Drug Class Review:
Quick-relief Medications for Asthma

Preliminary Scan Report #7

February 2018

This report is intended only for state employees in states participating in the Drug Effectiveness Review Project (DERP). Do not distribute outside your state Medicaid agency and public agency partners.

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Objective

The purpose of this preliminary updated literature scan process is to provide the Participating Organizations with a preview of the volume and nature of new research that has emerged subsequent to the previous full review process. Provision of the new research presented in this report is meant to assist with Participating Organizations' consideration of allocating resources toward updating the report. The literature search for this report focuses on new randomized controlled trials and comparative effectiveness reviews as well as actions taken by the U.S. Food and Drug Administration (FDA) since the last report. Other important studies could exist. Comprehensive review, quality assessment, and synthesis of evidence are not included in a scan.

Date of Last Update Report

Update #1, October 2008 (searches through May 2008)

Date of Last Preliminary Update Scan Report

Scan #6, January 2017

METHODS FOR SCAN

Scope and Key Questions

1. What is the comparative efficacy and effectiveness of quick-relief medications used to treat outpatients with bronchospasm due to asthma, or to prevent or treat exercise-induced bronchospasm?
2. What is the comparative incidence and severity of adverse events reported from using quick-relief medications to treat outpatients with bronchospasm due to asthma, or to prevent or treat exercise-induced bronchospasm?
3. Are there subgroups of patients for which quick-relief medications used to treat outpatients with bronchospasm due to asthma or to prevent or treat exercise-induced bronchospasm, differ in efficacy, effectiveness, or frequency and severity of adverse events?

Inclusion Criteria

Populations

1. Adults or children with asthma including those with exercise-induced bronchospasm

Interventions

1. Inhaled short-acting beta$_2$-agonists (SABA) via MDI or nebulized solution
    a. Albuterol, levalbuterol, pirbuterol
2. Short-acting anticholinergics
    a. Ipratropium bromide
3. Combination products
    a. Ipratropium bromide with albuterol

Excluded interventions:

1. Systemic corticosteroids
2. Inhaled Corticosteroids
3. Inhaled Cromolyn
4. Long-acting beta-agonists
5. Long-acting anticholinergics

Effectiveness Outcomes

1. Symptoms: e.g., cough, wheezing, shortness of breath
2. Change in treatment regimen for the exacerbation
3. Healthcare utilization: length of stay in the ER or other clinical facility, need for re-treatment within 24 hours, hospital admissions, length of hospital stay
4. For exercise induced bronchospasm: exercise tolerance, symptoms
5. Mortality

Harms Outcomes

1. Overall adverse events reported
2. Withdrawals due to adverse events
3. Serious adverse events

Setting

1. Outpatient settings including urgent care facilities and the emergency room

Study Designs (from Update Report)

1. For effectiveness: Head-to-head RCTs or controlled clinical trials with total sample size ≥ 20. No minimum duration of follow-up.
2. For adverse events: Head-to-head RCTs, controlled clinical trials, or observational studies with sample size ≥ 10. No minimum duration of follow-up.

Literature Search

To identify relevant citations, we searched Ovid MEDLINE® and Ovid MEDLINE® In-Process & Other Non-Indexed Citations from November 2016 through December 2017, as well as the Cochrane Central Register of Controlled Trials from 2016 through 2017, using terms for specific included drugs and limits for English language and humans. Literature searches included any new drugs identified in the present scan in addition to those included in Table 1. We also searched the FDA website to identify new drugs, new populations, and new serious harms (e.g., boxed warnings). To identify new drugs, we also searched CenterWatch (http://www.centerwatch.com), a privately-owned database of clinical trials information, and conducted a limited internet search. To identify comparative effectiveness reviews, we searched the websites of the Agency for Healthcare Research and Quality), the Canadian Agency for Drugs and Technology in Health, the VA Evidence-based Synthesis Program, and University of York Centre for Reviews and Dissemination.

Study Selection

We included only potentially relevant randomized controlled trials and comparative effectiveness reviews. One reviewer assessed abstracts of citations identified from literature searches for inclusion, using the criteria described above.

RESULTS

New Drugs

Identified in this Preliminary Update Scan

None.

Identified in previous Preliminary Update Scans

Albuterol sulfate (PROAIR RESPICLICK): a $beta_2$-adremergic agonist approved March 31, 2015 and indicated for the treatment or prevention of bronchospasm in patients 12 years of age and older with reversible obstructive airway disease and prevention of exercise-induced bronchospasm in patients 12 years of age and older.

