

Review article

Pharmacotherapy of allergic rhinitis: a pharmaco-economic approach

This article reports on a systematic literature review of the costs of allergic rhinitis (AR), the economic value of pharmacotherapy of AR, and the factors affecting costs and economic value of pharmacotherapy. Included studies had carried out a cost-of-illness analysis, cost analysis, cost-effectiveness, cost-utility or cost-benefit analysis. Allergic rhinitis imposes a substantial economic burden on society, with indirect costs of productivity loss being larger than the direct healthcare costs. Cost estimates were biased because of difficulties of diagnosis; exclusion of patients who do not seek healthcare; exclusion of over-the-counter medication; difficulties in estimating productivity loss. There is limited evidence on costs of seasonal/perennial and intermittent/persistent AR. Little is known of the economic value of pharmacotherapy of AR, although levocetirizine appears to be cost-effective as compared with placebo. Economic evaluations suffered limitations from small sample sizes, short trial duration, lack of standardized effectiveness measure, restricted scope of costs. Finally, the economic value of pharmacotherapy of AR is influenced by the perspective of the economic evaluation, relative effectiveness and costs of available drugs, patient compliance with treatment.

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Allergic rhinitis (AR) is a disease characterized by a symptomatic disorder of the nose induced after allergen exposure by an IgE-mediated inflammation (1). Allergic rhinitis is caused by indoor allergens, such as dust mites, animal danders, insects and moulds; and outdoor allergens, including pollens and moulds (2). Allergic rhinitis symptoms include rhinorrhea, nasal obstruction, nasal itching and sneezing (3). Previous studies have drawn on the time of exposure to classify AR into seasonal allergic rhinitis (SAR) or perennial allergic rhinitis (PAR) (4, 5). A different classification distinguishing between intermittent allergic rhinitis (IAR) and persistent allergic rhinitis (PER) has been proposed in the Allergic Rhinitis and its Impact on Asthma (ARIA) 2001 document (1).

Although AR may be diagnosed on the basis of clinical symptoms, immune response tests or nasal function, many patients are not diagnosed because AR is not perceived to greatly impair their social life, schooling and work (6). Estimates of AR prevalence vary between 10% and 20% in the general population (7) and between 10% and 40% in children (8). Allergic rhinitis may also be a co-morbidity in patients with asthma, otitis media or sinusitis (9). For instance, an ARIA update of the literature concluded that most patients with asthma have rhinitis; many patients with AR have asthma; and there is a temporal relationship between the onset of AR and

asthma, with rhinitis often preceding the development of asthma (10).

The literature shows that AR harms quality of life (11, 12); work performance (13, 14); social life (15) and school performance (16). Allergic rhinitis patients may also suffer from sleep disturbance (17), impaired cognitive function (18), depression and anxiety (19). The burden of AR underlines the importance of appropriate management strategies. A number of literature reviews have explored the effectiveness of the two main management strategies of AR: allergen immunotherapy (20, 21) and pharmacotherapy (6, 22, 23). With respect to the latter, these studies show that intranasal glucocorticosteroids are the most effective drugs to treat AR. Second-generation oral or intranasal H₁-antihistamines are recommended for the treatment of AR in adults and children. Oral decongestants may be used to treat AR in adults, but have side-effects. A modest beneficial effect of cromoglycate has been demonstrated. Pharmacotherapy of AR should take into account a number of factors, including costs and economic value of alternative drugs (6).

In a context of spiralling healthcare costs and limited resources, policy makers and healthcare payers are concerned about disease costs and the economic value of disease management strategies. Cost estimates can

underline the importance of a disease to society when considered alongside its impact on morbidity and mortality and when compared with the economic burden of other diseases. Furthermore, cost studies may allow the identification of the drivers of costs. Information about the economic value can be used by policy makers and healthcare payers to ascertain the efficiency of various management strategies by examining their effectiveness in relation to their costs.

The aim of this study is to systematically review the pharmaco-economic literature on pharmacotherapy of AR, SAR/PAR and IAR/PER by exploring three specific aspects: (i) the level and distribution of costs; (ii) the economic value of pharmacotherapy and (iii) the factors influencing costs and the economic value of pharmacotherapy. Methodological issues surrounding the evaluation of costs and economic value of pharmacotherapy were also explored. This study is carried out as part of the Supportive Initiatives for the Global Management of Allergy (SIGMA) of the UCB Institute of Allergy.

