLINE, published within the past 7 years, covers all topics I was looking for
- Systematic review offers one of the highest levels of evidence from conclusions made from multiple sources
- it is published in Cochrane Database of Systematic Reviews, which is a well-known and trusted source.

Citation
BMC Pulm Med. 2016 Apr 30;16(1):65. doi: 10.1186/s12890-016-0223-3.

https://bmcpulmmed.biomedcentral.com/track/pdf/10.1186/s12890-016-0223-3

Title and Authors

Efficacy and safety of ipratropium bromide/albuterol compared with albuterol in patients with moderate-to-severe asthma: a randomized controlled trial.

Donohue JF, Wise R, Busse WW, Garfinkel S, Zubek VB, Ghafouri M, Manuel RC, Schlenker-Herceg R, Bleecker ER

Abstract

BACKGROUND:

Many patients with asthma require frequent rescue medication for acute symptoms despite appropriate controller therapies. Thus, determining the most effective relief regimen is important in the management of more severe asthma. This study's objective was to evaluate whether ipratropium bromide/albuterol metered-dose inhaler (CVT-MDI) provides more effective acute relief of bronchospasm in moderate-to-severe asthma than albuterol hydrofluoroalkaline (ALB-HFA) alone after 4 weeks.

METHODS:

In this double-blind, crossover study, patients who had been diagnosed with asthma for ≥1 year were randomized to two sequences of study medication "as needed" for symptom relief (1-7 day washout before second 4-week treatment period): CVT-MDI/ALB-HFA or ALB-HFA/CVT-MDI. On days 1 and 29 of each sequence, 6-hour serial spirometry was performed after administration of the study drug. Co-primary endpoints were FEV1 area under the curve (AUC0-6) and peak (post-dose) forced expiratory volume in 1 s (FEV1) response (change from test day baseline) after 4 weeks. The effects of "as needed" treatment with ALB-HFA/CVT-MDI were analyzed using mixed effect model repeated measures (MMRM).

RESULTS:

A total of 226 patients, ≥18 years old, with inadequately controlled, moderate-to-severe asthma were randomized. The study met both co-primary endpoints demonstrating a statistically significant treatment benefit of CVT-MDI versus ALB-HFA. FEV1 AUC0-6h response was 167 ml for ALB-HFA, 252 ml for CVT-MDI ($p < 0.0001$); peak FEV1 response was 357 ml for ALB-HFA, 434 ml for CVT-MDI ($p < 0.0001$). Adverse events were comparable across groups.

CONCLUSIONS:

CVT-MDI significantly improved acute bronchodilation over ALB-HFA alone after 4 weeks of "as-needed" use for symptom relief, with a similar safety profile. This suggests additive bronchodilator effects of β2-agonist and anticholinergic treatment in moderate-to-severe, symptomatic asthma.

Reason I chose it

- indexed for MEDLINE, published within the past 4 years
- it covers the variables I am looking for in my PICO search
- it was published the United States
- included 226 subjects, and was a double-blind RCT

Citation

J Pak Med Assoc. 2016 Mar;66(3):243-6.
https://jpma.org.pk/article-details/7648?article_id=7648

Title and Authors

Response to nebulized salbutamol versus combination with ipratropium bromide in children with acute severe asthma.

Memon BN, Parkash A, Ahmed Khan KM, Gowa MA, Bai C

Abstract

OBJECTIVE:

To compare the efficacy of nebulised salbutamol alone and in combination with ipratropium bromide in acute

