

An update on the management of hay fever in adults

Allergic rhinitis is a common disorder occurring in about one in four people in Britain with a peak onset during adolescence.¹⁻³ Although not necessarily a serious illness, it can adversely affect quality of life and disrupt normal activities, and is a risk factor for asthma.^{2,3} The symptoms of seasonal allergic rhinitis/rhino-conjunctivitis caused by an IgE-mediated type 1 hypersensitivity reaction to airborne allergens, particularly pollens, and which typically occur between spring and autumn are commonly referred to as hay fever.³ There are a number of management options available including drug therapy. Several drugs can be bought over the counter in the UK, and so people with allergic rhinitis may commonly present to the pharmacy or to general practice. The choice of treatment will be influenced by the spectrum, intensity and frequency of symptoms, and should take into account safety, efficacy, cost and patient preferences. Some of the treatments now available have been developed since our previous review was published and include the newer antihistamines, oral leukotriene receptor antagonists (LTRA),ⁱ and sublingual allergen desensitisation immunotherapy.⁴

About hay fever

The symptoms of allergic rhinitis include sneezing, nasal itching, and rhinorrhoea, sometimes accompanied by conjunctivitis and nasal obstruction.³ Diagnosis is largely based on the history, presenting symptoms and exclusion of infectious or irritant causes of rhinitis.⁵ If necessary, skin prick testing or blood testing for serum total and specific IgE may be carried out to confirm the identity of the allergen, or, in rare cases, allergen provocation tests may be indicated.^{3,5}

Although allergic rhinitis has traditionally been classified as seasonal or perennial, it is now more usually classified by duration and severity. A distinction between moderate and severe is considered to make diagnosis more complex and does not make a difference to the therapeutic options (see Box).²

Box: Classification of allergic rhinitis²

Duration	
Intermittent	<4 days/week or <4 consecutive weeks
Persistent	>4 days/week and >4 consecutive weeks
Severity	
Mild	Symptoms not troublesome and normal activities and sleep not affected
Moderate/severe	Symptoms are troublesome and/or normal activities affected and/or sleep disturbed

What do the guidelines say?

Although bodies such as the National Institute for Health and Clinical Excellence (NICE) and the Scottish Intercollegiate Guidelines Network have not produced guidance, other organisations including the British Society for Allergy and Clinical Immunology (BSACI)⁶ and the Allergic Rhinitis and its Impact on Asthma (ARIA) initiative² have published guidelines for the management of allergic rhinitis. Both sets of guidelines are based on evidence, and for areas where there is limited evidence a consensus of expert opinion is used.

ⁱ Of the two LTRAs available in the UK, only montelukast is licensed for the treatment of seasonal allergic rhinitis, and only in people with concomitant asthma.

Several decision support tools provide summaries of guidance and treatment options, and these include Clinical Knowledge Summaries (provided by NICE) and Best Practice (provided by the BMJ Group).^{5,7}

Most guidelines and decision support tools recommend a stepwise approach. First-line treatment for mild intermittent symptoms is an oral or intranasal new generation antihistamine (typically defined as 'newer', 'second generation' or 'non-sedating').^{2,6} Alternatives include a nasal decongestant or an LTRA.^{2,7}

For persistent mild or intermittent moderate symptoms, the additional options include intranasal corticosteroids or intranasal cromoglicate.^{2,6,7}

The first choice for persistent moderate-to-severe symptoms is an intranasal corticosteroid.^{2,6-8} Alternatives include new generation oral antihistamines or an LTRA.² If response is inadequate, the diagnosis and adherence to treatment, including the technique for instilling nasal drops and using nasal sprays, should be checked before stepping up treatment by increasing the corticosteroid dose or giving an antihistamine and intranasal corticosteroid in combination.^{2,6}

Additional therapy may be considered depending on symptoms:

- intranasal ipratropium—for watery rhinorrhoea;
- oral or local new generation antihistamines—for nasal itching or sneezing;
- LTRA—for catarrh for people with rhinitis and asthma;
- short course (5–7 days) of an oral corticosteroid or an intranasal decongestant (e.g. ephedrine or xylometazoline) for severe nasal congestion or blockage, for symptoms uncontrolled by conventional pharmacotherapy (rescue therapy), for important social or work-related events or to facilitate absorption of intranasal corticosteroids or antihistamines.^{6,8}

People with allergic conjunctivitis may be treated with an antihistamine (oral or as eye drops) or cromoglicate eye drops.^{2,6,8}

People with persistent severe symptoms despite optimised drug therapy should be considered for referral to an allergy specialist.

