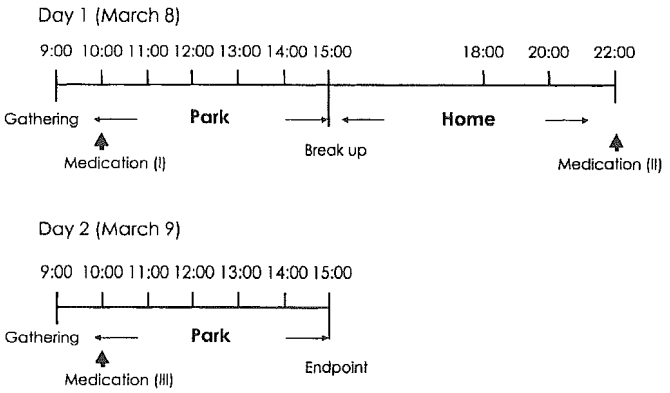

Figure 1. Study sequence. Nasal symptom scores and Japanese version of the Rhinoconjunctivitis Quality of Life Questionnaire scores were recorded before administration of the study agents at 10 AM on day 1.

and placebo were administered for 2 days to clarify the early effects on suppression of nasal symptoms, as evaluated by total symptom scores, and on improvement in scores on the Japanese version of the RQLQ (JRQLQ).

PARTICIPANTS AND METHODS

Participants

Eighty-five men and 92 women were recruited to the study from the general public through the Clinical Research Center of Osaka Medical College. For inclusion, individuals had to experience moderate or worse nasal symptoms of SAR between February and April 2002 and had to exhibit Japanese cedar specific IgE. Individuals with upper respiratory tract infections and sinusitis were excluded. Finally, 52 men and 61 women aged 20 to 57 years (mean, 34 years) were selected. All the participants resided in Osaka. Informed consent was obtained from each patient before entry into the study, which was approved by the ethics committee of Osaka Medical College.

Study Agents

Patients were randomly assigned to receive cetirizine hydrochloride, 10 mg daily; fexofenadine hydrochloride, 120 mg daily (administered as two 60-mg doses); loratadine, 10 mg daily; or placebo (lactose), twice daily. The medication doses used in this study are the standard daily doses used in Japan. All test agents, including placebo, were prepared at the Department of Pharmacologic Research Graduate School, Nihon University (Funabashi, Japan). Patients were not allowed to take any antiallergic agents beginning 3 days before the start of the study. However, the use of clemastine fumarate as a rescue drug was permitted on an as-needed basis between 3 PM and midnight on the first day of the study. Patients were instructed not to use antiasthma medications, antibiotics, H_1-antagonists, or decongestants for the duration of the study.

Methods

This was a 2-day, randomized, double-masked, parallel-group study conducted during the peak of the Japanese cedar pollen season (March 8 and 9, 2003) at Osaka Expo Park. The study sequence is outlined in Figure 1. All eligible patients visited the study site at 9 AM on day 1 and were questioned concerning their nasal symptoms and QOL during the baseline period. Individuals were given the first dose of study agent at 10 AM, and then they were asked to walk around the park without wearing a hat or cap, accompanied by a guide. Patients recorded their symptoms in diaries hourly between 11 AM and 3 PM while in the park and at 6, 8, and 10 PM at home. Individuals in the fexofenadine group took their second dose of fexofenadine and the others took placebo at 10 PM.

The next morning, all the patients returned to the park and took their third dose of study medication, including placebo, at 10 AM. Patients were then asked to complete their nasal symptom diaries hourly between 10 AM and 3 PM in the park. At the end of the study, patients completed their second JRQLQ.

Recording and Assessing Symptoms and QOL

The numbers of paroxysmal sneezes and occasions when patients blew their noses were recorded on nasal symptom forms. Nasal congestion, nasal itching, eye itching, and watering of the eyes were recorded on an analog scale from 0 (none) to 10 (very severe). In addition, QOL was surveyed in accordance with the JRQLQ.[7] This questionnaire includes 17 questions in 6 domains designed to measure the effects of rhinoconjunctivitis symptoms on disease-specific QOL. The JRQLQ was developed from the original 28-item RQLQ with permission from the Japan Academic Association for Copyright Clearance (Tokyo, Japan) and the Copyright Clearance Center Inc (Danvers, MA). An overall JRQLQ score was computed by taking the mean scores of the 17 items in the instrument; scores, therefore, ranged from 0 to 4, with higher scores indicating poorer QOL, which is different from the original RQLQ (7-point scale from 0 to 6).[7]

Airborne Japanese Cedar Pollen Count

A Durham pollen collector[8] was set up in the park to measure the amount of pollen during the study. In addition, the amount of airborne pollen in Osaka was measured at 8 locations on the study days.

Statistical Methods

Nasal symptom scores at 10 AM on day 1 in the 4 treatment groups were compared using the Tukey test. Baseline comparability of the 4 groups was analyzed using longitudinal analysis of variance. Evaluation of change in QOL status between baseline and the end of the study in each group was compared using the Wilcoxon signed rank test. Comparisons among the 4 groups were made using nonparametric methods (Mann-Whitney U test).

RESULTS

Participants

Seven individuals did not participate because of sickness on the study days. Background characteristics of the study groups are given in Table 1. No significant differences were observed among the 4 groups in terms of the number of

Table 1. Patient Background Characteristics

	Treatment group			
	Cetirizine (n = 30)	Fexofenadine (n = 28)	Loratadine (n = 28)	Placebo (n = 27)
Sex, No.				
Male	14	13	14	11
Female	16	15	14	16
Age, mean, y	34.1	34.1	32.5	34.6
Total symptom score, mean	12.1	11.7	10.0	12.3
Overall QOL score, mean	1.11	1.12	0.94	1.18

Abbreviation: QOL, quality of life.

paroxysmal sneezes, the number of times patients blew their noses, nasal congestion, nasal itching, eye itching, and watering of the eyes before administration of the study agents at 10 AM on day 1 (Table 2).

Airborne Japanese Cedar Pollen Count

The mean pollen counts at 8 facilities located in different areas of Osaka were 43.6 grains/cm^2 on day 1 and 40.9 grains/cm^2 on day 2. At Osaka Expo Park, the mean pollen counts were 34 grains/cm^2 between 9 AM and 3 PM on day 1 and 18 grains/cm^2 during the morning of day 2.

Changes in Symptom Scores

Reduction rates of mean values of total symptoms recorded by patients at all times by drug group are shown in Figure 2. Cetirizine use produced a 45% to 48% mean reduction in total

Table 2. Changes in Rhinoconjunctivitis Symptom Scores During the Study

Date and time	Change in symptom score						
	Sneeze	Nose blow	Stuffiness	Nasal itch	Eye itch	Eye watering	Total
			Cetirizine Group				
March 8							
10:00	0.50	1.63	2.79	2.15	2.75	2.26	**12.08**
12:00	0.13	0.63	1.49	1.16	1.85	0.99*	**6.25**
15:00	0.66*	1.20	1.78*	1.37	1.74*	1.32*	**8.07**
March 9							
12:00	0.03	0.80	2.21*	1.03	1.51*	1.14*	**6.72**
15:00	0.26*	0.83	1.93*	0.98	2.27*	1.19*	**7.46**
			Fexofenadine Group				
March 8							
10:00	0.61	1.18	2.66	2.79	2.88	1.60	**11.72**
12:00	0.07	0.36	1.49	1.37	1.79	0.90*	**5.98**
15:00	0.25*	1.43	2.11	1.69	2.12*	1.39*	**8.99**
March 9							
12:00	0.21	0.71	2.68	1.70	2.25	1.12*	**8.67**
15:00	0.25*	1.14	2.91	1.88	1.65*	0.82*	**8.65**
			Loratadine Group				
March 8							
10:00	0.82	1.21	1.88	1.91	2.37	1.82	**10.01**
12:00	0.36	0.64	1.80	1.80	1.70	0.92*	**7.22**
15:00	1.43	1.43	2.41	2.75	2.58	1.60*	**12.20**
March 9							
12:00	0.29	0.61	2.01*	1.94	1.33*	0.74*	**6.92**
15:00	0.75	0.82	2.09	1.73	1.56*	0.96*	**7.91**
			Placebo Group				
March 8							
10:00	0.67	1.29	2.77	2.19	2.87	2.52	**12.31**
12:00	0.15	0.74	2.41	1.81	2.56	2.34	**10.01**
15:00	2.14	2.14	3.48	2.66	4.03	3.70	**18.15**
March 9							
12:00	0.48	1.04	3.98	2.02	3.33	2.59	**13.44**
15:00	1.00	1.78	4.11	2.61	4.05	2.58	**16.13**

* $P < .05$ compared with baseline.

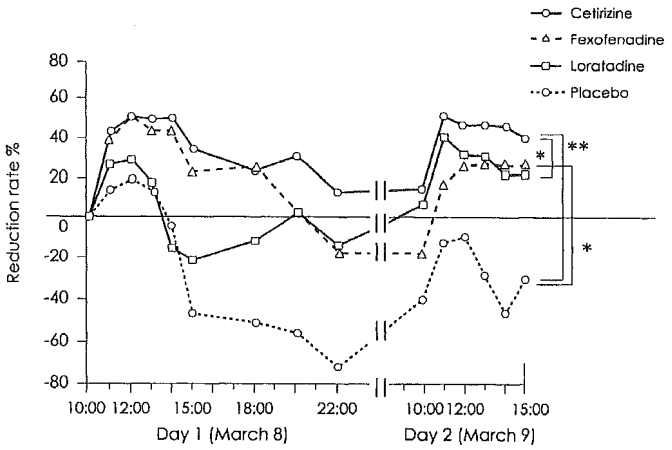

Figure 2. Mean hourly reductions in total symptom scores vs baseline. Asterisk indicates $P < .05$ (cetirizine vs loratadine and fexofenadine vs placebo); double asterisk, $P < .01$ (cetirizine vs placebo).

