

Asthma Medications Should Be Available for Over-the-Counter Use: Con

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Abstract

The United States Food and Drug Administration recently considered a policy to transfer inhaled short-acting bronchodilators to over-the-counter status if conditions of safe use can be established. The American Thoracic Society filed a comment in opposition to the proposal. This article examines the negative consequences that might result from allowing nonprescription access to bronchodilators and other inhaled asthma medications. Such a proposed policy change

conflicts directly with current guidelines for asthma management and would undermine efforts to achieve adequate asthma control in patients. In addition, a policy change to convert asthma medications to over-the-counter status could result in increased costs to patients as well as increased health care costs to society overall due to a worsening of asthma control in the population.

Keywords: health policy; asthma treatment; over-the-counter medications

(Received in original form March 23, 2014; accepted in final form May 8, 2014)

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Ann Am Thorac Soc Vol 11, No 6, pp 975–979, Jul 2014

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DOI: 10.1513/AnnalsATS.201403-129AR

Internet address: www.atsjournals.org

Asthma affects 18.7 million American adults and 6.8 million American children, representing 8% of all adults and close to 10% of all children in the United States (1). Asthma is the most common chronic disease of childhood (2). The economic and health care costs associated with asthma are staggering, and increasing over time. When comparing the time periods 1998–1999 and 2008–2009, average annual total health care expenditures (adjusted for inflation) for adults with asthma increased nearly fourfold from \$27.8 billion in 1998–1999 to \$104.6 billion in 2008–2009, and average annual total out-of-pocket health care expenditures tripled from \$4.5 billion to \$14.3 billion for the same periods (3). Further, during the same time periods, average annual total expenditures on all prescribed asthma medications quadrupled from \$2.5 billion to \$10.2 billion (3).

With respect to classes of asthma medications, annual expenditures for controller medications, including inhaled corticosteroids (alone or in combination with long acting β -agonists) and

leukotriene antagonists, quadrupled from \$1.7 billion in 1998–1999 to \$7.8 billion in 2008–2009, while expenditures for reliever medications, primarily short-acting β -agonists, tripled from \$793 million in 1998–1999 to \$2.4 billion in 2008–2009 (3).

The economic impact of asthma derives not only from direct medical costs, but also indirect costs from lost school and work days. In addition, the morbidity associated with both partly or poorly controlled asthma is great for both children and adults, with significant limitations in daily functioning, exercise, sleep, and school and work performance. Furthermore, asthma remains a chronic condition, with a death rate in the United States of 0.15 per 1,000 persons with asthma (period of 2001–2010) (4).

In an effort to explore the potential to address some of the costs and possible barriers to medication access associated with asthma treatment and management, the U.S. Food and Drug Administration (FDA) in March 2012 considered a policy to transfer certain asthma medications, namely short-acting bronchodilators, to over-the-counter

status, if conditions of safe use could be established (5). The American Thoracic Society offered a letter of comment to the FDA in which multiple concerns were raised against the proposed policy (6).

Asthma pharmacologic management rests heavily on the use of both short-acting bronchodilators for “rescue” therapy in the setting of an acute exacerbation and the use of maintenance medications, primarily inhaled corticosteroids, for “controller” therapy. Although the FDA was considering the possibility of transitioning only short-acting bronchodilators to over-the-counter status, there have been others who have raised the question of transitioning inhaled corticosteroids as well as short-acting bronchodilators to over-the-counter status. These two classes of medications raise different safety concerns and could have very different implications for care if either class is made available to the public without a prescription.

This article aims to expound upon the concerns raised by the American Thoracic Society with regard to transitioning

short-acting bronchodilators to over-the-counter status, and to explore further reasons why transitioning either short-acting bronchodilators or “controller” inhaled corticosteroid asthma medications to over-the-counter status could have grave negative implications for asthma control and management.

