

Management of asthma in the elderly patient

Andrea S Melani

Fisiopatologia e Riabilitazione
Respiratoria, Dipartimento Vasi,
Cuore e Torace, Policlinico Le Scotte,
Azienda Ospedaliera Universitaria
Senese, Siena, Italy

Abstract: A significant number of older asthmatics, more often than in previous ages, have poorly controlled asthma, leading to increased morbidity and mortality. On the other hand, current guidelines suggest that most asthmatics can obtain achievement and maintenance of disease control and do not include sections specific to the management of asthma in the elderly so that it is more evident the contrast between poor control of asthma in the elderly and the lack of specific guidance from guidelines on asthma management in older asthmatics. Inhaled corticosteroids are the cornerstone for older asthmatics, eventually with add-on inhaled long-acting beta-agonists; inhaled short acting beta-agonists can be used as rescue medications. Triggers exacerbating asthma are similar for all ages, but inhaled viruses and drug interactions have greater clinical significance in the elderly. Older asthmatics have an increased likelihood of comorbidities and polypharmacy, with possible worsening of asthma control and reduced treatment adherence. Physicians and older asthmatics probably either do not perceive or accept a poor asthma control. We conclude that specific instruments addressed to evaluate asthma control in the elderly with concomitant comorbidities and measurements for improving self-management and adherence could assure better disease control in older asthmatics.

Keywords: asthma, beta2-agonists, inhaled corticosteroids, asthma control, elderly

Introduction

Asthma is a chronic inflammatory bronchial disease associated with airway hyperresponsiveness, variable airflow obstruction, and episodes of wheezing, breathlessness, and cough; although these symptoms are common to many other diseases, in asthma they have a marked variability in response to a range of environmental stimuli, such as inhaled viruses, allergens, and drugs, often permitting the suspicion of diagnosis on a clinical basis (see Table 1).¹⁻⁵

Asthma is widespread for all classes of age, including the elderly. The term elderly usually refers to persons aged 65 years or older, a largely increasing population worldwide. The physician-diagnosed prevalence of asthma in older adults is between 6% and 10%, just as in any other age group.⁶ Asthma in older adults is either diagnosed after the age of 65 years or with a history of long-standing disease. In a cohort study of 1485 older asthmatics recruited by chest physicians, almost a quarter were diagnosed after 65 years.⁷

The goal of asthma treatment is achievement and maintenance of disease control.¹⁻⁵ Uncontrolled asthma is more common in older adults than in previous ages with a substantial clinical burden, a greater proportion of asthma medications prescriptions, hospitalizations, and death.⁸⁻¹³

Correspondence: Andrea S Melani
Fisiopatologia Respiratoria, Azienda
Ospedaliera Universitaria Senese,
Policlinico Le Scotte, Viale Bracci,
53100 Siena, Italy
Tel +39 0577 586 761
Fax +39 0577 586 196
Email a.melani@ao-siena.toscana.it

Table 1 Diagnosis of asthma based on medical history, physical examination, and objective measurements¹⁻⁴

Key elements of medical history

- Cough
- Wheezing
- Breathlessness
- Chest tightness
- Family or personal history of allergic or atopic disease

Assess for symptom patterns typical of asthma

- Episodic or recurrent
- Occur or worsen upon exposure to allergens, respiratory infections, irritants such as pollutants, exercise, tobacco smoke, or drugs
- Good response to a bronchodilator

Physical examination

- Wheezing on lung auscultation
- Concomitant rhinitis

Objective measurements

- Spirometry showing reversible airway obstruction: reduced FEV₁/FVC and increase in FEV₁ after a bronchodilator $\geq 12\%$ and ≥ 200 mL or after a course of controller therapy
- Alternative: peak expiratory flow variability: ≥ 60 lpm or $\geq 20\%$ based on multiple daily readings

If spirometry (or PEF) is normal, but symptoms are present consider

- Challenge testing

Allergy testing

- Skin testing
- Specific serum IgE testing

Abbreviations: FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; IgE, serum immunoglobulin E; PEF, peak expiratory flow.

The aim of this study is to assess the current modalities of asthma management in the elderly with reference to causes of uncontrolled disease and possible adjustments. Management of acute asthma is beyond the scope of the present work and interested readers are referred to other reviews.¹⁻⁴

This review includes results from the literature judged to be relevant on the topic. The PubMed database was searched using the keywords “asthma” in combination with “elderly” or “aging” or “older” up to March 2013. The selection of

articles was not systematic. Studies were not graded by criteria defined a priori.

Asthma control

Guidelines emphasize the need to use disease control to base adjustments on treatment for all ages.¹⁻⁵ With slight differences among guidelines,¹⁴ asthma control is usually established using some clinical and physiological outcomes assessed by the patient's recall of the previous 4 weeks, as shown in Table 2. Likewise, although the concept of asthma control is the same for all ages, its proper recognition in the elderly may be complicated because older asthmatics have a reduced perception of bronchoconstriction,^{15,16} tend to attribute cough or exertional breathlessness to age alone,^{17,18} and confuse symptoms of asthma with those of other chronic concomitant comorbidities, such as chronic obstructive pulmonary disease (COPD) and heart failure.¹⁹ Some questionnaires, mainly based on some clinical variables, can help clinicians to assess asthma control. However, they are validated in a range of ages, but not specifically in the elderly.²⁰⁻²² Other variables, namely treatment side effects, frequency and severity of exacerbations, and decline in lung function are also used for a full evaluation of disease control, but require longer observation over time.¹⁻⁵ Some physiologic measurements, such as peak expiratory flow monitoring, are used to evaluate asthma control, although offer no advantage over symptoms monitoring in older adults with moderate to severe asthma.²³ Monitoring with spirometry is underused in the elderly.⁸ Other variables, such as fractional exhaled nitric oxide measurements, are not routinely useful for assessing asthma control, at least in the elderly.²⁴

Guidelines recommend a stepwise approach for management according to the individualized assessment of asthma

Table 2 Classification of asthma control according to guidelines³

Components of control	Controlled (all of the following)	Partly controlled	Uncontrolled
Symptoms	≤ 2 days per week	> 2 days per week	Three or more features of partly controlled asthma present in any week
Night time awakenings	None	Any	
Interference with normal activity	None	Any	
SABA use for symptoms control	≤ 2 days per week	> 2 days per week	
FEV ₁ or PEF	Normal ($> 80\%$ of predicted/personal best)	$< 80\%$ of predicted/personal best	
Validated questionnaires	Score		
ATAQ ^o	0	1–2	3–4
ACQ ^o	≤ 0.75	0.75–1.5	≥ 1.5
ACT*	≥ 20	16–19	≤ 15

Notes: ^oHigher score indicates worsening of asthma control; *lower score indicates worsening of asthma control.