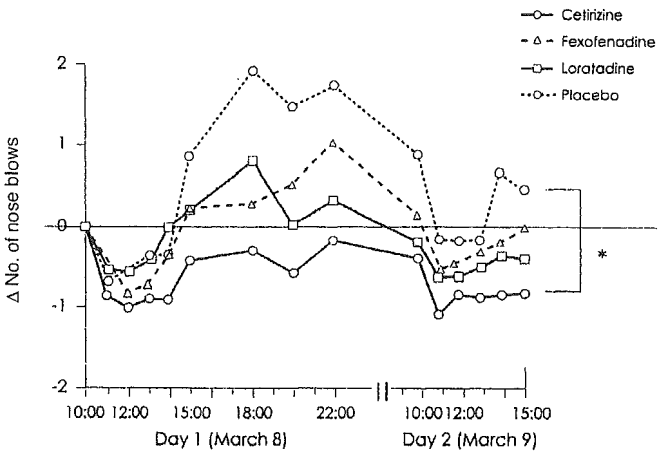

Figure 3. Change in the number of nose blows from baseline. Asterisk indicates $P < .05$ (cetirizine vs placebo).

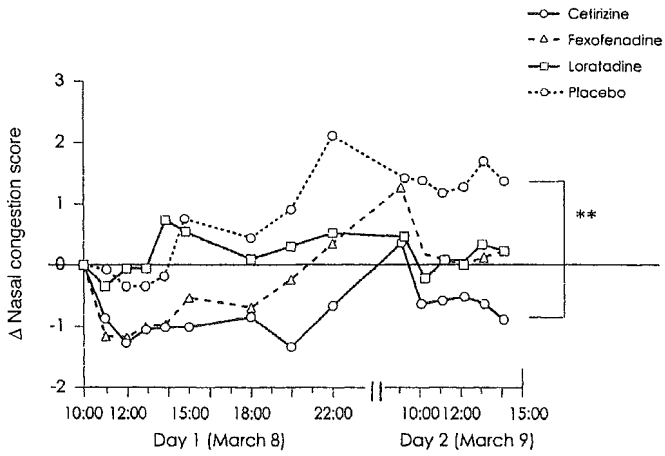

Figure 4. Change in visual analog scale scores for nasal congestion. Double asterisk indicates $P < .01$ (cetirizine vs placebo).

symptom scores compared with baseline 1 to 3 hours after administration on both days (Table 2). Mean percentage reductions with cetirizine use were consistently larger than those with fexofenadine, loratadine ($P = .04$), and placebo ($P = .006$) use.

Fexofenadine use produced a 42% to 48% mean reduction in total symptom scores within 1 to 3 hours of administration on day 1, but the reduction rate on day 2 was much lower than that observed on day 1 (Table 2). However, fexofenadine therapy significantly reduced total symptom scores compared with placebo use ($P = .04$). Loratadine use produced no significant reductions in total symptom scores overall compared with placebo use, although a 30% to 40% mean reduction was observed in this group on day 2 (Table 2). The effect of the first dose of loratadine on nasal symptoms disappeared within 4 hours on day 1. However, the second administration of loratadine continued to suppress nasal symptom through 3 PM on day 2.

The checkpoint analysis obtained at 3 PM on day 1 showed greater reductions in total symptom scores with cetirizine (34.0%; $P = .001$ vs baseline) and fexofenadine (22.8%; $P = .03$ vs baseline), whereas loratadine (−21.9%) and placebo (−47.5%; $P = .008$) showed significant increases compared with baseline. Similarly, the end point analysis obtained at the end of the study revealed the greatest reductions in total symptom scores in the cetirizine group (38.9%; $P = .005$ vs baseline), followed by the fexofenadine (25.9%) and loratadine (20.9%) groups. Aggravation of symptoms was noted in the placebo group. Total symptom scores in the 4 groups at 4 checkpoints are given in Table 2.

Group Comparisons by Symptom

Each symptom was compared at all times in the 4 groups. Cetirizine therapy significantly reduced the number of times the nose was blown (Fig 3) and nasal congestion (Fig 4) relative to placebo use and suppressed nasal itching more than loratadine and placebo use (Fig 5). Fexofenadine therapy was significantly more effective at reducing nasal itching than was placebo use. The 3 active treatments were better than placebo use in terms of reducing sneezing, eye itching, and eye watering. No differences were observed among the 3 active treatment groups in reducing these symptoms.

The onset of action of cetirizine, fexofenadine, and loratadine was observed as a reduction in eye watering within 2 hours of administration. Sneezing and eye itching in the cetirizine and fexofenadine groups and nasal congestion in the cetirizine group were significantly reduced compared with in the placebo group at 3 PM on days 1 and 2. Loratadine therapy significantly reduced nasal congestion and eye itching compared with placebo use at midnight on day 2 (Table 2).

Use of Rescue Drug

The use of rescue drug in the cetirizine, fexofenadine, loratadine, and placebo groups was calculated to be 7% (2/30),

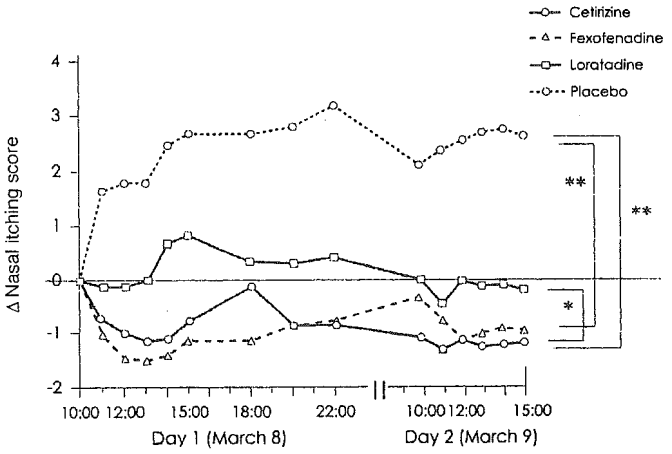

Figure 5. Changes of visual analog scale scores for nasal itching. Asterisk indicates $P < .05$ (cetirizine vs loratadine); double asterisk, $P < .01$ (cetirizine vs placebo and fexofenadine vs placebo).

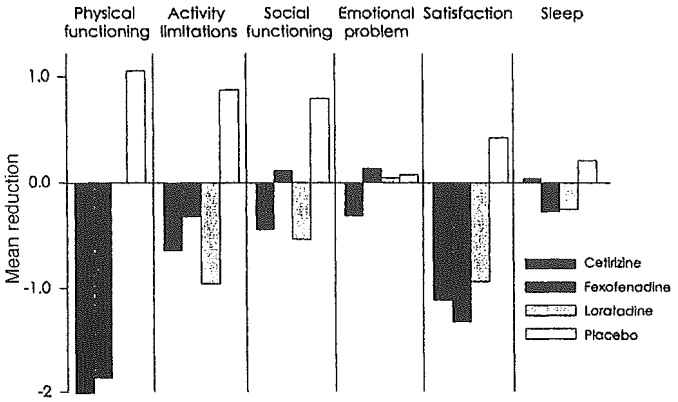

Figure 6. Mean reductions in 6 item scores in the Japanese version of the Rhinoconjunctivitis Quality of Life Questionnaire during the double-masked study with the administration of cetirizine, fexofenadine, loratadine, or placebo.

18% (5/28), 21% (6/28), and 22% (6/27), respectively. Although use of rescue medication was not statistically different among the 4 groups, use in the cetirizine group was markedly lower than that in the other groups. The use of clemastine as a rescue drug decreased total symptom scores for several hours. The time of peak plasma concentration after a single oral administration of clemastine was 3 hours. The rescue drug was administered on day 1 to 2 patients in the cetirizine group (at 4:35 PM or 11:20 PM), 5 patients in the fexofenadine group (at 3:05 PM, 3:15 PM, 5:00 PM, 8:30 PM, or 12:00 AM), 6 patients in the loratadine group (at 3:05 PM, 3:15 PM, 4:00 PM, 11:00 PM, 11:00 PM, or 12:55 AM), and 6 patients in the placebo group (at 3:00 PM, 3:30 PM, 4:30 PM, 5:15 PM, 11:15 PM, or 12:00 AM). The effect of clemastine therapy may have disappeared by morning (10 AM) on day 2. If clemastine use was still effective at the beginning of day 2, a reduction in nasal symptom scores would have been expected in the fexofenadine, loratadine, and placebo groups. However, only patients in the cetirizine group showed a significant improvement.

Changes in QOL Scores

No significant differences were observed in total QOL scores in the 4 study groups at baseline (Table 1). At the end of the study, overall QOL was significantly improved from baseline in all 3 active treatment groups, whereas patients in the placebo group exhibited significant QOL impairment. Reductions in mean total QOL scores at the end of the study were 24.7%, 19.3%, 33.2%, and −12.9% in the cetirizine, fexofenadine, loratadine, and placebo groups, respectively. No differences in QOL scores were observed among the 3 active treatment groups at the end of the study.

