performed using a 1.5-T MRI unit (Sigma Scanner; GE Medical Systems, Milwaukee, Wisc.) with three-dimensional spoiled gradient-recalled acquisition of 1.5 mm contiguous sections under the following conditions: field of view = 230 mm, matrix = 256 × 256 pixels, repetition time (TR) = 25 msec, echo time (TE) = 5 msec, and flip angle = 45°.

We used the manual tracing method and ANALYZE-PC software, Version 6 (Biomedical Imaging Resource, Mayo Foundation, Rochester, Minn.) to analyze the hippocampal and amygdalar volumes. The volumetric procedure has been described previously.[14] The intraclass correlation coefficients for intrarater variability based on the assessment of 20 subjects and the interrater reliability based on the assessment of 13 subjects were 0.99 and 0.96 for the hippocampus, respectively, and 0.98 and 0.81 for the amygdala, respectively. The intracranial volumes (sums of the gray matter, white matter, and CSF volumes) were calculated from non-normalized segmented images using Statistical Parametric Mapping Software 2 (Welcome Department of Cognitive Neurology, London).

### Memory Function

The memory function of the subjects was assessed as a surrogate marker of hippocampal function using the Wechsler Memory Scale—Revised (WMS-R)[15] This test examines both logical and figural memory, producing immediate and delayed memory scores for each parameter. We also calculated the percentage of retention, defined as delayed/immediate × 100.

### Statistical Analyses

The normalized volume values, defined as the absolute volume/intracranial volume, were analyzed by repeated-measures analyses of covariance (ANCOVA) with side as the repeated-measures (within-group) factor and age and alcohol consumption as covariates among the groups. A chi-square test, two-tailed Student's t test, and one-way analysis of variance (ANOVA) with post hoc Tukey's honestly significant difference tests were used to compare the subjects' characteristics. The indexes of the WMS-R and absolute regional brain volumes were also compared using an ANOVA. Additionally, we examined a partial correlation between the Impact of Event Scale subscores and volumetric variables, controlled for age and alcohol consumption, in the PTSD group (two-tailed). A p value of less than 0.05 was considered statistically significant. All data analyses were performed using statistical software SPSS version 12.0 J for Windows (SPSS Japan Institute Inc., Tokyo).

## RESULTS

No statistical differences in demographics (age, height, education, and lifetime alcohol consumption) were seen among the three groups (Table 1). The lifetime history of major depression and the past history of benzodiazepine medication were significantly different between the PTSD and non-PTSD groups, but other medical background characteristics, including the use of adjuvant chemotherapy or endocrinological treatments, were not significantly different. As expected, the PTSD subjects had significantly higher intrusion, avoidance, and total Impact of Event Scale scores compared with the non-PTSD subjects.

A repeated-measures ANCOVA showed no significant main effect among the three groups according to side, and no significant group-by-side interactions for the normalized hippocampal and amygdalar volumes (Table 2). We confirmed the absence of associations between these volumes and possible confounding background characteristics with trend-level differences between the groups, as shown in Table 1 ($p<0.10$). In addition, a repeated-measures ANCOVA after including these factors as covariates did not show any significant main (group) or interaction effects on the hippocampal (main: $p=0.44$, interaction: $p=0.13$) or amygdalar (main: $p=0.76$, interaction: $p=0.34$) volumes. None of the WMS-R indexes differed significantly among the three groups (Table 2).

Additional analyses examining the relationship between PTSD symptoms and volumetric variables revealed an inverse association between the left or right hippocampal volume and the intrusion subscale score, but not the avoidance subscale score, of the Impact of Event Scale in the PTSD group (Table 3). No significant correlations were found between the amygdalar volume and the Impact of Event Scale subscale scores.

We also examined the correlations between each WMS-R index, as surrogate markers for hippocampal function, and the Impact of Event Scale scores in the PTSD group, but did not find any significant correlations (data not shown).

## DISCUSSION

This is the first study examining the hippocampal and amygdalar volumes in subjects with cancer-related

PTSD compared with those not only in healthy comparison subjects but also to those in matched non-PTSD cancer survivors. Cancer-related PTSD was not associated with either hippocampal or amygdalar volume at approximately 1 year after cancer diagnosis. Furthermore, memory functioning in the PTSD group did not differ significantly from that in the non-PTSD or healthy groups.

The lack of association between the hippocampal volume and PTSD in the present study can be explained as follows. First, the duration of PTSD in this study was relatively short. Second, the severity of the PTSD might not be sufficient to alter the hippocampal volume. Kitayama et al.[6] summarized previous studies demonstrating that smaller hippocampi were typically observed in adults with long-standing and severe PTSD. Bonne et al.[16] reported that the hippocampal volumes of subjects with moderate PTSD did not differ from those without PTSD at 1 week or 6 months. Moreover, smaller hippocampi were not related to PTSD at 16 months after trauma[17]; meanwhile, the follow-up period of the present study was about 12 months. Although one positive study[18] showed smaller right hippocampi in PTSD subjects who had experienced trauma 158 days on average prior to the study, it did not set up the traumatized control group. Third, the distinctive features of the cancer experience as a traumatic event might contribute to the present results. Cancer-related PTSD might have a different neurological basis from that of other PTSDs because of its unique characteristics.

The present study did not demonstrate the presence of smaller hippocampi in breast cancer survivors with PTSD at about 1 year after the first experience of their traumas. To date, various authors have discussed whether a smaller hippocampal volume may be a predisposing factor in the development of PTSD[19,20] or the consequence of traumatic events and subsequent PTSD.[20,21] The present negative findings, considering the relatively short period since the onset of trauma, may indicate that a smaller hippocampal volume is not likely to predispose cancer subjects to developing PTSD. However, further longitudinal studies investigating hippocampal volume in cancer-related PTSD are needed to form a definite conclusion.

Although cancer-related PTSD was not associated with hippocampal volume, additional analyses revealed an inverse association between intrusive symptoms and hippocampal volume, which is in line with our previous study reporting smaller hippocampi in cancer survivors with intrusive symptoms.[4] These results may suggest

