

# The Effects of Antidepressants on the Results of Skin Prick Tests Used in the Diagnosis of Allergic Diseases

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## Key Words

Antidepressants • Asthma • Histamine reactivity • Rhinitis • Selective serotonin reuptake inhibitors • Skin prick test • Tricyclic antidepressants • Visual Analog Scale

## Abstract

**Background:** Some drugs may cause false negative results by suppressing the reactivity of the skin prick tests (SPTs). The aim of this survey was to show whether escitalopram, fluoxetine and sertraline had any effect on the reactivity of SPT. **Methods:** Twenty-four patients who were admitted to the outpatient clinic of the Psychiatry Department at the Hacettepe University Hospital and planned to be treated by these antidepressants were included in the study between May and October 2008. SPTs with positive control (histamine), negative control and 3 common aeroallergens were performed in the beginning, at the first and fourth weeks. A questionnaire including 26 questions about respiratory symptoms and allergic diseases was filled in face to face by the fellow-in-training. The Visual Analog Scale (VAS) of current respiratory and nasal symptoms was recorded at all 3 visits. **Results:** There were no statistically significant differences between the 3 mean diameters measured at 3 time points in addition to the mean diameters of the wheals between groups using escitalopram, sertraline and fluoxetine

( $p > 0.05$ ). There was a statistically significant decrease between the VAS of nasal symptoms at the 3 visits ( $p < 0.05$ ). **Conclusions:** Escitalopram, fluoxetine and sertraline do not seem to affect the reactivity of SPTs. Nasal symptoms might have been decreased due to both the allergic treatment suggested and the end of the pollen season.

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## Introduction

The skin prick test (SPT) is a widely used method for the determination of allergens which cause allergic diseases, the results of which can be influenced by the test technique used, application site, age, gender, race and the drugs used [1–6].

Some drugs are known to decrease the sensitivity of the skin. New- and old-generation antihistamines as well as tricyclic antidepressants (TCAs) can interfere with the results of SPTs. These characteristics of TCAs originate from their H<sub>1</sub> blocking effects. Several studies have investigated the duration of suppression on SPTs by these agents [3–8]. Nowadays, selective serotonin reuptake inhibitors (SSRIs) are used widely not only in depression, but also for many other reasons in the daily clinical practice of psychiatry. Although there are some controversial

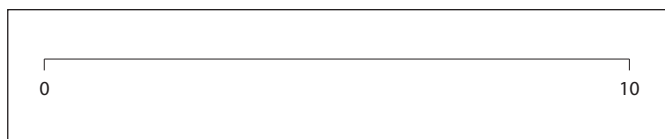


**Fig. 1.** Visual Analog Scale.

hypotheses, H<sub>1</sub> receptor-blocking features have been attributed to some of these agents [9–12]. Nowadays, the effect of these widely used drugs on SPTs has gained importance as a current problem. In our daily clinical practice decrease in histamine sensitivity was observed. There are no data about the suppressive effects of SSRIs on SPTs which are used widely nowadays. When all of these are taken into consideration, this study was planned to demonstrate the effect of SSRIs on SPTs.

## Material and Methods

The study was approved by the Ethics Committee of Hacettepe University. Twenty-four adult patients referred to the outpatient clinics of the Department of Psychiatry at the Hacettepe University Faculty of Medicine between May 2008 and October 2008 for any reason and started on antidepressant treatment (fluoxetine, escitalopram and sertraline) were enrolled in the study. Patients who used an antidepressant or antipsychotic within a year, new- or old-generation antihistamines within the last 10 and 3 days, respectively, and those who demonstrated dermatographism during allergy testing were excluded from the study, and enrolled patients were warned against usage of these drugs during the study. After the patients signed informed consent forms, a 26-item questionnaire (Appendix) about their allergic history was filled in face to face by the same fellow-in-training. Cases with history of allergy as well as those with respiratory and nasal symptoms at the onset of the study were evaluated using the Visual Analogue Scale (VAS). VAS has horizontal and vertical graded lines where the individual marks the severity of his/her symptoms [13]. One end of the scale represents absence of symptoms and the other end the most severe symptom (zero: absence of symptoms; 10 cm: severe symptoms) (fig. 1) [13]. Respiratory symptoms as dyspnea, cough, wheezing and tightness on chest, and nasal symptoms as sneezing, nasal discharge, nasal itching and congestion were evaluated. The patients were requested to mark the scale according to the severity of their symptoms.