Abbreviations: ACQ, Asthma Control Questionnaire; ACT, Asthma Control Test; ATAQ, Asthma Therapy Assessment Questionnaire; FEV₁, forced expiratory volume in 1 second; PEF, peak expiratory flow; SABA, short-acting β_2 -agonists.

Table 3 Stepwise approach to asthma therapy¹⁻⁴

Step 1	Step 2	Step 3	Step 4	Step 5	Step 6	
Preferred: SABA as needed	For 6–8 weeks Preferred: Low-dose ICS Alternative: LTRA	Preferred: Low-dose ICS + LABA or medium-dose ICS Alternative: Low-dose ICS + LTRA	Preferred: Medium-dose ICS + LABA Alternative: Medium-dose- ICS + LTRA	Preferred: High-dose ICS + LABA and LTRA. Consider omalizumab for patients with allergies	Preferred: High-dose ICS + LABA and LTRA. Consider tiotropium and omalizumab for patients with allergies	Step up when needed (first check adherence, inhaler technique, and environmental control) Assess control: Step down if possible when asthma is well-controlled for at least 3 months

Abbreviations: ICS, inhaled corticosteroids; LABA, long-acting β_2 -agonists; LTRA, leukotriene receptor agonists; SABA, short-acting β_2 -agonists.

control, as shown in Table 3. At each step, a preferred option and alternatives are identified: when asthma is uncontrolled, treatment is required to be increased to the next step; by contrast, when asthma is controlled, a reduction in the amount of treatment may be organized.¹⁻⁵ This process requires that asthma control is monitored by health care professionals and, preferably, by the patient at regular intervals.¹⁹ The frequency of follow-up assessments depends upon the patient's initial clinical severity and the patient's confidence in playing a role in his/her ongoing asthma control (self-management). Typically, patients are seen 1–3 months after the initial visit and every 3 months thereafter, but the interval is shorter after an exacerbation. A document specifically created to manage older asthmatics confirms these recommendations.²⁵

Inhaled corticosteroids

Inhaled corticosteroids (ICS) are the cornerstone of asthma anti-inflammatory therapy. Guidelines recommend regular daily long-term ICS use for all subjects with uncontrolled or partly controlled asthma.¹⁻⁵ In these conditions, several studies have demonstrated the efficacy of ICS in assuring asthma control.^{5,26} The decision of proper ICS dosing is based on the clinician's judgment of the response to treatment.¹⁻⁵ However, most benefits are achieved in adults at relatively low doses, equivalent to 0.2–0.4 mg of beclomethasone dipropionate (BDP) or equivalent per day that seldom sustain systemic effects even for long-term regular use.²⁷ Increasing to higher doses provides relatively little further benefit in terms of asthma control, but increases the risk of side effects.²⁷ The estimated comparative daily doses of different ICS through inhalers are reported in Table 4.¹⁻⁵ Different ICS may marginally influence safety and effectiveness by several factors, such as oral bioavailability, different pharmacokinetics, and on-site activation into the lung.²⁹ ICS are usually delivered via inhalers, either metered dose inhalers (MDI) or dry powder inhalers (DPI); although ICS can also be nebulized, this method of delivery is seldom used as current formulations

are available as suspensions that have poor and variable lung drug delivery.³⁰ Recently, the replacement of MDI propellants with more ecological formulations has permitted the modification of the characteristics of some ICS, delivering extra fine particles and increasing lung drug delivery; perhaps targeting smaller airways, some studies of real-life use attribute some advantages to these extra fine ICS with respect to traditional MDI, even at equipotent doses.³¹⁻³³ ICS do not cure asthma and when they are discontinued, deterioration of control follows within weeks to months in most patients.³⁴ However, not all asthmatics respond to ICS; failure of ICS treatment occurs in up to 25%–35% of patients.²⁸ Asthmatic phenotypes characterized by neutrophilic inflammation of the airways are less likely to respond to ICS than those with prevalent eosinophilic inflammation.³⁵ In older asthmatics neutrophilic airway inflammation is more common than in previous ages.³⁶ Likewise, although extensive specific information is not available, clinical studies do not support that ICS in older adults have less efficacy than in younger ages.⁵ Probably, in real life nonadherence to ICS is a more important problem and particularly in older asthmatics.¹⁹ In a large US survey, elderly asthmatics received a greater undertreatment

Table 4 Estimated comparative daily dose of different ICS in milligrams for adults based upon the available efficiency data in the literature

Name	Low	Medium	High dose
BDP–CFC MDI	<0.4	0.4–0.8	>0.8
BDP–HFA MDI	<0.25	0.25–0.5	>0.5
Budesonide DPI	<0.4	0.4–0.8	>0.8
Ciclesonide–HFA MDI	<0.2	0.2–0.4	>0.4
Fluticasone–HFA MDI or DPI	<0.25	0.25–0.5	>0.5
Triamcinolone–CFC MDI	<0.75	0.75–1.5	>1.5
Flunisolide–CFC MDI	<1	1–2	>2
Flunisolide–HFA MDI	<0.32	0.32–0.64	>0.64
Mometasone DPI	<0.4	0.4–0.8	>0.8

Abbreviations: ICS, inhaled corticosteroids; CFC, chlorofluorocarbon; DPI, dry powder inhaler; HFA, hydrofluoroalkane; MDI, metered dose inhaler; BDP, beclomethasone dipropionate.

of ICS than previous ages.³⁷ Most older patients admitting to emergency departments for asthma symptoms were not using ICS.¹⁰ In another group of 6254 elderly adults consecutively admitted to hospital with asthma in Ontario, those patients identified as users of ICS post-discharge were respectively 29% readmitted referrals to hospital and 30% of those who died over a 1-year follow-up period.³⁸

Inhaled beta-agonists

Inhaled β_2 -agonists are the most effective reliever in asthma.^{1–5} According to the duration of action, they are classified into either short-acting β_2 -agonists (SABAs) or long-acting β_2 -agonists (LABAs). Albuterol is by far the most commonly used SABA. Formoterol and salmeterol are the most commonly used LABAs. Formoterol, like albuterol, is a fast-acting reliever. Albuterol and (in some countries) formoterol are not only available by inhalation, but also by nebulization. There is no clinical difference between different devices for β_2 -agonists' delivery.³⁹ However, inhalers are less cumbersome and more convenient than nebulizers and preferred if proper inhaler technique is obtained.