**TABLE 1. Characteristics of Cancer Survivors with and without PTSD and Healthy Comparison Subjects**

| | PTSD (n = 15) | | | Non-PTSD (n = 15) | | | Healthy Comparison Subjects (n = 15) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mean | SD | Range | Mean | SD | Range | Mean | SD | Range | F[a] | p |
| Age (years) | 44.8 | 7.4 | 32–55 | 45.0 | 7.2 | 31–55 | 44.9 | 7.2 | 31–57 | <0.01 | 0.997 |
| Height (cm) | 156.4 | 6.5 | 148–172 | 158.4 | 5.1 | 153–171 | 155.3 | 5.2 | 145–162 | 1.13 | 0.332 |
| Education (years) | 13.3 | 1.5 | 12–16 | 12.8 | 2.0 | 9–16 | 14.1 | 2.0 | 10–17 | 2.04 | 0.143 |
| Lifetime alcohol consumption (kg) | 23.6 | 44.0 | 0–127.4 | 10.6 | 24.0 | 0–92.8 | 7.0 | 13.0 | 0–37.9 | 1.29 | 0.286 |
| Period from first diagnosis to MRI (days) | 304.0 | 103.0 | 96–406 | 374.9 | 94.0 | 241–575 | — | — | — | 0.30 | 0.586 |
| IES Intrusion | 10.0 | 5.4 | 2–18 | 3.9 | 3.0 | 0–9 | — | — | — | −3.82 | 0.001 |
| Avoidance | 7.1 | 6.2 | 0–22 | 2.0 | 3.0 | 0–8 | — | — | — | −2.83 | 0.010 |
| Total | 17.1 | 8.1 | 2–32 | 5.9 | 5.2 | 0–15 | — | — | — | −4.49 | <0.01 |
| Duration of PTSD (days) | 199.3 | 122.0 | 56–378 | — | — | — | — | — | — | — | — |
| | N | % | | N | % | | | | | Chi-square[b] | p |
| Lifetime major depression | 6 | 40 | — | 0 | 0 | — | — | — | — | 13.85 | 0.001 |
| Depression before cancer | 3 | 20 | — | 0 | 0 | — | — | — | — | 3.33 | 0.068 |
| Depression after cancer | 4 | 27 | — | 0 | 0 | — | — | — | — | 4.62 | 0.032 |
| Past history of benzodiazepine medication | 3 | 20 | — | 0 | 0 | — | — | — | — | 6.43 | 0.040 |
| Past history of antidepressant medication | 0 | 0 | — | 0 | 0 | — | — | — | — | <0.01 | 1.000 |
| Clinical stage of breast cancer (0 or 1) | 5 | 33 | — | 5 | 33 | — | — | — | — | <0.01 | 1.000 |
| Tamoxifen (received) | 6 | 40 | — | 5 | 33 | — | — | — | — | 0.14 | 0.705 |
| Total mastectomy | 7 | 47 | — | 8 | 53 | — | — | — | — | 0.13 | 0.715 |
| Had received chemotherapy | 12 | 80 | — | 7 | 47 | — | — | — | — | 3.59 | 0.058 |
| Had received radiation therapy | 7 | 47 | — | 7 | 47 | — | — | — | — | 0.00 | 1.00 |

PTSD = posttraumatic stress disorder; IES = Impact of Event Scale
[a]Differences in continuous variable were analyzed by ANOVA
[b]Differences in categorical variables were analyzed by the chi-square test

TABLE 2. Brain Volume and Performance on the WMS-R in Cancer Survivors with and without PTSD and Healthy Comparison Subjects

| | PTSD (N = 15) | | Non-PTSD (N = 15) | | Healthy Comparison Subjects (N = 15) | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Absolute Volume ($cm^3$)** | **Mean** | **SD** | **Mean** | **SD** | **Mean** | **SD** | **F[a]** | **p** | |
| Hippocampus | | | | | | | | | |
| Left | 3.39 | 0.30 | 3.26 | 0.42 | 3.23 | 0.28 | 0.98 | 0.38 | |
| Right | 3.49 | 0.35 | 3.45 | 0.38 | 3.4 | 0.30 | 0.30 | 0.74 | |
| Amygdala | | | | | | | | | |
| Left | 1.48 | 0.16 | 1.49 | 0.19 | 1.43 | 0.14 | 0.47 | 0.63 | |
| Right | 1.61 | 0.18 | 1.57 | 0.18 | 1.57 | 0.14 | 0.23 | 0.80 | |
| Gray matter | 664 | 52 | 652 | 43 | 662 | 52 | 0.28 | 0.76 | |
| White matter | 408 | 37 | 410 | 34 | 404 | 41 | 0.12 | 0.89 | |
| Whole brain | 1073 | 84 | 1062 | 73 | 1066 | 91 | 0.07 | 0.94 | |
| Cerebrospinal fluid | 442 | 56 | 453 | 51 | 470 | 51 | 1.09 | 0.35 | |
| Intracranial volume | 1515 | 126 | 1516 | 113 | 1523 | 120 | 0.15 | 0.86 | |
| **Normalized Volume $\times 10^{-3}$** | **Mean** | **SD** | **Mean** | **SD** | **Mean** | **SD** | **F (Group)[b]** | **F (Side)[b]** | **F (Group $\times$ Side)[b]** |
| Hippocampus | | | | | | | 0.98 (df = 2, 40) | 3.28 (df = 1, 40) | 0.98 (df = 2, 40) |
| Left/ICV | 2.24 | 0.17 | 2.16 | 0.26 | 2.11 | 0.18 | | | |
| Right/ICV | 2.31 | 0.18 | 2.28 | 0.21 | 2.21 | 0.18 | | | |
| Amygdala | | | | | | | 0.47 (df = 2, 40) | 0.14 (df = 1, 40) | 0.98 (df = 2, 40) |
| Left/ICV | 0.98 | 0.09 | 0.98 | 0.10 | 0.94 | 0.09 | | | |
| Right/ICV | 1.06 | 0.08 | 1.04 | 0.11 | 1.03 | 0.11 | | | |
| **WMS-R** | **Mean** | **SD** | **Mean** | **SD** | **Mean** | **SD** | **F[a]** | **p** | |
| Logical memory | | | | | | | | | |
| Immediate recall | 21.1 | 5.7 | 22.6 | 9.0 | 26.2 | 6.9 | 1.94 | 0.156 | |
| Delayed recall | 16.3 | 5.6 | 16.9 | 8.4 | 22.4 | 9.7 | 2.60 | 0.086 | |
| Percent retention | 76.7 | 13.0 | 71.5 | 17.0 | 82.4 | 24.0 | 1.27 | 0.292 | |
| Figural memory | | | | | | | | | |
| Immediate recall | 37.9 | 2.4 | 36.4 | 2.9 | 36.4 | 4.1 | 1.14 | 0.330 | |
| Delayed recall | 34.1 | 6.0 | 34.8 | 3.6 | 33.5 | 5.9 | 0.24 | 0.789 | |
| Percent retention | 89.7 | 14.0 | 95.6 | 6.8 | 91.7 | 11.0 | 1.16 | 0.233 | |

SD = standard deviation; PTSD = posttraumatic stress disorder; ICV = intracranial volume; WMS-R = Wechsler Memory Scale—Revised
[a]Differences were analyzed with one-way ANOVA
[b]Differences were analyzed with repeated-measures ANCOVA

TABLE 3. Partial Correlations between Normalized Hippocampal or Amygdalar Volume and IES Scores in Cancer Survivors with PTSD (n = 15)

| | Left Hippocampus | | Right Hippocampus | | Left Amygdala | | Right Amygdala | |
|---|---|---|---|---|---|---|---|---|
| Characteristics | r | p | r | p | r | p | r | p |
| IES intrusion | −0.665 | 0.013* | −0.555 | 0.049* | −0.380 | 0.200 | −0.425 | 0.147 |
| IES avoidance | 0.138 | 0.652 | 0.296 | 0.326 | 0.224 | 0.462 | 0.007 | 0.981 |
| Total | −0.313 | 0.298 | −0.115 | 0.708 | −0.061 | 0.842 | −0.266 | 0.380 |

PTSD = posttraumatic stress disorder; IES = Impact of Event Scale
*$p<0.050$
Covariated: alcohol, age

that intrusive symptoms, rather than cancer-related PTSD, are associated with hippocampal volume. Moreover, this association was significant in the PTSD group but not in the other groups, suggesting that intrusions in subjects with PTSD might be pathophysiologically different from those in non-PTSD subjects. This conclusion, however, remains speculative.

With regard to the amygdala, no previous reports have described volumetric alterations in patients with PTSD. However, we previously reported smaller amygdalae in cancer survivors who experienced intrusive recollections more than 3 years after their surgeries.[5] Nevertheless, the present study did not show any association between amygdalar volume and cancer-related PTSD 1 year after trauma. These results may indicate that a longer duration of PTSD or intrusive symptoms is needed to cause volumetric alterations in the amygdala, but this topic also requires further longitudinal investigations.

