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Eur J Clin Pharmacol (2007) 63:991–996
DOI 10.1007/s00228-007-0355-8

PHARMACOGENETICS

Effects of CYP2D6 polymorphisms on neuroleptic malignant syndrome

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Received: 5 May 2007 / Accepted: 23 July 2007 / Published online: 14 August 2007

Abstract
Objective Neuroleptic malignant syndrome (NMS) is one of the most serious adverse reactions to antipsychotic medications. We accumulated data on Japanese NMS patients and, in a study designed to examine the effects of drug metabolism on the occurrence of NMS, tested the possibility of association between NMS and *CYP2D6* polymorphisms.
Methods We studied 53 patients who had experienced NMS and 112 healthy individuals. We determined what drugs the patients with NMS had been given and retrospectively identified candidates for drugs causing NMS. We screened the prevalence of *CYP2D6* genotypes using polymerase chain reaction and restriction fragment length polymorphism analyses.
Results The prevalence of **5* alleles in the group of all patients with NMS was higher than that in the controls, though this difference was not statistically significant (10.4% vs. 5.4%; P=0.107; odds ratio (OR) 2.05; 95% confidence interval (CI) 0.87–4.80). No association was found between the frequency of **10* alleles and the occurrence of NMS. We found **4* and duplicated alleles in only one patient each among the patients with NMS. A total of 29 patients appeared to have developed NMS as a result of having taking CYP2D6 substrates. The prevalence of **5* alleles in these 29 patient was significantly higher than that in the controls (15.5% vs. 5.4%; P=0.020; OR 3.25; 95% CI 1.30–8.13).
Conclusion Our findings suggest that the *CYP2D6*5* allele is likely to affect vulnerability to development of NMS.

Keywords Adverse reaction · CYP2D6 · Gene deletion · Neuroleptic malignant syndrome · Polymorphism

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Introduction

Neuroleptic malignant syndrome (NMS) is a well-recognized, severe, and potentially lethal adverse reaction to antipsychotic administration [1]. In addition to neuroleptic drugs, NMS can be caused by antidepressants, lithium carbonate, and other psychotropic agents. NMS is characterized by hyperthermia, extrapyramidal signs, altered consciousness, fluctuating blood pressure, incontinence, and dyspnea, as well as other features [2]. The frequency of its occurrence with conventional antipsychotic agents has been reported to vary from 0.02% to 2.44%, whereas a review of case reports has indicated that atypical antipsychotic agents can cause NMS, which can in some instances be severe enough to be fatal [3]. Caroff et al. and Ananth et al. reported the mortality rate is 4.4–11.3% [4, 5].

CYP2D6, an isozyme among the CYP mono-oxygenases, is responsible for the hepatic metabolism of various psychotropic agents. More than 40 polymorphic alleles that affect enzymatic activity have been described for the *CYP2D6* genes (http://www.imm.ki.se/cypalleles/cyp2d6.htm). The phenotypes of CYP2D6 activity resulting from these polymorphisms can be divided into extensive, poor,

and ultrarapid metabolizers (EM, PM, and UM) according to enzymatic activities [6]. The PM phenotype, lacking CYP2D6 expression, is caused by total gene deletion or single-nucleotide polymorphisms in a gene inherited in an autosomal recessive fashion. Together with the gene deletion allele (**5*), the polymorphic *CYP2D6* alleles **3* and **4* account for most instances of PM phenotype in Caucasians, although **3* and **4* are rare in Eastern Asians. Instead, the **10* allele, which encodes an unstable enzyme with decreased catalytic activity, is relatively frequent in Eastern Asia [7]. The frequency of the **5* allele is similar (4 to 6%) in Caucasian and East Asian populations [6]. Nishida et al. reported that the allelic frequencies of **10*, **5*, **4*, and **3* were 38.1%, 4.5%, 0.2%, and 0%, respectively, in 206 healthy Japanese subjects [8].

The PM phenotype is clinically important, as lack of the associated metabolic pathway may lead to toxicity and adverse reactions upon administration of certain drugs in standard doses [6, 9]. On the other hand, several studies have identified individuals with NMS who possessed *CYP2D6* polymorphisms resulting in defective CYP2D6 activity [10–12]. In this study, we performed systematic screening for *CYP2D6* polymorphisms and assessed genetic associations with the occurrence of NMS in Japanese patients.

Methods

We studied 53 patients (29 men and 24 women) who had experienced NMS. The patients had been recruited from several hospitals since 1996. NMS was diagnosed according to the criteria of Pope et al. [13]. Psychiatric diagnoses were made according to the criteria of the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*). Our control subjects were 112 healthy individuals without psychiatric diagnoses (33 men and 79 women). We recruited control subjects from personnel in hospitals and students, and we carried out the Mini-International Neuropsychiatric Interview (MINI) to exclude psychiatric patients. All subjects were Japanese and unrelated. We presented all NMS patients and healthy controls that we have accumulated so far. The prevalence of *CYP2D6*3*, **4*, and **10* in a part of our samples were previously reported elsewhere [7, 14].

We determined the drugs that the patients with NMS had been given and retrospectively identified candidates for drugs causing NMS. If NMS occurred after increase of an antipsychotic drug, we regarded the drug as a candidate. If sudden discontinuation of antipsychotics or antiparkinsonian drugs caused NMS, we mentioned it in the Table 1. In the other cases, we listed all psychotic drugs the patients were given.

This study was approved by the ethics committee of the Yokohama City University School of Medicine. Written informed consent was obtained from all of the patients and control subjects.

Genetic analysis

Genomic DNA was extracted from peripheral white blood cells from all patients and control subjects using the Wizard Genomic DNA Purification Kit (Promega, Madison, WI, USA) according to manufacturer guidelines. Polymerase chain reaction (PCR) and restriction fragment length polymorphism (RFLP) analyses were performed to screen for **10* and **4* alleles according to the method of Wang et al. [15] and Kawanishi et al. [14]. Long PCR was performed to screen for *CYP2D6* gene deletion allele (*CYP2D6*5*) and duplicated alleles according to the method of Lundqvist et al. [16] for duplication and that of Johansson et al. [17] and Wennerholm et al. [18] for deletion using two sets of oligonucleotide primers in each PCR reaction. Alleles for which neither **10*, **5*, **4* nor duplicated alleles could be identified were classified as *CYP2D6*1* (wild-type) alleles. Genetic analyses were performed by an investigator unaware of which subjects had developed NMS.

Statistical analysis

Statistical analyses were performed using the χ^2 tests with Fisher's exact test. Statistical tests were two-tailed, with P values less than 0.05 considered significant. These analyses were performed using SPSS 11.0 for Windows (SPSS Japan, Tokyo).

