



REVIEW

Continuous versus on-demand pharmacotherapy of allergic rhinitis: Evidence and practice

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Summary

This review aims to compare continuous with on-demand pharmacotherapy of allergic rhinitis by focusing on pharmacodynamic, pharmacokinetic, safety, effectiveness, cost and cost-effectiveness considerations. A working party of experts reviewed and discussed the literature and guidelines, and conducted a qualitative analysis of the Summary of Product Characteristics of specific medicines. With respect to medicines, the working party limited itself to antihistamines, nasal corticosteroids and leukotriene antagonists. Based on a review of the evidence from a multidisciplinary perspective, this article makes pharmacotherapeutic recommendations that are easy, functional and applicable to daily practice in primary care.

The pharmacotherapeutic evidence for continuous versus on-demand treatment of allergic rhinitis was limited. Clearly, for corticosteroids, their mechanism of action in allergic rhinitis of reducing allergic inflammation requires continuous therapy at least for the duration of symptoms. For H₁-antihistamines, some trials suggest that continuous treatment is preferable

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but more studies are needed to confirm this conclusion. For both H₁-antihistamines and nasal corticosteroids safety data indicate that continuous treatment may be given without fears of adverse consequences, although a distinction can be made between the first and the second generation antihistamines. With regard to the cost and cost-effectiveness implications of continuous therapy versus on-demand therapy, more studies are necessary before definitive conclusions may be made.

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Introduction

An estimated 20–30% of the adult population in the western world is affected by allergic rhinitis. According to some sources 1 out of 5 children is sensitive to inhalant common allergens. Others estimate to over 40% the number of children suffering from this condition.^{1–3}

Allergic rhinitis is not life-threatening and considered by many to be a trivial disease with mild symptoms. However, sufferers tell a different story. Assessment of the disease through both general health questionnaires and disease specific questionnaires shows a dramatic impairment of the quality of life and usual daily activities with the patients with more severe disease experiencing the highest level of impairment.⁴ Although the presence of the symptoms is perceived as a disturbing element in itself, in a recent patient survey, 85% of the patients felt that their daily activities, particularly those relating to their professional, personal and social life, their outdoor activities and their ability to function properly at work or at school and their sleep were impaired either moderately or severely.⁵ Furthermore, a large proportion of patients report that their disease causes sleep disturbances, such as trouble in going to sleep or awakening during the night and more than 50% report that they felt tired upon waking.^{5–7} In a survey performed in South Africa in 1181 patients with allergic rhinitis, symptoms of allergic rhinitis affected the quality of sleep in 76.6% of sufferers and for more than a third this was every night.⁸

Almost 40% of children suffering from allergic rhinitis reported that they have to miss school due their disease.⁵ In addition, allergic rhinitis can impair cognitive function and compromise learning, placing afflicted children at

a disadvantage. In a survey of 83 adolescents with seasonal allergic rhinitis, 78% reported that they had difficulty doing schoolwork, 75% could not concentrate on solving problems and 70% were less able to get school activities accomplished.⁹ In addition, both the acquisition and application of knowledge are slowed and short-term memory is reduced in allergic children compared with healthy children.¹⁰

In adults, allergic rhinitis can also be a cause of both work absenteeism and of reduced work performance with an European survey finding that a quarter of patients had to take time off work due to their disease.⁵ These figures were confirmed in another population-survey¹¹ which assessed the relative impacts on work loss and decreased productivity of allergic rhinitis and asthma in 400 adults in Northern California. The results showed that work loss, assessed as any partial or complete lost work days during the previous 4 weeks due to the condition, was similar in the two conditions, 23% for allergic rhinitis and 24% for asthma. However, of those persons who stayed at work and tried to "work through" their symptoms, 36% of patients with allergic rhinitis were less effective at their jobs compared with 19% for asthma.¹¹ These data suggest that allergic rhinitis, which is more common than asthma, may actually have a bigger impact among those who stay at work "working through" their symptoms.

