

Pharmacotherapy in the management of asthma in the elderly: a review of clinical studies

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Asthma in the elderly is a disease with emerging concern. Despite some recent advances in our understanding of epidemiology and pathophysiology, there is a considerable lack of clinical evidence specific to elderly patients. Currently available high quality clinical evidence has been mostly obtained from younger adults, but rarely from elderly patients. Under-representation of elderly patients in previous randomized trials may have been due to being, old age, or having comorbidities. Thus, a question may be raised whether current clinical evidence could be well generalized into elderly patients. Further clinical trials should address clinical issues raised in elderly population. In this review, we aimed to overview the efficacy and safety of pharmacological management, and also to summarize the literature relevant to elderly asthma.

Keywords: Drug Therapy; Asthma; Aged

INTRODUCTION

It is now increasingly recognized that asthma in the elderly (≥ 65 years) is a major health problem [1]. Prevalence of current asthma appears to be similar to, or even higher in the elderly than that in younger adults [2]. Incidence data also indicated

that asthma is not a rare disease in the elderly, reporting that the incidence was as high as 7% in the elderly, which was similar across adult age groups [3]. Significantly higher morbidity and mortality burden in the elderly, compared to that in younger patients [4], highlights its major unmet clinical needs.

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There are many challenges in the management of asthma in the elderly, including distinct risk factors, multiple comorbidities, decreased cognitive function, lack of caregiver, and poor adherence [2]. However, another major challenge would be the lack of clinical evidence on the efficacy of therapeutic agents obtained from elderly patients. Recent Global Initiative for Asthma (GINA) guideline allocated a section for the management of asthma for the elderly, but still in a brief way [5]. As commented in the guideline [5], elderly patients have been often excluded from major clinical trials, probably because of old age and multiple comorbidities. According to a recent retrospective analysis in Italy, about 40% of adult asthma patients virtually belonged to ineligible group in asthma inhaler trial with usual selection criteria, simply because of being older than 65 years [6]. This problem indicates a major gap between current evidence and real-world practice for elderly patients.

In this review, we aimed to overview the literature on the efficacy of asthma controller medications and to specify clinical issues related to the elderly. Through this, we aimed to identify current status and gaps in the clinical evidence for managing elderly asthma patients.

CORTICOSTEROIDS

Inhaled corticosteroids

Inhaled corticosteroid (ICS) is a mainstay in the pharmacotherapy for asthma, as chronic airway inflammation is a key feature of the disease [5]. ICS improves symptom control, quality of life, lung function, exacerbation risk and asthma-related mortality [7-10]. Considering many different immune cells involved in asthma pathogenesis, it may be natural that broad anti-inflammatory effects of corticosteroids offer more therapeutic gain than more specific anti-inflammatory drugs.

As ICS largely targets eosinophilic inflammation, the effects could vary with inflammatory profiles of asthma patients. Thus, it could be also questioned if ICS is equally effective in the elderly patients, as they are less atopic. However, degree of airway eosinophilia, based on induced sputum studies, appears to be similar between elderly and younger patients [11, 12]. One observational data from TENOR (The Epidemiology and Natural history of asthma: Outcomes and treatment Regimens) study suggests that active ICS therapy could improve asthma outcomes effectively in elderly patients [13]. Also in a population-

based study in Canada, ICS was beneficial in reducing the risks of rehospitalization and all-cause mortality in elderly asthma patients, compared to those who did not receive ICS over a one year follow-up after discharge [14].

Safety issues of ICS in the elderly have been recently reviewed in details by Battaglia et al. [15]. Briefly, ICS is considered to be generally safe at low dose, but may have concerns in the elderly at high dose. Higher cumulative dose of ICS could influence bone mineral density and increase the risk of nonvertebral fracture among adults [16, 17]. Cumulative dose of ICS was significantly correlated with the risk of cataract extraction [18]. Also in a retrospective analysis of older asthma patients who received ICS treatment for longer than 6 months (mean age, 67.2 years), daily dose of ICS showed trends toward the risks of adrenal insufficiency or abnormal adrenocorticotrophic hormone responses, but the risks were strongly increased by concomitant oral steroid use [19]. Local side effects, such as oropharyngeal candidiasis, hoarseness and dysphonia, may increase with age due to poor inhaler technique or physical function [5].

