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# Economic Impact of Treatments for Controlling Symptoms Associated with Rhinitis: an Evaluation of Narivent® *vs* Standard Therapy

Valerio Damiani[1], Dilyana Vicheva[2], Angelo Camaioni[1], Claudio Viti[1], Giulia Schillani[3], Giada Morpurgo[4], Antonella Silvia Scirè[4], Dario Gregori[5,*]

[1]*ENT Department San Giovanni Addolorata Hospital, Rome, Italy*

[2]*Bulgarian Rhinologic Society, Department of Otorhinolaryngology, Medical University, Plovdiv, Bulgaria*

[3]*Department of Life Sciences, University of Trieste, Italy*

[4]*Zeta Research Srl, Trieste, Italy*

[5]*Unit of Biostatistics, Epidemiology and Public Health, Department of Cardiac, Thoracic and Vascular Sciences, University of Padova, Italy*

**Abstract:** *Rationale and aim:* Upper airway disorders, like allergic and non-allergic rhinitis, are common nasal conditions affecting millions of individuals worldwide. The prevalence of allergic rhinitis (AR), in particular, has been increasing in the last decades. The pervasiveness of this disorder therefore imposes a large burden both on individual patients and the society. A wide range of drugs exists for symptomatic treatment of rhinitis, such as corticosteroids, decongestants, and antihistamines, but standard therapies are often associated with several side effects. A new class of medical devices, based on bio-mechanically innovative triggers, has been proven to have a good clinical effectiveness with lower adverse reactions, particularly over prolonged administration periods.

The present study aims at evaluating the economic impact of rhinitis, with respect to direct and indirect costs, and analysing the use of the medical device Narivent® compared to standard therapies to manage the symptoms of this illness.

*Methods: Via* a Monte Carlo simulation study, data on disease prevalence, drug prescription and cost of both the specific therapeutic approach and the adverse events treatment will be combined to provide an estimate of the overall cost of the pharmacotherapy as compared with Narivent®.

*Results:* Lowering the impact of adverse reactions related to standard therapy through the use of novel therapeutic approaches like Narivent®, might reduce the overall burden of rhinitis by about 5 billion per year.

*Conclusion:* The use of the medical device Narivent®, as an alternative approach to manage symptoms associated with rhinitis, may contribute to bring down its costs by about 3.5% yearly as compared to the standard therapy.

**Keywords:** burden of rhinitis; cost impact analysis; allergic rhinitis costs; non allergic rhinitis costs.

## INTRODUCTION

Rhinitis is a common nasal disorder and represents a global health problem, involving millions of individuals across the world. The two major classifications are allergic and nonallergic rhinitis (NAR) [1, 2]. AR is the most common form of non-infectious rhinitis, affecting 400 million of people worldwide with a high prevalence in industrialised nations [3]. In the United States it affects between 10-30% of the adult population and up to 40% of children, while in Europe its prevalence is estimated to be 23% [1-4].

AR is a symptomatic disorder characterised by the inflammation of the nasal mucosa, induced by an IgE-mediated immune response against allergens. It is historically classified in seasonal or perennial depending on whether an individual is sensitized to cyclic pollens or year-round allergens such as dust mites and animal dander [5, 6]. A different classification has been proposed in the "Allergic Rhinitis and its Impact on Asthma (ARIA)" document [7] and distinguishes between intermittent allergic rhinitis (IAR) and persistent allergic rhinitis (PER) depending on the frequency of symptoms, and between mild or moderate/severe allergic rhinitis depending on symptoms' severity [8-10].

Initial allergen exposure in susceptible subjects results in the production of IgE antibodies, which become fixed to mast cells, a process known as sensitisation. Subsequent exposure causes the release of inflammatory mediators (such as histamine, bradykinin, prostaglandins, leukotrienes) generating an immediate, IgE-dependent allergic response and leading to increased nasal obstruction, tissue oedema and production of secretions [5].

