



Allergic rhinitis: pharmacotherapy in pregnancy and old age

E Ridolo, M Caminati, I Martignago, V Melli, C Salvottini, O Rossi, AR Dama, M Schiappoli, C Bovo, C Incorvaia & G Senna

To cite this article: E Ridolo, M Caminati, I Martignago, V Melli, C Salvottini, O Rossi, AR Dama, M Schiappoli, C Bovo, C Incorvaia & G Senna (2016): Allergic rhinitis: pharmacotherapy in pregnancy and old age, Expert Review of Clinical Pharmacology, DOI: [10.1080/17512433.2016.1189324](https://doi.org/10.1080/17512433.2016.1189324)

To link to this article: <http://dx.doi.org/10.1080/17512433.2016.1189324>



Accepted author version posted online: 13 May 2016.



Submit your article to this journal [↗](#)



Article views: 2



View related articles [↗](#)



View Crossmark data [↗](#)

Publisher: Taylor & Francis

Journal: *Expert Review of Clinical Pharmacology*

DOI: 10.1080/17512433.2016.1189324

Review

Allergic rhinitis: pharmacotherapy in pregnancy and old age

Ridolo E¹, Caminati M², Martignago I¹, Melli V¹, Salvottini C³, Rossi O⁴, Dama AR², Schiappoli M², Bovo C⁵, Incorvaia C⁶, Senna G²

¹ Clinical and Experimental Medicine, University of Parma, Parma, Italy

² Allergy Unit and Asthma Center, Verona University Hospital, Verona, Italy

³ Department of Molecular Medicine, University of Pavia, Italy

⁴ Allergy Unit, Azienda Ospedaliera Universitaria Careggi, Firenze, Italy

⁵ Medical Direction, Verona University Hospital, Verona, Italy

⁶ Allergy/Pulmonary Rehabilitation, ICP Hospital, Milano, Italy

Corresponding author:

Marco Caminati, Allergy Unit and Asthma Center, Verona University Hospital, piazzale Stefani 1, 37126

Verona, Italy. Phone +393289582878; Fax +390458123526

Authors' email address:

Erminia Ridolo: erminia.ridolo@unipr.it

Irene Martignago: irene.martignago@gmail.com

Valerie Melli: valerie.melli@gmail.com

Chiara Salvottini: chiara.salvottini@gmail.com

Oliviero Rossi: o.rossi@dm.unifi.it

Anna Rita Dama: annarita.dama@ospedaleuniverona.it

Michele Schiappoli: michele.schiappoli@ospedaleuniverona.it

Chiara Bovo: chiara.bovo@ospedaleuniverona.it

Cristoforo Incorvaia: cristoforo.incorvaia@gmail.com

Gianenrico Senna: gianenrico.senna@ospedaleuniverona.it

Abstract

Introduction: Allergic rhinitis (AR) affects 20-30% of women in reproductive age and may worsen during pregnancy. About 10% of the elderly suffer from AR, and it could be under-diagnosed in these patients. Many drugs are currently available, however AR treatment during pregnancy and old age represent a challenging issue.

Areas covered: A review of the literature on the topic has been performed.

Expert review: In pregnancy, drug avoidance should be carefully balanced with the need for AR optimal control. Topical drugs are suggested as a first approach. The safety and tolerability profile of second-generation antihistamines is well supported. If allergen immunotherapy (AIT) is ongoing and well tolerated, there is no reason for stopping it. AIT initiation in pregnancy is not recommended. For elderly patients, no specific concerns have been highlighted regarding topical treatments, except from nasal decongestionants. Second generation antihistamines are generally well tolerated. Old age should not preclude AIT.

Key words: allergic rhinitis, pregnancy, elderly, allergen immunotherapy, antihistamines, intranasal steroids

1. Introduction

Allergic rhinitis (AR) is a very common disease, often associated with other comorbidities and with an important burden on patient's quality of life. The prevalence of AR is increasing worldwide and it is estimated that 400 million people are currently suffering from AR. Moreover, at least 40% of them have concomitant asthma, and more than 80% of asthmatic patients are affected by rhinitis (1). The definition of AR is based on clinical symptoms after allergen exposure in sensitized patients, which include rhinorrhea, nasal obstruction, nasal itching and sneezing (2).

AR has an important negative impact on quality-of-life, impairing sleep, school and work activities (3). Diagnosis is based on the combination of clinical history with skin prick tests or in vitro tests detecting specific IgE. The most common allergens implied in AR in Europe are house dust mite, grass pollen, tree pollen, weed pollen, animal dander (cat and dog particularly) and molds (4).

According to the Allergic Rhinitis and Its Impact on Asthma (ARIA) guidelines (2), AR is classified as "intermittent", when symptoms are present less than 4 days per week or less than 4 consecutive weeks, or "persistent", if they are more frequent; and as "mild", when the patient does not complain about sleep disturbance, impairment of daily activities (leisure and/or sport, school or work), or "moderate/severe", if one or more of the previous items is present.

The management of AR includes patient education, prevention of exposure to environmental allergens and irritants, pharmacological therapies and allergen specific immunotherapy. Patient education and allergen avoidance are important to prevent the development and the exacerbation of AR symptoms. Allergen avoidance can be applied to animal's dander and house dust mite allergy, but the effectiveness of individual and environmental measures is controversial, because the systematic review of the available trials on dust mite allergy control measures was unable to provide definitive recommendations (5) and no systematic review is available for animal's dander. The drugs currently recommended to treat AR are summarized in Table 1 and 2. The approach is stepwise, according to the severity and frequency of symptoms.

While patient education must be obviously considered for any degree of severity of AR, the drug therapy, concerning molecules, dosage, route of administration, duration of treatment, etc, must be adapted to the level of AR severity.

The first pharmacotherapy step for the milder form of AR is represented by H1- blockers, through oral or intranasal route of administration. The ARIA (2) and European Academy of Allergy and Clinical Immunology (EAACI) guidelines consider the use of nasal corticosteroids as a step up in therapy (6). Leukotriene receptor antagonists are especially useful in patients with comorbid asthma. Decongestants and cromones are considered in ARIA guidelines, but their use has a minor impact on symptoms control. Oral corticosteroids are permitted only for brief periods of time in order to achieve good symptoms control and only in patients with severe AR, not fully responding to the aforementioned therapy. The patients must be reevaluated in order to decide a step down or a step up of therapy and reach the minimum therapy necessary. Allergen immunotherapy (AIT) must be considered in case of moderate/severe intermittent AR or in any kind of persistent AR (2). There are some limitations in the treatment of AR in pregnant women and in elderly patients, as defined by an age $\geq$ 65 years. It is estimated that approximately 20-30% of women in reproductive age suffer from AR and about one-third of them present worsening of symptoms during pregnancy (7). Concerning the elderly, about 10% of them suffer from AR, with a higher incidence in females, and there are data suggesting that AR could be underdiagnosed in these patients (8).