Another safety concern is a potential risk of pneumonia. This issue was initially raised from clinical trials of chronic obstructive pulmonary disease (COPD) patients. The TORCH (Towards a Revolution in COPD Health) study was the first report on the increased risk of pneumonia among COPD patients receiving ICS [20]. The overall risks of pneumonia were found to be significantly related to fluticasone but not budesonide [21, 22]; however, in a recent Cochrane group meta-analysis, no significant difference was found with respect to serious adverse events or mortality between fluticasone and budesonide among COPD patients [23]. Among patients with asthma, a recent case-control study reported a possible dose-response relationship between ICS dose and risk of pneumonia or lower respiratory tract infection [24]. However, the mechanisms of ICS to increase the risk of pneumonia in asthma are not clear. As asthma patients frequently have COPD together with ageing [2], the issue of pneumonia risk of ICS needs prospective investigation in elderly patients with asthma.

To maximize the efficacy of ICS therapy while minimizing dose-dependent risks of adverse effects, several steroid-sparing approaches have been made but mostly been unsuccessful, except for concomitant long-acting beta-2 agonist (LABA). However, which subgroups of asthma patients could benefit from specific steroid-sparing strategy remains to be investigated particularly in the elderly, as elderly patients frequently have

vitamin D insufficiency or metabolic comorbidities [25].

Collectively, ICS is the cornerstone of pharmacological treatment of asthma, which probably holds true also in the elderly. However, due to dose-dependent potential side effects, clinicians need to titrate the ICS dose regularly and also may need to consider steroid-sparing agents. Also clinicians should monitor for any local or systemic side effects, such as oropharyngeal candidiasis, bone mineral density reduction, nonvertebral fracture, cataract, adrenal insufficiency, or pneumonia.

Systemic corticosteroids

Systemic corticosteroid is more potent than ICS, but also has higher risks of side effects. Thus it is only recommended as step 5 management in the GINA guideline [5]. Also the use should be limited to patients who could have more benefits than side effects [26]. Chronic use of systemic corticosteroid is associated with many side effects including osteoporosis, fracture, infection, obesity, coronary artery disease, avascular necrosis, stroke, cataract, diabetes and skin thinning, in a dose-dependent way, which could be more problematic in severe or elderly asthma patients [27].

INHALED BETA-2 ADRENERGICS

Since the clinical study by Graeser and Rowe [28], inhalation treatment with adrenergic agonists (previously epinephrine) for asthmatic bronchoconstriction has long been applied in clinical practice. Beta-2 adrenergic receptor has been later found to be more specific in dilatation of bronchial smooth muscle cells, and thus its specific agonists have been developed successfully. Now several different types of inhaled beta-2 adrenergic agonists are available in clinical practice; short-acting beta-2 agonists (SABA) like salbutamol, LABA like salmeterol or formoterol, and ultra-LABA like indacaterol.

At present, LABA is recommended as add-on to ICS as asthma controller, particularly as a single combination inhaler [29]. Combination of ICS plus LABA exerts better efficacy than double-dose ICS or ICS plus LTRA [30, 31]. These 2 drugs may exert synergistic effects for each other; ICS increases the gene transcription of beta-2 receptors and protects the down regulation of the receptor in response to prolonged usage of LABA, whereas LABA could also enhance anti-inflammatory actions of ICS [32].

LABA as monotherapy has been related to risks of asthma-related morbidity and mortality, and thus is not recommended alone. In previous clinical trial comparing salmeterol with placebo added to usual therapy, salmeterol group had a higher rate of asthma-related deaths (odds ratio, 4.37) [33]. However, in *post hoc* analyses of the intention-to-treat population, the increased risks of deaths were observed only among the subjects who did not use concomitant ICS at baseline. In recent Cochrane group meta-analyses of randomized controlled trials (RCTs) comparing regular ICS+LABA (either salmeterol or formoterol) vs. same-dose ICS groups, no significant differences were found in fatal or nonfatal serious adverse events between two groups [34, 35].