severe asthma in children.
METHODS:
The randomised controlled trial was conducted at the National Institute of Child Health, Karachi, from October 2012 to March 2013, and comprised patients with acute severe asthma who were randomised into two equal groups. Group A patients received 3 doses of nebulised salbutamol alone (0.03 ml/kg/dose) at 15-minute intervals and Group B received 3 similar doses of salbutamol along with ipratropium (250 ug/dose). Acute severe asthma was categorised as serve exacerbation (clinical score >10) and moderate (5-10 score) based on Bentur Modification. Efficacy was measured after 5minutes of the last dose by change in severity score from severe exacerbation (baseline) to low score. SPSS 10 was used for statistical analysis.
RESULTS:
There were two groups of 100(50%) patients each. The mean age in Group A was 9.1±3 years and 9.3±2.8 years in Group B. Male-Female ratio in Group A was 1.5:1 and in Group B it was 1.2:1. In Group B, 93(93%) children showed improvement in clinical score (<10 score) while it was 84(84%) in Group A. There was better response in clinical score in Group A than Group B, but it was not significant (p>0.05).
CONCLUSIONS:
The combination of nebulised salbutamol along with ipratropium bromide in the treatment of acute asthma exacerbation was not superior to salbutamol alone.

Reason I chose it

- indexed for MEDLINE, published within the past 4 years
- it covers the variables I am looking for in my PICO search
- the 200 subjects were randomly assigned into groups to receive treatment

Summary of Evidence:

Author (Date) Level of Evidence	Sample/Setting (# of subjects/ studies, cohort definition etc)	Outcome(s) studied	Key Findings	Limitations and Biases
Kirkland et al. (2017) Meta-analysis	**MEDLINE, Embase, CINAHL, SCOPUS, LILACS, ProQuest Dissertations & Theses Global, EBM databases, and Cochrane Airways Group Register of Trials were searched. Articles searched ranged from 1946 to July 2016. **Inclusion criteria: 1) randomized/controlled studies that compared effectiveness of combined therapy of inhaled SABA + short-acting anticholinergics (SAAC) vs. SABA-only, in prevention of hospitalization of adults with acute asthma. 2) Subjects >16 years old. 3) Setting: acute care settings or emergency departments **Found 23 studies that fit criteria, totaling 2724 subjects. Studies included were from South Asia,	**primary: need of hospitalization as decided by physician **secondary: length of stay in ED, adverse events, PFT data, symptom scores, quality of life, amount of additional bronchodilator treatments needed, and amount of relapse	**patients with severe asthma exacerbations using the combination of SAAC + SABA, had lower hospitalizations. However, this finding was not seen in patients with mild to moderate exacerbations. **in combination therapy, the use of ipratropium bromide is as effective as the use of another SAAC **combination of SAAC + SABA, versus SABA monotherapy, had greater improvement in FEV1 and peak expiratory flow. **patients taking SAAC + SABA, versus SABA monotherapy, seemed to report more adverse effects (ie: dry mouth, nausea, headache, tremor, anxiety, agitation, palpitations, blurred vision, chest retractions) **there is not enough evidence to compare single vs. multiple doses of inhalation therapy, in the effectiveness in preventing hospitalizations	**authors noted: "Most studies were rated at unclear or high risk of bias", quality of evidence "ranged from very low to moderate", 14/23 of the studies were assessed to have high risk of bias due to "lack of double blinding, incomplete reporting of adverse events, and receiving industry funding with no clarification of the role that company had on outcome reporting or manuscript preparation" **the respective inclusion criteria of the studies and hospital admission criteria may impact the outcomes in the study **patients may have other pulmonary diseases that impact their outcome