The aim of this review is to provide an update on pharmacotherapy of AR in these two particular categories of patients. In fact, it is clear how much delicate is the choice of any treatment during pregnancy due to the potential adverse effects on the fetus, but assessing a therapy can be difficult also in elderly, that very often present comorbidities and are on daily-based multidrug regimen.

2. Therapy of AR during pregnancy

Rhinitis is often a problem during pregnancy. In fact, increasing circulating blood volume and hormonal influence (particularly by estrogens) to the nasal mucosa can cause not only a hormonal

rhinitis during pregnancy but also a worsening of pre-existing nasal symptoms from AR. This is true especially regarding nasal congestion (7).

Though the first recommendation for treatment in a pregnant woman with AR is allergen avoidance, sometimes this is not sufficient to guarantee an optimal control of symptoms. A controlled AR improves quality of life and sleep. In addition, the possible risk of a harmful treatment of AR for the fetus and for the mother must be considered, especially in patients who already suffer from asthma (9). Frequent exacerbations due to uncontrolled asthma during pregnancy are associated to a greater risk of low weight at birth (10), congenital malformations (11) and also to risk for the mother, such as pre-eclampsia, gestational diabetes and antepartum hemorrhage (11, 12). The five categories (A, B, C, D, X) established by Food and Drug Administration (FDA) to indicate the potential of a drug to cause birth defects is used during pregnancy have been recently updated (13). Actually, the manufacturers are currently required to provide information about the risks and benefits of drugs and/or biological products during pregnancy and lactation (14).

Anyway, no drug used for the treatment of AR was rated A, as adequate and well controlled studies demonstrating no evidence of risk to the fetus are not available. In fact, few observational studies on the use of AR medications during pregnancy have been conducted. Consequently, caution must be used when administering drugs because of the placental transfer, but also the benefits of treating AR must be considered; for example preventing exacerbation of asthma can outweigh any potential risks for the fetus.

2.1 Oral antihistamines

There are no data on humans that suggest that antihistamines have any kind of adverse effects on fetus, regardless the gestational age of administration (15). The main concern for the use of antihistamines in pregnancy is about their oxytocin-like effects, that, if large doses are administered just before labor, may cause contractions (16). Moreover, if the mother takes a high dosage of H1-blockers immediately before term, the newborn can show withdrawal symptoms

such as tremor and irritability (17). For the general population, ARIA guidelines recommend to use second-generation oral H1-antihistamines because of the well known sedative and anticholinergic effects of the first generation agents (18, 19).

A study conducted on 17266 women with 17776 deliveries and 18197 infants, using prospectively collected information on drug taken in early pregnancy, pointed out that the use of cetirizine and loratadine has no clear teratogenic effect (20).

A recent review confirmed the safety of both first and second generation antihistamines' use during pregnancy (21). After confirming the safety of cetirizine and loratadine, the authors analyzed only other two antihistamines of the second generation, i.e. terfenadine and astemizole, confirming that the frequency of birth defects among women exposed to them were not significantly different from the control group. Still, these two drugs present cardiotoxicity and are no longer approved in most countries (22). The principal limit of this review is represented by the fact that the authors considered only birth defects as outcome, but not other issues such as fetal loss, preterm delivery or low birth weight (21). Among the newest second generation H1-blocker there is an animal study about bilastine, which appeared to be well tolerated in pregnant/lactating rats and in their offspring. Besides, the authors did not observe adverse effects also on fetal development in rabbits at higher doses than the corresponding recommended daily human dosage (23). In conclusion, the greater part of the studies on safety is about cetirizine and loratadine, while studies on the other second generation H1-blockers in pregnancy are lacking. Anyway, it is reasonable to prefer as first approach a topical drug for treating AR in pregnant women, using them only in case of failure.

2.2 Intranasal antihistamines

intranasal antihistamines alone can be recommended due to their faster action on symptoms relief. However, there are no adequate and well controlled studies about their use in pregnant women. Azelastine hydrochloride has been shown to cause developmental toxicity in mice, rats and rabbits (24). In clinical practice, the same precautions used for oral H1-blockers must be considered also

for intranasal ones (25). Alternatively, nasal douching can be effective and harmless in pregnancy (see below in the text).

2.3 Decongestants

Intranasal decongestants for the treatment of nasal obstruction are effective in the short term, but they must not be used for more than 9 days due to the risk of drug-induced rhinitis (not only during pregnancy) (2). ARIA guidelines advise to avoid pseudoephedrine during pregnancy and to use the others with caution (2). In fact, the use of pseudoephedrine and phenylpropanolamine during the first trimester is related to the development of gastroschisis (26,27), while administration of phenylephrine, phenylpropanolamine and phenylpropanolamine in the first three months are associated respectively with endocardial cushion defects, ear defects and pyloric stenosis (28). For these reasons, some experts recommend not to use decongestants during pregnancy (29). Moreover, it should be useful to advise patients about the fact that the over-the-counter drugs can contain pseudoephedrine.

2.4 Leukotriene receptor antagonists

Leukotriene receptor antagonists (LTRAs) are more effective than placebo in AR, but their action is equivalent to oral H1-antihistamines and inferior to intranasal corticosteroids to treat AR (2). Montelukast is considered safe among the drugs used in pregnancy. The available data are derived from studies on asthmatic pregnant women (30, 31), while LTRAs in AR are less investigated. This makes it recommendable to use LTRAs during pregnancy only in patients with not-well controlled asthma and to prefer other drugs for AR (32).

2.5 Intranasal Corticosteroids

Intranasal corticosteroids (INS) are an important option for the management of AR thanks to their efficacy and pharmacokinetic properties (2). In fact, INS reach a high concentration on the receptor in the nasal mucosa and have low bioavailability, reducing the risk of systemic side effects and also the possibility to affect the fetus. However, even though there are differences in safety between the different molecules, beclomethasone, budesonide, mometasone, triamcinolone,

fluticasone and flunisolide are well tolerated, especially after the second trimester (15), and they seem not to cause significant adverse effects at therapeutic dosage.

There are several studies in literature on the safety of inhaled budesonide in pregnancy, as also observed for the intranasal route (8), while some authors suggest the use of fluticasone during pregnancy, underlining the absence of adverse outcomes (32, 33).

