

Effects of psychotherapy for middle-aged individuals with anxiety disorders in a general medicine practice

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Background: Anxiety disorders are mental disorders that cause somatic symptoms for which patients may seek care from general medicine departments. We focused on anxiety disorders in middle-aged patients and examined the effect of a psychotherapeutic intervention.

Materials and Methods: The participants were 14 middle-aged patients diagnosed with an anxiety disorder. Patients received pretreatment assessments and were randomly assigned to a pharmacotherapy group (n = 8) or a pharmacotherapy and psychotherapy group (n = 6). The duration of the study was three months. Pre- and post-treatment, the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36), State-Trait Anxiety Inventory (STAI), and a visual analog scale (VAS) were administered. In the pharmacotherapy and psychotherapy group, salivary cortisol was collected pre- and post-psychotherapy at the first and final psychotherapy sessions.

Result: Four patients in the pharmacotherapy group withdrew from the study. There were no significant differences in the total scores of the SF-36 or STAI between groups. Improvement was seen in the pharmacotherapy and psychotherapy group pre- and post-treatment. SF-36 subscales of bodily pain ($p = 0.02$) and mental health ($p = 0.04$) were significantly higher than post-treatment. The state anxiety score on the STAI improved post-treatment ($p = 0.03$). On the VAS, the pharmacotherapy and psychotherapy group's symptoms were significantly improved ($p = 0.02$).

Conclusion: This suggests that psychotherapy for middle-aged individuals contributes to the improvement of anxiety states and HRQoL in general medicine departments. It promotes the recognition of curative effects and prevents doctor shopping.

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Key words: anxiety disorders, general medicine, middle age, psychotherapy, salivary cortisol, visual analog scale (VAS)

Introduction

Anxiety disorders are a group of disorders marked by symptoms of uneasiness. Generalized anxiety disorder, social phobia, panic disorder, and acute stress disorder are in-

cluded in the anxiety disorder category in the DSM-IV-TR. The prevalence of anxiety disorders is substantial in the general population and their functional impact is significant. However, the causes of anxiety disorders have not been scientifically explained.

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Anxiety disorders are mental disorders that cause somatic symptoms for which patients may seek and receive treatment through a general medicine department^{1,2}. If medical care does not provide the appropriate diagnosis and treatment, the patient may not understand the illness and be dissatisfied with the treatment. This may lead to the patient visiting various hospitals and doctors until an explanation or appropriate treatment is found^{3,4}. Thus, the identification of anxiety disorders is required in general medicine departments^{1,5,6}.

In recent years, the physical factors of anxiety disorders, including brain dysfunction theory, have become influential, although social factors and psychological factors must also be considered. In addition in treatment effect studies, a variety of approaches, such as pharmacotherapy and cognitive behavioral therapy, have been attempted and studied⁷⁻⁹.

The examination of age group studies on anxiety disorders have focused on the elderly¹⁰⁻¹², long-term outcomes, and the need for early treatment¹³. There are relatively few studies except for the elderly. However, in middle age, individuals experience physical decline, children moving out of the family home, caring for aging parents, and changes in the workplace such as early retirement. Such social problems may lead to financial and psychological problems; thus, it may be difficult to feel settled¹⁴. Therefore, in this study, we decided to examine the effects of psychotherapy in middle age on such a psychosocial background.

In the evaluation of psychotherapy effects dropout rates are an issue¹⁵⁻¹⁷. Reasons of dropout have been examined from perspectives of disease differences, patient characteristics, and feelings of satisfaction. In psychotherapy, the clinical psychologist talks with a patient in a private room at a scheduled time. The topic focuses on the patient experience. We considered that stress in talking with psychologists might cause burden and be one of the reasons for dropouts. Therefore, we collected salivary cortisol to measure the burden of the psychotherapy objectively. Salivary cortisol attracts attention as one of the physiological evaluation methods of stress. Cortisol is the hormone that is important in assessing about psychological and physical health conditions¹⁸. It is shown that salivary cortisol rises with stress in the laboratory research¹⁹. We examined the burden of psychotherapy from a change in salivary cortisol.