Results

Table 1 shows characteristics of the patients with NMS. Mean age at the first NMS episode was 50.8 years [standard deviation (SD)=16.8). NMS relapsed in ten patients. The principal diagnoses were schizophrenia in 41 cases; mood disorders in four; delusional disorder, alcohol dependence, drug dependence, dementia, steroid-induced psychotic disorder, psychotic disorder due to viral encephalitis, autism, and personality disorder in one case each. CYP2D6 genotypes and allele frequencies of the NMS patients and control subjects are given in Table 2. The observed frequency of **5* alleles in patients with NMS was higher than that in controls, though the difference between groups was not statistically significant [10.4% vs. 5.4%; P=0.107; odds ratio (OR) 2.05; 95% confidence interval (CI) 0.87–4.80). No association was found between **10* alleles and the occurrence of NMS. The**4* and duplicated

Table 1 Characteristics of the patients with neuroleptic malignant syndrome (NMS)

Number	Sex (M/F)	Age of first NMS onset	Times of NMS	Diagnosis	Genotype	Possible causative drugs of NMS occurrence [1]
1	M	54	1	Schizophrenia	*1/*1	HPD
2	F	45	1	Schizophrenia	*1/*10	Bromperidol
3	M	46	1	Schizophrenia	*1/*10	Unknown
4	M	30	1	Schizophrenia	*1/*5	Fluphenazine
5	M	41	3	Schizophrenia	*10/*10	[a]Mosapramine, [b]HPD, [c]risperidone
6	F	72	2	Schizophrenia	*1/*10	[a]HPD, [b]sulpiride
7	M	40	1	Schizophrenia	*1/*1	Risperidone, thioridazine
8	M	59	2	Schizophrenia	*5/*10	[a]HPD, [b]HPD
9	M	76	1	Schizophrenia	*1/*5	Amoxapine, CPZ
10	M	43	2	Alcohol dependence	*1/*1	[a]Levomepromazine, [b]unknown
11	F	24	2	Schizophrenia	*1/*1	[a]Sulpiride, [b]CPZ, sultopride
12	M	28	1	Schizophrenia	*1/*1	HPD
13	F	60	1	Mood disorder	*1/*10	Amoxapine, amitriptyline
14	M	16	1	Schizophrenia	*10/*10	HPD
15	F	26	2	Schizophrenia	*1/*10	[a]HPD, propericyazine, [b]thioridazine
16	F	24	1	Schizophrenia	*1/*1	Bromperidol, discontinuation of biperiden
17	F	20	1	Schizophrenia	*1/*1	Risperidone
18	M	55	4	Psychotic disorder due to viral encephalitis	*1/*1	[a]Li , [b]unknown, [c]Li, HPD, [d]levomepromazine
19	M	30	1	Schizophrenia	*1/*10	Nemonapride
20	F	62	2	Schizophrenia	*4/*10	[a]Bromperidol, [b]Discontinuation of neuroleptics
21	M	57	1	Mood disorder	*1/*1	Amitriptyline, levomepromazine
22	F	74	1	Schizophrenia	*1/*10	HPD
23	M	48	1	Mood disorder	*1/*1	Mianserin
24	F	31	1	Schizophrenia	*5/*10	Risperidone, olanzapine
25	F	32	1	Schizophrenia	*10/*10	HPD
26	M	21	1	Schizophrenia	*10/*10	HPD
27	F	62	1	Schizophrenia	*1/*1	Discontinuation of HPD and bromperidol
28	F	38	1	Personality disorder	*1/*1	Sultopride
29	M	30	1	Drug dependence	*1/*1	Mianserin, levomepromazine
30	F	51	1	Schizophrenia	*1/*10	Risperidone, perospirone
31	F	31	1	Schizophrenia	*1/*5	Levomepromazine, propericyazine, perospirone
32	M	34	1	Schizophrenia	*10/*10	HPD
33	M	73	1	Schizophrenia	*10/*10	Risperidone, tiapride
34	M	19	1	Schizophrenia	*1XN/*1	Quetiapine
35	F	38	1	Schizophrenia	*1/*1	HPD, CPZ
36	M	21	1	Schizophrenia	*1/*1	Zotepine, bromperidol
37	F	65	1	Schizophrenia	*1/*1	Risperidone, nemonapride, CPZ
38	M	9	1	Autism	*1/*5	HPD
39	M	66	1	Dementia	*1/*5	Quetiapine
40	F	68	1	Mood disorder	*1/*1	Reduced amantadine
41	F	54	2	Schizophrenia	*1/*5	[a]HPD, CPZ, levomepromazine, sulpiride, tiapride, [b]CPZ
42	F	58	2	Steroid-induced psychotic disorder	*10/*10	[a]Perospirone [b]reduced bromocriptine
43	M	47	1	Schizophrenia	*1/*1	HPD
44	M	21	1	Schizophrenia	*1/*10	Sultopride
45	M	34	1	Schizophrenia	*1/*1	Sultopride, zotepine
46	M	49	1	Schizophrenia	*1/*5	Risperidone, quetiapine
47	M	26	1	Schizophrenia	*10/*10	Discontinuation of antipsychotics
48	M	66	1	Schizophrenia	*1/*1	Risperidone, zotepine

Table 1 (continued)

Number	Sex (M/F)	Age of first NMS onset	Times of NMS	Diagnosis	Genotype	Possible causative drugs of NMS occurrence [1]
49	M	58	1	Schizophrenia	*5/*10	HPD
50	F	71	1	Schizophrenia	*1/*10	Levomepromazine
51	F	56	1	Delusional disorder	*10/*10	Quetiapine
52	F	35	1	Schizophrenia	*1/*5	Risperidone, levomepromazine
53	F	71	1	Schizophrenia	*1/*10	Zotepine

[1] *HPD* haloperidol, *CPZ* chlorpromazine, *Li* lithium carbonate
[a], [b], [c], and [d] indicate the first, second, third, and fourth episodes of NMS, respectively.

alleles were found in only one patient each among the NMS group.

To estimate the clinical effects of deletion, NMS patients were classified into those whose NMS-causative drugs had been CYP2D6 substrates. A total of 29 patients had been given CYP2D6 substrates (risperidone, olanzapine, fluphenazine, thioridazine, haloperidol, chlorpromazine, amitriptyline, or mianserin [9]) (Table 1). The prevalence of **5* alleles in these 29 patients was significantly higher than that in controls (15.5% vs. 5.4%; P=0.020; OR 3.25; 95% CI 1.30–8.13).

Discussion

Since NMS was first proposed as a clinical entity in the 1960s, various case descriptions and clinical studies of it have been reported from psychiatric and neurologic units, though the mechanisms underlying NMS remain unclear. Dopaminergic systems of the central nervous system appear likely to be involved in the onset of NMS, as all neuroleptics known to cause NMS act as dopamine receptor antagonists [1]. Certain predisposing conditions such as dehydration, malnutrition, exhaustion, infection, and organic brain diseases are risk factors for the development of NMS [19–23]. High or rapidly increasing antipsychotic doses, large numbers of intramuscular injections, and psychomotor agitation are additional risk factors that tend to be interrelated [19, 20]. On the other hand, NMS often recurs despite absence of acquired risk factors. In addition, occurrences of familial NMS have been reported. Deuschl et al. reported NMS in twin brothers with schizophrenia [24], and Otani et al. described familial occurrence involving a mother and her two daughters [25]. Furthermore, patients who have experienced NMS remain at increased risk for its occurrence [1, 26–29]. These findings suggest that constitutional factors under genetic control play roles in the onset of NMS, which has spurred mutation analyses and genetic association studies. Although minimization of risk factors and increased awareness of NMS could decrease its incidence, and detection of prodromal symptoms could decrease the morbidity of NMS, prediction and prevention are still difficult, as there are individual differences in responses to drugs, and no biological marker is available to identify individuals who are inherently at increased risk for NMS.