The number of β_2 -adrenergic receptors on the smooth airway muscles decrease with aging.⁴⁰ The response to SABAs has been shown to decline with age⁴¹ and older asthmatics admitting to emergency rooms may be less responsive to albuterol than younger asthmatics.¹⁰ By contrast, current studies do not support that LABA use in older adults is less effective than in younger ages.^{1–5}

Guidelines recommend that asthmatics should have access to an inhaled fast-acting bronchodilator for rescue from acute symptoms.^{1–5} SABAs should not be utilized more than 2–3 times a week because regular use of SABAs alone is dangerous.⁴² LABAs should never be used alone as long-term regular monotherapy for asthma because they may be dangerous.^{43,44} When a low to medium ICS dose alone is unable to control asthma, the addition of an LABA has advantageous effects on lung function, symptoms, and exacerbations.⁴⁵ LABAs and ICS can be administered either separately or combined. Manufacturers have produced a combination of LABAs and ICS in a single inhaler, suggesting that it can optimize adherence with respect to separate inhaler use.^{46,47} Effectively, they ensure that LABAs are necessarily accompanied by ICS and their use is now widespread in real life. Even if used concomitantly with ICS, adverse effects of LABAs are not necessarily a nonissue⁴⁸ and they should be stopped when possible.⁴⁹ Concerns remain about the ultimate major cardiovascular safety of LABAs. Nevertheless, minor adverse outcomes are common in older asthmatics using LABA/ICS

combinations at daily recommended dosages: a survey found that, 41% and 51% of patients reported side effects attributed to ICS and LABA, respectively; the most common side effects were voice changes, sore throat, and tremors.⁵⁰

LABAs/ICS are currently used as a twice – daily regimen, but efforts have been made to develop a once-daily combination to simplify treatment and, possibly, increase adherence: indacaterol/mometasone, and vilanterol/fluticasone furoate are being developed and are two possible options.

Leukotriene receptor antagonists

Several studies have demonstrated that leukotriene receptor antagonists (LTRAs) are well tolerated and improve asthma control at all ages,⁵¹ including the elderly.⁵² LTRAs seem to be particularly useful in asthmatics with concomitant rhinitis,⁵³ and who smoke.⁵⁴ Once-daily orally administered montelukast is the most prescribed LTRA. When used alone, LTRAs are not as effective as ICS,⁵¹ but they are the first alternative to ICS in older asthmatics who prefer a nonsteroid drug or who cannot tolerate ICS. LTRAs are used as an alternative to LABAs in addition to ICS, but the combination treatment of LABAs/ICS has more efficacy.⁵⁵ Recently, LTRAs have been proposed in the elderly with difficult-to-treat asthma for steroid resistance.¹¹

Biological agents

Several biological agents are in advanced phases of study in asthma, but only omalizumab, a monoclonal antibody directed against serum immunoglobulin E (IgE), is currently a therapeutic option in severe asthmatics,⁵⁶ including the elderly.⁵⁷ Omalizumab is used as add-on therapy in allergic patients with elevated serum levels of IgE and severe asthma uncontrolled with high doses of ICS, or requiring systemic corticosteroids, where it reduces the incidence of exacerbations, emergency room visits, and improves quality of life.⁵⁶ Omalizumab is administered as a subcutaneous injection every 2 to 4 weeks depending on dose. Its cost is higher than that of other asthma therapies. There is no evidence of a persistent beneficial effect after stopping its use.⁵⁸ It has marked variability in response, being, to date, not clear what differentiates a responder from a nonresponder. The most common side effects of omalizumab are local symptoms at the site of injection, and with a small risk of anaphylaxis, corresponding to 0.09% of cases in post-marketing surveillance studies.⁵⁹

Systemic corticosteroids

A goal of asthma management is to achieve disease control with no or minimal use of systemic corticosteroids. In fact,

although systemic corticosteroids are very effective in asthma, their prolonged use is limited by the risk of significant adverse effects, such as adrenal failure, osteoporosis, diabetes mellitus, cataract, glaucoma, hypertension, psychosis, skin bruising, muscle weakness, gastritis, and peptic ulcer that warrant caution and monitoring.¹⁻⁴ However, long-term systemic corticosteroid use is sometimes required for severely uncontrolled asthma or as a burst to treat exacerbations. To this aim, oral prednisolone at daily dose of 0.5–1.0 mg/kg or equivalent is often given for at least 5 days,^{4,60} but the doses and duration should be individualized based on previous or current response. In addition, corticosteroids are also used for controlling a variety of diseases and in the elderly their weaning is a bigger challenge than in younger ages. Tapering is necessary after long-term use or recurrent bursts with systemic corticosteroids. Out of emergency oral preparations are preferred to intravenous and intramuscular formulations because they are equally effective and more practical.

Inhaled anticholinergics

Inhaled ipratropium, the most commonly used short-acting anticholinergic, is not a first-choice as a reliever, being less effective than β_2 -agonists. However, some elderly patients have a particularly good response to anticholinergics.⁶¹ In uncontrolled asthma, despite ICS/LABA use, the addition of once-daily tiotropium may give a significant improvement in forced expiratory volume in 1 second (FEV₁) and symptoms.⁶² In many countries, tiotropium is available with either the DPI HandiHaler® (Pfizer, Inc, New York, NY, USA) or the soft mist inhaler Respimat® (Boehringer Ingelheim, Ingelheim, Germany). However, the release of tiotropium via Respimat has been associated with an increase in deaths, mainly in the elderly with known cardiac rhythm disorders, so it is advisable to use the DPI for its delivery until the current concerns are excluded.⁶³ Possibly, tiotropium and other long-term anticholinergics might be useful as add-on treatment in moderate to severe asthma, but currently their use is off-label and has not yet translated into specific treatment guidelines.⁶²

Other treatments

Theophyllines, usually used as oral sustained-release formulations, are a third-choice, but may provide a benefit as add-on therapy in patients who do not achieve control with ICS/LABAs.¹⁻³ They have a relatively small therapeutic index with significant side effects, particularly at higher doses and in the elderly.²⁵

Long-term use of macrolides is gaining popularity in neutrophilic forms of difficult-to-treat asthma.⁶⁴⁻⁶⁶ It is not

clear if the beneficial effect of macrolides is due to antibiotic or immunomodulatory effects.

Roflumilast, a phosphodiesterase-4 inhibitor with anti-inflammatory properties, has shown some efficacy with tolerable gastrointestinal side effects in patients with mild to moderate asthma.⁶⁷ Further trials are necessary to determine its role in asthma treatment.