MATERIALS AND METHODS

Study Participants

In this study, ages 40–60 were defined as middle age. Fourteen patients who had a diagnosis of an anxiety disorder in a general medicine practice were recruited through general physician referral. Diagnostic assessments included the administration of the Structured Diagnostic Interview for DSM-IV. The selection criteria included the DSM-IV diagnoses of anxiety disorders, middle age, willingness to participate in the study, and willingness to consider psychotherapy. We excluded individuals receiving medical treatment for anxiety disorders at another hospital. Participants were given pretreatment assessments and randomly assigned to a pharmacotherapy group ($n = 8$) or a pharmacotherapy and psychotherapy group ($n = 6$). The pharmacotherapy group received a periodic medical examination and medicine prescription by a general physician. The pharmacotherapy and psychotherapy group received psychotherapy with the clinical psychologist in addition to medical examination and medicine prescription by a general physician. The psychologist was a qualified clinical psychologist with eight years of experience. The duration of the study was three months (Figure 1).

At the beginning of the psychotherapy, the clinical psychologist explained the purpose and method of psychotherapy and began psychotherapy with patient consent. Psychotherapy lasted about 60 minutes. We completed the medical examination and the psychotherapy in another room. The patient sat on a chair with a backrest and talked with a psychologist across a table. The psychotherapy schedule was established by the patients' circumstances and schedules. The patient and the psychologist talked and scheduled appointments for the next time as the psychotherapy session

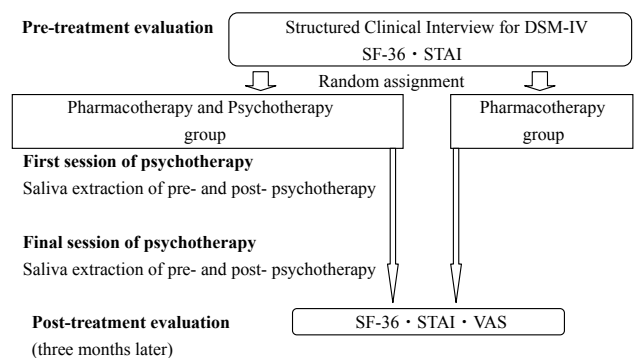


Figure 1. Progress and evaluation of research

ended. The schedule began at the rate of once or twice a week and the interval gradually increased. We conducted an average of six psychotherapy sessions during the study.

Measures

Outcome measures included the State-Trait Anxiety Inventory (STAI) for Japan (Form X), the Medical Outcomes Study Short Form-36 (SF-36)^{20,21}, a visual analog scale (VAS), and a salivary cortisol measure.

Questionnaires

Anxiety was measured with the Japanese version of the State-Trait Anxiety Inventory (Form X). The State-Trait Anxiety Inventory was developed by Spielberger, et al.²² to determine individuals' separate state and trait anxiety levels and has been standardized for Japan. The State-Trait Anxiety Inventory consists of a State Anxiety Scale (STAI-S) and a Trait Anxiety Scale (STAI-T). The STAI is a self-evaluation scale containing 40 expressions. This questionnaire was completed pre- and post-treatment.

Health-related quality of life (HRQoL) was measured with the SF-36 (Japanese version 2, Acute; iHope International, Japan)²³ to determine the range of functional impairment of anxiety disorders in primary care patients^{24,25}. The questionnaire consists of 36 items in eight dimensions of functioning. Physical functioning, physical role, bodily pain, general health, vitality, social functioning, emotional role, and mental health concepts of the SF-36 were measured on a five point Likert scale with varying answers. This questionnaire was completed pre- and post-treatment.

Visual analog scale

Patient treatment achievement was measured with a visual analog scale. Pre-treatment, we confirmed the achievement level the participant expected from the treatment. Post-treatment, all patients were asked to plot their treatment achievement on a 10-cm horizontal line. Marks were made on a 10-cm line with 0= pre-treatment at one end and 10= full treatment achievement expected by the participant at the other end.