Methods

Search strategy

The studies were identified by searching PubMed, Centre for Reviews and Dissemination databases (Database of Abstracts of Reviews of Effects, NHS Economic Evaluation Database and Health Technology Assessments Database), Cochrane Database of Systematic Reviews and EconLit up to May 2008. Additionally, the bibliography of included studies was checked for other relevant studies. Search terms included 'AR', 'seasonal', 'perennial', 'intermittent', 'persistent', 'pharmacotherapy', 'drugs', 'pharmaco-economics', 'costs', 'cost-of-illness', 'economic burden', 'productivity', 'economic evaluation', 'cost-effectiveness', 'cost-minimization', 'cost-consequence', 'cost-utility', 'cost-benefit' alone and in combination with each other.

Inclusion/exclusion criteria

Cost studies can take the form of cost-of-illness analyses or cost analyses. A cost-of-illness analysis quantifies the economic burden to society by measuring the costs of diagnosis and treatment as well as the costs arising as a result of the disease (for instance, productivity loss because of time taken off work). Such studies can measure direct costs related to healthcare resource use (e.g. medication, physician visits), direct nonhealthcare costs (e.g. transportation to physician visits), and indirect costs arising from time lost from work or reduced productivity at work. A cost analysis compares costs of at least two management strategies.

Information about the economic value of pharmacotherapy was derived from economic evaluations: studies had to compare at least two drugs in terms of both costs and consequences (24). A drug is said to 'dominate' the comparator when the drug is more effective and less expensive than the comparator. Three main techniques can be used to conduct an economic evaluation of pharmacotherapy of AR: cost-effectiveness analysis, cost-utility analysis and cost-benefit analysis.

Cost-effectiveness analysis denotes an economic evaluation where a single consequence is quantified in a natural unit, such as the percentage of patients who respond to treatment or for whom

treatment is successful. There are two specific cases of a cost-effectiveness analysis. In a cost-minimization analysis, only costs are analysed and the least costly management approach is chosen provided that consequences are known to be equal between pharmacotherapeutic approaches. In a cost-consequence analysis, costs and more than one consequence are compared between treatment alternatives.

A study that measures consequences by specific health-related quality of life measures, such as quality-adjusted life years (QALYs), is referred to as a cost-utility analysis. The QALY takes into account the quantity and quality of life. Quality of life associated with a health state is measured on a scale of 0 (reflecting death) to 1 (reflecting perfect health). Quality of life data are then combined with estimates of the time period for which the health benefits last to generate QALYs.

Cost-benefit analysis refers to an economic evaluation where consequences are valued in monetary terms. As a result, benefits can be directly compared with costs of pharmacotherapy and the net worth (benefits minus costs) of each of the treatment alternatives can be estimated. The results of a cost-benefit analysis may be stated in the form of the net benefit or loss of one alternative over another or in the form of a ratio of benefits to costs.

Inclusion was restricted to articles published in peer-reviewed journals. Congress abstracts were not considered because they do not provide sufficient details of methodology and results. As the literature review focused on pharmacotherapy, studies of immunotherapy were excluded. With respect to the economic burden of AR, exclusion criteria included studies that did not convert healthcare resource utilization into costs and studies that did not distinguish costs of AR from costs of co-morbidities. Economic evaluations of pharmacotherapy of AR were excluded if studies analysed a single intervention without a comparator, if data on either costs or consequences were absent, if data on costs and consequences were not integrated.

Assessment of methodological quality

A qualitative appraisal was carried out of the methodological quality of cost-of-illness analyses by investigating study population, data sources, methods of data collection, scope of included costs and time horizon. The quality of economic evaluations was assessed by considering the perspective, study design (trial- or model-based economic evaluation); scope, measurement and valuation of costs and consequences; and incremental analysis of costs and consequences (24).

Results

Economic burden

The results of the literature search are presented in Fig. 1. Our analysis was based on three literature reviews of AR costs (25–27), four studies on SAR/PAR costs (28–31) and one study on PER costs (32). No study of IAR costs was identified.

AR costs. Even though the cost of an individual case of AR is low, the total economic burden is considerable given that it has a high prevalence and affects people for significant periods of time of the year (25–27). Annual AR costs have been estimated to range from US\$1.7 to 4.3 billion in the United States in 2003 values (25).