The inclusion of subjects with a past history of PTSD and the lack of information on PTSD severity are two limitations of the present study. Despite these limitations, our study also has several strengths. Our study was a well-matched control study with adequate statistical power, and all the subjects were right-handed women without any current psychiatric comorbidity. Moreover, we used both traumatized and nontraumatized comparison subjects, whereas most previous studies used one or the other.

In conclusion, hippocampal volume is not associated with cancer-related PTSD but may be associated with intrusive symptoms in cancer survivors. A future study focusing on intrusive symptoms, rather than full PTSD, is needed to resolve the neurobiology of distress in cancer survivors.

*This study was supported in part by a third-term Comprehensive Research for Cancer Control from the Japanese Ministry of Health, Labour and Welfare and a Grant-in-Aid for Scientific Research (KAKENHI WAKATE B-16790711) from the Japanese Ministry of Education, Culture, Sports, Science and Technology. We would like to thank Prof. Toru Nishikawa for his thoughtfulness, Dr. Noriyuki Kitayama for his valuable advice, and Ms. Nobue Taguchi, Ms. Yukiko Kozaki, and Ms. Yuko Kojima for their research assistance.*

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Stress and Health

*Stress and Health* 24: 407–412 (2008)
Published online 9 July 2008 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/smi.1193
*Received 21 May 2007; Accepted 2 April 2008*

# Short Communication: Psychological impact and associated factors after disclosure of genetic test results concerning hereditary non-polyposis colorectal cancer

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**Summary**

*The purpose of this study is to elucidate the psychological impact of disclosure of genetic test results concerning hereditary non-polyposis colorectal cancer (HNPCC) and to assess factors associated with it, with particular focus on memory function. The subjects were persons who were suspected of having HNPCC and given the choice of undergoing genetic testing. The post-genetic testing psychological impact was evaluated by means of the Impact of Event Scale-Revised (IES-R), and personality tendencies and memory function were evaluated. Final data were obtained from 46 subjects. The results of the genetic testing were 'mutation-positive' in 18 subjects, 'uninformative' in 18 subjects, and 'mutation-negative' in 10 subjects. Comparison of the IES-R scores showed that they tended to be higher in the mutation-positive group, but the differences were not statistically significant. The personality tendency 'nervousness' and verbal memory assessed prior to disclosure were significantly associated with total score on the IES-R. Based on the results of this study it seems possible to minimize the risk of a psychological impact of disclosure of genetic test results by reassessing the follow-up system for persons at high risk of a psychological impact.*


**Key Words**

*cancer; genetic testing; HNPCC; memory function; psychological impact*

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## Introduction

Advances in genetics in recent years have made major contributions to the development of medical genetics. The existence of 'familial

tumours' has been recognized, and genetic testing is now being attempted and has the potential to be of incalculable benefit to humanity (Offit, 1998). Numerous gene analyses related to the genesis and development of colorectal cancer have been conducted, and the existence of hereditary colorectal tumours in the form of hereditary non-polyposis colorectal cancer (HNPCC) and familial adenomatous polyposis has been identified.

However, in contrast to the advances in genetic techniques there has been a great deal of apprehension in regard to the psychological factors associated with their application (Offit, 1998). For this reason some recent studies have investigated the psychological aspects of undergoing genetic testing for hereditary colorectal tumours, especially HNPCC, and being informed of the results (Aktan-Collan, Haukkala, Mecklin, Uutela, & Kääriäinen, 2001; Codori et al., 2003; Esplen et al., 2001; Gritz et al., 2005; Murakami et al., 2004), and many of the studies have shown that genetic testing does not result in short- or long-term adverse psychological outcomes, including depression or anxiety.

Some studies that have investigated the psychological aspects of genetic testing in recent years have been conducted from the standpoint of post-traumatic stress disorder (PTSD; Claes, Denayer, Evers-Kiebooms, Boogaerts, & Legius, 2004; Meiser et al., 2004). PTSD develops as a result of exposure to a traumatic event, and the sensitivity and vulnerability of the individual to stress are considered factors in its aetiology. PTSD is manifested by a decline in ability to concentrate and remember, and since hippocampal atrophy has been observed on diagnostic images in a high percentage of patients clinically, interest has increased in the parenchymal factors that underlie the symptoms. There have been particularly numerous reports of studies on PTSD and decreased memory function (Bremner et al., 1993; Golier et al., 2002; Lindauer, Olff, van Meijel, Carlier, & Gersons, 2006). While reduced memory function has been reported in PTSD in many prior studies, some reports claim that the hippocampal damage reflects stress vulnerability before the traumatic experience, while others claim that it develops as a result of traumatic experiences or PTSD. As a result of these conflicting findings, whether the hippocampal damage is a cause or a result remains unclear. Furthermore, hardly any studies have attempted to identify factors, especially biological factors, which are associated with the psychological effects of being informed of the results of genetic testing for HNPCC.

The purpose of the present study was to investigate the psychological impact of disclosure of genetic test results and the factors associated with it, especially focusing on memory function, in subjects who underwent genetic testing for HNPCC and were informed of the results.

## Methods

### *Subjects*

The subjects were persons who fulfilled the following eligibility criteria amongst those examined for the first time in the genetic counselling outpatient clinic of the National Cancer Center Hospital in Japan: (1) HNPCC was suspected based on a survey that included a pedigree chart, and the choice of undergoing genetic testing was offered and (2) 20 years of age or more.

Subjects to whom the following factors applied were considered ineligible, and they were excluded: (1) subjects for whom it was difficult to understand the purpose of the study (dementia, etc.), (2) subjects in serious physical condition and (3) subjects from families in which the proband was unknown.

### *Measures*

**Sociodemographic variables.** Information regarding the interval between genetic counselling and the disclosure of the test results, age at the time of the examination, gender, marital status, whether the subject had children, history of cancer, household size, occupation, education level, and whether the subject had a religious faith was collected by means of a questionnaire.

**Psychological impact.** We used the revised version of the Impact of Event Scale (IES-R; Asukai et al., 2002; Horowitz, Wilner, & Alvarez, 1979), which evaluates the effect of psychological trauma. It is a self-report questionnaire devised by Weiss and Marmar (1997) and consists of 22 items. The IES-R is composed of three subscales, that is, a hyperarousal subscale in addition to the previous intrusion subscale and avoidance subscale.





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DOI: 10.1002/smi

**Personality characteristics.** We used the Eysenck Personality Questionnaire-Revised (EPQ-R) to assess personality characteristics. The EPQ-R is a self-report questionnaire prepared by Eysenck and Eysenck (1985) and consists of 48 items that evaluate personality traits. It is composed of four scales: Psychoticism, Neuroticism, Extraversion or Introversion and Lie.

**Memory.** We used the revised version of the Wechsler Memory Scale (WMS-R) to assess memory. The original WMS was developed as a scale to objectively measure memory function (Wechsler, 1981). WMS-R measures four memory functions: verbal memory, visual memory, attention or concentration and delayed memory, but only verbal memory and visual memory were evaluated in this study. Since a reduction in hippocampal volume in the brain had been described in PTSD in the past (Bremner, 1999), and the decrease in hippocampal volume has been reported to be associated with a decrease in memory function (Sass et al., 1990), we measured memory function as a means of evaluating hippocampal function.