Concerns Derived from Asthma Clinical Practice Guidelines

The National Asthma Education and Prevention Program was established by the National Heart, Lung, and Blood Institute in the late 1980s to develop clinical practice guidelines for the diagnosis and management of asthma aimed at helping health care professionals bridge the gap between current knowledge and practice. The most recent update to these clinical asthma guidelines was published in 2007 (2). These guidelines represent the current standard of care in the United States for the management of asthma. Since the first guidelines were published in 1991, there has been a reduction in asthma-related deaths, improvement in patient’s exercise tolerance, and improved access to patient education (7).

The National Asthma Education and Prevention Program guidelines focus on four major components of asthma management: use of objective measures to assess severity and monitor course of therapy; environmental control measures; patient and family education; and pharmacologic management (2). This multipronged approach highlights the fact that asthma is a multifactorial, highly variable chronic disease that is not adequately controlled by pharmacological management alone. Indeed, the diagnosis is one that cannot be established by a simple blood test and relies heavily on comprehensive and thorough history and physical examination for symptoms, daily functioning, frequency of exacerbation, and response to treatment.

Transitioning asthma medications, either rescue or controller therapy, to over-the-counter status may undermine the importance of initial and ongoing medical interaction for both diagnosis and management of asthma. Transitioning medications to over-the-counter status could potentially result in lack of attention

to multiple important aspects of asthma control, with decreased maintenance office visits, less patient education regarding monitoring of symptoms, use of asthma action plans, appropriate inhaler technique, assessment of disease severity and exacerbations, and managing environmental exposures and co-morbid conditions. The lack of attention to components of asthma management other than drug therapy could have the unintended consequence of overall worsening asthma control, likely resulting in increased acute care, urgent care, and emergency room costs for increased exacerbations. In addition, worse asthma control overall would result in increased indirect costs from lost work and school due to increased baseline symptoms and increased exacerbation rates. The current asthma guidelines are based on multidisciplinary expert opinion after comprehensive screening of 15,000 articles leading to full-text review of close to 1,700 articles on asthma care and management (2). Despite the fact that this represents the most comprehensive review of the current literature, there remains room for additional research aimed at establishing true connection between adequate asthma control and use of nonpharmacological measures aimed at achieving that control.

Potential for Increased Health Care Utilization

A number of studies have shown that poorly controlled asthma results in increased health care utilization and adverse health outcomes such as increased hospitalization and admission to an intensive care unit (8–10). In 2012, Gold and coworkers published a study looking at associations of patient outcomes with level of asthma control (11). This study used data from the Asthma Insights and Management survey to determine whether partly and uncontrolled asthma in respondents to the Asthma Insights and Management survey was associated with adverse outcomes as compared with well-controlled asthma. The Asthma Insights and Management survey, which was conducted in 2009, included 2,500 patients with asthma, 12 years of age and older. The survey classified patients into levels of control and compared use of health care services and limitations of

activities in patients with different levels of asthma control.

In this study, patients with uncontrolled asthma were more likely to report use of oral steroids (odds ratio [OR], 2.5) and over-the-counter medicine (OR, 2.7) compared with patients with well-controlled asthma. Patients with partly or uncontrolled asthma were more likely to report ever visiting doctors, specialists, or the emergency room or being hospitalized (ORs ranging from 2.1–5.6) for asthma compared with respondents whose asthma was well controlled. Finally, respondents with poorly controlled asthma had increased odds (ORs ranging from 14–34) of reporting that asthma limited their activities compared with respondents with well-controlled asthma. This study suggests that, in fact, worse asthma control is associated with greater impairment of daily functioning and increased use of health care resources.

It is possible that those patients whose asthma was less controlled or uncontrolled simply represented patients with a more severe asthma phenotype. However, any situation that may result in worsening asthma control, and most especially for patients who may have a more severe phenotype, then, would most likely result in increased health care costs, and, most importantly, worse clinical care of the patients. Even given allowances for potential variations in asthma phenotype, adequate asthma control is still largely dependent on adherence to the guidelines that stress ongoing monitoring, education, and focus on environmental factors, as well as pharmacologic management. Focusing strictly on transitioning medications to an over-the-counter status ignores the other key components of effective asthma control and will likely have negative impact on health care resources and patient care.