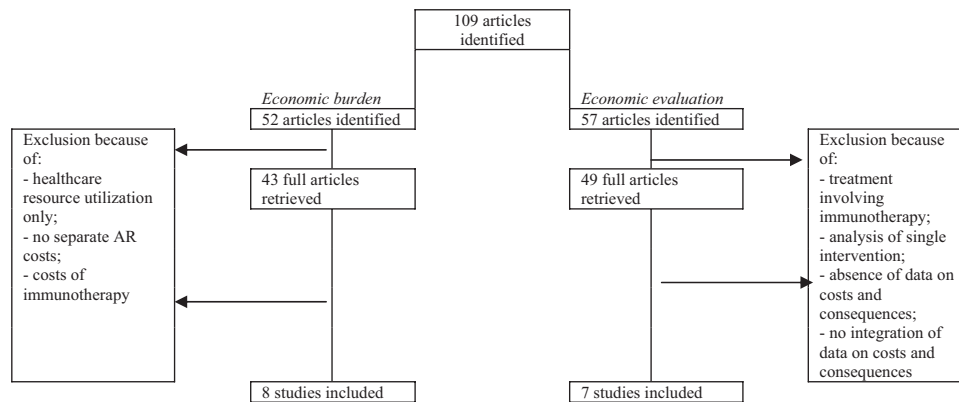


Figure 1. Flow chart of literature search.

A breakdown of AR costs reveals that indirect costs arising out of productivity loss are more important than direct healthcare costs: annual indirect costs ranged from US\$0.1 to 9.7 billion and annual direct healthcare costs amounted to US\$1.6–4.9 billion in the United States in 2003 values (25). Focusing on the distribution of direct costs of ambulatory care, Fig. 2 indicates that the principal cost driver is costs of physician visit, accounting for 31–76% of direct costs of ambulatory care. Medication accounted for 24–69% of direct costs (33–36). Variation in the distribution of costs between studies originated from differences in inclusion criteria for AR patients, treatment patterns, and in/exclusion of over-the-counter medication.

Allergic rhinitis generates higher indirect costs because of productivity loss than many other common medical diseases. A comparative analysis found that the indirect costs per employee per year amounted to US\$593 for AR, \$518 for high stress, \$277 for migraine, \$273 for depression, \$269 for arthritis/rheumatism, \$248 for anxiety disorder, \$181 for respiratory infections, \$105 for hypertension or high blood pressure, \$95 for diabetes, \$85 for asthma and \$40 for coronary heart disease in the

United States in 2002 values (37). The authors concluded that the significant impact on work productivity and health-related quality of life of AR should encourage employers to pay more attention to the indirect costs of this high-prevalence, low-intensity condition. Indirect costs of AR principally relate to reduced productivity while at work ('presenteeism') and, to a lesser extent, to work absence ('absenteeism'). A US panel estimated that annual indirect costs of AR because of work absence amounted to US\$0.5 billion and indirect costs because of reduced productivity while at work were US\$2.7 billion (38).

Costs of SAR/PAR. Two studies provided evidence of the costs of SAR and showed that costs rise when SAR and asthma are concomitant. A Turkish cost-of-illness analysis determined that SAR costs per patient during the pollen season of US\$79 without co-morbidity increased to \$139 in the presence of asthma and/or conjunctivitis (28). A German cost-of-illness analysis of moderate-to-severe SAR computed an average annual cost of 1089€ per child/adolescent and 1543€ per adult in 2000 values (29). Costs increased to 2202€ per child/adolescent and 2745€ per adult when SAR was accompanied by moderate asthma. Costs amounted to 7928€ per child/adolescent and 9286€ per adult in patients suffering from SAR and severe asthma. This retrospective study suffered from patient recall bias and a physician selection bias in that physicians interested in AR may have been more likely to participate in the study and in that physicians enrolled patients.