Observed changes in each of the 6 domains of the JRQLQ are shown in Figure 6. Administration of cetirizine on days 1 and 2 led to significant improvement in 3 items of physical functioning, 2 of activity limitations, and 1 of satisfaction with treatment compared with baseline. Administration of fexofenadine produced significant improvement in 2 items of physical functioning, 2 of activity limitations, and 1 of satisfaction. Administration of loratadine produced significant improvement in 1 item each of activity limitations and satisfaction.

Safety

All study medications were well tolerated. No serious adverse effects were reported during the study. The most frequently reported adverse effect was drowsiness, experienced by 7 participants (2 each in the cetirizine, fexofenadine, and loratadine groups and 1 in the placebo group).

DISCUSSION

The purpose of this study was to compare the efficacy, with special focus on the onset of action, and safety of cetirizine, fexofenadine, and loratadine vs placebo in Japanese patients with JCP. The results suggest that cetirizine is the most effective of these medications overall given its ability to suppress individual symptoms, improve JRQLQ scores in several domains, and reduce the need for rescue medication.

Second-generation oral antihistamines are believed to act fast. Pharmacokinetic studies of the 3 drugs used in this study demonstrate rapid absorption rates after single and multiple oral doses. Times to peak plasma concentration after single oral administrations of cetirizine, fexofenadine, and loratadine are 1, 2, and 1.4 to 1.6 hours, respectively.[9] Oral antihistamines have been demonstrated to be highly effective against eye symptoms occurring when pollen counts are high.[10–14] In the present study, a significant reduction in eye watering was found within 2 hours of administration of the first dose in all 3 active treatment groups. Antihistamines have also been reported to be highly effective against paroxysmal sneezing and nasal discharge as well as eye and nasal itching in general.[10–14] However, in the present study, only

cetirizine suppressed sneezing, nasal discharge, and nasal itching compared with placebo.

There is little reported effect of these drugs on nasal congestion. However, we demonstrated that cetirizine therapy significantly decreases nasal congestion compared with placebo use. This finding may be supported by indirect evidence; for example, it has been shown that administration of cetirizine in patients with allergic rhinitis results in a significant decrease in serum RANTES (regulated upon activation, normal T-cell expressed, and secreted), a major chemoattractant protein for eosinophils, and MCP-1.[15] Furthermore, eosinophil infiltration was significantly reduced by cetirizine treatment in patients with SAR after allergen-specific challenge.[16] In vitro, cetirizine has been shown to inhibit eotaxin-induced eosinophil transendothelial migration.[17] Furthermore, administration of cetirizine in mice reduced not only interleukin 4 (IL-4) and IL-5 expression but also eosinophil infiltration in nasal mucosa.[18] These results seem to support the effect of cetirizine on the improvement in nasal congestion observed in this study.

Intercellular adhesion molecule 1 is a transmembrane glycoprotein that promotes adhesion in inflammatory reactions. All 3 antihistamines reduce the expression of intercellular adhesion molecule 1 on epithelial cell membranes, as shown by in vitro[19,20] and in vivo[21] studies. Fexofenadine and loratadine possess anti-inflammatory properties. Treatment with fexofenadine in vitro reduces the eosinophil-induced release of IL-8 and granulocyte-macrophage colony-stimulating factor from human nasal epithelial cells[22] and inhibits the production of IL-4 and thymus- and activation-regulated chemokine by human peripheral blood lymphocytes.[23] In addition, fexofenadine treatment of sensitized mice in vivo prevented tissue eosinophilia and T_H2 cytokine production.[24]

Loratadine treatment inhibited histamine-induced P-selectin expression and IL-6 and IL-8 secretion by human endothelial cells.[25] Incubation of loratadine in vitro attenuated the nitric oxide–induced release of RANTES by human bronchial epithelial cells[26] and leukotriene B4 production by neutrophils.[27] However, the effects of fexofenadine and loratadine on nasal congestion were not found. This result might be due to the medication period. It is possible that prolonged administration of fexofenadine and loratadine results in a more comfortable nasal passage.

Natural exposure to an allergen by walking in a park is a clinical research method first used by Meltzer et al.[10] The obvious advantage of this method is that it replicates the real-life situation of patients with pollinosis. However, a disadvantage is that the drug effects can only be evaluated for short durations. The main concerns in the present study were the weather and the amount of airborne pollen. Average amounts of airborne pollen for the time of year were present (90 grains/cm^2 for >2 days). Consequently, sufficient natural exposure for assessing this study was obtained. A characteristic of JCP is that it can easily be aggravated owing to Japan's long pollen season and the large amount of airborne pollen. Nonetheless, in terms of treatment planning, screening of fast-acting drugs is an extremely important point of clinical research. In this regard, cetirizine's onset of action occurred at 1 hour, and maximum effects were seen at 2 hours, suggesting that cetirizine is a highly useful antihistamine for patients with JCP.

Recently, environmental exposure units have been used not only to provide constant exposure to pollen but also, more accurately, to determine experimental conditions rather than going outdoors during the peak pollen season.[28,29] Although innovations in outdoor park study design and methods have proved successful in the rating of antihistamines, environmental exposure units provide reproducible exposure environments for testing at any time. The onset of action and the efficacy of cetirizine therapy observed in this study are consistent with those observed in other multidrug comparative studies[28,29] using environmental exposure units and park tests.

Improving patient well-being and health-related QOL is widely recognized as an important goal in the treatment of patients with JCP. Cetirizine therapy provided the greatest number of improved items in the JRQLQ. The 3 antihistamines tested in this study provided safe and effective symptomatic relief, as shown by JRQLQ scores. Although moderate correlations between symptom severity and RQLQ score have been found in several studies,[30–32] the nasal symptom score may be more sensitive than the JRQLQ score to compare the effectiveness of anti-JCP medications in short-term studies. One reason is the duration of such studies; reliable improvement in the QOL score usually requires 1 or more weeks of treatment.[33] Another reason apparently is problems of recording symptoms using the visual analog scale used in the JRQLQ, at least in our study population. Similar studies conducted in Japanese patients using the original RQLQ, with scores ranging from 0 to 7, suggested that these patients hesitated to check the mark. Therefore, we reduced the range to 0 to 4 for the JRQLQ used in this study. Total score represented as a number seems easier for Japanese patients.

Ranking of antihistamines is important for patients with JCP and physicians in primary care. We rank cetirizine as having the best effectiveness, followed by fexofenadine and then loratadine. This supports the trend already observed by other research groups.[10,11,13,14,28,29] It is possible that in the present study the duration was too short to observe benefits in the loratadine group. However, it has been reported that cetirizine performed better than loratadine in a 7-week, double-masked study, although the results were not significant.[34] Several other reports have found that cetirizine is superior to loratadine in the suppression of nasal symptoms in patients with SAR.[10,11,28,29] In Europe, it has been reported that there are no differences in efficacy between fexofenadine and cetirizine in patients with SAR.[35,36] Furthermore, fexofenadine has been demonstrated to be significantly more effective than loratadine in relieving nasal congestion and eye symptoms and in improving QOL.[13,14]

In this study, patients treated with cetirizine hydrochloride and loratadine received the full dose of medication in the

morning, whereas those taking fexofenadine hydrochloride received 60 mg at 10 AM and 10 PM. In the United States, the customary dose of fexofenadine hydrochloride is 180 mg once daily. In general, Japanese people are of smaller stature than American people, and it has not been established whether 180 mg of fexofenadine hydrochloride once daily can be taken safely by Japanese patients. Further studies are needed to determine the optimal dose of fexofenadine in the Japanese. In this study, all 3 antihistamines tested were well tolerated. Although there were no significant differences among the treatment groups regarding adverse effects, significant differences were seen in terms of time to onset of action, duration of effect, and efficacy. This study provides some insights into the clinical responses to 3 antihistamines that may prove helpful in the management of JCP.