	Australia, Canada, Colombia, Japan, New Zealand, Spain, UK, USA, and Uraguay.			
Griffiths et al. (2013) Systematic Review	**MEDLINE, EMBASE, and CINAHL were searched. Articles searched ranged from 1966 to July 2000. ** Inclusion criteria: 1) RCT that compares the use of combined inhaled anticholinergic drug + SABA versus SABA-only, in treating acute asthma exacerbations. 2) Subjects from 18 months to 18 years old. 2) Setting: acute care settings or emergency departments **Found 20 studies that fit criteria, 2697 total subjects, majority had moderate to severe exacerbations.	**primary: hospital admission **secondary: change in PFT, change in baseline clinical score, oxygen saturation, amount of additional bronchodilator treatments needed, need for systemic corticosteroids, adverse effects, relapse rate	**objective to see if the addition of anticholinergic to SABA will improve symptoms in children with asthma exacerbations, as well as if there is a difference in adverse effects between the two regimens. **the combination of anticholinergics with SABA, versus SABA monotherapy, showed a reduction in hospital admission (17/100 vs 23/100 respectively) **the combination regimen had better outcomes in lung function, clinical improvement within 2 hours, oxygen saturation within 1 hour, and the need for additional bronchodilators before discharge. **the combination regimen had fewer reports of nausea and tremor, compared with SABA monotherapy.	**multiple tools were used to assess risk of bias in the included studies. 9/20 trials were considered low risk of selection bias, 9/20 has unclear risk, and 1/20 was high risk. **results are limited to the younger age groups; and outcome of admission is dependent on individual physician's deliberation **over 50% of the studies were published in the US, so outcome may not be as applicable in other countries. **the quality of the review depends on the quality of the data provided from the included studies.
Donohue et al. (2016) RCT-crossover	**double blind, crossover design, to study whether combination of ipratropium bromide/albuterol metered-dose inhaler (Combivent) (CVT-MDI) is more effective at relieving moderate to severe asthma exacerbation, than Albuterol HFA alone. ** Inclusion criteria: 1) 18+ years old with diagnosis of asthma for at least 1 year, baseline FEV<80% with post-bronchodilator reversibility. >12%, and Asthma Control Questionnaire (ACQ) score ≥1.5 2) Setting: "study centers in the United States" **226 subjects randomly assigned into either the group first given Albuterol HFA inhaler then CVT-MDI; or the other group given CVT-MDI then Albuterol HFA. With the crossover design,	**primary: FEV1 area-under-the-curve compared to baseline, and peak FEV1 response. **secondary: mini Asthma Quality of Life Questionnaire response, ACQ response, and the # of puffs of respective medication used during each treatment	**bronchodilator response was longer in CVT-MDI use (137.5min), compared to Albuterol HFA (66.6min). **peak-FEV1 response noted at 4 weeks compared with response at baseline, was better in CVT-MDI (59.2%), compared to Albuterol HFA (45.6%). **reported adverse effects were greater in CVT-MDI (22.8%, more cough), compared to Albuterol HFA (14%); severe asthma exacerbations were seen in 7 patients on CVT-MDI, compared with 2 patients on Albuterol HFA.	**proper assessment of medication effectiveness depends on individual patient's compliance, self-reporting, and competence in using asthma monitor at home. **potential bias due to funding provided by Boehringer Ingelheim Pharmaceuticals, Inc. **study results may have been skewed by those patients who prematurely stopped the trial medications. **crossover studies have the inherent limitation of a "carryover" effect that may carry the experience from the first treatment phase to the second treatment phase.

	222 patients were treated with Albuterol, and 219 were treated with CVT-MDI.			
Memon et al. (2016) RCT	**RCT was conducted at the National Institute of Child Health in Karachi, Pakistan. **200 subjects, ranging from 2-14 years old, presented in the setting of the ER with severe asthma exacerbation, randomly assigned to the two groups of either Albuterol-only, or combined Albuterol + Ipratropium bromide.	**clinical score by BenturModification measured acute severe asthma (ASA) by assessing respiratory rate, heart rate, presence of wheezing, and usage of accessory muscle; each part graded from 0-3, where 5-10 showed moderate asthma, and >10 severe.	**this RCT wanted to see if there was a difference between nebulized Albuterol as monotherapy, versus having it combined with Ipratropium bromide. **Duo-therapy had 93% improvement, while the monotherapy had 84% (the study stated that this is not statistically significant)	**published in Pakistan, where patients' asthma triggers may differ from those in the US, and they may have different health issues. Therefore, the outcome from medication may not relate. **has limitation of small sample size, and unclear conclusion of whether or not findings were significant.