As allergic rhinitis is one of the most frequent diseases encountered in clinical practice, the cost implications to society are enormous.¹² It was calculated that in the United States in 1994, there were 811,000 missed workdays, 4,230,000 reduced productivity days, and 824,000 school absences caused by allergic rhinitis.¹³ These work and school lost days account for a significant economic loss (for

example, indirect loss from school absenteeism was estimated to \$13,000,000). For 1996, it was calculated that the direct financial cost of rhinitis in the United States exceeded \$3 billion and there were additional costs of \$4 billion for its effect on concomitant conditions such as asthma and otitis.¹⁴ In Germany, the average annual cost of seasonal allergic rhinitis has been estimated to be €1089 per child/adolescent and €1543 per adult¹⁵ while a study using 2002 French costing data calculated an annual cost of €4260 per patient for allergic rhinitis of which only 2% could be attributed to direct medical costs, the remainder constituted by workdays lost due absence from work or poor productivity and the inability to perform usual daily activities.¹⁶

These facts justify the search for optimizing the pharmacotherapy of allergic rhinitis. The main objective of this review is to find an answer to the research question: what is the pharmacotherapeutic evidence supporting continuous treatment of allergic rhinitis in comparison with an on-demand regimen? The purpose is to make recommendations applicable to daily practice. The recommendations should be easy and functional to primary care. They must be based upon a multidisciplinary approach.

Methodological considerations

In order to make a multidisciplinary approach, a working party with experts in the field of pharmacology, pharmacokinetics, pharmacotherapy, pharmaco-epidemiology and pharmaco-economics was formed.

The activities of the working party had to yield a draft paper containing: (a) a survey of evidence and expert opinions; (b) an identification of the knowledge gaps; (c) a summary of the findings and recommendations; (d) a proposal for future research initiatives.

To reach the objectives five physical meetings of the working party took place over a period of 18 months to discuss the evidence on these questions.

During the first meeting a concept paper was discussed. The outcomes of this meeting were defined as actions: (a) each member should have taken a task according to the concept agreed upon; (b) a time schedule for delivering draft working papers. During the second meeting the first draft papers were discussed and a time schedule was accepted to deliver a second draft. During the third meeting a schedule of a manuscript for publication was agreed upon, starting from the draft papers. Because the working papers were mostly quite extensive, limits had to be set of what could be incorporated. The fourth meeting was organised in order to comment the first draft of the manuscript. The fifth meeting was the decisive one with regard to the content of the manuscript. From that time on the – mostly formal – finalising was left to one principal author.

The members of the working party reviewed the literature and guidelines, and conducted a qualitative analysis of the Summary of Product Characteristics (SmPC) of specific medicines. The working party limited itself to antihistamines, nasal corticosteroids and leukotriene antagonists as the therapeutic agents and considered the following questions:

- What is the clinical approach used at present with regard to continuous or 'on-demand' therapy?
- Do pharmacokinetic and pharmacodynamic considerations indicate a preference for continuous or 'on-demand' therapy?
- To what extent do safety considerations influence the choice between continuous versus 'on-demand' therapy?
- What are the cost and cost-effectiveness implications of continuous therapy versus 'on-demand' therapy?

Cochrane reviews, Web of Science, PubMed and International Pharmaceutical Abstracts were used as scientific databases. The following search terms were all or not combined: allergic, allergy, antihistamine, antileukotrienes, atopic, benefit, congestion, corticosteroids, cost, continuous, decision, duration, guideline, kinetic, leukotriene, nasal, on-demand, outcome, pharmaco-economic, pharmacology, risk, side effects, sneezing, steroids, symptomatic, symptoms, therapeutic, therapy.

When selecting the studies, special attention was paid to the continuous versus on-demand concept and the duration of therapy. Searches were made in parallel with different search terms as entry. The outcomes of these searches were discussed during the meetings of the working party and selection of references was made by consensus.

This study was carried out as part of the Supportive Initiatives for the Global Management of Allergy (SIGMA) of the UCB Institute of Allergy.

What is the clinical approach used at present with regard to continuous or 'on-demand' therapy?

The ARIA (Allergic Rhinitis and its Impact on Asthma) guidelines in 2003¹⁷ and updated most recently in 2008¹⁸ were the first to recommend an international approach to the treatment of allergic rhinitis. According to these guidelines first line treatment of allergic rhinitis consists of three steps:

1. oral or intranasal H₁-antihistamines with limited use of decongestants for mild intermittent rhinitis
2. oral or intranasal H₁-antihistamines or intranasal corticosteroids with limited use of decongestants and chromones for moderate-to-severe intermittent and mild rhinitis
3. intranasal corticosteroids with step-down and step-up options, in conjunction with H₁-antihistamines, nasal decongestants, ipratropium and oral corticosteroids for moderate-to-severe persistent rhinitis

The three-step approach seems easy to put into practice. But as clear-cut it may be, some considerations have to be made with regard to symptoms and co-pathology. In the ARIA guidelines special attention is given to co-morbidities, as allergic inflammation does not limit to the nasal airway. In case allergic rhinitis is accompanied by asthma, the inhaled therapy becomes continuous as from GINA step 2. In case the allergic rhinitis is not complicated by any co-morbidity, the level of severity should be taken into account when making the therapeutic approach. Starting from the symptoms a pharmacological

management can be proposed, according to the ARIA guidelines.