REFERENCES

1. Okuda M. Epidemiology of Japanese cedar pollinosis throughout Japan. *Ann Allergy Asthma Immunol.* 2003;91:288–296.
2. Juniper EF, Guyatt GH. Development and testing of a new measure of health status for clinical trials in rhinoconjunctivitis. *Clin Exp Allergy.* 1991;21:77–83.
3. Bousquet J, Bullinger M, Fayol C, et al. Assessment of quality of life in patients with perennial allergic rhinitis with the French version of the SF-36 Health Status Questionnaire. *J Allergy Clin Immunol.* 1994;94:182–188.
4. Juniper EF, Guyatt GH, Griffith LE, et al. Interpretation of rhinoconjunctivitis quality of life questionnaire data. *J Allergy Clin Immunol.* 1996;98:843–845.
5. Leynaert B, Neukirch C, Liard R, et al. Quality of life in allergic rhinitis and asthma. *Am J Respir Crit Care Med.* 2000;162: 1391–1396.
6. Noonan MJ, Raphael GD, Nayak A, et al. The health-related quality of life effects of once-daily cetirizine HCl in patients with seasonal allergic rhinitis: a randomized double-blind, placebo-controlled trial. *Clin Exp Allergy.* 2003;33:351–358.
7. Okuda M, Okubo K, Goto J, et al. Japanese version Rhinoconjunctivitis Quality of Life Questionnaire for Japanese cedar pollinosis. *Jpn J Allergy.* 2003;52:21–56.
8. Fujieda S, Noda I, Sugimoto C, et al. Effect of pretreatment with ketotifen on pollinosis: correlation with eosinophil cationic protein. *Am J Rhinol.* 1994;8:49–53.
9. Gonzalez MA, Estes KS. Pharmacokinetic overview of oral second-generation H_1 antihistamines. *Int J Clin Pharmacol Ther.* 1998;36:292–300.
10. Meltzer EO, Weiler JM, Widlitz MD. Comparative outdoor study of the efficacy, onset and duration of action, and safety of cetirizine, loratadine, and placebo for seasonal allergic rhinitis. *J Allergy Clin Immunol.* 1996;97:617–626.
11. Day JH, Briscoe MP, Clark RH, et al. Onset of action and efficacy of terfenadine, astemizole, cetirizine, and loratadine for the relief of symptoms of allergic rhinitis. *Ann Allergy Asthma Immunol.* 1997;79:163–172.
12. Bernstein DI, Schoenwetter WF, Nathan RA, et al. Efficacy and safety of fexofenadine hydrochloride for treatment of seasonal allergic rhinitis. *Ann Allergy Asthma Immunol.* 1997;79: 443–448.
13. Kaiser HB, Capano D, Harris A, et al. A double-blind, placebo-controlled comparison of the safety and efficacy of loratadine (Claritin), fexofenadine HCl (Allegro), and placebo in the treatment of subjects with seasonal allergic rhinitis. *Allergy.* 1999; 52:322.
14. Van Cauwenberge P, Juniper EF. Comparison of the efficacy, safety and quality of life provided by fexofenadine hydrochloride 120 mg, loratadine 10 mg and placebo administered once daily for the treatment of seasonal allergic rhinitis. *Clin Exp Allergy.* 2000;30:891–899.
15. Bruno G, Andreozzi P, Graf U, et al. Cetirizine, a second-generation H_1 antagonist, modulates RANTES and MCP-1 levels in allergic rhinitis. *Int J Immunopathol Pharmacol.* 2002; 15:113–118.
16. Ciprandi G, Buscaglia S, Pesce G, et al. Cetirizine reduces inflammatory cell recruitment and ICAM-1 (or CD54) expression on conjunctival epithelium in both early- and late-phase reactions after allergen-specific challenge. *Allergy Clin Immunol.* 1995;95:612–621.
17. Thomson L, Blaylock MG, Sexton DW, et al. Cetirizine and levocetirizine inhibit eotaxin-induced eosinophil transendothelial migration through human dermal or lung microvascular endothelial cells. *Clin Exp Allergy.* 2002;32:1187–1192.
18. Jin HR, Okamoto Y, Matsuzaki Z, et al. Cetirizine decreases interleukin-4, interleukin-5, and interferon-γ gene expressions in nasal-associated lymphoid tissue of sensitized mice. *Am J Rhinol.* 2002;16:43–48.
19. Vignola AM, Crampette L, Mondain M, et al. Inhibitory activity of loratadine and descarboethoxyloratadine on expression of ICAM-1 and HLA-DR by nasal epithelial cells. *Allergy.* 1995; 50:200–203.
20. Paolieri F, Battifora M, Riccio AM, et al. Terfenadine and fexofenadine reduce in vitro ICAM-1 expression on human continuous cell lines. *Ann Allergy Asthma Immunol.* 1998;81: 601–607.
21. Campbell A, Chanal I, Czarlewski W, et al. Reduction of soluble ICAM-1 levels in nasal secretion by H1-blockers in seasonal allergic rhinitis. *Allergy.* 1997;52:1022–1025.
22. Abdelaziz MM, Devalia JL, Khair OA, et al. Effect of fexofenadine on eosinophil-induced changes in epithelial permeability and cytokine release from nasal epithelial cells of patients with seasonal allergic rhinitis. *J Allergy Clin Immunol.* 1998;101: 410–420.
23. Asano K, Kanai K, Suzaki H. Suppressive activity of fexofenadine hydrochloride on thymus- and activation-regulated chemokine production from human peripheral blood leukocytes in response to antigenic stimulation in vitro. *Int Arch Allergy Immunol.* 2004;133:267–275.
24. Gelfand EW, Cui ZH, Takeda K, et al. Fexofenadine modulates T-cell function, preventing allergen-induced airway inflammation and hyper-responsiveness. *J Allergy Clin Immunol.* 2002; 110:85–95.
25. Molet S, Gosset P, Lassalle P, et al. Inhibitory activity of loratadine and descarboxyethoxyloratadine on histamine-induced activation of endothelial cells. *Clin Exp Allergy.* 1997; 27:1167–1174.
26. Bayram H, Devalia JL, Khair OA, et al. Effect of loratadine on nitrogen dioxide–induced changes in electrical resistance and release of inflammatory mediators from cultured human bronchial epithelial cells. *J Allergy Clin Immunol.* 1999;104:93–99.
27. Amsellem C, Czarlewski W, Lagarde M, et al. Inhibitory effect of loratadine on leukotriene B4 production by neutrophils either alone or during interaction with human airway epithelial cells. *Pulm Pharmacol Ther.* 1998;11:245–252.

28. Day JH, Briscoe M, Widlitz MD. Cetirizine, loratadine, or placebo in subjects with seasonal allergic rhinitis: effects after controlled ragweed pollen challenge in an environmental exposure unit. *J Allergy Clin Immunol.* 1998;101:638–645.
29. Day JH, Briscoe M, Rafeiro E, et al. Comparative onset of action and symptom relief with cetirizine, loratadine, or placebo in an environmental exposure unit in subjects with seasonal allergic rhinitis: confirmation of a test system. *Ann Allergy Asthma Immunol.* 2001;87:474–481.
30. Mansmann HC Jr, Altman RA, Berman BA, et al. Efficacy and safety of cetirizine therapy in perennial allergic rhinitis. *Ann Allergy.* 1992;68:348–353.
31. Lockey RF, Widlitz MD, Mitchell DQ, et al. Comparative study of cetirizine and terfenadine versus placebo in the symptomatic management of seasonal allergic rhinitis. *Ann Allergy Asthma Immunol.* 1996;76:448–454.
32. Murray JJ, Nathan RA, Bronsky EA, et al. Comprehensive evaluation of cetirizine in the management of seasonal allergic rhinitis: impact on symptoms, quality of life, productivity, and activity impairment. *Allergy Asthma Proc.* 2002;23:391–398.
33. Burtin B, Duchateau J, Pignat JC, et al. Further improvement of quality of life by cetirizine in perennial allergic rhinitis as a function of treatment duration. *J Invest Allergol Clin Immunol.* 2000;10:66–70.
34. Nunes C, Ladeira S. Double-blind study of cetirizine and loratadine versus placebo in patients with allergic rhinitis. *J Invest Allergol Clin Immunol.* 2000;10:20–23.
35. Howarth PH, Stern MA, Roi L, et al. Double-blind, placebo-controlled study comparing the efficacy and safety of fexofenadine hydrochloride (120 and 180 mg once daily) and cetirizine in seasonal allergic rhinitis. *J Allergy Clin Immunol.* 1999; 104:927–933.
36. Horak F, Stubner P, Zieglmayer R, et al. Controlled comparison of the efficacy and safety of cetirizine 10 mg o.d. and fexofenadine 120 mg o.d. in reducing symptoms of seasonal allergic rhinitis. *Int Arch Allergy Immunol.* 2001;125:73–79.