Psychoneuroendocrine response

We also measured participants' salivary cortisol (a hormone) and examined the stress reaction to psychotherapy. Salivary cortisol was chosen because other measures, such as blood draws, may cause pain and uneasiness. Salivary

cortisol is easily collected and is not a burden for participants¹⁸. The pharmacotherapy and psychotherapy group members measured salivary cortisol pre- and post-psychotherapy at the first and final psychotherapy sessions. To exclude the measurement influence, the pre-psychotherapy measurements were collected after a ten-minute rest and the post-psychotherapy measurements were collected just after psychotherapy. They were collected at the same time in the first and final psychotherapy sessions. Salivary cortisol was collected using Salivette®. This is a container with cotton that doubled in size in a spitz pipe. The subject removes the cotton from the container and allows saliva to soak thoroughly. After collecting, the cotton was placed in a container, sealed, and cryopreserved.

Semi-Structured interview

A semi-structured interview was conducted at pre-treatment for all patients. The interview was completed with a questionnaire. Contents included a clinical history, family structure, life behavioral patterns, and work experience.

Ethical Considerations

The study protocol was approved by the Medical Ethics Committee of Nagasaki University. Written informed consent was obtained from each subject in accordance with the Helsinki Declaration.

Statistical Analysis

Intention-to-treat analyses were performed. The Mann-Whitney U test and Wilcoxon signed rank test were used to find pre- and post-treatment differences between the groups. Statistical significance was set at $p < 0.05$. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria)²⁶. More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics.

RESULTS

Participant characteristics

Among fourteen participants, four participants of the pharmacotherapy group withdrew from the study. One pa-

tient transferred to the psychiatry department and the other patient canceled study entry. We did not understand the reasons for the other two people. One had a history of six consultations and one medication experience. The other one had a history of one consultation without taking medicine. We hypothesized that they hoped for treatment unlike other hospitals or did not want to take medicine.

Demographic and clinical data for the participants are presented in Table 1. There were seven women and seven men ranging in age from 41 to 58 years. The period of anxiety symptoms, the number of hospitals patient had consulted for anxiety symptoms, and the medication history for anxiety disorders did not differ between groups. For pharmacotherapy, an antianxiety medication, a sleep medication, and an antidepressant were prescribed. We performed an equivalent conversion calculation to compare the prescription contents. We used diazepam as the reference anti-anxiety and sleeping drug, and imipramine as the reference

antidepressant (Table 2). There were no differences in the prescription contents of antidepressants, antianxiety medications, or sleeping medications for pharmacotherapy between groups.

SF-36 pre- and post-treatment in the pharmacotherapy and psychotherapy group

The scores of eight people in the pharmacotherapy group and six people in the pharmacotherapy and psychotherapy group were used for analysis. The median scores are included in Table 3. The groups did not differ at pre-treatment on any demographic or clinical variables. In the pharmacotherapy and psychotherapy group, the total SF-36 score improved from pre- to post-treatment. There was a significant difference in the reports of bodily pain scores ($p = 0.02$) and mental health scores ($p = 0.04$).

Table 1. Demographic and clinical participant characteristics (N = 14)

	Pharmacotherapy group (N = 8)	Pharmacotherapy and psychotherapy group (N = 6)
	n or <i>M</i> (range)	n or <i>M</i> (range)
Age	49.75 (41–53)	51 (46–58)
Gender		
Male	3	4
Female	5	2
Employment status		
Employed full-time	4	3
A part-time job	1	
Self-owned business		3
Not employed	2	
Unclear	1	
Marital Status		
Married	5	6
Unclear	3	
Existence of living together		
Family	5	6
Unclear	3	
Mean time of symptom duration by the report of the patient	208 days (7–730)	203 days (1–730)
The number of hospitals which patient had consulted for anxiety symptoms	2.25 (0–6)	1.8 (0–4)
Medication taken for the anxiety disorder		
Yes	2	1
No	6	5
Dropout from study	4	