A cost-of-illness analysis estimated PAR costs in a sample of 2033 French patients (30). Annual costs totalled FF 9.4 billion in 1997 values. Total costs were broken down into FF 3.4 billion of direct healthcare costs and FF 6 billion of indirect costs because of productivity loss. Consequently, the authors remarked that, with a view to reducing the economic burden, more attention needs to be paid to decreasing the productivity loss associated with PAR. Direct healthcare costs could be

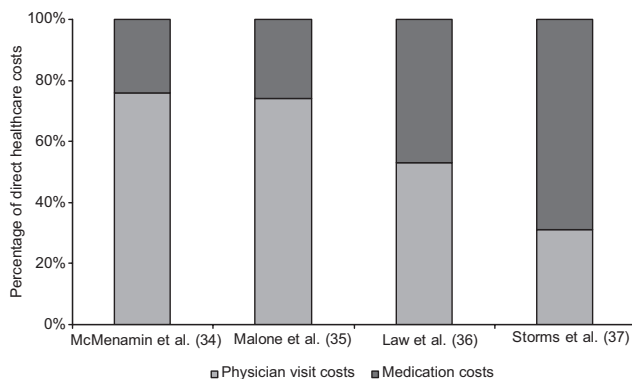


Figure 2. Distribution of direct costs of ambulatory care of allergic rhinitis.

attributed to medication costs (FF 1.3 billion), costs of physician visits (FF 1.2 billion), and costs of diagnostic tests (FF 1 billion).

One study compared costs of PAR with those of SAR (31). This US study classified patients into PAR or SAR groups based on their pattern of allergy drug use over the course of 1 year. Out of a sample of over 80 000 patients, 79% of patients were classified to have SAR and 21% had PAR. Perennial AR patients had higher annual average costs of allergy-related outpatient visits (US\$568 vs \$471, $P < 0.0001$) and higher annual average costs for second-generation antihistaminics (i.e. fexofenadine, loratadine and cetirizine) (US\$531 vs \$162, $P < 0.0001$) as compared with SAR patients in 1998 values. Higher PAR costs may originate from the fact that PAR patients were significantly older and had higher rates of co-morbidities (i.e. asthma, depression, migraine, otitis media and sinusitis) than SAR patients.

Costs of IAR/PER. A cost analysis of PER conducted in Belgium, France, Italy, Germany and Spain compared patients without long-term treatment with patients treated with levocetirizine (32). Total costs per patient per month without long-term treatment amounted to 355€ in 2002 values. Total costs consisted of direct healthcare costs of 8€ per patient per month (2% of total costs), indirect costs of work absence of 34€ (10%), indirect costs of reduced productivity at work of 79€ (22%), indirect costs of inability or restriction to perform usual daily activities of 234€ (66%). Costs per patient per month with long-term treatment with levocetirizine amounted to 202€. These costs consisted of direct healthcare costs of 18€ per patient per month (9% of total costs), indirect costs of work absence of 13€ (6%), indirect costs of reduced productivity at work of 49€ (24%), indirect costs of inability or restriction to perform usual daily activities of 122€ (60%). The authors acknowledged that the cost analysis was performed alongside a randomized controlled trial (RCT) and that their estimates, therefore, may not reflect costs in real clinical practice settings.

Factors affecting costs. Cost estimates vary between studies as a result of adoption of different methodologies to define the patient population. For instance, cost studies have used estimates of the number of AR patients in the United States ranging from 12 to 39 million (33–36, 38). Two cost studies enrolled patients with the primary diagnosis of AR, but did not consider patients with a primary diagnosis of asthma, sinusitis or otitis media and a secondary diagnosis of AR (33, 34). As symptom-based definitions may lead to underdiagnosis (6), one study defined SAR/PAR based on the pattern of allergy drug use over the course of 1 year (31). Defining SAR/PAR in terms of healthcare resource use recognizes that PAR is associated with higher resource use, but inhibits international comparison because treatment

patterns and, thus, classification systems of SAR/PAR vary across countries.

Cost estimates are influenced by patients' decision to seek healthcare and by the use of over-the-counter medication. In two studies, patients seeking healthcare were defined as those patients who visited a healthcare provider or received a prescription drug for AR (34, 35). Using this definition, 12% and 66% of patients experiencing AR sought healthcare respectively. Although patients not seeking healthcare do not impose an economic burden on the healthcare system, they still generate indirect costs because of productivity loss. Also, cost studies underestimate medication costs as they focus on prescription drugs only. One study indicated that costs of over-the-counter medication make up 60% of AR medication costs (36).