Immunosuppressors, such as methotrexate, cyclosporins, tacrolimus, azathioprine, and gold salts are seldom used in asthma because they sustain a variety of side effects that usually do not offset their steroid-sparing effect.³

Bronchial thermoplasty is a relatively safe bronchoscopic procedure in which radiofrequency energy is used to reduce bronchial smooth muscle wall thickness. If more clinical data will confirm its potential, bronchial thermoplasty might eventually become an option in severe asthma resistant to pharmacological management.⁶⁸

Trigger avoidance and the role of comorbidities

Allergy has a well-known role in asthma, even if, overall, it seems to wane with age.^{69,70} However, asthma in the elderly may be associated with allergic triggers.⁷⁰ There is scarce evidence about whether measures to create a low-allergen environment are effective for improving asthma control in the elderly. The role of specific immunotherapy in elderly asthmatics is limited, but specific allergen immunotherapy may be an appropriate adjunctive therapy when a clear relationship exists between symptoms, allergen exposure, and positivity to a skin test.⁷¹

Asthma exacerbations are often sustained in the elderly by a variety of nonallergenic triggers, such as viral infections, pollutants, and drugs. Elderly asthmatics often perceive viral infections as common triggers and two thirds reported seasonal worsening in winter.⁷² Patients with moderate to severe asthma should be advised to receive an influenza vaccination every year; they are safe and have a small risk of pulmonary complications.⁷³ From the 1991–2002 Medicare Survey, 72% of older subjects received influenza vaccinations.⁷⁴

Several epidemiologic studies suggest an association between outbreaks of asthma exacerbations and exposures to air pollutants;⁷⁵ environmental tobacco smoke is an important and modifiable air pollutant.⁷⁵ Surprisingly, active smoking is common among asthmatics.⁷⁶ Asthmatics who smoke often have poor disease control⁷⁶ and diminished responsiveness to ICS^{54,77} and systemic corticosteroids.⁷⁸ It is generally believed that the damage from smoking has already been done in the elderly, but, although more beneficial when achieved early,

quitting is always useful⁷⁹ and has to be encouraged for all asthmatics who smoke, because clinically useful, traditional drugs used for support in smoking cessation have been safely and successfully used in the elderly.⁸⁰

Physical activity is important for patients with chronic respiratory diseases. It has been found that exercise training improves quality of life in older asthmatics.⁸¹

Older asthmatics have an increased risk of comorbidities, as shown in Table 5.⁸² In a survey, the prevalence of comorbidities in asthmatics was 22% higher than in healthy counterparts of similar age.⁸³ Several studies have also found an association between uncontrolled asthma and comorbidities and the proper treatment of some comorbidities may successfully contribute to asthma control.⁸² On the other hand, treatment of other comorbidities, such as hypertension, congestive heart failure, arthrosis, and glaucoma can sustain or worsen asthma.⁸² Possibly nonsteroidal anti-inflammatory drugs⁸⁴ and β -blockers,⁸⁵ including topical formulations,⁸⁶ are the most well-known drugs causing asthma exacerbations and should be avoided in patients with a history of unfavorable outcomes with these agents. Paracetamol and some selective cyclooxygenase-2 inhibitors, such as celecoxib and etoricoxib, and some newer beta-blockers may be a safer alternative.^{87,88}

Role of education

The role of education in asthma management is essential and its key components are displayed in Table 6.¹⁻⁴

The main goals of education are to achieve the patient's self-management and improve adherence. Self-management requires not only the acquisition of knowledge and skills, but also behavior changes in order to achieve positive health effects.⁸⁹ Even if older asthmatics may be more prone to accept a passive approach and be less involved or not seek

Table 5 Main asthma-related comorbidities

Rhinitis/rhinosinusitis
Gastro-esophageal reflux disease
Obesity
Obstructive sleep apnea syndrome and other sleep-disordered breathing
Chronic obstructive pulmonary disease
Psychopathologies, mainly depression
Tobacco smoking
Osteoporosis
Dysfunctional breathing/vocal cord dysfunction
Hormonal disorders
Hypertension, diabetes, ischemic heart disease, degenerative joint disease/arthritis, cardiac arrhythmia, congestive heart failure, cerebrovascular disease/atherosclerosis ^a

Note: ^aProbably increased.

Table 6 Key components of a personalized asthma education program

Develop good patient–doctor partnership
Discuss the nature of the disease and its pathophysiology
Evaluate patient's triggers
Identify patient's goals and preferences
Develop a self-monitoring plan in how to monitor symptoms and lung function
Discuss patient's lifestyle and change options that are useful for better asthma control according to patient's goals and preferences
Evaluate treatment regimen according to patient's goals and preferences
Discuss comorbidities and their treatment including over-the-counter medications, drops, and health food preparations
Share and document decisions about treatment, lifestyle regimens, and trigger avoidance according to the patient's goals
Share a written asthma action plan for the early recognition and treatment of exacerbations, including when and how early to access health care providers for unscheduled visits or emergencies
Teach proper inhaler technique with practical examples using the prescribed placebo inhaler
Schedule follow-up appointments according to patient's availability
Control and document asthma control at each follow-up visit
Control and document comorbidities, their treatment, and possible drug–drug interactions at each follow-up visit
Control and document effectiveness of the trigger avoidance program at each follow-up visit
Control and document effectiveness of lifestyles program at each follow-up visit
Control and document adherence to shared treatment at each follow-up visit
Control and document inhaler technique at each follow-up visit

out information,⁹⁰ self-management is possible and effective even in the elderly and may also contribute to improve adherence.⁹³⁻⁹⁵

Adherence is defined as the degree to which patient behaviors coincide with the recommendations of health care providers.⁹⁶ Adherence is a major problem for treatment of all chronic diseases, including asthma. Nonadherence significantly contributes to asthma mortality,⁹⁷ hospitalizations,⁹⁸ high health care costs,⁹⁵ and increased exacerbations.⁹⁹ It is useful to distinguish between intentional and unintentional nonadherence. Intentional nonadherence occurs when the patient decides either not to take the drug, to only take it from time to time, or to take a different dosage than prescribed.⁹⁶ Possibly, at similar baseline conditions, older asthmatics have the same degree of intentional nonadherence with respect to previous ages, even if in real life they often suffer from conditions predisposing them to nonadherence, such as polypharmacy and depression.^{100,101} Unintentional nonadherence occurs when a patient involuntarily does not follow medical prescriptions.⁹⁶ Poor inhaler technique is a variety of unintentional nonadherence⁹⁶ and it is common in asthma, as the most important drugs used for its manage-

ment are administered by inhalation. The effective use of inhalers is critically dependent upon the patient's ability to utilize the device properly. Although inhaler misuse may be due to a poor device choice for an individual patient, more often it occurs for lack of proper education.¹⁰² Unfortunately, poor inhaler technique is commonly observed for all inhaler devices, is associated with poor asthma control,¹⁰³ and with increased age.¹⁰² The most important modifiable factors associated with improved inhaler use for both MDI and DPI are the provision of instructions (practical education being better than verbal) at the first prescription and regular checks at each follow-up visit by trained health caregivers.¹⁰² Because the problem of inhaler misuse is neglected by patients and physicians, inhaler education should be an integral part of the routine management of any asthmatic patient.