Recent findings of pharmacogenetic studies have indicated that polymorphisms of the *CYP2D6* gene are associated with interindividual differences in drug responses. PM individuals who are homozygous for either point mutations in or deletion of the *CYP2D6* gene are unable to metabolize CYP2D6 substrates, resulting in higher plasma drug concentrations. The PM phenotype is clinically important, as lack of the associated metabolic pathway may lead to toxicity and adverse reactions upon administration of drugs in standard doses [6, 9]. Dose effect of the *CYP2D6* gene has been shown to be associated with CYP2D6 activity, and this activity is decreased in individ-

Table 2 CYP2D6 genotypes and allele frequencies in patients with neuroleptic malignant syndrome (NMS) and control patients (%)

	Controls (n=112)	Patients with NMS (n=53)	Patients with NMS caused by drugs including CYP2D6 substrates (n=29)
Genotypes			
*1/*1	46 (41.1)	20 (37.7)	11 (37.9)
*1/*10	32 (28.6)	11 (20.8)	4 (13.8)
*10/*10	21 (18.8)	9 (17.0)	5 (17.2)
*1/*5	8 (7.1)	8 (15.1)	6 (20.7)
*5/*10	4 (3.6)	3 (5.7)	3 (10.3)
*4/*10	0	1 (1.9)	0
*1XN/*1	1 (0.9)	1 (1.9)	0
Alleles			
*1	133/224 (59.4)	60/106 (56.6)	32/58 (55.2)
*10	78/224 (34.8)	33/106 (31.1)	17/58 (29.3)
*5	12/224 (5.4)	11/106 (10.4)	9/58 (15.5)[a]
*4	0	1/106 (0.9)	0
*1XN	1/224 (0.4)	1/106 (0.9)	0

[a] $\chi 2$, Fisher's exact test, $p<0.05$

uals heterozygous for deletion [6]. Several studies have suggested that adverse reactions to neuroleptics are associated with decreased or deficient CYP2D6 activity. PM is more prevalent among patients with than those without drug-induced extrapyramidal symptoms [30, 31]. For example, tardive dyskinesia (TD) has been linked to decreased CYP2D6 activity. Kapitany et al. genotyped patients with schizophrenia for the *3, *4, and *5 alleles and found that frequency of TD was higher in patients heterozygous for these alleles [32]. Ohmori et al. also found an association between TD and the *10 allele in Japanese patients with schizophrenia [33]. Similar conclusions were obtained in another study [30, 34].

Genetic association studies also have sought to identify *CYP2D6* polymorphisms affecting susceptibility to NMS. We also reported the finding of homozygosity for the *CYP2D6*10* allele in two psychiatric patients who had previous episodes of NMS, although we failed to identify an association between the *3, *4, or *10 allele and NMS in previous studies [7, 11, 14]. Recently, we reported two NMS patients with schizophrenia who were found to possess a *CYP2D6* gene-deletion allele [12].

Thus, in the study reported here, we reexamined the possibility of an association between CYP2D6 polymorphisms including the *5 allele and NMS in 53 patients with NMS. We found that the prevalence of *5 alleles in the 29 patients whose NMS-causative drugs were CYP2D6 substrates was significantly higher than that in controls (15.5% vs. 5.4%; P=0.020), though we did not find a significant difference in prevalence of *5 alleles between the group of patients with NMS and controls (10.4% vs. 5.4%; P=0.107).

On the other hand, no association was found between NMS and *10 or *10/*10 genotypes. The frequency of genotype of either *5/*10, *4/*10, *10/*10, or *1/*5 tended to be higher in NMS patients whose NMS-causative drugs were CYP2D6 substrates than that in controls (P= 0.076). Kubota et al. found that no difference was observed in metabolic activity of dextromethorphan O-demethylation between individuals with *10/*10 and *1/*5 genotypes [35]. Mihara et al. reported that the steady-state plasma concentrations of equal doses of risperidone were not significantly different between *10/*10 and *5/wt [36]. Another study investigating haloperidol metabolism indicated that *5 might have stronger impact than *10 [37]. The two polymorphic alleles, *10 and *5, possibly have different impacts in drug metabolism.

CYP2D6 substrates taken by patients with a *5 allele were metabolized at a reduced rate, resulting in higher plasma levels of the CYP2D6 substrate; it is the same condition as that brought on by known risk factors of NMS: rapidly increasing or greater numbers of intramuscular injections of neuroleptic drugs. We speculate that accumulation or high plasma concentrations of CYP2D6 substrates may have induced cellular toxicity and/or aberrant neurotransmission linked to the pathogenesis of NMS. Screening for at least the *CYP2D6*5* allele before initiating antipsychotic therapy including CYP2D6 substrates might be useful in identifying subjects at risk of developing NMS.

The following limitations to our study should be noted: we did not know whether sulpiride, sultopride, levomepromazine, propericyazine, and mosapramine are CYP2D6 substrates; we did not consider causes of NMS other than medications because physical conditions of the patients were not fully investigated in this study; and we lacked laboratory data concerning serum concentrations of antipsychotics because this study was retrospective and we could measure only a few serum concentrations of antipsychotics, given the constraints of the Japanese health insurance system.

NMS may be a heterogeneous condition with respect to etiology. We believe that by themselves, *CYP2D6* gene polymorphisms such as the *5 allele cannot explain all occurrences of NMS. Systemic analyses involving functional genetic polymorphisms of drug targets, such as dopamine receptors [38], may also be needed to improve understanding of this disorder. Our findings do suggest, though, that the *CYP2D6*5* allele is likely to affect vulnerability to development of NMS. Although 53 patients is a small number for an association study, NMS occurs only rarely, and this number is the greatest in a genetic study of NMS to date. Whereas our sample size has been the greatest for an association study regarding NMS to date, it is still small. Larger case-control studies will be needed to assess the effects of *CYP2D6* gene polymorphisms on the occurrence of NMS.

Acknowledgements This study was supported in part by a Grant-in-Aid for Scientific Research (No. 16790698) from the Ministry of Education, Science, Sports, and Culture, Japan.

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Jpn J Clin Oncol 2008;38(12)867–870
doi:10.1093/jjco/hyn115

Short Communication

Problem-Solving Therapy for Psychological Distress in Japanese Cancer Patients: Preliminary Clinical Experience from Psychiatric Consultations

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Received August 25, 2008; accepted September 22, 2008; published online November 12, 2008

Problem-solving therapy (PST) is a brief, structured psychological treatment. Preliminary clinical findings regarding the effectiveness of PST for treating psychological distress experienced by Japanese cancer patients are presented. Our actual clinical experience in administering PST to four consecutive distressed cancer patients was reviewed. All of the patients were breast cancer survivors who were referred to us after undergoing surgery. Three cases received six PST sessions each and one case received three PST sessions. The depression and anxiety scores decreased after PST. Our preliminary experience suggests that PST is an effective treatment for alleviating psychological distress in Japanese cancer patients and that this treatment should be further examined in a clinical trial.

Key words: cancer – psychological distress – problem-solving therapy – psychological intervention

INTRODUCTION

The experience of cancer causes considerable stress in patients. Depression and anxiety, including adjustment disorders and major depression, are the most prevalent forms of psychological distress experienced by cancer patients (1). Patients sometimes seek psychological treatment to help them cope with their cancer even though their psychological status does not meet the criteria of a formal psychiatric diagnosis (1). Previous Japanese studies investigating the prevalence of psychological distress in cancer patients have reported rates of 15–40% (2,3). Psychological distress not only causes great suffering, but also diminishes quality of life, amplifies pain and other symptoms, and sometimes leads to suicide.

