

Wyoming Drug Utilization Review

Chronic Obstructive Pulmonary Disease: Long-Acting Beta-Agonists Steroid Options

Brianna Earl, PharmD. Candidate 2019

As discussed in a previous newsletter, chronic obstructive pulmonary disorder (COPD) is a common, yet preventable disease. Globally, COPD is a major cause of morbidity and mortality, characterized by persistent airflow limitation and respiratory symptoms.¹

The standard treatment of COPD includes the use of pharmacologic agents, individualized based on the patients' symptoms and future risk of exacerbations. While there are currently no clinical trials demonstrating modification of lung function long-term, medications are able to reduce the severity and frequency of exacerbations, reduce symptoms, and improve exercise tolerance and overall health status.¹

Long-acting beta²-agonists (LABAs), such as formoterol and salmeterol, are bronchodilators used in the maintenance treatment of COPD. LABAs work through the local and selective stimulation of beta₂-receptors in the lung, resulting in an increase of cyclic AMP. Subsequently, bronchial smooth muscle relaxes and allows for increased bronchial airflow.^{2,3}

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines separate patients into four individual treatments groups: A, B, C, or D. Each group has a set of therapeutic recommendations based on the patient's symptoms and frequency of exacerbations. LABAs may be used as monotherapy in group B, if the patient's symptoms are well controlled. Persistent, uncontrolled symptoms require escalation of treatment to combination therapy. LABAs are recommended as combination therapy with long-acting muscarinic agents (LAMAs) or inhaled corticosteroids (ICS) in groups C and D. Group A does not require the use of a long-acting bronchodilator due to the presence of less severe symptoms and a low risk of exacerbation.¹ Please refer to the table on page 3.

There are both advantages and disadvantages to consider when using LABAs in the treatment of COPD. LABAs are able to significantly improve both lung function and dyspnea, while also reducing the rate of exacerbation. However, LAMAs are more effective in reducing exacerbations, as well as hospital admission rates when compared to LABAs.¹ Additionally, consistent use of beta₂-agonists over an extended period may result in the downregulation of beta₂-receptors in the airways, reducing the effectiveness of the medication. Thus, patients may require increased doses in order to achieve the same effect.⁴ Use of LABAs does not result in a decreased rate of lung function decline.¹

As with any drug therapy, LABAs are not without side effects. While the desired effect of LABAs is through the activation of beta₂-receptors in the lung, off-target effects can occur. The heart also contains beta₂-receptors, which can result cardiovascular effects including tachycardia, hypertension, angina, palpitations, and QT prolongation.^{2,3} Cardiovascular effects are not typically seen at therapeutic doses, but become a concern in patients requiring higher doses of LABAs, especially

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WY-DUR

University of Wyoming
School of Pharmacy
Dept. 3375
1000 E. University Ave
Laramie, WY 82071
307-766-6750
www.uwyo.edu/DUR

Edited by

Aimee Lewis, PharmD, MBA
Laura Miller, MS

P&T Committee Meeting Update

The P&T Committee met for its quarterly business meeting on February 14, 2019.

Highlights of this meeting include:

Emgality will require a three-month trial and failure of both an anticonvulsant and a beta blocker, in line with the other two CGRP inhibitors for migraine.

Epidiolex and Dupixent will be limited to indication. Cequa and Yupelri were referred to the Department of Health for cost analysis and PDL placement.

Onfi criteria will be updated to allow for Lennox-Gastaut Syndrome in patients aged 2 and older.

The proposed prior authorization criteria will be posted for public comment at www.uwyo.edu/DUR. Comments may be sent by email to alewis13@uwyo.edu or by mail to: Wyoming Drug Utilization Review Board, Dept. 3375, 1000 E. University Avenue, Laramie, WY 82071. Comments should be received prior to March 29, 2019.

The next P&T Committee meeting will be held May 8, 2019 in Cheyenne. An agenda will be posted approximately two weeks prior to the meeting.

Chronic Obstructive Pulmonary Disease

in patients with pre-existing cardiac disease. While hyperglycemia and hypokalemia rarely occur, they can also be seen when higher doses are warranted. Common side effects include headache, musculoskeletal pain, somatic tremor, and paradoxical bronchospasm.