Cost studies fail to separate AR costs from costs of co-morbidities. Generally, existing cost-of-illness analyses have identified AR patients, but did not have a control group of patients without the disease. Such case series analyses may be misleading because attribution of healthcare resource utilization to AR, asthma, otitis media and sinusitis is difficult. To calculate AR costs, studies need to compare patients with AR and with a co-morbidity to equivalent patients with the co-morbidity, but without AR. A case-control study design comparing patients with/without AR seems to be suited for this purpose because it allows identification of additional healthcare resource use related to AR. No cost study was identified that adopted such a case-control study design. Also, no study was found that investigated the potential relationship between disease severity and costs.

Economic evaluations of pharmacotherapy

Figure 1 shows results of the literature search. The economic literature consisted of one cost-consequence analysis and one cost-benefit analysis of pharmacotherapy of AR (39, 40); two cost-consequence analyses, one cost-minimization analysis and one cost-benefit analysis of SAR/PAR (41–44), and one cost-consequence analysis of PER (45). No economic evaluation of pharmacotherapy of IAR was identified. The findings of economic evaluations of pharmacotherapy of AR are summarized in Table 1.

Pharmacotherapy of AR. A cost-consequence analysis investigated continuous treatment vs on-demand treatment in a small sample of children during 6 months (39). 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 albuterol, inhaled fluticasone and short courses of systemic corticosteroids. The assessment of costs was limited to drug costs. The authors found that continuous

Table 1. Economic evaluations of pharmacotherapy of allergic rhinitis

Sample	Type	Perspective	Comparators	Design	Follow-up period	Year of costing	Costs	Consequences	Costs/consequences	References
Pharmacotherapy of AR 20 patients	CCA	Healthcare system	Cetirizine (5 mg once daily) or placebo Rescue medication when needed	Evaluation alongside prospective, double-blinded RCT	6 months	1997	Average drug costs per child for 6 months of treatment amounted to US\$279 with placebo and US\$192 with cetirizine	Average weekly rhinitis symptom scores and asthma symptom scores were lower in the cetirizine group vs the placebo group	Continuous treatment with cetirizine results in better symptom control and lower drug costs as compared to on-demand treatment	(39)
Patient taking first-generation anti-histamine	CBA	Society	First-generation antihistamine, no treatment	Decision analytic model	1 year	2001	Costs of first-generation antihistamines amounted to US\$697 million Costs of antihistamine-associated sedation were US\$11.3 billion	Benefits of first-generation antihistamines amounted to US\$7.7 billion	Net benefits of first-generation antihistamines amounted to –US\$4.2 billion	(40)
Pharmacotherapy of SAR 155 patients	CCA	Healthcare system	Intranasal fluticasone propionate 200 µg once daily or terfenadine 60 mg twice daily	Evaluation alongside prospective, double-blinded RCT	14 days	1995	Drug costs amounted to US\$18.14 with fluticasone and US\$24.81 with terfenadine	Average percentage decrease in symptom score was 41% with fluticasone and 29% with terfenadine Percentage of patients that experienced improvement was 86% with fluticasone and 68% with terfenadine Percentage of patients that experienced significant improvement was 38% with fluticasone and 19% with terfenadine	Treatment with fluticasone dominated treatment with terfenadine	(41)
123 patients	CCA	Healthcare system	Mometasone furoate (200 µg once daily), levocabastine hydrochloride (200 µg twice daily) or disodium cromoglycate (5.6 mg four times daily)	Evaluation alongside prospective, open RCT	23 days	2003	Average daily drug costs amounted to 0.4632€ with mometasone furoate, 1.4894€ with levocabastine, and 0.4659€ with disodium cromoglycate	Number of treatment successes was 37 with mometasone furoate, 32 with levocabastine, and 26 with disodium cromoglycate	Treatment with mometasone furoate dominated treatment with levocabastine, and dominated treatment with disodium cromoglycate	(42)

Table 1. (Continued)