SPTs were performed in the Adult Allergy Laboratory at the beginning, in the 1st and 4th weeks after starting on an antidepressant drug using negative and positive controls, and 3 aeroallergens which contained cat, *Dermatophagoides pteronyssinus* and *Phleum pratense*. Symptomatic patients with history of allergy who completed questionnaires at the beginning were requested to complete the questionnaire again at the 1st and 4th week, and then their symptoms were re-evaluated using VAS at each visit. The standard allergen solutions used for SPTs were pre-

**Table 1.** Demographic data and clinical characteristics of patients and the prevalence of allergic diseases according to the questionnaire

|                                                                | n = 24       | %    |
|----------------------------------------------------------------|--------------|------|
| Gender, female                                                 | 22           | 91.7 |
| Age, years                                                     | 39.7 ± 9.8   |      |
| Median age, years <sup>1</sup>                                 | 39.5 (22–60) |      |
| Smoking                                                        | 10           | 41.7 |
| Antidepressant drugs                                           | 24           | 100  |
| Fluoxetine                                                     | 12           | 50   |
| Escitalopram                                                   | 10           | 41.7 |
| Sertraline                                                     | 2            | 8.3  |
| Concomitant systemic diseases                                  | 14           | 54.2 |
| Concomitant allergic diseases                                  | 6            | 25   |
| Metal allergy                                                  | 6            | 25   |
| Asthma                                                         | 5            | 20.8 |
| Rhinitis                                                       | 4            | 16.7 |
| Food allergy                                                   | 3            | 12.5 |
| Drug allergy                                                   | 3            | 12.5 |
| Urticaria/Angioedema                                           | 1            | 4.2  |
| The prevalence of allergic diseases according to questionnaire |              |      |
| Allergic rhinitis <sup>2</sup>                                 | 13           | 54.2 |
| History of asthma                                              | 6            | 25   |
| Urticaria <sup>2</sup>                                         | 5            | 20.8 |
| Angioedema <sup>2</sup>                                        | 4            | 16.7 |
| Food allergy                                                   | 3            | 12.5 |
| Drug allergy                                                   | 3            | 12.5 |
| Eczema <sup>2</sup>                                            | 0            | 0    |

<sup>1</sup> Figures in parentheses represent the range.

<sup>2</sup> Current or past.

pared by Stallergen. Histamine (10 mg/ml) and glycerol solution with phenol were used as positive and negative controls, respectively. Testing was performed as mentioned in the position paper by EAACI [14]. At all 3 stages, tests were conducted by the same 3 healthcare technicians who have expertise on allergy tests. During the evaluation process, the largest diameter of the wheal (R<sub>1</sub>) and the second diameter intersecting the first one vertically at its midpoint (R<sub>2</sub>) were recorded separately. Arithmetic means [ $r = (R_1 + R_2)/2$ ] of these 2 measurements were calculated to find the mean diameter of the wheal, and a mean diameter of 3 mm and above was considered as positive reaction.

To demonstrate the effect of antidepressants, the new values of the wheal diameter formed in response to allergens and histamine were evaluated at each visit.

## Statistical Analyses

The data recorded were expressed as means, standard deviation, median and range of values for continuous variables, and as quantity and percentage for categorical variables. In the main comparison, the difference between arithmetic means of diameters of reactive wheal compared to histamine was recorded in various measurements. Serial changes in VAS assessment scores of

**Table 2.** Diameters and changes in diameters of wheals produced by histamine

|                                                                          | b             | 1w             | 4w             | p (b–1w) | p (b–4w) | p (b–1w–4w) |
|--------------------------------------------------------------------------|---------------|----------------|----------------|----------|----------|-------------|
| Diameter of wheal produced by histamine                                  |               |                |                |          |          |             |
| Mean $\pm$ SD, mm                                                        | 5.9 $\pm$ 1.0 | 6.1 $\pm$ 0.8  | 6.1 $\pm$ 0.9  | 0.27     | 0.25     | 0.42        |
| Median                                                                   | 5.6 (5; 8)    | 6 (5; 8)       | 6 (4; 8)       |          |          |             |
| Changes in the diameter of the wheals produced by histamine <sup>1</sup> |               |                |                |          |          |             |
| Mean $\pm$ SD, mm                                                        |               | –0.2 $\pm$ 1.1 | –0.3 $\pm$ 1.4 |          |          |             |
| Median                                                                   |               | 0 (–2; 2)      | 0 (–3; 8)      |          |          |             |

Figures in parentheses are minimum and maximum values.

