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Drug Class Literature Scan: Beta Agonists, Inhaled Short-Acting

Date of Review: July 2019

Date of Last Review: September 2015
Literature Search: September/01/2015 – 06/06/2019

Current Status of PDL Class:
See **Appendix 1**.

Purpose of Review:
The purpose of this literature scan is to provide new comparative effectiveness and safety evidence for short-acting beta agonists (SABA) medications published since the last literature scan.

Conclusions:
- New evidence to provide guidance for the preferred drug list (PDL) was synthesized from two new guidelines from the National Institute for Health and Care Excellence (NICE), and two systematic reviews from Cochrane Systematic Reviews.[1-4]
- The identified literature supports current policy and prior authorization criteria for short-acting beta agonist (SABA) medications in the treatment of asthma, chronic obstructive pulmonary disease (COPD), adults with cough or bronchitis as well as bronchiolitis in infants and children.

Hospitalizations
- Patients presenting to the emergency department (ED) who received combination SABA and inhaled anticholinergic therapy were less likely to be hospitalized (risk ratio [RR] 0.72, 95% confidence interval [CI] 0.59 to 0.87; participants = 2120; studies = 16; I^2 = 12%; moderate quality of evidence).[1] An estimated 65 fewer patients per 1000 would require hospitalization after receiving combination therapy (95% 30 to 95), compared to 231 per 1000 patients receiving SABA alone.[1] Although combination inhaled therapy was more effective than SABA treatment alone in reducing hospitalization 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).[1]

Recommendations:
- Recommend no changes to the current PDL for inhaled short-acting beta agonist medications (SABAs) based upon clinical efficacy.
- Evaluate comparative drug costs in executive session.

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Summary of Prior Reviews and Current Policy

- As of September 2015, SABAs were delineated into their own PDL class, separate from maintenance inhaler therapies for the treatment of asthma and COPD.
- In adults and children with asthma and adults with COPD there remained insufficient evidence to determine relative differences in efficacy or effectiveness between albuterol and levalbuterol and between the different inhalation formulations.
- There was insufficient evidence to determine a relative difference in efficacy, effectiveness, safety or adverse events in subgroups of patients' base demographics, comorbidities or pregnancy with short-acting, inhaled beta-agonist medications (SABAs).
- Albuterol solution, nebulized solution and HFA are preferred products on the PDL. There is 100% utilization of preferred therapies.

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. A summary of the clinical trials is available in **Appendix 2** with abstracts presented in **Appendix 3**. The Medline search strategy used for this literature scan is available in **Appendix 4**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:

Cochrane - Combined inhaled Beta-agonist and Anticholinergic Agents for Emergency Management in Adults with Asthma

Inhaled short-acting anticholinergics (SAAC) and SABA are effective therapies for adult patients with acute asthma who present to the ED.[1] A systematic search and meta-analysis was conducted regarding the effectiveness of combined inhaled therapy (SAAC + SABA agents) vs. SABA alone to reduce hospitalizations in adult patients presenting to the ED with an exacerbation of asthma. Randomized or controlled clinical trials comparing the effectiveness of combined inhaled therapy (SAAC and SABA) to SABA treatment alone to prevent hospitalizations in adults (16 y/o or older) with acute asthma in the emergency department were considered for inclusion. Studies which included less than 20% of the total patient population as having comorbid COPD and having data where by patients without comorbid COPD could be extracted were also included for analysis.[1] Included were 23 studies of high-risk or unclear bias that involved a total of 2724 enrolled patients. The primary outcome measure was inclusive of the proportion of patients requiring hospitalization. Secondary outcomes were also inclusive of ED length of stay, number of bronchodilator treatments required, adverse events, symptom scores, quality of life and continuous data from pulmonary function testing.