### *Evaluation procedure*

This study was approved by the Institutional Review Board of the National Cancer Center Hospital of Japan.

After the completion of genetic counselling, the physician in charge of the study explained the nature of the study according to the disclosure document to the potential subjects who fulfilled the eligibility criteria. Those who gave their consent were assessed in regard to socio-demographic variables, personality traits and memory function before disclosure of the genetic rest results, and that information was used as the baseline data. The IES-R was administered as a measurement of psychological impact 1 month after explanation of the genetic test results, and the scores were used as the data 1 month after disclosure of the test results.

### *Statistical analysis*

The data were not normally distributed, so non-parametric tests were used.

The Kruskal-Wallis test was performed in regard to each of the items that evaluated psychological impact in order to conduct a comparative assessment between groups classified according to the results of the genetic test.

Spearman's rank correlation coefficient, the Mann-Whitney *U*-test, or the Kruskal-Wallis test was used to assess the factors associated with degree of psychological impact, and the IES-R scores and other factors were analysed for associations.

The $p$ values in all of the tests are two-tailed, and $p < 0.05$ were considered significant. Statistical Package for the Social Sciences software version 14.0J for Windows was used to perform all of the statistical analyses.

## Results

### *Subjects' participation*

Eight potential subjects were ineligible because they refused to undergo genetic testing, or it was difficult for them to understand the purpose of the study, or the proband was unknown. There were 51 potential subjects who fulfilled the eligibility criteria, and consent to participate in the baseline survey was obtained from 47 of them. One of the 47 subjects later refused to take the memory function test (WMS-R), and ultimately there were 46 subjects of the final analysis.

### *Subjects' characteristics and results of genetic testing*

The socio-demographic variables, results of genetic testing, and scores on the EPQ-R of the 46 subjects who met the eligibility criteria are shown in Table I. The results of the genetic testing were 'mutation-positive' in 18 (39.1 per cent) subjects, 'uninformative' in 18 (39.1 per cent) subjects and 'mutation-negative' in 10 (21.7 per cent) subjects.

### *Psychological impact of the results of genetic testing*

The scores on the IES-R, the scale that was used to evaluate degree of psychological impact in this study, are shown in Table II.

The IES-R scores tended to be higher in the mutation-positive group than in either of the other two groups, but the differences were not statistically significant.

Table I. Subjects' characteristics ($n = 46$).

| | *n* | Mean | SD |
|---|---|---|---|
| Age | | 49.5 | 13.0 |
| Gender | | | |
| Male | 22 | | |
| Female | 24 | | |
| Number of days after receipt of the test results | | 78.7 | 48.8 |
| Marital status | | | |
| Married | 38 | | |
| Unmarried | 8 | | |
| Children | | | |
| Yes | 37 | | |
| No | 9 | | |
| History of cancer | | | |
| Unaffected | 14 | | |
| Affected | 32 | | |
| Proband | | | |
| Yes | 29 | | |
| No | 17 | | |
| Household size | | | |
| Alone | 4 | | |
| ≥2 | 42 | | |
| Employed | | | |
| Yes | 32 | | |
| No | 14 | | |
| Education | | | |
| ≤12 | 187 | | |
| >2 | 28 | | |
| Religion | | | |
| Yes | 7 | | |
| No | 39 | | |
| Genetic testing results | | | |
| Positive | 18 | | |
| Uniformative | 18 | | |
| Negative | 10 | | |
| EPQ-R | | | |
| Psychoticism | | 3.4 | 1.7 |
| Neuroticism | | 4.4 | 2.5 |
| Extraversion/Introversion | | 6.6 | 3.3 |
| Lie | | 5.5 | 3.0 |
| WMS-R | | | |
| Verbal memory | | 100.5 | 12.5 |
| Visual memory | | 118.3 | 12.1 |

EPQ-R: Eysenck Personality Questionnaire-Revised; WMS-R: Wechsler Memory Scale-Revised.

### *Factors associated with psychological impact*

The results of a univariate analysis showed that 'neuroticism' on the EPQ-R ($p = 0.010$) and 'verbal memory' on the WMS-R ($p = 0.037$) were significantly associated with total IES-R scores, which are an indicator of psychological impact.

Table II. Comparison of psychological impact between groups that were classified on the basis of the genetic test results.

| | Positive | Negative | Uninformative | $p^*$ |
|---|---|---|---|---|
| IES-R | | | | |
| Intrusion | 28.33† | 19.70† | 20.78† | 0.085 |
| Avoidance | 25.75 | 21.95 | 22.11 | 0.385 |
| Hyperarousal | 25.67 | 22.39 | 21.60 | 0.512 |
| Total | 28.78 | 19.44 | 21.30 | 0.070 |

* Kruskal-Wallis test, † Mean rank.
IES-R: Impact of Event Scale-Revised.

No significant associations were found with any other factors (Table III).

## Discussion

### *Factors associated with the psychological impact of the disclosure of genetic information*

**Personality tendencies; neuroticism.** The results of the analysis in this study showed that 'neuroticism' was significantly associated with greater psychological impact of disclosure of the genetic information. Previous studies have reported that neurotic, highly anxious and depressive personalities are the factors associated with psychological impact the results of this study supported the results of the studies of Tjemsland, Soreide and Malt (1998) Neuroticism is anxiety proneness, and hence we would expect persons who are more anxiety prone to be more prone to react to the threat of testing or the results of testing.

**Memory function; verbal memory.** A significant association was found between the psychological impact of disclosure of genetic information and verbal memory. Bremner et al. (1993) observed verbal memory impairment in a study of PTSD patients amongst American soldiers returning from combat in Vietnam. The same as in these earlier studies, the results of the present study support an association between psychological impact and memory disturbances, particularly verbal memory disturbances.

Knowledge of the pathology underlying PTSD and memory disorders has accumulated, and nervous system damage, primarily to the hippocampus, has been postulated in PTSD. The question of whether the memory disorder in PTSD





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DOI: 10.1002/smi

Table III. Factors associated with psychological impact (total score on the IES-R).

| | r | p* |
|---|---|---|
| Age | −0.11 | 0.458 |
| Number of days after receipt of the test results | −0.103 | 0.496 |
| EPQ-R | | |
| Psychoticism | −0.069 | 0.647 |
| Neuroticism | 0.377 | 0.010 |
| Extraversion/Introversion | −0.189 | 0.210 |
| Lie | −0.006 | 0.969 |
| WMS-R | | |
| Verbal memory | −0.308 | 0.037 |
| Visual memory | −0.172 | 0.254 |

| | n | Mean | p† |
|---|---|---|---|
| Gender | | | |
| Male | 22 | 21.57 | 0.320 |
| Female | 24 | 25.27 | |
| Marital status | | | |
| Married | 38 | 23.62 | 0.890 |
| Unmarried | 8 | 22.94 | |
| Children | | | |
| Yes | 37 | 23.11 | 0.669 |
| No | 9 | 25.11 | |
| History of cancer | | | |
| Unaffected | 14 | 23.07 | 0.879 |
| Affected | 32 | 23.69 | |
| Proband | | | |
| Yes | 29 | 23.86 | 0.799 |
| No | 17 | 22.88 | |
| Household size | | | |
| Alone | 4 | 21.00 | 0.678 |
| ≥2 | 42 | 23.74 | |
| Employed | | | |
| Yes | 32 | 23.97 | 0.703 |
| No | 14 | 22.43 | |
| Education | | | |
| ≤12 | 18 | 23.78 | 0.905 |
| >2 | 28 | 23.32 | |
| Religion | | | |
| Yes | 7 | 30.57 | 0.107 |
| No | 39 | 22.23 | |

| | n | Mean | p‡ |
|---|---|---|---|
| Genetic testing results | | | |
| Positive | 18 | 28.78 | 0.070 |
| Uninformative | 18 | 19.44 | |
| Negative | 10 | 21.30 | |