<sup>1</sup> Changes from the beginning are provided. b = Beginning; 1w = 1st week; 4w = 4th week.

symptoms were also investigated. Changes between the beginning and the 1st and 4th week were also analyzed. Changes between the beginning, the 1st and 4th week were tested with a nonparametric multidependent variable test (Friedman test). In cases where statistically significant differences were found, the differences between beginning, 1st- and 4th-week measurements were evaluated with Wilcoxon test.  $p < 0.05$  was considered as statistically significant. For statistical analyses, SPSS 10.0 for Windows was used.

## Results

The demographic data and clinical characteristics of 24 patients included in the study and the prevalence of allergic diseases according to the questionnaire are given in table 1.

According to the results of SPTs, the dimensions of wheal produced by histamine measured at the beginning and at the end of the 1st and 4th week are shown in table 2. The measurements performed at the 3 visits did not detect any significant difference with respect to dimensions of wheal produced by histamine, and when the effect of each drug was evaluated separately, no statistically significant difference was noted between measurements performed in the beginning and at 1st and 4th week. The difference in the dimensions of wheal produced by histamine between the beginning and the 1st week was not statistically significant compared to the one found between the beginning and the 4th week. Results related to these differences are also shown in table 2. There were no statistically significant differences in the variations of the diameters of the wheal produced by histamine according to drugs (fluoxetine, escitalopram and sertraline;  $p > 0.05$ ).

Rates of positivity against *D. pteronyssinus* and *P. pratense* were found to be 4.1 and 8.3% (total positivity = 12.5%) in SPT, respectively. The inadequate number of

**Table 3.** The evaluation of respiratory and nasal symptoms with VAS

|                 | Median VAS <sub>b</sub> , cm | VAS <sub>1w</sub> cm | VAS <sub>4w</sub> cm | p (b–1w–4w) |
|-----------------|------------------------------|----------------------|----------------------|-------------|
| Dyspnea         | 4 (0–6)                      | 2 (0–4)              | 2 (0–4)              | 0.07        |
| Wheezing        | 2.5 (0–6)                    | 1 (0–6)              | 1.5 (0–6)            | 0.15        |
| Nasal symptoms  | 3 (0–10)                     | 1 (0–8)              | 1.5 (0–8)            | 0.04        |
| Chest tightness | 0.5 (0–1)                    | 0.5 (0–1)            | 0.5 (0–1)            | –           |
| Cough           | 2 (0–7)                      | 1 (0–5)              | 0.5 (0–8)            | 0.7         |

Figures in parentheses are ranges. b = Beginning; 1w = 1st week; 4w = 4th week.

the positivity in SPT with aeroallergens precluded statistical analysis.

VAS was performed on patients describing dyspnea ( $n = 5$ ), nasal symptoms as sneezing, rhinorrhea and nasal stuffiness ( $n = 8$ ), wheezing ( $n = 3$ ), and chest tightness ( $n = 1$ ). The results of VAS are shown in table 3. When VAS scores were compared, only nasal symptoms recorded at the beginning, and at the 1st and 4th week decreased statistically significantly.

## Discussion

Various factors, including the technique used for this test, application area on the skin, timing of the test, age, gender and race of the subject, as well as concomitant drugs used at the time of testing can affect the results of SPTs. Various drugs can suppress skin reaction that will be induced by histamine and allergens, and thus affect potential wheal and erythema formation. This phenomenon consequently complicates the evaluation of the test

which necessitates investigation of concomitant drugs used during and before the test in daily allergy practice. Antihistamines, ketotifen, local skin preparations, some antidepressants, prominently TCAs, are the drugs which may affect sensitivity of SPT [3–5, 7, 8].

Four types of histamine receptors, H<sub>1</sub>, H<sub>2</sub>, H<sub>3</sub> and H<sub>4</sub>, are known to date. Interaction of histamine with the H<sub>1</sub> receptor causes early onset immunologic reactions. This receptor is found in nerve cells, airway and vascular smooth muscles, hepatocytes, endothelial and epithelial cells, neutrophils, eosinophils, monocytes, dendritic cells, as well as T and B lymphocytes [15]. Some drugs affecting SPT show their effects by binding to histamine receptors. When antihistamines are used at the time of testing, they block H<sub>1</sub> receptors, suppress wheal and flare responses, and interfere with SPT reactivity leading to false negative results [16].