Overall, patients receiving combination inhaled therapy were less likely to be hospitalized (RR 0.72, 95% CI 0.59 to 0.87; N = 2120; studies = 16; I^2 = 12%; moderate quality of evidence).[1] An estimated 65 fewer patients per 1000 would require hospitalization after receiving combination therapy (95% 30 to 95), compared to 231 per 1000 patients receiving SABA alone.[1] Although combination inhaled therapy was more effective than SABA treatment alone in reducing hospitalization in patients with severe asthma exacerbations, but not for participants with mild or moderate exacerbations (test for difference between subgroups P = 0.02).[1]
Patients 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.[1] 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).[1] 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.[1]

Cochrane: Beta-2-agonists for acute cough or a clinical diagnosis of acute bronchitis

A systematic review and sensitivity analysis was conducted in determining whether beta-2 agonists (oral and inhaled albuterol, and inhaled fenoterol [not available in the US]) improve acute bronchitis symptoms in people with no underlying pulmonary disease such as asthma, COPD or pulmonary fibrosis.[2] Primary study outcomes were daily cough scores, the number of patients still coughing at the end of the trial and adverse effects from the medication regimen being evaluated. Secondary outcomes were inclusive of but not limited to presentation characteristics of the cough, limitations in daily activities of living and general well-being. Randomized controlled trials (RCTs) which allocated patients (adults, or children over two years of age) with acute bronchitis or acute cough and without known pulmonary disease to beta-2-agonist versus placebo, no treatment or alternative treatment were considered for inclusion.[2] Excluded were studies which contained patients who had pre-existing pulmonary disease, cystic fibrosis and another acute respiratory illness such as sinusitis, pertussis or pneumonia. Eligible trials in children and adult population were analyzed separately.

Two trials of moderate quality in children (n = 134) with no evidence of airflow restriction did not find any benefits from oral beta-2- agonists.[2] Five trials in adults (n = 418) had mixed results but overall summary statistics did not reveal any significant benefits from oral (3 trials) nor from inhaled (3 trials) beta-2-agonists. Three studies with low-quality evidence demonstrated no significant differences in daily cough scores, nor in the percentage of adults still coughing after seven days (control group 71%; RR 0.86, 95% CI 0.63 to 1.18; 220 participants).[2] In one trial, subgroups with evidence of airflow limitation had lower symptom scores if given beta-2-agonists. However investigators noted quicker resolution of cough with beta-2-agonists were those with a higher proportion of people wheezing at baseline.

Authors concluded that at the time of this systematic review there was no evidence to support the use of beta-2-agonists in children (over 2 years of age) or adults with acute cough who do not have evidence of airflow restriction. Beta-2-agonists may reduce symptoms, including cough, in people with evidence of airflow restriction. However, this potential benefit is not well supported by the available data and must be weighed against the adverse effects associated with their use.

After review, twenty-four systematic reviews were excluded due to poor quality, wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

New Guidelines:

NICE- Diagnosis & Management of Bronchiolitis in Children

NICE developed and published guidance regarding diagnosis and management of bronchiolitis in children in 2015.[3] Bronchiolitis is the most common lower respiratory tract infection in the first year of life: one in five infants is affected and 2-3% are hospitalized. Mild cases of bronchiolitis can be managed at home, but infants with severe respiratory distress, difficulty taking adequate oral fluids, or with apnea require secondary care. Inhaled and nebulized SABAs, corticosteroids (ICS) and anticholinergic medications are not recommended in the management of bronchiolitis in infants. NICE guidelines regarding infant

bronchiolitis management also advise against the usage of any of the following medication s (nebulized, inhaled and/or oral): antibiotics, hypertonic saline, adrenaline, salbutamol, montelukast and/or systemic corticosteroids.[3]

NICE – Asthma Diagnosis, Monitoring and Chronic Asthma Management

A 2017 NICE guidance updated the management of chronic asthma in children, young people and adults.[4] The pharmacological recommendations for maintenance therapy were reviewed in a previous update; therefore, SABA use will be presented and discussed in this review. New guidance recommendations mirror previous statements of using SABA first line (**Table 1**).