* Spearman's rank correlation coefficient, † Mann-Whitney *U*-test, ‡ Kruskal-Wallis test.

patients is due to the PTSD, or whether persons who already have a memory disorder tend to develop PTSD has been debated, but no clear answer has been obtained. The finding of a significant association between the strength of the psychological impact after disclosure of the genetic information and poor memory function before disclosure of the genetic information in the present study suggests that the poorer a person's memory function is originally, the more susceptible the person is to a psychological impact. In other words, it was suggested that damage to the hippocampus existed before the traumatic experience, and that the traumatic experience in such individuals, and their vulnerability to stress, that is, the problem of dealing with the stress associated with it, governed the severity of the psychological impact on them.

### *Limitations and perspectives*

The first limitation of this study that can be cited is that since the subjects were persons who accepted the offer of genetic testing and genetic counselling, it would be difficult to claim that the subjects of this study adequately represented the parent population. The second limitation is that we used scales that measure psychological impact and made measurements that especially focused on PTSD. It seems that in the future it will also be necessary to evaluate other psychological parameters, such as depression, cancer worry and cancer-specific distress. Lastly, as the present study elucidated, only the short-term effects of disclosure of the results of genetic testing and the sample size was small, it cannot be concluded that there was no significant difference between IES-R scores according to mutation status groups. In order to determine the full psychosocial impact of genetic testing it will be necessary to extend the investigation to assessment of its long-term effects.

Despite the existence of these limitations, the results of this study suggest that the risk of a psychological impact of disclosure of genetic test results can be minimized by reviewing the counselling system for subjects who have neuroticism or a verbal memory disturbance.

#### Acknowledgments

This work was supported in part by Grants-in-Aid for Cancer Research (11-21) from the Japanese Ministry of Health, Labor and Welfare.

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*Stress and Health* 24: 407–412 (2008)
DOI: 10.1002/smi

*International Journal of Psychiatry in Clinical Practice*, 2008; 12(1): 11–18

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ORIGINAL ARTICLE

# Revised psychopharmacological algorithms for the treatment of mood disorders in Japan

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**Abstract**

*Objective.* To revise the psychopharmacology algorithms for the treatment of mood disorders published in 1999 in Japan. *Methods.* The algorithms were established based on clinical psychopharmacological evidence, the results of a questionnaire survey sent to 200 Japanese psychiatrists, and the consensus of all the research members. *Results.* Six categorized algorithms have been developed, i.e. mild or moderate major depression, severe non-psychotic major depression, psychotic depression, mania, bipolar depression, and rapid cycling mood disorder. *Conclusion.* The revised algorithms will be helpful for the treatment of mood disorders in Japan.

**Key Words:** *Psychopharmacology algorithm, bipolar disorder, Japan, major depression, mood disorders*

## Introduction

Collectively, mood disorders continue to be one of the greatest disease burdens in the world [1]. We previously published the first Japanese version of algorithms for the treatment of mood disorders in 1999 [2]. However, there were a limited number of drugs available at that time. For example, selective serotonin reuptake inhibitors (SSRIs) were not approved. Since then, two SSRIs, fluvoxamine and paroxetine, and a serotonin-noradrenaline reuptake inhibitor (SNRI), milnacipran, have been widely used for the treatment of mood disorders. Moreover, novel antipsychotics such as olanzapine and quetiapine were approved in 2001. In this study, we have revised the algorithms for the treatment of mood disorders. There are six algorithms in this report, i.e. mild or moderate depression, severe non-psychotic depression, psychotic depression, mania, bipolar depression, and rapid cycling bipolar disorder.

## Methods

The methods used for developing the algorithms were according to previous reports [2,3]. Although it is essential that algorithms should be developed on evidence-based medicine (EBM), everyday clinical practice is quite different from clinical trials. Thus, we sent a questionnaire survey to about 200 psychiatrists in 19 institutes (13 university hospitals, five national institutes and one private psychiatric hospital) throughout Japan. They worked in university hospitals, psychiatric hospitals or clinics. Their mean length of psychiatric practice was 8.5 years. As for typical cases presented, the questionnaire asked about the selection of drugs, dose, duration of treatment, use of concomitant drugs, alternative drug therapy for failures to the initial therapy, and so on. In this study, for example, SSRIs and an SNRI were selected in 57and 18% of the responders, respectively, as first-line treatment of

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*(Received 16 March 2006; accepted 8 February 2007)*

ISSN 1365-1501 print/ISSN 1471-1788 online © 2008 Taylor & Francis
DOI: 10.1080/13651500701330791

major depressive disorder, mild or moderate. Switching to another antidepressant was selected in 84% when the initial therapy failed. As for major depressive disorder, severe without psychotic features, TCAs, SSRIs, an SNRI and electroconvulsive therapy (ECT) were chosen as the initial therapy in 57, 19, 9 and 8% of the responders, respectively. When the initial treatment failed, switching to another antidepressant, augmentation and ECT were selected in 52, 25 and 20%, respectively [4]. The results of this survey were taken into consideration when developing algorithms. Evidence levels were rated as follows: A = good research-based evidence, i.e., multiple, randomized controlled trials (RCTs) and substantial group consensus supporting the guideline statement; B = fair research-based evidence, i.e., at least one RCT and some degree of group consensus supporting the guideline statement; C = based primarily on group consensus, with minimal research-based evidence but significant clinical experience. We tried to collect as many studies conducted in Japan as possible.

### Explanation of algorithms

*Algorithm for the treatment of major depressive disorder, mild or moderate (Figure 1)*

A diagnosis of major depression is made according to the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM-IV). We recommend SSRIs (fluvoxamine and paroxetine) and an SNRI (milnacipran) as first-line treatment, because they are as efficacious as tricyclic and related antidepressants, less toxic, and more tolerable [5–10]. It is preferable to start drug therapy at a low dose, and then increase the dose gradually. The concomitant use of benzodiazepines is useful for up to the first 4 weeks of treatment [11]. The goal of therapy in the acute phase is to eliminate the depressive symptoms and regain


Figure 1. Algorithm for the treatment of major depression, mild or moderate. *Dotted rectangle: evaluate outcome (remission or not) in case of efficacy. SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin-noradrenaline reuptake inhibitor; TCA, tricyclic antidepressant; non-TCA, non-tricyclic antidepressant; ECT, electroconvulsive therapy.

psychological and social functioning. If the patient is judged as "in remission", a continuation therapy should be kept for at least 4–6 months with the same dose of the effective drug [12]. If treatment at maximum dosage is not effective [13], a switch to another antidepressant or augmentation strategies should be considered. Augmentation is an option when the antidepressant is intolerable or its efficacy is partial. Lithium is by far the most effective drug for augmentation [14] (level A). Other drugs used for augmentation include thyroid hormones [15] (level A), olanzapine [16] (level B), and dopamine agonists such as bromocriptine [17] (level C). The results of buspirone and pindolol treatments are conflicting [18–20]. ECT should be considered when switching and augmentation strategies have failed [21] (level A).