2.6 Intranasal second generation antihistamine/nasal corticosteroid combination

A new combination of fluticasone propionate and azelastine (MP29-02) became commercially available in the last years (34). There are not studies in literature regarding its use in pregnant women. We suggest to apply the same precautions used for both single components (antihistamine and corticosteroid) administered intranasally.

2.7 Intranasal cromones

Cromoglycate and nedocromil are available as intranasal preparations and are very safe (9), but also modestly effective on nasal symptoms (2). There are no recent data about adverse effects on fetus and/or on mother caused by the use of cromones during pregnancy. Only a 1982 study on more than 600 asthmatic women assessed the safety of inhaled cromolyn sodium (35). Therefore, cromones can be suggested as first line treatment, but their scarce efficacy often limits their use.

2.8 Ipratropium

ARIA guidelines (2) suggest adding intranasal ipratropium in case of severe persistent AR with rhinorrhea that is partially responsive to the previously indicated drugs (see Table 1). Anyway, ipratropium was demonstrated not to improve nasal obstruction and sneezing, especially in persistent AR (36). Even though adverse effects from topical use of ipratropium are uncommon (2), there are no available studies in literature regarding its intranasal use during pregnancy.

2.9 Oral Corticosteroids

Oral corticosteroids (OC) are recommended for only brief courses in patients with AR who require a rapid improvement of symptoms (2). Use of OCs during the first trimester is associated with a

greater risk of development of cleft lip and cleft palate (37), but their side effects can involve also the mother, causing preeclampsia and preterm delivery (8, 15). However, OCs are rarely necessary to control AR symptoms.

2.10 Other treatment options

- Nasal douching: an Italian study demonstrated that nasal lavage with hypertonic saline solution in AR in pregnant women is a safe and effective therapeutic option (38).
- External nasal dilators at night are suggested in some studies as alternatives to drug therapy (8).
- Avoidance of irritant agents, such as smog and smoke, is always recommended (15).

2.11 Allergen specific immunotherapy

AIT is the only therapy able to modify the natural history of the disease, with a long lasting effect on symptoms also after cessation (39). The first controlled study on AIT during pregnancy dates back to 1978 (40). Metzger et al. conducted a retrospective study on 90 women with allergic asthma and/or rhinitis with a total of 121 pregnancies. The women underwent subcutaneous immunotherapy (SCIT) that was mostly started before pregnancy. In fact, during 7 of the total pregnancies SCIT was initiated with no fetal or maternal complications. Shaikh et al. reported that there were no differences in the incidence of prematurity, preeclampsia, abortion, neonatal death or congenital malformations compared to the control group (41). Such study not only confirmed that the continuation of SCIT during pregnancy did not lead to risk for fetus and/or for the mother, but also showed a lower incidence of abortion, toxemia and prematurity compared to the group of women who refused AIT (41).

Regarding sublingual immunotherapy (SLIT), there is only one trial conducted on pregnant women by the same group of authors, who analyzed data collected from 185 pregnant women receiving SLIT, who did not present any significant difference in presentation of congenital malformations, eclampsia and perinatal deaths (42). Among these 185 patients, 24 women started SLIT during pregnancy without any adverse reaction.

The EAACI position paper on contraindications to AIT (43) recommends continuing a well-tolerated AIT during pregnancy with caution, but advises against the initiation of AIT in pregnant women. In fact, even if the risk of anaphylactic reaction due to AIT is very low, it must be considered that anaphylaxis can cause fetal abnormalities as a consequence of placental vasoconstriction and can lead to preterm labor and high risk of miscarriage due to maternal hypoxemia (44, 45). These results were confirmed also in a recent review (46).

3. Therapy of AR in elderly patients

AR affects fraction of the population over 65 years up to 20% (47, 48). The most frequent allergen sensitizations in this population are towards indoor allergens, such as house dust mites, cockroaches, and furred pets, as a consequence of the fact the elderly use to spend great part of the day indoor (49). A study showed that quality of life in elderly is significantly more compromised than in young people (50). In fact, AR not only impairs quality of sleep, but is also potentially able to alter cognitive functions, mental health, glucose metabolism and endocrine functions (8).

Before prescribing any therapy for AR in elderly, there are several aspects to consider (51):

- collect a complete clinical history, with all the comorbidities (i.e. impairment of kidney and/or liver function, asthma, COPD...);
- consider any pharmacotherapy (chronic, on demand, ...), not only for the possible interaction among drugs, but also for the compliance, that usually decreases with the increase in number of drugs prescribed;
- elderly patients often have a poor perception of AR symptoms;
- a poor control of AR can worsen preexisting chronic low airway diseases and particularly asthma;
- compliance can be low also because of a not immediate treatment efficacy;

- the cost of some medications can compromise the adherence; this may concern patients of any age, but particularly the elderly because of the frequent co-morbidities and the consequent cost of the other drugs to treat them;
- the “corticosteroid fear” is present at any age, but it seems particularly important in elderly. However, in a recent study in UK in 2659 patients with asthma, older participants reported fewer concerns about both OC and ICS (52).

Therefore, it is fundamental to correctly approach the pharmacotherapy for AR in old people due to all these aspects in order to warrant an optimal control of symptoms and eventually a good quality of life.

3.1 Oral antihistamines

The recommendation to prefer second generation antihistamines (2) must be necessarily applied to older patients. In fact, the first generation H1 blockers act on H1 receptors of central nervous system (CNS) causing sedation, anxiety and decreased reaction times, that are more pronounced in elderly (22), also because they are not selective for H1 receptors. In fact, they act also on *a*) serotonin receptors, causing increase of appetite and weight gain; *b*) $\pm$ -adrenergic receptors, inducing dizziness and postural hypotension; *c*) muscarinic receptors, provoking dryness of mouth and eyes, blurred vision, urinary retention, constipation, sinus tachycardia; *d*) cardiac ion channels, favoring the prolongation of QT interval and potentially leading to polymorphic ventricular arrhythmias (22, 53). Elderly may also present preexisting cardiac disorders and consequently they are at higher risk of serious adverse effects. Similarly, patients with prostatic hypertrophy, bladder neck obstruction or narrow angle glaucoma should avoid first generation antihistamines. In any case, drug therapy of aged persons has its main issue in quantitative pharmacotherapeutic aspects, requiring an accurate assessment of co-morbidities and polymedication, which may lead to drug-drug interactions. Use of first-generation H1 receptor antagonists in the elderly should be considered carefully because of the large number of adverse effects and potential for interactions with these agents (53). Instead, recent studies based on

measurement of cerebral histamine H1-receptor occupancy by positron emission tomography showed that second generation antihistamines such as bilastine, fexofenadine and levocetirizine had the lowest occupancy, which accounted for the clinically observed absence of sedative effect (54, 55).