Table 2. The medicines that were prescribed for both groups

	Case		Dose that is equivalent to 5 mg diazepam (mg/day)	Dose that is equivalent to 150 mg imipramine (mg/day)
Pharmacotherapy group	Case 1	Etizolam 1 mg	3.3 (3.1–5.63)	37.5 (37.5–45)
	Case 2	Zolpidem Tartrate 10 mg Bromazepam 2 mg Milnacipran Hydrochloride 30 mg		
	Case 3	Paroxetine Hydrochloride 20 mg Etizolam 0.5 mg		
	Case 4	Fludiazepam 0.5 mg		
	Case 5	Etizolam 1 mg Sertraline Hydrochloride 25 mg		
	Case 6	Zolpidem Tartrate 5 mg		
	Case 7	Etizolam 1 mg Paroxetine Hydrochloride 10 mg		
	Case 8	Paroxetine Hydrochloride 10 mg Alprazolam 0.4 mg, Quazepam 15 mg		
Pharmacotherapy and psychotherapy group	Case 9	Hangekobokuto 7.5 g	6.67 (6.17–8.34)	75 (37.5–75)
	Case 10	Paroxetine Hydrochloride 20 mg		
	Case 11	Paroxetine Hydrochloride 10 mg Zolpidem Tartrate 10 mg Etizolam 0.5 mg		
	Case 12	Diazepam 4 mg, Etizolam 0.5 mg		
	Case 13	Sertraline Hydrochloride 50 mg		
	Case 14	Clotiazepam 20 mg		

Median (interquartile range)

STAI scores pre- and post-treatment of the pharmacotherapy and psychotherapy group

There was no significant difference between the pharmacotherapy group and the pharmacotherapy and psychotherapy group on the STAI. As shown in Table 3, the state anxiety score of the pharmacotherapy and psychotherapy group improved between pre- and post-treatment ($p = 0.03$).

VAS comparison of the pharmacotherapy group and the pharmacotherapy and psychotherapy group

The VAS scores were significantly different between the pharmacotherapy group and the pharmacotherapy and psy-

chotherapy group (Table 3). The pharmacotherapy and psychotherapy group reported higher degrees of treatment achievement than the pharmacotherapy group ($p = 0.02$).

Salivary cortisol pre- and post- psychotherapy

In the pharmacotherapy and psychotherapy group, there was no difference in pre- and post-psychotherapy salivary cortisol between first and final psychotherapy sessions. We compared the salivary cortisol of post-psychotherapy in the first psychotherapy session and final psychotherapy session. There was a tendency for salivary cortisol to decrease ($p = 0.06$; Table 4).

Table 3. SF-36 and STAI scores across groups

Scale	Subscale	Pharmacotherapy group		Pharmacotherapy and psychotherapy group	
		Pre-	Post-	Pre-	Post-
SF-36	Mental health	40	50	42.5	55
		(30–50)	(37.5–61.25)	(25–48.75)	(51.25–70)*
	Emotional role	75	50	45.85	66.65
		(47.93–87.48)	(43.75–50)	(29.18–56.23)	(45.85–93.75)
	General health	30	40	35	45
		(25–41.25)	(33.75–49.25)	(18.75–52.75)	(45–52)
	Physical functioning	92.5	87.5	77.5	87.5
		(87.5–100)	(68.75–96.25)	(66.25–88.75)	(77.5–93.75)
	Physical role	62.55	62.5	46.9	53.15
		(48.45–75)	(48.45–75)	(20.33–59.38)	(45.35–70.33)
Bodily pain	47	81	46.5	57	
	(19.5–57)	(54.25–100)	(26.75–58.75)	(43.75–69.5)*	
Social functioning	56.25	50	56.25	62.5	
	(37.5–75)	(43.75–53.13)	(40.63–71.88)	(62.5–71.88)	
Vitality	21.9	40.65	40.65	46.9	
	(12.5–29.7)	(15.68–67.2)	(28.13–48.45)	(43.8–64.1)	
STAI	Trait	54	56	61	48
		(51.5–57)	(49.25–57.5)	(53–66)	(40–59)
	State	57	53	56	47
		(53.75–61.25)	(44.75–57.5)	(51.5–65)	(39.52–54.75)*
VAS		2.2		7.7	
		(2.15–2.3)		(7.35–8.15)*	