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Ⅱ．平成17年度　研究成果（原著、総説）

著者名・発表論文名・学会雑誌名・巻号・発表年・最初と最後のページ・発表年

（主任研究者）

著書

1．大久保公裕：第２章、免疫、病気が分かるからだのビジュアル百科、服部光男岡島重孝監修、pp47-60、小学館、東京 2005

2．大久保公裕：第 5 章、感覚器、病気が分かるからだのビジュアル百科、服部光男岡島重孝監修、pp251-276、小学館、東京 2005

論文発表

1. Gotoh M, Okubo K: Sublingual immunotherapy for Japanese cedar pollinosis. Allergology International 54: 167-171, 2005.
2. Okuda M, Ohkubo K, Goto M, Okamoto Y, Konno A, Baba K, Ogino S, Enomoto M, Imai T, So N, Ishikawa Y, Takenaka Y, Manndai T, Crawford B: Comparative study of two Japanese rhinoconjunctivitis quality-of-life questionnaires. Acta Oto-Laryngologica 125: 10. 736-744, 2005
3. Gotoh M, Okubo K, Okuda M: Inhibitory effects of facemasks and eyeglasses on invasion of pollen particles in the nose and eye: clinical study. Rhinology 43, 8: 266-270, 2005.
4. 大久保公裕：アレルギー性鼻炎の QOL について－抗ロイコトリエン剤の有効性－．日気食会報 56．2(4 月)：194-196，2005.
5. 後藤穣、大久保公裕：アレルギー性鼻炎のかゆみの成因と治療．アレルギー科 19.4: 360-364, 2005.
6. 大久保公裕：ARIA と PG-MARJ2005．Prog Med 25.10: 2741-2747, 2005.
7. 奥田稔、大久保公裕、後藤穣：鼻正常者の鼻症状．アレルギー54.6: 551-554, 2005.
8. 奥田稔、大久保公裕、後藤穣、石田祐子：空中スギ花粉の着衣、皮膚への付着．アレルギー54.6: 555-558, 2005.
9. 奥田稔、大久保公裕、後藤穣、石田祐子：季節前スギ花粉症の高率発症への疑問－鼻内スギ花粉数の測定から．アレルギー54.7: 636-640, 2005.
10. 今井透、藤倉輝道、新井寧子、余田敬子、北島整、相田瑞江、小津千佳、酒主敦子、大久保公裕、森山寛、遠藤朝彦、宇井直也、吉村剛：2005 年のスギ花粉症に対するラマトロバンと抗ヒスタミン薬の併用効果－QOL 調査－．耳鼻咽喉科展望 48．6．12 月：427-438, 2005.
11. Okamoto Y, Matsuzaki Z, Matsuoka T, Endo S, Yamamoto H, Chazono H, Horiguchi S, Hanazawa T: Influence of viral infection on the development of nasal hypersensitivity. Clin Exp Allergy 35: 679-684, 2005.
12. 佐々木康二、三品朋子、鈴木あゆ美、湯田厚司、間島雄一：スギ花粉における秋の気象条件と花粉飛散の影響．東海花粉症 17: 59-63, 2006.
13. 湯田厚司、間島雄一、島田博匡、森正美、伊藤英樹、加藤淳也、平田圭甫、森外由美ほか：三重県におけるスギ・ヒノキ科花粉の 2005 年飛散結果と 2006 年飛散予想．東海花粉症 17: 28-33, 2006.

14. Okano M, Hattori H, et al. Nasal exposure to Staphylococcal enterotoxin enhances the development of allergic rhinitis in mice. Clinical and Experimental Allergy 35: 506-514, 2005.

15. Maeda M, Okano M, et al. Glycofrom analysis of Japanese cedar pollen allergen, Cry j 1. Bioscience Biotechnology Biochemistry 69: 1700-1705, 2005.

16. Hattori H, Okano M, et al. Signals through CD40 play a critical role in the pathophysiology of Schistosoma mansoni egg antigen-induced allergic rhinitis in mice. American Journal of Rhinology (in press).

17. Okano M, Fujiwara T, et al. Presence and characterization of PGD2-related molecules in nasal mucosa of patients with allergic rhinitis. American Journal of Rhinology (in press).

18. Sugimoto H, Okano M, et al. CRTH2-specific binding characteristics of ^{3}H-ramatroban and its effects on PGD_2-, 15-deoxy-^{12,14}-PGJ2- and indomethacin-induced agonist responses. British Journal of Pharmacology (in press).

19. Okano M, Sugata Y, et al. EP2/EP4-mediated suppression of antigen-specific human T cell responses by prostaglandin E2. Immunology (in press).

20. 石部司、久保伸夫： アレルギー性鼻炎に対するアルゴンプラズマ凝固療法。耳鼻臨床 ９９：２０３－２１０。２００６

21. Gotoh M, Okubo K: Sublingual immunotherapy for Japanese cedar pollinosis. Allergology International 54:167-171, 2005

22. Gotoh M, Okubo K, Okuda M: Inhibitory effects of facemasks and eyeglasses on invasion of pollen particles in the nose and eye: clinical study. Rhinology 43: 266-270, 2005.

23. Yamada T, Zhang K, Yamada A, Zhu D, Saxon A: B lymphocyte stimulator activates p38 mitogen-activated protein kinase in human Ig class switch recombination Am J Respir Cell Mol Biol. 32(5):388-94, 2005

24. Hyo S, Fujieda S, Kawata R, Kitazawa T, Takenaka H.: Comparison of efficacy by short-term administration of antihistamines cetirizine, fexofenadine, and loratadine versus placebo under natural exposure to Japanese cedar pollen. An Allergy Asthm Immunol, 94:457-64, 2005.

25. Takahashi N, Yamada T, Narita N, Fujieda S: Double-stranded RNA induces production of RANTES and IL-8 by human nasal fibroblast. Clin Immunol 118:51-8, 2006.

26. Yamada T, Takahashi N, Sunaga H, Narita N, Yamamoto H., Fujieda S: Roles of protein tyrosine kinese Syk in nasal polyps. Clin Exp All Rev. 5:72-6, 2005.

総説

1．大久保公裕：アレルギー性鼻炎・花粉症．医学と薬学 55.2: 177-182, 2006.

2．大久保公裕：スギ花粉症の舌下免疫療法．感染炎症免疫 35.2: 162-163, 2006.

3．大久保公裕：アレルギー性鼻炎．JOHNS21.9: 1287-1290, 2005.

4．大久保公裕：スギ花粉症の薬物療法のポイント．PTM2 12.1, 2006.

5．大久保公裕：新しい薬剤開発の動向．MB ENT57.12: 58-63, 2005

6．大久保公裕、後藤穣：花粉症．日本臨床 63 増刊 5: 145-150, 2005.

7．大久保公裕：花粉症に対する抗 IgE 抗体療法．Medical Science Digest31.13: 527-529, 2005

8．大久保公裕、奥田稔：花粉症を含むアレルギー性鼻炎の疫学．アレルギーの臨床 26.1: 23-26, 2006.

9．大久保公裕：免疫療法の実際 2.花粉症・アレルギー性鼻炎．アレルギーの臨床 26.3: 194-200, 2006.

１０．　大久保公裕、大西正樹：アレルギー性鼻炎(花粉症)に対する鼻噴霧用ステロイド薬治療の EBM アレルギーの臨床 25.11: 871-875, 2005.

１１．　大久保公裕：アレルギー性鼻炎の近未来の治療戦略．Q&A でわかるアレルギー疾患 1(3). 10: 238- 239, 2005.

１２．　大久保公裕：アレルギー性鼻炎の QOL．東京都医師会雑誌 59.3: 11-16, 2006.

１３．　岡本美孝：鼻アレルギー．日本臨床 63 増刊 5:96-101, 2005.

１４．　岡本美孝：小児の鼻アレルギー．Progress in Medicine25:2725-2728, 2005.

１５．　増山敬祐：わかりやすい免疫疾患　第 IV 章　免疫と病態　皮膚・感覚器疾患　アレルギー性鼻副鼻腔炎．日本医師会雑誌　134（特別号）：342-347, 2005.

１６．　増山敬祐：花粉症の治療　ガイドラインと評価．Mebio　22: 61-67, 2005.

１７．　増山敬祐：花粉症に対する鼻局所ステロイド薬の進歩とエビデンス．アレルギーの臨床 26: 117-123, 2006.

１８．　久保伸夫：花粉症に対する外科治療の適応と治療成績．アレルギーの臨床　２５（２）：３９～４５．２００５．

１９．　盛川宏、馬場廣太郎：外来偶発事故防止マニュアル－減感作療法－．ＪＯＨＮＳ　21：1113-1114、2005.

２０．　盛川宏、馬場廣太郎：アレルギーの衛生仮説－慢性副鼻腔炎とアレルギー－．Pharma Media　23：29-31、2005.

２１．　盛川宏：花粉症治療薬の選択－鼻閉に有効な薬剤：ENTONI 57：18-23、2005.

街頭QOLアンケート調査

■調査概要

■ 調査目的　本調査は、今シーズンの花粉症（アレルギー性鼻炎）の発症状況と、発症者が花粉症に対し、どのような認識・対処をしているかを把握する事により、今後の花粉症治療の参考資料とする事を目的とした。

■ 調査手法　街頭リクルートによる自記式アンケート

■ 調査対象とサンプル設計　計 200サンプル

・花粉症アレルギーを持っている人（対象者の自己申告）

※その時症状が出ていなくても「花粉症持ち」の人であれば可

※自分が「花粉症」だと思っていれば、医者の診断がなくても可

※今シーズンの発症の有無は問わない

→花粉の飛散状況を考慮し、2回にわけて実施（各回100sずつ）

→性別・年代によりサンプル割付

	計	10代	20代	30代	40代	50代以上
全体	100	20	20	20	20	20
男性	50	10	10	10	10	10
女性	50	10	10	10	10	10