First generation H1-blockers, but also some of the second one (loratadine, desloratadine, rupatadine), are metabolized by the hepatic system cytochrome P450. An impaired liver function or a concomitant therapy with P450 cytochrome (ketoconazole, erythromycin, grapefruit...) can cause an increase in plasma concentration, worsening any side effect (56).

The second generation antihistamines must be preferred because they have a better safety profile, thanks to their higher specificity for H1 receptors and the low ability to cross the blood brain barrier (57). They also have anti-inflammatory activity, by inhibiting pro-inflammatory cytokines (51), and cardiac safety, documented for loratadine, fexofenadine, mizolastine, ebastine, azelastine, cetirizine, desloratadine, levocetirizine, rupatadine and bilastine (56-59). Regarding the pharmacokinetic properties of these drugs, cetirizine and fexofenadine are excreted almost totally unchanged in the urine and in the feces, respectively (53), while 95% of bilastine is eliminated unaltered for 28% in urine and for 66% in feces (60). Moreover, bilastine does not act on hepatic cytochromes (60). Thanks to these reasons, second generation H1-blockers have a wider therapeutic index, making their use strongly recommended in elderly.

3.2 Intranasal antihistamines

Side effects are potentially the same as the oral route of administration, but the topical use decreases this risk. It is always recommended to use second generation antihistamines to reduce side effects due to absence of selectivity of the oldest H1-blockers. The most frequent adverse effects due to intranasal antihistamines include bitter taste, headache, dry mouth and local nasal mucosa irritation. Only one study on the use of intranasal antihistamines was conducted on patients over 65 years. Shin et al. analyzed the use of intranasal azelastine, showing its safety for older people (61). In fact, azelastine is excreted for 75% in feces and only for 25% in urine, thus

resulting safe also in case of renal dysfunction (62). Moreover, its bioavailability is about 40% (63). Another study evaluated the use of levocabastin in general population, showing that after nasal administration does not reach high blood concentrations, but it is excreted unaltered in urine, making it not safe in case of kidney failure (60). The same caution must be applied in case of simultaneous prescription of inhibitors of P450 cytochromes (ketoconazole and erythromycin, i.e.) (60).

3.3 Decongestants

Guidelines suggest using intranasal decongestants for short periods to avoid the risk of drug-induced rhinitis, as mentioned above (2). In fact, they can affect the cardiovascular, urinary, central nervous and endocrine systems, inducing anxiety, irritability, insomnia, arrhythmias, urinary retention and increases in blood pressure (61). Decongestant use is not indicated in elderly, especially in patients with cardiovascular diseases, bladder neck obstruction and vascular cognitive impairment.

3.4 Leukotriene Receptor Antagonists (LTRA)

LTRAs are suggested by ARIA and EAACI guidelines to treat milder forms and intermittent moderate AR (2). It has been demonstrated that LTRAs are particularly effective in improving nasal congestion and quality of sleep (62). There are no clinical trials about the use of LTRAs for AR in elderly, but there are some studies on their use in older patients with asthma, as reported in a recent review by Scichilone (63). The most common adverse effects of LTRAs are headache, abdominal pain, diarrhea, and nausea (63), but these studies did not show a significant higher risk of adverse effects in elderly patients. Liver damages are rarely reported, not only in older population (52, 64). The advantage to use them in this kind of patients can be given by the increase of adherence to the therapy, due to the preference and minor risk of mistake in taking a tablet instead of, for example, a spray. LTRAs can be also useful to reach a better control of a concomitant asthma.

3.5 Intranasal Corticosteroids

INS are very effective on nasal obstruction, nasal itching and rhinorrhea and their action reach the maximum effect after 24-48 hours, but the early benefit can be achieved after 12 hours (65) in any kind of rhinitis. Mometasone and fluticasone furoate act also on conjunctivitis symptoms (66). Such topical steroids have a very low bioavailability: from the 0,5% of fluticasone furoate to the 20% of flunisolide, but bioavailability increases up to 42% for beclomethasone (67-69). The safety of INS is documented in elderly in few clinical trials focused on this particular population. One randomized controlled study evaluated the efficacy and safety of mometasone furoate in patients over 65 years old (70), while another confirmed the same results with fluticasone propionate (71). The most frequent side effects include mouth and nose dryness, burning of the nasal mucosa, nasal crusting and epistaxis. Even though there is no evidence that INS can alter bone metabolism (72,73), they must be prescribed with caution in patient already suffering from osteoporosis and/or receiving steroids for other comorbidities. Another concern about INS use is glaucoma. A case-control study including 9793 patients over 66 years with a diagnosis of glaucoma (borderline or open angle) or of ocular hypertension showed that there was no increase of ocular adverse effects during therapy with INS (74). In conclusion, INS should be considered a sufficiently safe treatment option of AR in elderly.

3.6 Intranasal second generation antihistamine/nasal corticosteroid combination

A study investigated the efficacy and safety of the combination of fluticasone propionate and azelastine conducted on general adult population, showing that this formulation is superior in symptoms control to the two separate molecules (75). Concerning the safety, the results reported above (63, 67) on the two components (azelastine and fluticasone propionate) used separately can be also extended to their combination.

3.7 Intranasal cromones

Cromones vs placebo trials stated that sodium cromoglicate is more effective than placebo (76), but its efficacy is low compared to the other therapeutic options available for AR (2). Side effects are extremely rare with sodium cromoglicate nasal solutions (76), thus these drugs are very safe. Nonetheless, the need to take cromones several times a day makes it very difficult to maintain adherence (76), especially in elderly people.

3.8 Ipratropium

Ipratropium is effective in improving rhinorrhea, but it does not impact on the other nasal symptoms (36). Ipratropium is a short-acting anticholinergic agent and this can reduce the potential adverse effects. In fact, adverse reactions due to the anticholinergic action occur more commonly with long-acting molecules. Dry mouth, bad taste, reduction of gastrointestinal peristalsis, dilatation of pupil and blurred vision consequent to increase in intraocular pressure, mild cognitive impairment, and paradoxal bronchoconstriction are potential side effects (77). Even though the use of anticholinergics is not officially recommended in elderly patients, they are generally well tolerated both in nasal topical preparations and in inhaled formulations for bronchial obstruction (78).

3.9 Oral Corticosteroids

As previously stated, ARIA guidelines suggest to use systemic corticosteroids only for brief periods when it is necessary to obtain a rapid control of the symptoms (2). The potential effects of a prolonged therapy with OCs are well known and include glucose intolerance, mainly reversible, gastrointestinal bleeding, hypertension, mood alterations, cataract, glaucoma, osteoporosis (2). Therefore, older patients often discontinue therapies abruptly, causing not only a flare up of the symptoms, but also a possible acute adrenal insufficiency. However, AR only rarely requires the use of OCs.