Table 1. NICE Recommendations for the Use of SABA Therapy in Chronic Asthma[4]

Pharmacotherapy for Adults (17 years and older) with Newly Diagnosed or Uncontrolled Asthma
▪ Offer a SABA for reliever therapy: SABA monotherapy can be considered for adults who have infrequent, short-lived wheeze and normal lung function
▪ SABA can be used as reliever therapy in patients who continue to have uncontrolled asthma on a MART* regimen and are switching to a fixed-dose ICS and LABA
Pharmacotherapy for children and young people (5 to 16 years) with newly diagnosed or uncontrolled asthma
▪ SABA should be offered to children and young people with newly diagnosed asthma
▪ SABA monotherapy can be considered for infrequent, short-lived wheeze and normal lung function
▪ If asthma remains uncontrolled on pediatric low dose ICS and an LTRA, consider stopping the LTRA and starting a LABA in combination with the ICS
▪ SABA as reliever therapy should be used in combination with ICS and LABA in patients who continue to have uncontrolled asthma symptoms on a MART regimen*
Pharmacotherapy for Children Under 5 (5 to 16 year olds) with Suspected or Confirmed Asthma
▪ A SABA should be offered to children with suspected asthma for symptom relief and alongside maintenance therapy.
* MART – maintenance and reliever therapy which is a combination of an ICS and fast-acting LABA which is used for daily maintenance treatment and symptom relief. Abbreviations: ICS – inhaled corticosteroid; LABA – long-acting beta-agonist; LTRA – leukotriene receptor antagonist; MART – maintenance and reliever therapy; SABA – short-acting beta-agonist

Summary of Additional Guidelines & Clinical Trials for Clinical Context:

Global Initiative for Chronic Obstructive Lung Disease (GOLD) - 2019

The GOLD guidelines are produced on an annual basis to provide strategies for diagnosis, management and prevention of COPD.[5] GOLD guidelines are funded by sales of documents and resources. Seventy-six percent of GOLD board of directors and science committee have ties to industry, suggesting a high risk for publication bias. Other limitations to the guideline include the absence of the following: diversity in representation from professional groups, patient and public input, external review by experts in the field, and discussion on resource implications/barriers of recommendations.[5] Therefore, guideline recommendations for pharmaceutical management will be provided for clinical context but not relied upon for decisions regarding the PDL. Maintenance medications have been previously presented so only evidence related to SABAs will be presented. GOLD recommends the use of SABAs in patients with COPD who present with 0 to 1 moderate exacerbations. Inhaled bronchodilators are recommended over oral bronchodilators, which have demonstrated prevention and reduction in symptoms (Evidence level A [recommendation based on high-quality evidence]).[5] Regular and as needed use of SABA or short-acting muscarinic antagonists

(SAMA) have shown to reduce symptoms and improve FEV1 and are recommended based on level A evidence. Combination of SABA and SAMA are superior in reducing symptoms and improving FEV1 compared to either entity alone (Evidence level A).[5]

New Formulations:

- ProAir Digihaler – A dry powder inhaler that meters 117 mcg of albuterol (equivalent to 97 mcg of albuterol base) from the device reservoir and delivers 108 mcg of albuterol (equivalent to 90 mcg of albuterol base) from the mouthpiece per actuation was approved in 2019.[6] ProAir ® Digihaler™ is indicated for the treatment or prevention of bronchospasm in patients aged four years and older with reversible obstructive airway disease, and for prevention of exercise-induced bronchospasm (EIB) in patients aged four years and older. ProAir Digihaler contains a built-in electronic module which detects, records, and stores data on inhaler events for transmission to the mobile ProAir ® Digihaler™ contains built-in sensors that detect when the inhaler is used and measure inspiratory flow. Use of the App is not required for administration of medication to the patient.[6]
- Albuterol – A generic version of ProAir hydrofluoroalkane (HFA) albuterol metered dose inhaler, manufactured by Teva, was approved in 2019.[7]
- Albuterol – An authorized generic version of Ventolin metered dose inhaler, manufactured by GSK, was approved in 2019.[8]

New FDA Safety Alerts:

No new safety alerts identified.