*Address correspondence to this author at the Unit of Biostatistics, Epidemiology and Public Health, Department of Cardiac, Thoracic and Vascular Sciences, Via Loredan, 18, 35121 Padova – Italy; Tel: +39 049 8275384; Fax: +39 02 700445089; E-mail: dario.gregori@unipd.it

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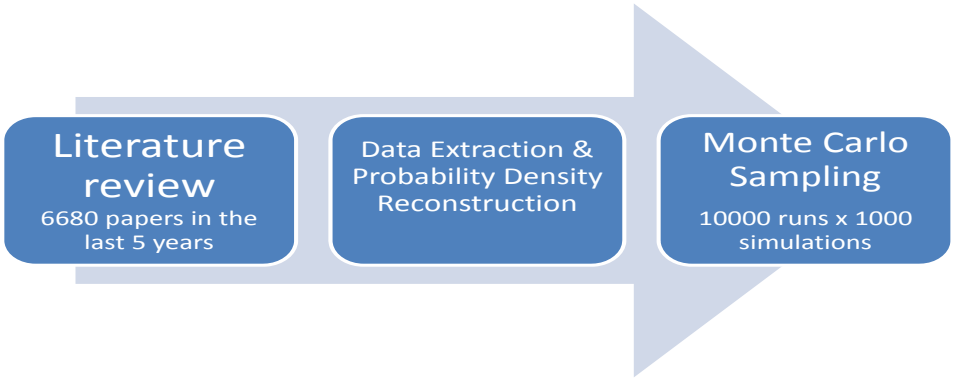


**Fig. (1).** Flow Chart of the Study Conduction.

Many subjects have symptoms that mimic allergic rhinitis, without any specific causal factor and with a lack of demonstrated IgE-mediated allergy. These patients have nonallergic rhinitis (NAR) and its prevalence in an adolescent/adult population diagnosed with rhinitis is estimated to be at least 25% [11]. NAR has 8 major subtypes which includes non-allergic rhinopathy (previously known as vasomotor rhinitis), non-allergic rhinitis with eosinophilia, atrophic rhinitis, senile rhinitis, gustatory rhinitis, drug-induced rhinitis, hormonal-induced rhinitis, and cerebral spinal fluid leak. Its exact pathophysiology remains uncertain but, like AR, NAR is characterized by persistent or intermittent nasal symptoms. Nasal obstruction and rhinorrhea are its hallmark features and more commonly seen than sneezing, nasal and palatal itch, and concurrent ocular symptoms, which are more suggestive of allergic upper airway disease [6]. A variety of stimuli may trigger NAR, including irritants such as smoke from tobacco and strong odors, climate changes, humidity, and changing barometric pressure and/or temperature. NAR may usually be differentiated from AR by characteristics including a relatively later age of onset, female sex, and a frequent lack of atopic comorbidities, such as atopic dermatitis, asthma, and food allergies. [6]. Rhinitis (in its multi-factorial etiology) is therefore a common rhinopathy and is characterized by the presence of at least one of the following nasal symptoms: anterior or posterior rhinorrhea, sneezing, nasal blockage and itching of the nose [12]. It can often be a debilitating condition which critically harms patients quality of life: several studies have demonstrated that poorly controlled symptoms of AR contribute to sleep disturbances, daytime fatigue, impaired learning and cognitive functioning and decreased long-term productivity. People with AR are also more likely to report problems with social activities, difficulties with daily activities, work/school performance and decreased feelings of mental well-being than people without AR [13]. Moreover, the presence of allergic rhinitis is closely linked to other inflammatory diseases affecting respiratory mucous membranes, such as asthma, allergic conjunctivitis, and sinusitis, and thus has additional important health implications [3, 13].

The goal of the treatment of rhinitis is to reach a good symptom control and for this purpose a variety of therapeutic options is available. The management of AR includes allergen avoidance, antihistamines (oral and intranasal), intranasal corticosteroids, intranasal cromones, leukotriene receptor antagonists, and immunotherapy in appropriately selected patients. Occasional systemic corticosteroids and decongestants (oral and topical) are also used [2]. The mainstay of treatment for NAR are intranasal corticosteroids. Topical antihistamines are also efficacious and topical anticholinergics (such as ipratropium bromide) nasal spray are effective in treating rhinorrhea symptoms. Adjunct therapy includes decongestants and nasal saline [2].

