The beta agonist paradox: why albuterol overuse is dangerous

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Clinical questions
Why is albuterol overuse dangerous?
In 1989, a case-control study was published suggesting that an asthma mortality epidemic that had plagued New Zealand for more than a decade was due to fenoterol—a short-acting beta agonist used to treat asthma. When this drug was pulled from the market shortly thereafter, asthma mortality in New Zealand markedly decreased. (Crane 1995)

How could a medication used to treat the bronchospasm of asthma actually make asthma worse?
The answer rests on two key facts:
1. In asthma, inflammation of the bronchial tubes (airway wall thickening and mucus production) results in airway obstruction.
2. Beta agonists such as albuterol are pro-inflammatory. Use of beta agonists has been associated with increased inflammatory markers including sputum inflammatory cells, and their overuse has been associated with increased airway hyper-responsiveness and impaired beta2-adrenergic receptor expression.

There have been concerns about adverse effects from overuse ever since the advent of beta agonist treatments 50 years ago. After the New Zealand experience, asthma guidelines around the world were modified to recommend that patients use beta agonists "as needed" rather than on a regular schedule. Around the same time, more effective anti-inflammatory treatments—namely, inhaled corticosteroids—became available. Together, more limited use of beta agonists and more effective treatment of asthma's inflammatory component have helped reduce asthma mortality dramatically in the U.S. (Moorman 2007) and worldwide since the 1990s.

With these improvements, however, the awareness of the risks of albuterol overuse has diminished, especially among patients.

How much albuterol is too much?
When used in moderation, albuterol is a safe, effective, and essential treatment for asthma. However, we now know that a patient's increasing use of albuterol reflects a lack of control of the inflammation that underlies the patient's asthma, and that the albuterol itself could be making this worse.

Recommendations
There are three methods to help identify albuterol overuse:
1. The rule of twos. We often invoke the "rule of twos" to identify when a patient is at risk for albuterol overuse. If patients use albuterol more than twice a week (except for exercise) or their asthma wakes them up more than twice a month, their asthma is likely not well controlled. (Another possibility is that they may be overusing albuterol to treat a different condition, such as GERD, anxiety, or cough induced by post-nasal drainage.)
2. **Albuterol refills.** Every canister of albuterol contains 200 puffs. For the majority of well-controlled asthmatics, one canister a year is sufficient for good asthma control. More than two in a year should at least raise the question of whether the patient's asthma is well controlled or not. For more information, read "Asthma Zero Albuterol Refills: 200 Puffs Is Enough" in the October 2017 issue of Pharmacy E-News.

3. The HEDIS® (Healthcare Effectiveness Data and Information Set) **asthma medication ratio** (AMR) measures asthma controller (anti-inflammatory) use against albuterol use: Individuals 5–85 years of age with persistent asthma who had a ratio of controller medication to total asthma medications of 0.50 or greater. (Note: In 2018, the age range will change to 5–65 years.)

   When patients are overusing albuterol, their AMR will go below 0.5 (Schatz 2010). Patients with AMR < 0.5 are at increased risk for asthma hospitalization and emergency department visits.

   **How could this change my practice?**
   - When prescribing albuterol for patients with asthma, know that one canister with zero refills will suffice for most patients. See "Asthma Zero Albuterol Refills: 200 Puffs Is Enough."
   - Remember the rule of twos when talking to patients about asthma, and always be wary of asthma mimics, even in patients with an established asthma diagnosis. See the recent Clinical Pearl "Asthma diagnosis in four easy steps."
   - Any time your patients need an albuterol refill, look to see how much they've used in the past year. If they've used more than one or two canisters (and it's not for exercise only or extra medication to keep at school, etc.) then it's time to intervene and help identify what is leading to so much albuterol use.

**References**