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Regarding therapy for psychological distress, two potentially effective management strategies are available: psychotherapy and pharmacotherapy. A previous Japanese study indicated that psychotherapy is deemed more acceptable than pharmacotherapy by cancer patients (4). Although previous reviews have highlighted the general efficacy of various psychosocial interventions, very few studies have addressed which kinds of psychotherapy are feasible or effective for Japanese cancer patients in actual clinical oncology practice. In this context, we have been interested in the effectiveness of problem-solving therapy (PST), which is a brief, structured psychological treatment (5). PST has been shown to be effective for the treatment of common mental disorders, including depression and anxiety, in primary care and oncology settings in Western countries (5).

The current report introduces our preliminary clinical findings regarding the effectiveness of PST for treating psychological distress experienced by Japanese cancer patients.

PATIENTS AND METHODS

Subjects

The subjects were four consecutive cancer patients who were referred to one of the authors for PST. The patients were referred for the treatment of psychological distress and were followed up by one of the authors. The patients received PST for several reasons, such as intolerability and/or reluctance to use medications and refractoriness to general supportive psychotherapeutic approaches. Psychiatric diagnoses were made using the *Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition (DSM-IV). As this study was conducted in the routine clinical setting, treatments of PST were provided under usual health national insurance system (we therefore could not charge the patients any special fee for PST). In the following, several items of personal information were modified to preserve the anonymity of the patients.

Problem-Solving Therapy

PST focuses on the present and helps patients to use their own skills and resources to function better. The patients are taught how their psychological symptoms may be linked to psychosocial problems that they are facing, and PST provides the patients with a structured strategy to solve them. If these problems can be resolved, their symptoms may improve. PST includes the following seven steps (5): (i) explanation of the treatment and its rationale, (ii) identification, definition and breakdown of the problem, (iii) establishing achievable goals, (iv) generating solutions, (v) evaluating and choosing the solution, (vi) implementing the chosen solution, (vii) evaluating the outcome after the solution has been implemented. We developed a PST manual for Japanese cancer patients. The manual was designed to help the patients list and summarize problems commonly encountered by cancer patients, including cancer treatment, symptoms of cancer, treatment side effects, fear of recurrence/metastasis, relationship with medical staff, family and other people, economic problems, information issues, employment/school issues. The manual also includes tips and worksheets for patients to use while progressing through each step of PST. The first treatment session lasted about 90 min, and subsequent sessions lasted 40–50 min. In principle, six treatment sessions were given. In addition, we incorporated a simple behavioral treatment skill, activity scheduling, into the PST (5). In activity scheduling, we helped the patients find and then engage in pleasurable activities on a more frequent basis to help alleviate their psychological distress.

Assessment

We used two psychological measures, the Beck Depression Inventory-II (BDI-II) (6) and the Hospital Anxiety and Depression Scale (HADS) (7), to evaluate psychological distress in clinical practice, depending on the patients' psychological status. The BDI-II is a 21-item self-reported questionnaire to evaluate the severity of depression. The total score can range from 0 to 63, with higher scores representing severer depression. The validity and reliability of the Japanese version of the BDI-II has been confirmed (8). Depression severity was assessed according to the following BDI scores (9): 0–13, minimal; 14–19, mild; 20–28, moderate; 29–63, severe. The HADS is a 14-item self-reported questionnaire consisting of an anxiety and depression subscale: the total score can range from 0 to 42. Higher scores indicate severer anxiety and depression. The Japanese version of the HADS has been validated for cancer populations, and the optimal cut-off point for screening for adjustment disorder and major depressive disorder was 10 of 11 (10). In this report, the results of these measures before and immediately after intervention were used.

Because of the small sample size, we presented the descriptive statistics of the BDI-II and HADS scores pre- and post-intervention only.

RESULTS

All of the patients were breast cancer survivors who were referred to us after undergoing surgery (Table 1). Their psychiatric diagnoses varied, ranging from normal reaction to major depression. Both the BDI-II scores [pre: 26.8 (SD = 14.0); post: 13.3 (SD = 7.7)] and the HADS scores [pre: 17.0 (SD = 2.6); post: 9.7 (SD = 3.5)] improved after PST. Three patients completed all six PST sessions, while one patient received only three PST sessions (one case, a 32-year woman, terminated PST early because she declined further treatment after finding a new job.). Patient adherences with each therapy session, including activity scheduling, was generally excellent for all the four patients.

Here, the clinical process of PST is introduced using one example case (Ms. D). Ms. D was a 52-year-old housewife who lived with her husband and two children. She was diagnosed as having early-stage breast cancer (Stage 0) and received a surgical resection (simple mastectomy). Because the results of a sentinel lymph node biopsy were negative, she was told that she would not need any further adjuvant therapy. However, she became nervous and anxious about the possible recurrence of her breast cancer and its development into a serious physical disease. Consequently, she could not sleep and began to feel several kinds of physical discomfort, including dizziness, tinnitus and palpitations. She visited an otolaryngologist and neurologist, but no evidence of organic disease was found. Three months after her operation, she consulted a psychiatric clinic and began to take psychotropic medications, including antidepressants and benzodiazepines, and was subsequently referred to one of the authors. An initial assessment revealed a depressive mood and a fear of recurrence, and she was diagnosed as having an adjustment disorder with mixed emotional features (BDI-II score, 31). Thereafter, we continued to provide her with general psychosocial treatment, including continuous medication and supportive psychotherapy. However, her condition remained unchanged during the

Table 1. Characteristics of the cancer patients

Age	Sex	Cancer site	Stage	Cancer treatment (period after cancer diagnosis at the start of PST)	Psychiatric diagnosis	PST	BDI-II score		HADS score	
							Pre PST	Post PST	Pre PST	Post PST
32	Female	Breast	Early	Hormone therapy after left mastectomy (18 months after diagnosis)	Major depression in partial remission	3 sessions during 4 weeks	21	17	19	13
47	Female	Breast	Early	Hormone therapy after left partial mastectomy + radiation (20 months after diagnosis)	Normal reaction, but having perceived distress	6 sessions during 10 weeks	12	2	14	6
47	Female	Breast	Locally advanced	None after right mastectomy + chemotherapy (53 months after diagnosis)	Major depression	6 sessions during 20 weeks	45	15	NA	8
52	Female	Breast	Early	None after left simple mastectomy (13 months after diagnosis)	Adjustment disorder with mixed emotional features	6 sessions during 12 weeks	29	21	18	10

BDI-II, Beck Depression Inventory-II; HADS, Hospital Anxiety and Depression Scale; PST, problem-solving therapy; NA, not applicable. One case, a 32-year-old woman, completed only three PST sessions.

next 8 months. We therefore introduced her to the concept of PST and she expressed an interest. At this time, her BDI-II score was 29. During the PST session, various problems were revealed, including a fear of recurrence, dissatisfaction with her communication with her physician, marital discord and tension with her husband, and frequent difficulties with her son. Interestingly, she selected the difficulties with her son as the first problem that she would like to deal with using PST. During the PST session, she stated that much of her distress resulted from quarrels with her son, and these quarrels often began after she had scolded him. Using the PST skills, she defined her problem ('I can't help scolding my son.') and defined an achievable goal ('I will refrain from scolding him for a couple of hours after his return from school.'). She generated nine potential solutions and finally selected three solution strategies. She was able to complete most of the solution strategies. During the evaluation process, she said, 'I feel better because I am having fewer quarrels with my son.' After the third PST session, she stated, 'Lately, I am not so worried about my disease' and 'I feel that I shall see what I shall see'. At this time, her BDI-II score was 19. She next tried to resolve her marital discord. Although this problem was not successfully solved, she understood that her goal was too difficult and that she needed to set a smaller goal. She completed a total of six PST sessions over a period of 3 months. By the completion of the PST, her feelings had improved (Table 1). Although the six sessions were not sufficient to deal with all of her problems and she partly failed to resolve one of her problems, as mentioned, she felt that 'I will be able to cope with my problems using the PST'.