Despite its general effectiveness in the management of rhinitis, pharmacotherapy is often associated with relevant adverse reactions and, depending on the severity of the disorder, may entail long-term treatments which can result in a considerable cost for the healthcare system. In addition, even when the symptoms of rhinitis are transient, the high incidence of these conditions imposes a substantial economic impact on society, regarding both the direct (medical and nonmedical) and the indirect costs (e.g.: disability, early retirement, reduced working capacity and absence from work).

The aim of the present study is to quantify the economic impact of standard treatments of rhinitis and to highlight how the use of the medical device Narivent® as an alternative approach to manage its symptoms, may contribute to bring down the economic consequences of rhinitis.

## METHODS

### Statistical Methods

A decision model was developed to evaluate the introduction of Narivent® (i.e. to compare competing treatment regimens of standard therapy vs Narivent®) for people suffering from rhinitis in the European Union. At each node of the decision tree, probabilities taken from published reports were used as the expected values of Binomial/Multinomial probability distributions.

A hypothetical cohort has thus been constructed based on epidemiological variables and probability tables Fig. (1). After determining the likely number of people affected by rhinitis in Europe, the hypothetical cohort was entered into a Markov model grafted onto the decision tree. Incorporation of a Markov sub-tree allows the representation of cumulative outcomes, such as symptoms relief and relapse. Although the decision tree is restricted to the finite time frame of 1 year, the Markov model reflects events, such as recurrence or chronicitization, that have an ongoing risk. The Markov model in the analysis consisted of four finite health states in which a member of the cohort might exist: (*i*) incidence of

**Table 1. Recommended Treatments for AR, According to Symptoms (Scores – in Italics - from 1 to 4 Indicate the Degree of Appropriateness). [2]**

| Symptoms | Oral Antishistamine | Nasal Antihistamine | Nasal Steroids | Nasal Decongestant | Nasal Ipratropium Bromide |
|---|---|---|---|---|---|
| Rhinorrea | 2 | 2 | 3 | | 2 |
| Sneezing | 2 | 2 | 3 | | |
| Nasal Itching | 2 | 2 | 3 | | |
| Nasal Congestion | 1 | 1 | 3 | 4 | |
| Ocular Symptoms | 2 | | 2 | | |
| Administration (%) | 25.63% | 9.81% | 31.33% | 4.75% | 5.38% |

**Table 2. Estimated Costs of Treatment with Narivent®**

| | Number of Administrations Per Day (1 Puff/Nostril) | Days of Treatment with Narivent | Treatment Cost |
|---|---|---|---|
| Rhinopathies (acute phase) | 3 | 7 | €3.42 |
| Chronic rhinopathies | 2 | 30 | €9.78 |

**Table 3. Costs Estimated for Europe Based on the Simulation Study [2]**

| | Mean | 95% C.I. | |
|---|---|---|---|
| Narivent® | €158,459,147,170.61 | €150,943,810,000.00 | €165,851,050,000.00 |
| Standard | €164,366,710,103.89 | €156,540,870,000.00 | €172,233,140,000.00 |
| Delta | -€5,907,562,933.28 | -€5,597,060,000.00 | -€6,382,090,000.00 |

rhinitis; (*ii*) acute treatment; (*iii*) chronic treatment; and (*iv*) recurrence. The model was employed in a cohort simulation (1000 simulations per 10000 runs each) in which hypothetical patients travelled through the decision tree and then entered the Markov model [14, 15]. In the Markov model, the cohort was distributed into the first three health states: subsequent transitions to the fourth state (i.e. recurrence) occurred at the end of each year at a rate reflecting age-specific recurrence rate.

All results have been presented with the corresponding Monte Carlo credibility intervals (95% if not otherwise specified). Analyses were performed using Model Risk® [16].

## RESULTS

### Simulation Scenario

Incidence and prevalence estimates of rhinitis have been set according to published literature with respect to the European Union. According to recent studies, AR prevalence is about 23% in Europe [1], whereas NAR prevalence is considered slightly higher, close to 25%, affecting more than 200 million of people worldwide, 50 million of which living in Europe [17]. Country-specific estimates report higher rates, like the 29% prevalence in Belgium [8] and about 45% in Turkey [18].