Improved asthma control and improved asthma outcomes have been demonstrated in studies that focus on quality improvement measures that provide ongoing education, care coordination, active outreach, and self-management support (12, 13). In Cincinnati (13) and San Francisco (12), researchers showed that quality improvement measures with more robust attention to guidelines-based care, enhanced follow-up for patients, and more aggressive outreach resulted in improved asthma control. Importantly, these studies both showed improved asthma control and

improved asthma outcomes in low-income, underserved, multi-ethnic patients, a group of patients who have routinely been shown in other studies to have worse asthma control compared with white patients of higher socioeconomic status (2, 11, 14–16). These quality improvement studies highlight the paramount importance of aspects of asthma management that require ongoing interaction with the patient for education and reinforcement. These efforts would be thwarted by a situation in which asthma medications were provided in a nonmedical retail setting.

Studies of Nonprescription Bronchodilators for Asthma Control

A few studies have examined nonprescription bronchodilator use in asthma (17–20). Australian studies have linked the use of nonprescription bronchodilators with both underutilization of inhaled corticosteroids and with infrequent physician consultation (18–20).

In the United States, researchers looked at three different groups of asthma medication users: those who exclusively used prescription asthma medications, those who were exclusive over-the-counter bronchodilator medication users, and those who combined both prescription and over-the-counter asthma medications to treat their asthma (17). Group assignment was based on self-reported medication use for the preceding 12 months. Demographic and clinical data was collected, spirometry was measured pre- and post-bronchodilator, and peak flow was monitored for 1 week.

The results of this study showed that nonprescription use was more common among male subjects, and that there was greater nonprescription medication use among patients who did not have a primary caregiver. None of the patients in the exclusive over-the-counter group had ever received systemic corticosteroids, in contrast to 50% of the patients in the groups who used prescription medications. This difference could be theorized to be because the patients in the exclusive over-the-counter group had more mild disease. Indeed, the over-the-counter subjects rated their asthma as less severe than the exclusive prescription drug user subjects. However, the spirometry data among the over-the-

counter subjects who rated their asthma as mild showed a greater change in FEV₁ after bronchodilator use, indicating both a level of obstruction at baseline and a severity of disease that was less mild than the patients perceived. The authors concluded that this discordance between perceived severity of disease and objective measures of lung function in the exclusive over-the-counter medication subjects suggests that “self-assessment of asthma severity may not be ‘on target,’ especially among individuals who self-medicate their illness with nonprescription bronchodilators” (17).

The above study again highlights the importance of more than just access to medication for adequate asthma control. Also, importantly, this study calls into question the patient’s ability to appreciate the severity of their illness. These potential limitations would make it almost impossible to conceive a situation for determining “conditions of safe use” for over-the-counter medications for asthma. Furthermore, poor patient perception of severity of baseline illness or exacerbation may result in a potentially dangerous situation of patients seeking out over-the-counter medications (in a drug store, for example) in an acute situation of respiratory distress, rather than seeking appropriate medical care for an exacerbation.

Cost Considerations for Patients

Heretofore, the negative impact on asthma control and management as a result of a transition to over-the-counter status for asthma medications has been considered. The most obvious question has yet to be addressed, namely: What would be the likely consequence of cost to the patient if asthma medications were transitioned to over-the-counter status?

