



# Prescription Profile and Clinical Outcomes in Patients with Allergic Rhinitis Treated with Oral Antihistamines or Nasal Corticosteroids

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## Abstract

**Introduction** Oral antihistamines and intranasal corticosteroids have been shown to be effective and safe for the treatment of allergic rhinitis; however, the evidence suggests a level of superiority of corticosteroids, so they should be preferred over the former.

**Objective** To know the prescription profile of two second generation antihistamines (cetirizine and levocetirizine) and two nasal corticosteroids (mometasone and furoate-ciclesonide) in a cohort of patients with allergic rhinitis, and to compare the clinical outcomes obtained.

**Methods** A cohort study was carried including patients with allergic rhinitis treated with cetirizine, levocetirizine, mometasone furoate or ciclesonide. The improvement was evaluated with the total nasal symptoms score (TNSS). This scale yields results between 0 and 12. Zero indicates absence of symptoms.

**Results** A total of 314 patients completed 12 weeks of follow-up. Seventy-five percent were treated with antihistamines, 20% with corticosteroids, and 5% with a combination of the above. The TNSS median for corticosteroid was 2.5 points; for antihistamines, it was 5 points, and for combination, it was 4 points. We found differences between corticosteroids and antihistamines.

**Conclusion** The prescription percentage of second generation oral antihistamines is higher than that of intranasal corticosteroids. However, patients with allergic rhinitis treated with the second option obtained better control of symptoms.


## Keywords

- ▶ perennial allergic rhinitis
- ▶ histamine antagonists
- ▶ mometasone furoate
- ▶ ciclesonide
- ▶ drug prescriptions
- ▶ cohort studies

## Introduction

Allergic rhinitis is a symptomatic disorder whose main effect occurs on the nasal mucosa. This effect is induced by exposure to allergens, which trigger an inflammatory process mediated by immunoglobulin-E (Ig-E).<sup>1</sup> This condition is relatively frequent and has a high prevalence between 13

and 14 years of age, a group in which it can reach 14.6%. According to the data reported by the International Study of Asthma and Allergies in Childhood (ISAAC).<sup>2</sup> From a global perspective, Africa and Latin America have the highest reported prevalence (18% and 17.3% respectively), and Colombia ranks 5th worldwide, reaching a percentage of 25.2% of cases in the adolescent population.<sup>2</sup> Due to the high burden of the disease, the volume of consultations generated by this condition is understandable, with examples such as the one reported by the national ambulatory care survey

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conducted in the United States between 1995 and 1998, in which rhinitis represented almost 3% of the total of family physicians' consultations, and it was located in the 12th position of frequent consultation reasons.<sup>3</sup>

The symptoms associated with this pathology, such as rhinorrhea, lacrimation, conjunctival injection, pruritus and nasal obstruction, significantly affect the quality of life, and social and work performances, which is why it is essential to offer the patient safe and effective therapeutic alternatives to keep them free of symptoms most of the day, preventing their onset or quickly controlling the symptoms.<sup>4,5</sup>

Within the therapeutic arsenal, there are multiple options, among which are oral and topical antihistamines, leukotriene inhibitors, intranasal decongestants and topical intranasal corticosteroids. Faced with all these alternatives, there is evidence in the scientific literature that suggests that treatment with second-generation antihistamines or intranasal aerosol corticosteroids are the first-choice option in all cases; however, when these two therapies are compared, the recommendation is aimed at preferring intranasal corticosteroids over antihistamines.<sup>4,6</sup>

Specifically, within the group of intranasal corticosteroids, it is worth highlighting mometasone furoate, which is a synthetic glucocorticoid, capable of inhibiting the formation, release, and activation of chemical and cellular mediators that facilitate the control and prevent the appearance of new episodes. This medication was introduced to the world market in 1998 and has been used with a high safety profile and effectiveness over many years.<sup>7</sup> In Colombia, this drug proved to be a cost-effective strategy compared with beclomethasone dipropionate.<sup>8</sup>

Despite the recommendation to prefer intranasal corticosteroids over antihistamines,<sup>4,6</sup> researchers have hypothesized that the treatment of this condition in the country is based mainly on the use of antihistamines, probably related to a low level of access to specialists in otorhinolaryngology, and due to the high availability of over-the-counter antihistamines at a low cost, compared with nasal corticosteroids. Despite this perception, it was not possible to document in the national literature studies that allowed establishing the distribution of the prescription or use of this type of medication in patients with allergic rhinitis.