Diseases are symptomatic in 83% of the cases [19], presenting serious comorbidities like wheezing, tightness, asthma attacks and chronic cough in about 23% of the cases [20]. Treatment prescription indications according to major symptoms are provided in Table **1**.

Burden for the health care system has been estimated for US, with about 23.41$ for office visits to generalists, 30.55$ for office visits to specialists and 29.28$ for allergy-related testing procedures [21]. Impairment of daily activities has been estimated being quite high. On average, the total number of days lost to work is 6.8 per person affected by AR or NAR, of which 2.5 are direct work absenteeism and 2.6 for providing support and care to other diseased relatives [22].

Adverse events for common therapeutic alternatives have been reported extensively, for corticosteroids mostly consisting in epistaxis (10-15% of the patients), for antihistamines conjunctival symptoms, and for others even more severe reactions up to increased risk of glaucoma for anticholinergics [3]. For what concerns Narivent®, so far no severe adverse effects are reported by the manufacturer in the post-market surveillance. In an experimental, unpublished study on a paediatric population, assessing the efficacy of Narivent® in the treatment of nasal congestion associated with allergic rhinitis, only mild adverse reactions were recorded, with an incidence of less than 1%.

Direct treatment costs for major therapeutic alternatives are estimates as about: (*i*) 378.56$ for intranasal antihistamines and steroids, (*ii*) 213.2$ for oral and ophthalmic antihistamines, (*iii*) 503.3$ for inhaled, oral, ophthalmic, and dermatologic corticosteroids and (*iv*) 168.58$ for inhaled and oral bronchodilators [21]. Direct treatment costs for Narivent® are presented in Table **2**.

### Cost-Impact Estimation

Using the data from the simulation scenario, overall impact of AR in Europe has been estimated at about 164 billion€/year (Table **3**). Lowering impact of adverse therapy with the introduction of novel approaches like Narivent® might reduce overall burden by about 5 billion per year