DISCUSSION

Many types of psychosocial interventions exist for reducing psychological distress among cancer patients. However, very few studies have confirmed the effectiveness of such interventions in Japan, and the available studies were limited to group psychosocial interventions (11,12) and progressive muscle relaxation (PMR) (13). Several barriers to providing such interventions exist in the Japanese medical system and/or culture, including the difficulty of accruing a homogeneous cancer patient group for appropriate interventions, disadvantages of group interventions for some patients (e.g. reluctance to share individual experiences), and the patient's dissatisfaction with simple behavioral interventions such as PMR. Furthermore, although Western studies have systematically reviewed the effectiveness of psychosocial interventions for cancer patients, demonstrating that cognitive behavioral therapy is recommended (14), our clinical experience suggests that most cancer patients do not have extreme distortions of cognition and that traditional cognitive therapeutic interventions are often not appropriate for cancer patients. Additionally, fewer trained clinical psychologists are available to provide formal psychological intervention for cancer patients in Japan, and this situation creates a barrier to its dissemination among them. In this context, we are interested in using PST to alleviate psychological distress in cancer patients within the Japanese medical system, based on the appropriateness and simplicity of PST.

The current findings suggest that PST can be used to alleviate common forms of psychological distress experienced by cancer patients, such as adjustment disorders and/or major depression. In addition, good adherence to the therapy suggests PST is an acceptable therapy for Japanese cancer patients. Furthermore because PST is a brief therapy that consists of six treatment sessions, PST can be a cost effective psychotherapy. The fact that the subjects were cancer survivors, including both short and long duration after cancer diagnosis, who continued to experience psychological distress after cancer diagnosis, suggests that one of possible subjects who benefit from PST may be distressing cancer

survivors, irrespective of duration after cancer. Although many cancer survivors experience a fear of recurrence and a previous Japanese survey indicated that the most common distress experienced by Japanese cancer patients is a fear of recurrence and/or disease metastasis (15), no standard interventions for alleviating this form of distress exist (16). Our experience suggests that PST may be useful for reducing fears of recurrence, although PST does not directly deal with fear or anxiety itself but instead focuses on present daily problems. In addition, a previous study suggested the usefulness of PST for alleviating distress among palliative care patients (17). These findings suggest that PST can be used for a broad range of psychological distress in clinical oncology settings. On the other hand, because we could not find the long-lasting effect of PST (e.g. 6 or 12 months after treatment), whether the effect of PST is persistent or not should be addressed in a future study. In addition, because treatment period ranged widely from 4 to 20 weeks in the current study, we could not determine the best treatment period for cancer patients' illness trajectory. We also need to address this issue in a future study.

The present findings are very limited because our case series is seriously flawed by many methodological weaknesses, especially many types of bias resulting from systematic and random errors. However, our experience indicates that the PST is a promising psychosocial intervention that should be investigated in further well-designed clinical trials in Japanese clinical oncology settings. We are now planning a clinical trial to investigate the effectiveness of PST on fear of recurrence among breast cancer survivors.

Funding

This study was supported in part by a Grant-in-Aid for Cancer Research from the Japanese Ministry of Labor, Health and Welfare.

Conflict of interest statement

None declared.

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Palliative and Supportive Care (2008), 6, 225–230. Printed in the USA.

doi:10.1017/S1478951508000369

Psychiatric disorders and background characteristics of cancer patients' family members referred to psychiatric consultation service at National Cancer Center Hospitals in Japan

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(RECEIVED May 10, 2007; ACCEPTED August 17, 2007)

ABSTRACT

Objective: Psychological distress of cancer patients' family members is treated by psychiatric consultation service for outpatients at National Cancer Center Hospitals in Japan. The purpose of this study was to identify psychiatric disorders and explore background characteristics of cancer patients' family members referred to psychiatric consultation service, so that we could better understand current utilization of this psychiatric consultation service for cancer patients' family members.

Methods: A retrospective descriptive study using clinical practice data obtained for 5 years (from January 2000 to December 2004) was conducted at two National Cancer Center Hospitals. We reviewed the psychiatric consultation database, computerized patient database of the National Cancer Center Hospitals, and medical charts of cancer patients' family members who were referred to psychiatry and their cancer patients.

Results: Out of a total of 4992 psychiatric consultations, 118 (2%) were for cancer patients' family members. The most common psychiatric disorders among cancer patients' family members were adjustment disorders ($n = 69$, 58%), followed by major depression ($n = 30$, 25%). Female ($n = 101$, 86%), spouse ($n = 87$, 74%), married ($n = 92$, 78%), and housewife ($n = 63$, 53%) were the most common background characteristics of the family members. Sixty-four percent of cancer patients ($n = 75$) were hospitalized at the time of their family members' referral and 34% of cancer patients ($n = 40$) had already received psychiatric consultation service and 55% of cancer patients ($n = 65$) had delivered bad news prior to their family members' referral.

Significance of the research: We found that very few family members were provided with psychiatric consultation service at two National Cancer Center Hospitals. Adjustment disorders are suggested to be the most common psychiatric disorders among cancer patients' family members.

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KEYWORDS: Psychiatric disorders, Background characteristics, Cancer patients', family members, Psychiatric consultation, Japan

INTRODUCTION

Cancer is recognized as a disease that influences all the family members (Rait & Lederberg, 1990; Saeki et al., 2000), and psychological distress of cancer patients' family members is considered to be equal to that of cancer patients themselves in Western countries (Kissane et al., 1994; Plumb & Holland, 1977). Previous studies using self-report questionnaires have reported that probable cases of clinical psychological distress were 20%–30% (Pitceathly & Maguire, 2003). The few studies using psychiatric interviews have found that approximately 10%–50% of family members experience some form of psychiatric morbidity (Sharan et al., 1999; Pitceathly & Maguire, 2003).

Psychological distress of cancer patients' family members is treated by psychiatric consultation service for outpatients at National Cancer Center Hospitals in Japan. We recently reported on psychiatric disorders among cancer patients' family members of the National Cancer Center Hospital East in Japan and showed that very few family members were provided with psychiatric consultation service (3% of total psychiatric consultations; Akechi et al., 2006). This result raises the possibility that psychological distress among family members may be underestimated; thus, the development of an efficient consultation service for cancer patients' family members is an urgent issue in Japan. Therefore, we need to examine the psychiatric consultation data of two National Cancer Center Hospitals to improve the institutional bias regarding psychiatric disorders and background characteristics in family members noted in our previous study (Akechi et al., 2006).

The clinical characteristics of cancer patients are important factors that influence the psychological distress of family members. For example, physical characteristics such as pain (Miaskowski et al., 1997), vomiting or delirium (Prigerson et al., 2003), and advanced disease status (Kurtz et al., 1994; Weitzner et al., 1999) were associated with psychological distress in family members. Furthermore, psychological distress in cancer patients was positively associated with psychological distress in caregivers in a recent meta-analysis (Hodges et al., 2005). Thus, the clinical characteristics of cancerpatients can be regarded as important information concerning the psychological states of family members. In particular, clinical characteristics of cancer patients including those both medical and psychological provide useful information for health care professionals because they can be used to determine the timing of family members' psychiatric consultations. Therefore, we examined two clinical characteristics of cancer patients as the background characteristics of family members: "patient had received psychiatric consultation service" and "patient had delivered bad news" prior to their family members' referrals.