■ 調査日時　1回目：3月1日～5日のうち、晴れた日（1日間）　→3月2日（水）実施

2回目：3月22日～25日のうち、晴れた日（1日間）　→3月25日（金）実施

花粉飛散状況を考慮し、実査時間帯は15時～19時を中心とした

■ 調査地点　新宿駅周辺　（調査条件を同一にするため、2回とも同じ地点で実施した）

■ 調査実施機関　株式会社 リサーチ・アンド・ディベロプメント

（R&D管理番号：50503-01/50503-02）

調査結果の要約・まとめ

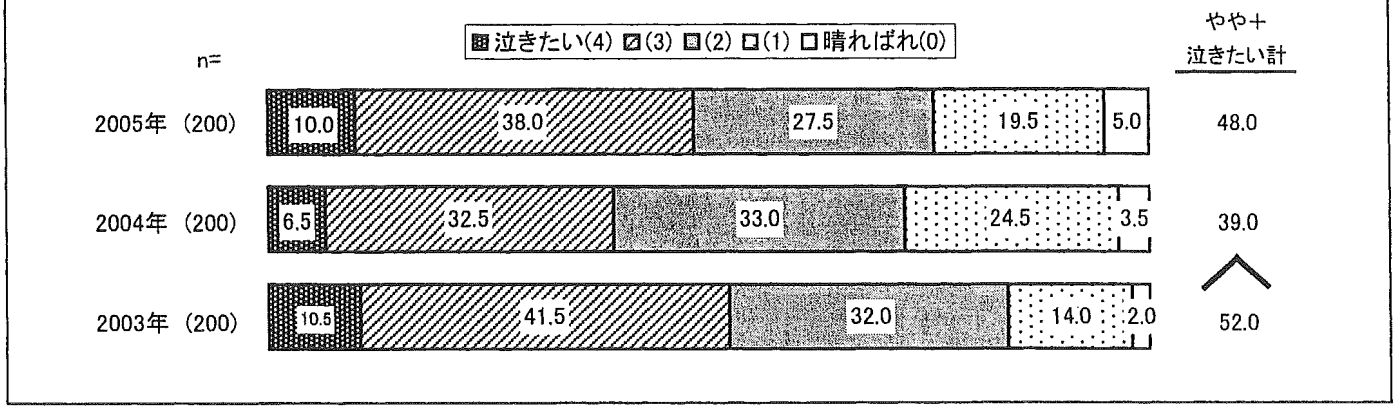
1．3年間の比較

◇昨年（2004年）と比べて、今年は症状は重く（ただし「泣きたい計」の割合で統計的有意差はない）、一昨年（2003年）のレベルに近い。

◇同様に、「今年、治療のために通院している」割合も昨年に比べると高く、また一昨年も上回っている。

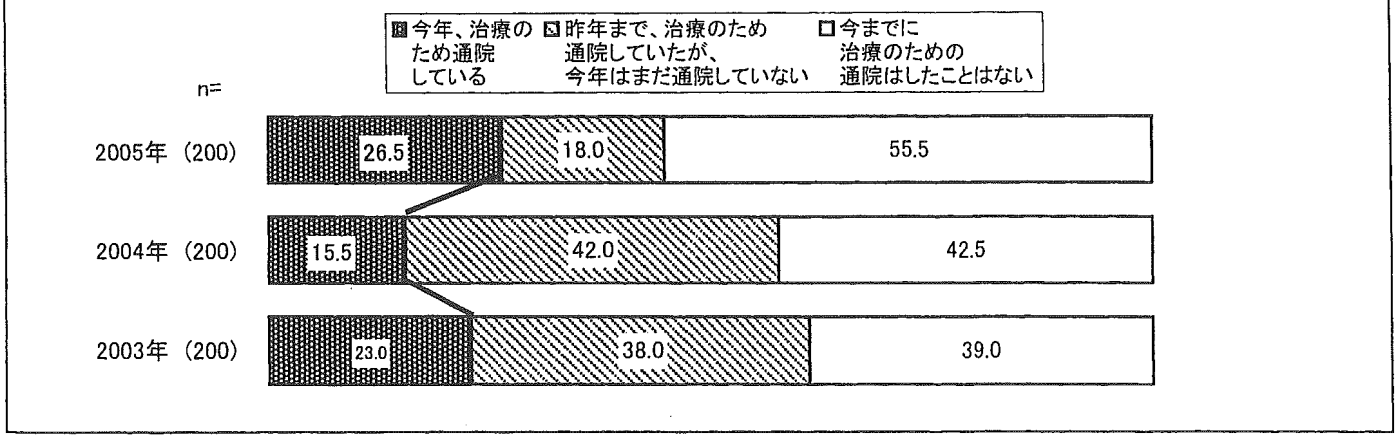
■【総括的状態】（3年間の比較）

＊＜統計的有意差あり　(%)



■【通院の有無】（3年間の比較）

(%)



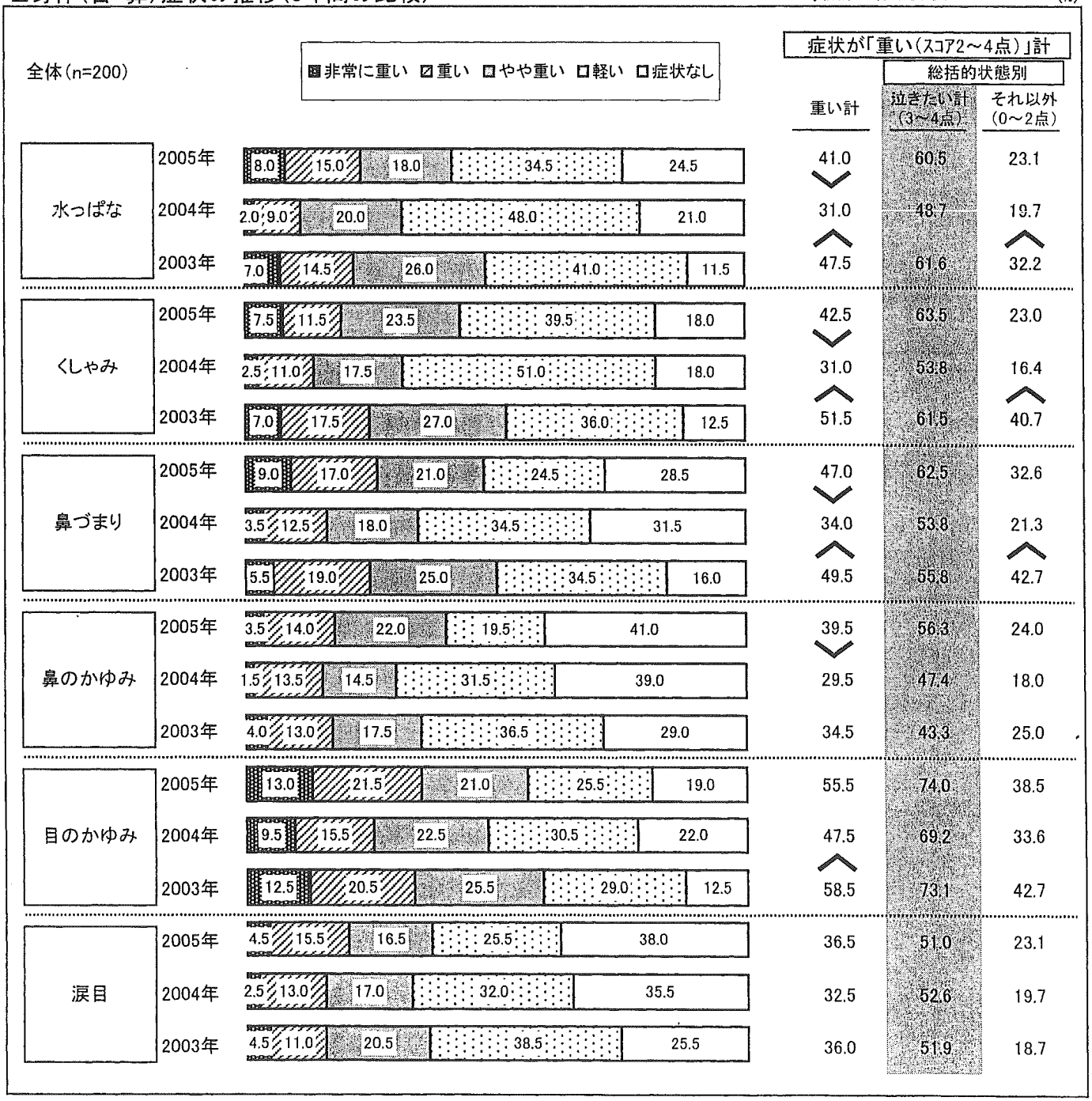
◇「目のかゆみ」の症状が最も重く、“症状が重い”（非常に重い＋重い＋やや重い）とした割合が5割を超えている。次いで「鼻づまり」の症状が重い。

◇昨年に比べると、全ての症状で“症状が重い”とした割合が高い。
その中で、統計的な有意差がみられたのは、「水っぱな」「くしゃみ」「鼻づまり」「鼻のかゆみ」。

	総括的状態	
	泣きたい計	それ以外
2005年	(96)	(104)
2004年	(78)	(122)
2003年	(104)	(96)