New Serious Harms (e.g. boxed warnings)

Identified in this Preliminary Update Scan

None.

Identified in previous Preliminary Update Scans

None.

Comparative Effectiveness Reviews

Identified in this Preliminary Update Scan

None.

Identified in previous Preliminary Update Scans

None.

Randomized Controlled Trials

Medline searches for the current scan resulted in 241 publications, with only 1 head to head trial of a combination of ipratropium and albuterol compared with albuterol alone for asthma symptom relief (Table 1). Cumulatively, since the last update report, we have identified a total of 9 head-to-head trials (Table 1). Five of the 9 head-to-head trials compared different delivery methods of the same drug. Abstracts of the head-to-head trials are available in the appendix. The abstracts of the active-controlled trial and the placebo-controlled trial are available upon request.

Table 1. Potentially relevant trials of drugs for quick relief of asthma symptoms (N=9)

Author, Year	Comparison	N	Focus
Head-to-head drug			
Andrews, 2009	Levalbuterol nebulized Racemic albuterol nebulized	81	Children aged 6-18
Punj, 2009	Levosalbutamol Racemic Salbutamol	60	Children aged 5-18
Wilkinson, 2011	Racemic albuterol nebulized Levalbuterol nebulized	99	Children aged 6-17
Donohue, 2016	Ipratropium bromide/albuterol Albuterol	226	Adults with moderate-to-severe asthma
Head-to-head delivery method			
Bar-Yishay, 2011	Salbutamol 0.30 mg/kg by mask Salbutamol 0.30 mg/kg by hood	26	Wheezy infants
Direkwatanachai, 2011	Salbutamol pMDI with spacer Salbutamol with DPI Salbutamol 0.15 mg/kg nebulized	216	Children aged 5-18 in Thailand
Dhuper, 2011	Albuterol with MDI/spacer Albuterol Cumulatively there are nebulized	60	Inner city adults; crossover study
Rotta, 2010	Salbutamol pMDI with spacer Salbutamol nebulized	46	Children aged 1-5
Sabato, 2011	Nebulized albuterol Albuterol MDI	149	Children aged 0-18

SUMMARY

Since the last update report, we have identified 1 newly approved drug: albuterol sulfate (PROAIR RESPICLICK). Cumulatively, there are 9 new head-to-head trials since the last report, including 1 new this scan, and 5 comparisons of different delivery methods, including nebulization. We have not identified any new serious harms or comparative effectiveness reviews in current or previous scans conducted since the last update report.

APPENDIX A. Abstracts of potentially relevant new trials for quick relief of asthma symptoms (N=9)

Head-to-head trials (drug vs. drug, N=4)

Andrews T. McGintee E. Mittal MK. Tyler L. Chew A. Zhang X. Pawlowski N. Zorc JJ. (2009). "High-dose continuous nebulized levalbuterol for pediatric status asthmaticus: a randomized trial."Journal of Pediatrics 155(2):205-10.

> OBJECTIVE: To assess the use of high-dose continuous levalbuterol (LEV), the single active (R)-enantiomer of racemic albuterol (RAC), in the treatment of status asthmaticus. STUDY DESIGN: Children age 6 to 18 years with severe asthma exacerbation were enrolled in this randomized, double-blind trial if they failed initial emergency department (ED) therapy with RAC and systemic steroids. Subjects received equipotent doses of RAC (20 mg/hour) or LEV (10 mg/hour) within a standardized inpatient protocol. Blood samples for measurements of albuterol enantiomer, potassium, and glucose levels were obtained from the first 40 subjects. The median time until discontinuation of continuous therapy was compared using the rank-sum test, and other outcomes were compared using general linear mixed models. RESULTS: A total of 81 subjects (40 in the RAC group and 41 in the LEV group) were enrolled; the 2 groups were similar at baseline. Both groups tolerated continuous therapy with similar changes in heart rate and serum potassium and glucose levels but higher serum (S)-albuterol concentrations in the subjects treated with RAC. The median time for continuous therapy was similar in the RAC and LEV groups (18.3 hours vs 16.0 hours), as were the other clinical measures. CONCLUSIONS: Substituting high-dose continuous LEV for RAC did not reduce the time on continuous therapy and had similar adverse effects in children who had failed initial treatment with RAC.