- Sneezing: intranasal corticosteroids, oral or intranasal antihistamines.
- Rhinorrhea: intranasal corticosteroids, oral or intranasal antihistamines, nasal anticholinergics.
- Nasal obstruction: oral decongestants, intranasal corticosteroids, antileukotrienes.
- Nasal itching: oral or nasal antihistamines, nasal corticosteroids.
- Eye symptoms: intraocular antihistamines, oral antihistamines, intranasal corticosteroids, intraocular chromones, antileukotrienes.

Of the above-mentioned medicines, oral decongestants should be used for a few days, especially in patients with cardiovascular co-morbidity, benign prostate hyperplasia, sleep disturbances and glaucoma.¹⁷

For mild intermittent rhinitis, the treatment should be when necessary and of short duration. For moderate-to-severe intermittent, the treatment should be continued to prevent the development of persistent rhinitis. For persistent rhinitis, continuous treatment is considered as more efficient than 'on-demand' therapy. Antihistamines and intranasal corticosteroids are perceived as being more effective if the therapy is continuous.¹⁹

The analysis of the SmPC of 24 medicines revealed that, apart from the leukotriene antagonists and some oral glucocorticoids, all other medicines contained the labelling 'allergic rhinitis' or 'allergic conditions of the respiratory tract'. Symptomatic as well as prophylactic and chronic treatment is mentioned in the indications.

Divergent information is given on the duration of treatment for different drugs:

- *Oral decongestants*: the duration of treatment should be as short as possible
- *H₁-antihistamines*: mostly no instructions with regard to duration of therapy are given. Cetirizine and levocetirizine are most explicit with specific durations according to the complaints. For both products time limits are specified (e.g. 3–6 weeks for levocetirizine in case of hay fever). Most probably limited experience in clinical trials causes this warning (SmPC dated January 2004), as for cetirizine clinical experience covers at least one year
- *Local corticosteroids*: it is recommended to use the spray 'regularly', preventively or continuously
- *Oral corticosteroids*: use of betamethasone is restricted to 10–14 days
- *Sodium cromoglycate*: preventive treatment does not allow an interruption of treatment

What do we learn from clinical studies focusing on continuous or 'on-demand' therapy?

H₁-antihistamines

Only two studies specifically designed to compare continuous versus on-demand therapy, both from the same research group, were retrieved. Some comparative data

were also obtained from a third study used to assess the use of rescue medication in children. Quantitative data from these studies are given in Table 1.

In the first study,²⁰ cetirizine was administered either continuously or on-demand to twenty adults with seasonal allergic rhinitis over a 4-week period of natural allergen exposure during the pollen season. The results showed that patients treated with continuous therapy achieved significant symptomatic relief and inflammatory control (decreases in numbers of infiltrating neutrophils and eosinophils) in comparison to patients treated on-demand. Interestingly, the authors comment that whereas continuous treatment reduces clinical and inflammatory variables more than on-demand therapy, the on-demand therapy can achieve acceptable clinical control but does not reduce allergic inflammation. Furthermore, the cost of therapy is lower for on-demand treatment.

The second study,²¹ compared two parallel groups of 31 adults with persistent allergic rhinitis, one group taking levocetirizine daily and the other taking it on-demand for six months. Both treatment regimens considerably decreased the total and individual symptom scores from baseline and achieved similar levels up to week 14. Continuous treatment was generally better than on-demand from week 15 onwards, reaching statistical significance from weeks 17–21 (from week 19 to 21 for nasal pruritus). Both regimens substantially improved quality of life and sleep quality. The authors concluded that continuous therapy showed a trend to be more effective in controlling the symptoms of rhinitis, improving quality of life and decreasing nasal inflammation compared with on-demand therapy.

The third study²² evaluated whether cetirizine administered regularly for 24 weeks reduced allergic symptoms and the use of rescue medications, such as antibiotics, paracetamol, β_2 -agonists, inhaled and systemic corticosteroids, in children with persistent allergic rhinitis and asthma due to house dust mite allergy. The results showed that symptom scores and consumption of rescue medication were significantly lower ($P < 0.05$) in the cetirizine-treated group versus the placebo group. Furthermore, the cost of treatment was lower with continuous therapy because more co-medication was taken in the placebo group due to poorer symptom control.