SABA is now indicated only for a rapid relief of bronchoconstriction (onset 5 to 10 minutes), but never recommended as a daily regular medication now. Regular use of SABA as monotherapy, particularly fenoterol, was previously found to have significant relationships with poor asthma control, compared to as-needed use of SABA [36]. In addition, regular use of fenoterol was strongly related to asthma-related mortality in a dose-dependent manner [37].

Data are scarce in relation to the efficacy in the elderly. In a retrospective observational study using a health claims database of elderly patients in United States (US), the subjects who received fluticasone-salmeterol combination had significantly reduced risks of inpatient hospitalization (32%) and Emergency Department/inpatient hospitalization (22%) than those who received ICS [38]. However, there is a concern that bronchodilator response to beta-2 adrenergic receptor stimulation may decrease with age [39] whereas the response to ipratropium may not [40]. With regard to safety, a particular concern is necessary if the subjects have cardiovascular or metabolic comorbidities. Nebulized beta2-agonist might increase the risk of dysrhythmia or hypokalemia among patients at risks (such as previous history myocardial infarction, or taking diuretics or insulin therapy) [41]. However, in a 1-year retrospective analysis of elderly asthma patients in Japan, the usual dose of budesonide/formoterol (320/9 mg twice per day) did not show significant adverse effects on serum potassium levels or pulse rate [42].

ANTICHOLINERGICS

Airway hyperresponsiveness to cholinergic stimulation is a hallmark of asthma, and thus the blockade of muscarinic receptor should be a potential therapeutic option. However, it

has been just recently that this drug started to be considered as clinically important in asthma. Despite a long history of using plant alkaloids in relieving asthma attack [43], previous short-acting anticholinergics, including ipratropium bromide, failed to show significant efficacy. This lack of efficacy is supposed to be due to their lack of selectivity in antagonism, as simultaneous stimulation of different muscarinic subtypes could result in the decrease in bronchodilator effects [44]. However, now anticholinergics finally started to show promise, along with recent advances in characterization of muscarinic receptor subtypes, particularly M3 [44] and development of M3 selective antagonists [45]. M3 receptor has been identified as to have more important roles in the cholinergic bronchoconstriction pathway than other subtypes, and is considered to be the main target for bronchodilation in the asthmatic airways [46].

Tiotropium bromide is one of the well-known long-acting anticholinergics with M3 kinetic selectivity. Since the first clinical observation in 2008 [47, 48], several clinical studies have demonstrated its efficacy in asthma patients who remained poorly controlled despite conventional therapy [49-53]. Among adult patients with asthma inadequately controlled on low-dose ICS, tiotropium 18-mcg add-on was superior to double ICS dose and noninferior to salmeterol 50-mcg bid add-on in improving morning peak expiratory flow [50]. More notable findings were that tiotropium add-on therapy provided additional gain in lung function parameters among severe asthma patients who were already receiving high-dose ICS and LABA [49, 52, 53]. The mechanisms of these additional benefits by tiotropium are still unclear, but could include potential nonneuronal anticholinergic actions of genetic determinants in β_2 -receptor responses (*ADRB2* gene polymorphism) [54, 55].

Direct clinical evidence is lacking, to our knowledge so far, in the elderly. However, considering potential age-related decrease in responsiveness to β_2 adrenergic receptors in the airways [39, 40], one could speculate that long-acting anticholinergics offer significant additive bronchodilator effects in elderly patients already receiving LABA. Also one could wonder if long-acting anticholinergics will be appropriate alternatives to LABA in the elderly. These questions warrant direct investigation. However, previous positive asthma trials showing the efficacy of tiotropium add-on therapy had characteristics of mainly being older adults (mean age 61.0 years [47], 59.6 years [48], 63 years [49], 54.8 years [52], and 53 years [53]).