The purpose of this study was to identify psychiatric disorders and explore background characteristics of cancer patients' family members referred to a psychiatric consultation service, so that we could better understand current utilization of this psychiatric consultation service for cancer patients' family members.

METHODS

Psychiatric Consultation Service at National Cancer Center Hospitals

As of January 2004, the National Cancer Center Hospital had 600 beds and staff members of the Psychiatry Service were one staff psychiatrist as outpatient clinician, one part-time adjunct psychiatrist, one part-time clinical psychologist, and one psychiatric clinical nurse specialist. The National Cancer Center Hospital East has 425 beds and staff members of the Psychiatry Service were two staff psychiatrists and three part-time psychiatrists as outpatient clinicians, one part-time adjunct psychiatrist, and one clinical psychologist.

Both Psychiatry Services provide two main services, one for outpatients and one for inpatients who were referred from physicians belonging to other divisions who are responsible for cancer patients. Psychological distress of cancer patients' family members is treated by psychiatric consultation service for outpatients at National Cancer Center Hospitals in Japan, and health care professionals pay attention to psychological distress of cancer patients' family members and recommend the use of the psychiatric consultation service, if necessary.

Furthermore, both Psychiatry Services share the psychiatric consultation database records, and information was input into the database by psychiatrists after they had conducted patient examinations. This computerized database (Akechi et al., 2001a) included demographic variables such as age, gender, marital status, and employment status as well as psychiatric diagnosis. The psychiatric disorders were diagnosed at the time of the family member's initial visit according to the *Diagnostic and Statistical*

Manual of Mental Disorders, 4th edition (DSM-IV). Each psychiatry division is independent; however, a case conference is held weekly to have consistency in psychiatric diagnosis and treatment.

Subjects and Procedure

First, we reviewed the psychiatric consultation database records of the Psychiatry Services of the National Cancer Center Hospital and the National Cancer Center Hospital East for the period from January 2000 to December 2004 to obtain characteristics of outpatients and background characteristics of family members who were referred to the Psychiatry Service. Family members were defined as first-degree relatives (spouse, parents, children, siblings) of cancer patients. Background characteristics of family members such as age, gender, marital status, employment status, and psychiatric diagnosis were obtained from psychiatric consultation database records.

Then, we examined family members' medical charts to identify other background characteristics such as their relationship to the cancer patient and history of psychiatric disorder.

Finally, we examined the overall computerized patient database of National Cancer Center Hospital and National Cancer Center Hospital East and the patients' medical charts to identify cancer patients whose family members had been referred to the Psychiatry Service. Thereafter, we reviewed the patients' medical charts to obtain clinical characteristics such as patient cancer site, patient setting, patient had received psychiatric consultation service prior to their family referrals (presence or absence, date, psychiatric disorders), and patient had delivered bad news prior to their family referrals (presence or absence, date, the type of information). Four types of bad news were categorized according to the main type of information given to the cancer patient: initial cancer diagnosis, treatment failure or disease progression, transition to palliative care, and poor prognosis or limited life expectancy.

Informed consent and the approval of our institutional review board were not obtained because this was a retrospective study using clinical practice data.

RESULTS

Characteristics of Patients Who Were Referred to a Psychiatric Consultation Service

Of a total of 4992 psychiatric consultation services, 1436 (29%) were for outpatients. Among psychiatric consultation services for outpatients, 1273 (26%) were for cancer patients, 118 (2%) were for family members, and 45 (1%) were for medical staff members at two National Cancer Center Hospitals. The proportion of family members who were referred to psychiatry as outpatients were 2% ($n = 56$) of the total of 3064 consultations at the National Cancer Center Hospital and 3% ($n = 62$) of the total of 1928 consultations at the National Cancer Center Hospital East.

Background Characteristics of Family Members Who Were Referred to a Psychiatric Consultation Service

We identified the most frequent background characteristics of the family members who were referred to each Psychiatry Service at two National Cancer Center Hospitals as shown in Table 1: female ($n = 101$, 86%), spouse ($n = 87$, 74%), married ($n = 92$, 78%), and housewife ($n = 63$, 53%).

Among background characteristics of family members, the most common patient cancer site was the lung ($n = 18$, 15%), followed by the stomach ($n = 12$, 10%). Many of the cancer patients were hospitalized at the time of their family members' referral ($n = 75$, 64%), and a few of them had died ($n = 9$, 8%).

Thirty-four percent ($n = 40$) had received psychiatric consultation service for cancer patients prior to their family members' referrals. The most common psychiatric disorder among cancer patients was adjustment disorders ($n = 13$, 11%), the second was major depression and no diagnosis ($n = 7$, 6%), and the third was delirium ($n = 6$, 5%) The period from patients' psychiatric consultation to family members' referrals ranged from 0 to 896 days (mean $\pm$ *SD*: 75 $\pm$ 149, median: 16).

Fifty-five percent of cancer patients ($n = 65$) had delivered bad news for patients prior to their family members' referrals. The types of bad news were initial cancer diagnosis ($n = 19$, 16%), treatment failure or disease progression ($n = 13$, 11%); transition to palliative care ($n = 9$, 8%), and poor prognosis or limited life expectancy ($n = 24$, 20%). The period from patients' delivery of bad news to family members' referrals ranged from 0 to 427 days (mean $\pm$ *SD*: 31 $\pm$ 63, median: 12).

Psychiatric Disorders of Family Members Who Were Referred to a Psychiatric Consultation Service

The most common psychiatric disorders among cancer patients' family members were adjustment disorders ($n = 69$, 58%: with anxiety, $n = 21$; with depressed mood, $n = 12$; with mixed anxiety and depressed mood, $n = 35$; and with mixed disturbance of emotions and conduct, $n = 1$), followed by major depression ($n = 30$, 25%) as shown in Table 2. The

Table 1. *Background characteristics of family members who were referred to psychiatric consultation service*

	Total (n=118)		NCCH (n=56)		NCCHE (n=62)	
	n	(%)	n	(%)	n	(%)
Age (years)						
Mean ± SD	51 ± 13		49 ± 13		52 ± 13	
Range	20–79		26–74		20–79	
Gender						
Male	17	(14)	7	(13)	10	(16)
Female	101	(86)	49	(88)	52	(84)
Relationship to patient						
Spouse	87	(74)	34	(61)	53	(85)
Parent	16	(14)	12	(21)	4	(6)
Children	13	(11)	9	(16)	4	(6)
Sibling	2	(2)	1	(2)	1	(2)
Marital status						
Married	92	(78)	41	(73)	51	(82)
Unmarried	11	(9)	8	(14)	3	(5)
Divorced	1	(1)	1	(2)	0	0
Widowed	14	(12)	6	(11)	8	(13)
Employment status						
Full time	29	(25)	15	(27)	14	(23)
Part time	15	(13)	6	(11)	9	(15)
Housewife	63	(53)	29	(52)	34	(55)
Retired	5	(4)	1	(2)	4	(6)
History of any psychiatric disorder						
Presence	14	(12)	9	(16)	5	(8)
Absence	104	(88)	47	(84)	57	(92)
Patient cancer site						
Lung	18	(15)	6	(11)	12	(19)
Stomach	12	(10)	7	(13)	5	(8)
Colon	8	(7)	4	(7)	4	(6)
Esophagus	8	(7)	3	(5)	5	(8)
Breast	6	(5)	1	(2)	5	(8)
Head and neck	7	(6)	1	(2)	6	(10)
Leukemia	6	(5)	2	(4)	4	(6)
Others	41	(35)	28	(50)	13	(21)
Patient setting						
Inpatient	75	(64)	40	(71)	35	(56)
Outpatient	22	(19)	9	(16)	13	(21)
Deceased	9	(8)	3	(5)	6	(10)
Patient had received psychiatric consultation service						
Presence	40	(34)	25	(45)	15	(24)
Absence	66	(56)	27	(48)	39	(63)
Patient had delivered bad news						
Presence	65	(55)	44	(79)	21	(34)
Absence	41	(35)	8	(14)	33	(53)

Some percentages do not add up to 100% because of missing data. NCCH: National Cancer Center Hospital. NCCHE: National Cancer Center Hospital East.