3.10 Other treatment options

- Saline douching represents a cheap, easy to use and free from adverse effects way to improve AR symptoms (25). The limit of its application could be secondary to the difficulty to manage the tools necessary to perform nasal lavages. In fact, comorbidities such as arthritis, osteoarthritis, cognitive impairment are frequent in elderly.
- There are not incontrovertible proofs of efficacy regarding acupuncture, homeopathy, herbal medicine, though their large diffusion in general population (2, 25, 79).
- Avoiding irritant and inhalant allergens is commonly suggested.

3.11 Allergen specific immunotherapy

The GA²LEN/EAACI pocket guide for AIT for allergic rhinitis and asthma (80) does not set an upper age limit to prescribe AIT. A recent EAACI position paper on the clinical contraindications to AIT confirmed this concept (43). The first study that proved the efficacy and safety of AIT in the elderly was conducted on 22 geriatric patients in 1993 (81). Other studies confirmed that SCIT was effective and safe in elderly as much as in younger patient (82, 83). The same results were obtained for SLIT (84, 85) and for the first time they were supported by two double-blind placebo-controlled trials, during which elderly were treated with SLIT for house dust mites and grass pollen (86, 87).

The contraindications for AIT stated in the EAACI position paper (43) include some frequent clinical conditions among elderly, such as malignant neoplasias, autoimmune diseases and uncontrolled asthma. These latter are considered as absolute contraindications. Cardiovascular diseases, psychiatric or mental disorders, chronic infections, such as HBV and HCV, and chronic therapy with β -blockers, ACE-inhibitors or immunosuppressive drugs are instead relative contraindications. Despite old patients with chronic diseases and on daily drug-regimen are very common in real-life, the available literature about AIT in elderly is scarce because they are often

excluded from controlled trials or are present in a limited number. In conclusion, old age does not preclude AIT, but the risk/benefit ratio must be considered individually for each patient before prescribing this treatment, considering its demonstrated capacity to improve significantly the quality of life, and to reduce symptoms and use of drugs (88).

4. Expert Commentary and Five Years View

Pharmacological treatment during pregnancy and old age represent a challenging issue. The potential adverse effects on the fetus should be always taken into consideration when prescribing a treatment to pregnant women. Concerning the elderly under multi-pharmacological treatment, the risk of potential negative interactions between drugs and side effects is highly increased.

Drug avoidance recommendation in pregnancy should be carefully balanced with the need for mother wellbeing. The potential risk of a bad AR treatment for the fetus has to be taken into consideration, particularly if AR affects quality of sleep and in asthmatic patients. Nasal inflammation is a well-known asthma exacerbations trigger and uncontrolled asthma during pregnancy is associated with a greater risk of low weight at birth, congenital malformations, pre-eclampsia, gestational diabetes and antepartum hemorrhage.

Due to ethical issues no clinical trials can be conducted to investigate the impact of drugs on pregnancy, but a great amount of published data support the safety of some pharmacological treatments in that particular lifetime. It is reasonable choosing a topical drug as first approach; intranasal budesonide is usually the suggested option, as no adverse events have been observed while treating pregnant women. As far as systemic drugs, the second-generation antihistamines provide a very good safety and tolerability profile; most of data on treatment in pregnancy concern cetirizine and loratadine. If pregnancy occurs while allergen immunotherapy is ongoing and it is

well tolerated, there is no reason for stopping it; on the other hand, AIT initiation during pregnancy is not recommended. Unless very rare, the risk of anaphylactic AIT related-reactions should be avoided. Furthermore, due to the specific immune and hormonal changes during pregnancy, in some cases rhinitis spontaneously improves.

Elderly patient are often affected by multiple comorbidities, even more severe than allergic rhinitis. Nevertheless poorly controlled AR can act as a trigger for respiratory diseases exacerbation and also heavily affect the patient's quality of life. For these reasons there is no sense in avoiding AR treatment if it is indicated. Of course a careful assessment of comorbidities and potential drug interactions should be carefully taken into consideration when prescribing any pharmacological therapy. No specific concerns have been highlighted regarding topical treatments, except for ipratropium and decongestionants, especially in patients with cardiovascular diseases, bladder neck obstruction and vascular cognitive impairment. The inability to properly use the device might represent a contraindication to topical treatment prescription. This aspect should be always assessed, even more in old aged patients. As far as systemic drugs is concerned, second generation antihistamines overall provide an optimal safety and tolerability profile, particularly concerning cardiac effects and interaction with Central Nervous System; furthermore their wide therapeutic index make their use strongly recommended in elderly, in comparison with first generation antihistamines. LTRAs are suggested in elderly as well, especially when they are affected by concomitant asthma. Though elderly are often excluded from controlled trials and few data are available about AIT in that specific lifetime, there is no evidence that old age should preclude allergen immunotherapy. On the opposite, once excluded the well-known general contraindications, it should be highly considered in elderly as well, at least for two main reasons: first, AIT might significantly improve the patient's quality of life; second, it can be able to provide a significant reduction of drug intake.

In conclusion, a great numbers of drugs are currently available for the management of allergic rhinitis and many of them provide an optimal safety and tolerability profile also during pregnancy

and old age. Thus it is mandatory for every clinician treating AR in every lifetime and carefully tailoring the pharmacological treatment.

5. Key issues

- Drug avoidance recommendation in pregnancy should be carefully balanced with the need for mother wellbeing and AR optimal control.
- Topical drugs are suggested as a first approach and intranasal budesonide has never been related to adverse events observed while treating pregnant women.
- Many data support the good safety and tolerability profile of second-generation antihistamines in pregnancy, particularly cetirizine and loratadine.
- If allergen immunotherapy is ongoing and it is well tolerated, there is no reason for stopping it during pregnancy; on the other hand, AIT initiation in that period is not recommended.
- No specific concerns have been highlighted regarding topical treatments in the elderly, except for ipratropium and nasal decongestionants.
- Second generation antihistamines do not have cardiac effects and do not interact with Central Nervous System; furthermore their wide therapeutic index make their use strongly recommended in elderly, in comparison with first generation antihistamines.
- LTRAs are suggested in elderly as well, especially when they are affected by concomitant asthma.
- There is no evidence that old age should preclude allergen immunotherapy.

- It is mandatory for every clinician treating curing AR in every lifetime and carefully tailoring the pharmacological treatment.