There is a suggestion from a small-scale study with children that long-term cetirizine treatment may reduce new sensitisations in monosensitised children. The study included two groups of 10 children with mite allergy, receiving either cetirizine or placebo daily. Cetirizine could be used as rescue medication. After six months continuously treated children remained on cetirizine during the following three years. The other children were treated on-demand during the same period. After 3 years only 2 continuously treated children showed polysensitization versus 5 symptomatically treated children. After 6 years the results were respectively 7 versus 9. ($P = 0.002$).²³

The results of these pilot studies support the continuous use of antihistamines as being more effective than on-demand therapy. The observation that inflammatory variables, such as nasal congestion, are suppressed better by

Table 1 Comparison of continuous versus on-demand therapy with cetirizine and levocetirizine.

Reference	Patients	Intervention	Outcome
Ciprandi et al., 1997 DB–R–Pl	N = 20 (19–48 years) (11 men/9 women) Rhinoconjunctivitis due to pollen	Natural pollen exposure Cetirizine 10 mg/day or Pl for 4 weeks C or OD Rescue medication = cetirizine 10 mg/day	Nasal symptoms: C < OD: from 3rd week* Rescue medication: C < OD: from 1st week** Neutrophils/eosinophils: C < OD: at 4 weeks ** Cost of therapy: OD < C
Ciprandi et al., 2001 DB–R–Pl	N = 20 (3–10 years) (15 boys/5 girls) Rhinoconjunctivitis (house dust mite) and/or mild intermittent asthma	Cetirizine drops 5 mg/day for 24 weeks Rescue medication = Cetirizine 5 mg/day Salbutamol 1 or 2 puffs of 100 µg Fluticasone 2 puffs of 125–250 µg Oral deflazacort 1 mg/kg AB or acetaminophen if needed	Weekly rhinitis symptoms: C < OD: 11 weeks on 24* Weekly asthma symptoms: C < OD: 6 weeks on 24* Additional drug intake: C < OD 16 weeks on 24 Additional cetirizine intake: C < OD*** Cost of therapy: C (191.83US \$) < OD (278.54US \$)
Canonica et al., 2008 R–O–P	N = 62 (31 in each group) Persistent allergic rhinitis	Levocetirizine 5 mg/day for 6 months C or OD	Drop out = 22/62 C = OD up to week 14 C > OD from week 17 on*

The abbreviations used are: DB = double blind, O = open label, R = randomized, P = parallel, Pl = placebo, C = continuous, OD = on-demand, AB = antibiotics. Significance levels are indicated by; * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

continuous therapy supports the hypothesis that reduction of allergic inflammation requires long-term therapy with antihistamines.^{14,24} However, there is a need for more clinical evidence, particularly with other antihistamines. In addition, pharmacological and pharmacokinetic parameters could help to look for a certain level of evidence. The studies mentioned above cannot be considered as pivotal: the number of patients per treatment group was low, especially when placebo was included in the study design. A type 1 statistical error (=outcome false positive) cannot be excluded.

Nasal corticosteroids

Local administration of corticosteroids to the nose has three primary effects:

- A vasoconstrictor effect which develops slowly over a period of up to 72 h²⁵
- A reduction of allergic inflammation following down-regulation of pro-inflammatory cytokines involved in the recruitment and activation of inflammatory cells, including eosinophils, dendritic cells and T-lymphocytes.^{26,27} These effects become apparent only slowly, taking days or even weeks to become maximal.
- A reduction of mast cell accumulation and maturation resulting from the downregulation of the transcription of stem cell factor, the primary growth factor for mast cells.²⁸ This is the slowest of the effects to become apparent due to the long life span of mast cells in allergic responses.²⁹

The 'lag'-time before significant therapeutic results are obtained with intranasal corticosteroids differs from study

to study being dependent both on the glucocorticoid used and the experimental conditions. The fastest response for significant changes in the nasal index score and peak nasal inspiratory flow has been obtained 4 h after the first administration of nasal budesonide or mometasone.³⁰ In another study³¹ mometasone improved the composite nasal and non-nasal symptom score after 5 h but required 7 h to reduce nasal symptoms.