Considering the above, the aim of this study was to know the prescription profile of two second-generation antihistamines (cetirizine, levocetirizine) and two nasal corticosteroids (mometasone, furoate-ciclesonide), and to compare the clinical outcomes after a 12-week follow-up of a Colombian patient's cohort with allergic rhinitis treated by a group of general practitioners.

## Methods

### Design

An observational cohort analytical study was performed, within the framework of the activities of a follow-up program to monitor adverse events, clinical outcomes and profiles of use of a group of drugs from the Abbott laboratory portfolio, called the Biomedical Monitoring Registry of med-

ical care and clinical outcomes in frequent pathologies (RBDC). This project complied with all the national and international research ethics regulations and was approved by an independent ethics committee.

### Population and Sample

Within the program *Registro biomédico de desenlaces clínicos* (RBDC, in the Spanish acronym), through a sequential sampling, patients diagnosed with allergic rhinitis were included, according to the classification criteria proposed in the Allergic Rhinitis and its Impact on Asthma (ARIA) study,<sup>1</sup> without age restriction, who were candidates to be treated—according to medical criteria—with cetirizine, levocetirizine, ciclesonide or mometasone furoate for nasal application, and who attended the private consultation of a group of 21 general practitioners, between July and December, 2016, in 12 cities of Colombia (Bogotá, San Juan del Cesar, Manizales, Florida Blanca, Bucaramanga, Medellín, Florida, Palmira, Cali, Santa Marta, Barranquilla and Cartagena). Patients with a diagnosis of allergic rhinitis adequately controlled with other medications, and those who did not agree to participate voluntarily were not included in this cohort. The final sample was given by the totality of subjects that were enrolled by the group of program physicians, in a lapse of 6 months.

### Procedure for Enrollment and Follow-up

In real-life conditions, each doctor gave attention to their patient, made the corresponding diagnosis and assigned the treatment according to their clinical criteria. When the patient was a candidate to be part of the registry, the doctor requested their informed consent to be able to document and analyze the data of the clinical evolution of their condition, during a period of 12 weeks. In each case, the professionals prescribed the treatment according to their clinical criteria and allowed the research group to know the baseline and follow-up data. Clinical control appointments were defined by the attending physician, but for the purposes of the analysis, the last available control was recorded at week 12 of follow-up ( $\pm 2$  weeks).

### Variables of Interest

Sociodemographic variables of age and gender were evaluated and the type of prescribed treatment was documented, differentiating between antihistamine prescription and corticosteroid prescription. The symptoms associated with the disease were evaluated, using the total nasal symptom score (TNSS) domains,<sup>9</sup> which include rhinorrhea, nasal pruritus, sneezing and nasal obstruction, measured with the Likert scale (0: no symptoms, 1: mild symptoms, 2: moderate symptoms, 3: severe symptoms). This scale yields possible values between 0 and 12, in which 0 is absence of symptoms and 12 is the greatest possible intensity of symptoms. Finally, serious adverse events, defined as hospitalizations, mortality, and serious infections, were evaluated.

### Statistical Analysis

A general description of the study variables was made, using frequency measurements, and central tendency and

dispersion statistics, according to the measurement scale of each parameter. For the type of prescription variable, absolute and relative frequencies were calculated by specific medication and grouped into three alternatives (intranasal corticosteroids, antihistamines, and combination). Clinical outcomes were estimated using the TNSS scale. The initial and final scores for the entire cohort were documented, and the improvement gradient was calculated, subtracting the final score from the initial score. The initial, final, and gradient scores were described for the three groups, reporting the minimum, 25th percentile, median, 75th percentile, and maximum. Since the values of the TNSS variable did not present a normal distribution, the statistical contrast was performed using the non-parametric Kruskal-Wallis test and the Dunn posthoc test. To assess possible confounding factors, a multivariate linear regression model was performed, using the final TNSS as the dependent variable, and the type of treatment as the independent variable, controlling by age, gender and the initial TNSS. Serious adverse events were described through absolute and relative frequencies. For hypothesis testing, an  $\alpha$  value of 0.05 was defined, considering that a  $p$ -value below this cut-off point would be statistically significant.