Conclusion

Current guidelines do not include specific sections for the management of asthma in the elderly, supporting the view that drugs that are useful in managing asthma in the elderly are as effective as for other age groups. This is only partially evidence-based, as many randomized trials of treatment exclude older asthmatics.¹⁰⁴ According to this view, other reasons explain the greater percentage of uncontrolled asthma in the elderly, with increased morbidity and mortality.

A first cause is that many elderly patients perceive or tolerate substantial asthma symptoms, perhaps having low expectations about the degree of control that is possible. A second cause is that older asthmatics often suffer from many other comorbidities, which, directly or by treatment, may worsen the control of asthma. Possibly, patients and physicians often make tradeoffs with these comorbidities and do not treat asthma, considering it to be less dangerous. Importantly, guidelines do not include specific extensive sections for patients with multiple comorbidities and polypharmacy, a very common situation in the elderly; when guidelines describe possible interactions between diseases and with other drugs taken concomitantly, the discussion is superficial and limited to a few generic warnings, while drug–drug interactions often largely contribute to worsen asthma control in older adults. This calls for a shift in clinical research towards more pragmatic trials to generate more applicable evidence according to the peculiarities and the needs of older asthmatics.^{105,106} A third cause is poor adherence. It also includes inhaler misuse, which is particularly common in the elderly and often not contrasted efficiently.

We conclude that despite the fact that a variety of treatment options for good asthma management are available,

in real life many elderly asthmatics suffer from poor disease control. The main reasons are that older asthmatics tolerate or do not perceive poor symptom control, are not encouraged to develop self-management, and have poor adherence to medications including common inhaler misuse. Concomitant comorbidities and/or related treatments may also contribute to poor asthma control. Identification and use of specific instruments addressed to evaluate asthma control in the elderly with concomitant comorbidities as well as measurements for improving self-management and adherence are needed for better asthma control in the elderly.

Disclosure

AS Melani has served as an advisory board member, has been reimbursed for speaker honoraria, and has received fees as a consultant for Chiesi, Menarini, Novartis, Mundipharma, GSK, Sanofi-Aventis, and Artsana. There was no source of financial support for the present manuscript. The author reports no other conflicts of interest in this work.

References

1. National Heart, Lung, and Blood Institute; National Asthma Education and Prevention Program. *Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma*. Bethesda: National Heart, Lung, and Blood Institute; 2007. Available from: <http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.pdf>. Accessed March 31, 2013.
2. British Thoracic Society; Scottish Intercollegiate Guidelines Network. *British Guideline on the Management of Asthma. A national clinical guideline*. Edinburgh: Scottish Intercollegiate Guidelines Network; 2012. Available from: <http://www.sign.ac.uk/pdf/sign101.pdf>. Accessed March 31, 2013.
3. Global Initiative for Asthma [homepage on the Internet]. Global strategy for asthma management and prevention [updated 2009]. Available from: <http://www.ginasthma.org/guidelines-gina-report-global-strategy-for-asthma.html>. Accessed March 31, 2013.
4. Loughheed MD, Leniere C, Ducharme FM; Canadian Thoracic Society Asthma Clinical Assembly. Canadian Thoracic Society 2012 Guideline update: diagnosis and management of asthma in preschoolers, children, and adults: executive summary. *Can Respir J*. 2012;19(6):e81–e88.
5. Jonas DE, Wines RCM, DelMonte M, et al; Oregon Health and Science University. *Drug Class Review: Controller Medications for Asthma. Final Update 1 Report*. 2011. Available from: <http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0032860/pdf/TOC.pdf>. Accessed March 31, 2013.
6. Zureik M, Orehek J. Diagnosis and severity of asthma in the elderly: results of a large survey in 1,485 asthmatics recruited by lung specialists. *Respiration*. 2002;69(3):223–228.
7. Simpson CR, Sheikh A. Trends in the epidemiology of asthma in England: a national study of 333,294 patients. *J R Soc Med*. 2010;103(3):98–106.
8. Enright PL, McClelland RL, Newman AB, Gottlieb DJ, Lebowitz MD. Underdiagnosis and undertreatment of asthma in the elderly. Cardiovascular Health Study Research Group. *Chest*. 1999;116(3):603–613.
9. Plaza V, Serra-Batlles J, Ferrer M, Morejón E. Quality of life and economic features in elderly asthmatics. *Respiration*. 2000;67(1):65–70.
10. Banerji A, Clark S, Afilalo M, Blanda MP, Cydulka RK, Camargo CA Jr. Prospective multicenter study of acute asthma in younger versus older adults presenting to the emergency department. *J Am Geriatr Soc*. 2006;54(1):48–55.