＊《統計的有意差あり

■身体（目・鼻）症状の推移（3年間の比較）



◇「気分が晴れない」の症状は、“症状がひどい”（とてもひどい＋ひどい＋ややひどい）割合が5割で最も高い。

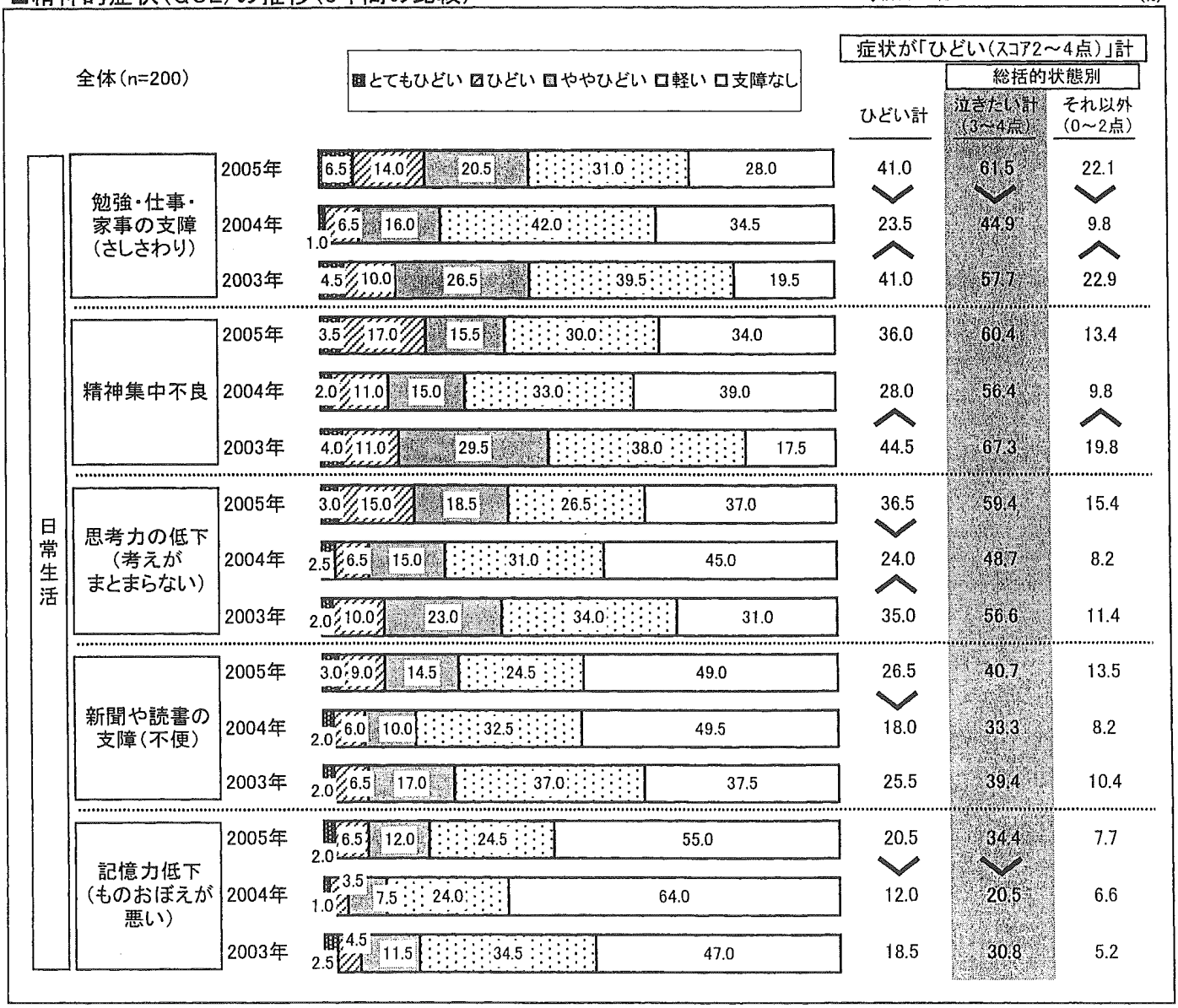
◇昨年に比べると、全ての症状で“症状がひどい”とした割合が高くなっている。
その中で、統計的な有意差がみられたのは、「勉強・仕事・家事の支障」「思考力の低下」「新聞や読書の支障」「記憶力低下」「スポーツ、ピクニックなど野外生活の支障」「外出の支障」「人とつき合いの支障」「睡眠障害」「気分が晴れない」「いらいら感」「ゆううつ」「生活に不満足」。
特に、「外出の支障」「気分が晴れない」は20ポイント以上高くなっている。

◇総括的状態別に症状をみると、『泣きたい計』層は昨年より「倦怠感」「疲労」の症状が悪くなっている（統計的有意差はある）のに対し、『それ以下』層は症状が良くなっており、症状の変化にギャップが見られる。

	総括的状態	
	泣きたい計	それ以外
2005年	(96)	(104)
2004年	(78)	(122)
2003年	(104)	(96)

＊《統計的有意差あり

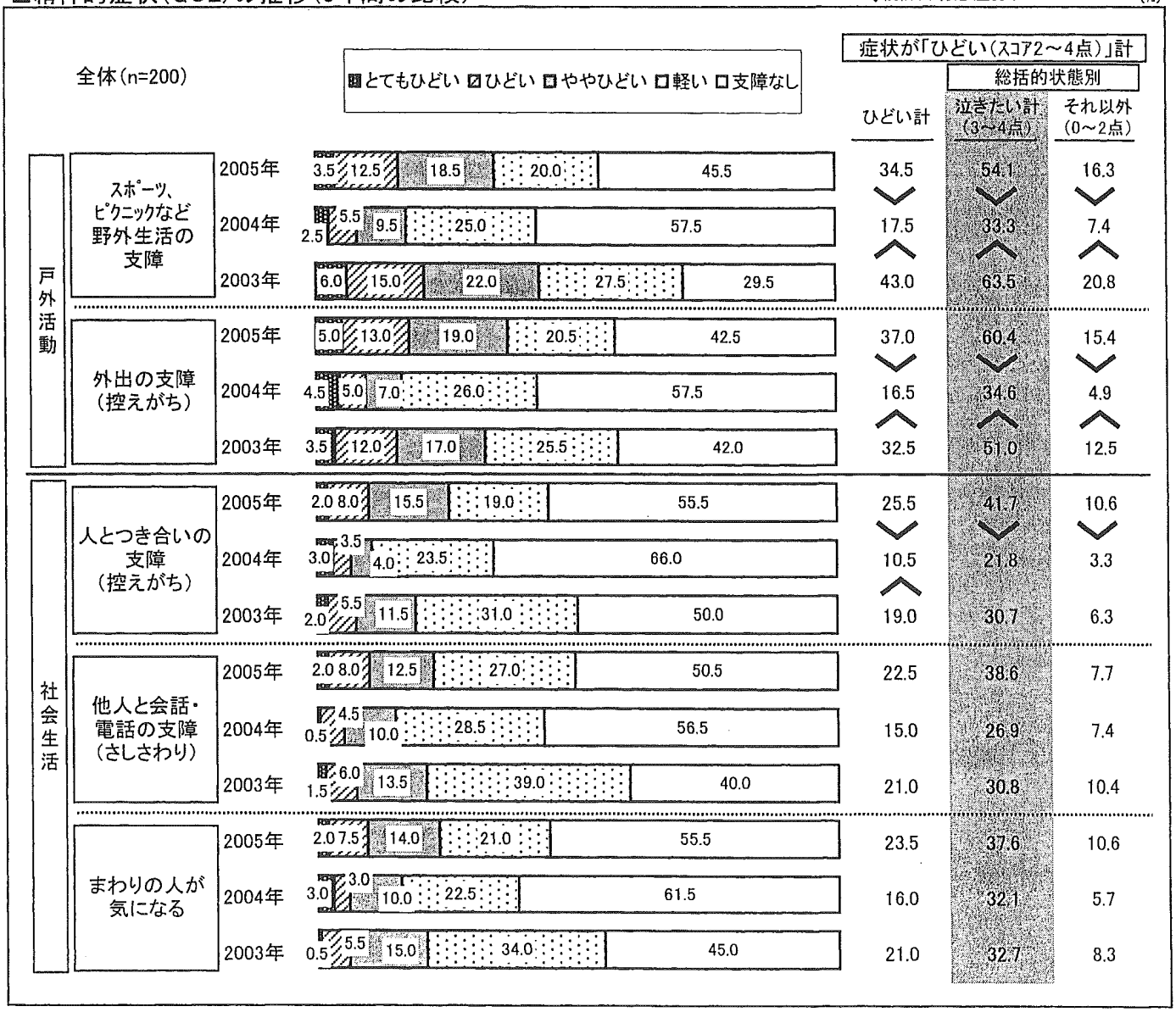
■精神的症状（QOL）の推移（3年間の比較）



■精神的症状（QOL）の推移（3年間の比較）

	総括的状態	
	泣きたい計	それ以外
2005年	(96)	(104)
2004年	(78)	(122)
2003年	(104)	(96)