Punj A. Prakash A. Bhasin A. (2009) "Levosalbutamol vs racemic salbutamol in the treatment of acute exacerbation of asthma." Indian Journal of Pediatrics 76(11):1131-5. 2009 Nov.

> OBJECTIVE: To compare efficacy and tolerability of levosalbutamol (Group 1) and racemic salbutamol (Group 2) for the treatment of acute exacerbation of asthma in children age 5 to 18 yr. METHODS: A randomized double blind clinical study involving 60 children was undertaken between October' 06 to December' 07. RESULTS: The following baseline clinical characteristic were recorded initially and after giving 3 nebulizations at 20 min intervals in the Ist hour of presentation viz respiratory rate (RR), heart rate (HR), oxygen saturation in room air SPO2, PEFR (peak expiratory flow rate), serum K+ level and asthma score. In Group 1 patients (levosalbutamol), there was significant increment in SPO2 and PEFR (P CONCLUSION: Levosalbutamol appears to be more efficacious than racemic

salbutamol in terms of improvement in PEFR, SPO2 and asthma score while deleterious effects of tachycardia and fall in serum K+ were seen with racemic salbutamol.

Wilkinson M. Bulloch B. Garcia-Filion P. Keahey L. Efficacy of racemic albuterol versus levalbuterol used as a continuous nebulization for the treatment of acute asthma exacerbations: a randomized, double-blind, clinical trial. Journal of Asthma. 48(2):188-93, 2011 Mar.

OBJECTIVE: To compare racemic albuterol (RAC) with levalbuterol (LEV) in continuous form for the treatment of acute pediatric asthma exacerbations in the emergency department.

STUDY DESIGN: Children between the ages of 6 and 17 inclusive were enrolled if they had a history of asthma, presented to the emergency department with an acute asthma exacerbation, and had an initial forced expiratory volume in 1 second (FEV1) <70% predicted. Patients were then randomized to receive either 7.5 mg of RAC or 3.75 mg of LEV over 1 hour, in addition to standard asthma therapies. Spirometry and asthma scoring were performed at the end of the first hour, and a second hour-long nebulization with the same drug was administered if deemed necessary. Spirometry and asthma scoring were again performed and the final disposition was recorded. As a second, optional part of the study, baseline serum albuterol levels were collected on some patients before treatment.

RESULTS: A total of 99 patients completed the study (44 RAC and 55 LEV). Baseline characteristics were similar except that the RAC group had a higher baseline asthma score. Children in the RAC group had a greater improvement in their FEV1 (p = .043) as well as in their asthma scores (p = .01) after 1 hour of continuous treatment compared to the LEV group. The greater improvement in asthma scores was maintained after the second hour of continuous therapy in the RAC group (p = .008) but not for FEV1 measurements (p = .57). There were no differences between groups for changes in heart rate, respiratory rate, oxygen saturation, or rates of admission.

CONCLUSIONS: At the doses used, RAC appears to be superior to LEV with respect to changes in FEV1 and asthma score. There was no significant difference between the drugs with respect to admission rates or side-effect profile.

Donohue, J. F., et al. (2016). "Efficacy and safety of ipratropium bromide/albuterol compared with albuterol in patients with moderate-to-severe asthma: a randomized controlled trial." BMC Pulmonary Medicine **16**(1): 65.

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 beta2-agonist and anticholinergic treatment in moderate-to-severe, symptomatic asthma.

TRIAL REGISTRATION: ClinicalTrials.gov No.: NCT00818454 ; Registered November 16, 2009.

Head-to-head trials (delivery method vs. delivery method, N=5)

Bar-Yishay E. Avital A. Springer C. Amirav I. Lung function response to bronchodilator nebulization via hood in wheezy infants: a pilot study. Israel Medical Association Journal: Imaj. 13(1):39-43, 2011 Jan.

BACKGROUND: In infants, small volume nebulizers with a face mask are commonly used to facilitate aerosol therapy. However, infants may be disturbed by mask application, causing poor mask-to-face seal and thus reducing the dose delivered.

OBJECTIVES: To compare lung function response to bronchodilator nebulization via two delivery devices: hood versus mask.

METHODS: We studied 26 recurrently wheezy infants aged 45.8 weeks (95% confidence interval 39.6-52.0). Inhalations of 0.30 mg/kg salbutamol were administered in two alliqots 30 minutes apart using mask and hood in alternating order (M+H or H+M). Response to inhalations was measured by maximal expiratory flows at functional residual capacity (V'maxFRC) at 5 minute intervals after each dose, and area under the V'maxFRC curve (AUC) was documented.