While the above studies show that statistically significant improvement may occur quite rapidly, it takes much longer for nasal corticosteroids to become truly effective. For example, by 12 h after the first administration of mometasone during the pollen season, only 28% of patients experienced clinically significant relief 28% while by 72 h 64% of the patients experienced at least moderate relief.³² In another study, 4–8 days was needed for significant clinical improvement with beclomethasone and mometasone.³³ Patients on mometasone and beclomethasone have less non minimal symptom days as compared to placebo after 2 days. The proportion of symptom free days was 83% (mometasone), 77% (beclomethasone) and 64% (placebo). The difference with placebo was significant for both active treatments ($P < 0.01$).³⁴

In most studies with nasal corticosteroids, patients have at least one week of treatment before the first assessment is made. Sometimes there is significant relief after one week of the daytime, but not the night-time symptoms³⁵ Even for provocation tests, at least two weeks pre-treatment is often given.³⁶ Also, whether the scoring is performed by the physician or by the patient can make a difference. In one study,³⁷ subjective assessments made by the physician showed a clinical difference after one week whereas assessments by the patients themselves required two weeks to achieve significant differences.

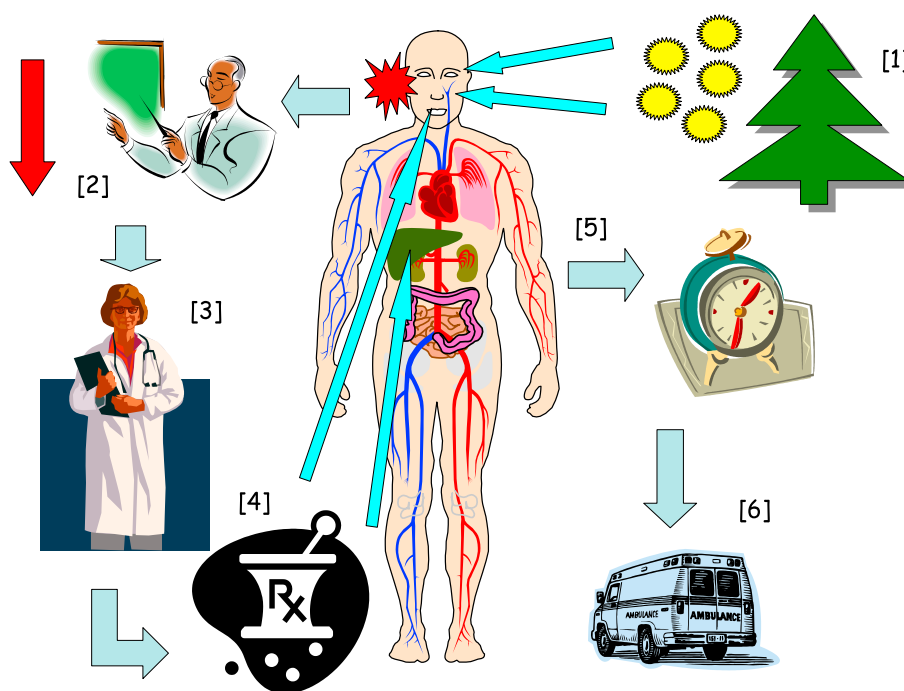


Figure 1 [1] Challenge of allergic rhinitis can be multifold. Causal relationship between pollen and seasonal allergy is fading as pollen seem to penetrate into the bronchioles. [2] Allergic rhinitis has a considerable influence on professional performance and cannot be foreseen in all circumstances. Direct as well as indirect costs play a role when considering the interference. [3] Medicines can be prescribed according to guidelines. The prescription can have an intermittent or a continuous character. [4] Treatment can be systemic (antihistamines, leukotriene antagonists) or local (corticosteroids, antihistamines). [5] There is a lag-time between starting the pharmacotherapy and the onset of action. [6] Intermittent and continuous therapies are not hampered by serious side effects.

As continuous therapy with corticosteroids may reduce mast cell numbers,³⁸ some authors strongly recommend starting the treatment with nasal glucocorticoids before the pollen season to achieve a prophylactic reduction of mast cells in the nasal epithelium. To this end, the SmPC for mometasone states: *...The start of the pollen season may vary, depending mainly on the geographic area and the prevailing weather conditions, so 'safe' advice is to start pre-treatment 2 to 4 weeks before start of the pollen season and to continue treatment throughout the pollen season....* The study that stimulated this recommendation³⁹ was one which started administration of nasal mometasone as prophylactic treatment 2–4 weeks before the pollen season and continued for four months. An overwhelming majority of patients (84%) were satisfied with this type of treatment. There was, however, no control group, as this was 'a real life' study.