Median (interquartile range)

SF-36: Medical Outcomes Short Form-36; STAI: State-Trait Anxiety Inventory-JYZ.

*P < 0.05 is considered statistically significant comparisons of scores pre- and post-treatment in the psychotherapy group.

Table 4. Salivary cortisol concentration of pre- and post-psychotherapy at the first and final psychotherapy sessions

	First session		Final session	
	Pre-psychotherapy	Post-psychotherapy	Pre-psychotherapy	Post-psychotherapy
$\mu\text{g}/\text{dl}$	0.18 (0.16–0.27)	0.25 (0.23–0.3)	0.21 (0.16–0.26)	0.155 (0.14–0.24)

Median (interquartile range)

DISCUSSION

In this study, we investigated the effect of psychotherapy interventions for anxiety disorders in middle-aged patients who visited a general medicine department.

We compared the HRQoL subscale scores on the SF-36. Vitality scores, mental health scores, and bodily pain scores improved pre- to post-treatment in the pharmacotherapy and psychotherapy group. Anxiety sensitivity is an independent predictor of bodily pain scores and social functioning scores on the SF-36²⁷. The association between anxiety sensitivity and pain is of interest. Anxiety sensitivity predicts bodily pain score since individuals with high anxiety sensitivity usually have beliefs about the harmfulness of certain bodily sensations²⁸.

In the pharmacotherapy and psychotherapy group, the state anxiety score on the STAI significantly improved. The VAS score showed that the pharmacotherapy and psychotherapy group felt closer to expected treatment achievement than the pharmacotherapy group. This suggests that psychotherapy contributed to the improvement of anxiety states.

Psychotherapy includes listening to patients' thoughts and feelings. We addressed not only the anxiety symptoms but also patient action and changes in disease consciousness. There was an opportunity to "restructure" the patients' past experiences. Psychotherapy decreases the influence of vague unease and offers the opportunity to improve the state of uneasiness. Of course, pharmacotherapy also includes listening to patients' thoughts and feelings. However, pharmacotherapy required shorter consultation hours for one patient than psychotherapy. In a medical examination, the progress of anxiety symptoms is evaluated. Evaluation of the benefits and the side effects of medication were important in physician examinations.

Anxiety disorders are often accompanied by anticipatory anxiety. Even if anxiety symptoms were improved by pharmacotherapy, a patient with an anxiety disorder may have continuing anticipatory uneasiness²⁹. Patient with anxiety disorders tend to be sensitive to symptoms and avoid events that cause uneasiness in their daily life. Therefore, we can expect a decrease in action restrictions by talking about anticipation uneasiness by psychotherapy.

Studies on psychotherapy for anxiety disorders have been reported recently^{8,24,30}. However, psychotherapy may not only affect but also burden a patient. The patient may face the problem at some other time.

In this study, we collected salivary cortisol to examine objectively the burden that psychotherapy itself caused a pa-

tient. There was a tendency for stress, as measured by salivary cortisol, to decrease over time in the pharmacotherapy and psychotherapy group. Before psychotherapy, the patient may have found it difficult to talk with a psychologist in the first psychotherapy session and been uncertain about the procedures. Such anxiety may have caused stress for the patient. However, the tendency for stress seen in the cortisol values decreased post-psychotherapy of the final session. This suggests that any stress associated with psychotherapy diminishes over time.