Though there are various different views about affinity of SSRIs to histamine receptors, data is lacking on their effects on SPT [8–12]. The objective of this study was to investigate the variations induced by SSRIs whose effects we have partially observed in daily allergy practice on sensitivity to SPT. For this aim SPT was applied to patients for whom antidepressant therapy was planned to begin mostly with fluoxetine and escitalopram, before the initiation of drug therapy, at the 1st and 4th week when antidepressants were expected to exert their efficacy. In this study a significant decrease in histamine sensitivity, that is, in the diameter of wheal, was not detected at the 1st week and at the end of the 4th week.

Some studies suggest that some frequently used SSRIs such as citalopram, escitalopram and fluoxetine have lower H<sub>1</sub>-blocking effects, however, others, though controversial, assert that they have these characteristics [9–12]. Our study drug fluoxetine which belongs to this group has statedly lower H<sub>1</sub> affinity compared with escitalopram [11, 12]. It was observed that these 2 drugs did not affect the diameter of wheal induced by histamine in SPT, and there was no significant difference between the drugs according to the diameter of the wheal.

It was demonstrated that doxepine, which is a TCA, inhibited wheal produced by histamine [17]. In a study performed with TCAs, during a 7-day follow-up period, doxepine and desipramine were compared with respect to their duration of suppression of histamine sensitivity, and doxepine was found to suppress histamine sensitivity for longer periods. Since any significant change in the diameter of wheal did not occur in this study it can be concluded that the duration of SSRI therapies does not influence the results of SPT testing.

In studies performed with drugs affecting SPT results, placebo or antihistamines were used as controls and applied either as single doses or during 5–7 days [8, 18]. In a study conducted with doxepine, healthy individuals were enrolled in the study, while in trials with montelukast and ranitidine, cases with pollen allergies were enrolled [8, 18, 19]. In the present study, patients with an established indication for antidepressant usage who did not receive the drug were included, and the patients themselves were used as controls. In this study the positive control dose was 10 mg/ml, while in other studies a dose of 1.7 mg/ml had been used. In our survey, tests were repeated using the same laboratory, technique, standard solutions and laboratory team to prevent technical factors from interfering with the sensitivity of tests. During the study period the patients were warned against use of antihistamines which might affect the results of SPT.

It was observed that age did not effect changes in arithmetic means of wheal produced by histamine. The majority of the study group were females. In adult populations psychiatric and allergic diseases are more frequently seen in women [20–22]. For the cases in this study, antidepressants were indicated because of depression and other psychiatric etiologies, and some of them had been followed-up for allergic diseases. The higher number of female patients might be attributed to these etiologic factors.

Although application of VAS requires a patient's compliance and longer explanations, it is used in many fields, especially related to pain [23]. It is used widely in diseases of allergy in order to evaluate the severity of rhinitis and treatment efficacy [24, 25]. According to the results of VAS used in this study, only nasal symptoms of 3 measurements differed significantly. Since these cases had a history of allergy and treatment had already been recommended, it was thought that this improvement could not be attributed to antidepressants only. This study started in May and ended in October, which is the end of the pollen season, which might be another explanation for the decrease in the severity of symptoms.

In conclusion, this study suggests that fluoxetine and escitalopram do not affect sensitivity to SPT or at least have no blocking effects on histamine receptors of the skin. Since only 2 cases used sertraline, it is not appropriate to arrive at a definite conclusion, however, in these 2 cases no effect was observed. It can be concluded that withdrawal of fluoxetine and escitalopram before SPT is not required. In addition to fluoxetine, escitalopram and sertraline, it is necessary to investigate other SSRIs whose associations with H<sub>1</sub> receptors are not clearly defined.