*Algorithm for the treatment of severe non-psychotic depression (major depressive disorder, severe without psychotic features) (Figure 2)*

The diagnosis of severity is based on the DSM-IV criteria. For severe cases, hospitalization should be planned as a general rule because the impairment of social/occupational function is severe. Although TCAs and an SNRI, venlafaxine, seem to be more effective than SSRIs in inpatients [5,22], a meta-analysis demonstrated that paroxetine is as efficacious as TCAs in patients with severe depression [6]. Thus, any of TCAs, non-TCAs, SSRIs, and SNRIs can be selected as the first-line treatment. Another option is ECT [21] (level A). ECT is useful for patients with a high risk of suicide or in poor general condition. In the case of partial or no efficacy, augmentation, switching, or ECT can be chosen as the second- and third-line treatments.

*Algorithm for the treatment of psychotic depression (major depressive disorder, severe with psychotic features) (Figure 3)*

The diagnosis is based on the DSM-IV criteria. The treatment strategies should be considered according to suicide risk, severity of agitation, and oral intake ability. If the patient shows no suicidal risk and is without agitation, monotherapy with

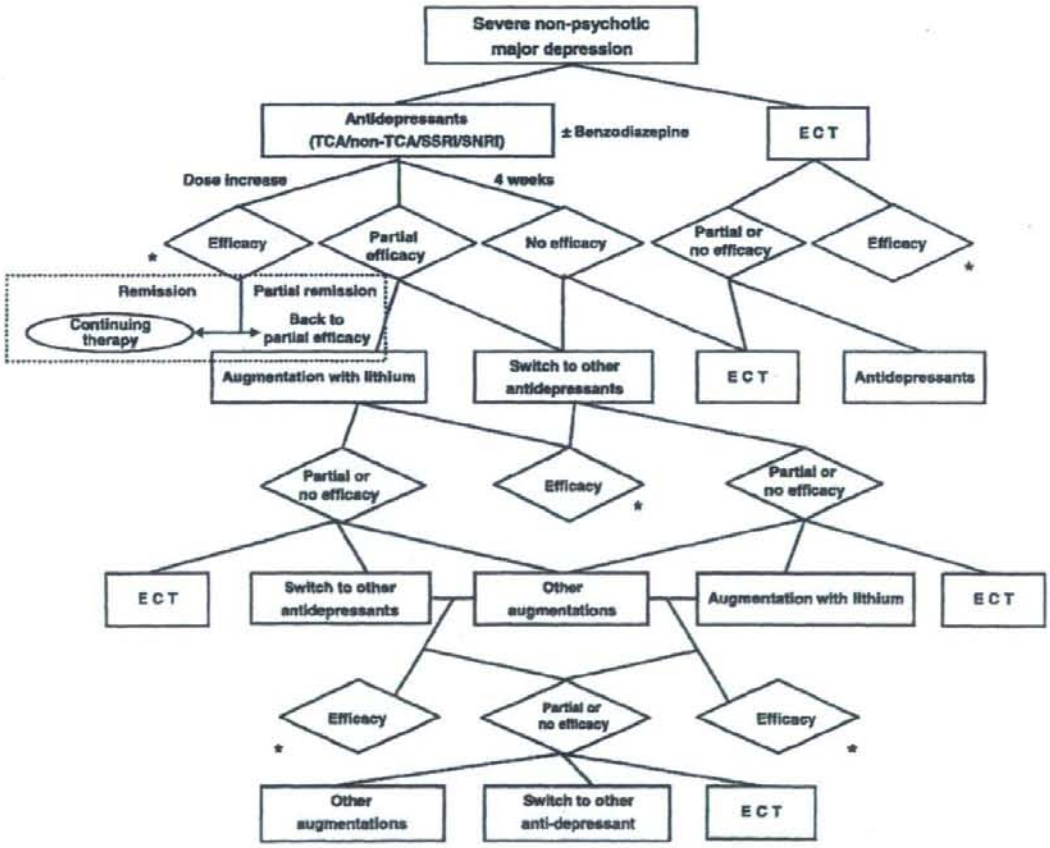


Figure 2. Algorithm for the treatment of non-psychotic severe depression. *Dotted rectangle: evaluate outcome (remission or not) in case of efficacy. SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin-noradrenaline reuptake inhibitor; TCA, tricyclic antidepressant; non-TCA, non-tricyclic antidepressant; ECT, electroconvulsive therapy.

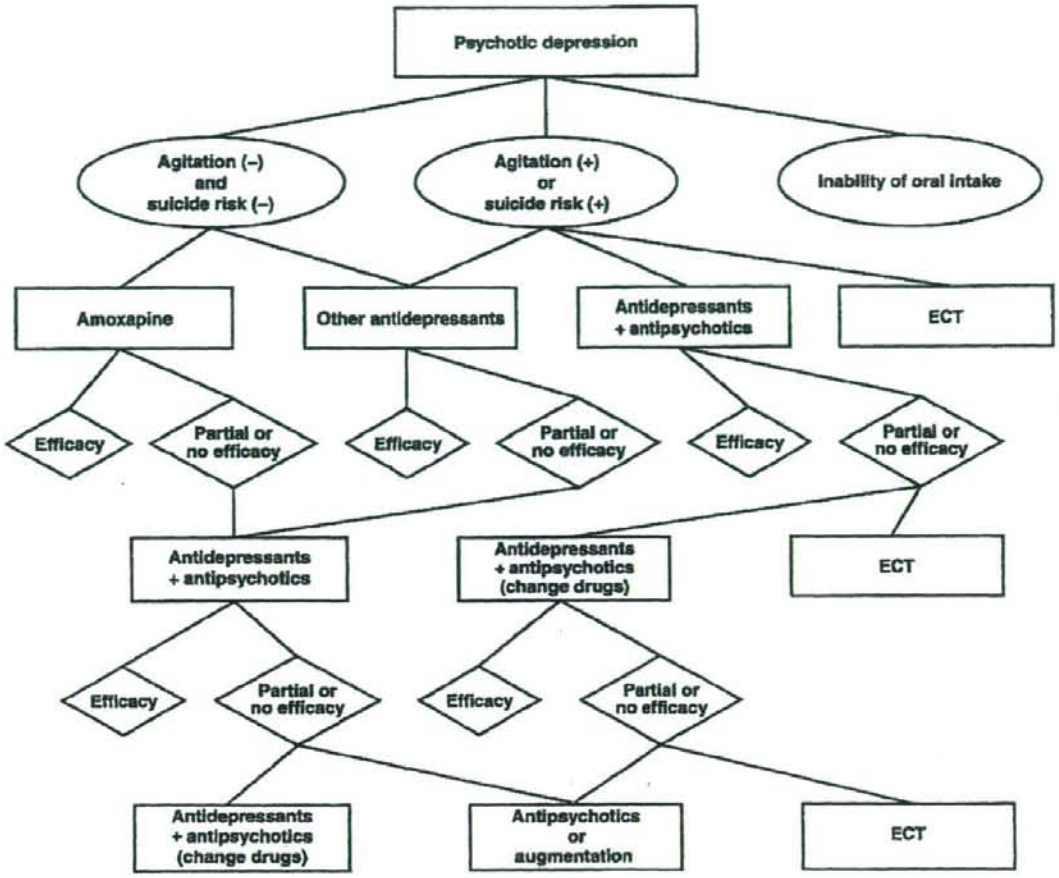


Figure 3. Algorithm for the treatment of psychotic depression.

antidepressants such as amoxapine or fluvoxamine is recommended as one of the first choices [23–25] (level B). For the treatment of psychotic depression with a high risk of suicide or agitation, an antidepressant-antipsychotic combination [23,24,26] or ECT [27] (level A) is recommended. Combination therapy with SSRIs and atypical antipsychotics may be helpful [28] (level B). In the case of partial or no efficacy, augmentation, switching to another combination of antidepressant and antipsychotic, or ECT can be chosen as the second- and third-line treatments.