References:

1. Kirkland SW, Vandenberghe C, Voaklander B, et al. Combined inhaled beta-agonist and anticholinergic agents for emergency management in adults with asthma. *Cochrane Database Syst Rev*. 2017;1:CD001284.
2. Becker LA, Hom J, Villasis-Keever M, et al. Beta 2-agonists for acute cough or a clinical diagnosis of acute bronchitis. *Cochrane Database Syst Rev*. 2015(9):CD001726.
3. National Institute for Health and Care Excellence. Bronchiolitis in children: diagnosis and management. *NICE Guideline* [NG9] Published date: June 2015 https://www.nice.org.uk/guidance/ng9. Accessed April 23, 2019.
4. National Institute for Health and Care Excellence. Asthma: diagnosis, monitoring and chronic asthma management. NICE Guideline. November 2017. Available at: nice.org.uk/guidance/ng80. Accessed April 23, 2019.
5. GOLD 2019 Global Strategy for the Diagnosis, Management and Prevention of COPD. Glob Initiat Chronic Obstr Lung Dis - GOLD. http://goldcopd.org/gold-2018-global-strategy-diagnosis-management-prevention-copd/. Published November 2018. Accessed April 23, 2019.17.
6. ProAir Digihaler Prescribing Information. Teva Respiratory LLC, Frazer PA. December 2018
7. Albuterol HFA. Prescribing Information. Teva Respiratory LLC, Frazer, PA. March 2019.
8. Albuterol HFA. Prescribing Information. Prasco GlaxoSmithKline, LLC, Research Triangle Park, NC. March 2019.

Appendix 1: Current Preferred Drug List

Short-Acting Beta-Agonists

Generic	Brand	Form	PDL
albuterol sulfate	ALBUTEROL SULFATE HFA	HFA AER AD	Y
albuterol sulfate	PROAIR HFA	HFA AER AD	Y
albuterol sulfate	PROVENTIL HFA	HFA AER AD	Y
albuterol sulfate	VENTOLIN HFA	HFA AER AD	Y
albuterol sulfate	ALBUTEROL SULFATE	SOLUTION	Y
albuterol sulfate	AIRET	VIAL-NEB	Y
albuterol sulfate	ALBUTEROL SULFATE	VIAL-NEB	Y
albuterol sulfate	PROAIR RESPICLICK	AER POW BA	N
albuterol	ALBUTEROL	AER REFILL	N
levalbuterol HCl	LEVALBUTEROL CONCENTRATE	VIAL-NEB	N
levalbuterol HCl	LEVALBUTEROL HCL	VIAL-NEB	N
levalbuterol HCl	XOPENEX	VIAL-NEB	N
levalbuterol HCl	XOPENEX CONCENTRATE	VIAL-NEB	N
levalbuterol tartrate	LEVALBUTEROL TARTRATE HFA	HFA AER AD	N
levalbuterol tartrate	XOPENEX HFA	HFA AER AD	N

Appendix 2: New Comparative Clinical Trials

A total of 29 citations were manually reviewed from the initial literature search. After further review, 25 were excluded because of wrong study design (eg, observational), comparator (eg, no control or placebo-controlled), or outcome studied (eg, non-clinical).

Appendix 3: Medline Search Strategy

Database(s): **Ovid MEDLINE(R)** 1946 to May Week 5 2019

Search Strategy:

#	Searches	Results
1	Albuterol/ or albuterol.mp.	10220
2	levalbuterol.mp. or Levalbuterol/	133
3	1 or 2	10231
4	limit 3 to (english language and humans and yr="2015 -Current")	577
5	limit 4 to (clinical trial, phase iii or guideline or meta analysis or practice guideline or "systematic review")	29

Appendix 5: Key Inclusion Criteria

Population	Patients with asthma, chronic obstructive pulmonary disease and other lung diseases treated with SABAs
Intervention	SABA listed in Appendix 1
Comparator	Active comparisons of drugs listed in Appendix 1
Outcomes	Symptom Improvement Morbidity Mortality Serious Adverse Events Discontinuation from Serious Adverse Events
Timing	Any study duration; literature search from 9/1/2015 to 6/6/2019
Setting	Outpatient