Thus, with corticosteroids, which act primarily to reduce allergic inflammation, continuous therapy is essential for them to be clinically effective.

To what extent do safety considerations influence the choice between continuous versus 'on-demand' therapy?

For drugs used for symptomatic relief of non-lethal conditions, such as allergic diseases, safety is of paramount importance. As no comparative data are available for

continuous versus on-demand therapy with respect to safety, this review will consider the long-term safety aspects of antihistamines and intranasal corticosteroids in relation to their use in both situations.

H₁-antihistamines

It is now over 65 years since the introduction of phenox-ybenzamine, the first H₁-antihistamine introduced for clinical use.⁴⁰ It should be remembered that the first-generation antihistamines came from the same chemical stem as anticholinergic drugs, a stem from which tricyclic antidepressants, antipsychotics and many other drugs were developed. Indeed, the antihistamine, promethazine, was initially introduced as an antipsychotic drug. As a consequence, first-generation antihistamines are associated with a number of adverse events, including central nervous system depression and anticholinergic and cardiovascular effects. Nevertheless, first-generation H₁-antihistamines, including dexchlorpheniramine, diphenhydramine, hydroxyzine and promethazine are still regularly used.

The introduction of terfenadine in 1978⁴¹ saw the first of the minimally sedating H₁-antihistamines, a list which now contains many drugs including azelastine, cetirizine, desloratadine, ebastine, fexofenadine, levocetirizine and loratadine. Second generation H₁-antihistamines are recognised as being highly effective treatments for allergic disease and are among the most frequently prescribed and safest drugs in the world.⁴² There are many second

generation H₁-antihistamines available and at first examination these appear to be comparable in terms of safety and efficacy. However, the newer antihistamines in fact represent a heterogeneous group of compounds, having markedly differing chemical structures, physico-chemical properties, pharmacokinetic characteristics (e.g. half-lives of elimination, protein binding, tissue distribution, absolute bioavailability), being differently recognised by drug metabolising enzymes and transporters, and producing different adverse effects.

When comparing the duration of action with the plasma elimination, there is not always a concordance. First-generation antihistamines tend to have a longer plasma half-life as compared to their duration of action. That is in contrast with the second generation antihistamines where duration of action mostly exceeds the plasma elimination half-life. Translated into risk-benefit it means that circulating concentrations of first-generation antihistamines can still have secondary effects without resulting in therapeutic benefits. Respecting therapeutic regimens with first-generation antihistamines in order to obtain a 24 h protection against allergic symptoms may provoke unnecessary side effects. Theoretically the second generation of antihistamines may allow for a continuous therapy without imposing a kinetic burden on the patient (see Table 2). As all first-generation antihistamines are Over-The-Counter (OTC) medicines, it should be carefully examined which type of antihistamine should be delivered. When no additional anticholinergic activity is wanted, second generation antihistamines are preferable.⁴³ The pharmacoeconomic outcome of using first-generation antihistamines seems to be negative by the loss of productivity due to sedation.⁴⁴

However, some other events occurred with newer substances. The most serious toxic event reported was the

association between the consumption of astemizole or terfenadine and the occurrence of prolongation of the QT interval, leading to the appearance of polymorphic ventricular arrhythmias, syncope, and even cardiac arrest.²⁵ Both astemizole and terfenadine were essentially pro-drugs which required hepatic first-pass metabolism by CYP3A4, a member of the hepatic cytochrome P450 family. In most normal subjects, CYP3A4, activity was sufficient to ensure that the levels of astemizole and terfenadine in the plasma were below the detection limits. As the cardiac adverse effects are related directly to high plasma levels of the unmetabolised parent drug, it follows that in patients with pre-existing cardiac dysfunction, such as congenital QT prolongation, the presence of impaired liver function, due to conditions such as cirrhosis or ethanol abuse, or concomitant use of inhibitors of CYP3A4, such as ketoconazole, itraconazole, and macrolide antibiotics, was one of the main predisposing factors for the occurrence of cardiotoxicity.⁴⁵ Following the recognition of over 200 cases of potentially fatal cardiac arrhythmias, both terfenadine and astemizole have been withdrawn from the market in most countries. Finally, the finding that an interaction with HERG1K⁺ channels is the mechanism by which terfenadine and astemizole caused potentially fatal cardiac arrhythmias has allowed the development of pre-clinical tests, both *in vitro* and *in vivo*, to predict such activity. Thus, all H₁-antihistamines on the market today are free from clinically demonstrable cardiotoxicity.