Therapeutic roles of anticholinergics in elderly patients with

asthma and comorbid COPD are still not proven. However, in a 12-week randomized double-blind placebo-controlled study involving 472 older adults (mean age, 59.6 years) with heavy smoking history (>10 pack-year) and physician diagnosis of asthma and comorbid COPD, tiotropium add-on provided significant improvement in the primary endpoint forced expiratory volume in 1 second (FEV_1) area under the curve from 0 to 6 hours at 12 weeks compared to placebo [48]. Comorbid COPD in elderly patients with asthma is significantly related to risks of future asthma exacerbation [56]. Thus whether the addition of anticholinergics could reduce exacerbation in these patients warrants investigation.

Long-term safety issues have not been addressed in asthma patients, as the longest trial so far had a just 48-week duration [53]. Once in COPD trials, previous RCTs had raised a particular concern over major adverse cardiovascular events from inhaled anticholinergics [57]. However, later large-scale RCTs of longer duration (2.3 to 4 years), including the UPLIFT (Understanding Potential Long-term Impacts on Function with Tiotropium) and the TIOSPIR (Tiotropium Safety and Performance in RespiMat) trials which assessed the risks as pre-specified primary or key secondary outcomes, virtually contradicted previous concerns over the risks [58, 59]. *Post hoc* analyses of the UPLIFT trial further supported the cardiac safety of tiotropium, using the data of 400 COPD patients who experienced major cardiac events (cardiac arrhythmia, myocardial infarct, or cardiac failure) but completed the study; they found that tiotropium did not increase the risk of subsequent cardiovascular events, compared to placebo [60].

Other potential adverse effects of anticholinergics should be paid attention in the elderly, such as dry mouth, blurred vision, constipation, or urinary retention. However, in an open-label, single-arm, prospective pilot study on 25 COPD patients with benign prostatic hyperplasia (mean age, 72.9 years), tiotropium 18 mcg did not have adverse effects on lower urinary tract function [61]. These issues also warrant further clarification in elderly asthma patients.

ANTILEUKOTRIENES

Cysteinyl leukotrienes (cysLTs; LTC₄, LTD₄, and LTE₄) are potent bronchoconstrictors and chemoattractant for eosinophils, and thus have been important therapeutic targets in asthma patients [62]. CysLTs are produced by myeloid cells including

mast cells, basophils and eosinophils [63]; and cysLT1 receptors are expressed in airway smooth muscle cells and myeloid cells, and upregulated by several cytokines of Th2 inflammation [64, 65]. The enzyme 5-lipoxygenase (5-LO), which regulates the production of leukotrienes, can also be upregulated by interleukin-5 [66]. Thus, cysLT1 receptor and 5-LO have been therapeutic targets.

Currently, two types of drugs are available in clinical practice—leukotriene receptor antagonists (LTRA) and 5-LO inhibitors. LTRAs (montelukast, pranlukast, and zafirlukast) mostly antagonize cysLT1 receptor only, but 5-LO inhibitor (zileuton) can inhibit the production of all the leukotrienes including cysLT and LTB₄ [62]. Thus one may wonder if 5-LO inhibitor has wider application. However, the clinical relevance of additional blockade effects by 5-LO inhibitor is still unclear in asthma treatment. Thus, here we mostly discuss clinical evidence of LTRA.

Clinical evidence from RCTs among adult patients indicates a consistent but modest efficacy of LTRA, compared to ICS (as monotherapy) or LABA (as add-on to ICS). As a monotherapy, montelukast offers a rapid bronchodilator effect in asthma patients, regardless of their concurrent ICS treatment status [67]; however, when compared to ICS, the effect size of LTRA appears to be small in terms of exacerbation, lung function parameters, and symptoms [68]. As add-on therapy to ICS, LTRA appears to have a modest steroid-sparing effect among symptomatic patients [69]; however, LTRA was inferior to LABA as adjunctive therapy among adults who remained symptomatic in spite of regular ICS treatment, according to the meta-analyses of Cochrane Group [30]. However, as LTRA has oral formulation, it may have better adherence profile and appears to be similarly effective option in real-world practice settings, compared to inhaled steroids or LABA [70].