When looking at other classes of medications such as long-acting antihistamines that have been transitioned to over-the-counter status, the American Thoracic Society points out in its letter that these medications were subsequently excluded from insurance coverage (6). In a similar situation, transitioning of asthma medications to over-the-counter status would almost assuredly result in insurance coverage being dropped for asthma medications. The costs for short-acting

bronchodilator rescue therapy remain high, as generic versions of albuterol are not available after the switch to hydrofluoroalkane (HFA) propellant for pressurized metered-dose inhalers. Cost data obtained from Epocrates shows the price for an 18-g (200 dose actuations) albuterol HFA inhaler to range between \$55 and \$65 per inhaler for all major manufacturers, including Ventolin, Proventil, and Proair (21). Furthermore, costs for inhaled corticosteroids are significantly higher, ranging from \$130 to \$380 for a 1-month supply (21).

In a proposed situation in which both short-acting and controller medications are transitioned to over-the-counter status, the monthly cost to the patient could be as high as \$300 to \$400. The greatest likelihood in this scenario would be that patients would forego the more expensive controller medications and would rely on short-acting medications, provided they could even afford those. In the National Asthma Education and Prevention Program guidelines, regular use of short-acting β_2 -agonists is not recommended for maintenance therapy, and need for regular short-acting β_2 -agonists indicates inadequate asthma control (2).

The burden of cost imposed on the patients as a result of a transition to over-the-counter asthma medications would be further magnified when one considers that most individuals with asthma have other co-morbid conditions that require additional therapy that is also over-the-counter and not covered by insurance. The association between asthma and allergic rhinitis has been long established, with multiple studies confirming sensitization to indoor and outdoor allergens as a risk factor for development of asthma (22–26). Also a chronic condition, allergic rhinitis requires ongoing regular use of medications for adequate control. The combined burden of cost of both asthma and allergy medications could be staggering if none of these medications is covered by insurance, as would likely be the case once they were all transitioned to over-the-counter status. Furthermore, many individuals with asthma also have co-morbid gastroesophageal reflux (27), another chronic condition requiring regular use of medications that have also been transitioned to over-the-counter status, and, as such, are no longer covered by insurance.

Safety Concerns

In addition to cost, the safety implications of a transition of asthma medications to over-the-counter status should be considered. Although both β_2 -agonists and inhaled corticosteroids generally have favorable safety profiles, they are not completely benign classes of medications. Ongoing monitoring for side effects, as well as monitoring for adjustment of dosing strategy, is recommended by the National Asthma Education and Prevention Program (2). Inhaled corticosteroids have been shown to reduce growth velocity in children (28–31) and decrease bone mineral density in adults (32). Less significant, but other side effects from inhaled corticosteroids, such as oral candidiasis (33), also need to be monitored and potentially treated. It is not clear that an over-the-counter dispensing regime for inhaled corticosteroids would result in any higher incidence of side effects, but consideration would need to be given to ensure that there was appropriate education of the patient regarding potential side effects and that there was still a mechanism in place to monitor for those side effects.

The dangers of excessive cardiac stimulation from overuse of β -agonists are well established with less selective β -adrenergic receptor agonists (34). Although the selective β_2 -agonists have a more favorable cardiac safety profile, they still require ongoing monitoring for their use. The ongoing monitoring of use of short-acting β -agonists is important because increasing use of short-acting β -agonists has been associated with increased risk for death or near death in patients who have asthma (35). In addition, other studies have identified problems with chronic use of albuterol in some subsets of patients, especially when used without

inhaled corticosteroids (36, 37). The much-needed ongoing monitoring for side effects as well as monitoring for severity of disease as indicated by short-acting β -agonist use would be compromised by a transition to over-the-counter status, as patients could be using these classes of medications without any physician supervision.

There are further safety concerns that can be conceived as a result of the transition of asthma medications to over-the-counter status. The cheapest medication to treat asthma is systemic prednisone, which costs anywhere from \$5 to \$10 for 30 10- or 20-mg pills (21). In a situation in which patients may make decisions on which medications they can afford, coupled with a likely situation of worsening asthma control as a result of transition of medications to over-the-counter status, it is likely that the use of systemic corticosteroid would increase. The side effects of systemic corticosteroid use are well known and include adrenal suppression, growth suppression, dermal thinning, hypertension, Cushing syndrome, cataracts, and muscle weakness (38).