This psychotherapy intervention study was completed in general medicine^{31,32}. In mental health care, physician-patient alliance and communication are associated with more favorable patient adherence³³. In the general medicine department, the patient has already consulted multiple hospitals including psychiatry, refuses consultation and psychiatric medication, and may feel a limit to pharmacotherapy. In this study, the curative effect may have increased because a general physician and a psychologist treated cooperatively. The combination of pharmacotherapy and psychotherapy can provide appropriate treatment for the patient. It promotes the recognition of curative effects. If a patient can recognize a curative effect, doctor shopping may be prevented³⁴.

The limitations of this study included the small number of cases and the treatment duration. We intended to study middle age. However, we were not able to clarify whether the result was peculiar to middle age. We think that the background of the uneasiness of each generation is different. Based on this result, we will adopt a qualitative psychotherapy study as the next step to clarify characteristic factors and curative effects for middle age.

References

- 1) Rangaraj J, Pélioso A. Identification des troubles anxieux [Identification of anxiety disorders in general medicine.]. *Annales Médico-psychologiques* 161(3): 250-254, 2003
- 2) Deacon B, Lickel J, Abramowitz JS. Medical utilization across the anxiety disorders. *J Anxiety Disord* 22(2): 344-350, 2008
- 3) Sato T, Takeichi M, Shirahama M, Fukui T, Gude JK. Doctor-shopping patients and users of alternative medicine among Japanese primary care patients. *Gen Hosp Psychiatry* 17(2): 115-125, 1995
- 4) Callahan EJ, Jaen CR, Crabtree BF, Zyzanski SJ, Goodwin MA, Stange KC. The impact of recent emotional distress and diagnosis of depression or anxiety on the physician-patient encounter in family practice. *J Fam Pract* 46(5): 410-418, 1998
- 5) Herzig L, Mühlemann N, Bischoff. Troubles émotionnels en médecine de famille ou le visage caché d'une souffrance. [Mental disorders in primary care.] *Rev Med Suisse* 6(249): 1000-1005, 2010
- 6) Baldwin DS, Rafiq R, Talat B. Overcoming barriers in the pharmacological treatment of anxiety disorders. *Neuropsychiatry* 3(1): 33-44, 2013