Conclusions from clinical studies on efficacy are still controversial in the elderly patients. Previous data was rather negative, suggesting that the effects might decrease with aging. In the 4-week open-label ACCEPT (Accolate Clinical Experience and Pharmacoeconomics) trial involving 3,700 asthma patients, the addition of zafirlukast provided clinical improvement in asthma patients as overall, but the clinical effect was less evident in the elderly, compared to younger patients [71]. Also in a retrospective pooled analysis of 5 RCTs comparing zafirlukast to fluticasone as monotherapy, the effects of zafirlukast appeared to be lost in older adults (aged ≥ 50 years) [72]. However, recent trials hinted toward different conclusions. In a recent 12-week

randomized open-label trial of 140 elderly patients with mild asthma (aged 60–75 years), the addition of montelukast to low-dose budesonide had comparable efficacy to that of double dose budesonide [73]. Also in a 24-month long-term clinical observation study, LTRA add-on to ICS improved clinical outcomes in elderly patients with severe asthma [74]. As LTRA has good safety and adherence profiles, LTRA may potentially be a good option in the real-world practice of elderly asthma patients [75].

THEOPHYLLINE

Theophylline has been widely used in the treatment of asthma since 1922, as it is less expensive and oral form is available [76]. Theophylline is a weak nonselective inhibitor of phosphodiesterase isoenzymes, which lead to increase intracellular concentrations of cyclic adenosine monophosphate and cyclic 3', 5' guanosine monophosphate concentration by breaking down cyclic nucleotides. As a bronchodilator, it is less effective than beta2-agonist [77]. Also as an anti-inflammatory drug, it is less effective than ICS. Thus, in the GINA guideline for adult asthma, theophylline is just recommended as an alternative to low dose ICS (step 2), to LABA (in combination with ICS; step 3), or as an add-on therapy to medium to high dose ICS/LABA (step 4 or 5) [5].

Relatively high dose of theophylline is required to exert bronchodilator effects (serum level 10–20 mcg/mL) [76]. In addition, therapeutic window is rather narrow and thus serum level of theophylline should be monitored to avoid overdose or adverse reactions such as nausea, vomiting, or arrhythmia. Serum theophylline levels can be influenced by drug interactions which share P450 enzyme pathway, or comorbid conditions such as old age, smoking, or cardiac/hepatic diseases [76].

Despite concerns on efficacy and safety, however, there is also a positive speculation on its anti-inflammatory “steroid-sparing” effects at low dose (1–5 mcg/mL) in chronic obstructive airway diseases [78]. In a pilot study of 68 smoking patients with mild-to-moderate asthma, the addition of low dose oral theophylline sustained-release form (400 mg per day; mean serum level, 4.3 mcg/mL) to 200 mcg per day beclomethasone further improved in peak expiratory flow and asthma control [79]. In subsets of steroid-resistant asthma patients, such as smoking asthma or severe asthma, reduced histone deacetylase 2 (HDAC2)

activity has been related to the resistance mechanism. Notably, theophylline at low dose may restore HDAC2 activity and reverse steroid insensitivity to normal in susceptible patients [76]. These findings warrant prospective instigation to examine whether low dose theophylline has acceptable safety and benefit profiles in the elderly asthma patients with steroid resistance or smoking history.

Sustained release form of theophylline is easier to control serum level and considered to be safer [76]. In an analysis of 3,810 elderly patients with asthma or COPD in Japan (mean age, 73.8 years), the incidence of adverse events was 4.71% during using low-dose sustained-release theophylline; 5 most frequent events were nausea (1.05%), loss of appetite (0.56%), hyperuricemia (0.42%), palpitation (0.39%) and increased alkaline phosphatase (0.28%) [80].