Sample	Type	Perspective	Comparators	Design	Follow-up period	Year of costing	Costs	Consequences	Costs/consequences	References
241 patients	CBA	Society	Intranasal budesonide as a dry powder (400 µg) or budesonide as an aqueous spray (256 µg)	Evaluation alongside prospective, double-blinded RCT	4 weeks	1993	Not available	Mean willingness-to-pay was Can\$12.95/week for all patients, Can\$13.13/week for patients receiving budesonide as a dry powder, and Can\$12.77 for patients receiving budesonide as an aqueous spray	Net benefits equaled Can\$5.80/week for all patients, Can\$4.99/week for patients receiving budesonide as a dry powder, and Can\$6.60 for patients receiving budesonide as an aqueous spray	(43)
Pharmacotherapy of PAR 314 patients	CMA	Healthcare system	Budesonide as an aqueous nasal spray (256 µg) or fluticasone propionate nasal spray (200 µg)	Evaluation alongside prospective, double-blinded RCT	6 weeks	1998	Total annual costs of drugs, side-effects, lack of efficacy and general management amounted to Can\$389.85 per patient with budesonide and Can\$508.6 per patient with fluticasone	No differences were observed in improvement of combined nasal symptoms between budesonide and fluticasone	Budesonide was equally effective and less expensive than fluticasone	(44)
Pharmacotherapy of PER 551 patients	CCA	Society	Levocetirizine 5 mg or with placebo	Evaluation alongside prospective, double-blinded RCT	6 months	2001	Total costs amounted to 108.18€ per patient per month with levocetirizine and 160.27€ with placebo	Levocetirizine was associated with a greater improvement in quality of life and AR symptoms	Treatment with levocetirizine dominated placebo	(45)

AR, allergic rhinitis; CBA, cost-benefit analysis; CCA, cost-consequence analysis; CMA, cost-minimization analysis; PAR, perennial allergic rhinitis; PER, persistent allergic rhinitis; RCT, randomized controlled trial; SAR, seasonal allergic rhinitis.

treatment dominated on-demand treatment: continuous treatment with cetirizine resulted in better symptom control of AR and of asthma, and in lower drug costs as compared with on-demand treatment.

An economic evaluation set up a decision-analytic model to calculate the net benefits of treating AR with first-generation antihistamines (40). Benefits of pharmacotherapy were elicited using the willingness-to-pay technique, although the authors noted some methodological concerns when applying this technique to AR. Costs of pharmacotherapy consisted of two components: costs of antihistamines and costs of antihistamine-associated sedation. The latter included costs of unintentional injuries (e.g. motor vehicle, occupational and home injuries) and costs of lost productivity. Costs of first-generation antihistamines amounted to US\$697 million and costs of antihistamine-associated sedation were US\$11.3 billion. Benefits of first-generation antihistamines amounted to US\$7.7 billion. Thus, net benefits of first-generation antihistamines amounted to –US\$4.2 billion. Based on probabilistic sensitivity analyses, the probability that first-generation antihistamines had a negative net benefit was 97%. These findings indicate that first-generation antihistamines are not cost-beneficial in treating AR when the costs of antihistamine-associated sedation are taken into account.

Pharmacotherapy of SAR/PAR. Two cost-consequence analyses assessed the economic value of intranasal glucocorticosteroids in treating SAR. A US study investigated 14 days of treatment with intranasal fluticasone propionate 200 µg once daily as compared with terfenadine 60 mg twice daily (41). A German study examined 23 days of treatment with mometasone furoate (200 µg once daily) as compared with levocabastine hydrochloride (200 µg twice daily) or disodium cromoglycate (5.6 mg four times daily) (42). Efficacy data of both studies were derived from prospective RCTs. Efficacy was defined in terms of symptom ratings, response to treatment or treatment success. Drug costs were calculated in 1995 and 2003 values respectively. Both cost-consequence analyses indicated that treatment with the glucocorticosteroid was more effective and less expensive than treatment with the comparator drug, irrespective of efficacy measure used.

These two cost-consequence analyses suffered from important methodological shortcomings. First, the studies considered drug costs only, implying that other healthcare costs (e.g. physician visits, adverse events) and indirect costs were not included. Secondly, the time horizon of RCT was relatively short. Thirdly, the studies computed average cost-effectiveness ratios. However, estimates of average cost-effectiveness ratios have limited relevance to decision makers. This is because insight into the economic value of a drug requires that the additional costs and effectiveness of the drug as compared with the alternative is calculated. This necessitates the calculation

of incremental rather than average cost-effectiveness ratios.

