Safety in Respiratory Therapy
A Drug Utilization Review

Reduction of symptoms and future risk of exacerbations, while minimizing side effects of treatment.

The National Asthma Education and Prevention Program (NAEPP) published guidelines for the treatment of asthma in 2007.[1] The guidelines outline goals of therapy that include the prevention of recurrent exacerbation and need for emergency department or hospital care, the prevention of reduced lung growth in children or loss of lung function in adults, and the optimization of pharmacotherapy with minimal or no adverse effects.[2] Pharmacological treatment follows a stepwise approach that is based on the severity of asthma symptoms and extent of symptom control. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) published guidelines for the management of Chronic Obstructive Pulmonary Disease (COPD) in 2019.[3] The guidelines outline goals of therapy that focus on the reduction of symptoms and future risk of exacerbations, while minimizing side effects of treatment. Pharmacological management is based on an individual assessment of severity of symptoms and exacerbation risk.

Inhaled Medications for Asthma and COPD

The different classes of inhaled medications used in the management of asthma and COPD include short-acting beta-agonists (SABAs), long-acting beta-agonists (LABAs), inhaled corticosteroids (ICS), short-acting muscarinic antagonists (SAMAs), and long-acting muscarinic antagonists (LAMAs).[1-3]

SABAs, albuterol and levalbuterol, are agonists at adrenergic beta^2 receptors that cause rapid relaxation of bronchial smooth muscle and bronchodilation with a duration of effect of 4-6 hours. SABAs should be used on an as-needed basis, as scheduled doses are not associated with improved patient outcomes.[4] **LABAs,** including salmeterol, formoterol, vilanterol, indacaterol, and olodaterol, are also agonists at beta$_2$ receptors;however, they have a duration of effect of 12-24 hours.[4]

Adverse effects include jitteriness, tachycardia, dysrhythmias, and tremor. Additionally, LABAs carry a boxed warning of increased risk of asthma-related death and are contraindicated as monotherapy in the treatment of asthma.[4] Both SABAs and LABAs should be used with caution in those with pre-existing cardiovascular disorders.[1]

Inhaled Corticosteroids (ICS), including beclomethasone, budesonide, fluticasone, and mometasone, are agonists at glucocorticoid receptors that result in anti-inflammatory, immunosuppressive, and anti-proliferative effects. They should be used as scheduled maintenance inhalers in the treatment of asthma, and have been shown to improve asthma control and quality of life.[1] There is less clinical benefit seen in the management of COPD.[3]

Adverse effects include oral candidiasis (thrush), upper respiratory infection, pneumonia, growth retardation, reduced bone density, and adrenal insufficiency. To minimize adverse effects, the lowest effective dose that maintains symptom control should be used.[5]

SAMAs, ipratropium, and **LAMAs,** aclidinium, tiotropium, umeclidinium, and glycopyrronium, work through competitive inhibition of cholinergic receptors in bronchial smooth muscle, resulting in bronchodilation. They are used in the management of COPD and severe asthma not fully responsive to beta-agonists.[6]

Adverse effects are anticholinergic in nature and include xerostomia, blurred vision, urinary retention, tachycardia, and closed-angle glaucoma.[6] They should be used with caution in those with pre-existing glaucoma and prostatic hyperplasia.[5]

Drug Utilization Review Findings:

Respiratory Medication Therapy

An analysis of the concurrent drug utilization review (DUR) point of sale rejects was conducted to determine the effectiveness of alerting pharmacists of duplication in therapy of respiratory medications.

In reviewing UnitedHealthcare Community Plan data from the first two quarters of 2019, there were 16,613 rejected claims for duplicate therapy for 8,160 members. Of the rejected claims, 8,050 (48%) of them were overridden.

The use of multiple agents with the same component results in additive toxicity and increases the risk of adverse effects. The overuse of SABAs and LABAs increases the risk of cardiovascular events and fatality.[4] Concurrent use of multiple ICS increases the risk of oral candidiasis, pneumonia, growth retardation in children, and osteoporosis in adults.[5] The use of multiple SAMAs and LAMAs increases the risk of anticholinergic side effects.[6]

Both NAEPP and GOLD guidelines recommend using the lowest dose of medication necessary to maintain symptom control.[1,3] This recommendation is aimed at decreasing the potential for adverse effects, as toxicity is dose-related. Additionally, both guidelines recommend frequent assessment of pharmacologic treatment and de-escalation of therapy if appropriate, with the idea that step-down therapy is essential to identify the minimum medication necessary. NAEPP guidelines cite evidence that the dose-response curves of ICS are relatively flat, and that there is little benefit seen with increased dose in most patients.[1,5] Instead, guidelines recommend addition of another class of maintenance medication, such as a LABA, rather than increasing the dose or adding an additional ICS. Guidelines also state that LABA dose should not exceed 100 mcg of salmeterol or 24 mcg of formoterol daily, which could easily occur if a patient is prescribed more than one LABA. GOLD guidelines recommend combining medications with different mechanisms and durations of action due to increased effectiveness of bronchodilation and decreased risk of side effects.[3]

In summary, NAEPP and GOLD guidelines recommend combining different classes of medications in inadequately controlled patients, as addition of different medications within the same class exhibits a lack of benefit and increased risk of toxicity.

Goal of the Drug Utilization Review Team

The UnitedHealthcare Community Plan retrospective drug utilization review program is administered to promote the safe and efficacious use of medications. These interventions do not take into consideration patient-specific variables. The intent of this newsletter is to bring attention to potential medication-related issues that have been found during an analysis of the DUR data regarding respiratory medications. UnitedHealthcare Community Plan is committed to continuing to provide the best possible care for our members.

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[4]Lemanske R. Beta Agonists in Asthma: Controversy Regarding Chronic Use. UpToDate. www.uptodate.com. Updated January 16, 2019. Accessed July 29, 2019.
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