ANTI-IgE MONOCLONAL ANTIBODY

IgE is a key mediator in several allergic reactions involving type I hypersensitivity mechanism. Thus, the invention of omalizumab, a recombinant humanized monoclonal IgG antibody [81], has provided a breakthrough in clinical practice for IgE-mediated diseases including allergic asthma. In RCTs of adult patients with moderate or severe allergic asthma, omalizumab add-on therapy significantly improved asthma outcomes such as exacerbation and hospitalization rates, compared to placebo [82]. However, elderly asthma patients are frequently nonatopic (also called as "intrinsic asthma") [2]; thus, the efficacy of omalizumab may be questioned in these patients.

Interestingly, however, recent findings suggest that the efficacy of anti-IgE therapy is not restricted to "atopic" patients. A case report of 52-year-old man with severe nonallergic asthma, who benefited from 3-year long-term omalizumab treatment, was one of the first clinical observations related to this issue [83]. In the analysis of multicenter registry database of severe asthma patients in Spain (29 nonatopic and 266 atopic patients; mean age mid-50s), omalizumab was similarly effective in between nonatopic and atopic patients [84]. Also, in a proof-of-concept 16-week RCT to examine biologic and clinical effects of omalizumab in 41 adult patients with severe nonatopic asthma (mean age, 55 years), omalizumab significantly reduced high affinity IgE receptor (FcεRI) expression on basophils and plasmacytoid dendritic cells (pDCs) as primary outcomes, and also significantly improved

mean FEV₁ (by 250 mL and 9.5% predicted) as a secondary outcome [85]. These clinical benefits observed in severe nonatopic asthma patients may be plausible, as asthma severity among older adult patients were not related to the presence of atopy, but significantly to high total IgE and staphylococcal enterotoxin-specific IgE (SE-IgE) levels [86]. High serum total IgE levels also showed strong correlations with SE-IgE levels [87], probably due to the biological property of SEs to promote polyclonal IgE production [88].

Clinical evidence from elderly patients are still sparse. In a pooled analysis of 5 RCTs on moderate-to-severe "allergic" asthma patients, the efficacy of omalizumab in older adults (>50 years; n = 601; mean age, 58 years) was similar to that of overall study participants (n = 2,236; mean age, 40 years), in the outcomes of asthma exacerbation, patient/investigator-reported global effectiveness, asthma symptom scores, and rescue medication use [89]. In prospective postmarketing surveillance trials to examine the efficacy and tolerability of omalizumab in a real-life setting, omalizumab reduced asthma exacerbations and symptoms, improved lung function, and was well tolerated among severe "allergic" asthma patients, regardless of age (≥50 years or <50 years) [90]. In a retrospective, observational data analysis of elderly veteran population with severe allergic asthma, omalizumab add-on improved asthma exacerbation, FEV₁ by 280 mL and asthma control test score. Moreover, the needs for systemic prednisone therapy were also markedly reduced by omalizumab treatment [91]. These data suggest potential efficacy of omalizumab in the elderly patients with severe "allergic" (or atopic) asthma.

Data are still lacking in severe "nonatopic" asthma in the elderly; however, asthma severity in the elderly appears to be unrelated to atopy but significantly associated with IgE responses [86], possibly driven by SE which is thought to originate from *Staphylococcus aureus* colonized in nasal mucosa [88]. Thus, we speculate that omalizumab would be also effective in elderly patients with severe asthma and high IgE levels, irrespective of their atopic status.

As omalizumab may modulate innate immune functions like FcεRI expression in pDCs which are important in antiviral responses [85], the agent could hopefully have additional benefits to reduce asthma exacerbation by viral infection. Cross-link of FcεRI in pDCs is reported to lead to the suppression of antiviral cellular functions [92].

The efficacy and safety considerations of asthma controller

medications in the elderly were summarized in Table 1.