11. Hanania NA, King MJ, Braman SS, et al; Asthma in Elderly workshop participants. Asthma in the elderly: Current understanding and future research needs – a report of a National Institute on Aging (NIA) workshop. *J Allergy Clin Immunol*. 2011;128(Suppl 3):S4–S24.
12. Talreja N, Baptist AP. Effect of age on asthma control: results from the National Asthma Survey. *Ann Allergy Asthma Immunol*. 2011;106(1):24–29.
13. Tsai CL, Delclos GL, Huang JS, Hanania NA, Camargo CA Jr. Age-related differences in asthma outcomes in the United States, 1988–2006. *Ann Allergy Asthma Immunol*. 2013;110(4):240–246.
14. O'Byrne PM, Reddel HK, Eriksson G, et al. Measuring asthma control: a comparison of three classification systems. *Eur Respir J*. 2010;36(2):269–276.
15. Connolly MJ, Crowley JJ, Charan NB, Nielson CP, Vestal RE. Reduced subjective awareness of bronchoconstriction provoked by methacholine in elderly asthmatic and normal subjects as measured on a simple awareness scale. *Thorax*. 1992;47(6):410–413.
16. Ekici M, Apan A, Ekici A, Erdemoglu AK. Perception of bronchoconstriction in elderly asthmatics. *J Asthma*. 2001;38(8):691–696.
17. Goeman DP, O'Hehir RE, Jenkins C, Scharf SL, Douglass JA. 'You have to learn to live with it': a qualitative and quantitative study of older people with asthma. *Clin Respir J*. 2007;1(2):99–105.
18. Allen SC, Vassallo M, Khattab A. The threshold for sensing airflow resistance during tidal breathing rises in old age: implications for elderly patients with obstructive airways diseases. *Age Ageing*. 2009;38(5):548–552.
19. Gibson PG, McDonald VM, Marks GB. Asthma in older adults. *Lancet*. 2010;376(9743):803–813.
20. Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. *Eur Respir J*. 1999;14(4):902–907.
21. Nathan RA, Sorkness CA, Kosinski M, et al. Development of the asthma control test: a survey for assessing asthma control. *J Allergy Clin Immunol*. 2004;113(1):59–65.
22. Vollmer WM, Markson LE, O'Connor E, et al. Association of asthma control with health care utilization and quality of life. *Am J Respir Crit Care Med*. 1999;160(5 Pt 1):1647–1652.
23. Buist AS, Vollmer WM, Wilson SR, Frazier EA, Hayward AD. A randomized clinical trial of peak flow versus symptom monitoring in older adults with asthma. *Am J Respir Crit Care Med*. 2006;174(10):1077–1087.
24. Columbo M, Wong B, Panettieri RA Jr, Rohr AS. Asthma in the elderly: the role of exhaled nitric oxide measurements. *Respir Med*. 2013;107(5):785–787.
25. NAEPP Working Group Report. *Considerations for Diagnosing and Managing Asthma in the Elderly*. Bethesda: National Heart, Lung, and Blood Institute; 1996. Available from: http://msdh.ms.gov/msdhsite/_static/resources/2107.pdf. Accessed on March 20, 2013.
26. Barnes PJ, Pedersen S, Busse WW. Efficacy and safety of inhaled corticosteroids. New developments. *Am J Respir Crit Care Med*. 1998;157(3 Pt 2):S1–S53.
27. Lipworth BJ. Systemic adverse effects of inhaled corticosteroid therapy: A systematic review and meta-analysis. *Arch Intern Med*. 1999;159(9):941–955.
28. Szefer SJ, Martin RJ, King TS, et al; Asthma Clinical Research Network of the National Heart Lung, and Blood Institute. Significant variability in response to inhaled corticosteroids for persistent asthma. *J Allergy Clin Immunol*. 2002;109(3):410–418.
29. Derendorf H, Nave R, Drollmann A, Cerasoli F, Wurst W. Relevance of pharmacokinetics and pharmacodynamics of inhaled corticosteroids to asthma. *Eur Respir J*. 2006;28(5):1042–1050.
30. Melani AS. Nebulized corticosteroids in asthma and COPD. An Italian appraisal. *Respir Care*. 2012;57(7):1161–1174.
31. Price D, Martin RJ, Barnes N, et al. Prescribing practices and asthma control with hydrofluoroalkane-beclomethasone and fluticasone: a real-world observational study. *J Allergy Clin Immunol*. 2010;126(3):511–518.
32. Müller V, Gálffy G, Eszes N, et al. Asthma control in patients receiving inhaled corticosteroid and long-acting beta2-agonist fixed combinations. A real-life study comparing dry powder inhalers and a pressurized metered dose inhaler extrafine formulation. *BMC Pulm Med*. 2011;11:40.
33. Brusselle G, Peché R, Van den Brande P, Verhulst A, Hollanders W, Bruhwyler J. Real-life effectiveness of extrafine beclomethasone dipropionate/formoterol in adults with persistent asthma according to smoking status. *Respir Med*. 2012;106(6):811–819.
34. Rank MA, Hagan JB, Park MA, et al. The risk of asthma exacerbation after stopping low-dose inhaled corticosteroids: A systematic review and meta-analysis of randomized controlled trials. *J Allergy Clin Immunol*. 2013;131(3):724–729.
35. Wenzel SE. Asthma: defining of the persistent adult phenotypes. *Lancet*. 2006;368(9537):804–813.
36. Thomas RA, Green RH, Brithling CE, et al. The influence of age on induced sputum differential cell counts in normal subjects. *Chest*. 2004;126(6):1811–1814.
37. Navaratnam P, Jayawant SS, Pedersen CA, Balkrishnan R. Asthma pharmacotherapy prescribing in the ambulatory population of the United States: evidence of nonadherence to national guidelines and implications for elderly people. *J Am Geriatr Soc*. 2008;56(7):1312–1317.
38. Sin DD, Tu JV. Inhaled corticosteroid therapy reduces the risk of rehospitalization and all-cause mortality in elderly asthmatics. *Eur Respir J*. 2001;17(3):380–385.
39. Dolovich MB, Ahrens RC, Hess DR, et al; American College of Chest Physicians; American College of Asthma, Allergy, and Immunology. Device selection and outcomes of aerosol therapy: Evidence-based guidelines: American College of Chest Physicians/American College of Asthma, Allergy, and Immunology. *Chest*. 2005;127(1):335–371.
40. Pfeifer MA, Weinberg CR, Cook D, Best JD, Reenan A, Halter JB. Differential changes of autonomic nervous system function with age in man. *Am J Med*. 1983;75(2):249–258.
41. Connolly MJ, Crowley JJ, Charan NB, Nielson CP, Vestal RE. Impaired bronchodilator response to albuterol in healthy elderly men and women. *Chest*. 1995;108(2):401–406.
42. Sears MR, Taylor DR, Print CG, et al. Regular inhaled beta-agonist treatment in bronchial asthma. *Lancet*. 1990;336(8728):1391–1396.
43. Lazarus SC, Boushey HA, Fahy JV, et al; Asthma Clinical Research Network for the National Heart, Lung, and Blood Institute. Long-acting beta2-agonist monotherapy vs continued therapy with inhaled corticosteroids in patients with persistent asthma: a randomized controlled trial. *JAMA*. 2001;285(20):2583–2593.
44. Nelson HS, Weiss ST, Bleecker ER, Yancey SW, Dorinsky PM; SMART Study Group. The Salmeterol Multicenter Asthma Research Trial: a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. *Chest*. 2006;129(1):15–26.
45. Bateman ED, Boushey HA, Bousquet J, et al; GOAL Investigators Group. Can guideline-defined asthma control be achieved? The Gaining Optimal Asthma Control study. *Am J Respir Crit Care Med*. 2004;170(8):836–844.
46. Stempel DA, Stoloff SW, Carranza Rosenzweig JR, Stanford RH, Ryskina KL, Legorreta AP. Adherence to asthma controller medication regimens. *Respir Med*. 2005;99(10):1263–1267.
47. Perrin K, Williams M, Wijesinghe M, James K, Weatherall M, Beasley R. Randomized controlled trial of adherence with single or combination inhaled corticosteroid/long-acting beta-agonist inhaler therapy in asthma. *J Allergy Clin Immunol*. 2010;126(3):505–510.
48. McMahon AW, Levenson MS, McEvoy BW, Mosholder AD, Murphy D. Age and risks of FDA-approved long-acting β_2 -adrenergic receptor agonists. *Pediatrics*. 2011;128(5):e1147–e1154.
49. Brozek JL, Kraft M, Krishnan JA, et al. Long-acting β_2 -agonist step-off in patients with controlled asthma. *Arch Intern Med*. 2012;172(18):1365–1375.
50. Goeman DP, Jenkins CR, Crane MA, Bosnic-Anticevich SZ, Douglass JA. Unmet needs of older people with asthma: cross-sectional survey. *J Asthma*. 2011;48(9):865–875.