Declaration of Interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

References

*-Papers of interest

** -Papers of particular interest

1. Pawankar R, Canonica GW, Holgate ST, et al. WAO White Book on Allergy: update 2013. 2013. <http://www.worldallergy.org> Accessed December 2015.
2. Bousquet J, Schünemann HJ, Samolinski B, et al. Allergic Rhinitis and its Impact on Asthma (ARIA): Achievements in 10 years and future needs. *J Allergy Clin Immunol*. 2012;130:1049-62.
3. Juniper EF, Stahl E, Doty RL, et al. Clinical outcomes and adverse effect monitoring in allergic rhinitis. *J Allergy Clin Immunol* 2005;3(Suppl.1):S390–S413.
4. Bubach GJ, Heinzerling LM, Edenharter G, et al. GA(2)LEN skin test study II: clinical relevance of inhalant allergen sensitizations in Europe. *Allergy*. 2009; 64:1507-15.
5. Nurmatov U, van Schayck CP, Hurwitz B, Sheikh A. House dust mite avoidance measures for perennial allergic rhinitis: an updated Cochrane systematic review. *Allergy* 2012;67:158-65.
6. Roberts G, Xatzipsalti M, Borrego LM, et al. Paediatric rhinitis: position paper of the European Academy of Allergy and Clinical Immunology. *Allergy* 2013;68:1102–16.
7. Incaudo GA, Takach P. The diagnosis and treatment of allergic rhinitis during pregnancy and lactation. *Immunol allergy Clin N Am* 2006;26:137-154.
8. Ventura MT, Scichilone N, Gelardi M, et al. Management of allergic disease in the elderly: key considerations, recommendations and emerging therapies. *Expert Rev Clin Immunol*. 2015;11:1219-28.
9. Bousquet J, Van Cauwenberge P, Khaltaev N; Aria Workshop Group; World Health Organization. Allergic Rhinitis and its impact on asthma. *J Allergy Clin Immunol* 2001; 108: S147-S334.
10. Murphy VE, Clifton VL, Gibson PG, et al. Asthma exacerbations during pregnancy: incidence and association with adverse pregnancy outcomes *Thorax*. 2006;61:169–76.
11. Hodyl NA, Stark MJ, Scheil W, et al. Perinatal outcomes following maternal asthma and cigarette smoking during pregnancy. *Eur Respir J*. 2014;43:704–16.
12. Enriquez R, Griffin MR, Carroll KN, et al. Effect of maternal asthma and asthma control on pregnancy and perinatal outcomes. *J Allergy Clin Immunol*. 2007;120:625–30.
13. Food and Drug Administration, HHS. Content and format of labeling for human prescription drug and biological products; requirements for pregnancy and lactation labeling. Final rule. *Fed Regist*. 2014;79:72063-103.
14. Food and Drug Administration. Labeling and prescription drug advertising: content and format for labeling for human prescription drugs (final rule). *Fed Regist* 1979;44:37434-67.
15. Yawn B, Knudtson M. Treating Asthma and Comorbid Allergic Rhinitis in Pregnancy. *J Am Board Fam Med*. 2007;20:289-98.

16. Brost BC, Scardo JA, Newman RB. Diphenhydramine overdose during pregnancy: lessons from the past. *Am J Obstet Gynecol.* 1996;175:1376–77.
17. Ito S, Blajchman A, Stephenson M, et al. Prospective follow-up of adverse reactions in breast-fed infants exposed to maternal medication. *Am J Obstet Gynecol.* 1993;168:1393–99.
18. Plaut M, Valentine MD. Clinical practice. Allergic rhinitis. *N Engl J Med.* 2005 3;353:1934–44.
19. Blaiss MS. Diphenhydramine vs desloratadine comparisons must consider risk-benefit ratio. *Ann Allergy Asthma Immunol.* 2006;97:121-2.
20. Källén B. Use of antihistamine drugs in early pregnancy and delivery outcome. *J Matern Fetal Neonatal Med.* 2002;11:146-52.
21. Gilboa SM, Ailes EC, Rai RP, et al. Antihistamines and Birth Defects: A Systematic Review of the Literature. *Expert Opin Drug Saf.* 2014;13:1667–98.
22. Church MK, Maurer M, Simons FE, et al; Global Allergy and Asthma European Network. Risk of first-generation H(1)-antihistamines: a GA(2)LEN position paper. *Allergy.* 2010; 65:459–66.
23. Lucero ML, Arteche JK, Sommer EW, et al. Preclinical toxicity profile of oral bilastine. *Drug Chem Toxicol.* 2012;35(Suppl 1):25-33.
24. Berger WE. Pharmacokinetic characteristics and safety and tolerability of a reformulated azelastine hydrochloride nasal spray in patients with chronic rhinitis, *Expert Opin Metab Toxicol* 2009;5:91-102.
25. Scadding GK. Optimal management of allergic rhinitis. *Arch Dis Child* 2015; 100:576-82.
26. Torfs CP, Katz EA, Bateson TF, et al. Maternal medications and environmental exposures as risk factors for gastroschisis. *Teratology* 1996;54:84–92.
27. Werler MM, Mitchell AA, Shapiro S. First trimester maternal medication use in relation to gastroschisis. *Teratology* 1992 April; 45 (4):361–7.
28. Yau WP, Mitchell AA, Lin KJ, et al. Use of decongestants during pregnancy and the risk of birth defects. *Am J Epidemiol.* 2013;178:198- 208.
28. Demoly P, Piette V, Daures JP. Treatment of allergic rhinitis during pregnancy. *Drugs* 2003; 63: 1813–20.
29. Rocklin RE. Asthma, asthma medications and their effects on maternal/fetal outcomes during pregnancy. *Reprod Toxicol.* 2011;32:189-97.
30. Gluck JC, Gluck PA. Asthma controller therapy during pregnancy. *Am J Obstet Gynecol* 2005; 192: 369–80.
31. Gilbert C, Mazzotta P, Loebstein R, Koren G. Fetal safety of drugs used in the treatment of allergic rhinitis: a critical review. *Drug Saf* 2005;28:707–19.
32. Ellegaard EK, Hellgren M, Karlsson NG. Fluticasone propionate aqueous nasal spray in pregnancy rhinitis. *Clin Otolaryngol Allied Sci.* 2001;26:394-400.