*Algorithm for the treatment of bipolar disorder, manic episode (Figure 4)*

The diagnosis of mania is according to the DSM-IV criteria. The first-line treatment is mood stabilizers. There is no difference in antimanic efficacy among lithium, carbamazepine, and valproate [29–31] (level A). Valproate seems to be favorable in the treatment of mixed mania [31] (level B). Antipsychotics such as sultopride [32] (level B) and zotepine [33] (level B), alone or in combination with mood stabilizers, are often used for the treatment of mania. Recently, atypical antipsychotics, olanzapine [34] (level A), quetiapine [35] (level A), and risperidone [36–38] (level A) are preferred because of their low incidence of extrapyramidal side effects. A combination of mood stabilizers may be helpful [39] (level B). Furthermore, ECT could be chosen when pharmacotherapy fails [40] (level A).

*Algorithm for the treatment of bipolar disorder, depressive episode (Figure 5)*

Patients with bipolar disorder sometimes become depressed even under treatment with lithium. However, there are a limited number of studies available in these cases. An increase in the dose of lithium, the use of carbamazepine or valproate, or the addition of antidepressants such as SSRI or SNRI can be selected [41–43] (level B). ECT is an option for the treatment of refractory bipolar depression.

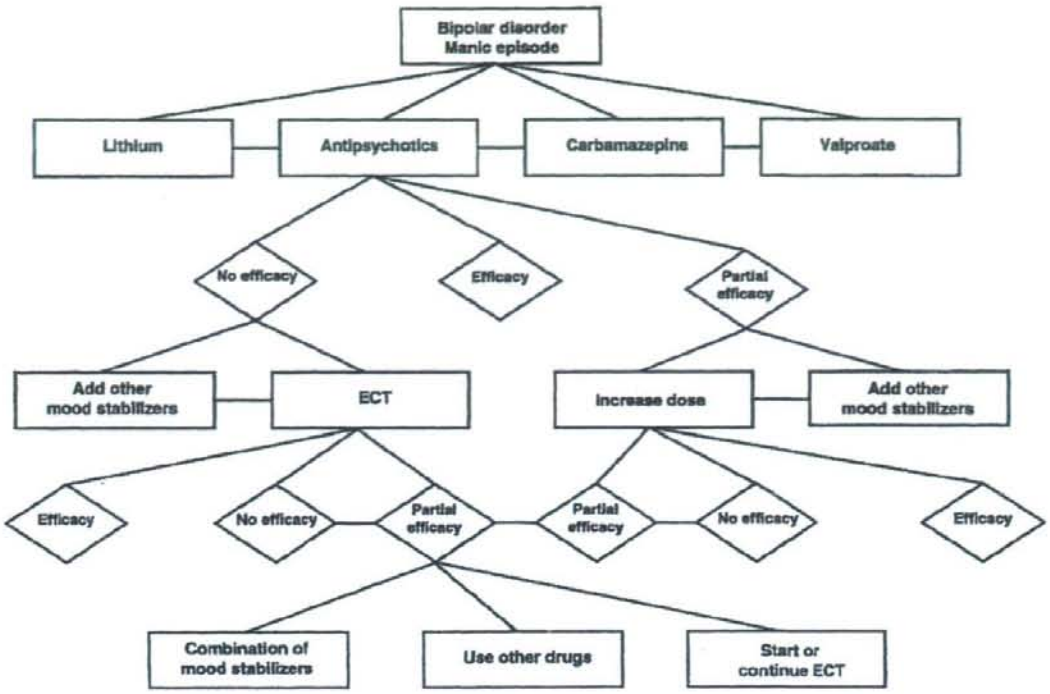


Figure 4. Algorithm for the treatment of bipolar disorder, manic episode.

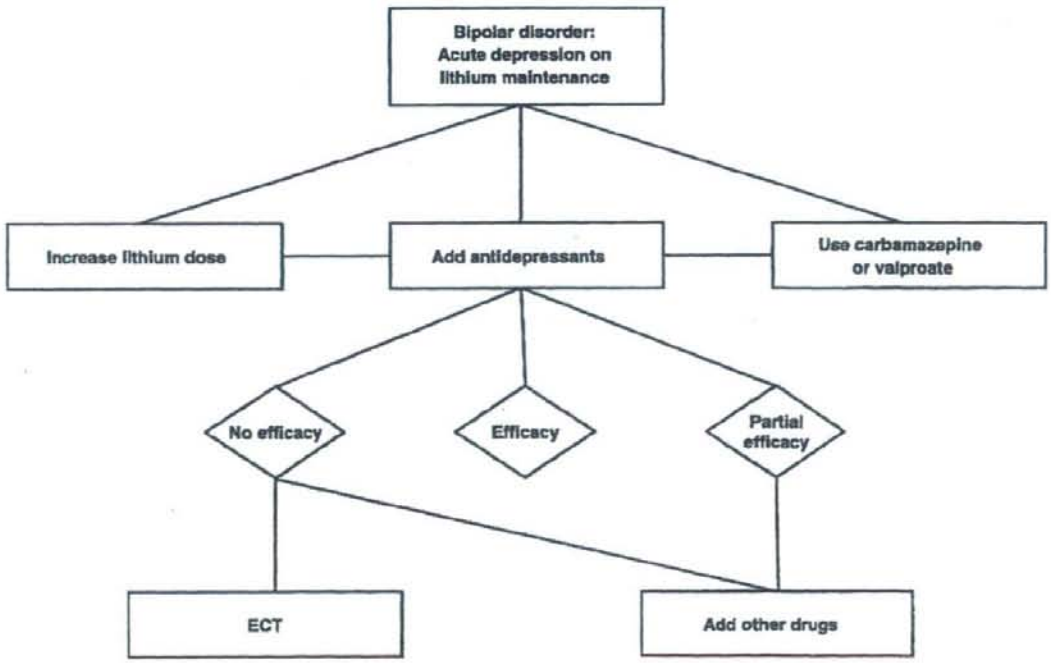


Figure 5. Algorithm for the treatment of bipolar disorder, depressive episode.

*Algorithm for the treatment of rapid cycling mood disorder (Figure 6)*

The diagnosis of rapid cycling (RC) is according to the DSM-IV criteria. RC is sometimes induced by hypothyroidism, female hormone disturbance, organic brain syndrome, or antidepressant treatment. Most clinical studies on RC are based primarily on group consensus, with minimal research-based evidence but significant clinical experience (level C). The first-line treatment is valproate or carbamazepine [44,45]. Because carbamazepine might induce severe side effects, valproate may be preferable. Although RC is usually resistant to lithium, the combination of lithium and valproate (or carbamazepine) may be helpful in cases of partial or no efficacy. Another option is to add levothyroxine to mood stabilizers [46]. Where the above treatment does not show any efficacy, clonazepam [47], atypical antipsychotics such as olanzapine [48], or ECT [49] can be used.