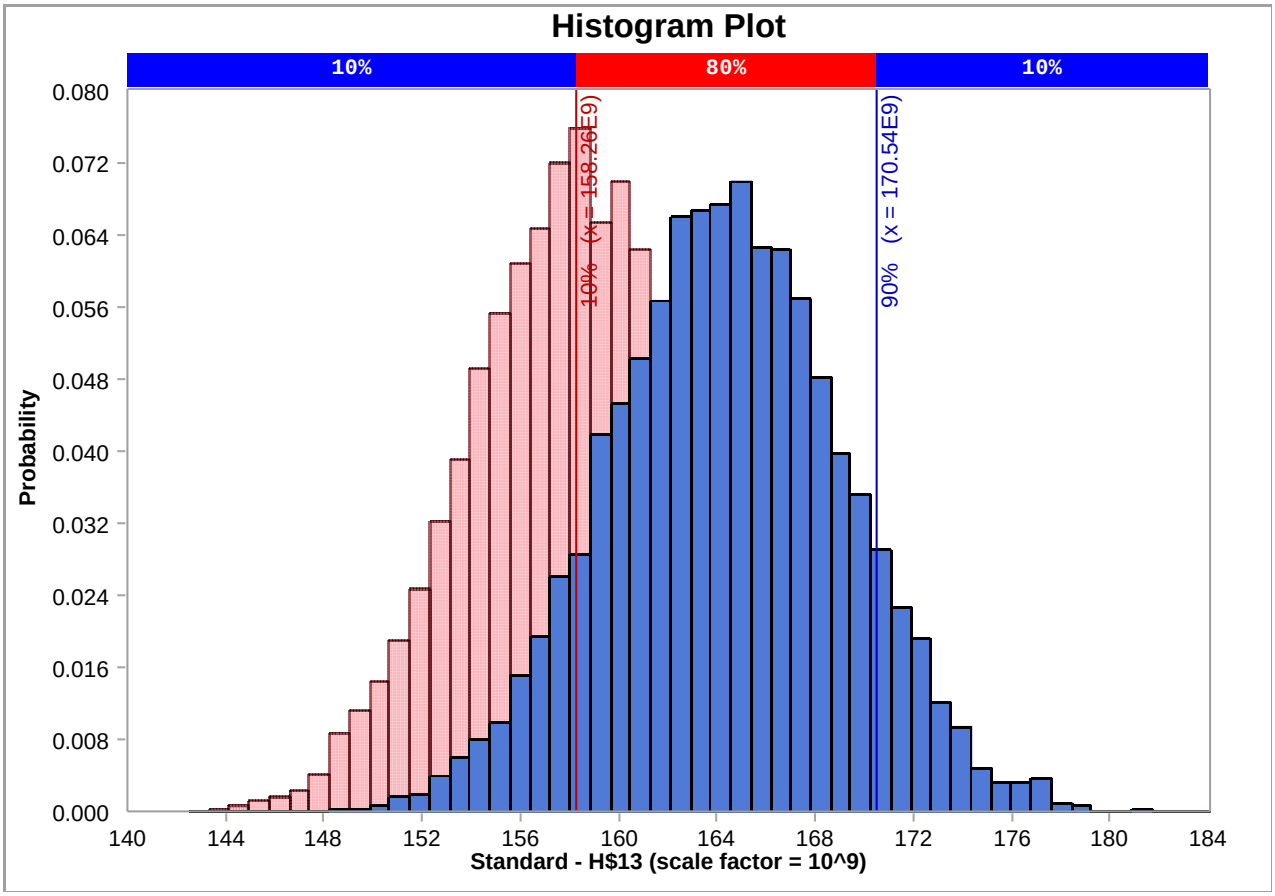


**Fig. (2).** Histograms of the cost distributions (blue standard therapeutical approach, red Narivent®) after simulation (10% - 90%).

Table **3**, with a significant shift downward of the overall therapeutic costs Fig. (2).

## DISCUSSION

Rhinitis is a highly impacting disease in Europe, due to the high prevalence and significant costs of care. Our estimates of the costs of the standard therapeutic approach being about 160 billion € per year, are consistent with previous estimates of 120-140 billion € overall [23, 24]. This is largely attributable to the high prevalence of symptomatic disease forms, to which part of the therapeutic agents are targeted, but also to the high rates of adverse reactions related to such therapies [25, 26].

The adoption of milder therapeutic strategies, like Narivent®, might represent an interesting option in view of its lower adverse reactions rates in front of a proven efficacy [27]. Narivent® has been shown to have: (*i*) an anti-oedematous action, due to the presence of mannitol, a naturally occurring sugar alcohol, widely used in pharmaceutical formulations and food products, and employed therapeutically for its known osmotic action; (*ii*) an anti-inflammatory action, due to the presence of glycyrrhizin, a glucosidic triterpene extracted from the roots of the liquorice plant, which is the first direct inhibitor of HMGB1 (High-mobility group box 1 protein; intranuclear protein), which acts as a potent pro-inflammatory mediator when released in the extracellular environment; and (*iii*) as lubricant, due to the presence of copolymer of methyl vinyl ether and maleic anhydride (PVM/MA copolymer), which is classified as a Poly vinyl methyl ether (PVME or PVM). It is a viscous, balsam-like substance and acts promoting and increasing the adhesion time of glycyrrhizin to the nasal mucosa, with a lengthening of the anti-inflammatory action.

Our estimates show that the adoption of milder therapeutic options based on the medical device class of Narivent® could induce a reduction of the overall economic burden of AR and NAR of about -3.59% (95% C.I. from -3.71% to -3.58%), estimated as a reduction yearly such as 5 billion €.

### Study Limitations

The simulation exercise which has been performed is relying on published aggregated data, and suffers therefore from all major limitations of ecological studies. In addition, although the cost-impact analysis has been performed using the most updated stochastic techniques, biases could have been introduced in the analysis due to neglecting complex interactions among treatments and patients characteristics, which have been ignored due to lack of information.

### Final Remarks

Our simulation study on the economic advantages of adopting Narivent® as a standard therapeutic agent for targeting AR and NAR has shown that the overall economic impact of the two diseases could be reduced by about 3.5% yearly.

## CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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Declared none.

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