51. Chauhan BF, Ducharme FM. Anti-leukotriene agents compared to inhaled corticosteroids in the management of recurrent and/or chronic asthma in adults and children. *Cochrane Database Syst Rev*. 2012;5: CD002314.
52. Korenblat PE, Kemp JP, Scherger JE, Minkwitz MC, Mezzanotte W. Effect of age on response to zafirlukast in patients with asthma in the Accolate Clinical Experience And Pharmacoepidemiology Trial (ACCEPT). *Ann Allergy Asthma Immunol*. 2000;84(2):217–225.
53. Price DB, Swern A, Tozzi CA, Philip G, Polos P. Effect of montelukast on lung function in asthma patients with allergic rhinitis: analysis from the COMPACT trial. *Allergy*. 2006;61(6):737–742.
54. Lazarus SC, Chinchilli VM, Rollings NJ, et al; National Heart Lung and Blood Institute's Asthma Clinical Research Network. Smoking affects response to inhaled corticosteroids or leukotriene receptor antagonists in asthma. *Am J Respir Crit Care Med*. 2007;175(8):783–790.
55. Ducharme FM, Lasserson TJ, Cates CJ. Addition to inhaled corticosteroids of long-acting beta2-agonists versus anti-leukotrienes for chronic asthma. *Cochrane Database Syst Rev*. 2011;(5):CD003137.
56. Tan R, Corren J. Omalizumab in the treatment of asthma. *Expert Rev Respir Med*. 2011;5(6):747–756.
57. Buhl R, Fox H, Blogg M, Reisner C. Add-on omalizumab therapy reduces clinically significant and severe asthma exacerbations, and improves FEV1 in patients with severe persistent allergic asthma irrespective of age. *Eur Respir J*. 2005;26(Suppl 49):48S, P418.
58. Lowe PJ, Renard D. Omalizumab decreases IgE production in patients with allergic (IgE-mediated) asthma; PKPD analysis of a biomarker, total IgE. *Br J Clin Pharmacol*. 2011;72(2):306–320.
59. Cox L, Lieberman P, Wallace D, et al. American Academy of Allergy, Asthma and Immunology/American College of Allergy, Asthma and Immunology Omalizumab-Associated Anaphylaxis Joint Task Force follow-up report. *J Allergy Clin Immunol*. 2011;128(1):210–212.
60. Tattersfield AE, Postma DS, Barnes PJ, et al. Exacerbations of asthma: a descriptive study of 425 severe exacerbations. The FACET International Study Group. *Am J Respir Crit Care Med*. 1999;160(2):594–599.
61. Ullah MI, Newman GB, Saunders KB. Influence of age on response to ipratropium and salbutamol in asthma. *Thorax*. 1981;36(7):523–529.
62. Lipworth BJ. Emerging role of long-acting muscarinic antagonists for asthma. *Br J Clin Pharmacol*. Epub March 28, 2013.
63. Singh S, Loke YK, Enright PL, Furberg CD. Mortality associated with tiotropium mist inhaler in patients with chronic obstructive pulmonary disease: systematic review and meta-analysis of randomised controlled trials. *BMJ*. 2011;342:d3215.
64. Simpson JL, Powell H, Boyle MJ, Scott RJ, Gibson PG. Clarithromycin targets neutrophilic airway inflammation in refractory asthma. *Am J Respir Crit Care Med*. 2008;177(2):148–155.
65. Sutherland ER, King TS, Icitovic N, et al; National Heart, Lung and Blood Institute's Asthma Clinical Research Network. A trial of clarithromycin for the treatment of suboptimally controlled asthma. *J Allergy Clin Immunol*. 2010;126(4):747–753.
66. Brusselle GG, Vanderstichele C, Jordens P, et al. Azithromycin for prevention of exacerbations in severe asthma (AZISAST): a multicentre randomised double-blind placebo-controlled trial. *Thorax*. 2013;68(4):322–329.
67. Bateman ED, Izquierdo JL, Harnest U, et al. Efficacy and safety of roflumilast in the treatment of asthma. *Ann Allergy Asthma Immunol*. 2006;96(5):679–686.
68. Gildea TR, Khatri SB, Castro M. Bronchial thermoplasty: a new treatment for severe refractory asthma. *Cleve Clin J Med*. 2011;78(7): 477–485.
69. Slavin RG, Haselkorn T, Lee JH, Zheng B, Deniz Y, Wenzel SE; TENOR Study Group. Asthma in older adults: observations from the epidemiology and natural history of asthma: outcomes and treatment regimens (TENOR) study. *Ann Allergy Asthma Immunol*. 2006;96(3): 406–414.
70. Scichilone N, Callari A, Augugliaro G, Marchese M, Toggias A, Bellia V. The impact of age on prevalence of positive skin prick tests and specific IgE tests. *Respir Med*. 2011;105(5):651–658.
71. Bozek A, Ignasiak B, Filipowska B, Jarzab J. House dust mite sublingual immunotherapy: a double-blind, placebo-controlled study in elderly patients with allergic rhinitis. *Clin Exp Allergy*. 2013;43(2):242–248.
72. Jackson DJ, Johnston SL. The role of viruses in acute exacerbations of asthma. *J Allergy Clin Immunol*. 2010;125(6):1178–1187.
73. Pesek R, Lockey R. Vaccination of adults with asthma and COPD. *Allergy*. 2011;66(1):25–31.
74. Centers for Disease Control and Prevention (CDC). Influenza vaccination and self-reported reasons for not receiving influenza vaccination among Medicare beneficiaries aged ≥ or = 65 years – United States, 1991–2002. *MMWR Morb Mortal Wkly Rep*. 2004;53(43):1012–1015.
75. Bentayeb M, Simoni M, Baiz N, et al; Geriatric Study in Europe on Health Effects of Air Quality in Nursing Homes Group. Adverse respiratory effects of outdoor air pollution in the elderly. *Int J Tuberc Lung Dis*. 2012;16(9):1149–1161.
76. Boulet LP, FitzGerald JM, McIvor RA, Zimmerman S, Chapman KR. Influence of current or former smoking on asthma management and control. *Can Respir J*. 2008;15(5):275–279.
77. Tomlinson JE, McMahon AD, Chaudhuri R, Thompson JM, Wood SF, Thomson NC. Efficacy of low and high dose inhaled corticosteroid in smokers versus non-smokers with mild asthma. *Thorax*. 2005;60(4): 282–287.
78. Chaudhuri R, Livingston E, McMahon AD, Thomson L, Borland W, Thomson NC. Cigarette smoking impairs the therapeutic response to oral corticosteroids in chronic asthma. *Am J Respir Crit Care Med*. 2003;168(11):1308–1311.
79. Gellert C, Schöttker B, Brenner H. Smoking and all-cause mortality in older people: systematic review and meta-analysis. *Arch Intern Med*. 2012;172(11):837–844.
80. Tait RJ, Hulse GK, Waterreus A, et al. Effectiveness of a smoking cessation intervention in older adults. *Addiction*. 2007;102(1): 148–155.
81. Turner S, Eastwood P, Cook A, Jenkins S. Improvements in symptoms and quality of life following exercise training in older adults with moderate/severe persistent asthma. *Respiration*. 2011;81(4):302–310.
82. Boulet LP, Boulay MÈ. Asthma-related comorbidities. *Expert Rev Respir Med*. 2011;5(3):377–393.
83. Gershon AS, Guan J, Wang C, Victor JC, To T. Describing and quantifying asthma comorbidity: a population study. *PLoS One*. 2012;7(5): e34967.
84. Szczeklik A. Aspirin-induced asthma: a tribute to John Vane as a source of inspiration. *Pharmacol Rep*. 2010;62(3):526–529.
85. Ashrafian H, Violaris AG. Beta-blocker therapy of cardiovascular diseases in patients with bronchial asthma or COPD: the pro viewpoint. *Prim Care Respir J*. 2005;14(5):236–241.
86. Odeh M, Oliven A, Bassan H. Timolol eyedrop-induced fatal bronchospasm in an asthmatic patient. *J Fam Pract*. 1991;32(1):97–98.
87. Martín-García C, Hinojosa M, Berges P, Camacho E, García-Rodríguez R, Alfaya T. Celecoxib, a highly selective COX-2 inhibitor, is safe in aspirin-induced asthma patients. *J Invest Allergol Clin Immunol*. 2003;13(1):20–25.
88. Hanania NA, Singh S, El-Wali R, et al. The safety and effects of the beta-blocker, nadolol, in mild asthma: an open-label pilot study. *Pulm Pharmacol Ther*. 2008;21(1):134–141.
89. Gibson PG, Powell H, Coughlan J, et al. Self-management education and regular practitioner review for adults with asthma. *Cochrane Database Syst Rev*. 2003;(1):CD001117.
90. Schneider A, Körner T, Mehring M, Wensing M, Elwyn G, Szecsenyi J. Impact of age, health locus of control and psychological co-morbidity on patients' preferences for shared decision making in general practice. *Patient Educ Couns*. 2006;61(2):292–298.
91. Patel RR, Saltoun CA, Grammer LC. Improving asthma care for the elderly: a randomized controlled trial using a simple telephone intervention. *J Asthma*. 2009;46(1):30–35.
92. Baptist AP, Ross JA, Yang Y, Song PX, Clark NM. A randomized controlled trial of a self-regulation intervention for older adults with asthma. *J Am Geriatr Soc*. 2013;61(5):747–753.