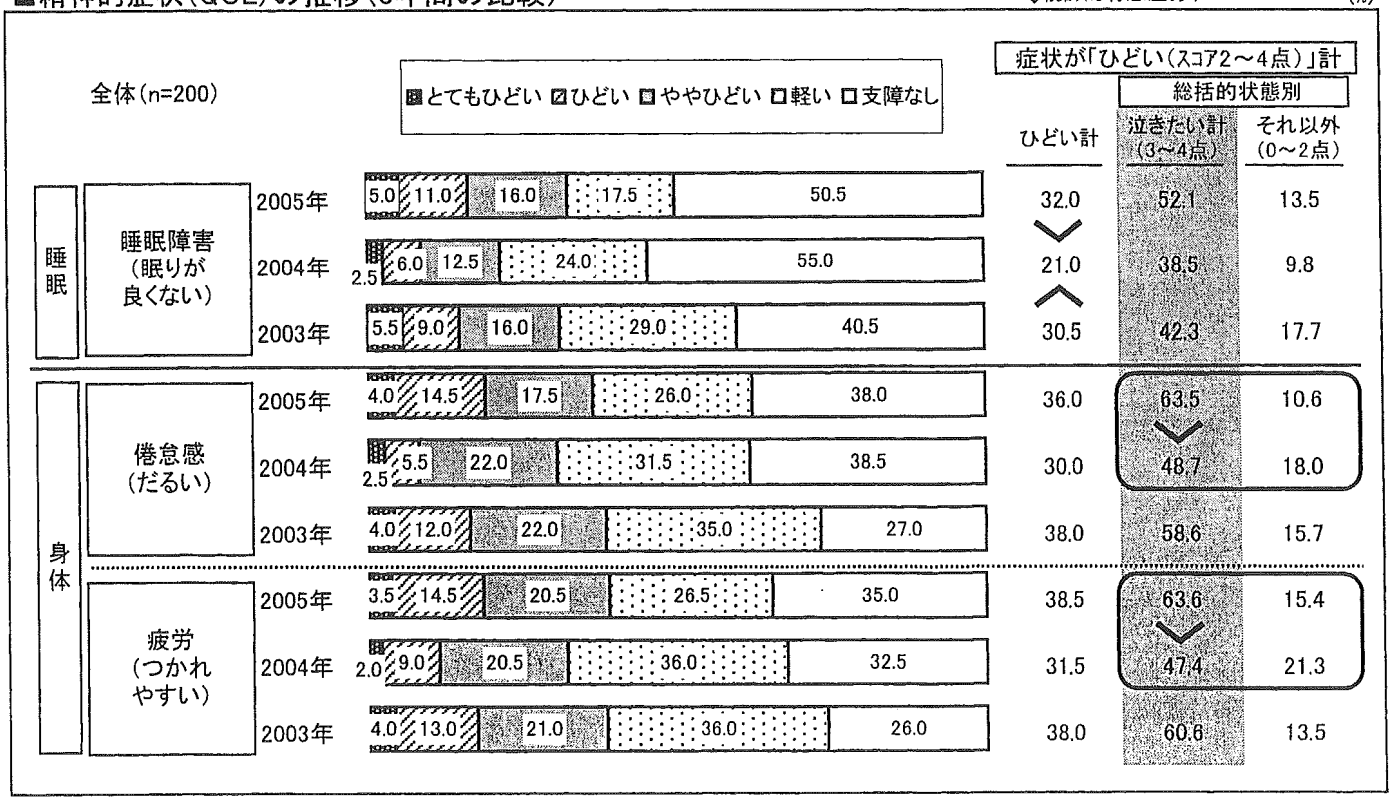
＊《統計的有意差あり　(%)



	総括的状態	
	泣きたい計	それ以外
2005年	(96)	(104)
2004年	(78)	(122)
2003年	(104)	(96)

＊≪統計的有意差あり　(%)

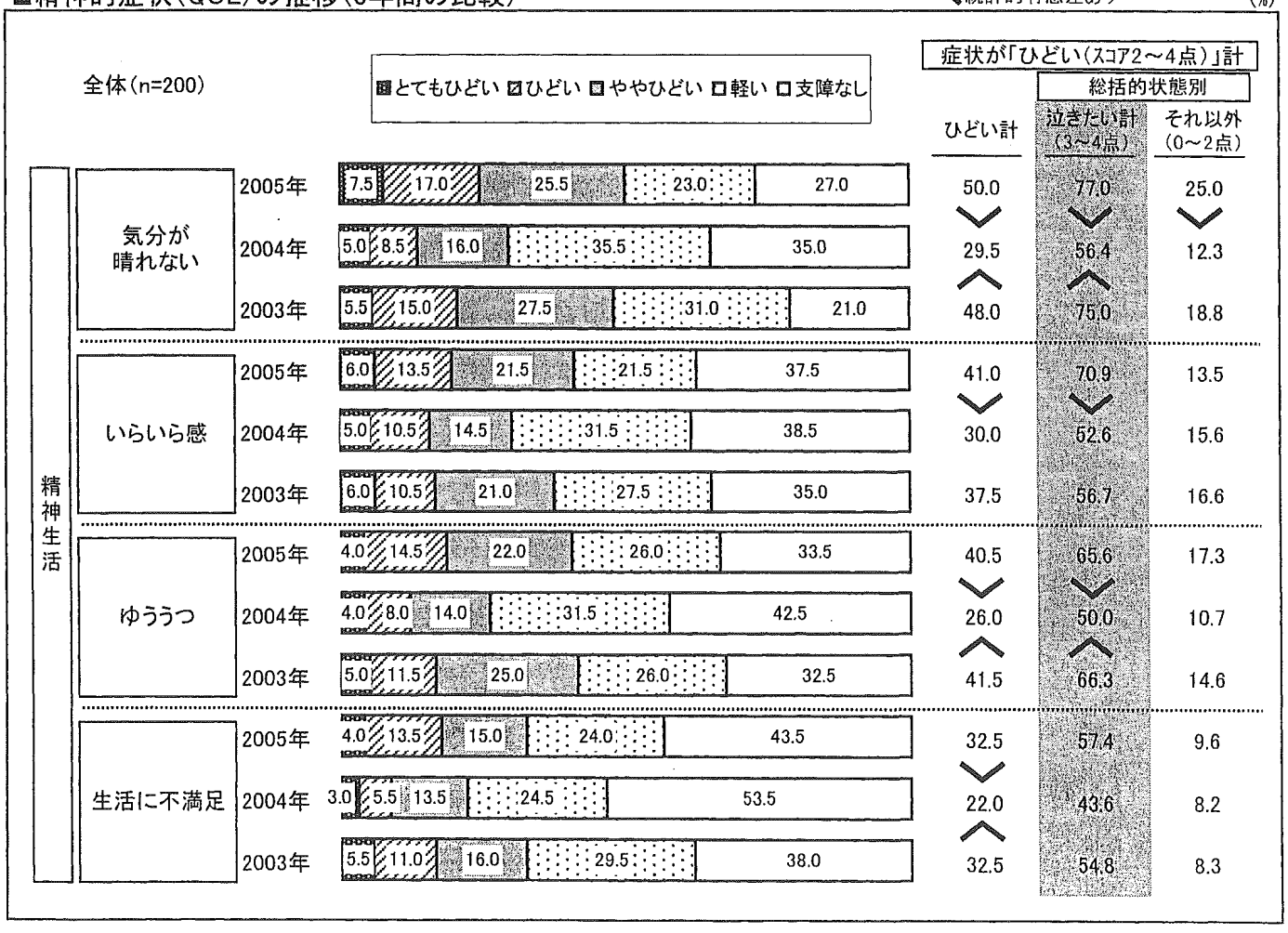
■精神的症状(QOL)の推移(3年間の比較)



	総括的状態	
	泣きたい計	それ以外
2005年	(96)	(104)
2004年	(78)	(122)
2003年	(104)	(96)

＊≪統計的有意差あり

■精神的症状(QOL)の推移(3年間の比較)



(%)

2.総括的状態との相関係数

◇総括的状態と身体症状の相関係数(影響度合い)をみると、昨年に比べ「くしゃみ」「目のかゆみ」「水っぱな」の相関が強くなっているものの、影響度合いのレベルはさほど強くない。

◇総括的状態と精神的症状(QOL)の相関係数をみると、「精神生活スコア」の相関が最も高い。次いで高いのが「身体スコア」「日常生活スコア」。
昨年に比べると、「身体スコア」との相関が強くなっており、2003年に近いレベルとなっている。

■総括的状態と身体症状の相関係数

*濃い網掛け:相関係数0.6以上、薄い網掛け0.5以上　(相関係数)

		2005年	2004年	2003年
身体症状	水っぱな	0.3914	0.3333	0.3627
	くしゃみ	0.4585	0.3917	0.3570
	鼻づまり	0.3467	0.3691	0.2331
	鼻のかゆみ	0.3469	0.4067	0.2460
	目のかゆみ	0.4373	0.3909	0.3700
	涙目(なみだめ)	0.3994	0.4078	0.3820

■総括的状態と精神的症状(QOL)の相関係数

(相関係数)

		2005年	2004年	2003年
領域別スコア	①日常生活スコア	0.5008	0.5314	0.5323
	②戸外活動スコア	0.4416	0.4430	0.5247
	③社会生活スコア	0.4676	0.4610	0.4607
	④睡眠スコア	0.3972	0.3514	0.3734
	⑤身体スコア	0.5128	0.4027	0.5477
	⑥精神生活スコア	0.6032	0.6108	0.6484
精神的症状(QOL)	勉強・仕事・家事の支障	0.4345	0.4977	0.4579
	精神集中不良	0.4737	0.5427	0.4518
	思考力の低下	0.4566	0.4384	0.4557
	新聞や読書の支障	0.4315	0.4065	0.4100
	記憶力の低下	0.3620	0.3125	0.4032
	スポーツ等野外生活支障	0.3423	0.3908	0.4775
	外出の支障	0.4603	0.4186	0.4676
	人とつき合いの支障	0.4505	0.3781	0.4727
	他人と会話・電話の支障	0.4009	0.3769	0.3752
	まわりの人が気になる	0.3893	0.4590	0.3404
	睡眠障害	0.3972	0.3514	0.3734
	倦怠感	0.4891	0.4227	0.5223
	疲労	0.4901	0.3426	0.5315
	気分が晴れない	0.5354	0.5993	0.5963
	いらいら感	0.5636	0.5213	0.5044
	ゆううつ	0.5406	0.4787	0.6402
	生活に不満足	0.5159	0.5602	0.5535

■領域別スコア(合計の平均)

(スコア/合計の平均点)

	n=	QOL スコア計	① 日常生活 スコア	② 戸外活動 スコア	③ 社会生活 スコア	④ 睡眠 スコア	⑤ 身体 スコア	⑥ 精神生活 スコア
2005年	(200)	18.99	5.55	2.26	2.46	1.03	2.46	5.24
2004年	(200)	14.45	4.24	1.44	1.82	0.77	2.14	4.05
2003年	(200)	19.84	5.84	2.50	2.51	1.10	2.64	5.25