RESULTS: A small but significant response to salbutamol was observed following the second inhalation with V'maxFRC, improving by 31.7% (7.2-56.2, P (0.02) and AUC by 425% x min (-154, 1004; P < 0.02). The improvement following salbutamol was similar by both delivery modalities but with a small but significantly better response when H was used after M (P < 0.01).

CONCLUSIONS: Nebulized salbutamol induced a variable but positive response in wheezy infants. Salbutamol via hood was as effective as conventional face mask delivery. Since it is simple and patient-friendly, it could replace the face mask method particularly with uncooperative infants.

Direkwatanachai C. Teeratakulpisarn J. Suntornlohanakul S. Trakultivakorn M. Ngamphaiboon J. Wongpitoon N. Vangveeravong M. Comparison of salbutamol efficacy in children--via the metered-dose inhaler (MDI) with Volumatic spacer and via the dry powder inhaler, Easyhaler, with the nebulizer--in mild to moderate asthma exacerbation: a multicenter, randomized study. Asian Pacific Journal of Allergy & Immunology. 29(1):25-33, 2011 Mar.

BACKGROUND: Beta(2) agonist administered via a nebulizer is the standard treatment for acute asthma exacerbation. There are some limitations for the use of nebulization. We conducted a study to determine the efficacy of salbutamol administered via the pMDI with Volumatic spacer and the Easyhaler (DPI) compared to nebulization in mild to moderate asthma exacerbations in children.

METHODS: A multicenter, randomized, controlled study was conducted in children between 5 and 18 years of age who presented at an emergency or outpatient department. They were randomized to receive either 6 puffs of salbutamol via the pMDI with Volumatic spacer, or via the Easyhaler, or 0.15 mg/kg of salbutamol nebulized via oxygen (or compressed air). The primary outcome was the clinical response which was assessed using the modified Wood's asthma score. The secondary outcomes were: hospitalization, asthma revisit within 3 days, systemic corticosteroid use and adverse events. The clinical score, oxygen saturation, PR, RR, BP and adverse events were recorded at time 0 (before treatment) and 20, 40 and 60 minutes after drug administration.

RESULTS: There were no statistically significant differences in the clinical response between the three groups at the 1st, 2nd or 3rd dose or for the SpO(2) or the respiratory rate while the children in the Easyhaler group had significantly less tachycardia after the 2nd dose. No significant adverse events were noted among the three groups.

CONCLUSIONS: Salbutamol administered via pMDI with Volumatic spacer or DPI (Easyhaler) are as effective as salbutamol given via a nebulizer in providing effective relief of mild to moderate severity acute asthma exacerbation in children between 5 and 18 years of age.

Dhuper S. Chandra A. Ahmed A. Bista S. Moghekar A. Verma R. Chong C. Shim C. Cohen H. Choksi S. Efficacy and cost comparisons of bronchodilatator administration between metered dose inhalers with disposable spacers and nebulizers for acute asthma treatment. Journal of Emergency Medicine. 40(3):247-55, 2011 Mar.

BACKGROUND: Despite demonstration of equivalent efficacy of beta agonist delivery using a metered dose inhaler (MDI) with spacer vs. nebulizer in asthma patients, use of a nebulizer remains standard practice.

OBJECTIVES: We hypothesize that beta agonist delivery with a MDI/disposable spacer combination is an effective and low-cost alternative to nebulizer delivery for acute asthma in an inner-city population.

METHODS: This study was a prospective, randomized, double-blinded, placebo-controlled trial with 60 acute asthma adult patients in two inner-city emergency departments. Subjects (n = 60) received albuterol with either a MDI/spacer combination or nebulizer. The spacer group (n = 29) received albuterol by MDI/spacer followed by placebo nebulization. The nebulizer group (n = 29) received placebo by MDI/spacer followed by albuterol nebulization. Peak flows, symptom scores, and need for rescue bronchodilatator were monitored. Median values were compared with the Kolmogorov-Smirnov test.

RESULTS: Patients in the two randomized groups had similar baseline characteristics. The severity of asthma exacerbation, median peak flows, and symptom scores were not significantly different between the two groups. The median (interquartile range) improvement in peak flow was 120 (75-180) L/min vs. 120 (80-155) L/min in the spacer and nebulizer groups, respectively (p = 0.56). The median improvement in the symptom score was 7 (5-9) vs. 7 (4-9) in the spacer and nebulizer groups, respectively (p = 0.78). The median cost of treatment per patient was $10.11 ($10.03-$10.28) vs. $18.26 ($9.88-$22.45) in the spacer and nebulizer groups, respectively (p < 0.001).