Conclusions:

Kirkland et al. (2017)	SAAC + SABA combination lowered hospitalizations and improved FEV1 and peak expiratory flow in patients with acute asthma, better than SABA monotherapy. The combination was particularly effective in severe exacerbations, than in mild to moderate exacerbations. Unfortunately, it was the combination therapy that seemed to report more adverse effects (ie: dry mouth, nausea, headache, tremor, anxiety, agitation, palpitations, blurred vision, chest retractions).
Griffiths et al. (2013)	Supports the use of the combination of anticholinergics with SABA, over SABA monotherapy to treat acute moderate to severe asthma in children (since most included studies had managed moderate/severe asthma, and not mild asthma), and reduce hospital admission. It is suggested to give "three doses of 250 mcg or two doses of 500 mcg of ipratropium bromide administered by nebulizer over 60 to 90 minutes, in combination with a SABA". The combination regimen had fewer reports of nausea and tremor, compared with SABA monotherapy.
Donohue et al. (2016)	Concludes that fixed-dose combination of short-acting anticholinergic with a SABA is more effective at improving lung function in patients with moderate to severe asthma, as compared to having SABA monotherapy. It should be noted, however, that adverse effects were reported more in the combination therapy, compared with SABA alone.
Memon et al. (2016)	Combination therapy of Albuterol + Ipratropium bromide showed 93% improvement in clinical scores, while the Albuterol monotherapy had 84%. The study stated that this is not statistically significant, however, conclude that clinical score is reduced more in combination therapy.

These articles are listed in the order of how I weigh them in terms of strength of evidence. Kirkland (2017) is weighed the most because it is a Meta-analysis, published the most recently of the collected articles. Next comes Griffiths (2013), which was published earlier, but is a Systematic review. These two types of articles help provide the most comprehensive review of articles, a high number of total patient subjects (2724 and 2697 respectively), and are the highest level of evidence to help answer the PICO question. Additionally, they were published in Cochrane Database of Systematic Reviews, a highly trusted database. Donohue (2016) and Memon (2016) are RCTs that also helped answer the PICO question. They are ranked in this order because the former was conducted in the United States, while the latter was from Pakistan and had a questionable conclusion. Also, they had 226 and 200 total patient subjects respectively; which is relatively low, and takes away from the power of the study.

The conclusions formed from these articles indicate the effectiveness of combination therapy of anticholinergics with SABA, over SABA monotherapy to treat acute moderate to severe asthma in children and adults. Three of the articles compared adverse effects in both therapies: Kirkland (2017) and Donohue (2016) suggest that the combination therapy has more adverse effects, while Griffiths (2013) reported fewer reports of nausea and tremor

in combination therapy compared with SABA monotherapy.

Magnitude of any Effects

According to the articles, there is shown to be a greater effect with the use of combined therapy of anticholinergics with SABA, over SABA monotherapy, to treat acute moderate to severe asthma in children and adults. This positive effect was not studied in the treatment of mild asthma. In regards to which therapy has more adverse effects, there is no mutual conclusion between the studies.

Clinical Significance

There is enough evidence to show that combined therapy of anticholinergics with SABA should be considered over SABA monotherapy when treating moderate to severe asthma exacerbations. It can reduce the need for hospitalization of these patients. Additionally, in three of the studies that measured outcomes in terms of improved lung function, the combined therapy showed to be more effective.

Clinical Bottom Line

The question to be answered was: In asthma patients with exacerbations, is nebulized Albuterol as effective as DuoNeb at relieving symptoms? From searching on Cochrane, PubMed and Google Scholar, 4 articles that were relevant to the search terms were picked. In all, there is 1 meta-analysis, 1 systematic review, and 2 RCTs which all covered the topics and variables in question.

Based on the articles and information gathered, there is enough evidence proving that a combination of anticholinergics (ie: Ipratropium bromide) with a SABA (ie: Albuterol sulfate) is more effective at resolving the symptoms of asthma exacerbations, than with monotherapy of SABA. Three out of four studies reviewed specified that that the combination is more effective and recommended to be used in moderate to severe asthma, as compared to mild asthma. Also, the use of ipratropium bromide may be as effective as the use of another anticholinergic drug. There are conflicting conclusions regarding which regimen has more adverse effects: two out of three studies report more adverse effects from combination therapy, while one study reported less.

If a colleague asks about which therapy to consider to treat their patient with moderate to severe asthma exacerbation, it is recommend to prescribe the combination of anticholinergics with the SABA. To prevent potential complications with combination therapy, a period of observation should be considered.