- 7) Bouwknecht JA. Behavioral studies on anxiety and depression in a drug discovery environment: Keys to a successful future. *Eur J Pharmacol* 753: 158-176, 2015
- 8) Hanrahan F, Field AP, Jones FW, Davey GC. A meta-analysis of cognitive therapy for worry in generalized anxiety disorder. *Clin Psychol Rev* 33(1): 120-132, 2013.
- 9) Pinquart M, Oslejsek B, Teubert D. Efficacy of systemic therapy on adults with mental disorders: A meta-analysis. *Psychother Res* 17: 1-17, 2014
- 10) Bryant C, Jackson H, Ames D. The prevalence of anxiety in older adults: methodological issues and a review of the literature. *J Affect Disord* 109(3): 233-250, 2008
- 11) Ayers CR, Sorrell JT, Thorp SR, Wetherell JL. Evidence-based psychological treatments for late-life anxiety. *Psychol Aging* 22(1): 8-17, 2007
- 12) Blay SL, Marinho V. Anxiety disorders in old age. *Curr Opin Psychiatry* 25(6): 462-467, 2012
- 13) Bradford A, Cully J, Rhoades H, Kunik M, Kraus-Schuman C, Wilson N, et al. Early response to psychotherapy and long-term change in worry symptoms in older adults with generalized anxiety disorder. *Am J Geriatr Psychiatry* 19(4): 347-356, 2011
- 14) Lang IA, Llewellyn DJ, Hubbard RE, Langa KM, Melzer D. Income and the midlife peak in common mental disorder prevalence. *Psychol Med* 41(7): 1365-1372, 2011
- 15) Swift JK, Greenberg RP. A treatment by disorder meta-analysis of dropout from psychotherapy. *J Psychother Integr* 24(3): 193-207, 2014
- 16) Simon GE, Imel ZE, Ludman EJ, Steinfeld BJ. Is dropout after a first psychotherapy visit always a bad outcome? *Psychiatr Serv* 63(7): 705-707, 2012
- 17) Jaeschke R, Siwek M, Dudek D. Compliance in anxiety disorders. *Neuropsychiatri Neuropsycholog* 6(2): 51-59, 2011
- 18) McEwen BS. Allostasis and allostatic load: implications for neuropsychopharmacology. *Neuropsychopharmacology* 22:108-124, 2000
- 19) Dickerson SS, Kemeny ME. Acute stressors and cortisol responses: a theoretical integration and synthesis of laboratory research. *Psychol Bull.* 130:355-391, 2004
- 20) Fukuhara S, Bito S, Green J, Hsiao A, Kurokawa K. Translation, adaptation, and validation of the SF-36 Health Survey for use in Japan. *J Clin Epidemiol* 51(11): 1037-1044, 1998
- 21) Fukuhara S, Suzukamo Y. *Manual of SF-36 v. 2, Japanese version.* (Institute for Health Outcomes & Process Evaluation Research, Kyoto, Japan), 2004
- 22) Spielberger CD, Gorsuch RL, Lushene RE, Vagg PR, Jacobs, GA. *Manual for State-Trait Anxiety Inventory.* (Consulting Psychologists Press, Palo Alto, CA) 1970
- 23) Fukuhara S, Ware Jr. JE, Kosinski M, Wada S, Gandek B. Psychometric and clinical tests of validity of the Japanese SF-36 Health Survey. *J Clin Epidemiol* 51(11): 1045-1053, 1998
- 24) Beard C, Weisberg RB, Keller MB. Health-related quality of life across the anxiety disorders: Findings from a sample of primary care patients. *J Anxiety Disord* 24(6): 559-64, 2010
- 25) Weisberg RB, Beard C, Pagano ME, Maki KM, Culpepper L, Keller MB. Impairment and functioning in a sample of primary care patients with generalized anxiety disorder: Results from the primary care anxiety project. *Prim Care Companion J Clin Psychiatry* 12(5): e1-8, 2010
- 26) Kanda Y. Investigation of the freely available easy-to-use software 'EZ' for medical statistics. *Bone Marrow Transplant* 48(3): 452-458, 2013
- 27) Kang E-H, Kim B, Choe AY, Lee J-Y, Choi TK, Lee S-H. Panic disorder and health-related quality of life: The predictive roles of anxiety sensitivity and trait anxiety. *Psychiatry Res* 225(1-2): 157-163, 2015
- 28) McNally RJ. Anxiety sensitivity and panic disorder. *Biol Psychiatry* 52(10): 938-946, 2002
- 29) Helbig-Lang S, Lang T, Petermann F, Hoyer J. Anticipatory anxiety as a function of panic attacks and panic-related self-efficacy: an ambulatory assessment study in panic disorder. *Behav Cogn Psychother* 40(5): 590-604, 2012
- 30) Hans E, Hiller W. A meta-analysis of nonrandomized effectiveness studies on outpatient cognitive behavioral therapy for adult anxiety disorders. *Clin Psychol Rev* 33(8): 954-964, 2013
- 31) Fernández C, Fernández R, Amigo DI. Characteristics and one-year follow-up of primary care patients with health anxiety. *Primary Care Commun Psychiatry* 10(3): 81-101, 2005
- 32) Menchetti M, Rucci P, Bortolotti B, Bombi A, Scocco P, Kraemer HC, et al. Moderators of remission with interpersonal counselling or drug treatment in primary care patients with depression: Randomised controlled trial. *Br J Psychiatry* 204(2): 144-150, 2014
- 33) Thompson L, McCabe R. The effect of clinician-patient alliance and communication on treatment adherence in mental health care: A systematic review. *BMC Psychiatry* 12: 87, 2012.
- 34) Sato T, Takeichi M, Hara T, Koizumi S. Second opinion behaviour among Japanese primary care patients. *Br J Gen Pract* 49(444): 546-550, 1999