## Appendix

### Questionnaire

- 
- 1 During the last 12 months, have you noticed for any reason wheezing, whistling sounds or murmurs coming from your chest?  
☐ yes ☐ no  
If your answer is 'No' go to question 2, and if 'Yes' proceed with 1a.
- 1a At that time have you felt any shortness of breath associated with sounds coming from your chest?  
☐ yes ☐ no
- 1b Have you ever heard these sounds when you were not suffering from viral infection of the upper respiratory system or flu?  
☐ yes ☐ no
- 2 During the last 12 months have you ever awakened at night from your sleep with tightness and/or squeezing sensation on your chest?  
☐ yes ☐ no
- 3 During the last 12 months have you ever awakened at night from your sleep with shortness of breath?  
☐ yes ☐ no
- 4 During the last 12 months have you ever awakened at night from your sleep with cough?  
☐ yes ☐ no
- 5 During the last 12 months have you ever had an asthmatic attack?  
☐ yes ☐ no
- 6 Are you using any antiasthmatic drug (tablet, syrup, spray, suppository)?  
☐ yes ☐ no
- 7 Have you had perennial allergic rhinitis lasting all year long or seasonal allergic rhinitis occurring during the spring/summer months?  
☐ yes ☐ no  
If your answer is yes;  
Perennial rhinitis: ☐ yes ☐ no  
Seasonal hay fever: ☐ yes ☐ no  
Age at onset: \_\_\_\_\_  
Treatment: \_\_\_\_\_ Surgical: \_\_\_\_\_  
Medical: \_\_\_\_\_
- 8 During the last 12 months, have you ever had a pet at your home?  
☐ yes ☐ no  
If your answer is yes then specify \_\_\_\_\_
- 9 Previously, when you were a child, have you ever had a house pet at your home?  
☐ yes ☐ no  
If your answer is yes, then specify: \_\_\_\_\_
- 10 Are you a current smoker? (If you quit smoking within the last year or smoke cigarettes or cigars only a few times a week, check 'Yes'. The World Health Organization considers a regular smoker of one cigarette a day as an addict.)  
☐ yes ☐ no
- 11 Have you had any eczemas on your knee(s) and/or elbow(s)?  
☐ yes ☐ no  
If yes, state age at onset: \_\_\_\_\_
- 12 Have you ever had eczemas on your knee(s) and/or elbow(s)?  
☐ yes ☐ no  
If yes, at what age did it resolve? \_\_\_\_\_
- 13 Have you had an eczema on any other region of your body?  
☐ yes ☐ no  
If present, where? \_\_\_\_\_
- 14 Have you ever had an asthmatic disease up to a year from now?  
☐ yes ☐ no  
Age at onset: \_\_\_\_\_  
At what age did it resolve? \_\_\_\_\_
- 15 Have you ever felt that you had allergic reaction against any food (sudden swelling on your lips and tongue, sudden onset of rhinitis/ sneezing/stuffy nose, shortness of breath, wheezing, sudden onset of itching and swellings, fainting etc.)?  
☐ yes ☐ no
- 16 If you ever had such a reactive disorder, what was the responsible food? \_\_\_\_\_
- 17 Have you ever had an allergy against any drug?  
☐ yes ☐ no  
Age at onset: \_\_\_\_\_
- 18 If you have a drug allergy, do you remember the name and category of this drug (i.e.: penicillin, aspirin, pain reliever, antibiotics etc.)? \_\_\_\_\_
- 19 Does any particular tree, flower or grass pollen (flower powder) make you feel uncomfortable?  
☐ yes ☐ no
- 20 Have you had any known allergies against animals like cats, dogs, horses, rabbits, and birds? ☐ yes ☐ no
- 21 If you have asthma, have you been using your medications for at least 2 weeks before? ☐ yes ☐ no
- 22 If you have perennial rhinitis lasting a year or allergic rhinitis during pollen seasons only, have you been using your drugs for at least 2 weeks before?  
☐ yes ☐ no
- 23 If you have eczema, have you been using your drugs for at least 2 weeks before? ☐ yes ☐ no
- 24 Have your mother, father and siblings had asthma, chronic (continuous) bronchitis, skin eczema, perennial rhinitis or seasonal hay fever?  
☐ yes ☐ no  
If yes, who had which disorder?
- 25 Have you ever had hives (sudden onset of itching, swelling, rashes and blisters)? ☐ yes ☐ no  
Age at onset: \_\_\_\_\_  
Are you still suffering from it?  
☐ yes ☐ no
- 26 Have you ever had swelling on your lips and tongue?  
☐ yes ☐ no  
At what age?: \_\_\_\_\_  
Are you still suffering from it?
-