In Canada, an analysis calculated the cost-benefit of treatment with intranasal budesonide for patients suffering from SAR (43). The study was based on a double-blinded RCT comparing 4 weeks of daily treatment with intranasal budesonide as a dry powder (400 µg) with 4 weeks of daily budesonide as an aqueous spray (256 µg). Benefits of treatment were measured using a willingness-to-pay questionnaire, although the authors acknowledged that design issues may have led to an underestimation of willingness to pay. Costs of drugs, physician visits, outpatient visits, time off work and school were collected in 1993 values. The net benefit (= benefits – costs) equalled Can\$5.80/week for all patients, Can\$4.99/week for patients receiving budesonide as a dry powder, and Can\$6.60 for patients receiving budesonide as an aqueous spray. No differences were observed in net benefits between delivery modes of budesonide. The authors concluded that intranasal budesonide is cost-beneficial in the treatment of SAR.

A Canadian cost-minimization analysis analysed 6 weeks of daily treatment with budesonide as an aqueous nasal spray (256 µg) or fluticasone propionate nasal spray (200 µg) for patients suffering from PAR (44). A double-blinded RCT showed no difference between budesonide and fluticasone in terms of compliance, nasal symptoms and tolerability. Equal efficacy as shown by the 6-week trial was assumed to be maintained at 1 year. Information about resource utilization related to general management, management because of lack of efficacy and management of side-effects were based on the expert opinion of five specialists in allergy or immunology and five general practitioners. This resource utilization was assumed to be equal between pharmacotherapies as the RCT pointed to similar clinical outcomes. Therefore, in practice, only resource utilization of budesonide and fluticasone varied between study groups. Resource utilization was multiplied by the respective unit costs pertaining to Ontario in 1998 values. Total annual costs of drugs, side-effects, lack of efficacy and general management amounted to Can\$389.85 per patient with budesonide and Can\$508.6 per patient with fluticasone in 1998 values. Therefore, budesonide as an aqueous spray generates the same clinical benefit at a lower cost than fluticasone propionate nasal spray.

Pharmacotherapy of IAR/PER. A cost-consequence analysis compared treatment with levocetirizine 5 mg or with placebo for patients suffering from PER sensitized to both grass pollen and house dust mite (45). Efficacy data on quality of life and symptoms were based on a double-blinded RCT set in Belgium, France, Germany, Italy and Spain. This was a large trial examining treatment over a period of 6 months. However, the authors did not combine data on quality of life and treatment period into QALYs. As most patients were enrolled in France, a

French costing model was used to calculate direct healthcare costs (drugs, physician visits) and indirect costs (productivity loss) related to PER and associated co-morbidities in 2001 values. Levocetirizine generated a greater improvement in quality of life and symptoms at a lower cost per patient per month over the 6-month treatment period as compared with placebo.

Factors affecting economic value of pharmacotherapy. The economic value of pharmacotherapy is influenced by the perspective of the economic evaluation, the relative effectiveness and costs of available drugs, and patient compliance with treatment.

Some economic evaluations took the perspective of the healthcare system, implying that they considered direct healthcare costs (39, 41, 42, 44). On the one hand, this is acceptable as interest in management strategies tends to focus on drug use, intensity and length of treatment in outpatient settings. On the other hand, such a perspective is too restrictive as treatment has wider implications on time off work or school. Three out of the six economic evaluations adopted a societal perspective (40, 43, 45).

The relative effectiveness of available drugs plays a key role in determining the economic value of pharmacotherapy. The literature has shown that intranasal glucocorticosteroids are the most effective drugs in adults and children (6, 23). If glucocorticosteroids are more effective and less expensive than other pharmacotherapies, no formal economic evaluation is necessary because glucocorticosteroids would be dominant. If glucocorticosteroids are more effective, but also more expensive than other pharmacotherapies, an economic evaluation needs to be carried out and the improvement in effectiveness needs to be weighed against the additional costs.

The economic value is also determined by the costs of pharmacotherapy. In particular, the switch from prescription to over-the-counter status may alter the relative costs of pharmacotherapies. For instance, a model simulated the cost-effectiveness of switching loratadine to over-the-counter status for the treatment of AR in the United States from a societal perspective (46). Information about costs and effectiveness originated from the medical literature and national surveys. The findings showed that the availability of over-the-counter loratadine was accompanied by annual savings of US\$4 billion dollars and 135 061 QALYs. In other words, making loratadine available over-the-counter saved costs and enhanced effectiveness.