* DTB CME/CPD

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Allergen immunotherapy may be an option for such patients.² Immunotherapy carries a risk of anaphylaxis and severe bronchospasm and should be carried out under the supervision of an experienced physician in a hospital or clinic where immediate access to cardiopulmonary resuscitation facilities are available.⁹ Patients should be observed for a minimum of 60 minutes following each injection, and for 20–30 minutes after the first sublingual dose.^{9,10}

Which drug?

In practice, the treatment of hay fever is not as straightforward as the preceding summary of the guidelines might suggest. Patients may have preferences for the oral or intranasal route, for episodic or preventive treatment and for buying over the counter medicines rather than obtaining them on prescription. The range of presenting symptoms will also influence the choice of therapy and systemic administration may be more effective for patients with multiple symptoms (see table).

Table: Effects of therapies on hay fever symptoms⁶

Drug class	Sneezing	Rhinorrhoea	Nasal obstruction	Nasal itching	Eye symptoms
Antihistamines					
Oral	++	++	+	+++	++
Intranasal	++	++	+	++	–
Eye drops	–	–	–	–	+++
Corticosteroids					
Intranasal	+++	+++	+++	++	++
Mast cell stabilisers					
Intranasal	+	+	+	+	–
Eye drops	–	–	–	–	++
Decongestants					
Intranasal	–	–	++++	–	–
Oral	–	–	+	–	–
Anticholinergics					
–	–	++	–	–	–
Leukotriene receptor antagonistⁱ					
–	–	+	++	–	++

In addition, ARIA considers that the most important barrier to implementation of guidelines is the scarcity of high-quality evidence supporting treatment decisions.⁸ Their review of the literature identified many areas where there were few studies or only studies with a high risk of bias. They also identified many areas that required more rigorous systematic reviews or where existing systematic reviews required updating. The ARIA guidelines used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach¹¹ to evaluate the evidence. Under this approach, recommendations are graded as strong or weak (conditional) based on four key factors: the balance between desirable and undesirable consequences of treatment (net clinical benefit); available evidence; values and preferences; and cost.

Antihistamines

The new generation of antihistamines (e.g. cetirizine, loratadine) are preferred to the older generation (e.g. chlorphenamine) as they produce fewer unwanted effects including sedation.^{6,8} The functional designation 'non-sedating' is arbitrary as the degree of sedation is a continuum with no well-defined cut-off value and is not used by ARIA.⁸ Prescription-event monitoring in the UK found that loratadine and fexofenadine were associated with a lower incidence of sedation than acrivastine and cetirizine, although the risk of sedation was low with all four drugs and the clinical significance of the findings was unclear.¹² ARIA considers the evidence for using new generation antihistamines to be of low quality, but nevertheless gives a strong recommendation for those that do not cause sedation and a conditional recommendation for those that cause some sedation.⁸

In its review, ARIA concluded that intranasal antihistamines (e.g. azelastine) showed a small to moderate effect on nasal symptoms compared with placebo, based on evidence it classified as low quality.⁸ A small number of

comparative studies comparing intranasal antihistamines with new-generation oral antihistamines found them to be equally beneficial,^{8,13} although a pharmaceutical industry-funded review concluded that intranasal antihistamines were more effective than oral antihistamines for rhinitis symptoms.¹⁴ ARIA considered that patients would probably show a preference for oral over intranasal administration.⁸