With regard to systemic steroid use, the National Asthma Education and Prevention Program expert panel “recommends that, because the magnitude of adverse effects is often related to the dose, frequency of administration, and the duration of corticosteroid use, every consideration should be given to minimize systemic corticosteroid doses and maximize other modes of therapy” (2). Again, this strong recommendation of the National Asthma Education and Prevention Program guidelines would be challenged by a situation that could result in increased systemic corticosteroid caused by a transition of other asthma medications to over-the-counter status.

Asthma remains a highly complex, variable, multifactorial, potentially fatal

chronic illness that requires a multi-pronged approach for adequate diagnosis, management, monitoring, and treatment. The transition of asthma medications, either short-acting bronchodilators and/or preventative inhaled corticosteroids, to over-the-counter status would threaten the implementation of this multifaceted approach to disease control and would fly in the face of current standard of care guidelines. The end result of the transition of asthma medications to over-the-counter status could not only be an increase in health care costs overall, but, most importantly, worse health and clinical care for a large percentage of patients who suffer from asthma.

Conclusions

The current debate about prescription status of asthma medications highlights important gaps that remain in understanding asthma control overall and in understanding the variables that may influence the ability to achieve such control. There exist clear disparities in asthma severity and control among different racial groups, as well as likely disparities among different socioeconomic groups (2). Any potential change to prescription status for asthma medications, either short-acting medications or controller medications, should be accompanied by ongoing prospective research looking at potential effects of such change on asthma control, overall use of all classes of asthma medications, use of health care resources, and economic impact related to out-of-pocket costs to the patients and lost work and/or school days. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

References

- 1 National Center for Health Statistics, Centers for Disease Control and Prevention. Asthma FastStats [updated 2014 Feb 25 accessed 2014 Mar 6]. Available from: <http://www.cdc.gov/nchs/fastats/asthma.htm>
- 2 National Heart, Lung, and Blood Institute and the National Asthma Education and Prevention Program. Expert Panel Report 3 (EPR 3): Guidelines for the Diagnosis and Management of Asthma [accessed 2014 Feb 12]. Available from: <http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm>
- 3 Sarpong E. Changes in adult asthma medication use and expenditures, United States, 1998–1999 to 2008–2009. Statistical Brief #374. 2012 Jul [accessed 2014 Apr]. Agency for Healthcare Research and Quality, Rockville, MD. Available from: http://www.meps.ahrq.gov/mepsweb/data_files/publications/st374/stat374.pdf
- 4 Akinbami LJ, Sullivan SD, Campbell JD, Grundmeier RW, Hartert TV, Lee TA, Smith RA. Trends in asthma prevalence, health care use, and mortality in the United States, 2001–2010. NCHS data brief, no 94. Hyattsville, MD: National Center for Health Statistics, 2012.
- 5 Department of Health and Human Services, Food and Drug Administration. Using innovative technologies and other conditions of safe use to expand which drug products can be considered nonprescription; public hearing. Department of Health and Human Services, Food and Drug Administration; 2012 [accessed 2014