National Cancer Center Hospital had a higher proportion of adjustment disorders (73% vs. 45%) and lower proportion of major depression (14% vs. 35%) than the National Cancer Center Hospital East.

Table 2. *Psychiatric disorders of family members who were referred to psychiatric consultation service*

	Total (n=118)		NCCH (n=56)		NCCHE (n=62)	
	n	(%)	n	(%)	n	(%)
Adjustment disorders	69	(58)	41	(73)	28	(45)
Major depression	30	(25)	8	(14)	22	(35)
No diagnosis	9	(8)	1	(2)	8	(13)
Others	10	(8)	6	(11)	4	(6)

NCCH: National Cancer Center Hospital. NCCHE: National Cancer Center Hospital East.

DISCUSSION

In this study, we found that very few family members were provided with psychiatric consultation service at two National Cancer Center Hospitals (2% of total psychiatric consultation services). Considering psychological distress of cancer patients' family members is equal to that of cancer patients, this result shows the possibility that psychological distress among family members may be underestimated or psychiatric consultation services for family members might not be working enough. A recent study using consecutive sampling in the United States showed only 15% of caregivers with psychiatric disorders accessed a mental health professional (Vanderwerker et al., 2005), though cancer patients' family members are considered as "second order patients" (Rait & Lederberg, 1990). In addition, Japanese cancer patients' family members often devote more time to their role as caregiver (Long & Long, 1982), so this feature of Japanese people may prohibit the utilization of psychiatric consultation services. Cancer center hospitals have the advantage of being able to provide psychiatric treatment for family members at the same hospital at which the cancer patient is being treated, so the dissemination of psychiatric consultation services for family members is desirable.

More than half of family members who were referred to psychiatric consultation services suffered from adjustment disorders in this study; adjustment disorders are suggested to be the most common psychiatric disorders among cancer patients' family members. Recent study in the United States indicated that a total of 13% of the caregivers of advanced cancer patient had met criteria for psychiatric disorder; however, this study did not assess adjustment disorders (Vanderwerker et al., 2005). A future study using consecutive sampling of cancer patients' family members is needed to identify the prevalence of psychiatric disorders, including adjustment disorders.

Women, spouses, and housewives were the relatively common background characteristics of the

family members who were referred to psychiatric consultation services at both National Cancer Center Hospitals. A previous review study demonstrated that female primary caregivers had high levels of psychiatric morbidity attributable to caregiving: women spend more time on caregiving, report higher levels of caregiver burden and role strain, and are less likely to obtain informal support for caregiving (Yee & Schulz, 2000). Female spouses of cancer patients' may experience high level of psychological distress. However, the clinical setting for our psychiatric consultation service (during the daytime on weekdays) may have prevented male full-time workers from using this service.

Lung and stomach were the most common cancer sites among the patients; this result is consistent with the most common causes of death among men (Ministry of Health, Labour and Welfare, 2004), reflecting the high proportion of female spouses referred for psychiatric consultation in this study. Many of the patients whose family members were referred were hospitalized. Recent studies report that spousal hospitalization for cancer was associated with an increased risk of death among elderly people (Christakis & Allison, 2006), so careful attention to psychological distress and the appropriate recommendation for psychiatric consultation services for spousal caregivers of inpatients by health care professionals may be a strategy for early treatment of psychological distress among family members.

Among clinical characteristics of cancer patients whose family members were referred, 34% of the cancer patients had already received psychiatric consultation services because of psychological distress prior to their family members' referrals. The likelihood of a family member being recommended for outpatient consultation may increase if the cancer patient has already been referred for inpatient consultation, because such a situation increases the accessibility of the members of our psychiatric service to the family members. In addition, family members may be more likely to consult the psychiatric service on their own behalf if the cancer patient has already received consultation. Most family members did not know that psychiatric consultation service is available for cancer patients' family members as well as cancer patients when members of the Psychiatry Service recommend family members to consult, so dissemination of this information is also necessary. The proportions of psychiatric disorders among cancer patients whose family members were referred to psychiatric consultations were nearly equal to those for overall patient consultations (Akechi et al., 2001a), suggesting that no particular psychiatric disorder experienced by cancer patients leads to the need for psychiatric consultation service for family members.

In addition, 55% of the cancer patients had delivered bad news prior to their family member's referral and the types of bad news ranged from diagnosis to prognosis. Regardless of the content, having delivered bad news regarding cancer is a stressful life event for cancer patients, so this event might lead family members to psychological distress. Moreover, Japanese cultural background of delivering bad news and decision making after delivering bad news might be associated with family psychological distress: Information about cancer prognosis and treatment plans are usually given to the families before being given to the patient in Japan (Hattori et al., 1991; Ministry of Health and Welfare, 1994) and family opinions are accorded a larger role by a Japanese patient in decision making (Saeki et al., 2000). So further studies are needed to clarify the association between psychological distress of family members and these events: "patient had received psychiatric consultation service" and "patient had delivered bad news."

This study has several limitations. First, we were only able to examine families who used the psychiatric consultation service. So we could not discuss the association between family members' background characteristics and psychological distress because accessibility to this psychiatric consultation service may influence the results. Second, this study has some methodological limitations because of its retrospective study design: We could not identify all the cancer patients whose families were referred to psychiatric consultation service nor could we identify other characteristics such as actual triggers for family members' psychiatric consultations.

ACKNOWLEDGMENTS

This study was supported in part by a Third Term Comprehensive 10-Year Strategy for Cancer Control grant from the Japanese Ministry of Health, Labour and Welfare.