33. Choi JS, Han JY, Kim MY, et al. Pregnancy outcomes in women using inhaled fluticasone during pregnancy: a case series. *Allergol Immunopathol (Madr)*. 2007;35:239-42.
34. Meltzer EO, LaForceC, RatnerP, et al. MP29-02(a novel intranasal formulation of azelastine hydrochloride and fluticasone propionate) in the treatment of seasonal allergic rhinitis: a randomized, double-blind, placebo-controlled trial of efficacy and safety. *Allergy Asthma Proc*. 2012;33:324-32.
35. Wilson J. Use of sodium cromoglycate during pregnancy. *J PharmMed* 1982;8:45-51.
36. Mygind N, Borum P. Intranasal ipratropium: literature abstracts and comments. *Rhinol Suppl*. 1989;9:37-44.
37. Rodriguez-Pinilla E, Martinez-Frias ML. Corticosteroids during pregnancy and oral clefts: a case control study. *Teratology* 1998;58:2-5.
38. Garavello W, Somigliana E, Acaia B, et al. Nasal lavage in pregnant women with seasonal allergic rhinitis: a randomized study. *Int Arch Allergy Immunol*. 2010;151:137-41.
39. Demoly P, Cameron MA, Casale TB, et al. The value of pre- and co- seasonal sublingual immunotherapy in pollen-induced allergic rhinoconjunctivitis. *Clin Transl Allergy*. 2015 5:18.
40. Metzger WJ, Turner E, Patterson R. The safety of immunotherapy during pregnancy. *J Allergy Clin Immunol* 1978;61:268-72.
41. Shaikh WA. A retrospective study on the safety of immunotherapy in pregnancy. *Clin Exp Allergy* 1993;23:857-60.
42. Shaikh WA, Shaikh SW. A prospective study on the safety of sublingual immunotherapy in pregnancy. *Allergy* 2012;67:741- 743.
- ** To our knowledge the only prospective trial on allergen immunotherapy in pregnancy.
43. Pitsios C, Demoly P, Bilò MB, et al. Clinical contraindications to allergen immunotherapy: an EAACI position paper. *Allergy* 2015;70: 897-909.
44. Simons FE, Schatz MJ. Anaphylaxis during pregnancy. *J Allergy Clin Immunol* 2012;130:597-606.
45. Helbling A, Muller UR, Hausmann O. Uterine contractions are known side effects of venom immunotherapy. *J Investig Allergol Clin Immunol* 2011;21:330.
46. Oykman P, Kim HL, Ellis AK. Allergen immunotherapy in pregnancy. *Allergy Asthma Clin Immunol* 2015;11:31.
47. Cardona V, Guilarte M, Luengo O, et al. Allergic diseases in the elderly. *Clin Transl Allergy* 2011; 1:11.
48. Morais-Almeida M, Pite H, Pereira AM, et al. Prevalence and classification of rhinitis in the elderly: a nationwide survey in Portugal. *Allergy* 2013;68:1150-7.
49. Huss K, Naumann PL, Mason PJ, et al. Asthma severity, atopic status, allergen exposure and quality of life in elderly persons. *Ann Allergy Asthma Immunol*. 2001;86:524-30.

50. Ventura MT, Gelardi M, D'Amato A, et al. Clinical and cytologic characteristics of allergic rhinitis in elderly patients. *Ann Allergy Asthma Immunol.* 2012;108:141–4.

51. Scichilone N, Ventura MT, Bonini M, et al. Choosing wisely: practical considerations on treatment efficacy and safety of asthma in the elderly. *Clin Mol Allergy* 2015;13:7.

* An updated and extensive review on pharmacological treatments for asthma in the elderly

52. Cooper V, Metcalf L, Versnel J, et al. Patient-reported side effects, concerns and adherence to corticosteroid treatment for asthma, and comparison with physicians estimates of side-effect prevalence: a UK-wide, cross-sectional study. *NPJ Prim Care Respir Med* 2015;25:15026.

53. Hansen J, Klimek L, Hormann K. Pharmacological management of allergic rhinitis in the elderly: safety issues with of antihistamines. *Drugs Aging.* 2005;22:289-96.

54. Jauregui I, Ramaekers JG, Yanai K, et al. Bilastine: a new antihistamine with an optimal benefit-to-risk ratio for safety during driving. *Expert Opin Drug Saf* 2016;15):89-98.

55. Hiraoka K, Tashiro M, Grobosch T, et al. Brain histamine H1 receptor occupancy measured by PET after oral administration of levocetirizine, a non-sedating antihistamine. *Expert Opin Drug Saf* 2015;14:199-206.

56. Bom AT, Pinto AM. Allergic respiratory diseases in the elderly. *Respir Med.* 2009;103: 1614-22.

57. Demoly P, Chiriac AM, Berge B, et al. Reasons for prescribing second generation antihistamines to treat allergic rhinitis in real-life conditions and patient response. *Allergy Asthma Clin Immunol.* 2014 6;10:29.

58. Ridolo E, Montagni M, Bonzano L, et al. Bilastine: new insight into antihistamine treatment. *Clin Mol Allergy.* 2015;13:1.

59. Mullol J, Bousquet J, Bachert C, et al. Update on rupatadine in the management of allergic disorders. *Allergy.* 2015;70 (Suppl 100):1-24.

60. Bachert C, Kuna P, Sanquer F, et al; Bilastine International Working Group. Comparison of the efficacy and safety of bilastine 20 mg vs desloratadine 5 mg in seasonal allergic rhinitis patients. *Allergy.* 2009;64:158-65.

61. Shin MH, Barody F, Proud D, et al. The effect of azelastine on the early allergic response. *Clin Exp Allergy.* 1992;22:289–95.

62. Kempuraj D, Huang M, Kandere K, et al. Azelastine is more potent than olopatadine in inhibiting interleukin-6 and tryptase release from human umbilical cord blood-derived cultured mast cells. *Ann Allergy Asthma Immunol.* 2002;88:501–6.

63. van Bavel J, Howland WC, Amar NJ, et al. Efficacy and safety of azelastine 0.15% nasal spray administered once daily in subjects with seasonal allergic rhinitis. *Allergy Asthma Proc.* 2009;30:512–8.

61. Jonson DA, Hricik JG. The pharmacology of alpha-adrenergic decongestants.

Pharmacotherapy. 1993;13(6 Pt 2):110S-115S.

62. Xu Y, Zhang J, Wang J. The efficacy and safety of selective H1-antihistamine versus leukotriene receptor antagonist for seasonal allergic rhinitis: a meta-analysis. *PLoS One*. 2014 10; 9:e112815.

63. Scichilone N, Battaglia S, Benfante A, et al. Safety and efficacy of montelukast as adjunctive therapy for treatment of asthma in elderly patients. *Clinical Interv Aging* 2013;8: 1329–37.