## Results

A total of 420 patients diagnosed with moderate to severe rhinitis entered the registry, 314 of whom attended the medical follow-up up to week 12 ( $\pm 2$  weeks), leading to a percentage of adherence with the medical control of 75%. The cohort was composed of 62% women (196/314). The ages of the patients ranged from 1 to 96 years old, with a median of 25.5 years and 50% of the subjects between the ages of 6 and 52 years; 37% of the patients were under the age of 18 (116/314).

### Prescription Profiles

Among the 314 patients who attended control visits, different treatment schemes were formulated, including two types of oral antihistamines (levocetirizine and cetirizine), two types of intranasal corticosteroids (mometasone furoate and ciclesonide) and combinations of these products.

Regarding the use of antihistamines, levocetirizine accounted for 41% of the total prescriptions, while cetirizine accounted for 34%. The participation of intranasal corticosteroids was 15% for mometasone furoate and 4% for ciclesonide. For purposes of the analysis, the treatment groups were reorganized into intranasal corticosteroids, oral antihistamines and combinations of intranasal corticosteroid and oral antihistamine. Antihistamines accounted for 75%, aerosol corticosteroids for intranasal application for 20%, and the combination of the two groups for 5%. The detail of the prescription is presented in ► **Table 1**.

### Clinical Performance

The baseline TNSS assessment for the entire cohort reported values ranging from 5 to 12, with a median of 8. In the group treated with corticosteroid the initial median was 7, while for the groups of treatment with antihistaminic and combined

**Table 1** Prescription distribution

Medications	n	%
Levocetirizine	130	41
Cetirizine	107	34
<b>Total antihistamines</b>	<b>237</b>	<b>75</b>
Ciclesonide	14	4
Mometasone furoate	48	15
<b>Total corticosteroids</b>	<b>62</b>	<b>20</b>
Ciclesonide-cetirizine	1	0
Mometasone furoate-levocetirizine	8	3
Mometasone furoate-cetirizine	6	2
<b>Combined total</b>	<b>15</b>	<b>5</b>
<b>Total prescriptions</b>	<b>314</b>	<b>100</b>

therapy the median was 8, without significant baseline differences between groups being documented ( $p$ -value: 0.14).

The results after the end of the follow-up reported values between 1 and 12, with a median of 5. In the group treated with corticosteroid, the median was 2.5; in the antihistamine group, it was 5, and for the combined group, it was 4. The non-parametric Kruskal-Wallis test showed significant differences between the groups ( $p$ -value: 0.0001), and the Dunn posthoc test allowed to establish that this difference is significant in favor of corticosteroids compared with antihistamines ( $p$ -value: 0.0000). It was not possible to establish differences between antihistamines and combined therapy ( $p$ -value: 0.12) and between corticoid and combined therapy ( $p$ -value: 0.16).

The difference in TNSS for each subject was calculated, seeking to establish the reduction gradient in the score. The median reduction for the entire cohort was 4 points. In the group treated with corticosteroid, median reduction was 5 points, while in the antihistamine group it was 3, and for combined 4 points. The Kruskal-Wallis nonparametric test allowed establishing that at least one of the groups was different ( $p$ -value: 0.0008), and the Dunn posthoc test allowed establishing that this difference is significant in favor of corticosteroids compared with antihistamines ( $p$ -value: 0.0003). It was not possible to establish differences between antihistamines and combined therapy ( $p$ -value: 0.37) and between corticosteroid and combined therapy ( $p$ -value: 0.66). The descriptive statistics can be seen in ► **Table 2**.

The multivariate analysis model shows that, controlling by potential confounder factors, the nasal corticoids can reduce the final TNSS by 4.5 points (95% confidence interval: 3.5–5.5). The multivariate analysis model is presented in ► **Table 3**.

### Serious Adverse Events

No serious adverse events were recorded in any of the treatment groups, and, in no case, any suspension of treatment related to an adverse event was documented.