Patient compliance with drug regimens plays a role in the economic value of pharmacotherapy. The literature indicates that compliance of AR patients is influenced by a number of aspects including comfort and ease of administration, time to onset and duration of action, the number of daily doses required, tolerability, side-effect profile and patients' knowledge of their disease (47). Tailoring treatment to patient preferences for these aspects has been proposed as a strategy to enhance

patient compliance (48). Also, lack of effective communication between healthcare provider and patient has been shown to lead to poor patient compliance (47). A general model was recently published recommending that healthcare providers follow five steps in communicating with patients: (i) understand patients' experience and expectations; (ii) build partnership and check for patient understanding; (iii) provide evidence; (iv) present recommendations based on clinical judgement and patient preferences; (v) check for patient understanding and agreement (49).

Discussion

The cost-of-illness literature on AR is limited and the evidence mainly relates to the United States. The available evidence has shown that AR imposes a substantial economic burden on society, with indirect costs because of productivity loss being more important than direct healthcare costs. Cost estimates were biased as a result of difficulties involved in diagnosing AR; exclusion of patients who do not seek healthcare and absence of data on over-the-counter medication; and difficulties involved in estimating indirect costs because of productivity loss. There is limited evidence on the costs of SAR/PAR and IAR/PER. With a view to informing the methodology of future cost-of-illness studies, European studies are required that draw on a prospective collection of primary data on healthcare resource utilization and costs associated with the different forms of AR.

It is difficult to determine the economic impact of AR on patients, the healthcare system and society. Therefore, Table 2 identifies the major cost items that need to be considered when calculating AR costs 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 calculating 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.

Little is known of the economic value of different pharmacotherapeutic approaches to the management of AR, SAR/PAR and IAR/PER. There is some evidence supporting the cost-effectiveness of levocetirizine as compared with placebo. Existing economic evaluations suffered from a number of methodological limitations including small sample sizes, short duration of RCTs, lack of standardized effectiveness measure and restricted scope of costs. There is a need for more, better-designed and comprehensive economic evaluations examining the economic profile of pharmacotherapy of the different forms of AR.

Studies need to be carried out that prospectively collect primary data on cost-effectiveness. Current analyses based on RCTs provide a degree of internal validity,

Table 2. Items to be considered in cost studies of allergic rhinitis

Direct healthcare costs				
Medication	Healthcare providers	Other	Direct nonhealthcare costs	Indirect costs
Oral and intranasal antihistamines	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

but do not necessarily reflect real-life practice. Alternatively, modeling approaches can be employed based on high-quality data taken from the literature. Also, the comparability of results between cost-effectiveness analyses has been hampered by the variety of effectiveness measures that are used in studies. Further work is required to reach consensus on the most appropriate measure of effectiveness to be used in the field of AR.

Given that AR has a considerable impact on patient quality of life (11, 12), there is a place for cost-utility analyses of pharmacotherapy that account for quality of life. The Rhinoconjunctivitis Quality of Life Questionnaire is a disease-specific and validated instrument to measure quality of life (50). Alternatively, a generic quality-of-life instrument such as the EuroQol (51) or the Medical Outcomes Survey Short Form 36 (52) can be used to calculate QALYs. The advantage of using a generic measure is that the additional cost per QALY gained of pharmacotherapy of AR can be compared with the efficiency of therapeutic approaches to other diseases. Such information is used by decision makers to allocate scarce resources in healthcare.

Also, the technique of cost-benefit analysis may be suited to contrast costs of pharmacotherapy with the patient's willingness to pay for the clinical benefit of treatment. A cost-benefit analysis has the advantage that the economic value of pharmacotherapy can be determined in absolute terms by calculating net benefits (i.e. benefits-costs). This contrasts with cost-effectiveness and

cost-utility analyses, which express the economic value in relative terms by calculating, for instance, the additional costs per 1% symptom reduction or the extra costs per QALY gained. Two cost-benefit analyses of pharmacotherapy were identified (40, 43). However, assigning monetary values to health benefits remains controversial and further research is needed to clarify methodological issues surrounding the monetary valuation of health benefits.

Conclusions

The economic burden of AR is considerable because of its high prevalence during substantial periods of time of the year. Few studies have focused specifically on estimating costs of SAR/PAR or IAR/PER. Little is known of the economic value of pharmacotherapeutic approaches to the management of AR, although levocetirizine appears to be cost-effective as compared with placebo.

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