- Jun 13]. Available from: <http://www.gpo.gov/fdsys/pkg/FR-2012-02-28/pdf/2012-4597.pdf>
- 6 The American Thoracic Society. Utilizing innovating technologies and other conditions of safe use to expand access to nonprescription drugs. Letter of response to public hearing, submitted May 7, 2012.
- 7 National health interview survey (NHIS 2005). Hyattsville, MD: National Center for Health Statistics (NCHS), Centers for Disease Control and Prevention, 2005 [accessed 2014 Jun 13]. Available from: http://www.cdc.gov/nchs/about/major/nhis/reports_2005.htm
- 8 Lai CK, Ko FW, Bhome A, DE Guia TS, Wong GW, Zainudin BM, Nang AN, Boonsawat W, Cho SH, Gunasekera KD, et al. Relationship between asthma control status, the Asthma Control Test™ and urgent health-care utilization in Asia. *Respirology* 2011;16:688–697.
- 9 Murphy KR, Meltzer EO, Blaiss MS, Nathan RA, Stoloff SW, Doherty DE. Asthma management and control in the United States: results of the 2009 Asthma Insight and Management survey. *Allergy Asthma Proc* 2012;33:54–64.
- 10 Nguyen K, Zahran H, Iqbal S, Peng J, Boulay E. Factors associated with asthma control among adults in five New England states, 2006–2007. *J Asthma* 2011;48:581–588.
- 11 Gold LS, Smith N, Allen-Ramey FC, Nathan RA, Sullivan SD. Associations of patient outcomes with level of asthma control. *Ann Allergy Asthma Immunol* 2012;109:260–265, e2.
- 12 Fox P, Porter PG, Lob SH, Boer JH, Rocha DA, Adelson JW. Improving asthma-related health outcomes among low-income, multiethnic, school-aged children: results of a demonstration project that combined continuous quality improvement and community health worker strategies. *Pediatrics* 2007;120:e902–e911.
- 13 Britto MT, Vockell AL, Munafo JK, Schoettker PJ, Wimberg JA, Pruett R, Yi MS, Byczkowski TL. Improving outcomes for underserved adolescents with asthma. *Pediatrics* 2014;133:e418–e427.
- 14 Cope SF, Ungar WJ, Glazier RH. Socioeconomic factors and asthma control in children. *Pediatr Pulmonol* 2008;43:745–752.
- 15 Stanford RH, Gilsenan AW, Ziemiecki R, Zhou X, Lincourt WR, Ortega H. Predictors of uncontrolled asthma in adult and pediatric patients: analysis of the Asthma Control Characteristics and Prevalence Survey Studies (ACCESS). *J Asthma* 2010;47:257–262.
- 16 Bacon SL, Bouchard A, Loucks EB, Lavoie KL. Individual-level socioeconomic status is associated with worse asthma morbidity in patients with asthma. *Respir Res* 2009;10:125.
- 17 Kuschner WG, Hankinson TC, Wong HH, Blanc PD. Nonprescription bronchodilator medication use in asthma. *Chest* 1997;112:987–993.
- 18 Henry DA, Sutherland D, Francis L; Newcastle Retail Pharmacy Research Group. The use of non-prescription salbutamol inhalers by asthmatic patients in the Hunter Valley, New South Wales. *Med J Aust* 1989;150:445–449.
- 19 Gibson P, Henry D, Francis L, Cruickshank D, Dupen F, Higginbotham N, Henry R, Sutherland D. Association between availability of non-prescription β_2 agonist inhalers and undertreatment of asthma. *BMJ* 1993;306:1514–1518.
- 20 Comino EJ, Henry RL, Mitchell CA, Bauman A, Monaco R. Asthma management and mode of acquisition of inhaled bronchodilators. *Aust N Z J Med* 1995;25:496–502.
- 21 Epocrates Essentials for Apple iOS (Version 14.1) [Mobile application software] [accessed 2014 Feb]. Available from: <http://www.epocrates.com/mobile/iphone/essentials>