Corticosteroids

The corticosteroids available in the UK for intranasal administration include beclometasone dipropionate, betamethasone sodium phosphate, budesonide, flunisolide, fluticasone propionate, mometasone furoate and triamcinolone acetonide.¹⁰ Reviews have concluded that there were no striking differences in the efficacy or safety of intranasal corticosteroids, but that there was considerable variation in the daily cost.^{13,15} One review applied a 'therapeutic index' (TIX) in an attempt to reflect efficacy and safety; meta-analysis of 84 studies concluded that intranasal mometasone furoate and triamcinolone had the highest TIX scores, indicating high efficacy and low potential for adverse effects, budesonide and fluticasone propionate had moderate TIX scores and beclometasone dipropionate and fluticasone furoate had the lowest TIX scores.¹⁶ The authors noted shortcomings in the trials that were used and pointed out that cost had not been taken into account. Furthermore, the clinical significance of differences in TIX scores is not known.

Reduction of symptoms can take several days and the maximum effect may not be seen for up to 2 weeks.^{2,3,6} Although intranasal administration is rarely associated with systemic adverse effects, it can produce unpleasant local effects including epistaxis (nose bleeds), dryness and irritation of the nose and throat, and unpleasant taste and smell.^{6,10} In addition, the Medicines and Healthcare Products Regulatory Agency has warned about possible psychiatric effects associated with the use of inhaled and intranasal corticosteroids and problems associated with the use of high dose inhaled and intranasal corticosteroids.^{17,18}

Long-term treatment with oral corticosteroids is associated with significant adverse effects. Short-term administration may be helpful in patients with allergic rhinitis not responding to other therapy, but the benefit is very uncertain and is based on clinical observations.⁸

It was considered unlikely that intramuscular corticosteroids would be of clinical benefit compared with other treatments of allergic rhinitis, and the possible unwanted effects do not justify their use in this condition.⁸

Intranasal corticosteroids or new generation antihistamines?

Several reviews and meta-analyses have found intranasal corticosteroids (sprays or drops) to be more effective than either oral^{8,13,19} or topical^{8,13,20} antihistamines for the relief of nasal symptoms. It should be noted that several of the studies included in reviews involved astemizole or terfenadine, which have since been withdrawn due to cardiotoxicity. ARIA did not include these studies in its analysis and regards the remaining evidence for the superiority of intranasal corticosteroids compared with oral antihistamines to be of low quality; although, evidence for the superiority of intranasal corticosteroids compared with intranasal antihistamines was classified as high quality.⁸

Intranasal corticosteroids are also reported to be effective for ocular symptoms and may be at least as effective as oral antihistamines.^{16–22}

The preference for antihistamines may be based on their availability, their rapid onset of effect making them suitable for intermittent use, and patient preference for the oral route.

Leukotriene receptor antagonistsⁱ

The evidence from clinical trials of LTRAs showed a small benefit in reducing symptoms and improving quality of life with a low incidence of adverse effects and was judged by ARIA to be high quality.⁸ However, there is no evidence that they are superior to antihistamines and some evidence, albeit of low quality, that they have a lower net clinical benefit compared with intranasal corticosteroids.⁸ Furthermore, in the UK only montelukast is licensed for use in seasonal allergic rhinitis in asthmatic patients in whom it is indicated for their asthma.²³

Anticholinergics

Intranasal ipratropium bromide is effective for rhinorrhoea but not for other symptoms of rhinitis, and is recommended on the basis of moderate quality evidence.⁸

Decongestants

The net clinical benefit of intranasal decongestants in allergic rhinitis was concluded to be very uncertain, although there may be a net clinical benefit from prompt relief of nasal obstruction with a short course (not longer than 5 days) of intranasal decongestant administered along with other medications.⁸ However, ARIA found very little evidence, classified as very low quality, to support their conditional recommendation.⁸ There is concern that use of intranasal decongestants for more than 3–5 days may lead to rebound swelling of the nasal mucosa and drug-induced rhinitis (rhinitis medicamentosa).⁸

The evidence for the benefits of oral decongestants such as pseudoephedrine was judged to be low quality.⁸ Review of the literature suggested that they are only weakly effective in rhinitis and may cause systemic side effects, and are not recommended for regular use.⁸