ISSUES SURROUNDING PHARMACOLOGICAL TREATMENT

Choosing inhaler device

Inhalation is the major route of drug administration for asthma, including corticosteroids, beta2-agonists or anticholinergics. However, cognitive dysfunction and decreased dexterity pose difficult problems with using inhalers in the elderly. As reported in an earlier study by Allen and Ragab [93], the competence of using asthma inhaler, metered dose inhaler (MDI) here, is significantly related to intellectual function in the elderly. MDI requires multiple stages for inhalation, and thus the technique learning is also hindered by dementia, cognitive impairment or dyspraxia [94]. Dry powder inhaler (DPI) has less steps (less requiring coordination) and may be easier to use; however, it

requires sufficient inspiratory flow to aerosolize the powder [95]. In an elderly asthma cohort study in US, 52.6% had correct DPI technique, whereas 37.6% had proper MDI technique [96]. Thus jet nebulizer may need to be considered as an alternative route of delivery in cases necessary, although it is not portable [95]. Using MDI with spacer could also be an alternative way [95]. Whether using a single type of inhaler for both of controller and relieve could bring better clinical outcomes [97], compared to using mixed types of devices, needs to be examined in the elderly. Collectively, physicians should always discuss with elderly patients on difficulties in using inhalers, and also prescribe the device that individual patients can use effectively.

Adherence

Clinical significance of adherence also applies to elderly asthma patients [98], but may be a complex issue [2]. In the US elderly asthma cohort study, 57.0% had poor adherence to daily controller medication [99]; of note, poor adherence

Table 1. Efficacy and safety considerations in pharmacological management of elderly asthma patients

Type of medication	Efficacy	Safety
Inhaled corticosteroids (ICS)	Active ICS therapy could improve asthma outcomes effectively in elderly patients [13]. ICS prescription at discharge could reduce rehospitalization and all-cause mortality in elderly asthma patients [14].	Risks of following adverse reactions could increase in a dose-dependent manner [16-19, 24]; adrenal insufficiency, cataract, diabetes, decreased bone mineral density, fracture, oropharyngeal candidiasis, pneumonia?
Inhaled beta-2 adrenergics	Bronchodilator effects of beta-2 agonists might decrease with aging whereas anticholinergics might not [39, 40].	Following concerns may be raised in patients with cardiovascular or metabolic comorbidities; dysrhythmia, hypokalemia, QT prolongation, tachycardia
Inhaled anticholinergics	Positive trials showing the efficacy of tiotropium add-on to ICS and long-acting beta2 agonist therapy had characteristics of mainly being older adults (mean age, 53-63 years) [49, 52, 53].	Following concerns may be raised in susceptible patients; dry mouth, blurred vision, constipation, urinary retention,
Anti-leukotrienes	Zafirlukast add-on had less efficacy in elderly patients than younger patients [71]. Zafirlukast as monotherapy had less efficacy in older adults [72]. Montelukast add-on had comparable efficacy to doubling the dose of budesonide in elderly patients with mild asthma [73]. Montelukast add-on lead to improvement in clinical outcomes in elderly patients with severe asthma [74].	No specific issues were raised in the elderly.
Theophylline		Risks of adverse reactions may depend on serum drug level and comorbidities [76]. Sustained-release form is preferred; Incidence of adverse reactions was 4.71% among elderly patients with asthma or chronic obstructive pulmonary disease in Japan, which were mostly mild [76].
Anti-IgE monoclonal antibody	In trials of adult patients, efficacy of omalizumab was not restricted to "atopic" patients [84, 85]. In trials of older adult patients with severe "allergic" asthma, omalizumab had significant clinical benefits [89-91].	No specific issues were raised in the elderly.

Table 2. Summary of individual studies on the efficacy of pharmacotherapy in chronic management of elderly asthma patients