Use of LABAs is contraindicated in patients with a hypersensitivity to any component of the formulation.^{2,3} In particular, salmeterol is contraindicated in patients with a severe milk protein hypersensitivity, as the formulation contains lactose and milk protein. LABAs are also contraindicated in patients with status asthmaticus. Caution is warranted in patients with cardiovascular disease, diabetes, hyperthyroidism, hypokalemia, and seizure disorders.^{2,3}

Long-acting beta₂-agonist medications also have possible interactions with other medications. Extreme caution is necessary with the co-administration of LABAs and other QT prolonging agents, including tricyclic antidepressants, fluoroquinolones, macrolides, and antiarrhythmic medications.^{2,3} LABAs are not to be given in combination with beta-blockers, especially nonselective agents, as this may diminish the effect of the beta₂-agonist.^{2,3}

COPD is a common and progressive disease, with significant morbidity and mortality worldwide. While no current medication has shown evidence of preventing the decline of lung function, adequate disease control can

help to improve a patient's overall quality of life. LABA bronchodilators are central to symptom management in COPD and decrease the frequency of exacerbations. Whether used as monotherapy or as combination therapy, LABAs are a viable treatment option in the maintenance of stable COPD.

References:

1. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease (2019 report). Available at: <http://gold.copd.org/gold-reports/>. Accessed: November 13, 2018.
2. Long-acting beta2-agonists. Lexi-Drugs. Lexi-Comp Online™. Hudson (OH): Wolters Kluwer Clinical Drug Information, Inc.; 2018. Available from: <http://online.lexi.com>. Accessed: October 5, 2018.
3. Long-acting beta2-agonists. Monographs. Clinical Pharmacology [database online]. Tampa (FL): Elsevier Inc.; 2018. Available from: <https://www.clinicalkey.com/pharmacology>. Accessed: October 5, 2018
4. Almadhoun K, Sharma S. Bronchodilators. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2018. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK519028/>. Accessed on: October 10, 2018.

Training: Safe Prescribing of Opioids in Pregnancy and Postpartum

Please join us for a free training on safe prescribing practices for opioids in the pregnancy and postpartum periods. This training is open to all healthcare providers who serve pregnant and/or postpartum women, and will include free CMEs.

Training Topics include Safe Prescribing of Opioids, Laws and Regulations, Non-pharmacological Pain Management, and An Introduction to Medication-Assisted Treatment (MAT) for Pregnant or Postpartum Women and Their Infants.

When: Thursday, March 28th from 5pm to 8pm.
Dinner will be provided.

Where: Cheyenne Regional Medical Center, Auditorium A, 214 E 23rd St, Cheyenne, WY 82001; Participants will be able to join virtually via Zoom if needed.

Trainers: Kaylin Klie, MD, MA; Lesley Brooks, MD; Ryan Jackman, MD

For more information and how to register, please contact Christina Taylor at christina.taylor@wyo.gov.

Pocket Guide:

Tapering Opioids for Chronic Pain*

The Centers for Disease Control and Prevention (CDC) recently released guidelines for tapering opioids. Successful tapering can be difficult and should be individualized to minimize symptoms of opioid withdrawal. The CDC guidelines recommend evaluating patients within one to four weeks of initiation of opioids or dose escalation. The risk of overdose with long-acting opioids is particularly high within the first two weeks of treatment. The CDC's pocket guide can be found online at https://www.cdc.gov/drugoverdose/pdf/clinical_pocket_guide_tapering-a.pdf.

*Recommendations focus on pain lasting longer than 3 months or past the time of normal tissue healing, outside of active cancer treatment, palliative care, and end-of-life care.

Treatment Group	Treatment Recommendations ¹
A	Initial treatment: a short- or long-acting bronchodilator <ul style="list-style-type: none"> • If the bronchodilator is ineffective, may continue, stop, or try an alternative bronchodilator class
B	Initial treatment: a long-acting bronchodilator (LABA or LAMA) <ul style="list-style-type: none"> • If symptoms persist, use a LABA/LAMA combination
C	Initial treatment: LAMA monotherapy <ul style="list-style-type: none"> • If further exacerbations occur, use a LAMA/LABA combination (preferred) OR a LABA/ICS combination
D	Initial treatment: LAMA monotherapy OR LABA and LAMA combination (if highly symptomatic) OR a LABA/ICS combination (patients with a history and/or findings suggestive of COPD/asthma overlap) <ul style="list-style-type: none"> • Further exacerbations on LABA/LAMA combination: <ol style="list-style-type: none"> 1. Escalate to LABA/LAMA/ICS 2. Switch to LABA/ICS, though there is no evidence of better exacerbation prevention • If patients on LABA/LAMA/ICS therapy still experience exacerbations: <ol style="list-style-type: none"> 1. Roflumilast may be considered in patients with an FEV₁ less than 50% predicted and chronic bronchitis 2. Add a macrolide antibiotic → azithromycin preferred due to best available evidence 3. Stopping ICS → elevated risk of adverse events

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University of Wyoming
School of Pharmacy
Dept. 3375
1000 E. University Avenue
Laramie, WY 82071**

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