CONCLUSION: There is no evidence of superiority of nebulizer to MDI/spacer beta agonist delivery for emergency management of acute asthma in the inner-city adult population. MDI/spacer may be a more economical alternative to nebulizer delivery.

Rotta ET. Amantea SL. Froehlich PE. Becker A. Plasma concentrations of salbutamol in the treatment of acute asthma in a pediatric emergency. Could age be a parameter of influence?European Journal of Clinical Pharmacology. 66(6):605-10, 2010 Jun.

OBJECTIVE: The objective was to determine if the plasma concentrations of salbutamol, obtained during inhalation treatment of infantile acute asthma, are influenced by age range and by the aerosol system used.

METHOD: A randomized clinical trial was conducted in 46 children (1-5 years of age) with a diagnosis of acute asthma crisis, established in an emergency room pediatric service. Twenty-five children received salbutamol using a pressurized metered-dose inhaler with spacer (50 microg/kg), and 21 children received salbutamol by nebulization (150 microg/kg),three times during a 1-h period. At the end of the treatment, one blood sample was drawn and the plasma was stored for later determination of salbutamol concentration (liquid chromatography). Salbutamol plasma concentrations were compared in two age groups (< or =2 years and >2 years of age). The type of device used (pressurized metered-dose inhaler or nebulizer) and the need of hospitalization were also tested. The Mann-Whitney U test was used with the level of significance set at 5% ($P < 0.05$).

RESULTS: No differences were detected regarding either the aerosol delivery system used or the need for hospitalization in relation to the plasma concentrations of salbutamol. However, higher plasma levels were found in patients >2 years vs patients < or =2 years [median (IQR): 9.40 (6.32-18.22) vs. 4.65 (2.77-10.10) ng/mL], demonstrating a significance difference ($P = 0.05$).

CONCLUSION: Salbutamol plasma concentrations were influenced by age group of the patients submitted to inhalation therapy, even with doses adjusted for body weight. After correcting for the differences in the biovailabilities of the delivery systems, the concentrations were independent of the aerosol delivery device used.

Sabato K. Ward P. Hawk W. Gildengorin V. Asselin JM. Randomized controlled trial of a breath-actuated nebulizer in pediatric asthma patients in the emergency department.

Respiratory Care. 56(6):761-70, 2011 Jun.

BACKGROUND: Bronchodilator treatment for asthma can be provided with various aerosol-generating devices and methods. There have been no randomized trials of a breath-actuated nebulizer versus continuous 1-hour nebulization and/or small-volume constant-output nebulizer in pediatric asthma patients.

METHODS: We conducted a randomized study of one-time albuterol treatment with the AeroEclipse breath-actuated nebulizer versus standard therapy (single treatment via small-volume nebulizer or 1-hour of continuous nebulized albuterol) in pediatric asthma patients in the emergency department. Eligible patients were those admitted to the emergency department, 0 months to 18 years of age, who presented with asthma or wheezing. We assessed all the patients with our clinical asthma scoring system and peak-flow measurement if possible. We stratified the patients by clinical asthma score and weight, and then randomized them to receive their initial albuterol treatment in the emergency department via either AeroEclipse or standard therapy. We recorded time in the emergency department, change in clinical asthma score, need for additional bronchodilator treatments, need for admission, patient response, ability to actuate the AeroEclipse, and adverse effects.

RESULTS: We enrolled 149 patients between October 14, 2004 and November 11, 2005, and we randomized 84 patients to AeroEclipse and 65 to standard therapy. The cohort's average age was 5.5 years. There were no significant differences in demographics. The initial mean clinical asthma scores were 5.1 +/- 2.4 in the AeroEclipse group, and 5.1 +/- 2.1 in the standard-therapy group. Time in the emergency department was not different (AeroEclipse 102 min, standard therapy 125 min, P = .10), but the AeroEclipse group had a significantly greater improvement in clinical asthma score (1.9 +/- 1.2 vs 1.2 +/- 1.4, P = .001) and respiratory rate (P = .002), and significantly lower admission rate (38% vs 57%, P = .03). There was no difference in adverse effects.

CONCLUSIONS: Although AeroEclipse did not reduce the time in the ED, it significantly improved clinical asthma score, decreased admissions, and decreased respiratory rate.