Source	Study design	Participants	Intervention and comparison	Main findings
Sin and Tu (2001) [14]	Population database analysis	6,254 Elderly patients who were hospitalized for asthma (≥ 65 years)	ICS vs. no ICS prescription within 90 days postdischarge	Patients who received ICS at discharge had 29% lower risk of rehospitalization and 39% lower all-cause mortality risk for 1 year.
Stanford et al. (2012) [38]	Retrospective observational study of large health claims database	10,837 Elderly asthma patients (65–79 years)	Fluticasone-salmeterol vs. ICS	Fluticasone-salmeterol had lower rates of asthma exacerbation compared with ICS.
Korenblat et al. (2000) [71]	Open-label, noncomparative study, 4 weeks	263 Adolescents (12–17 years), 2,602 adults (18–65 years), and 321 elderly patients with asthma (>65 years)	Addition of zafirlukast 20 mg twice daily for 4 weeks (no comparison arm)	Zafirlukast improved symptom outcomes similarly across age groups, but had less improvements in lung functions and beta2-agonist rescue therapy in the elderly group.
Creticos et al. (2002) [72]	Retrospective analysis of 5 randomized double-blind double-dummy trials, 4–12 weeks	243 Older adult patients with asthma (>50 years)	Fluticasone propionate 88 mcg twice daily vs. zafirlukast 20 mg twice daily for 4 to 12 weeks	Fluticasone propionate significantly improved lung functions, increased symptom-free days and rescue-free days, and reduced exacerbations, compared to zafirlukast.
Bozek et al. (2012) [74]	Prospective observation study, 24 months	512 Elderly patients with severe asthma (>60 years)	Addition of montelukast vs. non for 12 months (random selection in the second period)	Montelukast addition to ICS/LABA significantly improved asthma control.
Ye et al. (2015) [73]	Randomized, open-label trial, 12 weeks	128 Older adult asthma patients who remained not fully controlled with 400 mcg/day of budesonide (60–75 years)	800 mcg of budesonide vs. 400 mcg of budesonide plus 10 mg of oral montelukast for 12 weeks	Montelukast addition had improvement in asthma control status in a comparable degree with doubling budesonide.
Maykut et al. (2008) [89]	Pooled analysis of 5 double-blind placebo-controlled trials, 28–32 weeks	601 Older adult patients with moderate-to-severe atopic asthma (>50 years)	Omalizumab vs. placebo for 28 to 32 weeks	Omalizumab showed significant improvement in asthma exacerbation risk, asthma symptom score and rescue medication use.
Korn et al. (2010) [90]	Pooled analysis of 2 postmarketing surveillance trials, 4 months	174 Older adults with uncontrolled severe persistent allergic asthma (>50 years)	Omalizumab: pretrial vs. trial period (for 4 months)	Omalizumab significantly reduced the rates of severe exacerbation, daily asthma symptoms, nocturnal awakening, and lung functions (by 68.9%, 67.8%, 72.6%, and 60%, respectively) in older adults.
Verma et al. (2011) [91]	Retrospective observational data analysis over 2 years	17 Elderly veteran patients with severe allergic asthma (49–90 years)	Omalizumab: 1 year prior vs. 1 year of active treatment	Omalizumab significantly reduced severe exacerbation, improved FEV ₁ and asthma control test score.

ICS, Inhaled corticosteroids; LABA, long-acting beta2 agonist; FEV₁, forced expiratory volume in 1 second.

was significantly associated with erroneous “no symptoms, no asthma” belief. Besides, poor adherence to controller medication was related to low level of health literacy [96].

Polypharmacy and drug interactions

Comorbidity is a major consideration in the pharmacological management of asthma in the elderly, as multiple comorbidity is frequent [2]. Comorbidity leads to polypharmacy and polypharmacy could in turn lead to more drug interaction issues. Polypharmacy could also influence adherence. Pharmacokinetics, pharmacodynamics, and drug interactions could be complex in the elderly; however, there is a still lack of relevant information.

CONCLUSION

In this review, we tried to identify clinical evidence on pharmacological therapy in elderly asthma patients. However, only a few literatures were retrieved (Table 2). We believe that general rules of pharmacotherapy hold true across various age groups; however, external validity of current guideline recommendations needs to be proven in the elderly population. Also efficacy and safety issues, which could arise from aging-related comorbidities and physical dysfunction, warrant direct investigation in the elderly.

We are now in the rapid transition of our population age structure and also perspective of asthma pathophysiology. “Old age” has been the frequent exclusion criteria (38.5%) in previous RCTs for various medical conditions published in major medical journals [100]. It is time to move on to make clinical evidence which could be generalized to older patients. Also further clinical studies need to address elderly specific issues in efficacy, safety, or indication.

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