**Table 2** Distribution of total nasal symptom score by treatment group. Initial-final difference

Treatment	TNSS	Minimum	p25	p50	p75	Maximum
Antihistaminic (n = 237)	Initial	5	5	8	12	12
	Final (12 weeks)	1	4	5	6	12
	Difference (basal-final)	-1	1	3	6	11
Corticosteroid (n = 62)	Initial	5	5	7	11	12
	Final (12 weeks)	1	1	2.5	3	6
	Difference (basal-final)	0	3	5	7	10
Combination (n = 15)	Initial	5	7	8	11	12
	Final (12 weeks)	1	3	4	5	7
	Difference (basal-final)	1	2	4	5	11
Total (n = 314)	Initial	5	5	8	12	12
	Final (8–12 weeks)	1	2	5	5	12
	Difference (final-basal)	-1	1	4	6	11

Abbreviations: p, percentile; TNSS, total nasal symptom score.

**Table 3** Multivariate linear model

Outcome: Final TNSS			
Predictor	Coefficient ( $\beta$ )	95% CI	p-value
Nasal corticosteroid	-4.5	-3.5; -5.5	0.000
Antihistaminic	1.05	-0.18; 2.2	0.09
Combination	-0.62	-1.9; 0.67	0.34
Age	0.004	-0.007; 0.01	0.48
Sex (0: female; 1: male)	0.32	-0.23; 0.88	0.25
Initial TNSS	0.27	0.18; 0.36	0.000
Model p-value: 0.000. R-squared: 0.2			

Abbreviations: CI, confidence interval; TNSS, total nasal symptom score.

## Discussion

Second generation antihistamines are considered today an effective alternative for the treatment of allergic rhinitis, due to their safety profile and the control of the most frequent nasal symptoms.<sup>6</sup> However, when compared with corticosteroids for intranasal application, evidence suggests that corticosteroids are superior for the control of symptoms, which is why, in some publications, they are recommended over antihistamines.<sup>6,10</sup>

In the context of the present investigation, most patients were treated with antihistamines (75%), and only in 20% of cases doctors prescribed intranasal corticosteroids. It is worth noting that the behavior displayed by these doctors is reasonable, since despite the evidence suggesting superiority in the effectiveness of intranasal corticosteroids, different clinical practice guidelines recommend the use of antihistamines as the first alternative of choice.<sup>5,6,11</sup> Notwithstanding the foregoing, it is important to note that the most recent systematic review, published in 2017, concluded, with a meta-analysis of five clinical trials and a narrative description of nine, that

intranasal corticosteroids are superior to oral antihistamines in terms of the control of nasal symptoms and the improvement of the quality of life of patients with allergic rhinitis<sup>10</sup>; consequently, it would be expected that future guidelines will state this with greater clarity, and primary care physicians will modify their behavior toward a profile of greater use of intranasal corticosteroids as the first line of treatment for patients with allergic rhinitis.

Within the distribution of prescriptions, it was found that only a low percentage (5%) indicated combined antihistamine treatments with intranasal corticosteroids. This behavior was studied in the 2016 update of the ARIA clinical practice guide, in which the following question was posed: "Should a combination of oral H1-antihistamine and intranasal corticosteroid versus intranasal corticosteroid alone be used for treatment of allergic rhinitis?"<sup>4</sup>. After evaluating the evidence, the authors recommend the choice of intranasal corticosteroid, rather than the combination. This recommendation is consistent with the findings of a subsequent systematic review, which concluded that treatment with intranasal corticosteroid plus oral antihistamine has similar efficacy to that of treatment with intranasal corticosteroid monotherapy, and, in turn, these treatments are superior to treatment with oral antihistamines.<sup>12</sup> Therefore, the prescribing profiles performed by this group of physicians are reasonably adjusted to the existing evidence, but nevertheless, based on the most recent evidence, intranasal corticosteroids should be preferred for the management of allergic rhinitis.