Mast cell stabilisers

Sodium cromoglicate and nedocromil (also known as chromones) act by inhibiting the degranulation of mast cells, reducing the release of inflammatory mediators and allergic mediators.⁶ The review by ARIA concluded that, despite the limited efficacy, treatment with intranasal or ophthalmic chromones may be of net clinical benefit for some patients because of mild side effects.⁸ The need for several applications per day may be a disadvantage.³

Other interventions

Allergen avoidance and nasal douching/nasal wash

Although allergen avoidance is recommended for the management of allergic rhinitis,⁶ the only method for pollen avoidance that has been shown to reduce symptoms significantly is the use of nasal filters. Other commonly

recommended measures, including staying indoors during periods of high pollen count, keeping windows in the home and car closed and using air conditioning, are based on expert consensus rather than clinical trial data.⁶

Nasal douching with saline is used more commonly in mainland Europe than in the UK.⁶ A systematic review and meta-analysis concluded that nasal irrigation with isotonic saline solution decreased nasal symptoms and medicines consumption with no reported adverse effects.²⁴ Both nasal douching and the use of sterile saline eye drops are considered to be helpful, non-toxic and inexpensive and can be recommended as an adjunct to other therapy.⁶

Allergen immunotherapy

Despite pharmacotherapy given in accordance with guidelines, symptoms will not be adequately controlled in 20% of patients.³ People with persistent symptoms that are inadequately controlled by optimised therapy and significantly interfere with quality of life should be considered for referral to an allergy specialist.²⁷ If the sensitising allergens can be identified and there is a suitable vaccine available, they may be considered for immunotherapy.²

Extracts of appropriate allergens are administered for several years in order to reduce the response to subsequent exposure to the allergen.²⁵

In the UK, vaccines for a variety of allergens are available for subcutaneous immunotherapy (SCIT) or sublingual immunotherapy (SLIT) as proprietary preparations or on a named-patient basis.^{25,26}

Reviews of injectable and sublingual allergen immunotherapy by the Cochrane Collaboration found statistically significant improvements in symptom control and reductions in the requirements for anti-allergic therapy.^{27,28} SLIT was found to have an extremely low incidence of significant side-effects.²⁸ A review of meta-analyses and another review of SLIT came to similar conclusions.^{29,30} However, some reviewers regard the benefit to be clinically modest, and the Cochrane review commented that the omission of cost-effectiveness data needs to be addressed.^{27,30,31} Individual studies of SCIT and SLIT have suggested that they may be cost effective compared with symptomatic treatment alone in appropriately targeted patients.^{32,33} A recent DTB review of the SLIT preparation Grazax concluded that the effects were modest and, given the high cost, that it could not be recommended for the majority of patients.³¹ In addition, Grazax (standardised allergen extract of grass pollen from Timothy [*Phleum pratense*]) is only licensed for grass pollen induced rhinitis and conjunctivitis in people who have a positive skin prick test and/or specific IgE test to grass pollen.³⁴

Conclusion

Hay fever is a common disorder with symptoms that affect the quality of life. Treatment guidelines on the management of hay fever are based on a mixture of evidence and expert consensus and provide a practical approach to management, using a stepwise escalation of therapy based on symptoms and response. However, many studies reviewed by the guideline developers were of low quality. Choice of treatment is influenced not only by the efficacy of the treatment options but also by patient preferences as to route and frequency of administration, availability over the counter and whether preventive or episodic treatment is required. Intranasal corticosteroids are widely recognised as the most effective symptomatic treatment available but oral or intranasal new generation antihistamines are usually offered as first-line treatment for intermittent symptoms. There is little compelling evidence to suggest that there are significant clinical benefits between many of the newer agents and choice will be driven by considerations of concordance, patient preference and cost. Although leukotriene receptor antagonists are included in some treatment guidelines, there is very limited evidence of efficacy. In the UK, montelukast is licensed for seasonal allergic rhinitis in patients with asthma. Referral to an allergy specialist for consideration for immunotherapy may be an option for people who fail to respond to conventional pharmacotherapy and are significantly incapacitated by symptoms. However, access to such services is often limited. The place of sublingual immunotherapy is still not clear.

[R = randomised controlled trials, M=meta-analysis]

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