Another adverse effect of H₁-antihistamines that has given cause for concern is their potential to cause a degree of somnolence in some individuals, despite the relatively short plasma elimination half-life (see Table 2). Most of the clinical trials report drowsiness, sedation, or somnolence as

Table 2 Plasma $T_{1/2}$ and duration of action of anti-H₁-antihistamines.

Class and nonproprietary names; I = 1st generation; II = 2nd generation	Duration of action (approximate values in hours)	Plasma $T_{1/2}$ (approximate values in hours)
Ethanolamines		
Diphenhydramine·HCl (I)	12	8
Alkylamines		
Dexchlorpheniramine maleate (I)	4–6	20–24
Acrivastine (II)	6–8	1.5 (Active metabolite: 2.5)
Piperazines		
Hydroxyzine·HCl (I)	6–24	20
Cetirizine·HCl (II)	12–24	8–10
Levocetirizine (II)		
Phenothiazines		
Promethazine·HCl (I)	4–6	10–14
Phthalazinones		
Azelastine·HCl (II)	12–24	20 (Active metabolite: 45)
Piperidines		
Loratadine (II)	24	12 (active metabolite 20)
Desloratadine (II)	24	27
Ebastine (II)	24	15–19
Mizolastine (II)	24	13
Fexofenadine (II)	12–24	11–15

a common adverse effect. In a post-marketing surveillance study of fexofenadine, acrivastine, cetirizine, and loratadine involving 43,363 people, the main outcome measure was sedation or drowsiness.⁴⁶ It found a significantly higher incidence of sedation for acrivastine (Odds Ratio 2.79, 95% CI 1.69–4.58; $P < 0.0001$) and cetirizine (Odds Ratio 3.53, 95% CI 2.07–5.42; $P < 0.0001$) compared with loratadine. However, it found no difference between fexofenadine and loratadine (Odds Ratio 0.63, 95% CI 0.36–1.11; $P = 0.1$). No increase in risk of accident or injury was found with any of the four antihistamines. There were also no considerations with regard to intermittent or continuous use.

The majority of sedation studies with H₁-antihistamines are performed in either healthy individuals or individuals with mild disease rather than in conditions, such as severe allergic rhinitis or chronic urticaria, both of which cause sleep deprivation.^{47–49} So is drug-induced daytime somnolence a problem with such patients. Two studies, one with fexofenadine and the other with levocetirizine, found that chronic urticaria patients taking regular H₁-antihistamine therapy experienced significantly less interference with sleep and improved daily activities.^{50,51} Two possible reasons may be suggested to explain the decreased somnolence. The first possibility is the relief from physical discomfort ensuing from the psychological status of the patients and the associated sleep deprivation. The second possibility is the development of tolerance to the central nervous sedative effects of the H₁-antihistamines which has been reported repeatedly to occur after 4–5 days of administration of both first and second generation.^{52–54} Thus, although direct comparisons between continuous and on-demand therapy with H₁-antihistamines have not been performed, it is tempting to speculate that continuous therapy may be preferable to reduce somnolence.

An evaluation was made for azelastine (topical use) long-term continuous treatment versus on-demand. Continuous use achieved better therapeutic outcomes, as on-demand use did not significantly reduce allergic inflammation.⁵⁵

In conclusion, H₁-antihistamines are very safe medicines when taken long term. Of the major H₁-antihistamines, cetirizine and loratadine have been on the market for 20 years and desloratadine, fexofenadine and levocetirizine for more than 8 years without safety issues arising. In adults, formal studies of two to three years duration have shown cetirizine to be safe when given continuously^{56,57} while in children of 1–2 years of age, both cetirizine and levocetirizine have been shown to be safe when given for periods of 18 months. No serious side effects occurred over that period. There were no significant differences on behavioural, cognitive or psychomotor development as compared to placebo treated children. The tools used were: the Behavior Screening Questionnaire, the McCarthy Scales of Children Abilities, the General Cognitive Index and the Global Medical Questionnaire.^{58–60}

Nasal corticosteroids

Intranasal corticosteroids are considered relatively safe.^{7,38} Local adverse effects are usually mild and include mucosal

irritation and epistaxis. Nasal septal perforation is rare. The most commonly reported adverse effects for individual intranasal corticosteroids are as follows:

- **Beclometasone:** epistaxis, upper respiratory tract infection and headache
- **Betamethasone:** sore throat, flushing and headache
- **Budesonide:** unpleasant taste, headache, coughing, nose dryness and epistaxis
- **Flunisolide:** nasal burning, drowsiness, and nasal irritation
- **Fluticasone:** headache, epistaxis, sore throat, nasal dryness/blowing and diarrhoea. There have been case reports of anaphylaxis and flushing as well as central nervous system, cardiac, and dermatological reactions
- **Mometasone:** headache, epistaxis, and pharyngitis. In clinical trials, the rate of treatment discontinuation with mometasone furoate nasal spray because of adverse events was $\leq 3\%$, a rate similar to those reported with placebo and active controls; the most frequently reported adverse effects were headache, viral infection, pharyngitis, and epistaxis
- **Triamcinolone:** headache, sneezing, and nasal irritation

As for the antihistamines, no comparative data are available for continuous versus on-demand therapy. Clinical and histopathological examination of nasal mucosa after long-term intranasal budesonide or mometasone use has failed to show significant changes.³⁸ Although intranasal steroids can result in systemic bioavailability, no significant adverse effects have been reported on bone metabolism. Influence of adrenal function should be considered. Based on morning salivary cortisol concentrations, for 58% of patients on nasal betamethasone sodium phosphate and for 4% of patients on mometasone furoate biochemical evidence of adrenal suppression was apparent.⁶¹ Mometasone 100 µg/day does neither influence growth in children between 3 and 9 years old, nor interfere with the hypothalamic–pituitary–adrenocortical-axis function. The compliance was high, but no details are given about the therapeutic efficacy.⁶²

What are the cost and cost-effectiveness implications of continuous versus 'on-demand' therapy?

To date, no study has compared costs of continuous and on-demand treatment of allergic rhinitis. As it is difficult to determine the economic impact of allergic rhinitis, Table 3 identifies the major cost items that need to be considered when contrasting costs of continuous and on-demand treatment of allergic rhinitis from a societal perspective. In addition to direct healthcare costs, studies need to focus on eliciting direct non-healthcare costs and indirect costs. With respect to the latter, attention needs to be paid to calculate the indirect costs of days lost to education and work, costs of reduced productivity at work, and the costs of reduced ability to carry out usual daily activities. Indirect costs need to be calculated for patients suffering from allergic rhinitis.

Table 3 Cost items of continuous/on-demand treatment of allergic rhinitis.

Direct healthcare costs			Direct non-health care costs	Indirect costs
Medication	Healthcare providers	Other		
Oral and intranasal antihistaminics	General practitioner	Diagnostic tests	Transportation to healthcare provider	Absence from work
Intranasal corticosteroids	Pneumologist	Immunotherapy	Child care costs while in treatment	Reduced productivity at work
Oral and intranasal decongestants	Ear, nose and throat specialist	Accident and Emergency visit	Home adaptations	Time lost from education
Intranasal anticholinergic agents		Alternative medicine (e.g. homeopathy)		Reduced ability to carry out usual daily activities

One cost-effectiveness analysis investigated continuous versus on-demand treatment in a small sample of children during six months.²² Continuous treatment consisted of the daily administration of cetirizine 5 mg. Alternatively, children received placebo. However, both groups of children were allowed to use rescue or symptomatic drugs when needed. Suggested rescue medication was cetirizine, inhaled salbutamol, inhaled fluticasone and short courses of systemic corticosteroids. The assessment of costs was limited to drug costs. The authors found that continuous treatment dominated on-demand treatment: continuous treatment with cetirizine resulted in better symptom control of allergic rhinitis and of asthma, and in lower drug costs as compared to on-demand treatment. There is a need for prospective economic evaluations alongside clinical trials comparing continuous and on-demand treatment of allergic rhinitis, with a sufficient number of patients and length of treatment period.

Conclusions

This review has examined the pharmacotherapeutic evidence for the use of continuous treatment in comparison with an on-demand regimen (Fig. 1). Clearly, for corticosteroids, their mechanism of action in allergic rhinitis of reducing allergic inflammation requires continuous therapy at least for the duration of symptoms. For H₁-antihistamines the conclusion is equivocal. Some trials suggest that continuous treatment is preferable but more studies are needed to confirm this. For both H₁-antihistamines and nasal corticosteroids safety data indicate that continuous treatment may be given without fears of adverse consequences. With regard to the cost and cost-effectiveness implications of continuous therapy versus on-demand therapy, more studies are necessary before definitive conclusions may be made.

Conflict of interest

Financial support for this study was received from the UCB Institute of Allergy. Some of the authors are or were employed by UCB. None of the authors has a conflict of interest that is directly relevant to the content of this manuscript.

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