The clinical results of the present investigation, based on the evaluation of the TNSS scale, showed greater effectiveness for patients who were treated with intranasal aerosol corticosteroids. This behavior was corroborated in the value obtained in the evaluation of symptoms at the 12-week follow-up and in the gradient results between the initial TNSS evaluation minus the final TNSS. It is important to highlight that this result was confirmed, in a multivariate model, adjusting for possible confounding factors. This result is consistent with the report by Juel-Berg et al, who, in their

systematic review, documented greater effectiveness of intranasal corticosteroids, compared with antihistamines; However, it is worth noting that the studies included in this review compared several molecules, among which are loratadine, levocetirizine, budesonide and fluticasone.<sup>10</sup>

Other specific studies have compared some of the molecules included in the present study, and the results are consistent with the findings described in the present investigation, although it is worth pointing out that the designs and outcomes evaluated were not the same. In 2015, the results of a clinical trial comparing ciclesonide with levocetirizine and a combination of the two molecules were published. These authors established the superiority of ciclesonide over levocetirizine, and could not demonstrate differences between ciclesonide and the combination of treatments, both in effectiveness and safety.<sup>13</sup> On the other hand, an observational study compared mometasone furoate with oral antihistamines in patients with allergic rhinitis, finding symptom control in 74% of those treated with intranasal corticosteroid, versus 68% in patients treated with oral antihistamines.<sup>14</sup> In summary, we can affirm that, despite the differences in design and outcomes evaluated, there are consistent results that validate the findings obtained in the present study and, consequently, the evidence suggests that intranasal corticosteroids should be preferred in monotherapy, compared with antihistamines or combinations.

Historically, first-generation antihistamines have been associated with adverse events, such as feeling dizzy, sedation and drowsiness. For this reason, their use has been limited and some have been discontinued. Currently, there are different second-generation antihistamines, for which lower frequency of adverse events has been reported.<sup>15</sup> Specifically, levocetirizine and cetirizine have been widely studied, and the data suggest that these are two safe molecules that can be used for the treatment of children and adults,<sup>15</sup> but preferably under medical supervision, since cases of seizures have been reported in children.<sup>16</sup> In the present study, 237 patients were treated with second-generation oral antihistamines (cetirizine and levocetirizine), and no serious adverse events or situations in which the treatment was discontinued due to an event were documented. These findings in real-life conditions in a large sample of children and adults, under medical supervision, allow to corroborate an adequate safety profile for these two molecules.

Regarding inhaled corticosteroids, there is sufficient evidence about their safety profile, for which mainly mild adverse events have been documented.<sup>7,17</sup> The risk of adrenal suppression has been studied in unusually high doses, and the results have shown minimal effects on the functioning of the hypothalamic-pituitary-adrenal axis.<sup>18</sup> The results of the present study are consistent with the findings described in the literature, since no serious adverse events or events that required suspension of treatment were documented.

This investigation, of observational character, in a context of habitual clinical practice, sought to find out the distribu-

tion of the profiles of prescription for the treatment of patients with allergic rhinitis, of a group of Colombian general practitioners. These results are interesting because simultaneously they allowed to know how the clinical practice of these doctors is developed, and, at the same time, the performance of the drugs in real life conditions was evaluated, which could become their main attribute as contribution to scientific knowledge. At the same time, it is important to recognize that, because it is an observational study, it presents the inherent limitations of the design, including a natural way of assigning interventions, instead of a random method, with the consequences of some risks of bias (observer and observed bias), which to some extent could overestimate the final effect. However, we assume that on the basis of a possible overestimation of the effect, all comparison groups would be affected by this phenomenon,<sup>19</sup> which is why the comparisons between the groups and the differences found could be close to reality.

## Conclusion

It is important to emphasize that the percentage of prescription of second-generation antihistamines (cetirizine and levocetirizine), by a group of general practitioners who develop their clinical practice in 12 cities of Colombia, is markedly superior to that of corticosteroids of intranasal application for the treatment of allergic rhinitis, and that the use of combination therapy is proportionately low. Although these behaviors adhere to the recommendations issued by different clinical practice guidelines, it is possible to reinforce among doctors the evidence that, despite the effectiveness of antihistamines, corticosteroids of intranasal application, such as mometasone furoate and ciclesonide, have been shown to be superior for the control of nasal symptoms. Additionally, it has been demonstrated that the combined treatments are not superior to the treatment with antihistamines or with intranasal corticosteroids in monotherapy, which is the reason why the routine use of this type of combinations should not be recommended, as corroborated with the results of this investigation.

## Conflicts of Interest

The authors declare that there were no conflicts of interest.