## Discussion

We have demonstrated the revised Japanese version of the algorithms for the treatment of mood disorders. As compared to the first version of the algorithms [2], major differences are the availability of newer antidepressants (fluvoxamine, paroxetine, and milnacipran) and antipsychotics (quetiapine and olanzapine). Moreover, an anticonvulsant, valproate, was approved for the treatment of bipolar disorder in 2002.

As for major depressive disorder, mild or moderate, the first-line treatment is SSRIs or SNRIs instead of TCAs, nonTCAs, or sulpiride. With regard to sulpiride, its clinical efficacy is not definite [50] (level B) and it is sometimes associated with side effects such as hyperprolactinemia, weight gain, and extrapyramidal signs. Thus, we do not recommend it as the first-line treatment in this version.

While lithium, carbamazepine, and antipsychotics such as zotepine and sultopride were recommended

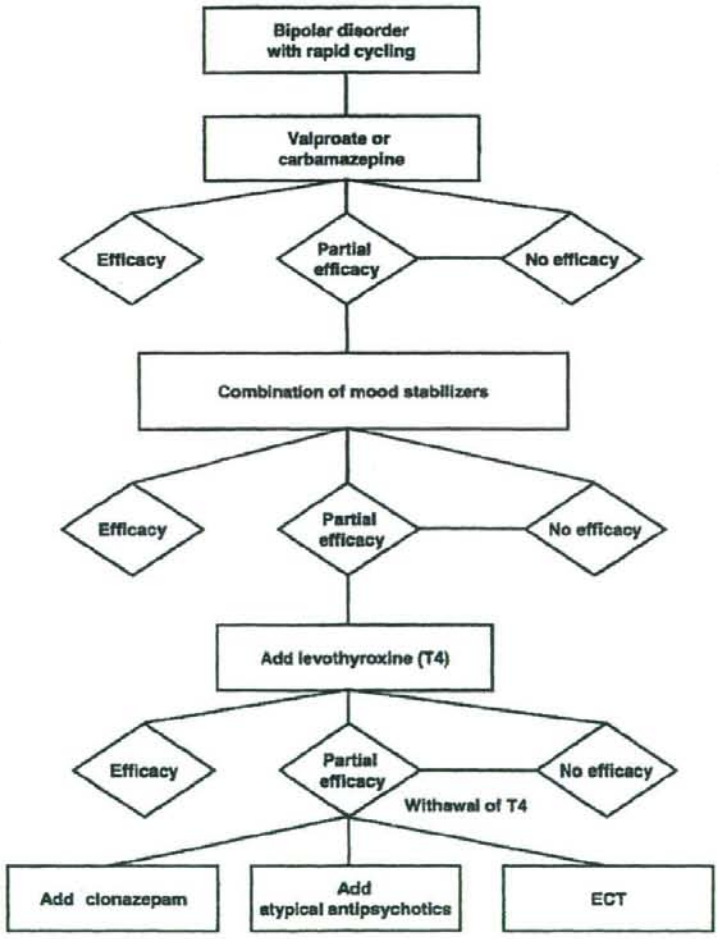


Figure 6. Algorithm for the treatment of rapid cycling mood disorder.

for the initial treatment of mania in the first version, valproate and novel antipsychotics such as quetiapine and olanzapine can be chosen in this revised version. Furthermore, valproate is also preferred for the first-line treatment of rapid cycling mood disorders because of its safety.

As for severe non-psychotic depression, psychotic depression, and bipolar depression, the revised treatment algorithms are similar to the original ones.

Except for clinical trials to approve new drugs, only a few RCTs have been conducted in Japan. Thus, most of the studies useful for the development of these revised algorithms were not conducted in Japan. Because clinical psychopharmacological evidence is insufficient, more and more randomized, placebo-controlled studies should be conducted to accumulate good research-based evidence in Japan. Furthermore, we have just begun to evaluate clinical outcomes following the use of these algorithms.

## Key points

- Revised psychopharmacology algorithms for the treatment of mood disorders have been presented
- These algorithms have been developed according to methods based on clinical psychopharmacological evidence, the results of a questionnaire survey sent to 200 Japanese psychiatrists, and the consensus of all the research members
- The algorithms consist of six categories including major depression and bipolar disorder
- Clinical psychopharmacological evidence is insufficient in Japan

## Statement of interest

The authors have no conflict of interest with any commercial or other associations in connection with the submitted article.

## Acknowledgement

A part of this work was supported by a grant from the Ministry of Health, Welfare, and Labour in Japan.

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**Psycho-Oncology**
*Psycho-Oncology* 17: 154–160 (2008)
Published online 27 April 2007 in Wiley InterScience (www.interscience.wiley.com). **DOI**: 10.1002/pon.1213

# Clinical experience of the use of a pharmacological treatment algorithm for major depressive disorder in patients with advanced cancer

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Received: 3 August 2006
Revised: 7 March 2007
Accepted: 12 March 2007

## Abstract

**The objective of this study was to describe the applicability and the dropout of the pharmacological treatment algorithm for major depressive disorder in patients with advanced cancer.**

**Psychiatrists treated major depressive disorder in advanced cancer patients on the basis of the algorithm. For discussing the problems related to the algorithm, we reviewed the reasons for the non-application of the algorithm and the reasons for dropout of patients within a week of initiation of treatment.**

**The algorithm was applied in 54 of 59 cases (applicability rate, 92%). The reasons for the non-application of the algorithm were as follows: the need to add a benzodiazepine to an antidepressant in 4 cases and the need to choose alprazolam despite the depression being moderate in severity, in order to obtain a rapid onset action and reduce anxiety in a patient with short prognosis. Nineteen of the 55 patients dropped out within a week of initiation of treatment based on the algorithm. Delirium was the most frequent reason for dropout.**

**The applicability rate was high, but several problems were identified, including those related to the combination of antidepressants and benzodiazepines, pharmacological treatment of depression in patients with short prognosis, and delirium due to antidepressants.**


**Keywords: algorithm; major depressive disorder; advanced cancer; antidepressant; clinical experience**

## Introduction

Major depressive disorder is the most distressing psychiatric disorder in advanced cancer patients. Although the prevalence of major depressive disorder in the community is 3–4% [1], it rises to 5–26% in advanced cancer patients [2]. Several studies have indicated that depression can have a serious negative impact on the quality of life of patients with advanced cancer [3,4], causing severe suffering [5], and a desire for early death [6,7], or suicide [8], as well as psychological distress to the family members [9].

While pharmacological treatment is important in depression, advanced cancer patients have some characteristics that can influence the pharmacological treatment of depression. For instance, advanced cancer patients also have various somatic symptoms and physically compromised conditions [10,11], so the minimal deleterious effects of medication can be serious in these patients. Also there are often problems related to the drug delivery routes [12], and rapid onset of effects of the antidepressants is required in patients with a poor prognosis. Although a standard strategy has long been desired for the treatment of major depression in cancer patients, few controlled clinical studies have been conducted in this population [13–20]. In particular, there are very few studies on patients with advanced cancer, and few appropriate guidelines are available for the treatment of depression in this patient population. Though there is no pharmacological treatment algorithm for depression in this population, generally algorithms are a good idea and not only provide the framework for vast amounts of information, but can also shape the database in response to certain clinical questions around disease management or utilization of medical procedures. The several reasons why algorithms have grown in popularity include the following: reduced unnecessary variation in clinical practice