- 22 Halonen M, Stern DA, Wright AL, Taussig LM, Martinez FD. *Alternaria* as a major allergen for asthma in children raised in a desert environment. *Am J Respir Crit Care Med* 1997;155:1356–1361.
- 23 Sears MR, Burrows B, Herbison GP, Holdaway MD, Flannery EM. Atopy in childhood: II. Relationship to airway responsiveness, hay fever and asthma. *Clin Exp Allergy* 1993;23:949–956.
- 24 Sporik R, Holgate ST, Platts-Mills TA, Cogswell JJ. Exposure to house-dust mite allergen (Der p I) and the development of asthma in childhood: a prospective study. *N Engl J Med* 1990;323:502–507.
- 25 Reid MJ, Moss RB, Hsu YP, Kwasnicki JM, Commerford TM, Nelson BL. Seasonal asthma in northern California: allergic causes and efficacy of immunotherapy. *J Allergy Clin Immunol* 1986;78:590–600.
- 26 Creticos PS, Reed CE, Norman PS, Khoury J, Adkinson NF Jr, Buncher CR, Busse WW, Bush RK, Gadde J, Li JT, et al. Ragweed immunotherapy in adult asthma. *N Engl J Med* 1996;334:501–506.
- 27 Harding SM. Gastroesophageal reflux and asthma: insight into the association. *J Allergy Clin Immunol* 1999;104:251–259.
- 28 The Childhood Asthma Management Program Research Group. Long-term effects of budesonide or nedocromil in children with asthma. *N Engl J Med* 2000;343:1054–1063.
- 29 Guilbert TW, Morgan WJ, Zeiger RS, Mauger DT, Boehmer SJ, Szefer SJ, Bacharier LB, Lemanske RF Jr, Strunk RC, Allen DB, et al. Long-term inhaled corticosteroids in preschool children at high risk for asthma. *N Engl J Med* 2006;354:1985–1997.
- 30 Leone FT, Fish JE, Szefer SJ, West SL. Systematic review of the evidence regarding potential complications of inhaled corticosteroid use in asthma: collaboration of American College of Chest Physicians, American Academy of Allergy, Asthma, and Immunology, and American College of Allergy, Asthma, and Immunology. *Chest* 2003;124:2329–2340.
- 31 Kelly HW, Sternberg AL, Lescher R, Fuhlbrigge AL, Williams P, Zeiger RS, Raissy HH, Van Natta ML, Tonascia J, Strunk RC; CAMP Research Group. Effect of inhaled glucocorticoids in childhood on adult height. *N Engl J Med* 2012;367:904–912.
- 32 Wong CA, Walsh LJ, Smith CJ, Wisniewski AF, Lewis SA, Hubbard R, Cawte S, Green DJ, Pringle M, Tattersfield AE. Inhaled corticosteroid use and bone-mineral density in patients with asthma. *Lancet* 2000;355:1399–1403.
- 33 Shaw NJ, Edmunds AT. Inhaled beclomethasone and oral candidiasis. *Arch Dis Child* 1986;61:788–790.
- 34 Centers for Disease Control and Prevention (CDC). Adverse events associated with ephedrine-containing products—Texas, December 1993–September 1995. *MMWR Morb Mortal Wkly Rep* 1996;45:689–693.
- 35 Spitzer WO, Suissa S, Ernst P, Horwitz RI, Habbick B, Cockcroft D, Boivin JF, McNutt M, Buist AS, Rebuck AS. The use of beta-agonists and the risk of death and near death from asthma. *N Engl J Med* 1992;326:501–506.
- 36 Eisner MD, Lieu TA, Chi F, Capra AM, Mendoza GR, Selby JV, Blanc PD. Beta agonists, inhaled steroids, and the risk of intensive care unit admission for asthma. *Eur Respir J* 2001;17:233–240.
- 37 Lemaitre RN, Siscovick DS, Psaty BM, Pearce RM, Raghunathan TE, Whitsel EA, Weinmann SA, Anderson GD, Lin D. Inhaled beta-2 adrenergic receptor agonists and primary cardiac arrest. *Am J Med* 2002;113:711–716.
- 38 Schleimer RP, Spahn JD, Covar R, Szefer SJ. Glucocorticoids: B. Clinical science. In: Adkinson NJ, Bochner BS, Busse WW, et al., editors. Middleton's allergy principles and practice, 6th ed. Philadelphia: Mosby; 2003. pp. 887–913.

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