## References

- 1 Bousquet J, Khaltaev N, Cruz AA, et al; World Health Organization; GA(2)LEN; AllerGen. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). *Allergy* 2008;63 (Suppl 86):8-160
- 2 Ait-Khaled N, Pearce N, Anderson HR, Ellwood P, Montefort S, Shah J; ISAAC Phase Three Study Group. Global map of the prevalence of symptoms of rhinoconjunctivitis in children: The International Study of Asthma and Allergies in Childhood (ISAAC) Phase Three. *Allergy* 2009;64(01):123-148
- 3 Pace WD, Dickinson LM, Staton EW. Seasonal variation in diagnoses and visits to family physicians. *Ann Fam Med* 2004;2(05): 411-417

- 4 Brożek JL, Bousquet J, Agache I, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines-2016 revision. *J Allergy Clin Immunol* 2017;140(04):950–958
- 5 Plaut M, Valentine MD. Clinical practice. Allergic rhinitis. *N Engl J Med* 2005;353(18):1934–1944
- 6 Brożek JL, Bousquet J, Baena-Cagnani CE, et al; Global Allergy and Asthma European Network; Grading of Recommendations Assessment, Development and Evaluation Working Group. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines: 2010 revision. *J Allergy Clin Immunol* 2010;126(03):466–476
- 7 Passali D, Spinosi MC, Crisanti A, Bellussi LM. Mometasone furoate nasal spray: a systematic review. *Multidiscip Respir Med* 2016; 11:18
- 8 Rodríguez-Martínez CE, Sossa-Briceño MP, Vladimir Lemos E. Cost-effectiveness analysis of mometasone furoate versus beclomethasone dipropionate for the treatment of pediatric allergic rhinitis in Colombia. *Adv Ther* 2015;32(03):254–269
- 9 Downie SR, Andersson M, Rimmer J, et al. Symptoms of persistent allergic rhinitis during a full calendar year in house dust mite-sensitive subjects. *Allergy* 2004;59(04):406–414
- 10 Juel-Berg N, Darling P, Bolvig J, et al. Intranasal corticosteroids compared with oral antihistamines in allergic rhinitis: A systematic review and meta-analysis. *Am J Rhinol Allergy* 2017;31(01):19–28
- 11 Okubo K, Kurono Y, Ichimura K, et al; Japanese Society of Allergology. Japanese guidelines for allergic rhinitis 2017. *Allergol Int* 2017;66(02):205–219
- 12 Feng S, Fan Y, Liang Z, Ma R, Cao W. Concomitant corticosteroid nasal spray plus antihistamine (oral or local spray) for the symptomatic management of allergic rhinitis. *Eur Arch Otorhinolaryngol* 2016;273(11):3477–3486
- 13 Kim CH, Kim JK, Kim HJ, et al. Comparison of intranasal ciclesonide, oral levocetirizine, and combination treatment for allergic rhinitis. *Allergy Asthma Immunol Res* 2015;7(02):158–166
- 14 Price D, Kemp L, Sims E, et al. Observational study comparing intranasal mometasone furoate with oral antihistamines for rhinitis and asthma. *Prim Care Respir J* 2010;19(03): 266–273
- 15 Pampura AN, Papadopoulos NG, Spičák V, Kurzawa R. Evidence for clinical safety, efficacy, and parent and physician perceptions of levocetirizine for the treatment of children with allergic disease. *Int Arch Allergy Immunol* 2011;155(04):367–378
- 16 Motola D, Donati M, Biagi C, et al. Safety profile of H1-antihistamines in pediatrics: an analysis based on data from Vigibase. *Pharmacoepidemiol Drug Saf* 2017;26(10):1164–1171
- 17 Chur V, Small CB, Stryszak P, Teper A. Safety of mometasone furoate nasal spray in the treatment of nasal polyps in children. *Pediatr Allergy Immunol* 2013;24(01):33–38
- 18 Afrime MB, Kosoglou T, Thonoor CM, Flannery BE, Herron JM. Mometasone furoate has minimal effects on the hypothalamic-pituitary-adrenal axis when delivered at high doses. *Chest* 2000; 118(06):1538–1546
- 19 Delgado-Rodríguez M, Llorca J. Bias. *J Epidemiol Community Health* 2004;58(08):635–641