64. Russmann S, Iselin HU, Meier D, et al. Acute hepatitis associated with montelukast. *J Hepatol*. 2003;38:694–5.

65. Jen A, Baroody F, de Tineo M, et al. As-needed use of fluticasone propionate nasal spray reduces symptoms of seasonal allergic rhinitis. *J Allergy Clin Immunol*. 2000;105:732–8.

66. Bielory L. Ocular symptom reduction in patients with seasonal allergic rhinitis treated with the intranasal corticosteroid mometasone furoate. *Ann Allergy Asthma Immunol*. 2008;100:272–9.

67. Bryson HM, Faulds D. Intranasal fluticasone propionate. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in allergic rhinitis. *Drugs* 1992;43:760–75.

68. Daley-Yates PT, Baker RC. Systemic bioavailability of fluticasone propionate administered as nasal drops and aqueous nasal spray formulations. *Br J Clin Pharmacol*. 2001;51:103–5.

69. Daley-Yates PT, Kunka RL, Yin Y, et al. Bioavailability of fluticasone propionate and mometasone furoate aqueous nasal sprays. *Eur J Clin Pharmacol*. 2004;60:265–8.

70. Grossman J, Gopalan G. Efficacy and safety of mometasone furoate spray in elderly subjects with perennial allergic rhinitis [abstract]. *J Allergy Clin Immunol*. 2009;123(2 Suppl 1):S271.

71. Behncke VB, Alemar G, Kaufman DA, et al. Azelastine nasal spray and fluticasone nasal spray in the treatment of geriatric patients with rhinitis. *J Allergy Clin Immunol*. 2006;117(Suppl 1):S263.

72. Wilson AM, Sims EJ, McFarlane LC, et al. Effects of intranasal corticosteroids on adrenal, bone, and blood markers of systemic activity in allergic rhinitis. *J Allergy Clin Immunol*. 1998; 102:598–604.

73. Lee DK, Robb FM, Sims EJ, et al. Systemic bioactivity of intranasal triamcinolone and mometasone in perennial allergic rhinitis. *Br J Clin Pharmacol*. 2003;55:310–3.

74. Garbe E, Suissa S. Inhaled corticosteroids and the risk of cataracts. *N Engl J Med*. 20;337: 1555.

75. Bousquet J, Bachert C, Bernstein J, et al Advances in pharmacotherapy for the treatment of allergic rhinitis; MP29-02 (a novel formulation of azelastine hydrochloride and fluticasone propionate in an advanced delivery system) fills the gap. *Expert Opin Pharmacother*. 2015;16:913–28

76. [No authors listed] Seasonal allergic rhinitis: limited effectiveness of treatments. *Prescrire Int*. 200;17:28–32.

77. Gupta P, O'Mahony MS. Potential adverse effects of bronchodilators in the treatment of

airways obstruction in older people: recommendations for prescribing. *Drugs Aging*. 2008;25:415-43

78. Tashkin DP. Long-acting anticholinergic use in chronic obstructive pulmonary disease: efficacy and safety. *Curr Opin Pulm Med* 2010;16:97-105.

79. Braido F, Sclifò F, Ferrando M, et al. New therapies for Allergic Rhinitis. *Curr Allergy Asthma Rep*. 2014; 14:422.

80. Zuberbier T, Bachert C, Bousquet PJ, et al. GA2LEN/EAACI pocket guide for allergen-specific immunotherapy for allergic rhinitis and asthma. *Allergy* 2010; 65:1525–30.

81. Armentia A, Fernández A, Tapias JA, et al. Immunotherapy with allergenic extracts in geriatric patients: evaluation of effectiveness and safety. *Allergol Immunopathol (Madr)* 1993; 21: 193-6.

82. Eidelman F, Darxentas N. Efficacy of allergy immunotherapy in the elderly. *J Allergy Clin Immunol* 2000; 105:313.

83. Asero R. Efficacy of injection immunotherapy with ragweed and birch pollen in elderly patients. *Int. Arch. Allergy Immunol*. 2004;21:135,332–35.

84. Marogna M, Bruno ME, Massolo A, et al. Sublingual immunotherapy for allergic respiratory disease in elderly patients: a retrospective study. *Eur Ann Allergy Clin Immunol*. 2008;40:22–9.

85. Baptistella E, Maniglia S, Malucelli DA, et al. Allergen-Specific Immunotherapy in Patients 55 Years and Older: Results and Review of Literature. *Int Arch Otorhinolaryngol* 2013;17:375–9.

86. Bozek A, Ignasiak B, Filipowska B, et al. House dust mite sublingual immunotherapy: a double-blind, placebo-controlled study in elderly patients with allergic rhinitis. *Clin. Exp. Allergy* 2013;43:242–8.

87. Bozek A, Kolodziejczyk K, Warkocka-Szolytysek B, et al. Grass pollen sublingual immunotherapy: a double-blind, placebo-controlled study in elderly patients with seasonal allergic rhinitis. *Am J Rhinol Allergy*. 2014;28:423-7.

88. Canonica GW, Cox L, Pawankar R et al. Sublingual immunotherapy: World Allergy Organization position paper 2013 update. *World Allergy Organ J*. 2014;7:6.

** The most extensive and updated review and statement on allergen sublingual immunotherapy for respiratory allergic diseases.

Table 1 Suggested pharmacotherapy in pregnant women with AR

RHINITIS	DRUG THERAPY	
----------	--------------	--

MILD INTERMITTENT	• Nasal douching Or • Second generation oral H1-Blockers	A L L E R G I C
MODERATE/SEVERE INTERMITTENT OR MILD PERSISTENT	• Second generation oral H1-Blockers Or • Intranasal CS	S A V O I D A N C E
MODERATE/SEVERE PERSISTENT	• Intranasal CS AND • Second generation oral H1-blockers <i>If failure:</i> • Increase intranasal CS	

Table 2 Suggested pharmacotherapy in elderly with AR

RHINITIS	DRUG THERAPY	
-----------------	---------------------	--

MILD INTERMITTENT	• Second generation oral H1-Blockers Or • Intranasal H1-Blockers	A	I
MODERATE/SEVERE INTERMITTENT OR MILD PERSISTENT	• Second generation oral H1-Blockers Or • Intranasal H1-Blockers Associated with • Intranasal CS	G	
MODERATE/SEVERE PERSISTENT	• Intranasal CS AND • Second generation oral H1-blockers <i>If failure:</i> • Increase intranasal CS • Add a short oral SC therapy if nasal blockage • Add ipratropium if rhinorrhea (and asthma)	E	
		R	M
		N	M
		E	U
		S	N
		A	O
		V	T
		O	H
		I	E
		D	R
		A	A
		N	P
		C	Y
		E	