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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
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

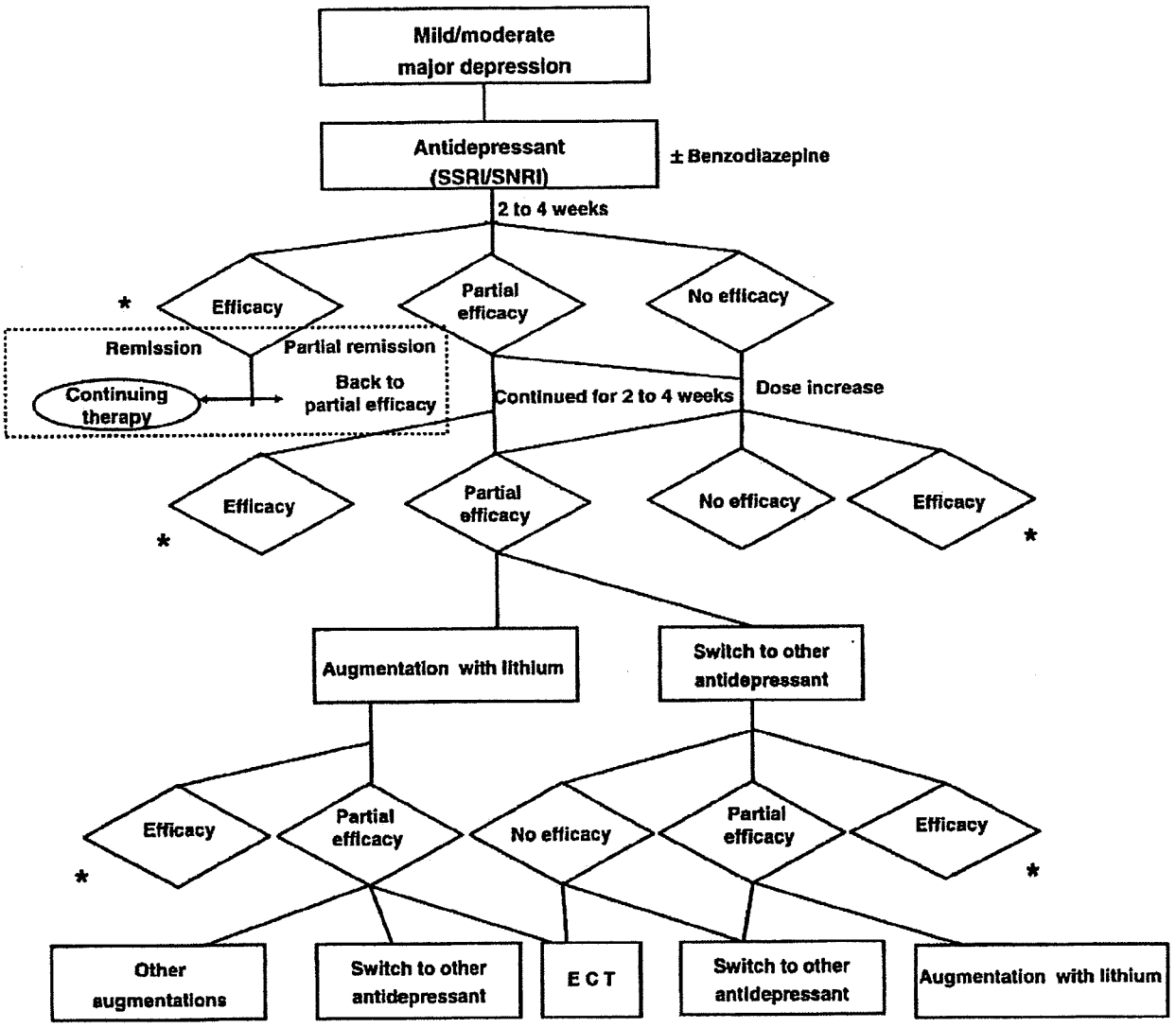

Figure 1. Algorithm for the treatment of major depression, mild or moderate. *Dotted rectangle: evaluate outcome (remission or not) in case of efficacy. SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin-noradrenaline reuptake inhibitor; TCA, tricyclic antidepressant; non-TCA, non-tricyclic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

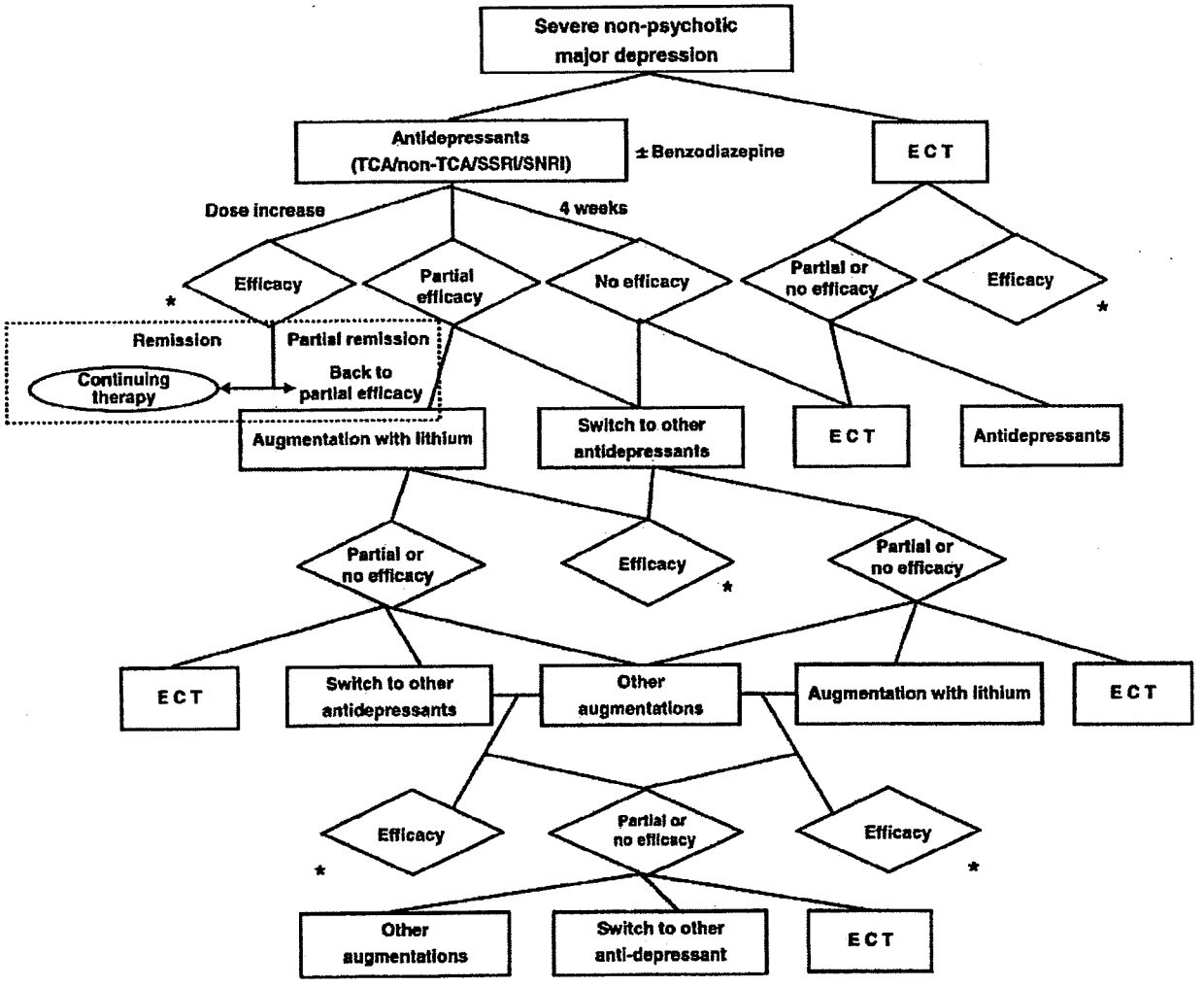

Figure 2. Algorithm for the treatment of non-psychotic severe depression. *Dotted rectangle: evaluate outcome (remission or not) in case of efficacy. SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin-noradrenaline reuptake inhibitor; TCA, tricyclic antidepressant; non-TCA, non-tricyclic antidepressant;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