Indian Health Service
IHS National Pharmacy and Therapeutics Committee
Inhaled Anticholinergics
Last Reviewed: July 2011

Background: The IHS National Pharmacy and Therapeutics Committee (NPTC) reviewed the inhaled anticholinergics at the July 2011 meeting. The clinical review of this class included ipratropium (current formulary agent), ipratropium/albuterol combination and tiotropium. In addition, the other agents used in the treatment of chronic obstructive pulmonary disease (COPD) that were currently included on the IHS National Core Formulary (NCF) were discussed, namely Proventil HFA® (albuterol), Serevent® (salmeterol), Asmanex® (mometasone) and Advair® (salmeterol/fluticasone). The NPTC voted to **add** tiotropium (Spiriva®) to the NCF. In addition, the committee voted to **remove** Serevent® (salmeterol) from the NCF.

Clinical Review: COPD is a respiratory disease involving airflow obstruction due to chronic bronchitis or emphysema. It is the 4th leading cause of chronic morbidity and mortality in the US and the underlying cause of 1 of every 20 deaths[1]. Seventy-five percent of COPD cases are associated with tobacco use. Although rates of COPD are less for AI/AN than for the general US population, it still impacts 4.6% of this group[2]. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) has established criteria for dividing patients into four stages of the disease[1]. GOLD recommends as needed treatment with a short-acting bronchodilator (short-acting beta agonist or short-acting anticholinergic) for mild disease, the addition of regular treatment with a long-acting bronchodilator (long-acting beta agonist or long-acting anticholinergic) for moderate disease, the addition of an inhaled corticosteroid for severe disease, and the addition of oxygen for very severe disease. In addition, guidelines recommend that when using combinations of long-acting maintenance therapy and short-acting rescue medications, agents with differing mechanisms of action be used (e.g., a short-acting beta agonist paired with a long-acting inhaled anticholinergic).

Efficacy:
Ipratropium- Ipratropium is associated with a mean increase of FEV_1 of 15% compared to placebo for at least 4 hours after treatment[3]. In head-to-head trials with albuterol, ipratropium and albuterol showed similar responses in patients, though declines in responsiveness was slower to develop with ipratropium compared to albuterol[4]. The use of ipratropium with or without albuterol has been shown to decrease the number of COPD exacerbations and to lower costs[5], though the combination was shown to provide a great mean peak % increase in FEV_1 compared to either agent alone[6]. The combination of ipratropium and salmeterol was not associated with significant differences in symptom control or need for rescue inhalers compared to salmeterol alone[7-9].

Tiotropium- Tiotropium has been shown to increase vital capacity, inspiratory capacity, post-dose exercise endurance, tidal volume and minute ventilation. As well, it has been shown to decrease residual volume, functional residual capacity, dyspnea, exacerbations, and hospitalizations[10, 11]. In head-to-head trials with salmeterol, tiotropium showed higher average post-dose FEV_1 over 12 hrs, higher peak FEV_1, and higher peak and average FVC[12]. Compared to salmeterol, tiotropium was associated with a 17% reduction in risk of first exacerbation, an increased time to first severe exacerbation, reduced annual number of moderate or severe exacerbations and reduced annual number of severe exacerbations with similar serious adverse events[13]. A trial comparing tiotropium to salmeterol/fluticasone showed that the combination product was associated with greater improvements in respiratory symptoms, but with a greater risk of patients developing pneumonia[14]. In this study, tiotropium was associated with a greater rate of patients withdrawing from the study. Annual exacerbation rates were not significantly different. Compared to ipratropium, tiotropium was associated with improved FEV1, a reduction in exacerbations by 24%, reduced hospitalizations, and greater improvements in PEF, health-related quality of life, reduced short-acting beta-agonist use, and reduced dyspnea[15].

Safety: A 2008 systematic review and meta-analysis of randomized, controlled trials of inhaled anticholinergics for the treatment of COPD for at least 30-days showed an increased risk of MI (RR, 1.53 [95% CI 1.05-2.23]; p=0.03) and cardiovascular death (RR, 1.80 [95% CI, 1.17-2.77]; p=0.008), but no statistically significant increase in the risk of stroke (RR, 1.46 [95% CI, 0.81-2.62]; p=0.20)[16].

Conclusions: The NPTC voted to **add** tiotropium to the NCF based on its role as a long-acting bronchodilator in the management of patients with COPD of moderate or greater severity. Since salmeterol monotherapy is contraindicated in asthma management due to increased risk of death and was shown in studies to be inferior to long-acting anticholinergics in COPD management, salmeterol was removed from the NCF.

If you have any questions regarding this document, please contact the NPTC at nptc1@ihs.gov.

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