93. Goeman DP, Sanci LA, Scharf SL, et al. Improving general practice consultations for older people with asthma: a cluster randomised control trial. *Med J Aust.* 2009;191(2):113–117.
94. Bozek A, Jarzab J. Adherence to asthma therapy in elderly patients. *J Asthma.* 2010;47(2):162–165.
95. Wilson SR, Strub P, Buist AS, et al; Better Outcomes of Asthma Treatment (BOAT) Study Group. Shared treatment decision making improves adherence and outcomes in poorly controlled asthma. *Am J Respir Crit Care Med.* 2010;181(6):566–577.
96. World Health Organization. *Adherence to Long-term Therapies: Evidence for Action.* Geneva: World Health Organization; 2003. Available from: http://www.who.int/chp/knowledge/publications/adherence_report/en/. Accessed March 20, 2013.
97. Harrison B, Stephenson P, Mohan G, Nasser S. An ongoing Confidential Enquiry into asthma deaths in the Eastern Region of the UK, 2001–2003. *Prim Care Respir J.* 2005;14(6):303–313.
98. Williams LK, Pladevall M, Xi H, et al. Relationship between adherence to inhaled corticosteroids and poor outcomes among adults with asthma. *J Allergy Clin Immunol.* 2004;114(6):1288–1293.
99. Williams LK, Peterson EL, Wells K, et al. Quantifying the proportion of severe asthma exacerbations attributable to inhaled corticosteroid nonadherence. *J Allergy Clin Immunol.* 2011;128(6):1185–1191.
100. DiMatteo MR, Lepper HS, Croghan TW. Depression is a risk factor for noncompliance with medical treatment: meta-analysis of the effects of anxiety and depression on patient adherence. *Arch Intern Med.* 2000;160(14):2101–2107.
101. Krauskopf KA, Sofianou A, Goel MS, et al. Depressive symptoms, low adherence, and poor asthma outcomes in the elderly. *J Asthma.* 2013;50(3):260–266.
102. Sestini P, Cappiello V, Aliani M, et al; Associazione Italiana Pneumologi Ospedalieri Educational Group. Prescription bias and factors associated with improper use of inhalers. *J Aerosol Med.* 2006;19(2):127–136.
103. Melani AS, Bonavia M, Cilenti V, et al; Gruppo Educazionale Associazione Italiana Pneumologi Ospedalieri. Inhaler mishandling remains common in real life and is associated with reduced disease control. *Respir Med.* 2011;105(6):930–938.
104. Travers J, Marsh S, Williams M, et al. External validity of randomised controlled trials in asthma: to whom do the results of the trials apply? *Thorax.* 2007;62(3):219–223.
105. Krishnan JA, Schatz M, Apter AJ. A call for action: Comparative effectiveness research in asthma. *J Allergy Clin Immunol.* 2011;127(1):123–127.
106. Price D, Hillyer EV, van der Molen T. Efficacy versus effectiveness trials: informing guidelines for asthma management. *Curr Opin Allergy Clin Immunol.* 2013;13(1):50–57.

Clinical Interventions in Aging

Publish your work in this journal

Clinical Interventions in Aging is an international, peer-reviewed journal focusing on evidence-based reports on the value or lack thereof of treatments intended to prevent or delay the onset of maladaptive correlates of aging in human beings. This journal is indexed on PubMed Central, MedLine, the American Chemical Society's 'Chemical Abstracts

Submit your manuscript here: <http://www.dovepress.com/clinical-interventions-in-aging-journal>

Dovepress

Service' (CAS), Scopus and the Elsevier Bibliographic databases. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.