## References

- 1 Averbeck M, Gebhardt C, Emmrich F, Treudler R, Simon JC: Immunologic principles of allergic disease. *J Dtsch Dermatol Ges* 2007;1015–1028.
- 2 Kay AB: Allergy and allergic diseases. *N Engl J Med* 2001;344:33–37.
- 3 Demoly P, Piette V, Bousquet J: In vivo methods for study of allergy skin tests, techniques, and interpretation; in Middleton EJ, Reed CE, Ellis Ef, Adkinson NF Jr, Yunginger JW, Buse W (eds): *Allergy: Principles and Practice*, ed 5. St. Louis, Mosby Year Book, 2003, pp 631–642.
- 4 Dreborg S: Methods for skin testing. *Allergy* 1989;44(suppl 10):22–30.
- 5 Nelson HS: Variables in allergy skin testing. *Allergy Proc* 1994;15:265–268.
- 6 Bordignon V, Burastero SE: Age, gender and reactivity to allergens independently influence skin reactivity to histamine. *J Invest Allergol Clin Immunol* 2006;16:129–135.
- 7 Li JT: Allergy testing. *Am Fam Physician* 2002;66:621–624.
- 8 Rao KS, Menon PK, Hilman BC, Sebastian CS, Bairnsfather L: Duration of the suppressive effect of tricyclic antidepressants on histamine induced wheal and flare reactions in human skin. *J Allergy Clin Immunol* 1988;82:752–757.
- 9 Baumann P: Pharmacology and pharmacokinetics of citalopram and other SSRIs. *Int Clin Psychopharmacol* 1996;11(suppl 1):5–11.
- 10 Gupta MA, Gupta AK: The use of antidepressant drugs in dermatology. *J Eur Acad Derm and Vener* 2001;15:512–518.
- 11 Carrasco JL, Sandner C: Clinical effects of pharmacological variations in selective serotonin reuptake inhibitors: an overview. *Int J Clin Pract* 2005;59:1228–1234.
- 12 Owens MJ, Knight DL, Nemeroff CB: Second-generation SSRIs: Human monoamine transporter binding profile of escitalopram and R-Fluoxetine. *Biol Psychiatry* 2001;50:345–350.
- 13 Wewers ME, Lowe NK: A critical review of visual analogue scales in the measurement of clinical phenomena. *Res Nurs Health* 1990;13:227–236.
- 14 Position paper: Allergen standardization and skin tests. The European Academy of Allergology and Clinical Immunology. *Allergy* 1993;48(14 suppl):48–82.
- 15 Jutel M, Blaser K, Akdis CA: Histamine in chronic allergic responses. *J Invest Allergol Clin Immunol* 2005;15:1–8.
- 16 Almind M, Dirksen A, Nielsen NH, Svendsen UG: Duration of the inhibitory activity of histamine-induced skin wheals of sedative and non-sedative antihistamines. *Allergy* 1988;43:593–596.
- 17 Sullivan TJ: Pharmacologic modulation of the whealing response to histamine in human skin: identification of doxepine as a potent in vivo inhibitor. *J Allergy Clin Immunol* 1982;69:260–267.
- 18 Kupczyk M, Kupryś I, Bocheńska-Marciniak M, Górski P, Kuna P: Ranitidine (150 mg daily) inhibits wheal, flare, and itching reactions in skin-prick tests. *Allergy Asthma Proc* 2007;28:711–715.
- 19 Kupczyk M, Kupryś I, Górski P, Kuna P: The effect of montelukast (10mg daily) and loratadine (10 mg daily) on wheal, flare and itching reactions in skin prick tests. *Pulm Pharmacol and Ther* 2007;20:85–89.
- 20 Vesga-López O, Schneier FR, Wang S, Heimberg RG, Liu SM, Hasin DS, Blanco C: Gender differences in generalized anxiety disorder: results from the national epidemiologic survey on alcohol and related conditions (NESARC). *J Clin Psychiatry* 2008;69:1606–1616.
- 21 Regitz-Zagrosek V, Schubert C, Krüger S: Gender differences in psychopharmacology. *Internist (Berl)* 2008;49:1516–1519.
- 22 Chen W, Mempel M, Schober W, Behrendt H, Ring J: Gender difference, sex hormones, and immediate type hypersensitivity reactions. *Allergy* 2008;68:1418–1427.
- 23 Price DD, McGrath PA, Rafii A, Buckingham B: The validation of visual analog scales as ratio scale measures for chronic and experimental pain. *Pain* 1983;17:45–56.
- 24 Bousquet J, Lund VJ, Van Cauwenberge P, Bremard-Oury C, Mounedji N, Stevens MT, El-Akkad T: Implementation of guidelines for seasonal allergic rhinitis: a randomized controlled trial. *Allergy* 2003;58:733–741.
- 25 Bousquet PJ, Combescure C, Neukirch F, Klossek JM, Méchin H, Daures JP, Bousquet J: Visual analog scales can assess the severity of rhinitis graded according to ARIA guidelines. *Allergy* 2007;62:367–372.