

Wyoming Drug Utilization Review

Short-acting Beta2-agonists Overuse

WRITTEN BY BEN ZOLLER

Asthma is a common chronic respiratory disease affecting approximately 5.8% of children and 8.4% of adults in the United States in 2020 (1). In 2019, asthma was associated with 1.8 million emergency department visits and 170,000 hospital stays (1). Asthma development is associated with genetic predisposition in combination with environmental factors (2). Asthma is characterized by airflow obstruction, bronchial hyperresponsiveness (BHR), and airway inflammation, leading to symptoms of wheezing, shortness of breath, and chest tightness (2,3).

Inhaled short-acting beta2-agonists (SABA) were historically first-line treatments for asthma (3). Inhaled SABAs are relatively cheap and effective treatments for quick relief of asthma symptoms. Inhaled SABAs relax bronchial smooth muscle by stimulating beta-2 receptors. This relieves bronchospasm, reduces airway resistance, and facilitates mucous drainage (4).

The 2022 Global Initiative for Asthma (GINA) guidelines no longer recommend as-needed (PRN) inhaled SABAs as first-line asthma treatment. The guidelines now recommend low dose inhaled corticosteroids (ICS)-formoterol PRN for asthma symptom relief in adults and adolescents (3). These changes were based on evidence that SABA-only treatment can adversely affect exacerbation risk.

The preferred treatment for adults and adolescents (>12 years of age) is low dose ICS-formoterol PRN for symptom relief (3). If further therapy is required, patients can also use their ICS-formoterol as maintenance therapy. The alternative treatment recommends using a low dose ICS and SABA together PRN. This therapy is only recommended if the preferred treatment is not possible, the patient is stable, and they will be adherent to both inhalers. Assessing inhaler technique, medication adherence, correct diagnosis, comorbidities, and exposure to environmental irritants, should occur before increasing therapy to avoid unnecessary changes (3).

Regular SABA use is associated with downregulation of beta-2 receptors on bronchial epithelial cells and alveolar macrophages, increased BHR, increased eosinophils, and reduced bronchodilator response (5,6). These detrimental effects can cause a cycle of overusing inhaled SABAs. Patients with poor symptom control are at increased risk of asthma exacerbations (3).

SABA overuse increases the risk of exacerbations leading to emergency department visits, hospitalization, and death (3). An increased risk of emergency department visits or hospitalization is associated with dispensing three or more 200-dose SABA canisters per year, as this indicates more than daily use. An increased risk of death is associated with dispensing twelve or more canisters per year. Nebulized SABA use is associated with a higher risk of emergency department visits and hospitalizations (3,7).

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Several studies have shown detrimental outcomes in patients with asthma overusing SABAs (3). A 2020 retrospective, population-based cohort study evaluated asthma exacerbations and mortality in 365,324 Swedish patients aged 12-45 years who collected two or more 150-dose SABA canisters in a 1-year period from 2006-2014 (8). Overuse was defined as collecting three or more SABA canisters in a year, indicating SABA use of more than twice a week. 30% of participants were found to have overused SABAs. SABA overuse increased the risk of exacerbations and mortality in a dose-dependent manner, as seen in table 1. Mortality included all-cause and asthma related mortality. SABA overuse may be a surrogate marker for increased risk of all-cause mortality as the majority of deaths were not linked to asthma (8).

Table 1. Findings from Nwaru, et al.⁸

Number of 150-dose SABA canisters collected per year	Exacerbation hazard ratio compared to patients using ≤2 canisters/year (95% CI)	Mortality hazard ratio compared to patients using ≤2 canisters/year (95% CI)
3-5	1.26 (1.24–1.28)	1.26 (1.14–1.39)
6-10	1.44 (1.41–1.46)	1.67 (1.49–1.87)
>=11	1.77 (1.72–1.83)	2.35 (2.02–2.72)

Paris et al. (7) evaluated the relationship between SABA use and asthma exacerbations in 2,056 patients aged 5-56 years in a 2008 retrospective study (7). SABA use was distinguished by preparation, either metered-dose inhaler (MDI) or nebulized solution. Daily SABA nebulizer use was associated with an increased risk of asthma related emergency department visits and hospitalizations, while SABA MDI use was not, as seen in table 2. This may be due to practitioners prescribing nebulizers for patients suffering from severe asthma who appear not to respond to MDI administered SABA (7).

Table 2. Findings from Paris, et al.⁷

Type of SABA used daily	Emergency department visit adjusted hazard ratio, asthma related (95% CI)	Hospitalization adjusted hazard ratio, asthma related (95% CI)
Nebulized	6.32 (2.38–16.80)	21.62 (3.17–147.57)
MDI	1.05 (0.97–1.14)	1.17 (0.98–1.40)

The use of PRN low dose ICS-formoterol for patients with asthma reduces the risk of severe exacerbations compared to PRN SABA use alone (3,9). A 2018 double blind, randomized phase 3 trial evaluated the efficacy of PRN budesonide-formoterol compared to PRN terbutaline in 3849 patients with asthma over a 52-week period (9). All participants were 12 years of age or older. The rate of severe exacerbations was reduced by 64% in patients using PRN budesonide-formoterol (rate ratio, 0.36; 95% CI 0.27-0.49). The annualized exacerbation rate was 7% in the budesonide-formoterol group compared to 20% in the terbutaline group. Budesonide-formoterol also increased the number of weeks of well-controlled asthma compared to terbutaline (9).

A 2021 Cochrane review of six studies found that use of PRN ICS-formoterol was clinically effective in reducing negative outcomes associated with asthma compared to PRN SABA use (10). PRN ICS-formoterol use reduced the odds of asthma exacerbations requiring systemic steroids by 55% and emergency department visits or hospitalizations by 65% compared to PRN SABA use alone. Two of the studies included children 12 years of age and older, while two were open-label. The authors rate the evidence as moderate to high quality as the studies included were well designed, but still had some potential for bias (10).

Current evidence demonstrates the efficacy and safety of PRN ICS-formoterol use compared to PRN SABA use. Patients using three or more canisters of SABAs a year are at higher risk of asthma-related complications and mortality. The 2022 GINA guidelines address these findings by recommending PRN ICS-formoterol in adults and adolescents with asthma. These evidence-based recommendations are the start of a new chapter in the management of patients with asthma.

References

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The P&T Committee met for its quarterly business meeting on February 8, 2024

Highlights of this meeting include:

Vtama will be allowed for treatment of plaque psoriasis following a trial of a preferred medium and high potency corticosteroid.

Fluticasone and Asmanex HFA will be allowed for children aged 8 and under without prior authorization.

Topiramate will be allowed for treatment of alcohol use disorder following a four-week trial of naltrexone or acamprosate.

Xphozah, Zurzuva, Fabhalta and Pombility + Opfolda were reviewed. All were limited to indication. Velsipity, Bimzelx, Omvoh, and Opvee were reviewed with no evidence of a significant difference in safety or efficacy versus the current products in their respective classes. All were referred to the Department of Health for cost analysis and Preferred Drug List placement.

All prior authorization criteria are open for public comment. Comments should be sent by email to alewis13@uwyo.edu by April 15, 2024.

The next P&T Committee meeting will be held May 9, 2024 in Cheyenne. An agenda will be posted approximately two weeks prior to the meeting.

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